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Handbook of Minerals as Nutritional Supplements
Robert A. DiSilvestro
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Handbook of Minerals as Nutritional Supplements

Robert A. DiSilvestro

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Preface

The Internet, television, and magazines are flooded with nutrition supplement advertisements, with many claims being made for various products. One area with an especially large recent growth spurt is the mineral supplement area. Moreover, a number of nutrition business trade journals are projecting that the mineral supplement market should see sustained growth over the next few years. As claims continue to be made for various mineral supplement products, major questions are arising, such as:

- What research, if any, is behind these claims?
- Do different forms of mineral supplements have different efficacies?
- Are these supplements beneficial only for correcting deficiency, or can there be benefits of eating more than the levels currently recommended as adequate?
- What are the safety issues of mineral supplements?

These questions are being asked not only by the general public, but also by many health care professionals, biomedical researchers, and people involved in the nutrition industries themselves. This last group is especially important to public health because their marketing can drive the sales of supplements. Therefore, the players in nutrition industries, as well as health care professionals and researchers, need a way to evaluate mineral supplement claims. Some information can be obtained using a quick search of the Internet, or by using a program like Medline. However, interpretation of the information obtained can be hampered by the lack of a specialized background and time available. For example, if one study says that a calcium supplement has no effect on blood pressure, and another study says the opposite, how does one reconcile the conflict? Someone with a good biomedical background can search out the issue, but this can be very time consuming.

This book is intended to provide a concise, yet informative presentation and interpretation of the current state of research on various mineral supplements. Each of the above-noted questions are addressed. The information should be technical enough to satisfy a biomedical audience but will avoid jargon used mainly by mineral specialists. Even so, it’s hard to write this type of a book without using some words for which the definition may not be known. Therefore, this book includes a glossary for some words that appear often.

As author of this book, I have tried to present more than one perspective for controversial areas, but I have also given my opinions on many of them. When I have given my opinion, I have tried to clearly state that this is what I am doing.

There is no doubt that more research is needed in almost all the areas I cover in this book. In that regard, I have pointed out some of what I think should come
next in research. At the same time, I recognize that a lot of people, from the general public to the most dedicated researcher, sometimes get frustrated if a report on nutrition or any other subject is totally noncommittal. So, I state what I feel is safe to conclude right now, and I provide some conjectures.

My hope is that this book can spur many of us to further consider how mineral supplements should and should not be used for health promotion and health care.
Acknowledgments and Conflicts of Interest

I would like to thank Gordon Wardlaw for reading and giving feedback on every chapter, and Elizabeth Joseph for a great deal of assistance with the reference aspects of the book preparation. I would also like to thank Emily Dy for help with references in the chapter on iron. In addition, I appreciate the help of each of the following for comments on individual subjects: Michael Bergeron, Priscilla Clarkson, Steve Abrams, Connie Weaver, Greg Miller, and Greg Wiet. I also appreciate my wife, Janet, and children, David, Daniel, and Lisa, for allowing me the enormous amount of time it took to complete this writing. Finally, I want to express great appreciation to Stacey Bell for having the original concept for the book and helping me get it off the ground.

I endeavored to present the issues in this book as honestly as I could, without trying to make any product supplier look better or worse than reality dictated. Even so, I do want to note the companies that have supported parts of my own mineral research: Albion Laboratories, Nutrition 21, Glanbia, and Purac of America.
Author

Dr. Robert DiSilvestro is professor of nutrition at The Ohio State University.

He earned his Ph.D. in Biochemistry from Texas A&M University in 1982 after receiving his Bachelor of Science from Purdue University, where he majored in Biochemistry.

DiSilvestro is the author or co-author of more than 70 peer-reviewed, research journal articles. He has also authored several reviews, including an invited review of a trace mineral manual for Free Radical Biology & Medicine, a journal.

He’s been a featured speaker for a National Institute of Health workshop on the current state of zinc research as well as speaking on minerals for a functional food symposium at an annual meeting of the Institute of Food Technology.

This is his first book.
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Calcium

Calcium is currently one of the most used nutritional supplements. Most of this interest comes in relation to osteoporosis prevention or treatment, though other uses also spring up. There are many types of supplements on the market and different messages on how they should be taken. One thing seems certain: Calcium supplementation will remain popular for the foreseeable future.

OVERVIEW OF FUNCTION

Calcium, as part of calcium phosphate, is the main structural component of bones and teeth. In addition, calcium is involved in a long list of reversible activating and regulatory actions. In fact, calcium movements in and out of cells or cell organelles are essential to many basic physiological functions, including neurological actions and cardiac muscle contraction. Part of calcium’s functions inside cells is to act as what is called a “second messenger.” This name arises because the shifting of calcium between pools is often a way that a hormone or other signaling molecule starts a process within a cell. In addition to intracellular second messenger functions, calcium also seems to serve as an extracellular messenger outside cells. Calcium is well suited to the activator/regulator roles, because this metal is a strong enough chelate former to complex with a signaling molecule, such as a receptor, but a weak enough chelate former to also fall back off the molecule.

The bone function of calcium seems to be better preserved than the activator/regulator functions, since bone releases some calcium if the body’s supply falls off. However, not all activating/regulatory functions are necessarily preserved perfectly in times of low calcium supply.

OVERVIEW OF METABOLISM

The activator/regulator functions are so essential to life, and are so sensitive to changes in calcium concentrations, that the body needs powerful mechanisms to maintain calcium homeostasis. These mechanisms exist especially for plasma calcium levels, and for the transport of calcium in and out of cells and in and out of cell organelles. This movement maintains the cytoplasmic concentration of ionized calcium (calcium ion in a relatively unbound state) in the micromolar range (over a thousand-fold less than plasma calcium concentrations). This low cytoplasmic calcium ion concentration is essential to calcium’s second messenger functioning.
Otherwise, small calcium ion fluxes would not impact the cellular environment enough to send signals.

About 1% of bone calcium exchanges freely with extracellular fluid and, therefore, is available for resisting changes in plasma calcium concentrations. Normally, about 40% of blood calcium is bound to plasma proteins, primarily albumin. The remaining 60% includes ionized calcium plus calcium complexed with phosphate and citrate.

Calcium absorption from the intestine, as well as movement between bone and blood, revolves around vitamin D-derived hormones, parathyroid hormone, and, to a lesser extent, calcitonin. Parathyroid hormone is released into the blood in response to decreases in plasma calcium. This action rapidly increases plasma calcium due to actions such as increased intestinal absorption of calcium, increased calcium retention by the kidney, and release of calcium from bone (bone resorption). Vitamin D hormones, especially 1′25-dihydroxycholecalciferol, also increase intestinal calcium absorption and bone resorption. The intestinal effect works in part by increasing calcium binding proteins, which increase calcium absorption. This type of absorption regulation is the opposite of what is seen for iron or zinc. With these metals, intestinal binding proteins decrease absorption. Thus, calcium absorption is increased by active regulation, but iron and zinc absorption is increased passively by diminishing barriers to absorption.

Calcitonin tends to lower plasma calcium concentration by increasing cell uptake, renal excretion, and bone formation. The effects of calcitonin on bone are much weaker than those of either PTH or vitamin D.

Vitamin D hormones, in addition to regulating calcium absorption and bone resorption, are involved in promoting some of calcium’s regulatory functions.

**NUTRITIONAL STATUS ASSESSMENT**

Plasma or serum total or ionized calcium is sometimes used to assess calcium nutritional status and for short-term assessments of calcium absorption. When there are large changes in calcium status, such as with the correction of severe calcium-deficiency rickets, serum calcium can show small changes. However, usually serum calcium measurement is not useful for assessing calcium status because, as just mentioned, serum calcium levels are regulated heavily. Sometimes, parathyroid hormone readings are done since they respond to fluxes in plasma calcium, though this is not the only influence. Other alternatives are reviewed by Cashman and Flynn. One is a calcium retention test, which utilizes urinary calcium. Another approach is the use of functional indices such as blood and urine markers of bone metabolism. Since these markers are affected by multiple factors, their prime use is for monitoring calcium intervention studies (i.e., to compare values before and after increased calcium intake). For population, long-term calcium status assessment, sometimes diet analysis is used, with the results compared to bone density or markers of bone metabolism.
Calcium absorption from different foods is known to vary. The classic “high bioavailability” food group is diary products, while the classic “low bioavailability” food is spinach, where most calcium is in the water-insoluble oxalate form. Some food components, such as the compound phytate, are known to inhibit calcium absorption.

High dietary protein has been said to both increase and decrease calcium balance, and consequently bone strength. One attempt to reconcile this conflict has been made by Dawson-Hughes. She notes that on the one hand, dietary protein stimulates the production of insulin-like growth factor-1 (IGF-1), which promotes osteoblast-mediated bone formation. On the other hand, dietary protein also increases urinary calcium losses by several proposed mechanisms. According to the Dawson-Hughes hypothesis, the influence that predominates depends on dietary calcium intake (at high intake, the positive effect is more prominent). By that author’s own admission, some but not all studies support the hypothesis. Possibly, the hypothesis is generally true, but some other factors may come into play.

In this author’s opinion, the key to the protein–calcium issue is to eat adequate calcium. If that is done, then even if high protein intake does have negative effects, they may not be enough to seriously affect calcium functional status.

Many different calcium complexes have been marketed for pill or capsule consumption or to fortify foods. A number of these have been used in studies where the supplement produces some effect associated with improved bone health (Table 1.1).

**TABLE 1.1**

Examples of Calcium Complexes That Give Positive Results in Bone Studies

<table>
<thead>
<tr>
<th>Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbonate*</td>
</tr>
<tr>
<td>Citrate</td>
</tr>
<tr>
<td>Citrate malate</td>
</tr>
<tr>
<td>Acetate</td>
</tr>
<tr>
<td>Phosphate</td>
</tr>
<tr>
<td>Gluconate</td>
</tr>
<tr>
<td>Lactate</td>
</tr>
</tbody>
</table>

* Calcium carbonate can be in a relatively isolated form or part of a natural preparation such as eggshell or coral calcium.
The fact that all forms of calcium named in Table 1.1 have been able to produce positive effects on bone health suggests that all can be used effectively by people. There are also a few studies that show similarities in absorption rates between different calcium supplements. For example, in rats, the apparent calcium absorption is reported to be the same from carbonate, gluconate, oyster shell, and bovine bone.\textsuperscript{10} On the other hand, calcium citrate has been reported to have better absorption than calcium carbonate, though this finding is not completely uniform.\textsuperscript{11,12,13} One reason for the diverse results could be that a number of different evaluation criteria have been used. It has also been suggested that the vitamin D and estrogen status of the subjects may affect comparisons between different types of calcium supplements.\textsuperscript{13} Whatever the reason for the differing results, some health care professionals and some researchers emphasize the better absorption potential of calcium citrates, while others point out that carbonate, at worst, still works nearly as well, is cheaper, and requires smaller delivery vehicle mass (due to more calcium per total complex weight). Another consideration can be GI tract tolerability. Some people have some distress with carbonate, though this may be lessened by splitting the daily dose into two ingestion times. Also, the GI tract distress may be temporary in many people. However, for people with health problems, the antacid effect of calcium carbonate may be undesirable in the long term.

Another kind of calcium supplement is milk extract calcium, such as that sold by Glanbia Ingredients Inc. This author’s laboratory has completed a small pilot study with this product. In a short intervention (six weeks), the milk calcium product produced a small decrease in a marker of bone degradation, which was not seen for calcium carbonate (Figure 1.1).

Calcium phosphate, due to its high water solubility, is used to fortify drinks like soy milk and is part of the calcium fortification in some orange juices. This form of calcium is also used in some pills because it is well tolerated by people who may have GI tract issues with calcium carbonate.

Calcium lactate finds its way into some food and pharmaceutical applications, sometimes mixed with calcium gluconate. For food applications, calcium lactate has desirable properties in terms of neutral flavor and stability. Calcium lactate is well absorbed\textsuperscript{14} and, in a rat study,\textsuperscript{15} shows better bone-stimulating activity than calcium carbonate or citrate. Calcium lactate is also sold as pills and as powder that a consumer can mix into drinks at home. This can be an economical alternative to some other forms of calcium supplementation.

Coral calcium, which is a type of calcium carbonate supplement, has been the subject of many extravagant claims. Along these lines, some Internet sites state that the many merits of coral calcium have been extensively researched. However, the papers cited on these websites generally do not actually involve studies of coral calcium. Instead, the research deals with calcium function in general, including many regulatory functions that are not even known to be affected by typical variations in calcium intake. In reality, only one original research paper relevant to coral calcium supplements appears in a Medline search of “coral + calcium + human.”\textsuperscript{16} This paper reports that in an acute test of calcium uptake, in a small number of people, one type of coral calcium preparation fares better than another type of calcium carbonate.
FIGURE 1.1 Bone specific alkaline phosphatase response to calcium supplementation as calcium carbonate or a milk calcium extract. Young adult females were given about 700 mg calcium/day for six weeks. Values are Units/L ± SEM. *Significantly different from pretreatment (p < 0.05, paired t-test).
However, this study does not compare coral calcium with calcium citrate, which may be better absorbed than calcium carbonate.

Some coral calcium advertisements claim superiority to other calcium supplements based partly on the inclusion of magnesium. However, the amount of magnesium varies. Moreover, there is no data presented to demonstrate how well this magnesium is absorbed in the presence of the calcium. Another highly advertised claim of coral calcium is that it can affect various aspects of health by manipulating body pH. This claim has no research backing. In regard to another issue, coral calcium is often presented as the reason for the longevity of certain Okinawans. However, there is no actual research data to indicate that coral calcium intake is what is responsible for any of the longevity. Therefore, considering all these issues related to coral calcium, there is no clear research justification for the extra expense compared to other calcium supplements.

Some calcium complexes have found a niche for specialized applications. In these applications, attention must often be given to the effects of calcium complex on pH as well as other chemical actions. For example, calcium gluconate is used for some infant formulas and TPN solutions. On the other hand, this form of calcium has not had tremendous popularity in pill or capsule form because of the relatively low percentage of calcium. This means a person has to take more or bigger calcium gluconate pills per dose compared to calcium carbonate. Even so, based on a rat study, calcium gluconate may have one selling point: Rats fed a calcium gluconate diet had a higher apparent absorption of magnesium than the rats fed the other calcium supplements, possibly because the gluconate stimulates magnesium absorption.

This observation for gluconate contrasts a concern that calcium supplements can antagonize magnesium absorption. For this reason, some people avoid taking a mixture of the two minerals, since each mineral may impair the absorption of the other. In contrast, some people take supplements that mix calcium and magnesium. The feeling is that the possible loss in absorption of each mineral is compensated by the increased intake of each. There is also another reason why some people feel that if one takes calcium, then one should also take magnesium. This reason is that high body calcium-to-magnesium ratios have been stated to be problematic. The concerns about this ratio, as well as possible impairment of magnesium absorption by calcium, are covered below in the Toxicity section. The opposite issue, magnesium impairing calcium absorption, is covered in the Magnesium chapter under Toxicity.

Calcium supplement bioavailability may be affected by the ability of the pill itself to dissolve. A website put out by Kansas State University (http://www.oznet.ksu.edu/ext_f&n/_timely/calcium.htm) suggests buying brand-name calcium supplements because the solubility may be better. The site also suggests testing the ability of a calcium pill to dissolve in 6 ounces of vinegar in 30 minutes.

Two other factors have been considered in regard to calcium supplement bioavailability. These are the timing around meals and the splitting of the daily dose into different ingestion times. The latter seems to help with calcium absorption, with 500 mg or less per single ingestion time as a common recommendation. The timing with meals is a less-settled issue. Calcium carbonate may be better taken
with meals, since the acid involved in food digestion can help dissolve calcium carbonate. Some groups, including an NIH panel, have recommended between meals as the time to take other calcium supplements. For these other forms of calcium, an empty stomach may work fine, but is it an advantage to taking between meals? One advantage may be avoiding food components that may interfere with calcium absorption. However, it should be noted that some calcium supplements have shown good absorption properties even when taken with a meal. Thus, this author feels that at present, as far as calcium supplement absorption goes, there is no compelling reason to favor either with meals or between meals. On the other hand, for people prone to kidney stones, taking calcium with meals may present a distinct advantage (see below).

TYPICAL INTAKES VERSUS NEEDS

There has been considerable debate as to what constitutes “needs” for calcium. It is safe to say that many people of different ages and circumstances do not eat RDA levels of calcium consistently. Possible consequences of such eating behavior are being elucidated by supplement studies (considered in the next section).

Calcium is rather unique among nutrient minerals in that when discussing this mineral, the phrase “deficiency” is not mentioned very often. This is a little strange since, in essence, most proposed calcium supplement uses are primarily intended as correction of marginal calcium deficiency. Even so, this term is not brought up much.

Severe calcium deficiency is not reported to any large degree in the biomedical literature. The one exception pertains to childhood rickets. Although vitamin D deficiency is the typical diagnosed cause of this, calcium deficiency can also play a role. The use of calcium supplements in this situation is discussed in the next section.

CURRENT RESEARCH ON SUPPLEMENT USE

RICKETS

Rickets is a name for a pattern of bone development impairment generally ascribed to a vitamin D deficiency. Since vitamin D promotes calcium absorption, it stands to reason that calcium deficiency can also cause or contribute to rickets. If this is the case, then calcium supplementation can reverse, or help reverse, rickets in some situations. This concept has been verified by a series of studies in children in Nigeria. It remains to be seen whether similar findings would occur in other settings.

BONE IN CHILDREN AND ADOLESCENTS WITHOUT RICKETS

Calcium supplements are often given to children by parents, with or without the advice of their physicians, because it makes sense to be concerned about calcium intake. The feeling is that adequate calcium intake is important to reach full bone growth, plus to help prevent osteoporosis later in life. There are studies to support
this feeling. One review\textsuperscript{19} notes that a number of studies show that in children and adolescents, increased calcium intake, via supplement or foods, impacts at least one measure of bone mass and growth. Despite these successes, there are a number of unanswered questions, which are summarized in Table 1.2.

As far as the first question in Table 1.2, some early returns are in. In a Chinese study, calcium supplements are effective in children with a mean starting calcium intake of 567 mg/day.\textsuperscript{20} In a U.S. study, calcium supplementation is more effective if the mean calcium intake is below about 900 mg/day.\textsuperscript{21} Since this intake is not extremely low, perhaps even a relatively good calcium intake does not preclude a benefit of supplements. On the other hand, a different study of calcium supplementation in adolescent girls finds an effect on bone across a wide range of habitual calcium intakes.\textsuperscript{22} In fact, the starting average calcium intake is over 900 mg. The different results may be partly age-dependent, though this may not be the whole story.

This last study\textsuperscript{22} is also relevant to another issue raised in Table 1.2. In this study, exercise did not enhance the calcium effect. However, since exercise–diet interactions can vary with different circumstances, many more trials are needed before conclusions can be reached.

As far as the last question in Table 1.2, retention of the benefits of calcium supplementation after termination, a few results are available. What is available presents a conflicting picture:\textsuperscript{23,24} In fact, in one study, it appears that an increased bone acquisition rate during the supplement phase is almost balanced by a reduced acquisition rate after supplement withdrawal.\textsuperscript{23} Unfortunately, there is just not enough data to make a conclusion at present.

\textbf{OSTEOPOROSIS PREVENTION AND TREATMENT IN ADULTS}

The term “osteoporosis” describes a certain condition of low bone density that can have multiple causes and ages of onset. However, this term is most often used to describe a specific state that occurs in older women and sometimes in older men.\textsuperscript{1} Prevention is preferable to treatment, since it is impossible to produce high bone density once osteoporosis is present. Treatment is limited to inhibiting disease progression.\textsuperscript{1}

It makes sense that calcium intake can be a factor in osteoporosis prevention, since calcium is so intimately connected to bone health. Still, it should be noted that

\begin{table}
\centering
\caption{Questions Concerning Calcium Supplementation in Children Without Rickets}
\begin{tabular}{|l|}
\hline
At what level of dietary calcium intake would supplements become helpful? \\
Would dairy intervention have a bigger effect than calcium supplements? \\
If supplements are used, what is the ideal dose? \\
Do calcium supplements create currently undetected magnesium deficits in children? \\
Can the effects of calcium supplements on bone growth be improved by adding other interventions (e.g., weight bearing exercises, increased vitamin D intake, etc.)? \\
Are the gains in bone lost if calcium supplementation is discontinued? \\
\hline
\end{tabular}
\end{table}
osteoporosis is very multifactorial in nature, and the relative contributions of various factors are not well characterized. The general strategy for osteoporosis prevention is to maximize bone mass gain at younger ages and minimize bone loss at older ages. Bone mass tends to peak about age 30, and bone loss accelerates in women after menopause. Thus, most studies on osteoporosis prevention look at bone gain in young adult women or bone loss in postmenopausal women. In this light, it can be asked: How much does calcium intake contribute to osteoporosis prevention? This is not an easy question to answer. When examining the pre-30-year-old population, one is looking into a crystal ball (predicting future osteoporosis development). When examining older women, and asking what caused or prevented osteoporosis, one is taking a trip in a time machine (interpreting distant past history’s contribution to a current state). What is generally done for intervention studies, such as those for calcium supplementation, is one of two approaches. One approach is to study postmenopausal women for slowing of bone loss and reduction of fracture incidence. The other approach is to examine bone mass gain in young adult women, even though we cannot quantitatively translate a given gain into a degree of osteoporosis risk reduction.

Calcium intervention studies in older women are not easy to conduct because bone density changes occur slowly, while health states can be constantly changing. In addition, previous long-term history prior to study initiation could conceivably influence how well calcium interventions work. Nonetheless, studies have been carried out. Along these lines, a meta-analysis concludes that intake of calcium, from supplement or foods, can have a small effect on bone loss after two or more years. Moreover, the data shows a non-statistically significant trend toward reduction in vertebral fractures, though the variation is high. The variation is even more of a problem for non-vertebral fractures, where no conclusion is reached. Therefore, this analysis paper suggests that in postmenopausal women, a good calcium intake, from diet or supplements, can be a factor in reducing risk of osteoporosis. However, this analysis cannot really say just how important the calcium intake is by itself, or how it might synergize with other factors, such as vitamin D intake. In fact, it may be hard for any study to do this unless it includes a very large subject number, uses interventions that last several years, examines calcium plus and minus many combinations of other dietary and non-dietary interventions, considers women with different starting bone densities and histories, compares different supplement doses, and controls the diet for calcium intake and factors that influence calcium absorption. Such a research project would be quite an ambitious undertaking, which would be enormously expensive, and would require incredible effort by a lot of researchers. This explains why such a study has never been done.

As hard as it would be to do the project just described, it would even be harder to directly study premenopausal women in regard to calcium and osteoporosis risk. Such a project would have all the issues noted for postmenopausal women, plus there would be a lag time of decades before osteoporosis evaluation. So, such a study has never been done. Instead, studies on calcium supplementation and bone in premenopausal women have focused on bone mass gains for a year or more. Some studies have also used evaluations of urine/blood markers of bone metabolism, which can also be used in short-term studies of intervention effects on bone turnover.
There are studies in young adult women that say that adequate calcium intake, by supplements or diet, can increase peak bone mass. In addition, a meta-analysis finds that calcium supplementation of approximately 1000 mg/day in premenopausal women can prevent the loss of 1% of bone/year at all bone sites except in the ulna. Once again, though, an exact value for optimal intake and an exact effect on osteoporosis risk is unknown. Also, we don’t have a good handle on how the effectiveness of any given calcium intake varies with race, genetics (especially in regard to bone density), exercise and other lifestyle issues, and dietary factors other than calcium.

Although the research emphasis on calcium and osteoporosis has been on women, there are a few studies on bone density in men. For example, in a placebo-controlled study, in both men and women over 65 years of age, three-year daily supplementation with calcium and vitamin D moderately reduces bone loss at several sites. In addition, this treatment significantly decreases the rate of non-vertebral fractures. In two other studies, calcium plus hormone treatment increases bone mineral density in male patients with osteoporosis. However, these studies do not examine placebo or calcium alone. There are also some studies that show that calcium supplementation can have short-term effects on markers of bone metabolism in men.

**Hyperparathyroidism**

Certain medical situations produce high plasma concentrations of parathyroid hormone. This could produce a degree of calcium deficiency, since parathyroid hormone reduces calcium absorption and increases calcium excretion. Thus, it would make sense that a moderately high calcium intake would help prevent calcium deficiency during hyperparathyroidism. It would also make sense that a moderately high calcium intake can reduce high plasma concentrations of parathyroid hormone. This is stated because parathyroid hormone secretion increases when serum calcium starts to fall. Therefore, keeping calcium intake high would prevent stimulation of parathyroid hormone secretion.

The ability of calcium supplementation, especially in conjunction with vitamin D, to normalize parathyroid hormone levels is still controversial, but the efficacy may depend on the nature of the hyperparathyroidism. For hyperparathyroidism that is secondary to another disease, such as renal failure, (calcium supplementation sometimes plus vitamin D) may be able to serve as a sole treatment. Good adherence to treatment seems to be a necessity. Calcium supplementation also may help with bone health in secondary hyperparathyroidism. For instance, a calcium–vitamin D combination reverses senile secondary hyperparathyroidism, and reduces hip bone loss and risk of hip fracture in elderly institutionalized women.

For primary hyperparathyroidism, calcium or vitamin D supplementation is not considered a practical alternative to surgical parathyroidectomy, though some other non-surgical treatments are under consideration. However, calcium supplementation may be useful for mild, primary hyperparathyroidism. In 17 such people with a calcium intake below 450 mg/day, calcium supplementation (500 mg) gives a significant increase in femoral neck bone mineral density and a decrease
in circulating parathyroid hormone values. It would be interesting to see what would have happened with subjects eating more calcium. At present, we don’t know if there is a minimum dietary calcium intake where supplements would no longer be helpful.

When surgery is used for primary hyperparathyroidism, there can be a need for calcium supplementation after surgery. One study has concluded that an ionized calcium reading after surgery can identify the need for calcium treatment in the majority of patients. 35

**Blood Pressure**

The regulatory functions of calcium can affect blood pressure, but a practical question asks: Are typical variations in calcium intake a major factor in regulating blood pressure in many people? A number of years ago, there was a rush of interest in this question following an epidemiological study published in a prominent journal. However, over time the findings of this study became thought to be more relevant to intake just before the survey rather than long-term diet patterns. However, other epidemiological studies support relationships of chronic calcium intake to blood pressure. In addition, some intervention studies examine blood pressure responses to increased calcium intake via foods or supplements. Three meta-analyses of calcium intervention–blood pressure studies find a statistically significant effect. However, in each of these analyses, the conclusion is that any effect is small.

These results suggest that calcium supplementation would not make a good standalone (or even adjuvant) treatment for high blood pressure. However, it is possible that the effects of supplemental calcium on blood pressure could be enhanced greatly by some co-treatment. However, this author questions the value of a search for such a possibility when there are already known, non-pharmacological strategies to lowering blood pressure. These strategies are good not only for lowering blood pressure but for health in general. Therefore, the public may be better served by being encouraged to follow these strategies rather than search for some way to make calcium supplements work better.

A special class of hypertension is pre-eclampsia of pregnancy. The results for calcium supplementation in this regard are mixed. One review contends that calcium supplementation may not show effects in groups with no demonstrated risk of pre-eclampsia, but may show effects in high-risk groups. However, the review notes that this contention is based on negative results in a large study and positive results in a small number of subjects for this type of issue. Another review concludes that positive results have occurred primarily where there is low calcium intake, but also points to low subject numbers in these studies.

In this author’s opinion, calcium status is not the prime factor in dividing someone into a high-risk or low-risk category for pre-eclampsia. However, for someone in the high-risk category, marginally low calcium intake may increase the risk even more. If this is true, then eating adequate calcium may prevent pre-eclampsia in some women, but adequate calcium intake does not guarantee prevention of pre-eclampsia. In this author’s opinion, pregnant women should try to eat
adequate calcium via food (and in some cases, supplements) because this intake is a good idea in general, and it may sometimes prevent pre-eclampsia. However, at present, the basis for eating high amounts of calcium to prevent pre-eclampsia is still speculative.

**Blood Lipid Alterations**

A high calcium intake is proposed to reduce serum cholesterol and produce other desirable blood lipid changes. The mechanisms are thought to involve calcium binding to lipids and forming insoluble complexes. This action can inhibit intestinal absorption of cholesterol, reduce re-uptake of bile acids (which could accelerate cholesterol degradation), and lower fat absorption.

There are a series of experimental animal studies and human intervention trials that support the concept that high calcium intake, via supplements or foods, can affect lipid profiles. However, the picture is not completely clear cut. Epidemiological work is not fully supportive, and two large intervention studies in hypertensive and non-hypertensive people don’t find an effect for calcium. In addition, among the intervention studies showing an effect, in some cases, the effect is small, or is studied in a small number of people. Nonetheless, this author feels that the calcium effect could be real, at least in some people. This opinion is based on the fact that effects are seen by different research groups, and there is a considerable effect seen in some studies. Since the effect is not totally consistent between studies, either in terms of whether an effects is seen at all, or whether the effect is small or large, possibly a strong effect will only occur when certain processes are strongly affecting serum lipid profiles. More research should be done to determine if this notion is true and, if so, to identify the relevant processes.

**Colon Cancer**

Calcium has been considered as an influence on colon cancer risk. The exact mechanism by which calcium would work is not known. However, it is expected to involve a complex series of signaling events that affect the structural and functional organization of colon cells. There is also the possibility that calcium can work through intraluminal precipitation of hydrophobic, cytotoxic substances, in particular fatty and bile acids, which can promote colorectal cancer development. The idea that calcium intake is inversely correlated with colon cancer risk is supported by some, though not all, epidemiological population studies and work in experimental animals. A calcium–colon cancer prevention relationship is also supported by a number of calcium intake intervention studies, which measure precancer cellular and biochemical parameters. For example, in one study, subjects considered at high risk for colon cancer took 900 mg calcium/day as either calcium carbonate supplement or as low fat dairy products. Both interventions lower epithelial cell proliferation indexes from a higher- to a lower-risk pattern. However, not all studies on calcium and cell proliferation in humans have shown a clear-cut effect, and some studies are not very large or may not be well controlled. On the other hand, some differences in results may be due to how the proliferation is evaluated.
In this author’s opinion, at present, the calcium–colon cancer connection is interesting but unconfirmed. Full confirmation would require an actual calcium intervention–cancer incidence study, which would be a lengthy and costly undertaking with ethical issues to consider. In addition, there are questions about how many and what doses of calcium should be tested, and whether maximal effects would require attention to vitamin D intake. Thus, in this author’s opinion, there is not yet a clear picture of the role of calcium intake and colon cancer prevention, but the picture is worth clarifying by further precancer intervention research.

**WEIGHT LOSS**

Low dietary calcium has been theorized to influence fat weight gain by increasing secretion of hormones such as 1,25-OH-vitamin D and parathyroid hormone, which in turn influence fat production and breakdown. In addition, high dietary calcium may decrease digestive tract absorption of fat.

A number of epidemiological and experimental animal studies have shown an inverse relationship between adiposity and calcium intake. There have also been some retroactive weight loss analyses of observational studies. Although these studies were not set up to evaluate weight loss, it is interesting that retroactive analysis yields a statistically significant negative association between calcium intake and body weight. Some of these studies involve dairy interventions and some involve calcium supplementation. Most of these studies do not report very large promotion of weight loss (e.g., 0.346 kg/year). One could argue that such a small weight loss continued over a long period of time is still valuable. One could also speculate the weight loss could be bigger if the study were actually designed to examine weight loss.

In another study, published as a meeting abstract, three-day records of diet, supplements, and activity for adolescent girls are examined for calcium intake from diet and supplements. The most striking finding is that in girls with similar calorie intake and physical activity, girls who consumed more calcium tended to weigh less and have lower values for certain body fat measures. This interesting study can be evaluated more fully when a full publication appears.

Conspicuously absent from the current published research is calcium intervention studies designed specifically to examine weight loss. This should change soon. In fact, one meeting abstract reports that in an intervention study, both calcium supplements and low-fat dairy products stimulate weight loss, with the dairy products being more effective. Dairy products have also been a little more effective than calcium alone in promoting weight differences in mice.

Certainly, this area merits more study. It is doubtful that calcium intake alone can overcome the fat-producing effects of extreme overeating and lack of physical activity. Nonetheless, calcium intake, via supplement or dairy products, may be able to make an important long-term contribution to body weight control.

**TOXICITY**

High-dose calcium supplementation can definitely cause problems and has been said to have done so in a few people. However, unlike many other minerals, there has
not been a lot of emphasis put on direct toxic effects of calcium intakes that are many times the RDA. This lack of concern occurs mainly because not that many people are likely to take calcium supplements at those doses. One reason is that such doses would require taking a lot of pills or capsules. In addition, the media and Internet has not encouraged high doses of calcium relative to the RDA as much as has been done for some other micronutrients. Nonetheless, there have been concerns about safety issues for calcium supplements: One has been lead contamination. At one time, this concern was expressed primarily for dolomite and bone meal as calcium supplements. More recently, though, a study found lead in other calcium supplements, especially the ones that are natural product extracts. The reaction to this has varied from one extreme to another. On one side, the attitude is that the lead in most supplements is still not that high. On the other side is the attitude that one should avoid any lead that one can. If consumers want to be on the safe side, they can look for calcium supplement labels that say “lead free.” Seeing a USP designation on the label is also a good sign.

Calcium supplements have also been reported to antagonize absorption of iron and zinc. The iron issue is controversial because the data is both pro and con on the idea. However, many of the pro-antagonism results are for short, highly controlled, experimental studies, which use test meals. Most long-term studies do not see an effect. In contrast, one three-day record study does see a weak inverse correlation between calcium intake and iron status. However, this study can’t really account for many factors that would restrict or enhance a calcium effect on iron absorption. Thus, it is hard to reach a final conclusion in this area. As with other nutrient antagonism issues presented in this book, in this author’s opinion, getting adequate amounts of each nutrient should minimize problems. If a person takes calcium supplements, and is concerned with effects on iron absorption, the person can take the calcium at a different time than an iron pill or a high-iron meal.

As far as calcium supplements and zinc, in postmenopausal women, chronically high calcium intake affects net zinc absorption and zinc balance, and acute calcium carbonate supplementation lowers acute zinc absorption. The chronic phase uses a calcium dose that is not all that high (under 500 mg) as a supplement or as milk. The acute study uses 600 mg, which exceeds what is usually recommended for single ingestion (see the Bioavailability from Foods and Supplements section).

Some negative effects of calcium supplementation are also seen for zinc status and absorption in rats. In contrast, in a study of human female girls (average age 11 years), adding 1000 mg/day calcium to a dietary intake of about 700 mg does not affect zinc balance. Similarly, in postmenopausal women, acute whole-body retention of zinc-65 is not affected by 500 mg of calcium as carbonate. In this author’s opinion, it is reasonable to say that calcium can antagonize zinc absorption, but we do not fully know when this is a problem and when it is not. Factors that may affect the situation include the age of the subjects, the type of calcium complex, the exact level of total calcium and zinc intake, and the zinc complexes ingested as foods or supplements. At present, this author recommends getting adequate intake of both minerals, with an emphasis on well-absorbed forms of zinc (see the Zinc chapter).
Another issue for calcium supplement safety is the concept that dietary calcium-to-magnesium ratios should not become too high. There are three concerns that have been raised. One, high intake of calcium can inhibit magnesium absorption and increase magnesium excretion, which can lead to marginal magnesium deficiencies. Two, if body calcium gets very high compared to the magnesium, hormonal changes can cause excess deposition of calcium in soft tissues and cause calcium loss from bones. Three, if dietary calcium-to-magnesium ratios get too high, this could alter normal extracellular Mg(2+)/Ca(2+) antagonism, which is needed for a variety of regulatory activities.

Although all three of these concerns are theoretically possible, are they of practical importance? As for the last concern, abnormal extracellular Mg(2+)/Ca(2+) antagonism, there is little direct study of this except for one rat study. In this work, there is some evidence that abnormalities in this extracellular antagonism are responsible for the pro-inflammatory state in magnesium-deficient rats. Even so, it should be recognized that this study deals with severely magnesium-deficient rats. Thus, this may not apply to more moderate states that are apt to exist in most human situations.

As far as high dietary calcium-to-magnesium ratios causing calcification of soft tissues or bone calcium loss, this is known primarily for magnesium-deficient rats. There is no data to say that this happens with marginally magnesium-deficient rats, or with humans where calcium supplementation is superimposed over a moderately low-magnesium diet. This does not mean that problems could not occur, only that these problems have not been ruled in or out yet.

The other issue, calcium supplements producing marginal magnesium by lowering magnesium absorption, could be true. However, the idea is unconfirmed for the typical situations that would be found in most people. It is known that in rats, high calcium intake lowers apparent magnesium absorption, as well as bone and serum magnesium, with the effect being worse if the rats are also fed low magnesium. Also, in an acute study, calcium can lower magnesium absorption in rat ileum in vivo. Once more, the applicability of these results to common human situations is unknown. In fact, in a controlled feeding study in humans, two types of calcium supplements and milk do not show strong depressions of magnesium absorption, and small effects are somewhat balanced by effects on magnesium excretion. Similarly, in another human study, magnesium balance is not affected by moderately high calcium intake (intake elevated with calcium citrate malate).

Thus, there is still a question as to whether typical calcium supplementation practices and typical magnesium intakes can produce marginal magnesium deficiency in a good number of people. To make matters more complicated, the answer may depend on the interactions of magnesium with other dietary components. In support of this concept, a rat study shows that calcium inhibition of magnesium absorption is abolished by manipulating the diet’s fiber content. In addition, high calcium intake does not impair absorption of magnesium in rats fed a soy-maize-based diet. On the other hand, in rats, the combination of high calcium and phosphorus can induce magnesium deficiency. In contrast, in this same study, feeding a certain polysaccharide inhibited the calcium plus phosphorus effect on magnesium status. In human very-low-birth-weight infants, when moderately low
magnesium intake is mixed with calcium and phosphorus supplementation, there is reduced magnesium absorption and retention.\textsuperscript{81} This occurs to the extent that the infants go into negative magnesium balance. Nonetheless, doubling magnesium intake negates the problem.

At present, it appears that calcium can impair magnesium absorption in some circumstances, but not in others. Thus, more research is needed to better characterize when this is a concern and when it is not. This author suspects that if people take in RDA levels of both calcium and magnesium via a balanced diet, they will likely avoid problems with balancing the two minerals. If calcium supplements are used, then people should pay attention to their dietary magnesium, or take a well-absorbed magnesium supplement. This could be done at a different time than calcium, though it is not yet certain if this separation is always necessary.

Another concern about calcium supplements is possible stimulation of kidney stone formation in susceptible individuals. At one time, people with a history of stone formation were told to eat as little calcium as possible. At the simplest level, this advice seemed reasonable since most kidney stones are made partly of calcium, especially calcium oxalate. Even so, the idea of a low-calcium diet for stone formers has now fallen into disfavor in most circles. In support of this disfavor, in a study of postmenopausal Thai women, calcium supplementation for three months, with or without vitamin D, has no group effects on urine markers considered relevant to stone formation.\textsuperscript{82}

Low dietary calcium may actually promote stone formation. For example, an epidemiological study in men finds low calcium intake to be associated with higher risk of stone formation.\textsuperscript{83} Similarly, in an epidemiology study of nurses, those with the highest dietary calcium intakes are much less likely to develop stones compared with the lowest intake group.\textsuperscript{84} However, in the nurse study, this relationship seems more related to calcium from diet rather than for supplements. In fact, the women taking supplemental calcium are rated 20\% more likely to develop stones. One explanation is that the seeming protective effect of calcium from foods is not due to the calcium, but rather to other factors in the high-calcium foods. Alternatively, as noted in the paper on the nurse study, the timing of calcium intake may be the key.

This rationale on timing involves one proposed mechanism by which calcium may prevent stone formation. According to this rationale, a fraction of dietary calcium, while in the GI tract, binds to oxalates from foods. This binding prevents the absorption of oxalates, which reduces their presence in the kidneys, which lowers the chances of calcium and oxalate forming stone crystals in the kidney. For this to happen, presumably, the calcium has to be eaten at the same time as the oxalate-containing foods. In the nurse study, the calcium supplements were generally not taken with meals, or were taken with breakfast, which may have less oxalates than other meals. Therefore, the supplemented calcium may not have done much oxalate binding in the GI tract. Unfortunately, these ideas on meal timing have not actually been verified directly. However, there is a study that shows that when calcium supplements and an oxalate load are given at the same time, both calcium carbonate and calcium citrate malate reduce urinary oxalate.\textsuperscript{85} It would have been interesting to see what would have happened if the calcium and oxalate were given at different
times. Nonetheless, this study does support the concept that calcium supplements may actually help prevent kidney stones.

There is one additional concern with some people for calcium supplementation. Calcium carbonate supplements can produce GI tract problems that can range from minor to serious, and can have some negative interactions with some drugs. For the former problems, a person can replace calcium carbonate with calcium citrate or another form of calcium. For the latter problem, professional guidance should be given based on the specific drug.

**SUMMARY AND CONCLUSIONS**

Calcium supplements are likely to remain among the most popular dietary supplements for quite some time. Their use seems to have some benefits in some circumstances, while some other applications are still speculative. An interesting future question for applications like weight loss is whether dairy products work better than calcium supplements. Calcium supplements may involve some risks, though at present, for most people, these risks have not been clearly verified.

**REFERENCES**


Magnesium biomedical research is currently both very exciting and very frustrating. It is exciting because there is the possibility that many people can benefit their health by increasing their magnesium intake. This excitement is reflected by the current and recent past existence of journals solely or mostly dedicated to magnesium research. On the other hand, magnesium research can be frustrating for two reasons. One, funding for nutrition-related magnesium research has not been a high priority among potential sources of research support. Two, in many areas of magnesium biomedical research, conclusions are hard to draw due to seemingly contradictory results. In fact, this author found this chapter to be the most difficult to write because hardly any issue is clear cut (including even relative bioavailabilities of different supplement forms).

The need for more research on magnesium is blatant, considering that there are a number of reports contending that marginal magnesium deficiency is not uncommon. In addition, a number of health applications are backed by some evidence, but need more research to make a definitive judgment.

OVERVIEW OF FUNCTION

Magnesium affects a multitude of physiological processes. The basis for these effects can be put into several categories. One category is that magnesium is needed as a cofactor for a large number of enzyme-catalyzed reactions, especially reactions that require ATP for energy. These ATP-requiring enzymes include those that add phosphate to other enzymes (enzyme phosphorylation) and the formation of the cell signaling molecule cyclic adenosine monophosphate (cAMP). Both these actions regulate many processes within cells. Another broad category of magnesium biochemical function is intracellular free magnesium ions acting as a physiological modulator. These modulations include competing with calcium for entrance into cells via cell membrane channel passage. Generally, mineral competitions are viewed from a negative perspective (i.e., one mineral competes with another for intestinal absorption, which can create a deficiency). In contrast, a competition between calcium and magnesium for cell membrane channels seems to keep many cellular processes in balance. This balancing act may also occur outside cells where magnesium is thought to antagonize calcium promotion of blood clotting.

Besides affecting calcium function, magnesium also modulates potassium function, though the effects are quite different. One action of magnesium on potassium is to block channels where potassium can leave cells. This helps maintain the
unequal distribution of intracellular and extracellular potassium in favor of the former. Magnesium also influences this potassium distribution via the need for magnesium for the enzyme Na,K-ATPase. This enzyme pumps sodium out of cells and potassium in. There may also be other ways that magnesium affects potassium distribution. These relationships between magnesium and potassium are manifest in severe magnesium deficiency, where there are body potassium depletion and low serum potassium readings.

The impact of intracellular magnesium ion concentrations on cellular processes appears to be far reaching, including effects on the synthesis of membrane phospholipids and lipid second messengers. These synthesis patterns are thought to be altered by low magnesium intake in a manner that can produce profound disturbances on cell function, especially in cardiac cells.

Magnesium also stabilizes certain structures by binding to phosphate groups. Examples include binding to the phospholipids in cell membranes and to the phosphates in nucleic acids. Magnesium has indirect antioxidant functions, which are likely mediated by the biochemical functions already mentioned. Although magnesium had not been traditionally viewed as an antioxidant, magnesium-deficient animals show signs of a pro-oxidant state. These signs include: high sensitivity of lipoproteins to oxidation, above-normal serum values for molecules associated with a pro-inflammatory state, high values for lipid peroxides, low plasma values for radical scavenging capacity, and activities for antioxidant enzymes, high magnitude of neurogenic oxidative responses in vivo, and poor myocardial tolerance to oxidant stress. In addition, magnesium deficiency in cultured cells can increase production of free radicals and the radical precursor hydrogen peroxide. The exact biochemical mechanisms responsible for each magnesium indirect antioxidant action are hard to identify since there are so many possibilities. Among these is the ability of magnesium to influence the stability and lipid composition of cell membranes, which in turn may influence cell tendencies to produce certain radicals. Another possibility is that since magnesium is needed for regulation of so many processes, some of these processes likely control production of pro-oxidant and antioxidant molecules. A lot of this regulation may be mediated by the pro-inflammatory molecule substance P, which reaches high levels in magnesium-deficient rats.

The magnesium functions just discussed only involve about a third of the body’s magnesium. This statement is made because about two thirds of the body’s magnesium is found in bone. This has led to the reasonable supposition that magnesium function includes a role or roles in bone health. The exact nature of this function has not been clear, but there is evidence for several possible functions. These functions include magnesium affecting hydroxyapatite crystal structure and controlling bone cell proliferation. Furthermore, magnesium antioxidant effects could restrict bone resorption. In addition, magnesium may affect bone health via effects that occur outside the bone. For example, magnesium affects secretion of parathyroid hormone (PTH) and insulin-like growth factor, both of which influence bone metabolism. The effects of magnesium deficiency on PTH are unusual. As a deficiency progresses, serum PTH levels can rise or fall at different times, but during the rise, there can be poor receptor reactivity to the hormone.
OVERVIEW OF METABOLISM

Magnesium absorption occurs by both a saturable carrier-mediated process and simple diffusion. Absorption does not appear to be regulated in the way that occurs for minerals such as calcium. There is some evidence that vitamin D status affects magnesium absorption, but in most circumstances, magnesium absorption appears to occur largely independent of vitamin D hormone influence. In addition, any increase in magnesium absorption due to vitamin D hormones may often be largely balanced by increased urinary excretion.

The main regulation of body magnesium content is via control of kidney magnesium reabsorption. This process is responsive to serum magnesium, which is responsive to magnesium intake. However, kidney reabsorption of magnesium can also be influenced by other factors such as certain drugs and hormonal changes. In fact, many situations that cause severe magnesium deficiency involve excess renal loss of magnesium.

As noted earlier, about two thirds of the body’s magnesium is found in the bone. Part of this magnesium is in equilibrium with the serum, while the majority is more stable. After bone, the biggest area of magnesium accumulation is the muscle, which has about a fourth of the body’s magnesium. Part of this magnesium is also in equilibrium with the plasma. Extracellular magnesium accounts for only 1% of total body magnesium. In the serum, over half the magnesium is ionized, while a third is bound to protein (especially albumin), and the rest is bound to low molecular weight anions.

NUTRITIONAL STATUS ASSESSMENT

By far, the most common means of assessing magnesium status is serum total magnesium. Serum is generally preferred over plasma due to possible magnesium contamination and interferences with some assays due to the anticoagulants in the collection tubes. Serum magnesium is definitely influenced by dietary magnesium and short-term changes in renal magnesium losses. However, serum magnesium values do not always reflect intracellular magnesium content or total-body magnesium content. Low tissue magnesium contents can sometimes occur despite normal serum magnesium values, and short-term changes in magnesium status are not always reflected by changes in serum magnesium. In addition, factors such as fluctuations in albumin or pH can affect serum magnesium. Nonetheless, serum magnesium is the starting point for any evaluation of magnesium status, and values under 0.7 mM usually mean that substantial magnesium depletion has taken place. Note that this is not a tremendously low value relative to the normal range, which is 0.70 to 1.05 mM. This reflects that as magnesium stores drop, homeostatic mechanisms work against big changes in serum values.

Muscle biopsy magnesium contents would seem to be an appropriate way to assess magnesium status, since over a fourth of the body’s magnesium is typically found in muscle. The main limitations for this method are that sample collection is rather uncomfortable for the subjects, and the sampling requires skill on the part of the person doing it. There have been rumblings that nuclear magnetic resonance...
(NMR) spectroscopy may eventually be used regularly as a non-invasive means of determining muscle-ionized magnesium. The basic method already exists, but has not yet been widely applied as a magnesium status assessment tool.

Total erythrocyte magnesium contents can respond to dietary magnesium interventions, but values do not always correlate with other tissue pools of magnesium. In addition, genetics may have a substantial influence. Also, anything that affects erythrocyte cell age distribution can affect mean magnesium values.

Mononuclear blood cell (MNC) total magnesium contents appear to reflect magnesium status in some but not all circumstances. For example, in some subjects, MNC magnesium correlates with muscle magnesium. In contrast, MNC magnesium values are reported as normal for a group of subjects with severe magnesium depletion. In other work, mononuclear cell magnesium is not a good marker of magnesium status in a study of short-term magnesium depletion in rats. In human magnesium supplementation studies, mononuclear cell magnesium is increased in some studies. In contrast, values are not increased in some other supplementation studies, though presupplementation magnesium status may have already been good in these studies. Thus, the utility of MNC magnesium for status assessment is still debatable. Two contributors to the variability in results could be technical considerations in the sample preparation and the effects of illness on the composition and size of the cells.

In contrast to total blood cell magnesium contents, erythrocyte-ionized magnesium seems to be a very good indicator of magnesium status. Although the utility of these measures has not been verified by an enormous number of studies, the existing work is generally supportive. Although there is some oscillation in erythrocyte-ionized magnesium content as the cells circulate, it may be small enough to still use this approach for magnesium status assessment. The most direct way to measure erythrocyte-ionized magnesium is by an NMR technique. The main drawbacks are that most laboratories are not fluent in this methodology and the amount of blood needed is substantial. Two alternative approaches are the use of fluorescent probes and a so-called zero point titration, which involves measuring total magnesium after sample fractionations. The fluorescent probe approach requires navigation around a number of procedural and interpretation pitfalls. The zero point titration approach has compared favorably with the NMR measures in three studies, especially for relative results. Thus, the zero point titration may be a viable option, though more comparisons to NMR results under more circumstances would be helpful.

Serum-ionized magnesium shows considerable promise in assessing magnesium status. Even so, there are still some researchers who question how often serum-ionized magnesium values can diagnose a marginal magnesium deficiency that would not be detected by total serum magnesium measurement. More research is needed to resolve this question.

Serum-ionized magnesium is usually done by means of a magnesium-specific electrode, though the quality of such electrodes may not be a constant. Another practical problem is that values for serum-ionized magnesium may change if blood samples are not centrifuged fairly quickly and, possibly, if not analyzed shortly after that. However, some studies use frozen serum samples, and others claim that serum samples can be refrigerated for a substantial time. Until this
conflict is resolved, rapid analysis would be the safest approach, though this may have some practical problems for some studies. Another concern is circadian rhythms in values during the day, which cause some magnesium researchers to recommend blood collection be carried out between 6 and 10 AM.\textsuperscript{29} There are also other technical considerations including even the position of the subject during blood collection.\textsuperscript{20}

Even if all the known technical concerns of sample collection and treatment are addressed, there is still room for improvement in sensitivity and specificity of the electrode method.\textsuperscript{20} Efforts on such improvement are supposed to be under way. Another aspect of this methodology that could use improvement is electrode availability. Commercial purchase of an electrode requires the simultaneous purchase of other apparatus that may be of no use to many researchers.

There is an alternative to the electrode approach for measuring serum-ionized magnesium. This alternative approach uses ultrafiltration, followed by a total magnesium reading in the low molecular weight fraction.\textsuperscript{40} Unfortunately, there can be a lot of technical pitfalls in this methodology, such as the magnesium partitioning during ultrafiltration being affected by pH changes.\textsuperscript{36,40} There seem to be ways of preventing this problem, or correcting for it during calculations, though the details of these approaches are still under some debate.

Urinary total magnesium is also used for assessing magnesium status, especially following an acute parenteral magnesium load (a type of magnesium tolerance test). For the measurements without the acute load, the applicability to status assessment can be rationalized by the fact that nearly all absorbed magnesium is eventually excreted in the urine.\textsuperscript{1} Thus, urinary excretion of magnesium in healthy subjects can be directly proportional to dietary intake and magnesium stores. However, this is not always true. High urinary magnesium can occur when there is excessive renal losses of magnesium.\textsuperscript{22} Thus, high urinary magnesium values can indicate either good or bad magnesium status. However, a combination of high urinary magnesium with low serum magnesium can serve as an indication of magnesium depletion due to excessive renal losses.\textsuperscript{1}

The magnesium loading test (also called magnesium tolerance test) is based on the assumption that a person in good magnesium status will excrete almost all of a parenterally administered magnesium load within 24 hours.\textsuperscript{2} On the other hand, someone with poor magnesium status will retain a good portion of the magnesium load. The test is run by collecting urine after infusion of a set amount of magnesium. The test is considered a good indicator of magnesium status in most circumstances. There are some exceptions, such as where there are problems with renal function. Still, this does not preclude use in most types of people. The main disadvantage to this approach is that it is not always possible from a practical standpoint.

In summary, serum magnesium is the most used magnesium assessment method, though it has some diagnostic limitations. Several other methods may be more reliable in some circumstances, though technical and practical considerations can affect their use.

**BIOAVAILABILITY FROM FOODS AND SUPPLEMENTS**

There is not a lot of data on magnesium absorption from different foods and diets in humans, though a few studies exist. Balance studies have set the percent absorption
at anywhere from about 20% up to about 70%. However, this would depend on the amount of magnesium being consumed, with low percent absorptions at higher acute intakes. However, an absorption of about 40 to 50% is often viewed as normal for children and young adults with Western diets, based on some balance studies.\textsuperscript{31–44} For a high-magnesium mineral water, the percent absorption on an empty stomach is about 46%, while the percent absorption jumps up to over 52% when consumed with a meal.\textsuperscript{45} All these percentages have to be interpreted with care, since values can vary with technique used, the subjects studied, and the amount of magnesium given. However, these percent absorptions show that magnesium is generally absorbed better than minerals like iron, and that magnesium from a number of sources have somewhat similar absorptions.

There is some work on food factors that influence magnesium absorption. Some carbohydrates, such as fructose, and fermentable carbohydrate polymers can increase magnesium absorption.\textsuperscript{46,47} Dietary fiber, which depresses absorption of some minerals, has shown mixed results for magnesium. Where there is inhibition, it does not seem to be as much as for some other minerals.\textsuperscript{48} In fact, fermentable polysaccharides actually increase absorption.\textsuperscript{48} In a worst-case scenario, even if high-fiber foods have a small negative effect on magnesium absorption, this effect could often be offset by these foods containing a relatively good amount of magnesium.\textsuperscript{49}

Phytates and oxalates can negatively affect magnesium absorption, though the actual impact these compounds have can vary. For example, spinach, which is high in oxalates, provides well-absorbed magnesium in studies of rats and humans.\textsuperscript{50–52} On the other hand, in rats, spinach can somewhat inhibit the absorption of magnesium added to the spinach-containing diet.\textsuperscript{52} One explanation is that the added magnesium binds to the oxalates in spinach, but the magnesium in the spinach itself is not predominantly bound to oxalates. Instead, most spinach magnesium may be present in complexes such as chlorophyll. The chlorophyll magnesium may be absorbed relatively independently of oxalate effects. In the case of phytates, the effects on magnesium absorption do not seem to be as strong as for other minerals, though at high phytate intakes, the effect on magnesium could be substantial.\textsuperscript{48,53,54}

Calcium is often stated to exert negative effects on magnesium absorption, but a major effect for most human circumstances is unconfirmed (see the chapter on calcium). On the other hand, high-dose zinc supplements may be an underappreciated cause of poor magnesium absorption.\textsuperscript{55} This concern is based primarily on just one study, but the study merits follow-up.

Magnesium supplements are available in many different complexes. All seem to be capable of impacting magnesium status, though there can be differences in bioactivity in certain studies. There is the general attitude that organic magnesium supplements are absorbed better than are inorganic versions, in part because the organic forms are more water soluble.\textsuperscript{56,57} However, this idea may not be clear cut. Many of the results are conflicting for organic versus inorganic supplements, as well as for comparisons between different organic magnesium complexes. A possible cause of the inconsistencies is that most studies lack a precise tool for measuring acute bioavailability. Short-term serum magnesium changes are not reliable due to renal adjustment of serum in the short run.\textsuperscript{57,58} For this reason, many studies examine acute responses of urinary magnesium. However, these measures may have variable...
responses for different types of people in different circumstances. It is noteworthy that one paper recommends that if this approach is used, then it should be preceded by a prestudy magnesium saturation period. This idea has some rationale, since magnesium absorption is not regulated by magnesium status, and saturated tissues will push magnesium toward urine. However, most studies on urinary magnesium don’t use this saturation pretreatment. Alternatively, stable isotope studies may provide better answers, but they have not been done much for this issue. Thus, at present, it is very difficult to make definitive statements about absorption differences for one supplement type versus another.

An indirect approach to this issue, which has not been used much, is to compare different magnesium complexes for long-term effects on magnesium status or some health benefit. A problem with this approach is that it requires far more time and money than acute studies. In addition, it is harder to use the same people for each supplement to be tested, which is typically done for acute studies. Therefore, for longer studies, either well-matched groups must be studied, or a single group must be committed for a substantial amount of time (to do multiple treatments and washout periods). In the latter case, compliance and lack of changes in diet would have to be monitored carefully. A very limited amount of this type of work has led to the idea that for some specialized effects, some forms of magnesium complexes may work better than others (discussed later in this section).

In addition to possible efficacy differences between supplement types, there may also be some differences in GI tract side effects. However, this is not well documented by extensive published studies. The limited data is discussed at the end of this section.

The inorganic magnesium supplement that tends to draw the most criticism for poor absorption is magnesium oxide. This complex is by far the most common form of magnesium supplement sold in a supermarket or drugstore setting, and is used for a lot of food-fortification applications. The attitude that magnesium oxide is not well absorbed derives in part from its low solubility in water. In addition, in two human studies of urinary magnesium responses, this form of magnesium shows less bioavailability than some other forms of magnesium. In fact, in one of these studies, the effect on urinary magnesium is so small that it is not significantly different from baseline. In the other study, magnesium citrate is absorbed 4.5 times as well as magnesium oxide. One drawback of the last study is that it is based on two-hour urines, which may underestimate total absorption for a slowly absorbed molecule. However, there is also an additional study reporting that magnesium absorption from magnesium oxide is less than from magnesium aspartate. In addition, in a four-week rat feeding study, magnesium oxide, when compared to magnesium citrate and two other magnesium complexes, shows lesser long-term effects on urinary magnesium and on diet-induced kidney stone formation.

Despite what was just said, the story on magnesium oxide is not as clear as it would first seem. For example, some finely ground preparations of magnesium oxide can dissolve to a good extent in water. Moreover, in a cattle study, different versions of magnesium oxide produced availabilities that paralleled their water solubility. In another cattle study, magnesium oxide preparations with small particle size have a better effect on urinary magnesium than do other magnesium oxide preparations.
Even so, one problem with applying these cattle studies to humans is that ruminant digestive processes differ from humans, which may cause differences in handling of magnesium oxide. Still, there are human studies of magnesium oxide supplementation where some desired health effect has been produced.\textsuperscript{66,67} Thus, it would be very helpful to have more human comparisons between different versions of magnesium oxide, as well as more comparisons of these versions vs. other types of magnesium supplements. These comparisons should include stable isotope absorption studies, long-term effects on magnesium status, and health effect end points.

Magnesium carbonate is another supplement that is very water insoluble. At present, magnesium carbonate is not used a lot in supplements or food fortifications, though it is sometimes used in both these fashions. The predominant human use for magnesium carbonate is as an antacid. Magnesium carbonate is not considered to be a well-absorbed form of magnesium,\textsuperscript{56} though actual studies of this point are very limited. In two studies, one in rats and one in humans, sustained magnesium carbonate supplementation actually decreases the magnesium content for plasma or certain tissues.\textsuperscript{68,69} In contrast, in a rat study,\textsuperscript{70} magnesium carbonate appears to be well absorbed, though that is in comparison to magnesium oxide and chloride, which are not considered “gold standards.” On the other hand, a different line of argument can be used to support a reasonably good bioavailability for magnesium carbonate. This argument is that in a human study, a magnesium carbonate supplement produces a small increase in serum magnesium and some apparent health benefits.\textsuperscript{71} This study is done with subjects with symptomatic mitral valve prolapse (MVP). However, an unanswered question is whether the benefits are due to improved magnesium status or just antacid effects. There is precedent that antacid use can have beneficial effects on a subcategory of subjects with mitral valve prolapse.\textsuperscript{72}

Magnesium sulfate is used for intramuscular and intravenous magnesium administration, and is sold as a laxative (e.g., under the name Epsom Salts). For the nonoral applications, there has not been much research consideration as to whether or not this is the optimal form of magnesium to use, but this form has certainly been the predominant one used. In the oral use area, magnesium sulfate laxative products are sometimes prescribed as magnesium supplements. In addition, to a limited extent, magnesium sulfate is marketed specifically for use as magnesium supplements, or used in powder form for food fortifications. There is little study on the efficacy of oral magnesium sulfate for impacting human magnesium status. Some researchers recommend against magnesium sulfate for supplementation purposes due to possible low absorption, though this has not been confirmed directly in humans. However, two rat studies are consistent with this idea. In one study,\textsuperscript{70} retention and absorption of magnesium sulfate is considerably less than magnesium carbonate, which may not be well absorbed itself.\textsuperscript{56} Similarly, in a four-week rat feeding study, magnesium sulfate, when compared to magnesium citrate and two other magnesium complexes, shows a lesser effect on urinary magnesium and on diet-induced kidney stone formation.\textsuperscript{63}

Another inorganic magnesium supplement with antacid and laxative properties is magnesium hydroxide (e.g., sold under the name of Maalox). Due to its poor water solubility, this form has been stated to have poor bioavailability.\textsuperscript{56} However, in one human study, magnesium hydroxide has the same acute effect on urinary
magnesium as some organic magnesium supplements.\textsuperscript{73} Still, as already noted above, there is some debate as to the value of this approach, though it is the way most studies of magnesium absorption are done. A selling point for supplement use of magnesium hydroxide is a beneficial effect on bone density in a human study.\textsuperscript{74} However, as discussed below in another section, there are some questions about this study. Another concern about magnesium hydroxide supplementation is that long-term use seems to increase the risk of developing a cardiac event in certain subjects.\textsuperscript{75}

In this author’s opinion, magnesium hydroxide can be a source of absorbable magnesium. However, since there are some unknowns about its bioactivity and safety, it would seem prudent to choose another magnesium complex if the goal is simply to increase magnesium intake. On the other hand, there may be some situations where the antacid effects of magnesium hydroxide on the stomach or urine may be useful. By the same token, there may be situations where those effects are not desirable. This same type of situational benefit–detriment effect can be true for another effect of magnesium hydroxide. This magnesium compound can influence the solubility and absorption of various agents such as drugs.\textsuperscript{76}

Magnesium chloride is another inorganic magnesium supplement, but it has better solubility properties than the others discussed so far.\textsuperscript{56} In one rat study, magnesium chloride is not as effective at raising serum magnesium as an organic form (magnesium gluconate).\textsuperscript{77} However, the study design, serum magnesium readings three days postsupplementation, is not a common approach to this area. In fact, short-term changes in serum magnesium following increased intake tend to be of limited use due to renal excretion responses.\textsuperscript{58} The time point in the rat study (three days) is somewhat longer than what would usually be termed “short term” in this context. Still, it is well below what would be called “long term.” In a human study, a magnesium chloride liquid has comparable acute effects on urinary magnesium to some organic magnesium supplements.\textsuperscript{73}

One way magnesium chloride is sometimes sold as a supplement is as an enteric-coated tablet under the trade name Slow-Mag\textsuperscript{®}. The enteric coating on a magnesium chloride pill is intended to reduce stomach upset and provide a slow, steady absorption. In one study, this type of preparation shows equal bioavailability to magnesium gluconate.\textsuperscript{78} However, the comparison is based on serum magnesium 24 hours after ingestion. As just noted, acute serum magnesium changes are not considered a good way to assess relative magnesium absorption.\textsuperscript{58} In another study, which is based on a GI tract lavage fluid collection, there is much less absorption with enteric-coated magnesium compared to magnesium from almonds, or compared to an acetate supplement.\textsuperscript{79} In other work, onetime supplementation with enteric-coated magnesium chloride does not affect urinary magnesium as much as liquid magnesium chloride or a magnesium gluconate tablet.\textsuperscript{80} However, there is some concern about this study. Neither the enteric-coated magnesium chloride nor the magnesium gluconate produce a statistically significant rise vs. no supplement. This is unexpected for gluconate, which casts doubt on the interpretation of the whole study. Therefore, the bioavailability of enteric-coated magnesium chloride is still an open question. Even so, it should be noted that in a study of cardiac rehabilitation patients, this form of magnesium does raise serum and urinary magnesium, as well as produce cardiovascular benefits.\textsuperscript{81}
There are many organic forms of magnesium supplements including lactate, fumarate, acetate, malate, citrate, picolinate, pidolate, glycinate, other amino acid chelates, taurate, gluconate, and orotate. There are not a lot of direct comparisons between the various organic complexes. A number of the individual complexes have been able to produce apparent benefits in human supplementation trials. Magnesium lactate may have especially good absorption based on very high water solubility, and a report of a very high percent absorption for a slow-release version. However, this report must be interpreted cautiously. The comparison made for different complexes uses different studies. In addition, the comparison is not based on very large-scale research. Moreover, two studies of urinary magnesium do not show any difference between magnesium lactate and some other types of magnesium supplement.

Again, though, it must be remembered that acute urinary magnesium change has been questioned as the final word on magnesium bioavailability. Therefore, it can be said that magnesium lactate appears to have very good absorption, which is proposed, but not confirmed, to be better than some other organic magnesium complexes.

Magnesium citrate is also considered a well-absorbed complex. As noted earlier, in one study, magnesium citrate is absorbed 4.5 times as well as magnesium oxide.

Magnesium taurate has some theoretical appeal because magnesium and taurine have been speculated to exert complementary roles in counteracting some health problems. However, to this author’s knowledge, no published human studies compare magnesium taurine to other types of magnesium supplements. There is an animal study of magnesium acetyltaurinate where this complex inhibits audiogenic seizures in magnesium-deficient mice. This effect is not completely duplicated by magnesium chloride plus vitamin B-6. There is also a rat study of magnesium acetyltaurinate in comparison to other magnesium complexes. In this case, magnesium acetyltaurinate is more effective than a variety of magnesium complexes in blocking symptoms caused by the combination of kainic acid plus magnesium deficiency. This is one of several examples where a particular magnesium complex may have an advantage for a specialized bioactivity. A few others are noted in this and other sections.

Magnesium pidolate may provide another example of where one magnesium complex shows better specialized bioactivity than other magnesium complexes. In rats, although magnesium deficiency-induced aggressive behavior is suppressed by a number of magnesium salts (chloride, pidolate, aspartate, gluconate, lactate), magnesium pidolate is the best at some subcategory measures. In another study, which examined some reactions to activity-altering drugs, magnesium as pidolate, but not as lactate or aspartate, induced a neurosedative effect.

Some Internet sites tout magnesium malate as a superior form of magnesium for certain applications. The main published study to support this concept is work in fibromyalgia patients where this complex reduces pain and tenderness measures. However, the positive results were obtained in an unblinded fashion, were not compared to specific effects on magnesium status, and were not compared to any other form of magnesium. Thus, at present, no special benefits can be ascribed to magnesium malate.
Magnesium diglycinate chelate has shown much better absorption properties than magnesium oxide in a subgroup of subjects who have undergone ileal resection.\textsuperscript{88} Ileal resection makes people prone to magnesium deficiency, but oral magnesium treatment is difficult due to sensitivity to the laxative effects of magnesium complexes. A crossover study was done in this population using stable isotope methodology.\textsuperscript{88} Magnesium absorption from magnesium diglycinate chelate is much better than from oxide in a subgroup of patients with the greatest impairment of magnesium absorption. A possible explanation for the better absorption is that the magnesium diglycinate chelate may be absorbed intact, possibly via a dipeptide transport pathway. However, it should be noted that this magnesium complex did not show a different absorption from the oxide form for the group as a whole. Despite this observation, and despite the fact that the subject number is not very large, the study does raise the possibility that magnesium diglycinate may be especially useful for these types of subjects. This usefulness is further enhanced by the good tolerability shown in this study in subjects with high sensitivity to GI distress.

This leads to the general subject of GI tract distress due to different forms of magnesium supplements. Unfortunately, there is no study that provides an extensive direct comparison of different magnesium complexes in this regard. The above-noted results for magnesium diglycinate suggest that this complex is one of the better magnesium complexes for GI tract tolerability. There is also a report of no diarrhea effect of magnesium aspartate at doses a little above the RDA.\textsuperscript{89} In addition, slow release preparations, such as some versions of magnesium lactate and enteric-coated magnesium chloride, would seem by design to be less irritating than most magnesium preparations. However, it is possible that one could produce some of the same effect as slow-release preparations by spacing out magnesium supplement ingestion (though this is more effort for the consumer). A number of Internet sites say that magnesium oxide produces 2 times, and magnesium chloride 3 times, the incidence of diarrhea than from an equal dose of magnesium gluconate. However, this author has been unable to find a published report on this comparison.

**TYPICAL INTAKES VERSUS NEEDS**

There are no commonly eaten foods that have extremely large percentages of the adult RDAs for magnesium.\textsuperscript{90} Among commonly eaten foods, nuts and seeds are the most concentrated per unit weight,\textsuperscript{90} but for most people, these foods are not a consistently eaten source of magnesium. Other relatively good sources of magnesium are whole grains and dark green leafy vegetables, due to the high content of chlorophyll, which contains magnesium. Milk and dairy products, though not outstanding sources of magnesium per serving, if consumed in high amounts, can contribute a reasonable amount of magnesium to the diet. Other reasonable sources are legumes, a few other vegetables, and a few fruits. Whole-grain products can also make some contribution if substantial amounts are eaten.

Estimates of magnesium intake from various dietary surveys indicate that many people eat less than recommended amounts of magnesium.\textsuperscript{91–93} One concern with such surveys is that they may not account for supplement use, though most multi-type supplements either omit magnesium or do not add a high percentage of the
RDA. Another issue is that most surveys do not account for the fact that some local drinking water can be a substantial magnesium source. Nonetheless, even if supplements and drinking water do cause an underestimation of some people’s magnesium intake, that would still leave many people consuming below recommended amounts.

The exact consequences of this seemingly widespread moderately low magnesium intake are not fully known yet. One concern is that this produces high susceptibility to acute magnesium depletion. Such depletion can be caused by impairment of intestinal magnesium, or more often, excess renal magnesium losses. In extreme cases, a serious magnesium deficit could occur even if previous magnesium intake had been very good. Still, if magnesium intake has not been very good, then depletion may occur more easily. Although the causes of such depletion are not extremely common, they can be a concern for some people. Examples of situations that can cause magnesium depletion are given below in the Overt Hypomagnesemia subsection. In other situations, marginal magnesium deficiency may have other consequences, especially when combined with physiological stress. These possible consequences come up in various supplementation studies that are discussed in the next section.

CURRENT RESEARCH ON SUPPLEMENT USE

Parenteral Pharmacological Uses

Parenteral magnesium has been proposed as helpful for a number of uses that are not intended primarily to correct magnesium deficiency. Examples include treatment and prevention of eclampsia and for treatment of acute myocardial infarction. Since this book is directed toward oral mineral supplements, the topic of parenteral magnesium for pharmacological purposes will not be covered here.

Overt Hypomagnesemia (Low Serum Magnesium)

Substantially low serum magnesium usually indicates magnesium deficiency due to excess renal losses. Examples of situations that can cause magnesium depletion are as follows:

- Very low calorie intakes (including self-imposed situations such as anorexia nervosa and so-called protein-sparing fasts)
- Parathyroid disease
- Chronic alcoholism
- Chronic diarrhea
- Certain drugs, especially some diuretics, certain antibiotics, and selected cancer chemotherapy drugs such as cisplatin
- Gitelman syndrome
- Uncontrolled diabetes (though body magnesium redistribution can also be a factor)
Besides being caused by renal magnesium losses, magnesium deficiency can also occur due to poor absorption, though this reason is less common. Examples of causes of poor magnesium absorption are gastrointestinal problems, such as malabsorption disorders as well as excessive vomiting and diarrhea.

On the basis of experimental magnesium depletion in human volunteers, the clinical manifestations of magnesium deficiency include anorexia, nausea, vomiting, lethargy, weakness, personality change, tetany (e.g., positive Trousseau’s or Chvostek’s sign or spontaneous carpopedal spasm), and tremor and muscle fasciculations. The neurological signs, particularly tetany, correlate with the development of low serum calcium and potassium.

In cases of substantial hypomagnesemia, oral magnesium supplements can often be effective, though in very severe cases, parenteral administration can be justified. It can also be important to treat the root cause of the problem, if possible. A first clue to the cause can be a measure of urinary magnesium to distinguish a case of excessive losses from poor absorption.

**Blood Pressure**

In theory, magnesium function could affect blood pressure via a number of different mechanisms. For example, magnesium effects on the sodium–potassium pump and on calcium ion flow can affect vascular tone and reactivity as well as dilation of blood vessels. Blood pressure could also be affected by the magnesium antioxidant actions named in the Function section, since oxidant stress is thought to contribute to hypertension. In addition, magnesium affects secretion of hormones, which can impact blood pressure. In light of these possible functional connections of magnesium to blood pressure, it is not surprising that in animals, magnesium deficiency can promote hypertension. However, these studies may depict situations that are more severe than would occur in most humans with hypertension. Still, a good number of human epidemiological studies show correlations between magnesium intake and blood pressure. In addition, there are some correlations between parameters of magnesium status assessment and blood pressure, though the results do not give a totally clear-cut relationship. Even with good results, epidemiological relationships may not actually reflect a major role for typical variations in magnesium intake and blood pressure. This statement is made because high-magnesium diets are typically high in other minerals as well as phytochemicals that could affect blood pressure. Thus, the apparent relationships of blood pressure with magnesium may just be a coincidental relationship that reflects other dietary patterns. One way to tease out what, if any, relationship magnesium has to blood pressure is the use of magnesium supplementation studies.

Unfortunately, studies of magnesium supplementation and blood pressure have not yielded consistent results. One problem can simply be that many studies have a small sample size for a blood pressure study. Blood pressure studies typically require a good number of subjects because the main end point is not very stable, and it is affected by many factors including emotional ones. Another reason for the variable results could be that magnesium intake may impact blood pressure only...
under a combination of certain conditions. Such a circumstance combination could be as follows:

- Subjects initially have at least a marginal magnesium deficiency.
- The deficiency is corrected by the given dose of the given magnesium complex.
- The subjects initially have high blood pressure, but it is not so far advanced that physical changes do not allow magnesium to make an impact.
- The high blood pressure is due to a specific process that responds to magnesium.

For the last issue, one proposition is that the specific process involves the renin–angiotensin-aldosterone system.\textsuperscript{108} Another proposition, based on a study comparing responders and non-responders, is that reduction in intraerythrocyte sodium is a discriminating factor.\textsuperscript{119}

The above-proposed scenario is supported by much of the research that has been done so far. However, in some cases, the study publications do not supply enough information to judge if this scenario is holding, especially for the last contention. Examples of where the scenario is supported, at least in part, are as follows:

- Virtually all studies on magnesium supplementation of people with normal blood pressure have not shown an effect.\textsuperscript{110,113}
- One study reports that responders to magnesium tended to have recently acquired hypertension.\textsuperscript{119}
- Some studies reporting no effect on blood pressure also report no effect on some markers of magnesium status.\textsuperscript{120–122}
- Some of the studies showing improvements in blood pressure also report increases in serum or plasma magnesium.\textsuperscript{57,111}
- One study separates responders and non-responders by starting urinary magnesium,\textsuperscript{123} while another study correlates rises in serum magnesium and falls in blood pressure.\textsuperscript{67}

A number of studies with positive results have used forms of magnesium that are considered well absorbed or have used above-RDA doses of magnesium oxide.\textsuperscript{111,119}

In a study where responders and non-responders are compared, discriminations can be found for starting plasma renin activities\textsuperscript{115} in another study, discriminations can be found based on the reduction in intraerythrocyte sodium.\textsuperscript{119}

This response model may not be 100% true but it does seem to have some explanatory power. Even so, not all studies directly support the model, though they may not actually contradict it. For example, magnesium aspartate supplementation lowers blood pressure in a study where there is no predictive value for starting magnesium status or dietary intake.\textsuperscript{118} However, dietary intake does not necessarily predict status if some types of hypertensive subjects have high magnesium needs. In addition, in this study,\textsuperscript{118} magnesium intake may have been low in most subjects,
which would mean that most would be good responders. The last comment can also apply to urinary magnesium data.

Two points should be clarified about the notion that already having high blood pressure may be a prerequisite to seeing a magnesium supplement effect on blood pressure. First, although this may be a general rule, some individuals with normal blood pressure may still respond to magnesium. This idea is supported by a study of normotensive subjects with signs of marginal magnesium deficiency.\textsuperscript{113} Magnesium supplementation does not produce a statistically significant decrease in blood pressure, but the mean value does decrease in two groups given magnesium. Another point about normotensive subjects is that even if increased magnesium intake doesn’t lower blood pressure, a good magnesium intake may help prevent future hypertension in some people.

If magnesium can affect blood pressure, how much of a change can be expected? In some studies, the change has been small, but in some cases, the systolic change has been in double digits.\textsuperscript{111} The difference may be in part due to starting blood pressure and change in magnesium status. It should also be recognized that blood pressure is affected by many factors, and maximal control is achieved by multiple interventions. This author recommends that people start by addressing the biggest known influences on blood pressure, then consider factors such as magnesium intake.

At present, it is still difficult to absolutely say specifically who, if anyone, can benefit blood pressure-wise from increasing magnesium intake. What is really needed is a study with large subject numbers of differing characteristics. It may be hard to get such a study funded while many people are not committed to changes already known to impact blood pressure. In the meantime, eating a diet high in magnesium is probably a good idea from multiple health perspectives, including boosting intake of other factors that can affect blood pressure. In addition, if people are in a high-risk group for low magnesium intake, or if they wonder if they have high magnesium needs, they should consult with a physician and a dietitian. In that case, a test of serum magnesium could be done, and if that is low, a trial of magnesium supplementation could be done. If blood pressure is lowered, and the dose of magnesium is modest and well tolerated, there is probably no danger in continuing this course (unless the patient tries to use this treatment to compensate for poor health habits).

**SERUM LIPIDS IN NON-DIABETIC SUBJECTS**

In some animal studies, moderately high magnesium intake affects serum or tissue lipid compositions in a manner that would be considered beneficial in humans.\textsuperscript{6,124,125} This effect does not necessarily involve prevention of a magnesium deficiency. One mechanism could be magnesium binding to lipids and bile salts in the GI tract and reducing their absorption.\textsuperscript{125} There also could be separate actions of magnesium on serum lipids that does involve correction of a marginal magnesium deficiency. Along these lines, in a few studies, serum- or platelet-ionized magnesium values show inverse correlations with certain serum lipid values.\textsuperscript{126-128} This could mean that marginal magnesium deficiency affects serum cholesterol. Alternatively, it could
reflect a comparison between moderately high magnesium intake vs. low to adequate intake. Another possibility is that the correlations just reflect other dietary factors that coincide with high magnesium intake.

There are two studies by overlapping authors that look at the response of serum lipids to increased magnesium intake. In these studies, which each involve about 400 subjects, magnesium intake is increased from about 400 mg/day to about 1000 mg by dietary intervention. The increased intake produces about a 10% decrease in serum cholesterol, LDL cholesterol, and triglycerides. Unfortunately, it is hard to decide whether these effects are due to magnesium alone, other dietary factors, or the combination of magnesium plus other dietary factors. This is one reason why supplementation studies can often make for cleaner results than diet intervention, though the latter can sometimes be the more effective treatment. There is one existing study on high-dose magnesium oxide that does not show lowered serum cholesterol.

In the just-discussed pair of studies, HDL cholesterol is not affected in the total subject population, but rises in subjects with initially low values for serum magnesium. This could mean that the effect on HDL cholesterol, unlike the effects on the other lipid parameters, involves correction of marginal magnesium deficiency. Although the average magnesium intake of the study subjects is reported to be above the adult RDAs, some individual subjects could have moderately low intake. Possibly, the HDL effect only occurs in the subjects with initially low magnesium intake, or in those with unusually high magnesium needs. Alternatively, low serum magnesium may just be a marker for a poor diet from other perspectives, which is corrected by the non-magnesium aspects of the diet intervention.

There is one other study where magnesium supplementation is reported to increase HDL cholesterol values. The initial magnesium status of the subjects is uncertain.

In another study, four weeks of magnesium supplementation (500 mg) plus a low-calorie, low-cholesterol diet is examined in subjects with hyperlipidemia of Frederickson types IV and IIb. The magnesium lowers serum triglycerides compared to the diet alone, but not serum cholesterol. There is also a study where magnesium aspartate does not alter total or HDL cholesterol when given at a dose a little above the RDA for six months. Possibly, the dose of magnesium has to be fairly high to see cholesterol effects.

In a final study, 1000 mg magnesium oxide supplementation of hyperlipidemic subjects actually increases serum cholesterol slightly due to an increase in LDL cholesterol. Values return to pretreatment levels after a washout period.

In summary, there is not yet conclusive evidence that high doses of magnesium can consistently produce beneficial effects on serum lipids, though this is a possibility. If this action exists, it may not always require correction of marginal magnesium deficiency.

**Prevention of Cardiovascular Disease in Non-Diabetic Subjects**

The possible relationship of magnesium to serum lipids and blood pressure would impact risk of cardiovascular diseases. In addition, magnesium could affect this risk.
via its antioxidant and anti-inflammatory actions.\textsuperscript{134} For example, magnesium-deficient rats have lipoproteins with high susceptibility to atherosclerosis-related oxidation.\textsuperscript{135} Magnesium also impacts cardiac muscle integrity, in part via regulatory effects on antioxidant enzymes,\textsuperscript{10} and cardiac phospholipid composition.\textsuperscript{6} Furthermore, magnesium restricting of calcium movements can affect heart beat, vasospasm tendencies, platelet aggregation, vasodilatation, and other cardiovascular-relevant processes.\textsuperscript{103,134} There is also an idea, though still controversial, that magnesium is part of a preischemia conditioning process that promotes later heart recovery from ischemic stress.\textsuperscript{11,103}

A number of epidemiological studies have found correlations between magnesium intake, or blood magnesium status indicators, and risk of certain types of cardiovascular disease including stroke and ischemic heart disease.\textsuperscript{94,102,138–140} These studies have included analysis of geographical regions with high magnesium contents in drinking water.\textsuperscript{94,138} In one notable recent epidemiological study, done in Honolulu, initial magnesium intake is correlated with later risk of coronary events in over 7000 men for over 15 years.\textsuperscript{141} There have also been autopsy studies showing lower myocardial and skeletal magnesium contents in subjects dying from ischemic heart disease rather than accidents.\textsuperscript{138} However, as already noted for other contexts, these studies do not distinguish direct effects of magnesium intake from magnesium intake just being a marker for other good dietary habits. On the other hand, studies in experimental animals with induced atherosclerosis show directly that low magnesium intake can enhance atherosclerosis progress.\textsuperscript{124,125} However, such studies usually use more severe magnesium deficiency than is common in humans.

Direct studies of magnesium supplementation have not been forthcoming. This is because studies of cardiac events in apparently healthy people require a lot of subjects and a long time. For such studies to receive funding, there has to be a sense of urgency, which has not yet happened in this area. One means of doing studies that cut down on subject numbers and reduce study time is to consider survivors of cardiovascular events. These types of studies can look at symptoms associated with risk of further occurrence of cardiovascular events. These symptoms can develop more quickly than major cardiac events in initially disease-free subjects. The approach of studying people who already have cardiovascular disease provides information useful for people in recovery, but may also have some predictive value for first-time events.

Several of these types of studies have been done in subjects with coronary artery disease. One such study finds that magnesium citrate supplementation (at about RDA levels) improves exercise tolerance, exercise-induced chest pain, and an index of quality of life.\textsuperscript{142} Similarly, in an earlier small pilot study, magnesium orotate improves left ventricular function and exercise tolerance.\textsuperscript{143} One problem with interpreting this study is that orotate itself may protect against cardiac stress.\textsuperscript{144} In another study, magnesium supplementation plus aspirin improves brachial artery endothelial function and exercise tolerance.\textsuperscript{145} In a different study, magnesium oxide (800 to 1200 mg/day), but not placebo, inhibits platelet-dependent thrombosis without affecting platelet aggregation.\textsuperscript{146} In one other study, enteric-coated magnesium chloride supplementation is alternated with placebo for six weeks.\textsuperscript{81} The subjects are 21 patients with stable congestive heart failure secondary to coronary artery disease,
who are treated with long-term loop diuretics, and who have initially low or normal serum magnesium concentrations. The magnesium treatment raises serum magnesium values, and decreases blood pressure, vascular resistance, the frequency of isolated ventricular premature complexes, couplets, and non-sustained ventricular tachycardia episodes.

One question about the above-mentioned studies is whether the apparent benefits involve correcting a marginal magnesium deficiency or not. In the study with the patients on diuretics, the mean value for serum magnesium increases, but not all subjects start with low values. Thus, it is hard to know if low serum magnesium is a prerequisite for seeing the changes. In the study on magnesium oxide effects on platelet-dependent thrombosis, serum magnesium is reported as normal, and it is not increased by magnesium supplementation. Although serum magnesium is not always an infallible guide to magnesium status, this study does raise the possibility that in this trial, the action of magnesium is not correcting a marginal deficiency. In one of the other studies, magnesium supplementation improves magnesium status based on sublingual cell ionic magnesium measured by x-ray dispersion. Unfortunately, it is hard to interpret this finding, since the method is not a common way to assess magnesium status (though it may ultimately prove to be a good method). Another issue with this study is that the magnesium supplement-induced increases in cell values are fairly small. In addition, even if magnesium status is improved, there is no direct evidence that the magnesium supplementation could not have worked if starting magnesium status was good. Thus, in subjects with coronary artery disease, any or all of the apparent benefits of magnesium supplementation may or may not depend on correcting marginal deficiency.

In contrast to the above results, in subjects with dilated cardiomyopathy, magnesium supplementation does not improve left ventricular ejection fraction nor prognosis compared to placebo. However, the co-treatments used in both groups already give substantial improvement in left ventricular ejection fraction. Thus, improvement may be somewhat "maxed out" in these subjects. Moreover, the particular magnesium treatment used does not increase serum magnesium. Thus, if improved magnesium status is needed to see the hypothesized benefits, then that improvement did not occur.

One study of magnesium supplementation in subjects with cardiovascular disease actually produces negative results. The study is done with survivors of an acute myocardial infarction. By one statistical analysis, though not another, cardiac events are higher in the magnesium group than in the placebo group. However, the magnesium supplement is the hydroxide form, which, as noted earlier, may not always be a good choice as a magnesium supplement due to antacid effects.

In summary, for subjects who have cardiovascular disease, magnesium supplementation produces apparent benefits in several studies. These results are promising but could use bolstering by more studies in more people. Some physicians may feel that there is already enough evidence to try a modest dose of magnesium in cardiac rehabilitation patients. Other physicians may be more cautious due to the possible detriment in one study. The detrimental actions, if they are a real concern, may possibly be avoided by not using magnesium hydroxide as the supplement, though this idea is unconfirmed.
It is not yet clear what, if anything, the studies discussed in this section imply for prevention of a first cardiac episode. One study along these lines does exist. The study involves 400 high-risk individuals consuming either a magnesium-rich diet or a control diet for 10 years. The group on the magnesium-rich diet shows less total complications, sudden deaths, and total mortality, and higher serum magnesium. These results are interesting, though this study should not be taken as a last word. One concern is that the subject number is not large for a study with prime end points of life expectancy and cardiac events. In addition, compliance tracking could have been challenging, though the difference in serum magnesium confirms at least some compliance. Finally, even if the study could be reproduced in more people, there would be doubt whether the benefits are due to magnesium, magnesium plus other dietary factors, or just the other dietary factors. For the moment, this study could inspire anyone concerned about initial or reoccurring cardiovascular disease to consume a magnesium-rich diet. This may help reduce cardiovascular risk, but if not, it still provides good amounts of magnesium for other uses, and it is likely to be high in many nutrients and phytochemicals.

**Diabetes**

Several lines of reasoning suggest that marginal magnesium deficiency occurs in a good number of diabetic subjects. For example, a number of studies report low serum magnesium values in many, though not all, subjects with type 1 or type 2 diabetes. The causes of the low serum magnesium are thought to be high renal magnesium loss plus some magnesium distribution away from the blood into certain tissues. Another connection between diabetes and magnesium is that erythrocyte-ionized magnesium, though not determined in all that many diabetic subjects, tends to show low values. This can occur even in subjects with normal serum magnesium values. Similarly, low serum-ionized magnesium can be found in type 2 diabetic adults and children, even with normal mean serum total magnesium values. There is also a report of low muscle magnesium contents in type 1 diabetic subjects. Finally, a series of studies in diabetic subjects show inverse correlations between serum magnesium and measures relevant to primary or secondary symptoms of diabetes (Table 2.1). If magnesium status is actually affecting the symptoms listed in Table 2.1, these effects may be related, at least partly, to insulin sensitivity. Magnesium function could have mechanistic connections to insulin sensitivity via magnesium effects on insulin receptor binding, activity of the receptors after binding, and signaling inside the cells.

These types of observations have led to the idea that many diabetic people would benefit from increased magnesium intake by diet or supplements. A number of studies of magnesium supplementation have occurred with type 2 diabetic subjects as well as a few studies with type 1 diabetic subjects (though one is not placebo controlled). These studies give some basis for benefits of increased magnesium intake, at least in some subjects. On the other hand, many of the studies do not examine large numbers of subjects, and some results conflict. Representative studies are summarized in Table 2.2.
In addition to these results, magnesium supplementation can also improve insulin responses and actions in elderly subjects without diabetes. 178

These results suggest that at least some diabetic people could benefit from increased magnesium intake. However, there is some doubt about the exact benefits, in the portion of the diabetic population that would reap the benefits, and the ideal magnesium treatment (dose, complex, length of treatment) to produce the benefits. The doubt derives from the low subject numbers in many studies, lack of placebo in a few studies, and conflicting results. The only way to settle these issues is a large, multi-center trial that examines many variations in subjects and treatments. As noted in the previous subsection, such trials are only funded where there is a high sense of urgency. In the meantime, some unconfirmed speculations on the causes of some of the conflicting results are given in the next few paragraphs.

For the lipid effects, there may be two different ways in which magnesium supplements can work. The first way may involve effects mediated by intracellular magnesium regulatory actions. For this process to be affected by increased magnesium intake, there may be two requirements. First, supplementation may have to correct a marginal magnesium deficiency. Some of the negative results noted in Table 2.2 for magnesium supplementation and serum lipids come in studies where magnesium status is not improved, is not reported, or is not initially poor in all the subjects. There may also be a minimal time of treatment needed to see an effect. It may take some time to correct magnesium deficiency and then some time for effects on lipid metabolism to replace the existing state of lipid compositions. This time-lag idea may also apply to some other possible effects of magnesium in diabetic subjects. For example, in the study finding no effect of magnesium supplementation on lipoprotein oxidation, the study’s authors propose that a longer treatment time may be needed to see an effect.161

A second way in which magnesium may affect serum lipids is the same as that hypothesized for effects in non-diabetic individuals. High oral magnesium intake may decrease absorption of lipids and bile salts. Doses of magnesium are not very high for many of the studies in Table 2.2.

### TABLE 2.1
Inverse Correlations with Serum Magnesium in Diabetic Subjects

<table>
<thead>
<tr>
<th>Measure</th>
<th>Type of Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
<td>Type 2157</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Type 1158,159</td>
</tr>
<tr>
<td>Diurnal rhythms of serum glucose*</td>
<td>Type 1 and 2160</td>
</tr>
<tr>
<td>Glucose clearance after a glucose load</td>
<td>Type 2155</td>
</tr>
<tr>
<td>Occurrence or progression of retinopathy</td>
<td>Type 1 and 2 in 149</td>
</tr>
</tbody>
</table>

* Comparison with diurnal rhythms of serum magnesium

In addition to these results, magnesium supplementation can also improve insulin responses and actions in elderly subjects without diabetes. 178
The specific magnesium complex used may also be important. One of the better effects seen on serum lipids is in a study using magnesium pidolate.\textsuperscript{168} This complex may work better due to better bioavailability than the inorganic magnesium complexes used in some of the negative studies. Alternatively, the pidolate may exert specialized effects, either independently of the magnesium or with it.

Insulin sensitivity and insulin reaction to glucose loading are improved in a number of studies in Table 2.2. In contrast, only one study reports any improvement of fasting serum glucose,\textsuperscript{169} and just one reports improvement in any other indicator of metabolic control.\textsuperscript{176} Some of the disparity for metabolic control results could be
tied to changes in magnesium status. In some negative result studies, initial magne-
sium status may not be poor for many of the subjects. In addition, in some studies, 
the magnesium treatment may not have corrected any marginal deficiency that was present. This lack of effect may be related to magnesium dose and bioavailability. 
In support of these last ideas, one of the two positive studies on magnesium sup-
plementation and metabolic control notes an effect only with the higher of two doses 
tested. In the other positive study, the supplement is liquid magnesium chloride, which shows good bioavailability in some studies. However, improvement in 
magnesium status cannot be the only factor in magnesium-induced improvement in 
metabolic control. There are studies noted in Table 2.2 where magnesium status is 
improved but metabolic control is unchanged. Thus, whether magnesium supple-
mentation can help with metabolic control in many diabetic subjects is still in doubt. 

In 1992, the American Diabetes Association made the following statement: “
“Adequate dietary magnesium intake can generally be achieved by a nutritionally 
balanced meal plan as recommended by the American Diabetes Association … only 
diabetic patients at high risk of hypomagnesemia should have total serum (blood) 
magnesium assessed, and such levels should be repleted only if hypomagnesemia 
can be demonstrated.” Since that statement, quite a few new studies have appeared, 
but this author feels that much of the statement still makes sense. On the other hand, 
this author feels that anyone with diabetes can have his or her serum magnesium 
checked. If a person shows low serum magnesium, in this author’s opinion, a low-
dose supplement with high bioavailability and low GI side effects is very likely to 
be safe and, possibly, could be helpful. If a diabetic person shows normal serum 
magnesium, this does not guarantee adequate magnesium intake, but a more detailed 
assessment of magnesium status is not available in most clinical settings. In this 
author’s opinion, if serum values come back normal, a subject should still strive to 
eat a moderately high magnesium diet. Supplements may or may not be helpful, 
though this decision should be made in consultation with a physician and a dietitian.

STRESS

Internet sites, as well as some scientific review articles, tout magnesium as an 
anti-stress mineral. Stress can be produced physiologically or psychologically. Mag-
nesium effects on physiological stress are part of the rationale for the possible effects 
of magnesium on blood pressure and other aspects of cardiovascular disease (see 
above). This is also part of the rationale for magnesium effects on exercise-related 
phenomena (see below). In addition, magnesium may affect reactions to psycholog-
ical stress.

Magnesium has a lot of theoretical ties with inhibiting responses to psychological 
stress. For instance, magnesium has a strong effect on neural excitability, since 
magnesium deficiency is characterized by neural and neuromuscular hyperexcitabil-
ity. In addition, blood vessel dilation or constriction can be very much influenced 
by magnesium. Magnesium can also have a variety of effects that involve systems 
thought to be involved in the pathophysiology of depression. One such effect is 
suppression of hippocampal kindling, which can reduce the release of adrenocorti-
cotrophic hormone (ACTH) and affect adrenocortical sensitivity to ACTH. A second
such effect is modulation of various receptors such as N-methyl-D-aspartate-antagonism, gamma-aminobutyric acidA-agonism, or angiotensin II-antagonism. In addition, magnesium can affect the function of the transport protein p-glycoprotein at the level of the blood-brain barrier, which may impact access of corticosteroids to the brain. Finally, magnesium depresses calcium ion–proteinkinase C-related neurotransmission and stimulates the sodium-potassium pump, both of which can impact neurological function.

It is of interest that magnesium and lithium, an anti-depression drug, have a number of functional overlaps, including effects on sleep electroencephalogram results.183

A big part of the relationship between magnesium and stress could be via interactions with the stress-related catecholamine hormones epinephrine and norepinephrine (adrenaline and noradrenaline). These hormones have three theoretically possible interactions with magnesium:

1. Epinephrine may increase magnesium needs, which could promote magnesium deficiency.
2. Norepinephrine and epinephrine secretion during stress may be inhibited by magnesium.
3. Magnesium may limit detrimental effects caused by these two hormones during stress.

In support of the first premise, low serum magnesium is reported for physiological stress situations associated with high serum catecholamine levels.180,184 These physiological stress situations include myocardial infarction, cardiac surgery, and insulin-induced hypoglycemia stress tests. This idea that catecholamine hormones depress serum magnesium is further supported by multiple studies showing that epinephrine infusion in humans depresses serum magnesium.193 In addition, emotional stress due to combat or threat of combat has been shown to produce low total and ionized serum magnesium values.186 Part of the mechanism for depressed serum magnesium in these situations has been thought to be epinephrine stimulation of adipose tissue fat breakdown.180 This breakdown liberates free fatty acids, which can then bind to magnesium and change its cell uptake patterns. However, this concept is not fully confirmed, because if plasma free fatty acids are elevated from an exogenous source, plasma magnesium does not drop.187 Thus, there may also be other ways in which epinephrine lowers serum or plasma magnesium.

It is not known if the lowering of serum magnesium by epinephrine is actually associated with a functional magnesium deficit. A deficit could be created by increased urinary loss of magnesium or a type of body magnesium redistribution that tends to deplete certain functional pools. Unfortunately, there is very little data as to whether either of these responses actually occurs. One study finds no short-term epinephrine infusion-induced increase of urinary magnesium,188 but there is not much additional work building on this observation. Also, in some situations, stress can actually produce a rise in plasma magnesium simultaneous to a loss of this element in blood cell and heart tissue. This pattern has been demonstrated by combining data from guinea pigs, rats, and humans undergoing noise stress.190–192 However, this rise may be temporary,
since noise stress can increase urinary magnesium. Thus, future studies may need to give attention to the time course of changes in magnesium metabolism.

The second possible interaction, magnesium inhibition of stress-induced norepinephrine secretion, is supported by a number of animal and human studies. Four examples are given here. One, in people with mitral valve prolapse, magnesium supplementation can decrease urinary norepinephrine and epinephrine, which is an indication of lower blood levels of these hormones. Two, in humans, magnesium sulfate infusion suppresses cardiac release of norepinephrine during a handgrip stress test, which is an indirect index of sympathetic efferent neuronal activity. Three, in stressed pigs, adding magnesium aspartate to a seemingly adequate diet produces lower norepinephrine concentrations. Four, high-dose magnesium gluconate reduces the catecholamine increase in response to immobilization stress. In the first example, the effect is thought to coincide with correction of marginal magnesium deficiency. On the other hand, this may not be the case in the last three examples. This raises the possibility that above-adequate magnesium intakes may counteract some stress effects.

On the other end of the spectrum, poor magnesium status can cause poor reaction to stress. For example, in comparing mice with genetically low blood magnesium to those with genetically high blood magnesium, the former have higher norepinephrine levels. Similarly, magnesium-deficient rats show high urinary norepinephrine. Also in rats, magnesium deprivation produces aggressive behavior. This effect can be reversed by supplementation by any of five magnesium complexes (chloride, pidolate, aspartate, gluconate, lactate). However, magnesium pidolate had the greatest efficacy by one assessment tool. The exact relationship of such animal studies to human situations is not yet clear.

The third premise, magnesium can modulate the detrimental effects of catecholamine hormones, is well supported by animal work. Three examples are given here. One, in magnesium-deficient rats, isolated aorta sensitivity to norepinephrine is higher than in control rats. Two, vascular reactivity to norepinephrine is higher in moderately magnesium-deficient rats than in controls. Three, in rats, high magnesium intake produces low pulmonary vascular reactivity and hypoxic pulmonary hypertension. Thus, this is another case where magnesium may have an effect that does not involve correction of a magnesium deficiency.

Despite these mechanistic rationales for magnesium interactions with psychological stress, there is not a lot of human studies of magnesium supplementation in this area. There is a study of magnesium supplement effects on sleep patterns, which is done in 12 elderly subjects. Based on sleep electroencephalogram results and nocturnal hormone secretion, magnesium supplementation partially reverses aging-related changes in sleep. The authors of the study note that these effects of magnesium resemble those of lithium, which supports the possible efficacy of magnesium as a mood stabilizer.

In another study, magnesium pidolate supplementation does not affect blood pressure during sympathetic neuro-stimulation by stresses of cold, isometric action, and tilt. Supplementation raises serum magnesium, though initial values are not very low.
There has been some attempt to use noise-induced hearing-loss studies to relate magnesium to protection against stress. In guinea pigs, and to a limited extent in humans, magnesium intake or body fluid magnesium levels (including perilymph values), have been shown to impact noise-induced hearing loss. However, the mechanisms of action may go well beyond a limitation of the general stress response. Instead, the magnesium effects may involve various physiological effects in the ear. Nonetheless, even if the magnesium actions on hearing loss do not primarily relate to general stress processes, the area of magnesium and hearing loss could use more human research. On the other hand, avoiding excess noise, when possible, may be a better approach to hearing maintenance than magnesium supplementation.

In conclusion, a connection between magnesium and resistance to the ill effects of psychological stress has a strong mechanistic basis. However, there are just not enough human intervention studies to rate the value of magnesium supplementation for anti-stress effects. One approach to such human intervention studies could involve noise and hearing loss, but this may not be ideal for studies on magnesium and general stress.

**EXERCISE**

Since a great deal of the body’s non-bone magnesium is found in muscle, it would be expected that there would be studies of magnesium supplementation relevant to exercise. Such studies yield differing results. This should not be all that surprising since many studies of a given theme in exercise give variable results. This can happen in part because of the many variables associated with designing an exercise study such as subject age, subject fitness, subject training level, subject motivation, the type of exercise examined, the exercise testing duration, the timing of the supplementation around the exercise tests, the project end points, how the data is analyzed (e.g., improvement versus just final results), and background diet (both for the component being studied and other components). In the case of magnesium supplementation, not only do these variations complicate interpretation, but as discussed below, there are also other design issues that cloud interpretation of many of the studies.

In principle, magnesium function should have many effects on exercise. For example, magnesium is important for regulating neuromuscular activity, excitation, and muscle contraction, as well as for aspects of protein synthesis. Magnesium is also needed for ATP-driven reactions, which include muscle contraction. In addition, the antioxidant and anti-inflammatory actions of magnesium could delay fatigue and promote muscle recovery, since fatigue and muscle recovery-related inflammation can be accelerated by oxidant stress. Another way magnesium can affect exercise capacities is via hormonal influences. For example, magnesium impacts secretion of insulin-like growth factor, which influences muscle growth and maintenance. Furthermore, magnesium promotes vasodilatation, which may impact blood flow to the muscles.

Besides a mechanistic link between magnesium and exercise, body magnesium distribution can be altered by exercise. Some short, intense exercise can increase
serum magnesium, possibly due to dehydration and movement of magnesium into the serum from muscle and other cells.\textsuperscript{57} In contrast, sustained strenuous exercise can reduce serum magnesium.\textsuperscript{57} Whether or not this action impacts magnesium functional status is controversial. Reductions in serum or plasma magnesium of 5 to 25\% have been reported immediately after prolonged strenuous exercise such as a marathon run, a half Ironman triathlon, prolonged cross-country skiing, 90 minutes of treadmill exercise, and a 120 km march.\textsuperscript{57} Some of this fall in serum magnesium may be mediated by catecholamines, as discussed for other types of stress in the previous subsection.

The drop in serum magnesium values seems to be especially pronounced in hot conditions.\textsuperscript{211,212} This could imply that sweat losses contribute greatly to the depression in serum magnesium in exercise, especially in heat. However, sweat losses of magnesium during exercise don’t appear to be big enough to account for the majority of the drop in serum magnesium.\textsuperscript{211,213}

Urinary magnesium can undergo some fluxes during and after prolonged exercise, but the net result is not thought to have major acute impact on body magnesium status.\textsuperscript{214} The effects of chronic exercise training on urinary magnesium, or on magnesium status in general, is poorly characterized. The fall in serum magnesium during acute, strenuous exercise may not involve body losses, but instead may be a movement of magnesium into cells including muscle cells, adipocytes, and erythrocytes.\textsuperscript{57} After exercise subsides, body magnesium distribution tends to gradually return back to normal.\textsuperscript{57} Whether or not prolonged repetition of this cycle raises magnesium needs is not known.

Magnesium movements during short-term or prolonged strenuous exercise could conceivably interact with dietary magnesium in the following ways:

1. If magnesium intake is chronically well below the RDA before exercise, performance could be impaired by sub-optimal amounts of magnesium moving to areas of need.
2. After exercise, the return to normal magnesium distribution may not be fully effective; if training keeps repeating this process, magnesium needs may be raised; if these increased needs are not met, exercise performance impairment and other effects of marginal magnesium deficiency may result.
3. An above-adequate intake of magnesium might enhance the efficiency of magnesium redistribution during exercise, which in turn might improve exercise performance.

The first possibility seems to be a safe assumption. Poor magnesium status has been shown in both humans and rats to have this effect.\textsuperscript{215,216} This could be true even in people of average fitness doing sub-maximal exercise. This contention is supported by a study where postmenopausal women are chronically fed different levels of magnesium.\textsuperscript{217} Marginally low intake affects sub-maximal exercise performance by increasing energy needs and adversely affecting cardiovascular function.

Although possibility number 1 was just stated to be a safe assumption, there are two unanswered questions. One, how bad does marginal magnesium deficiency have
to be before an effect is seen? And, two, how often does this state occur? Dietary surveys of competitive athletes and otherwise very active people show magnesium intake varying among different groups.\textsuperscript{57} Intakes range from well below the RDA to levels at or a little above the RDA. What these studies don’t say is whether the RDA is an appropriate standard for all types of athletes or highly active people. This leads to the second possibility, which says that chronic exercise training raises magnesium needs. As already stated, this issue has not been well addressed. A little support for the idea of raised needs is gathered from two studies\textsuperscript{31,218} In one, low serum magnesium persists long after a 120 km hike has ended.\textsuperscript{218} In the other study,\textsuperscript{31} certain female athletes show low serum magnesium levels despite dietary magnesium intakes above the RDA. Unfortunately, with both studies, it is hard to know if the results represent a true magnesium deficit or just metabolic regulatory action. The second study\textsuperscript{31} claims to have evidence for the latter. The contention is based on a lack of effect of three-week supplementation with magnesium oxide given to athletes with low to normal serum magnesium. The lack of effect is noted for both serum and cellular magnesium contents. However, this could simply indicate that the magnesium oxide supplement used has low bioavailability. This proposition is supported by the lack of a clear increase in urine magnesium from baseline in the supplemented group. If the supplemented magnesium was absorbed, but did not improve magnesium status, the urinary magnesium should increase. Thus, the question of whether chronic exercise training raises dietary magnesium needs is not yet answered.

The final possibility is that a dietary magnesium-induced improvement in exercise performance could go beyond any correction of marginal deficiency. This possibility is still unsettled, partly because most studies on magnesium supplementation and exercise performance do not fully address the issue of starting magnesium status.

There have been a number of studies on magnesium supplement effects on exercise performance. Most of these focus on just magnesium, though there are also a few dealing with specialized products such as magnesium–creatine, and a product that combines magnesium, zinc, and vitamin B\textsubscript{6}. These last two products are discussed briefly at the end of this subsection.

The following are brief summaries of 10 representative studies on magnesium supplementation and exercise performance (5 negative results and 5 positive results). In many of these studies, some details, such as magnesium status of the subjects, are not reported. In each of these studies, a placebo control is used.

**Negative**

1. Three weeks of magnesium oxide supplementation gives no effect on performance in multiple types of exercises; there is minimal impact on urine magnesium.\textsuperscript{31}
2. Magnesium aspartate supplementation has no effect on marathon race running performance in terms of muscle damage, rate of recovery of muscle function, or running time; no increase is seen for muscle or serum magnesium.\textsuperscript{219}
3. A 12-week exercise program plus magnesium supplementation is tried in active men; peak oxygen uptake is increased with or without magnesium; there is no change in urinary magnesium.220

4. Four weeks of magnesium oxide supplementation is done in young adults with a broad range of serum ionized magnesium values; there is a small increase in serum-ionized magnesium, but no change in exercise performance and recovery indices.221

5. Magnesium aspartate supplementation is done for three months in healthy young swimmers; there is no effect on performance data for laboratory or competition settings; there is some increase in serum magnesium values, which are initially in the lower end of normal range.222

Positive

6. Magnesium oxide is given during a seven-week strength training program for untrained subjects; both the magnesium and placebo groups gain strength, but the magnesium group does better based on knee-extension torque strength.223

7. Magnesium orotate is given to competitive triathletes for four weeks; there is no change in serum magnesium, which is initially in the normal range; swimming, cycling, and running times are lower in the magnesium group versus placebo; hormonal and metabolic changes in the supplemented group are more favorable than for placebo.224

8. Magnesium aspartate is given for three weeks to female rowers with plasma magnesium values at the low end of the normal range; exercise performance is improved.225

9. Magnesium picolinate given to moderately trained adults improves cardiopulmonary function during sub-maximal exercise.226

10. Short-term magnesium–potassium aspartate improves endurance on a bicycle ergometer.227

Some studies on both sides have questions about interpretation. For example, both study number 2 on the negative side219 and number 7 on the positive side224 have no before-intervention testing; there is just after-treatment testing. These types of studies require careful matching for initial fitness, plus either a very consistent, clear intervention effect or a high subject number. These studies have neither of the latter two traits. Study number 2 also uses both genders, which should not be done in an exercise study with a small number of subjects. In fairness to study number 7, the authors do not actually make a strong claim that the study demonstrates a magnesium effect on exercise performance. The authors present as their main goal analysis of magnesium modulation of exercise-induced effects on hormone metabolism and various physiological parameters. However, some other researchers have presented this study as a demonstration of exercise performance enhancement by magnesium.

Two of the five negative result studies cited use magnesium oxide,31,221 which does not always show good bioavailability. This may have been the case in both of these studies, since one reports no clear effect on urinary magnesium,31 and the other
reports just a small change in serum-ionized magnesium. Another of the negative result studies reports no effect on serum total magnesium. Similarly, one of the other negative studies finds no increase in serum or muscle magnesium. Thus, four of the five negative result studies do not necessarily involve improved magnesium status, which may be a requirement for seeing a magnesium supplement effect on exercise.

One of the positive results studies also uses magnesium oxide but still gets an effect on training-induced strength increase. It is noteworthy that pretraining strength of the subjects is pretty well matched between the magnesium and placebo groups. Unfortunately, this study does not report on subject magnesium status changes, but as noted earlier, some preparations of magnesium oxide can show enough bioavailability to affect magnesium status.

Study number 10 of the positive result studies has some question marks about interpretation due to low subject number (n = 6), the short duration of supplementation (one day before the first assessment), and the possible effects of potassium and aspartate independent of magnesium. The general idea of this last concern also applies to study number 7 of the positive results because orotate has biological activities independent of magnesium.

In conclusion, there are many questions about the studies of magnesium supplementation and exercise. Thus, no conclusions can be reached yet.

As mentioned earlier, two atypical magnesium supplements are marketed for exercise performance enhancement. One is a magnesium–creatine chelate. This complex may enhance creatine effectiveness by targeting creatine to muscle, slowing degradation of ingested creatine, and by magnesium functions complementing the actions of creatine. This author’s laboratory finds that short-term use of this supplement, at a relatively low dose for a creatine study, produces improved bench press performance. However, the improvement is no better than creatine alone. The short-term supplementation approach is used to test for a direct effect on performance that is relatively independent of a training enhancement effect. The negative results of this study do not rule out that magnesium–creatine might outperform creatine in a longer term training study of low-dose supplementation. Also, the initial work does not control for macronutrient content of the diet, which may affect the results. One other study has been published for magnesium–creatine, which when compared to our group’s study, uses a slightly longer intervention time and a considerably higher dose. The magnesium–creatine chelate increases intracellular and extracellular water as well as knee extension peak torque. This increase is not seen for placebo or for magnesium oxide mixed with creatine. The increased intracellular water may be indicative of more muscle synthesis of creatine or protein, though this is unconfirmed. In conclusion, work on magnesium creatine is still in the early stages.

A popular supplement for exercisers combines magnesium, zinc, and vitamin B₆, and is called ZMA. Although one website states: “There is a large body of scientific evidence supportive of ZMA,” there is not a single hit on Medline for the term “ZMA.” This author is aware of one meeting abstract on ZMA. This author is not aware of a follow-up as a full-length paper. Thus, it is difficult to assess the value of ZMA at this time.
OSTEOPOROSIS PREVENTION OR RESTRICTION

Since a high portion of the body’s magnesium resides in bone, and since magnesium has some possible mechanistic ties with bone health (see the Function section), it makes sense that magnesium intake could affect osteoporosis prevention or progression. This concept is supported by animal studies, but human intervention studies are very limited. The study that gets the most attention examines trabecular bone density in 31 postmenopausal women with osteoporosis. After a year, bone density is increased by magnesium supplementation as compared to a group of women who refused osteoporosis treatment. However, there are some bothersome aspects of the study. One concern is that bone density increases after one year, which is not a common finding in studies of this subject group. Usually, a good result is a slowing of bone loss. In addition, in 10 of the subjects given magnesium, continuation for a second year of supplementation loses the magnesium effect. Another problem is there is no placebo group. Instead, for a frame of reference, a group is used that may have been less motivated about their bone health than the supplementation group.

In a different study, done in healthy young adult females, the effects of 28 days of magnesium supplementation or placebo are examined for effects on biomarkers of bone metabolism. In this crossover study, values for serum and urine bone turnover markers are not affected by magnesium supplementation, but neither is serum magnesium. Thus, a marginal magnesium deficiency may not have existed, or if it did, it may not have been corrected. This may be the reason for no effect on bone turnover parameters. Alternatively, the supplementation intervention may have been too short. Or, it’s possible that boosting magnesium intake is not an effective way to promote bone health in this people group.

A few other studies on magnesium supplementation and bone have been done, though low subject number or design problems cause these studies to not carry much weight. Thus, at present, though magnesium protection against osteoporosis is theoretically very possible, we don’t know if increased magnesium intake would help osteoporosis prevention or restriction to a large degree in many people.

CHRONIC FATIGUE

Magnesium status in subjects with chronic fatigue syndrome does not seem consistent. One study states that erythrocyte magnesium is low, but a larger study does not. In the latter study, normal values are also reported for a magnesium loading test, though only six of the study subjects are tested. A different study reports normal serum total and ionized magnesium in subjects with chronic fatigue syndrome. In one other study, just under half of 97 subjects show evidence of magnesium deficiency based on a magnesium loading test. Magnesium supplementation was tested in 24 of these patients. Supplementation improves values for the loading test. However, not all the subjects in this study are declared to have chronic fatigue syndrome. Some are designated as having other types of chronic fatigue. Even so, this study adds to the idea that some degree of magnesium deficiency is not a consistent finding in chronic fatigue syndrome.
There are two other magnesium supplementation studies. One uses six weekly injections, which produces subjective symptom improvements in 12 of 15 subjects, while placebo gives improvement in 3 of 17 subjects. In this same study, there is also an energy scoring evaluation where seven of the supplemented group show improvement compared to just one in the placebo group. One other study examines a heterogeneous group of subjects, about half of which are said to have chronic fatigue syndrome. About half of the total subject group are designated as having “subclinical” magnesium deficiency based on a magnesium loading test. These subjects show lower values for some parameters of antioxidant defense. Of these subjects, 24 are given magnesium supplements, but only about half show improved magnesium status. The type of supplement is not stated. Supplementation increases serum vitamin E levels and improves one parameter of resistance to oxidant stress, but not two others.

At present, it is hard to reach a conclusion of the value of magnesium supplementation in chronic fatigue syndrome due to the inconsistency of results as to magnesium status, the very limited testing of symptom improvement with administered magnesium, and the mixing of different fatigue classifications in two studies.

**Asthma**

A number of Internet sites tout magnesium supplements for asthma patients. It is true that magnesium given by various non-oral routes has been tried pharmacologically in asthmatic subjects, particularly for treating acute stress. However, this does not necessarily indicate that oral supplements would be effective. There is one study of short-term intervention effects of magnesium intake on asthma symptoms. In this work, subjects eat a low-magnesium diet for three weeks, and then have a short-term treatment period for supplementation with magnesium or placebo. The subjects then repeat the diet protocol, after which they then take whatever supplementation treatment was not used the first time (magnesium or placebo). Magnesium supplementation improves subjective, but not objective, symptoms. Thus, at present, there is no direct, strong evidence that oral magnesium supplements would help asthma, though there are some epidemiological links between magnesium intake and some asthmatic symptoms.

**Beta-Thalassemia/Sickle Cell Anemia**

These two erythrocyte pathologies may be helped by magnesium supplementation. In the case of sickle cell anemia, one of the pathogenetic mechanisms responsible for sickling is decreased hydration of the cells. Erythrocytes require a high degree of hydration to keep the large amounts of hemoglobin soluble in the cells. In sickle cell anemia patients, a subset of the erythrocytes loses magnesium easily through cell membranes. This, in turn, affects cellular electrolyte transport, which in turn affects water movement in and out of the cells.

Besides the loss of magnesium from erythrocytes, there are reports of people with sickle cell anemia having high urinary magnesium excretion and low plasma
or serum magnesium. However, these reports do not encompass a tremendously large number of subjects. A small study in humans shows beneficial effects of magnesium pidolate supplementation on the erythrocytes. The benefits include effects on measures indicative of better cell hydration. In addition, in a mouse model for this disease, a low magnesium intake worsens the condition, and a high magnesium intake improves it. There is also a non-blinded study where magnesium supplementation strongly decreases the median number of painful days in a six-month period. However, as the authors of the study note, no firm conclusion on therapeutic efficacy can be drawn from this unblinded, open trial.

These results are certainly interesting. The next step would be large, placebo-controlled trials. Since all of the studies mentioned in the previous paragraph involve one particular researcher, it would be good to have some other groups also involved in the future studies. Some attention may need to be given to the particular magnesium complex used for the studies.

The same researcher who led the studies on magnesium supplementation and sickle cell anemia has also investigated magnesium in another erythrocyte disease, beta-thalassemia. This disease is also characterized by magnesium metabolism abnormalities, including low blood cell magnesium. In a small study of magnesium supplementation in humans, and in a study of a mouse model for the disease, erythrocytes are affected in ways that are reminiscent of those found for magnesium in sickle cell anemia. These results include effects on cell hydration, though the clinical importance of these effects for beta-thalassemia is not totally clear yet.

KIDNEY STONES

Magnesium–potassium citrate has been used as a preventive measure against kidney stone formation, but the main intended effect is citrate delivery. However, magnesium as part of this or other complexes may help inhibit kidney stone formation, particularly for calcium oxalate stones. There are several theoretical possibilities for how magnesium could work against such stone formation:

1. Inhibiting the formation of calcium oxalate crystal building in the kidney (supported by work in vitro)
2. Influencing body citrate metabolism, which influences urinary citrate, which inhibits stone formation
3. Non-citrate-related alkali effects in the urine, which reduce stone development (this could be especially true of complexes like magnesium hydroxide, which is an antacid)
4. Binding to oxalate in the GI tract to prevent oxalate absorption
5. Repression of internal oxalate production; this may only be relevant to avoidance of severe magnesium deficiency, and even then, increased production may be offset by increased oxalate secretion into the intestine

There have been some attempts to say that some chronic stone formers often have marginal magnesium deficiency, but the studies tend to be small and not overly...
compelling. For example, in a study in Thailand, 9 of 17 subjects with kidney stones show signs of marginal magnesium deficiency based on a magnesium tolerance test, but so do 6 of 16 controls. Even so, it is possible that a stone former would not have to have a marginal magnesium deficiency to benefit from increased magnesium intake. Conceivably, some mechanisms noted above could be promoted by consuming magnesium at levels beyond those needed to prevent or correct a marginal deficiency. Moreover, the effects of magnesium hydroxide as a urinary antacid may go beyond the effects of just providing extra magnesium. On the other hand, a low magnesium intake could aggravate a predisposition to renal stone formation via some of the possible mechanisms mentioned above. Thus, in principle, magnesium intake could be useful for kidney stone prevention as part of antacid complex, as a corrector of marginal magnesium deficiency, or by various actions that go beyond either antacid actions or correction of a marginal deficiency.

There are a number of studies on magnesium supplementation in regard to stone formation or kidney stone risk factors. Unfortunately, none make a strong case for or against supplementation. One reason is that most of the studies do not have a lot of subjects for the type of study done. In addition, some of the studies use end points that really don’t rule in or out a strong effect on stone formation. Another problem is that there is often little attention paid to the specific magnesium complex used, which could affect the results. Finally, many of the studies do not use a placebo control. As shown in one of the studies discussed below, a placebo effect can be very strong in these types of investigations. One reason for a placebo effect is that if subjects are motivated enough to be in this type of study, then they may also be motivated to take other steps to prevent stone formation (e.g., increasing water intake).

In one study, 13 stone formers are treated for one year with 400 mg magnesium oxide plus another agent in a non-placebo-controlled study. The treatment reduces urinary calcium to magnesium ratios, a result assumed but not confirmed to lower risk of forming calcium oxalate stones. A big issue for this study is that serum magnesium actually decreases with the treatment. This could mean that despite some positive effect, magnesium oxide might not be the best way to increase body uptake of magnesium. This concept is supported by a rat study suggesting that magnesium oxide is somewhat “middle of the road” among magnesium complexes for fighting kidney stone formation.

Another study examines only four subjects. Magnesium oxide supplementation shows no effect on urine parameters such as a measure of calcium phosphate complex formation tendencies. One problem with this study, besides the low subject number, is that the parameters measured may have limited value in predicting the formation of the most common kidney stones. An additional problem is the use of magnesium oxide, which as just mentioned may not be the best magnesium complex for fighting kidney stones. In another study with magnesium oxide in stone formers, there is no significant effect on urinary oxalate, while urinary calcium is increased. The supplementation does not increase in urinary magnesium, which could mean that the supplemental magnesium oxide is not absorbed well enough to be effective.
In contrast to these studies, some studies do show positive effects of magnesium oxide treatment. However, not one of the studies has a clear-cut interpretation. In one study, which is reported in two articles,\textsuperscript{250,259} stone formation per year is lower with magnesium oxide treatment. However, this assessment is based not on a blinded placebo comparison, but based on the subjects' previous history and in comparison to some subjects who were not undergoing preventative treatments. As already noted, placebo controls are very important for kidney stone studies. There is reason to believe that the effects seen in the just-mentioned study may have been a placebo effect, or due to the subjects making a general commitment to stone prevention steps. This reasoning is reinforced by the fact that the magnesium supplementation did not increase serum magnesium values long term.

The lack of a placebo group also applies to another study where magnesium oxide is reported to decrease the number of stones occurring in stone formers.\textsuperscript{260} In an additional study of magnesium oxide,\textsuperscript{261} the interpretation is clouded by the treatment consisting of magnesium plus vitamin B\textsubscript{6}. Thus, the role of magnesium versus that of the vitamin B\textsubscript{6} in the results is not clear. The same can be said for another study of the combination of magnesium oxide and vitamin B\textsubscript{6}.\textsuperscript{262} In this case, stone formation is not assessed. Instead, there is a report of increased urinary magnesium and citrate, along with a decrease in oxalate excretion in 16 calcium oxalate stone formers. The increase in urinary magnesium differs from some studies of magnesium oxide that don’t see a change in urinary magnesium. However, as noted in the Bioavailability section, physical differences in magnesium oxide preparations can give differences in bioavailability. In another study of urinary oxalate, seven normal subjects and four stone formers are given magnesium oxide or citrate for two weeks.\textsuperscript{263} If the supplements are taken with meals, urinary oxalate and urinary saturation of calcium with oxalate decreases. The low subject number and lack of placebo again put the results in question.

In a study of a different magnesium complex, nine subjects with low urinary magnesium excretion are given magnesium hydroxide (500 mg/day) for up to 18 months.\textsuperscript{264} Urinary magnesium increases while urinary oxalate decreases. The stone recurrence rate decreases from 0.75 to 0.11. Once again, though, there is no placebo control. Also, it is not known if the effect is due to magnesium in general, or due to the antacid effect of magnesium hydroxide.

There is a placebo-controlled study of magnesium hydroxide and kidney stone formation.\textsuperscript{265} A large improvement is seen for stone formation, but it is not statistically different from the placebo group. This emphasizes the need for a placebo group in this type of study. A problem with interpreting this particular study is that the improvement in the placebo group is so good. Possibly, with such a good placebo response, the study may have had to go longer to see a clear effect of the magnesium hydroxide (the improvement in the magnesium hydroxide group exceeds the placebo effect, but the difference is not statistically significant). Another question is whether another type of magnesium supplement could do better than magnesium hydroxide. Although the magnesium hydroxide has urine pH effects, an organic magnesium supplement may be more bioavailable.

There is one other study relevant to this area. In this work, magnesium and calcium are examined for short-term effects following an acute oxalate load in 24
healthy subjects. Magnesium is nearly as effective as calcium in reducing oxalate absorption and urinary excretion. This does not definitively show that magnesium supplements actually prevent kidney stone formation, but it does strengthen the case for one of the proposed mechanisms by which this could happen (reduced GI tract oxalate absorption).

After viewing the results and conflicting interpretations of these studies, a physician or a patient may ask: How can anyone make a decision on this issue? If one takes the approach of “it may help and it probably won’t hurt,” then a moderately high magnesium intake is appropriate. This could be done by diet. However, since a number of good magnesium sources are also high in oxalates, which are not desirable for stone formers, supplements can be a convenient option.

This issue has a practical side to this author, who has had a kidney stone. This author’s own approach, besides drinking large volumes of water, is to take about 320 mg of magnesium per day. This is not done as magnesium hydroxide, due to potential additive effects with one of his medications. Instead, an organic compound such as magnesium bisglycinate or magnesium lactate is used, even though neither has been tested in humans for kidney stone prevention. Still, these supplements at the stated dose are likely to be safe, should be well absorbed, and have the potential to affect most of the mechanisms noted above for magnesium and kidney stone prevention. This author would like to see a well-designed study of various magnesium complexes on kidney stone formation.

**Pregnancy: Premature/Low Birth Weight Outcomes**

Low serum magnesium values are common during pregnancy, though this could be a regulatory action or a hemodilution effect (increased water in the blood). On the other hand, some work with erythrocyte-ionized magnesium suggests that pregnancy can tend to deplete body magnesium. Moreover, there are some U.S.-based diet survey studies that show that magnesium intake by pregnant women is often well below the pregnancy RDA. This dietary pattern is seen even in middle- to upper-income women. These diet studies, plus the possibility that pregnancy may tend to deplete body magnesium, have fueled speculation that magnesium intake can affect pregnancy outcome. This attention has been especially focused on the risk of premature or other low-birth-weight pregnancy outcomes. Part of this focus has occurred because parenteral magnesium administration has been used to arrest preterm labor. Although this pharmacological application of magnesium may be very different from nutritional magnesium actions, in some people’s thoughts, the parenteral use connects magnesium with preterm delivery.

One line of evidence does support this connection. In Taiwan, there is an inverse relationship between risk of a very-low-birth-weight outcome and magnesium levels in drinking water. There is also a study reporting that women in preterm labor have even lower serum magnesium than most pregnant women. On the other hand, other studies find that preterm labor and delivery do not correspond to differences in dietary or serum magnesium levels.

There have been a number of studies of magnesium supplement effects on this type of pregnancy outcome, but they have been criticized for their design. For
instance, the author of a meta-analysis paper on this subject states that only one of seven reviewed studies were judged to be of high quality. This meta-analysis does report that oral magnesium treatment from before the 25th week of gestation is associated with a lower frequency of preterm birth. However, this effect disappears with exclusion of a cluster trial. Furthermore, the author says that the poor design just noted is likely to produce a bias favoring magnesium supplementation.

Thus, though oral magnesium supplementation may help prevent against pre-mature and low-birth-weight pregnancy outcome, this hypothesis has not yet been adequately tested.

**Premenstrual Syndrome (PMS)**

Due to magnesium functional ties with hormones and neurological processes, a role for magnesium in reducing PMS symptoms seems plausible. Some studies have reported low values of blood cell magnesium in women with PMS, but plasma magnesium can be normal. Since blood cell total magnesium may or may not be indicative of magnesium status, it is unclear if women with PMS are prone to marginal magnesium deficiency. However, the absence of such deficiency may not exclude the possibility of benefits for increased magnesium intake.

In a randomized, double-blind, placebo-controlled, crossover study, a daily supplement of 200 mg magnesium (as oxide) or placebo is administered for two menstrual cycles. In the second cycle, but not the first, the supplementation reduces mild premenstrual symptoms related to fluid retention. Since this study involves fairly low doses of a possibly poorly absorbed magnesium complex, the effects may have been better with a higher dose of a better absorbed magnesium complex. It is noteworthy that in this study, though urinary magnesium is increased, it is not to a great extent. Another crossover, placebo-controlled study uses the same dose and complex of magnesium, but also includes a treatment period where vitamin B₆ is tested (plus or minus the magnesium). Treatment times are all one menstrual cycle. One type of statistical analysis finds no difference between treatments, but another analysis shows a significant effect of the magnesium–vitamin B₆ combination on anxiety-related PMS symptoms. Urinary magnesium output is not affected by treatment. In the authors’ own words, the effects are modest, absorption from magnesium oxide is poor, and daily supplementation for longer than one month is necessary for tissue repletion.

In one other study, which is a double-blind, randomized design, 32 women with PMS are given placebo or magnesium pyrrolidone carboxylic acid for two cycles. The Menstrual Distress Questionnaire score of the cluster “pain” is significantly reduced during the second month in both groups, whereas magnesium treatment significantly impacts both the total Menstrual Distress Questionnaire score and the cluster “negative effect.” In the second month, supplementation increases lymphocyte and polymorphonuclear cell magnesium, but not magnesium in the plasma or erythrocytes.

Based on these three studies, it cannot be said that magnesium supplements can provide major PMS symptom relief, though there may be a modest effect on some symptoms. However, the relationship of increased magnesium intake to PMS symptoms may not have yet been tested in an ideal design.
Mitral Valve Prolapse

MVP can be fairly asymptomatic but it can also cause discomfort in many people. Magnesium could affect these symptoms via multiple direct effects on neurological function and by restriction of catecholamine rises in the blood (see the Stress subsection). There are three studies where magnesium is reported to improve symptoms in subjects with MVP. One of the studies only includes symptomatic MVP patients ($N = 141$) and finds low serum magnesium in 60% of the patients (as opposed to 5% of controls). Magnesium supplementation (five weeks) exceeds placebo in reducing symptoms and urinary epinephrine and norepinephrine (which indicates reduced blood levels of this hormone). However, it should be noted that symptoms are reduced, but not eliminated. Furthermore, not every subject shows improvement in every area. Perhaps with a longer treatment, the effects, though already respectable, could be even better. However, another issue here is that the form of magnesium used, magnesium carbonate, is an antacid. Antacids can relieve some MVP symptoms in some subjects. Thus, some of the effects shown here may not be due entirely to magnesium status changes. On the other hand, if antacid effects are not the main mechanism for the benefits, then the use of a different magnesium supplement might give better results. This contention is based on the supposition that magnesium carbonate may not be as well absorbed as some other magnesium complexes (see in Bioavailability from Foods and Supplements). In this study, magnesium carbonate does increase serum magnesium values, but the mean is still in the very low end of the normal range.

In another study, six months of magnesium orotate supplementation in MVP patients completely or partially reduces a variety of symptoms in more than half the patients. Similarly, 16 weeks of magnesium lactate supplementation, in 35 MVP patients, improves a number of symptoms. One particular symptom, called the sign of Trousseau, disappears in the 10 subjects initially showing this symptom. The latter study is partially placebo-controlled in that placebo is given to some of the subjects for the first half of the treatment time. No improvement is noted for the placebo time period.

In conclusion, the studies done thus far raise the possibility that increased magnesium intake can help with some MVP symptoms in at least some people with symptomatic MVP. However, more study is needed, especially a placebo-controlled study that well characterizes magnesium status before and after intervention, and relates status changes to symptom improvement.

Other Applications

There are a good number of other health applications that have been proposed for magnesium supplements based on one or more of the following:

- Abnormal values for some measure(s) of blood or urinary magnesium in a portion of subjects relevant to the application
- Mechanistic ties with the application
- One or a few studies on magnesium supplementation show a possible benefit
As should be clear from the above subsections, these three types of reasoning do not guarantee a clear demonstration of the efficacy of magnesium supplementation. This is especially true if the supplementation studies have design flaws. For some reason, a lot of such studies seem to show up in regard to magnesium supplementation. Thus, at this point, it has to be said that there are many claims for magnesium supplementation that could be true, but are not at all confirmed.

**TOXICITY**

The adult Upper Level (UL) for magnesium is odd in that the value (350 mg) is below the RDA for adult males and pregnant women. However, the UL for magnesium is designated as supplement intake, not total intake from food plus supplements. The UL is based on GI tract distress such as diarrhea rather than a toxic magnesium build-up. The actual intake that causes GI tract symptoms likely depends on the specific magnesium complex(es) ingested, the way the daily dose is taken (i.e., at one time vs. spread out), and whether the supplement is taken with food. However, none of these suppositions has been tested extensively from a published research standpoint.

Typical oral magnesium supplement doses are RDA levels to less than twice the RDA. These doses are not thought to generally pose an internal health problem. One exception is for subjects with renal failure, which slows magnesium excretion and can elevate risk for toxic build-up. In addition, the elderly can sometimes be at risk for magnesium toxicity because kidney function can decline with age. Also, elderly people are more likely than younger people to take

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**TABLE 2.3**

**Magnesium Supplements at a Glance**

**Adult RDA**: 420 mg (male), 320 mg (female)

**Typical dose in supplement studies**: 300–600 mg

**Best supplement complex**: organics are generally considered more active than inorganics, except chloride liquid; however, actual data is conflicting, possibly due to limitations in the methodology typically used; data is also conflicting for comparisons among the organics; amino acid chelates and lactate are among the best for GI tolerance; certain magnesium complexes may work best for certain specialized applications

**Applications**: use is established for treating substantial hypomagnesaemia; many other uses have some rationale, but are unconfirmed; the best supported of the unconfirmed uses are producing various benefits in diabetic subjects with low serum magnesium, modest lowering of blood pressure in certain types of people, giving various benefits in cardiac rehabilitation patients (though one study may show a use risk), and treatment of sickle cell anemia (though supplementation has been studied in just a few people)

**Upper Level**: 350 mg from supplements (based on GI tract symptoms); people may be able to exceed the UL without symptoms with magnesium from foods, with certain types of supplements, and possibly by spacing out daily doses

**Safety issues**: typical supplement doses are considered safe for people with good kidney function except for GI symptoms, especially diarrhea

As should be clear from the above subsections, these three types of reasoning do not guarantee a clear demonstration of the efficacy of magnesium supplementation. This is especially true if the supplementation studies have design flaws. For some reason, a lot of such studies seem to show up in regard to magnesium supplementation. Thus, at this point, it has to be said that there are many claims for magnesium supplementation that could be true, but are not at all confirmed.
magnesium-containing laxatives and antacids. Magnesium toxicity symptoms, besides diarrhea and nausea, include mental abnormalities, cardiac problems, reduced reflexes, and breathing difficulties.\(^2\)

**SUMMARY AND CONCLUSIONS**

Despite mounds of study on magnesium in general, and on supplementation in particular, very little can be said about the efficacy of magnesium supplements. The only established use for supplementation is for treatment of substantial hypomagnesemia due to “classical reasons” such as the use of certain diuretics. Many other applications may be useful, but this cannot be confirmed because so many studies are too small, too conflicting in results, too hard to interpret, too poorly designed, or simply require more follow-up.

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Potassium

If the average person is asked about potassium and nutrition, the person is likely to say two things. One, it is found in bananas, and two, it prevents cramps. Beyond that, there is not a tremendous amount of public awareness of this mineral, though there have been attempts to raise public consciousness. For example, a high-potassium diet was touted as an antidote to high blood pressure in the popular press book *The High Blood Pressure Solution: Natural Prevention and Cure with the K Factor* (by Richard D. Moore, Healing Art Press, 1993).

Although there are various medical uses of potassium compounds as prescription medicines, supplement companies have not given tremendous attention to potassium. One reason is that consumers have to take a lot of pills or capsules to make a major impact on their daily potassium intake. This is not an easy sell to consumers without compelling arguments. Thus, supplement companies have generally decided to put their efforts elsewhere. Nonetheless, there are some faint rumblings that potassium may become of more concern to the general public and biomedical community. If this does happen, we may see more of an advertising push for supplements, though food fortification may become more prominent (due to the pill or capsule dose issue just noted). The fortification approach may become especially prevalent with meal replacement products.

**OVERVIEW OF FUNCTION**

Potassium is of tremendous importance from a physiology standpoint, since potassium ion is the most abundant positively charged electrolyte inside cells. As noted in the next section, Overview of Physiology, potassium is actively pumped into cells. Intracellular potassium is a major determinant of intracellular osmolality. This gradient between intra- and extra-cellular potassium is needed for cell membrane polarization, which influences processes such as nerve impulses and muscle cell contraction (including cardiac muscle). Inside cells, potassium is needed for normal cell growth and protein synthesis. The charge movement by potassium through channels in cells has various regulatory actions. In addition, potassium channels in the kidneys participate in many diverse renal tubule functions.

Some very interesting but underappreciated work suggests that potassium may have indirect antioxidant actions by restricting excessive production of superoxide radical. This contention is based on a study where low potassium is fed to rabbits. When arteries are removed from these rabbits, superoxide production outside the body is very high. Unfortunately, this paper has not provoked follow-up studies in
humans, possibly due to technical limitations. Hopefully, some of the indirect approaches to evaluating superoxide production will be applied to human studies of potassium intake.

OVERVIEW OF PHYSIOLOGY

Since potassium acts as the prime electrolyte inside cells, this electrolyte is pumped into cells, while sodium is pumped out, by the so-called Na,K-ATPase. The sodium-potassium gradient created by this pump is essential for functions such as nerve impulse transmission. Only about 2% of total body potassium is outside cells, with much of the cellular potassium contained in muscle cells. Therefore, total body potassium is roughly proportional to lean body mass. Numerous factors affect the movement of potassium in and out of cells including insulin, which pushes potassium into cells. Stimulation of the sympathetic nervous system also affects potassium movement. β-agonists promote cellular uptake of potassium, while β-blockade or stimulation by α-agonists appear to do the opposite. Plasma potassium can also be affected by plasma pH. Acute metabolic acidosis increases movement of potassium out of cells, while acute metabolic alkalosis does the opposite. However, changes in plasma HCO₃ concentration may be more important than just pH changes.

Fecal potassium losses are fairly constant and small (roughly 10% of intake). In contrast, in healthy kidneys, urinary excretion is regulated to maintain balance. However, a large acute potassium load causes only about 50% of the load to appear in the urine over several hours. A rise in plasma potassium is minimized by transferring most of the potassium load into cells. If elevated intake continues, renal potassium excretion rises, probably due to aldosterone secretion. In renal failure, this process is impaired, which is why potassium intake is restricted in renal patients. During low potassium intake, potassium leaves cells, which partially maintains plasma concentrations.

NUTRITIONAL STATUS ASSESSMENT

Typically, serum or plasma potassium is used to assess potassium nutrition status. These measures can generally serve as a rough index to estimate body potassium stores, though normal or even high values do not always exclude some potassium depletion.

Severe potassium depletion is generally diagnosed by the combination of serum potassium readings plus medical history and symptoms often associated with potassium depletion. If a severe depletion is suspected, the root cause typically needs to be ferreted out. Then, the therapy should generally involve both potassium repletion and treating the root cause directly. Monitoring of repletion is then done by both serum potassium measures and evaluations associated with gross symptoms. This treatment and monitoring should not be done by “amateurs” but by medical professionals.

Besides concerns about potassium depletion, potassium status has also been studied to some extent from the standpoint of optimal intake. For example, some
studies have asked: Is there an optimal potassium intake that can beneficially impact blood pressure? For such purposes, potassium status is studied usually from the perspective of dietary intake assessment, or serum or plasma potassium. Occasionally, urinary potassium is also used, especially for considering short-term oral absorption of potassium from various sources. Although there may be other approaches that should be added, so far, there has not been a strong research demand for this addition. One possibility may be erythrocyte potassium ion content, which does show an inverse relationship with blood pressure in Venezuelan adolescents.9

**BIOAVAILABILITY FROM FOODS AND SUPPLEMENTS**

Potassium, because of its high water solubility, is generally absorbed very well, even up to about 90%.10 There is not a lot of information on absorption from individual foods, probably because it is assumed that potassium is absorbed well from most foods. For supplements, many different complexes of potassium are made for oral or intravenous use. In many cases, the molecule linked to the potassium is intended as the main biological modulator, not the potassium. In other cases, some specific molecule is combined with the potassium so that the complex has some specialized characteristic. For example, potassium is combined with chloride to have the taste characteristics suitable as a salt substitute for “shaker” use. In other cases, the binding molecule is chosen to avoid negative effects on certain medical conditions. In still other cases, the binding molecule is not chosen with a great deal of strategy.

As with food potassium, the potassium in supplements is assumed to be generally well absorbed. A few studies have examined the absorption of certain types of potassium supplements and have found the absorption to be very high.11,12,13 In some people, the types of encapsulation used for potassium supplements may influence tendencies for GI tract irritation.14

**TYPICAL INTAKES VERSUS NEEDS**

No RDA currently exists for potassium, and there is some question as to what constitutes an optimal intake under various circumstances. One problem with studying potassium needs is that it is hard to find a diet low or high in potassium that does not also have several other positive or negative aspects.

The concept that bananas are a good source of potassium is partially true. Compared to other foods, bananas contain one of the higher potassium contents per serving.15 On the other hand, there are a good number of other foods with equal or higher potassium per serving.15 These other foods include certain other fruits, dairy products, and even meats. It should be noted that one serving of any of these foods does not come close to providing most anyone’s definition of a full day’s supply. This points to the need to consider potassium intake from a full diet standpoint, rather than from a single food standpoint.

Since a lot of foods have some potassium, diet alone doesn’t usually cause severe potassium deficiencies unless total food intake is very low.1 Most cases of severe deficiency involve potassium losses.1
As noted earlier, there is some question as to what level of potassium intake is optimal. Some nutrition texts and Internet medical sites say that potassium intake in the U.S. tends to be fine except for extenuating circumstances (e.g., the use of certain diuretic drugs and some severe medical conditions). These texts and sites usually discourage potassium supplementation unless prescribed by a physician. In contrast to this attitude, there are popular press books and Internet sites claiming that many people in this country, especially those with high sodium intakes, do not eat less than optimal amounts of potassium. These sentiments are even echoed occasionally in scientific journals, though a somewhat speculative tone is often used. In this author’s opinion, it is hard to come to any conclusions on this matter until more creative research is done. There have been a few studies done on supplements. Some have supported the side that says all is usually well with potassium intake, while others have raised the possibility that increased intake may help some people.

CURRENT RESEARCH ON SUPPLEMENT USE

This section will be limited to applications where potassium is playing an active role in a chronic use. This will exclude situations where potassium is given by infusion or oral electrolyte solution to correct acute electrolyte depletions in medical care situations. This will also exclude applications directed by a physician to deal with drug side effects. A prime example of the latter is to counteract the potassium-depleting effects of certain diuretic drugs. Also excluded from this chapter will be the use of potassium chloride as a table salt substitute. To this author’s knowledge, there is not a lot of information on salt substitutes that differentiates the effects of decreased sodium intake vs. those of increased potassium intake. In addition, this section will not cover situations where potassium is given as part of a complex where the other part is considered the active ingredient. In such situations, the role of potassium is that of a “space filler.”

Once all these applications are eliminated, the main uses of potassium supplements that have been researched or given attention by the general public are those of Table 3.1. There could be other applications, but so far these have been given limited attention.

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<tr>
<th>TABLE 3.1</th>
<th>Areas of Prime Current Interest for Potassium Supplementation</th>
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<td>Hypertension</td>
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<tr>
<td>Athletic/exercise performance enhancement</td>
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<td>Kidney stone prevention</td>
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<td>Stroke prevention</td>
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<tr>
<td>Osteoporosis prevention</td>
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HYPERTENSION

The idea that potassium affects blood pressure derives from reasonable physiology involving electrolyte movement\textsuperscript{1,2} and possibly the indirect antioxidant effects noted earlier.\textsuperscript{3} However, just because potassium can affect blood pressure does not mean that typical variations in potassium intake have a major impact on blood pressure in many people. Some epidemiological studies show an inverse relationship between blood pressure and potassium intake or urinary potassium.\textsuperscript{16–19} However, it is not known if this relationship reflects actual potassium effects or other positive aspects of diets that happen to be high in potassium.

As far as potassium supplement studies go, a statistical analysis of a range of studies finds a statistically significant effect of potassium supplementation on blood pressure.\textsuperscript{20} This effect holds even with the exclusion of the most extreme results. This statistical analysis reports that the effects appear to be greatest when sodium intake is high. The average change in blood pressure for all the studies analyzed is not huge, but small average changes are not unusual for this type of overview analysis. This is because such overviews often must include studies that may not use the optimal conditions to see a change. This is not necessarily a negative comment about such studies. Such studies are needed to identify what the optimal conditions are for maximal changes. In addition, such studies define the range of circumstances where an effect can be seen. Nonetheless, when such suboptimal studies are included in an overview analysis, the average impact will be diminished.

Another issue here is that a new study of potassium chloride\textsuperscript{21} is not included in the overview analysis.\textsuperscript{20} This new study has a number of strong points:

- Placebo control
- A study group that should show high compliance
- Low to moderate potassium supplement dose
- Use of both a three- and six-week treatment duration (the effect is bigger at six weeks, which is longer than some studies showing no or low effects of potassium on blood pressure)
- A study group with fairly uniform, non-hypertensive starting blood pressure

An interesting speculation is brought up in the paper for this study.\textsuperscript{21} This speculation is that the relatively low dose of potassium chloride used might be more effective than a high dose. The reason given is that high intakes of chloride might counteract a blood pressure-lowering effect of potassium. It would be interesting to see a comparison of blood pressure effects between potassium chloride and potassium supplements that are not chloride based (e.g., tartrate).

Another overview analysis also reports a statistically significant effect of potassium supplementation on blood pressure.\textsuperscript{22} This analysis notes that the effect seems to be bigger in people with hypertension than in people with blood pressure in the normal range. Some studies of people with blood pressure in the normal range do not see an effect of potassium supplementation.\textsuperscript{23,24} On the other hand, the study discussed in the last two paragraphs does see an effect in such people.\textsuperscript{21} In addition,
another study of potassium supplementation in normotensive people also reports an effect.\textsuperscript{25} The latter study may differ from the negative result studies in that it is limited to subjects with moderately low potassium intakes. In these people, potassium supplementation raises total intake by an average of about 65\%. Importantly, the response is specific to potassium, since raising intake of two other minerals is not effective.

In this author’s opinion, sustained potassium supplementation can likely help at least some people lower blood pressure. Factors in how much potassium helps, or if it helps at all, could be starting blood pressure, dietary potassium intake, the dose and duration of potassium supplementation, and possibly whether or not potassium chloride is the form used. In this author’s opinion, potassium supplementation should not be viewed as a panacea for hypertension. One reason is that there is no clear indication that this step by itself can prevent or fully correct essential hypertension. In fact, even when drugs are used to correct essential hypertension, there is often the need to use more than one drug.\textsuperscript{26} Even so, increasing potassium intake can be one part of a dietary and non-dietary combination approach to preventing or reversing essential hypertension. With respect to the diet component, in this author’s opinion, high-potassium foods may be superior to supplements for most people. One reason is that unlike the case for most minerals, typical potassium supplement regimens tend to not provide more potassium than a few servings of various foods. Moreover, a high-potassium diet may have a variety of attributes that could aid with blood pressure control. Along these lines, the success of the so called Dash Diet for controlling blood pressure could be due partly to both the high potassium content and other factors.\textsuperscript{27}

**Kidney Stones**

Potassium/magnesium citrate has been used as a prescription drug to prevent kidney stones in people prone to this problem.\textsuperscript{28} The strategy has revolved more around the citrate part of the complex than the two minerals, but the minerals themselves may also be important (for the magnesium aspects, see the chapter on magnesium). Unfortunately, there are not an abundance of studies directly distinguishing the effects of supplementation of potassium apart from when it is “accompanying” citrate. However, there is one study that indirectly supports an effect of the potassium itself on kidney stone formation. In this study, children with high urinary calcium are examined for the effects of either supplemental potassium treatment or feeding a high-potassium diet. In both cases, there is a reduction of urinary calcium to creatinine ratios, which is considered a factor in kidney stone formation. Although this is not the same as examining adult kidney stone formation, it does say that potassium has the potential to reduce values for a risk factor for stone formation.

Epidemiological studies also support the idea that low-potassium intake increases the risk of kidney stone formation in high-risk subjects.\textsuperscript{29} Interpretation of these results can be clouded by the fact that low-potassium diets may also have other characteristics that influence stone formation.

In conclusion, an inverse relationship between potassium and kidney stone formation tendencies is unsettled, but possible.
CRAMPS

As noted earlier, a common notion among the general public is that potassium depletion, especially when combined with muscle exertion, causes muscle cramps. A connection certainly holds for severe potassium depletion and muscle tetany, which is a potentially dangerous form of cramps. However, this type of potassium depletion is associated mostly with non-routine medical treatments, not the more common cramping occurring in athletes or in everyday life. Surprisingly, in the last 35 years, very little study of this type of cramping and potassium is reported in the biomedical literature. Among the few studies reported, there is more than one suggesting that exercise-induced cramping often occurs independent of any role of potassium depletion. Therefore, in this author’s opinion, the role of potassium depletion and repletion in the most common types of cramps remains largely unknown. It is possible that potassium intake could be a factor some of the time, but adequate hydration and physical approaches (e.g., stretching or massage) may be more helpful more often. Therefore, taking potassium supplements to prevent common forms of cramps would seem to be unwarranted. On the other hand, if people want to eat good amounts of potassium, just in case it may help prevent them from cramping, this author recommends eating high-potassium foods. Even if the foods don’t prevent cramps, they will still provide a good share of various nutrients, and in many cases, a good deal of phytochemicals.

POTASSIUM AND EXERCISE PERFORMANCE

Besides the speculative influence on cramps, potassium has been tied to other aspects of muscle performance and fatigue during exercise. However, this tying has been from the metabolic perspective, not from the nutrition perspective. Numerous papers suggest that the leakage of potassium from muscle to serum during exercise contributes to fatigue. Despite this research, there is next to no research for actual studies of potassium intake on exercise performance. In one exception, potassium phosphate supplementation produces reduced effort perception during exercise, but it is not clear how much the potassium, rather than the phosphate, contributes to the effect. Therefore, in this author’s opinion, there is a need for new research on exercise-induced fatigue in relation to potassium nutrition.

POTASSIUM AND STROKE RISK

In the popular press, the Internet, and a few scientific journal articles, potassium supplements have been speculated to comprise a possible means of lowering stroke risk. It is thought that this effect, if it really exists, includes, but is not limited to, possible effects on hypertension. Still, there are no actual research studies of potassium supplementation and stroke. On the other hand, there are epidemiology and animal studies that raise the possibility that potassium intake can be linked with stroke risk. However, the results in the human epidemiology studies are far from clean. For example, in one study, which examined various types of people, an association of dietary potassium intake with stroke mortality is detected only among black men and hypertensive men. Furthermore, in other work, the possible effects
of potassium are difficult to tease out. The dietary potassium effect may require a combination with other dietary factors, or may not really be occurring at all. If the latter case is true, the seemingly protective action of potassium may simply be a coincidental association with other diet and lifestyle patterns. Therefore, at this point, in the author’s opinion, taking potassium supplements to lower stroke risk is still extremely speculative. On the other hand, eating a diet high in potassium, whether the potassium directly helps prevent strokes or not, is a good idea. Such diets are often health promoting due to their high content of various micronutrients, phytochemicals, and fiber.

**Potassium and Osteoporosis**

This possible relationship has been proposed primarily for protection against a deleterious action of a high-sodium diet. According to this idea, a high-salt diet alters calcium metabolism in a way that raises osteoporosis risk, but this action is blocked by a high-potassium diet. Although a major contribution to osteoporosis risk of a high-salt diet is still a long way from confirmed, there is a study showing that four weeks of high salt intake increases the rate of bone resorption in postmenopausal women. In this same study, the effect of the high-salt diet was inhibited by potassium citrate supplementation. There is also an epidemiological study linking salt intake and urinary calcium excretion. If these studies can be confirmed and expanded, then in some people, an anti-osteoporosis value may be ascribed for high potassium intake via diet or supplementation.

**Toxicity**

There is no doubt that too much potassium can be very dangerous due to potential cardiovascular effects and neuromuscular malfunctions. For most people, it would not be easy to reach toxic levels via supplements for two reasons. One, healthy kidneys can eliminate large excesses of orally ingested potassium. Two, due to the low potassium dose per pill or capsule, many of these would have to be taken to produce very high intakes. Not surprisingly, overdose of potassium is not frequently encountered in clinical practice except due to excess retention during renal disease. One concern can be a rapid build-up of body potassium, which could create problems before the kidney has a chance to eliminate the excess. A fairly recent report notes two cases of poisoning in people ingesting enormously high, single doses of sustained-release potassium preparations.

In this author’s opinion, in people with normal renal function, potassium supplement overload is not near as apt to occur as many other self-inflicted health problems. Nonetheless, due to the serious dangers of potassium poisoning, this possibility should not be taken lightly.

**Summary and Conclusions**

Potassium has tremendously important functions, but uncertainty exists about optimal intake levels and exactly what benefits can be ascribed to such an intake.
Prescription supplements are an important part of treatment for some medical conditions. Over-the-counter uses are less clear, though interesting. Such supplements are usually used safely and are not actually pushed all that much by most supplement companies. The best-studied application is for blood pressure, where it may help some people, though the benefit degree may vary with varying circumstances, and may work best when combined with other measures.

REFERENCES


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TABLE 3.2  
Potassium Supplements at a Glance

RDA: None set; optimal intake debatable
Typical dose in supplement studies: 900–2000 mg (minimal effective dose unknown)
Best supplement complex: a number seem to have good absorption
Applications: hypertension treatment possible, though not as a sole treatment; high-potassium foods may work better; a few other applications promising, but under-researched
Upper Level: none set
Safety issues: most people not apt to consume toxic levels

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Iron

Iron supplements have been studied since a time when many other minerals were not even known to be essential nutrients. For that reason, we have some clear tools for studying the outcomes of iron supplementation. Nevertheless, even with this knowledge base, there is still much more research needed concerning both the benefits and safety of iron supplements.

OVERVIEW OF FUNCTION

The best-known function of iron is to be part of the proteins hemoglobin and myoglobin, which participate in oxygen transport. In these proteins, the iron is not inserted directly into the amino acid structure of the proteins, but rather is inserted into chemical structures known as heme rings, which are inserted into the protein’s amino acid backbone. Iron also functions in enzymes that are iron–sulfur enzymes (iron is chelated by sulfur amino acids). Iron also is part of structures known as cytochromes, which are part of the electron transport chain of aerobic energy release, and are part of a family of enzymes called cytochrome P-450 dependent enzymes. The P-450 enzymes are involved in processes such as drug metabolism and steroid hormone synthesis.

Iron affects aerobic energy metabolism in at least three ways:

1. Oxygen transport to cells (needed for the electron transport chain)
2. The iron enzyme aconitase in the Krebs Cycle
3. Cytochromes and iron–sulfur proteins in the electron transport chain

Iron enzymes participate in an assortment of other biological processes including synthesis of neurotransmitters, peroxide conversions, purine metabolism, fatty acid synthesis, DNA synthesis, and nitric oxide production. Iron function also impacts the immune system. The exact molecular mechanisms for this last connection are hard to identify, since many iron functions could theoretically affect immune function. For example, iron can affect DNA synthesis, which can affect cell multiplication, which can affect immune responses.
OVERVIEW OF METABOLISM

Iron metabolism promotes iron function while inhibiting iron toxicity. Although this system doesn’t work perfectly if total body iron is very low or very high, it still works very well much of the time. Handling of iron is affected by a number of factors, but the most influential is body iron stores. If stores are low, the intestine becomes more efficient at iron absorption. If stores are high, iron absorption is inhibited.

Intestinal cells make a high molecular weight, iron-binding protein called ferritin in inverse proportion to body iron stores. A good deal of the regulation of ferritin synthesis is at the level of ferritin mRNA translation. If iron stores are low, little ferritin is made. This elevates iron absorption, since ferritin is a barrier to iron getting to the bloodstream. If iron stores are high, a lot of ferritin is made, which binds iron as it enters intestinal cells. A lot of this iron is kept from ever entering the bloodstream because, after just a few days, intestinal cells are sloughed off and excreted. Once iron is absorbed from the intestine, it can be stored in the liver. As with the intestine, ferritin is the primary liver iron binder.

Iron can be transported out of the liver to other body sites using a transport protein called transferrin. Attachment of iron to transferrin has been said to require an oxidation step catalyzed by the serum copper enzyme ceruloplasmin, though there has been some debate on this. Ceruloplasmin must have some relationship to iron metabolism since rodents or humans with genetic ceruloplasmin deficiency can become anemic. Less debatable is the idea that transferrin protein binds to receptors on cells, which take up the whole transferrin protein by endocytosis (an engulfing of the molecule by the membrane, which then forms a small capsule containing the engulfed material). The engulfed molecule then finds its way to the lysosomes, where acid releases the iron from transferrin. The released iron can then go to various iron molecules such as iron-containing enzymes, hemoglobin (if a red blood cell is being made), myoglobin (a protein that traps oxygen in tissues), and ferritin (which stores iron and helps prevent toxicity). In states of iron overload, ferritin is degraded to a water-insoluble iron-binding protein called hemosiderin. This helps reduce iron toxicity but cannot always prevent it. The main defense against iron toxicity is the ferritin in the intestine. If a lot of iron manages to get by this defense, then therapy steps need to be taken (see the Toxicity section below).

A good deal of the body’s iron is inserted into hemoglobin, which transports oxygen in red blood cells. These red blood cells eventually die but most of the iron from hemoglobin is conserved by the body. The same is true for iron used for other purposes. Nonetheless, some iron is lost each day via the GI tract, urine, and skin. Women who are menstruating also lose iron as part of blood losses.

NUTRITIONAL STATUS ASSESSMENT

Iron deficiency anemia is traditionally detected by a blood measurement called hematocrit, which is the percent of blood volume occupied by the red blood cells. Values below 34 to 37% are associated with iron deficiency anemia. Now, clinical laboratories tend to measure whole blood hemoglobin to assess anemia. For both
measurements, there can be causes of anemia other than iron deficiency, though this is a common cause. Generally, anemia testing is followed by more specific measures of iron status. These measures are also used to test for iron status in the absence of anemia. One method is serum ferritin, which is proportional to iron stores. One drawback to this evaluation is that ferritin values can be affected by factors other than iron status such as inflammatory stress. Another drawback to ferritin measurements is day-to-day variations within individuals.

Serum iron is also sometimes used for iron status assessment, but it has drawbacks, including its wide diurnal variation and its depression as a regulatory response to infection and inflammatory stress. In addition, values can fall after blood loss and with pregnancy or cancer. Serum transferrin or transferrin saturation (the ratio of serum iron to iron-binding capacity) can also be evaluated. The use of these measurements for iron status assessment has some of the same drawbacks as serum iron.

Another evaluation is erythrocyte protoporphyrin, a method requiring just a few drops of blood and minimal technical experience. Values are less subject to diurnal variations than some other iron assessment measurements. On the other hand, values are increased by lead poisoning, inflammation, and some uncommon situations. Protoporphyrin is used in population surveys but not typically in clinical applications.

The most recent addition to iron status assessment tools is serum transferrin receptors. These receptors are found on cell membranes but make their way into the serum. When iron supply falls, even to a mild degree, synthesis is increased for transferrin receptors. A few situations other than iron deficiency can affect these readings, but unlike values for serum ferritin or iron, serum transferrin receptor values do not change with inflammation. This assessment method may be particularly useful for diagnosing iron deficiency when chronic disease is prevalent, especially in elderly subjects. In the elderly, chronic diseases can cause anemia with high ferritin levels, even during iron deficiency. In contrast, diagnosis of iron deficiency has been reported to work well in the elderly using a TR-F index (the ratio of serum transferrin receptor level to log ferritin level).

**BIOAVAILABILITY FROM FOODS AND SUPPLEMENTS**

As already mentioned, iron absorption is strongly influenced by the iron status of the individual (iron-deficient individuals absorb a much higher percent of ingested iron than iron-replete individuals). However, iron absorption is also affected by the particular iron complex ingested, as well as by other dietary components, and by physiological factors such as stomach acid production.

Iron is consumed in two general classes: heme iron and non-heme iron. In meat (in a broad sense to include poultry and fish), some iron is associated with the proteins hemoglobin and myoglobin, which collectively are called heme iron. The rest of the iron in meat, as well as all the iron in vegetables, grains, and supplements, are non-heme iron. Heme iron is absorbed much better than non-heme iron. Another selling point for meat as a source of iron is that the amount of iron in meat is higher than the amount of iron occurring naturally in most other foods. Moreover, meat
contains a substance, termed meat protein factor, which actually improves absorption of the non-heme iron from other foods eaten at the same time.\textsuperscript{3}

Non-heme iron absorption can also be increased if the metal is in the +2 state rather than +3.\textsuperscript{3} This can be accomplished by eating the reducing agent ascorbic acid (vitamin C), which also may help iron by chelating it into a more absorbable complex.\textsuperscript{2} The iron in most supplements is already in the +2 state, which means that vitamin C will not have the same stimulating effect on absorption. Calcium supplements can be inhibitory to iron absorption, though the extent to which this occurs is controversial (see the chapter on calcium). Iron absorption can be reduced by a variety of food components such as phytic acid and some polyphenols such as the tannins in tea.\textsuperscript{5,13} However, one study gives evidence that promoters of iron absorption such as vitamin C and meat can more than compensate for any ill effects of tea on iron absorption.\textsuperscript{13} Also, one evaluation of a cross section of studies concludes that tea consumption does not influence iron status unless status is poor or borderline.\textsuperscript{14} This concept should be tested more directly before a final conclusion can be reached.

A substantial variation in absorption is reported for a series of multi-vitamin–mineral supplements, presumably due to the other nutrients and additives present, especially calcium and magnesium.\textsuperscript{15–19} Thus, such supplements may not always be a reliable means of getting as much absorbable iron as consumers think they are getting.

Supplemental iron is usually absorbed better when taken between meals.\textsuperscript{16} However, in some people, some iron complexes and doses taken between meals can produce GI tract discomforts, such as upset stomach.\textsuperscript{20}

Ferrous sulfate is the most common standalone iron supplement, partly because it is less costly than most other iron supplements. One downside of ferrous sulfate is that compared to other iron supplements, this complex is apt to produce gastrointestinal discomforts in some people.\textsuperscript{20,21} These discomforts can sometimes be reduced by taking the supplements with meals\textsuperscript{20,22} (though this can reduce absorption if the meal has absorption inhibitors), or keeping the doses low,\textsuperscript{3} or by splitting up the daily dose (though this can affect compliance).\textsuperscript{3} Other iron supplements include ferrous fumarate, which shows lower GI tract side effects than ferrous sulfate,\textsuperscript{23} ferrous citrate, ferrous succinate, ferrous gluconate, ferric pyrophosphate, ferric trimaltol, and iron bis-glycine chelate (Ferrochel®). Under most circumstances the first four ferrous compounds just named have similar oral absorptions to ferrous sulfate, and ferrous sulfate and the other compounds named have much better absorptions than ferric complexes.\textsuperscript{24–28} A number of these studies have compared the different iron complexes for absorption when mixed with different foods. For example, in a study of iron absorption from chocolate drink powder, the absorption of ferrous fumarate is 5.27%, ferrous sulfate 2.62%, and ferric pyrophosphate 0.55%.\textsuperscript{29} In a different study, which assesses iron absorption from a test meal, absorption of ferrous fumarate is 5.5 to 6.2%, while ferrous sulfate is 5.5%.\textsuperscript{26} In still another study,\textsuperscript{30} where iron is mixed with infant cereal, though fed to adults, there is no difference in absorption between ferrous fumarate and ferrous sulfate. In the same study, values for ferrous succinate and ferric pyrophosphate are 92% and 39% of the ferrous sulfate values, respectively.\textsuperscript{30}
In contrast to the studies just mentioned, in two other studies, Ferrochel®
(ferrous bis-glycine chelate) is reported to have far better bioactivity than ferrous
sulfate.\textsuperscript{31,32} In addition, compared to other forms of iron, Ferrochel® is reported to
show low GI tract upset tendencies,\textsuperscript{33} shows some resistance to absorption inhibition
by phytate,\textsuperscript{31} and in rats, requires a relatively high dose to produce toxicity.\textsuperscript{33} Fer-
rochel® has been successfully used to fortify dairy products in Brazil\textsuperscript{34} and on a
smaller basis in Saudi Arabia,\textsuperscript{35} since this complex does not damage dairy products
as easily as do some other iron complexes.\textsuperscript{36} The one down side to Ferrochel® is
that it is more expensive than ferrous sulfate, though less Ferrochel® can be used
to give the same absorbable iron as some higher concentrations of ferrous sulfate.

Iron mixed with EDTA also has some possible uses for fortification of certain
foods.\textsuperscript{36,37,38} In some cases, the EDTA addition can also improve iron absorption
substantially, though this seems to depend on what iron complex is mixed with
EDTA.\textsuperscript{38,39}

Another common iron form used in fortification is so-called reduced iron, which
is found in many breakfast cereal foods.\textsuperscript{40} The phrase “reduced iron” is a catch-all
term for several different types of finely powdered, elemental iron preparations.
These preparations can vary considerably in terms of particle size and other char-
acteristics. One type of reduced iron, know as electrolytic iron, has been recom-
mended as the best absorbed of the reduced iron family, though the absorption is
still not outstanding.\textsuperscript{40} Unfortunately, seeing the term “reduced iron” on a breakfast
cereal label does not guarantee that electrolytic iron is the form used; in fact, in
most cases, it probably isn’t the form used.\textsuperscript{41} Moreover, the preparations of even
electrolytic iron are not uniform.\textsuperscript{41}

Furthermore, according to one report, absorption of one of the better electrolytic
iron preparations is still only half that of ferrous sulfate.\textsuperscript{40} This means that in many
fortified cereal products, which use a reduced iron that is not electrolytic iron, the iron
absorption is considerably below 50% of ferrous sulfate. It also must be remembered
that the iron in cereal can be affected negatively by other components of the cereal
product, such as fiber and phytate.\textsuperscript{1} Besides all this, any form of iron in fortified cereal,
when expressed as a percent of the RDA, is actually a vastly inflated number. The
reason for this statement is that the RDA assumes that some iron is being consumed
as heme iron,\textsuperscript{1} whereas all the iron in fortified cereal is non-heme iron.

Despite all that was just said, iron-fortified infant cereal has been reported to
help prevent severe iron deficiency in the intended target group.\textsuperscript{52} However, the
amount of iron needed for this purpose is fairly small. On the other hand, for
menstruating adult women, it is not a good idea to rely on one serving per day of
fortified breakfast cereal as a main supply of iron.

Iron–carbohydrate preparations are also sometimes used for oral supplements.
Ferric trimalitol was mentioned above. This complex has less problem with GI tract
intolerance than ferrous sulfate.\textsuperscript{43} In one study, ferric trimalitol corrects anemia in
14 of 19 anemic individuals, most of which had inflammatory bowel disease (which
makes them very sensitive to GI track distress due to ferrous sulfate).\textsuperscript{43} This study
does not mean that ferric trimalitol is necessarily absorbed as well as ferrous sulfate,
only that the former compound, at certain doses, could correct anemia in some
individuals.
Another type of iron carbohydrate complex is iron bound to polysaccharides. For example, polymaltose–iron has shown similar absorption to ferrous salts in multiple circumstances. On the other hand, in some other studies using various end points in humans and rats, polymaltose–iron complex is not as bioactive as ferrous sulfate, though by some measures, the differences are not that large. Another polysaccharide that is attached to iron for human use is iron dextran. The main use of iron dextran is for non-oral administration (i.e., injections and IV infusions). Sodium ferric gluconate and iron–sucrose are also used for administration IV.

In conclusion, a number of different types of iron supplements can be absorbed well enough to impact iron status. Considerations in choosing a supplement include cost, GI reactions, and compliance when high doses are needed (e.g., a better absorbed supplement could involve smaller capsules or pills or fewer capsules or pills). Food fortification choices must consider the effects of the food components on the iron, as well as the iron effects on the food. Finally, multi-vitamin–mineral pills and iron-fortified cereals may not provide as much absorbable iron as implied by the label contents.

**TYPICAL INTAKES VERSUS NEEDS**

The RDA for iron is based on iron balance (losses vs. gains) with the assumption that 18% of the iron in the diet will be absorbed. Since a big source of iron loss can be menstrual blood loss, the iron RDA varies a lot with age and gender. For adult women, the RDA is 18 mg per day, while it is only 8 mg for adult men. The RDA is not intended to cover women with high menstrual losses, who may need to meet their extra needs with a supplement. The RDA for teenaged girls, 15 mg, is slightly lower than adult women. The RDA for teenaged boys, 11 mg, is slightly higher than adult men due to the need to support more lean body growth in the teenagers.

Iron deficiency is still a major problem around the world and could be considered the most common micronutrient deficiency worldwide. Deficiency occurs both in underdeveloped and industrialized countries. In fact, when describing people groups prone to iron deficiency, it is easier to name groups that are not overly prone than those who are. Probably every description of a group of people can be said to have some vulnerability to iron deficiency except for full-term, normal-birth-weight infants born to mothers of good iron status; healthy, male meat-eating teenagers; and male, meat-eating young adults (meat used in the broad sense to include fish and poultry). On the other hand, young adult women, as well as teenaged girls, are often at risk for iron deficiency due to blood iron losses plus a lower average meat consumption than their male counterparts. Women with heavy menstrual blood losses are especially prone to iron deficiency. The iron needs for such women can exceed the RDA. Supplements are considered helpful for at least some such women to meet iron needs.

Pregnant women don’t have to contend with menstrual blood losses, but iron is still a big concern. During pregnancy, a lot of body iron goes to making a new bloodstream and for other body changes.
As a person reaches the elderly stage of life, iron can become a problem as iron intake often falls, chronic diseases set in, and GI blood losses can occur. In some settings, poor iron status seems to occur more often in women than in men. However, this may not be universally true, and even in the studies where it is found, elderly men are not exempt from iron deficiency. On the other hand, not all elderly male or female populations have high percentages of iron deficiency. For example, one large group of non-institutionalized U.S. elderly subjects show a fairly low incidence of low iron stores. At the opposite end of the age spectrum, premature infants can have iron problems. During the early stages postbirth, iron stores are supposed to meet a lot of a baby’s needs. Because these iron stores are built mostly during the last trimester of pregnancy, a premature birth cuts iron storage short.

Two other groups of people particularly prone to iron deficiency are picky-eating, young children who avoid iron-rich foods, and vegetarians. The latter group has a challenge to get enough iron because as noted earlier, meat provides relatively well-absorbed heme iron, plus meat promotes iron absorption from other foods. Moreover, the high fiber or oxalic acid content of many vegetarian diets can further depress iron absorption. On the other hand, most vegetarian diets contain a good amount of vitamin C, which can promote iron absorption. Therefore, vegetarians should consume vitamin C-rich foods simultaneously with the few non-animal foods that contain respectable amounts of iron without oxalates (e.g., blackstrap molasses). A food such as spinach has a good amount of iron but oxalates, which block iron absorption, keep this food from being a good iron source. Consumption of an iron supplement can be useful for vegetarians even though this iron is not as well absorbed as meat iron. Adding milk to a vegetarian diet is not very helpful, since milk is not a good iron source. Some vegetarians rely heavily on iron-fortified breakfast cereals for this mineral. However, as noted earlier, such products may not provide as much bioavailable iron as what the label implies.

CURRENT RESEARCH ON SUPPLEMENT USE

GENERAL COMMENTS ON DOSES AND USES

The doses to use for iron supplementation are not always straightforward. Often, doses as high as 200 to 300 mg/day, which are well above the RDA, are used to correct problems because the goal is to make a big and quick impact on an iron-deficient state. Also, it should be realized that the RDA is built around iron in foods, with the assumption that some ingested iron will be heme iron. This heme iron can be absorbed several-fold higher than the non-heme iron in supplements. Thus, a supplement must greatly exceed the RDA to have the same impact as an RDA dose of iron from a meat-containing diet. In light of the percent absorptions discussed in preceding sections, it might seem reasonable to make mathematical comparisons between the absorbable iron in a supplement vs. absorbable iron in certain diets. For example, one could note that the RDA assumes 18% iron absorption, and that ferrous sulfate is absorbed at about 3 to 6% in some studies. On that basis, one could say that iron supplements must be given at three to six times the RDA to provide an RDA-equivalent amount of absorbable iron. However, a flaw in this
thinking is that supplements are often given to iron-deficient subjects who can absorb a higher percent of iron than normal. So, though it can be assumed that more iron is needed with supplements than with a meat-containing diet, an exact quantitative relationship cannot always be derived.

Since the ideal dose for iron supplementation may vary, iron supplements should ideally be used under the supervision of a knowledgeable health care professional team. In fact, a common theme in this section will be that iron supplementation should be carried out under the monitoring and supervision of health professionals such as physicians, dietitians, and, for community interventions, public health specialists. This may be the ideal approach for all mineral supplementation, but it is especially important for iron for three reasons:

1. Maximal efficacy of iron supplements may require some trial and error that needs to be monitored by tests that cannot generally be self-administered.
2. The margin for error for iron toxicity may be small and require monitoring.
3. For a number of health problems that can produce iron deficiency, the handling of iron repletion can have major health consequences, even life vs. death.

In many of the health problems associated with iron deficiency, the iron problem requires a choice of how to deliver the iron (i.e., oral vs. parenteral), and what co-treatments to use (e.g., other problems besides iron deficiency may co-exist).

Iron supplements are generally used for one of four general purposes (Table 4.1).

The first use in Table 4.1, treatment of iron deficiency anemia, is by far the most common use of iron supplements when prescribed by health professionals. While treating this anemic state, other effects can also occur. These effects could occur because correcting anemia can also correct secondary symptoms due to the anemia. In addition, the treatment of iron deficiency anemia can also treat symptoms of iron deficiency that are not caused by anemia, but by coexisting impairments in iron function.

The second use of iron supplements, prevention of anemia, is controversial and is discussed below. The third use of iron supplements, treatment of marginal iron deficiency, is also not settled, either in terms of what benefits can occur, or whether diet changes are the better approach. The final use, therapy for problems that are not solely a nutritional iron deficiency, have some basis, but are not all completely confirmed.

### Table 4.1

<table>
<thead>
<tr>
<th>General Uses of Iron Supplements</th>
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<td>Correction of iron deficiency anemia and coexisting deficiency symptoms</td>
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<tr>
<td>Prevention of iron deficiency anemia</td>
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<tr>
<td>Treatment of non-anemic iron depletion (marginal iron deficiency)</td>
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<tr>
<td>Therapy for problems not considered to be due solely to nutritional iron deficiency</td>
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TREATMENT AND PREVENTION OF ANEMIA IN INDIVIDUALS WITHOUT OTHER DIScernABLE HEALTH PROBLEMS

For a clinical setting, there is a fairly general consensus that oral iron supplements are usually the appropriate corrective measure for iron deficiency anemia in the absence of other major health problems. The exact dose used can vary with circumstances, but doses as high as 300 mg can be found. In some cases, reversal of anemia may require supplementation with other nutrients such as vitamin B12. In all cases of anemia, outcomes should be monitored by a team of health professionals. These professionals should also monitor general symptoms associated with anemia, such as lethargy and poor work performance, since these symptoms may not be entirely due to the anemia being treated.

Taking iron supplements to prevent anemia in susceptible individuals is more controversial. There is evidence that moderate doses of iron supplementation can reduce the frequency of anemia in certain populations of women. However, this does not automatically mean that this approach is the best. One reason is that iron supplementation, especially when self-prescribed, does not always prevent anemia in every individual, or even in the majority of every group that has been studied. On the other hand, some would contend that in certain women, iron supplementation is preferable to excess consumption of iron-rich meat products, which may help promote obesity and cardiovascular disease. Others would dispute this mind set. Along similar lines, some would contend that reliance on diet rather than supplements for iron may improve intake of certain other nutrients. It could also be argued that dietary approaches make iron toxicity less likely. Since the dangers of even moderately high iron intake are getting considerable publicity, many clinicians and public health specialists are leery of recommending widespread iron supplementation in non-anemic people (for discussion of moderate iron toxicity, see the Toxicity section below).

In this author’s opinion, iron supplementation may be the best option for preventing anemia in some, but not all, people. This author feels that this decision should be made by individuals in consultation with physicians and dietitians.

COMMUNITY INTERVENTIONS FOR ANEMIA TREATMENT AND PREVENTION

Anemia on a large-scale level can not only affect an individual’s health, but also impact a community’s productivity. Symptoms such as lethargy and reduced work capacity in adults, and impaired cognitive development in children, can impact a community’s economic growth. In addition, widespread anemia contributes to health care burdens on a community. In communities in many parts of the world, iron intake is clearly inadequate in a large percentage of people. In some cases, encouraging and educating the people about a dietary approach to this problem may make the best sense. This contention is supported by a study of Australian iron-deficient, premenopausal women. In this study, although a high-iron diet produces smaller increases in serum ferritin than iron supplementation, the former gives better continued improvements in iron status during a six-month follow-up. This may mean...
that individuals in Australia, when left to themselves, are more apt to sustain a dietary philosophy than persist with iron supplementation. Still, this pattern may not hold for all subjects in all circumstances.

In other cases, due to the economy, culture, or food supply, an iron deficiency problem cannot easily be fixed just by admonishing people to eat more of the best natural iron food sources. In these cases, it is more practical to consider community interventions that increase iron intake via either supplements or fortified foods. In some senses, food fortification is a form of supplementation, but the public health strategy has some differences. Food fortification has been successful at reducing iron deficiency rates in a number of places in the world. Whether food fortification or supplements are used to combat iron deficiency, there may also be the need to confront other dietary contributors to anemia, as well as non-dietary contributors such as intestinal parasites like hookworm.

If supplementation or food fortification is being considered for a community, be it an entire country or a country subsection, many factors need to be considered. These details are beyond the scope of this book, but it can be noted the details include the economics and politics of supplying the supplement or food fortification. Another consideration is whether specific subgroups within a community are being targeted, such as pregnant women or certain aged children. Another concern is whether the goal is correction of an existing problem or simply producing a modest rise in iron intake. The former situation may require supplements, since food fortification typically supplies far less iron per serving than a supplement. Another issue is considering treatment of non-nutritional contributions to iron deficiency such as hookworm.

Another issue for large-scale iron supplementation programs is daily supplementation versus once-a-week supplementation. This issue is not settled. The best answer may depend on the specific circumstances involved, and in some cases, both may work equally well. One concern had been the possibility that the body may not absorb the large weekly doses as well as the smaller daily doses. In reality, in the long run, though not always in the short run, the weekly approach seems to affect iron status about the same or just slightly better than the daily approach. GI tract side effects could be a concern in choosing between the daily or weekly approaches, but the tendencies are not clear. For example, in one study, GI tract upsets occur with both daily and weekly approaches, but the incidence is higher with the weekly approach. In another study, the pattern is the opposite. Despite the opposite observations on side effects, both studies find that compliance is better with the weekly approach. A possible explanation is that the weekly approach requires less effort by the subjects. In fact, this better compliance may explain why, in some studies, the weekly dose has a slightly better effect than the daily dose. At present, there is no consensus on the best approach, but practical issues such as product distribution and economics may become prime concerns. In addition, there has been some consideration of compromise approaches, such as twice weekly.
Premature/Low Birth Weight Infants

Iron deficiency occurs commonly in early childhood following premature birth or an otherwise extremely low weight birth. The prevalence of iron deficiency is even higher if cerebral palsy is also present.

The reasons for the iron deficiency could have to do with existing conditions in the mother, such as severe iron deficiency or diabetes. However, iron deficiency in these children can also have other causes. One has to do with limited storage of iron, which normally is accelerated in the three months before birth. A premature infant doesn’t have much, if any, of this storage period. Another problem can be due to the large number of blood draws required during their hospitalizations. In addition, in the months that follow birth, infants who were very low birth weight can have an accelerated “catch up” growth period that increases iron needs. These factors make iron deficiency a concern in these children, though sometimes over-treatment with iron or blood transfusions can actually put the children at risk for iron overload. These children are very vulnerable to that problem because their capacities for low iron-binding proteins and antioxidant systems are well below those of normal adults.

Treatments for anemia in premature or low-birth-weight infants can vary at different stages for the first year postbirth. Treatments can include blood cell transfusions, human recombinant erythropoietin administration, iron fortification of mother’s milk or formula, and parenteral iron (especially as iron dextran). The optimal procedure is not yet universally agreed upon and may actually vary for different individuals. For these reasons, treatment should be carried out by health care providers with specialized experience in this area. This is still an area where more research could be used.

One question that sometimes arises is whether non-anemic, marginally iron-deficient low-birth-weight infants could benefit from increased iron intake. This area has not been researched extensively. One study in Australia concludes that in extremely low-birth-weight infants without cerebral palsy, non-anemia iron deficiency does not impair development or affect behavior. However, since this issue can be examined with many different design details, one study cannot be the final word on the subject.

Renal Dialysis Patients

In end stage renal disease, where subjects are undergoing hemodialysis or peritoneal dialysis, iron deficiency is often a problem. The causes include poor iron absorption, increased iron needs due to red blood cell production in response to erythropoietin administration, and various causes of blood losses. Clinical care typically includes measures to prevent iron deficiency as well as monitoring for overt iron deficiency, which is then promptly treated. Common treatments are erythropoietin therapy and iron administration as either oral supplements or parenteral iron. The decision on the latter choice is best left to specialists, who consider several factors. Among the considerations are the low expense and usual safety of most oral iron supplementation plans. On the other hand, oral supplementation can be limited by...
poor patient compliance (dialysis patients are notorious for not complying with self-administered health interventions). In addition, low intestinal absorption of oral iron by renal patients may limit oral supplement effectiveness. Intravenous iron bypasses the absorption and compliance problems, but there can be a small risk of allergic reactions.

Some concern has been expressed about the possibility that chronic iron may increase infections in renal patients. Although iron can strengthen immune function, there is also the possibility that it can boost the growth of infectious organisms. Indeed, in experimental animals, iron injections can lead to increased susceptibility to bacterial infection. In addition, there are clinical studies in renal patients showing an association between high serum ferritin levels and increased infectious risk, but this could be an effect of infection rather than a cause.

Some physicians take the position that since we know that iron helps renal patients in some ways, and can only speculate that iron could be problematic for infections, priority should be given to what we know. A similar sentiment is expressed in a review article that, after reviewing the background research, states: “There is no reason to alter current iron treatment strategies based on this literature.”

Another concern about iron administration, either by oral supplement or parenteral administration, is increased oxidant stress, which in turn increases risk for cardiovascular disease. The whole issue of iron intake, oxidant stress, and cardiovascular disease risk is still controversial (see the Toxicity section). Thus, as with the infection issue, the attitude could be that iron, which is known to be helpful for renal dialysis patients, should not be withheld due to a risk that is speculative. In fact, in dialysis patients, anemia itself can be a risk factor for cardiac disease. Nonetheless, this is an area that could certainly use more research.

**Cancer Patients**

Anemia in cancer may be secondary to blood loss, displacement of normal bone marrow cells by malignant cells, myelotoxic therapy, or the tumor itself. It can also be speculated that poor iron status prior to cancer onset or initiation of cancer therapy may be a factor in anemia incidence. A recent review article notes that cancer-related anemia has detrimental effects on quality of life, adds the risk and inconvenience of blood transfusions, and may be associated with decreased survival or time to progression. Even so, this article also notes a high percentage of U.S. cancer patients have anemia, but are not treated adequately for this condition. The most common treatments for cancer-related anemia are iron supplementation, blood transfusion, and recombinant human erythropoietin. In addition, another erythropoietic agent, darbepoetin alfa (Aranesp), has been gaining attention for use in this context. Future research would be useful to clarify the benefits vs. risks, if any, of treating cancer-related anemia, and the best approach for various circumstances.

**The Elderly**

The elderly can be at risk for iron deficiency due to low iron intake, blood loss, chronic disease, and, occasionally, unknown reasons. In some cases, anemia can
be mild but, if untreated, can contribute to increased mortality, poor health, fatigue, and functional dependence, as well as increased risk of cardiovascular or neurological problems. As a first step, elderly patients with iron deficiency should undergo endoscopic examination, because if the reason for the anemia is GI blood loss, then that condition should be the first concern. In the opinion of some experts, the endoscopic exam should be done not just when there are very low hemoglobin values, but if there are any blood test signs of iron deficiency (even without a positive result in a fecal occult blood test).

Once blood loss is ruled out, iron supplementation is often a prime treatment for anemia in the elderly, just as it is for anemia at other ages. One study of U.S. rural elderly home-delivered-meals recipients finds iron deficiency to be more common in elderly females than in elderly males. This finding occurs despite a similar low dietary iron intake in both genders. The authors interpret this finding to result from lifelong poorer iron status in the women compared to the men.

As with other age groups, there is concern about excess iron promoting increase risk of cardiovascular disease. One study along these lines is mentioned below in the Toxicity section. However, as already stated for other situations, it would seem to make sense to treat anemia, when diagnosed, rather than withhold treatment for speculative reasons. On the other hand, it would seem prudent to monitor iron status in the elderly and not give more iron than is needed to restore and maintain good iron status.

**Iron Deficiency without Anemia**

This is a topic that is still very unsettled. In this author’s opinion, there is evidence for concern, but the exact range of consequences is far from clear. This issue badly needs more large-scale studies. As consequences are clarified, the next questions is: “Should supplements or diet be used to treat this state?” For research purposes, supplement studies make for cleaner result interpretation. For human health purposes, there may not be one right answer for everyone. The answer may depend on how much iron intake has to be boosted to obtain adequate iron status. If the amount is not too great, then diet may be the best course. If a person has very high iron needs, such as a woman with very high menstrual blood losses, a supplement approach may be better. That philosophy is already used widely for anemia prevention in women with very high menstrual blood losses. In addition, in one study of non-anemic, iron-deficient women, Ferrochel® supplementation makes a bigger impact on iron status than does diet counseling to improve iron intake and absorption.

For research purposes, iron deficiency without anemia, which can also be called non-anemia iron deficiency or marginal iron deficiency, has sometimes been based on a serum ferritin below 16 µg/L. This value is derived largely from a study of over 200 women (mean age 38) with known iron status based on absence or presence of stainable iron in bone marrow smears. In addition, marginal iron deficiency has also been shown to be reflected by serum transferrin receptor concentrations. For example, iron supplementation decreases these values in premenopausal female subjects having iron depletion without anemia (hemoglobin > 120 g/L and serum ferritin < 16 µg/L).
From a biochemical standpoint, marginal iron deficiency without anemia could conceivably affect iron’s non-hemoglobin-related functions in energy release, iron’s non-anemia-related impacts on immune function, and iron antioxidant actions. The latter would include iron’s role in the enzyme catalase, and possible iron protection against inactivation of non-iron antioxidant enzymes. The energy-related biochemical impairments could have general health consequences, such as impaired growth, reduced aerobic exertion capacities, reduced energy for non-strenuous tasks, negative effects on children’s cognitive development, and pregnancy outcome impacts.

Some of these possible consequences will be considered in this subsection, while pregnancy, childhood cognitive development, immune function, and exercise performance will be considered in their own subsections below. In the subsections, these topics are discussed in view of both anemia and non-anemia iron deficiency.

In very limited study, antioxidant function has not seemed to be improved by iron supplementation of marginally iron-deficient, college-aged females. In one study, oxidative damage, as indicated by protein carbonyl and lipid hydroperoxide concentrations, is not altered by eight weeks of iron supplementation despite improved measures of iron status. In another study, selenium-related antioxidant enzymes are not improved by iron supplementation of marginally iron-deficient subjects. Iron deficiency anemia had been shown to alter erythrocyte activities of non-iron metalloenzymes with antioxidant function, though the exact effect is inconsistent. There can be an increase, a decrease, or no change in different studies in different circumstances. These effects may have to do with dietary factors other than iron and anemia effects on blood cell life span and metabolism. More work could be done in this area, especially with other types of assessments, as well as with other types of subjects, including those prone to high degrees of oxidant stress.

Another issue for marginal iron deficiency is identifying what effects, if any, it has on symptoms that might be called “general feelings” and “general performance.” More severe iron deficiency, when accompanied by anemia, is known to be associated with these types of symptoms including lethargy, low energy for daily non-strenuous tasks, and reduced work capacity. Less is known about the same symptoms in regard to iron deficiency without anemia. One review of a series of studies on such topics concludes that what is termed “energetic efficiency” is affected at all levels of iron deficiency, including that without anemia. The expression “energetic efficiency” refers to the energy expended for a given work output. The expression can be used in the context of exercise performance (e.g., on a treadmill), or in the context of an occupational task or productivity. There have been studies tying both contexts to iron status, including non-anemia iron deficiency. Even so, more research would certainly be helpful.

There is also one study suggesting that non-anemic iron deficiency can impact cognitive function, particularly in the area of attention retention, for dieting, obese women. This contention is based on inverse correlations between evaluations of cognitive function and values for iron status indicators. The values for iron status indicators seem to indicate iron deficiency can occur in obese women despite iron intakes that would normally be considered adequate. It would be interesting to see follow-up studies assessing cognitive function after iron supplementation.
The subject of growth in children with non-anemia iron deficiency is another under-investigated area. Some studies have found iron supplementation in the absence of anemia to actually stunt growth.\textsuperscript{96} In contrast, a study of weekly iron supplementation of non-anemic school-aged children shows no negative effect on growth, while having a positive effect in preventing significant decreases in hemoglobin concentration.\textsuperscript{97} Thus, this whole area needs more research.

**PREGNANCY**

There are four questions regarding iron supplementation and pregnancy:

1. Should iron supplements be given to women who are anemic at the onset of pregnancy, as well as to those who become anemic during pregnancy?
2. Since iron needs rise during pregnancy, should iron supplements be given to prevent anemia in women who are not anemic at pregnancy onset?
3. If a woman is iron deficient, but not anemic, is there any benefit to iron supplementation besides possibly preventing later anemia development?
4. Is there any value to iron supplementation during pregnancy beyond correcting or preventing any deficiency?

For the first question, supplements effectively treat anemia in supervised studies, but are not always effective in clinical practices.\textsuperscript{62} Possible reasons for the latter include insufficient dose and time of supplementation and poor adherence.\textsuperscript{62} There has been debate as to the best dose, timing, and mode of administration. Another area of uncertainty is the full range of consequences of not treating iron deficiency anemia, especially in terms of maternal mortality, risk of preterm delivery, as well as the impact on iron stores of full-term offspring.\textsuperscript{98,99} In regard to the last area, recent data suggests that maternal iron status does influence iron status of the offspring for the first year of life.\textsuperscript{100} In another research area, some, but not all, data is consistent with anemia causing increased risks of maternal and child mortality, premature labor, and low birth weight.\textsuperscript{98,101} However, the “gold standard” studies, iron supplementation effects on these problems, have not consistently shown improvements in birth weight or avoidance of preterm labor.\textsuperscript{101,102,103} Still, it should be noted that the number of studies that clearly evaluate these issues for iron supplementation are not especially numerous. Moreover, for iron supplement effects on birth weight or the duration of gestation, one review claims that most studies have a bias toward false-negative findings.\textsuperscript{101} Thus, this area is still not clear and is difficult to evaluate due to ethical considerations.

The second question is even more controversial. Groups such as the World Health Organization recommend iron supplementation for all pregnant women, while other groups advocate iron supplements only with diagnosed anemia. A compromise between the two is stated in one review article\textsuperscript{99} as follows:

“In industrialized countries, iron supplements should be prescribed for pregnant women in the third trimester, when the need for iron is prominent. In developing countries, supplementation should be initiated as soon as possible after conception
because of the high prevalence of iron deficiency at the onset of pregnancy.” Which, if any, of these recommendations is the best option is still open to debate.

There are reasons to be wary of a general recommendation of iron supplementation for all pregnant women. Iron supplements during pregnancy can cause GI tract problems such as nausea and constipation,\textsuperscript{70,104} though the latter can sometimes be inhibited by stool softeners or high-fiber diets. In addition, iron supplementation, if too high, can inhibit absorption of zinc (see the Toxicity section). This is a concern because zinc is an important nutrient for pregnant women.\textsuperscript{105} Another concern for extremely high-dose iron supplementation is that it can cause iron poisoning in the child.\textsuperscript{106}

One compromise approach to this issue is routine use of a low-dose iron supplement. A trial in Australia of 20 mg iron/day (as ferrous sulfate) reduces the rate of anemia in pregnant women, though it does not totally prevent it.\textsuperscript{107} The dose used is too low to be expected to hinder zinc absorption or pose a toxicity threat to the child.

The third and fourth questions, correction of non-anemia iron deficiency and effects beyond correcting any deficiency, have received almost no real direct research. There is one study that seems to mix the third question with the fourth question.\textsuperscript{108} This work, which was done in the U.S., examines pregnant women who are initially iron-replete and non-anemic. The work involves giving a daily iron supplement (30 mg as ferrous sulfate) or placebo from early pregnancy to week 28 of gestation. At 28 and 38 weeks of gestation, women with a ferritin concentration of 12 to 20 g/L or < 12 g/L receive 30 or 60 mg iron/day, respectively, regardless of initial assignment. Compared with placebo, iron supplementation from enrollment to 28 weeks of gestation does not affect the overall prevalence of anemia or the incidence of preterm births, but leads to a significantly higher mean birth weight, a significantly lower incidence of low-birth-weight infants, and a significantly lower incidence of preterm low-birth-weight infants. One possible explanation is better transfer of iron to the baby despite not necessarily improving the mother’s iron status. The birth-weight effect was rather large compared to some other studies on iron and birth weight.\textsuperscript{109} Part of this may be due to the early initiation of supplementation in the recent study.\textsuperscript{108} In addition, this recent study may have been more poised to see big effects due to the study population. This population may have had a high inclusion rate of subjects who are not extremely malnourished, but who have high risks for variations in birth weights. This study is very interesting, but does not have a large subject number for a pregnancy outcome study. Follow-up studies would prove to be very interesting.

In conclusion, details about the use of iron supplements in pregnancy are still controversial, and the research that can be done has ethical limitations. In this author’s opinion, until more information is gathered, a modest-dose iron supplement throughout pregnancy, combined with good intake of other micronutrients, seems safe and possibly helpful. In light of the above-mentioned questions about iron absorption from multi-supplements, it may be helpful to combine a standalone iron supplement with a non-iron-containing multi-supplement such as One-A-Day For Men. Taking these two supplements at different times of day may also be helpful since, as noted in the toxicity
section, separating iron supplements from zinc ingestion may reduce the negative interactions. Although the iron-free multi-supplement may not provide 100% of pregnancy RDAs for most micronutrients, it should help meet many of the pregnant woman’s needs. Many clinicians would disagree with this approach to pregnancy supplementation, but it is offered up to start discussions.

**Cognitive and Behavioral Development**

Anemia in children seems likely to be associated with impaired cognitive function, but the picture is not completely clear. A review on this topic\(^\text{110}\) states that most correlational studies find associations between iron deficiency anemia and poor cognitive development, as well as motor development and behavioral problems. The review further states that longitudinal studies consistently indicate that children anemic in infancy continue to have poorer cognition and school achievement, and more behavior problems into middle childhood. On the other hand, the review also states that the results of some of these studies may be confounded by poor socioeconomic backgrounds, and further notes that in anemic children under 2 years old, short-term trials of iron treatment have generally failed to benefit development. In addition, most longer trials are said to lack randomized placebo groups and fail to produce benefits.

In contrast to the concern about socioeconomic confounders in the survey studies, two recent studies in the U.S. seem to have less problem with that issue. In one of the studies, a logistic regression analysis associates anemia with increased likelihood of mild to moderate mental retardation independent of birth weight, maternal education, sex, race–ethnicity, the mother’s age, or the child’s age at entry into the social program used for the study.\(^\text{111}\) In addition, analysis of data from the broad-based National Health and Nutrition Examination Survey III shows lower standardized math scores for iron-deficient school-aged children and adolescents, including those with iron deficiency without anemia.\(^\text{112}\)

Despite the above-mentioned, legitimate concerns about studies on iron status effects on cognitive and behavioral development, there are definitely some studies that show effects of iron supplementation. A number of the older studies are summarized in a paper that dwells more on the common message of several studies than on the design limitations.\(^\text{113}\) In addition, there are some newer studies that were published after the above-mentioned review\(^\text{110}\) that noted many design limitations in this research area. In one of these newer studies,\(^\text{114}\) iron supplements are tested beginning at six months in full-term, anemia-free Chilean infants. The results suggest that unsupplemented infants respond less positively to the physical and social environment and process information more slowly. The benefits may not be limited strictly to anemia prevention, though the study does not extensively explore this issue. In another study,\(^\text{115}\) which was done in Indonesia, iron supplementation is examined in children aged 6 to 60 months. No effect is seen for the whole group, but when supplementation is started by 18 months of age (n = 73), the supplemented children perform better than control children on the Sternberg test of working memory.
This last study suggests that in at least some settings, iron depletion and repletion has an effect on early development that can’t be duplicated later. However, there are also studies that indicate that later iron supplementation could still have other effects on cognitive and behavioral development. For example, in another study done in Indonesia, an iron supplement study in 3- to 6–year-olds finds that iron deficiency anemia alters cognitive processes related to visual attention and concept acquisition. In still another study in Indonesia, iron supplementation of iron-deficient anemic children improves school achievement test scores. In addition, positive results for cognition are reported by a review of four studies in India on iron supplementation in anemic schoolchildren up to 15 years old.

There are also a few studies in non-anemia iron deficiency that show benefits of iron supplementation. In one such study in a U.S. urban population, iron supplementation in adolescent girls improves verbal learning and memory. Another study examines non-anemic infants, 9 to 12 months old, with varying degrees of iron deficiency. In this study, iron supplementation impacts Mental Development Index scores. No effect is seen for infants in good iron status. This is a rather old study, which gets cited a lot. It would be good to see if the general results could be confirmed by other studies.

There is also a non-placebo-controlled study of iron supplementation of non-anemic children with attention deficit hyperactivity disorder. The supplementation produces a significant decrease on the parents’ Connors Rating Scale scores. Some people refer to this work as a study of non-anemic iron-deficient children, but the mean ferritin values are higher than those typically used to define that state. Thus, the iron could be having a pharmacological effect, possibly on dopaminergic activity, rather than correcting a nutritional deficiency. Another explanation is that the parents’ evaluation reflects wishful thinking. This is possible since there is no placebo control, and the iron does not affect blood parameters or teachers’ scores on the rating scale.

In conclusion, severe iron deficiency early in life likely has detrimental effects on cognitive and behavioral development, though the benefits of iron intervention, especially in terms of optimal starting age, are not fully clear. There may be cognitive benefits of treating iron deficiency, with or without anemia, later in childhood and adolescence, but there is hardly a wealth of studies in this area either. Still, it makes sense to try to treat or prevent iron deficiency in all ages of all children.

INFECTIONS

It is beyond argument that iron affects immune function. However, there are arguments concerning the particulars of the relationship of iron to infection occurrence. One of these issues is when to be concerned about too much iron intake promoting infection. Part of this concern is based on the idea that microbes themselves have a strong need for iron. In fact, the depression in serum iron that occurs with infections has long been speculated to give a host advantage by restricting microbe access to iron. Thus, it is theoretically possible that high intakes of iron could have negative effects on host defense.

Along these lines, there are human and animal studies associating parenteral iron with increased infection risk, though in some cases, this may be due to
contaminated administration instruments, and not the iron. There have also been studies reporting that iron supplementation increases the risk of malaria attack and morbidity, though other studies do not confirm this.\textsuperscript{125} Statistical analysis across these studies does not necessarily give a strong case for the idea that iron supplementation promotes poor resistance to malaria.\textsuperscript{126} In addition, the assessments criteria used in these studies has not always been precise. Even so, the studies raise the possibility of some connection between high iron intake and high malaria risk. This is problematic because malaria may cause anemia in some cases,\textsuperscript{127} which makes it gray as to whether iron should be given during malaria. To complicate the matter further, there are writings proposing that in some cases, iron supplementation can actually help with malaria treatment by boosting immune function.\textsuperscript{128} However, some review articles dispute this concept by saying that there are no clear demonstrations that iron supplementation helps recovery from, or prevention of, malaria.\textsuperscript{125} The whole area of iron and malaria could use more research.

Another approach to considering whether iron supplements can promote infections is a recent systematic review of 28 past randomized controlled trials of children.\textsuperscript{126} These trials deal with infection rate responses to oral or parenteral iron supplementation, or to fortification of formula, milk, or cereals. The studies vary considerably in terms of what types of children are studied (variations in age, degree of overall nutrition intake quality, etc.). The studies also vary in terms of the types of infections (some include malaria, some are not from areas of the world where malaria occurs). The conclusion of the review is that iron supplementation has no apparent harmful effect on the overall incidence of infectious illnesses in children. However, that conclusion does not rule out that specific supplement regimens in specific circumstances could have deleterious effects on resistance to certain infections.

On the opposite side of the issue, there are studies on iron deficiency and increased risk of infections. For example, a recent study in Israel has examined the association between iron deficiency anemia and the frequency of recurrent acute otitis media (ear infections) in 680 children.\textsuperscript{129} The paper concludes that anemic children have higher prevalence of episodes of acute otitis media in comparison to healthy, non-anemic children, and shows that there is a direct relationship between the degree of the anemia and the number of the episodes. However, not all studies on iron supplementation and infection incidence are clear cut. For example, there is not a clear protective effect of iron supplementation on overall infection rates in the above-noted systematic review on the safety of iron supplements in regard to infections.\textsuperscript{126} Thus, more research can be done to identify the circumstances where iron deficiency affects infection risk.

Another area that could use more research is how iron depletion effects on laboratory immune assessments relate to iron supplementation effects on resistance to infections. This area is difficult to study because in many settings, iron deficiency does not occur in isolation from other nutrient deficiencies that can affect immune function. A recent review article\textsuperscript{125} states the case well in saying: “Iron deficiency is associated with reversible abnormalities of immune function, but it is difficult to demonstrate the severity and relevance of these in observational studies.” Another review article declares that data on the relationship between iron deficiency and infection is conflicting.\textsuperscript{42} There are some reports of food iron or supplements
reducing infections in children in developing countries, but there are also reports of no effect. A recent study along these lines was done in western Kenya. Iron supplementation has no effect on reinfection with intestinal helminths and Schistosoma mansoni reports in children or adults. However, one limitation of this study is that the iron status of the subjects is not restricted to a narrow range.

Surprisingly, there are not a lot of recent human studies on iron supplementation and immune function. In one exception, in a study done with children in Sri Lanka, iron supplementation improves iron status and reduces morbidity from recurrent respiratory tract infections. Only half the children in the study were anemic, which raises the question of whether the iron supplements helped children with non-anemic iron deficiency. In contrast, in a study in Bangladesh, iron supplements had no effect on attack incidence or duration for diarrhea, dysentery, and acute respiratory tract infections. Thus, there is no real strong basis for definitive statements on iron supplementation and reduction of infection incidence.

In conclusion, based on cellular tests of iron status and immunity, iron deficiency can impair immune capacity. This means that correcting iron deficiency should impact resistance to infection, though demonstration of this concept has not been as strong as would be hoped. On the other end of the spectrum, iron supplements may sometimes increase the risk of problems with infections, but exactly when this is and is not a problem has not been well clarified.

**EXERCISE PERFORMANCE**

This area of research has been applied to both trained athletes and non-athletes. Athletes will be discussed here first. Trained athletes can often present with blood readings for hemoglobin or hematocrit that are consistent with anemia. This may or may not actually be indicative of anemia. In some cases, athletes involved in extensive endurance training can adapt to their training with a blood hemodilution effect (the blood accumulates a relatively high amount of water). This gives the appearance of low hemoglobin in a blood test, but in reality, the total hemoglobin may not be low. By analogy, one cup of orange juice can be diluted with one cup of water, which would halve the concentration of vitamin C per cup. However, the total vitamin C would not change.

This type of situation is sometimes called sports anemia, though others use this term to connote actual anemia in athletes. Some types of athletes can be prone to actual anemia for a number of reasons. One reason is simply that some athletes are females who are adolescents or young adults. This population is prone to anemia whether they are athletes or not. In addition, low body iron levels can develop in either gender due to mechanical hemolysis, GI blood loss, hematuria (blood in the urine), other causes of high urinary iron, sweating, low iron intake, or poor intestinal absorption. The relative contribution of any of these factors to iron status can be debated. For example, one article argues that the sweat and urine losses are negligible, but that there could be effects of increased rates of red cell iron and whole-body iron turnover. The latter could be due in part to increased GI blood loss, which has been observed in male runners. In these subjects, iron supplementation improves values for indicators of iron status.
A number of studies have shown that anemia and non-anemia iron deficiency can occur with some frequency in endurance athletes. Although female athletes may be more prone to iron deficiency than male athletes, males are not exempt, especially adolescent boys. For example, one study reports that in boys, endurance training brings about a significant decrease in serum ferritin and iron stores. Moreover, anemia is found in 10 to 15% of the subjects studied. Another study, of adolescent Israel gymnasts of both genders, shows results indicating that they are prone to non-anemia iron deficiency. Although the problem is more prevalent in the girls, it is reported for both genders. In another study, non-anemia iron deficiency is reported as common in a group of adolescent runners. In this study, iron deficiency is more common in females, but 20% of the males show iron depletion by the close of their season. This suggests that preseason screening alone is not adequate for detecting iron deficiency in athletes.

The logical question to ask is: Does correcting iron deficiency improve exercise or physical training performance in athletics? The use of training performance as an end point is easier than using sports performance, which would involve skill issues. When anemia is present, even if it is mild, iron supplementation seems to help performance. As far as correcting non-anemia iron deficiency, there have been some conflicting results in studying athletes. However, it is not surprising that the results in this area are not totally consistent. The results in studies of exercise performance in general, even if well designed, can be different for the different circumstances. In addition, for some specific studies of iron supplementation in non-anemia iron deficiency, design limitations may have been a problem. For example, some studies showing negative results may have had mixtures of marginally iron-deficient and non-deficient subjects. Moreover, one study uses a mixed mineral supplement, which, as noted above, may not always provide as much bioavailable iron as anticipated. In this study of the mixed supplement, there is no improvement of values for iron status indicators.

Another important consideration for these studies of iron supplementation is what is actually measured. Several of the positive result studies, which are discussed below, note that not all of their assessments give the positive results. Possibly, in the studies that give negative results, different assessments would have given positive results. In addition, as noted in a review article, not all studies have used one of the best choices for type of iron supplement, some have used doses that are low compared to the usual treatments for iron deficiency, some have not controlled for supplement timing and co-ingestion of foods that reduce iron absorption, some treatment periods are possibly too short, and the use of serum ferritin to monitor changes in iron status could be affected by inflammation responses to training or hemodilution. Another issue is that some studies with negative results did not use many subjects (though the same criticism can be made for some of the positive result studies). Finally, maximal iron improvement of exercise performance, since it involves better energy release, likely requires sufficient intake of calories, which may not always be a “given” in these studies. This point is supported by a study of iron and calorie supplementation in women in India. In this study, combined energy and iron deficits have a greater adverse effect on physical work capacity than energy or iron deficits alone. Although this study involves anemic subjects, the general idea could also apply to marginal iron deficiency.
A number of positive findings for iron supplementation and exercise performance in marginal iron deficiency have come forth. These findings are summarized in Table 4.2. As mentioned above, many of these studies report that iron supplementation effects do not occur for all the parameters considered in the study. There are a few other studies that could be put in Table 4.2. Two are excluded because the severity of iron deficiency of the subjects is unclear, and in another case, the assessments are subjective and have no placebo control.

It is worth mentioning that in the first study of Table 4.2, though the subject number is not large, all but one iron-supplemented subject show improvement, while the placebo group shows loss of endurance.

This research area of iron supplementation and exercise performance in non-anemia iron deficiency can still hardly be called clear. Even so, this author feels that in light of some questions about the negative studies, and the existence of positive findings, iron supplements likely enhance some aspects of exercise performance is some people with non-anemia iron deficiency. More research is definitely needed, especially for non-athletes, who have not been studied extensively in this area.

**MISCELLANEOUS HEALTH PROBLEMS**

Iron supplementation has been used with some apparent success for a number of health problems listed below:

- Restless leg syndrome
- Plummer-Vinson syndrome
- Breath-holding spells in children
- Obesity
- Goiter treatment (iron co-administered with iodine)

The first condition, restless leg syndrome, is a description of a symptom that can have a number of precipitating causes. Often, the best approach to treating this problem is to deal with a primary health condition that causes this symptom. As far as iron and restless leg syndrome, it does appear that some, but not all, people with the problem are iron deficient based on blood measurements. A simple approach to iron supplementation for people with restless leg syndrome is to only
give iron to people with blood measurement signs of iron deficiency. There are studies to support this approach. For example, there is a report that iron supplementation improves symptoms only in subjects with low ferritin. Similarly, another study finds no iron supplement-induced improvement of symptoms in the whole study group, but finds that responders show an increase in iron saturation values. However, there is some indication that iron metabolism can be abnormal during restless leg syndrome. In one study, though serum values for iron status are not abnormal, cerebral spinal fluid values are. In another study, autopsied brain tissue from seven subjects who had restless leg syndrome shows low iron and tranferrin receptors in certain types of brain cells. These two studies suggest the presence of a defect in iron transport in certain neurological tissue. The next question is whether high-dose iron could help some people by forcing iron into brain cells despite the transport defect. This is not yet established. Moreover, safety issues mean that such treatments may not be ideal, especially since there are other pharmacological and behavioral treatments available (though some have side effects). Perhaps, new treatments can be developed to specifically overcome the iron transport defect.

In this author’s opinion, at present, it seems prudent to try iron for this condition if there is evidence of iron deficiency, since that should be corrected anyway. If iron deficiency is not present, then low-dose iron supplements may not help and high-dose supplementation carries risk, plus its efficacy is uncertain. In that case, a decision should be made by individual subjects with their physician.

In the case of Plummer-Vinson syndrome, a condition where there is difficulty swallowing and web-like tissue membranes in the lower throat, the primary lesion may or may not involve iron deficiency. One review has contended that decreased incidence of Plummer-Vinson disease has been related to iron dietary intake and supplementation. However, not everyone in this medical area is convinced that iron deficiency is a prime cause of this problem. Obviously, the vast majority of people who are iron deficient do not develop this condition. Still, it is possible that iron deficiency plus some other circumstances are the root causes. It is also possible that the syndrome does not need iron deficiency to develop, but the lesion, especially if there is blood loss, can cause iron deficiency anemia, which can then worsen the symptoms. Whether or not iron deficiency is part of the prime cause, it does seem that iron supplementation can correct the anemia that is often present, and in at least some subjects, drastically reverse symptoms. However, if the lesion is far advanced, physical interventions may be necessary.

In some children, iron deficiency anemia can be associated with breath holding, possibly due to a problem in regulating autonomic nervous system reflexes. A number of studies find that giving iron supplements reduces the incidence of breath holding in subjects with anemia. An interesting question is whether the iron effect is due to eliminating anemia or eliminating another iron function impairment that co-exists with the anemia. The latter idea is supported by a case study, though it involves only one subject. In this subject, the breath-holding spells resolve before the anemia is completely eliminated. To this author’s knowledge, there is no evidence that iron supplements will help breath holding in subjects who are not iron deficient.
In fact, one study argues that the subjects most apt to be helped by iron supplementation are those with iron deficiency.\textsuperscript{160}

A relationship of iron to weight loss in overweight people has a theoretical basis. Iron status affects thyroid function,\textsuperscript{164} and thyroid function can affect weight loss.\textsuperscript{165} In fact, iron deficiency has been associated with impaired thermoregulation.\textsuperscript{166} There is one study\textsuperscript{167} where obese women on a very-low-calorie diet maintain better circulating thyroid hormone levels if supplemented with iron. The supplemented women lose more weight on average, but the difference is not statistically significant. Still, there is indication that the most weight was lost by women whose iron status and thyroid hormone levels were maintained the best. In any case, this whole area is still in the very speculative stage of research.

In terms of goiter, in some countries of Africa, many children are at high risk for both iodine deficiency-induced goiter and iron deficiency anemia. Since iron deficiency can impair thyroid metabolism,\textsuperscript{164} in theory, iron supplements can complement iodine effects on thyroid function. This possibility is supported by a study where goiter shrinkage by iodized salt is enhanced by also adding iron to the salt.\textsuperscript{168}

**TOXICITY**

Ironically (no pun intended), alongside the big concern for iron deficiency, there is also a big concern from the toxicity standpoint. There are a number of different implications that come up in this regard (Table 4.3).

Prominent symptoms of iron toxicity, such as organ damage and death, can be associated with the genetic condition hemochromatosis and repeated blood transfusions.\textsuperscript{1} The latter occurs because iron bypasses the body’s best defense against iron toxicity, namely using ferritin to block iron absorption from the GI tract. The former becomes problematic due to high absorption of iron. The typical treatment for the genetic condition is regular blood withdrawals.\textsuperscript{1} In other cases of iron overload, the iron chelator deferroxamine (Desferal®) or other oral iron chelators have been used.\textsuperscript{169} There is some speculation that a substantial number of people have mild forms of hemochromatosis. Such people would include those who are heterozygous carriers of a mutation commonly associated with hemochromatosis.\textsuperscript{20} However, this concept is not confirmed.\textsuperscript{20}

<table>
<thead>
<tr>
<th>TABLE 4.3</th>
<th>Iron Toxicity Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prominent symptoms due to non-nutritional toxicity or definite oral overdosing</td>
<td></td>
</tr>
<tr>
<td>Iron antagonism of copper and zinc absorption</td>
<td></td>
</tr>
<tr>
<td>GI tract irritation</td>
<td></td>
</tr>
<tr>
<td>Increased sensitivity to infections (covered above in the immune function section)</td>
<td></td>
</tr>
<tr>
<td>Increased risk of cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>Stimulation of oxidant stress (which may cause increased risk of various diseases)</td>
<td></td>
</tr>
</tbody>
</table>

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Since the intestine has a good defense against oral iron toxicity, it is not easy to produce severe iron toxicity due to oral iron consumption. However, it is possible to get a chronic or acute oral overdose in adults and children.\textsuperscript{170}

Iron supplements are definitely capable of impacting zinc status, largely via competition for intestinal absorption.\textsuperscript{20} The exact doses of iron that cause zinc problems is not fully clear, though a ratio of iron to zinc of 2.5:1 is too low to impair zinc absorption in one study.\textsuperscript{171} The exact problematic dose of iron for impairing zinc absorption may vary with different zinc intakes, timing of the supplementation, iron status of the person, and other health aspects of the person. In one interesting study,\textsuperscript{172} iron supplementation (100 mg iron/day as ferrous sulfate) at bedtime, is studied in young women with non-anemia iron deficiency. Zinc absorption, studied using zinc stable isotopes, does not change despite an improvement in iron status. One explanation is that the iron supplement is separated from the majority of zinc intake. Another aspect of timing has to do with taking both the zinc and iron with meals. In at least some circumstances, consuming iron and zinc supplements with a meal has little effect on the zinc absorbed.\textsuperscript{20} In summary, although iron supplementation can adversely affect zinc absorption, it is not clear how often this is actually a big concern.

Iron antagonism of copper, though not as publicized as iron effects on zinc, may be a concern. In livestock and experimental animals, high iron intake can negatively affect copper status.\textsuperscript{5,173} However, human studies on this subject are few, focus mostly on just serum copper, and give mixed results.\textsuperscript{174–177} In fact, in one study,\textsuperscript{177} iron supplementation of non-anemic iron-deficient subjects seems to improve copper status, though other interpretations of the results are possible. For example, serum copper is known to increase with inflammation (see the chapter on copper). Possibly, the increase in serum copper due to iron supplementation is a response to inflammation caused by the iron supplements.

In some people, a concern for high doses of iron complexes such as ferrous sulfate is the production of GI tract discomforts, such as upset stomach and constipation.\textsuperscript{20,21} In fact, this criterion has been used to set the Upper Levels (UL) for iron.\textsuperscript{20} As a result, the iron UL for adults (45 mg) is well below the doses of iron typically used to treat anemia. For people sensitive to iron-induced GI problems, but for whom high doses of iron are prescribed, the following solutions can help at least some of the time:

- Take the iron with meals.\textsuperscript{20,22}
- Use a form of iron that is not as irritating, such as iron bis-glycine chelate or ferrous fumarate.\textsuperscript{34,33}
- Spread out the daily dose over the day.\textsuperscript{3}
- Use a stool softener or eat a high-fiber diet (though the latter can cut down on iron absorption if the fiber and iron are consumed together).

The issue of moderate iron over-consumption and cardiovascular disease has been given a lot of attention by two epidemiological projects, one known as the Rotterdam Study\textsuperscript{84,178} and one done in Finland.\textsuperscript{179,180} In the Rotterdam Study,\textsuperscript{84,178} high dietary heme iron intake, as well as high serum ferritin, are related to an
increased risk of myocardial infarction in an elderly population. For the dietary heme iron, the relationship is more pronounced for the fatal cases of myocardial infarction. The Finland epidemiology project\textsuperscript{179,180} also related serum ferritin to risk of myocardial infarction. Although these studies are cited a lot, both in scientific literature and in writings for the general public, the studies have major limitations. First, it is often ignored that the Rotterdam Study finds no association of risk for myocardial infarction with serum iron, serum transferrin, or total dietary iron. It is also often ignored that in the Rotterdam Study, the association of myocardial infarction with serum ferritin is strongest for people with various health problems such as smoking and diabetes. Since ferritin is increased by physiological stress,\textsuperscript{181,182} the high ferritin values in both the Rotterdam and Finland studies could simply be identifying people with the most physiological stress. The last point can also be said of two studies finding that high serum ferritin levels after a stroke are associated with high risk of poor outcome.\textsuperscript{183,184} The Rotterdam Study does make some attempt to account for this issue by reanalyzing data after excluding subjects over a certain value for C-reactive protein, a marker of inflammation.\textsuperscript{84} However, the cutoff value is twice that of the value used as a minimum to assess relationships between C-reactive protein and metabolic syndrome.\textsuperscript{185}

One other potential problem with relating ferritin to risk of cardiovascular disease is that in at least some of the analysis, low ferritin could be associated with regular exercise. Serum ferritin can be reduced in some circumstances by exercise, including just moderate exercise in middle-aged or older people.\textsuperscript{186,187}

One study in western Australia,\textsuperscript{178} as well as some other studies,\textsuperscript{20} give results in conflict with the Rotterdam and Finland studies. For example, in the study in Australia, ferritin values are compared to first coronary heart disease event and time to first stroke event. There are some other studies that do show a relationship, but within these studies, there are some inconsistencies among the results for different indicators of iron status.\textsuperscript{20} Thus, the correlation study results for this subject are mixed. Moreover, even the studies with positive results do not have clear-cut interpretations. Thus, in this author’s opinion, the concept that dietary iron or iron stores play a major role in cardiovascular disease risk is still unconfirmed by population-based, correlation studies.

On the other hand, there are other lines of indirect evidence that iron can be involved in cardiovascular diseases, and the vast number of other diseases that involve oxidant stress. This involvement may not require overt iron toxicity to occur. The indirect evidence is that iron is very capable of generating free radicals that cause oxidant stress.\textsuperscript{188} This has mostly been demonstrated \textit{in vitro},\textsuperscript{188} but there is some evidence that iron can be found \textit{in vivo} in forms that could give rise to radicals.\textsuperscript{189,190,191} There is also data in rats showing that injection of the iron chelator desferrioxamine can slow chemically induced oxidant injuries.\textsuperscript{192,193,194} However, these chelators could also work via mechanisms other than iron chelation.\textsuperscript{195} Another issue here is that even if iron does generate radicals \textit{in vivo}, the dietary iron connection is not necessarily clarified. Dietary iron intake may not be a major determinant of how much iron-catalyzed radical generation occurs. The major determinant could be processes that put iron in a form that is free to generate radicals. By analogy, if in a car, the carburetor floods with gasoline, the problem is not too much gasoline
in the car. Instead, faulty carburetor mechanisms are to blame. Using a more biomedical analogy, just because atherosclerotic plaques contain calcium, a low-calcium diet is not advocated to prevent atherosclerosis.

Despite what was just said, there is one study supporting the idea that iron supplements can induce oxidant stress in intact people. Co-supplementation of relatively low doses of iron plus vitamin C increases oxidative DNA damage in white blood cells. However, the results are hard to interpret because the damage was found by one assay but not another. Also, the damage disappeared upon extending the supplement time, and in one study subgroup, oxidative DNA damage decreases with iron supplementation. It can also be noted that in another study with similar design, iron has modest beneficial effects on LDL oxidation, an indicator of free radical mediated oxidant stress. Although this study has a small subject number, the results are consistent with an earlier study. In that study, iron supplementation in subjects with high plasma vitamin C have no effect on oxidant-damaged DNA. In other work, eight weeks of iron supplementation has no effect on oxidant stress, as indicated by plasma protein carbonyl and lipid hydroperoxide concentrations. This work is done in college-aged females with either adequate iron status or with non-anemia iron deficiency.

In contrast to these last three studies, high-dose iron supplementation (100 mg/day) plus vitamin C supplementation in pregnant women lowers plasma vitamin E and increases plasma values for lipid peroxides, a measure of oxidant damage to lipids. One concern about this study is that the variances in values between individuals is extremely low for the method used. Also, even if oxidant stress does occur, this dose of iron may be outside the realm of moderately high iron intake. However, nobody has yet defined what constitutes moderately high iron intake.

There is a report of high-dose ferrous fumarate producing some signs of oxidant stress in Crohn’s disease patients. However, there is also an increase in GI tract irritation, a prime symptom of this disease. This high sensitivity to GI distress may have triggered the oxidant stress. Also, it should be noted that this study’s main indicators of oxidant stress are based on plasma sulfur compound levels, which may not always be indicative of oxidant stress changes.

In this author’s opinion, the studies with negative results on oxidant stress, and interpretation problems for the studies with positive findings, mean that moderately high iron supplements cannot be said to routinely produce oxidant stress. On the other hand, this area could use much more research, especially for defining the minimal intake of iron that is apt to cause oxidant stress.

In summary, there are certainly situations where iron toxicity is dangerous, but it is still unsettled as to whether subtle toxicities occur with modestly high dietary iron intakes.

**SUMMARY AND CONCLUSIONS**

There is no question that iron deficiency is still a major problem and that iron supplements benefit some people. Nonetheless, many unresolved issues still remain about iron supplements such as who should get them, how to give them (e.g., daily...
TABLE 4.4
Iron Supplements at a Glance

Adult RDA: 18 mg (male), 8 mg (female)

Typical dose in supplement studies: variable, but for correction of anemia, can be as high as 300 mg/day (RDA may not be the perfect guideline due to low absorption of supplements vs. meat products; however, high doses for all uses may be unwarranted)

Best supplement complex: ferrous sulfate is the cheapest and is absorbed as well or better than most iron supplements, but some doses cause GI tract irritations in some people; iron bis-glycine chelate Ferrochel® is better absorbed, has low GI irritation, but is more expensive than ferrous sulfate

Applications: beneficial to treat anemia; possibly beneficial to prevent anemia; helpful in pregnancy, though there are debatable issues such as the exact benefits, who should receive the supplements, and what protocol to use; a number of other uses are somewhat supported, but not fully confirmed

Upper Level: 45 mg (based on GI tract irritations; this dose is very often exceeded in anemia therapy)

Safety issues: many possible problems, but only overdosing is confirmed (especially in children)

vs. weekly), how much should be given, what benefits should be expected, and at what point safety issues become a concern.

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Zinc

Hundreds of papers have been published on various biological aspects of zinc. Many of these involve human supplementation studies. Yet, there is much that we still don’t know about zinc. We do know that zinc can affect numerous biological processes. In fact, it’s hard to think of a human body process where zinc is not involved. For this reason, many claims have been made about zinc supplementation and health. Some of these claims are supported by at least some research, but there are still a lot of uncertainties. The majority of the claims focus on correcting marginal deficiencies, though some claims involve getting “extra” zinc above the RDA.

OVERVIEW OF FUNCTION

Zinc is needed for the function of many enzymes. The exact number varies depending on how one defines separate enzymes, but some estimates say over 200 enzymes need zinc. Most of these enzymes are metalloenzymes where zinc is incorporated tightly into the protein structure, where zinc acts as a catalyst or to stabilize protein structure. For some other enzymes, zinc binds more transiently as an enzyme activator rather than a more permanent part of a metalloenzyme. In addition to roles with enzymes, zinc can also stabilize the structures of various other molecules, including non-enzyme proteins, certain hormones, transcription factors (e.g., zinc fingers), nucleic acids, and small regulatory molecules such as the peptide thymulin. This stabilizing function includes proteins in cell membranes, a function that seems to greatly affect cell membrane structure. This cell membrane stabilization function has wide implications because membrane stability affects receptors, which signal many actions in cells. If cell membrane stability is diminished, then some receptors may become less active while others become more active. So, some cellular functions may become sluggish while others may become overactive. Among the overactive processes seems to be secretion of superoxide and other reactive oxygen species by immune cells. Zinc, by maintaining membrane stability, can restrict this secretion and thus act as an indirect antioxidant. This and other indirect antioxidant actions of zinc are noted in Table 5.1.

Not all zinc functions diminish equally during progressive degrees of zinc deficiency. For example, in zinc-deficient rats, liver and erythrocyte activities for cytosolic superoxide dismutase 1 are not low at all. In contrast, zinc status in rats, humans, and a non-human primate does affect activities of extracellular superoxide dismutase, a protein distinct from superoxide dismutase 1. Among the most sensitive of all zinc functions to mild zinc deficiency is membrane stabilization,
which can affect multiple processes, probably including the third indirect antioxidant function listed in Table 5.1. This effect of zinc deficiency is a hyper-responsiveness of this aspect of the immune system, whereas other effects of zinc deficiency on immune function produce under-responsiveness. These opposite effects of zinc status on immune function may both be linked to membrane stabilization, though zinc can also affect the immune system in other ways, such as activating the T-cell regulator thymulin.

**OVERVIEW OF METABOLISM**

Zinc movement within the body is less chaperoned than is iron or copper. In fact, a lot of the zinc in serum just binds reversibly to albumin. Some other serum zinc is tightly bound to a protein called alpha-2-macroglobulin, though the metabolic or functional importance of that zinc is unknown.

Zinc movement in and out of cells is affected by cell concentrations of a protein family called metallothionein. Metallothionein I and II are structurally similar, high cysteine, low molecular weight proteins found in most cell types. The brain also contains a brain-specific metallothionein III. Metallothionein proteins bind a variety of metals such as zinc, copper, and cadmium. In the liver and kidney, this binding seems to play a role in inhibiting toxicity of these metals if they are present in high concentrations. Also, in intestinal cells, metallothionein levels rise with high body zinc, which appears to inhibit absorption of orally consumed zinc. In addition to such detoxification actions, metallothionein in various tissues seems to be important in drawing zinc into cells. This can be especially prominent during inflammatory stress, where serum zinc falls and there is a rise in zinc bound to metallothionein in the liver and kidney. Local inflammation in other body sites also brings about a metallothionein–zinc build-up at those sites. Besides roles in zinc distribution, metallothionein–zinc has other functions such as free radical scavenging. Synthesis and possibly degradation of metallothionein are very sensitive to zinc nutritional status as well as a number of other influences.

### TABLE 5.1
**Proposed Zinc Antioxidant Actions**

<table>
<thead>
<tr>
<th>Action</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase synthesis and likely inhibit degradation of the protein metallothionein, which can have antioxidant actions</td>
<td>6,7</td>
</tr>
<tr>
<td>Required for normal activity of superoxide dismutase antioxidant enzymes</td>
<td>8,9</td>
</tr>
<tr>
<td>Inhibit inappropriate activation of pro-inflammatory cells (activation causes secretion of superoxide radical and hydrogen peroxide, a radical precursor)</td>
<td>3,4,5</td>
</tr>
<tr>
<td>Limit intracellular free radical production</td>
<td>10</td>
</tr>
<tr>
<td>Block pro-oxidant reactions of redox-active transition metals</td>
<td>11</td>
</tr>
<tr>
<td>Protect protein sulfhydryl groups against oxidant damage</td>
<td>11</td>
</tr>
<tr>
<td>Protect against inflammatory cytokine-mediated activation of oxidative stress-responsive transcription factors</td>
<td>12</td>
</tr>
<tr>
<td>Promote absorption and reduce degradation of vitamin E</td>
<td>13,14</td>
</tr>
</tbody>
</table>

which can affect multiple processes, probably including the third indirect antioxidant function listed in Table 5.1. This effect of zinc deficiency is a hyper-responsiveness of this aspect of the immune system, whereas other effects of zinc deficiency on immune function produce under-responsiveness. These opposite effects of zinc status on immune function may both be linked to membrane stabilization, though zinc can also affect the immune system in other ways, such as activating the T-cell regulator thymulin.
NUTRITIONAL STATUS ASSESSMENT

Typically, serum or plasma zinc is used to assess zinc status.\textsuperscript{22} Very low values are associated with severe zinc deficiency, and moderately low values can be associated with marginal zinc deficiency.\textsuperscript{3,22,23} However, the use of serum or plasma zinc for identifying marginal zinc deficiency has two major limitations. One, values are not always sensitive to small changes in zinc status.\textsuperscript{24} Two, values are depressed by inflammation and other physiological stress even without any degree of zinc deficiency.\textsuperscript{6,20,25} This has led to the need for additional methods of assessing marginal zinc deficiency, though no ideal method has emerged. Even so, some methods seem to hold value for this purpose. In this author’s opinion, for research purposes, a marginal zinc deficiency can be declared if low values are seen for serum zinc plus one other indicator of zinc status, particularly if values for both indicators are raised by zinc supplementation. This author would also call a marginal zinc deficiency likely if serum zinc is not low, but values are low for two other indicators of zinc status, particularly if values for both are raised by zinc supplementation. Although these approaches are not ideal for clinical health care assessments, they can be valuable for clinical research. The methods for assessing zinc status, other than serum zinc, are discussed below.

One method that receives occasional use is plasma alkaline phosphatase activity.\textsuperscript{26} Values for this measure are influenced by zinc status, since zinc is needed for this enzyme activity.\textsuperscript{3} However, the activity values are also subject to so many other influences that the use for zinc status is limited mainly to highly controlled intervention studies (e.g., taking measures before and after a zinc supplementation period). As an alternative, some laboratories now use erythrocyte membrane alkaline phosphatase activities, since the activities are sensitive to small changes in zinc status.\textsuperscript{27}

Urinary zinc can also sometimes be a helpful measurement,\textsuperscript{22} but proper interpretation of the results can be tricky. For example, a high urinary zinc value could mean that zinc stores are high, or it could mean that excessive loss of zinc is adversely affecting zinc status. Thus, the use of this measurement should be done in the context of other measurements.

The zinc tolerance test is also sometimes used for zinc status evaluation.\textsuperscript{28,29} In this test, a single dose of oral zinc is given and serum zinc changes are followed over time. In principle, the faster the zinc is cleared, the less zinc is in the tissues. This test has not been directly compared very much to other markers of zinc status or to moderate dietary zinc depletion and repletion. One comparison to varying zinc intake does not yield a strong support for this tool.\textsuperscript{30} Therefore, though the test’s validity for assessing marginal zinc status may hold in some circumstances, there are still some questions. On the other hand, the zinc tolerance test does seem useful for studying acute, relative zinc absorption.\textsuperscript{31} An example of this use is the study of an acute effect of calcium on zinc absorption.\textsuperscript{32}

This author’s laboratory has assessed zinc status with plasma activities of the zinc metalloenzyme 5'-nucleotidase.\textsuperscript{24,33} The author’s group has found that these activities respond to moderate, relatively short-term changes in zinc intake in elderly subjects, even in the absence of a change in plasma zinc.\textsuperscript{24} Activities of 5'-nucleotidase activities...
are also low in mildly zinc-deficient rats (unpublished results), and extremely low in type 2 diabetic women,\textsuperscript{33} a group prone to marginal zinc deficiency.\textsuperscript{34} In type 2 diabetic women, 5′-nucleotidase activities are raised by zinc supplementation.\textsuperscript{35} The 5′-nucleotidase activity assay is a little quirky in that two long lag times must be monitored as part of the method.\textsuperscript{35} Nonetheless, our laboratory has obtained very good reproducibility (unpublished results). One limitation of this method of assessing zinc status is that certain types of tissue injury can raise values.\textsuperscript{36} Still, this does not preclude the use of this method in most types of studies. Blood cell membrane 5′-nucleotidase activities have also been used to study marginal zinc deficiency,\textsuperscript{37,38} though the need for specific blood sample processing can be a problem in some studies.\textsuperscript{3}

Erythrocyte metallothionein protein contents, or monocyte metallothionein mRNA, have also been shown to reflect zinc status.\textsuperscript{35,39} The protein values may change a little slowly in response to elevated zinc intake, but this may actually be helpful in studies where zinc intake varies a lot day to day. One limitation with either type of metallothionein measurement is the methodology. The RNA measurements require PCR, which is not routinely done by all research laboratories. The protein measurements require an antibody to metallothionein that works well with the assay employed. A number of antibodies from commercial sources and some antibodies made by individual investigators don’t always work well for metallothionein ELISA methods (based on this author’s own experience and conversations with others). Another issue for these methods is the influence of factors other than zinc status. Tissue metallothionein levels are affected by many regulators.\textsuperscript{6} It is not known how many of these same regulators affect blood cell levels.

Plasma activities of the peptide thymulin, a T-cell immune regulator,\textsuperscript{3} are very sensitive to marginal zinc deficiency in humans\textsuperscript{37,40} and in rats (DiSilvestro, R.A., unpublished data). Again, there are some factors other than zinc status that are known to affect activities,\textsuperscript{41} but a correction for this can be done by running the assay with and without added zinc. Adding zinc to the assay will increase activity in marginal zinc status even if synthesis of the peptide portion of thymulin is high. A bigger problem with the thymulin activity assay is that there are only two laboratories in the world that have routinely done the activity bio-assay for zinc studies (Dardenne’s group in France\textsuperscript{40} and Mocchegiani’s group in Italy\textsuperscript{42}). There are commercially available thymulin immunoassays, but they are not useful for zinc status assessments since this status affects activity, not peptide levels.

Various white blood cell zinc contents can also be used to diagnose marginal zinc status.\textsuperscript{3} The biggest issue here is that if the white cell subpopulations are not constant, then subpopulations must be separated to get meaningful results. Erythrocyte zinc contents have changed in response to dietary zinc in some controlled feeding studies, but this measure is not considered tremendously reliable for assessing zinc status.\textsuperscript{22}

One other assessment tool that is sometimes employed is hair zinc. This has been used as an initial screening tool for marginal zinc deficiency in children.\textsuperscript{43} If used for this purpose, care must be taken to minimize topical zinc contamination. This is the only documented use of hair mineral analysis, and at that, it is a fragile use in that it has many pitfalls.\textsuperscript{44,45} Nonetheless, some companies charge high fees for unfounded uses of a range of hair mineral analysis.
In conclusion, evaluation of marginal zinc status may often require more than one measurement and always requires attention to what else may be affecting values for the measurements. For research purposes, the best approach is to take measures before and after zinc supplementation.

BIOAVAILABILITY FROM FOODS AND SUPPLEMENTS

Zinc seems to be absorbed best from animal products, though plant sources can provide absorbable zinc. The best known inhibitor of zinc absorption is phytate, a phosphate-containing compound that is particularly high in certain grain products and some beans, including soybeans.

A number of types of zinc supplements are sold. Most multi-vitamin–mineral pills, as well as cereal fortificants, use zinc oxide. Most tests of this complex of zinc, either in humans or other species, have found the absorption to be lower than other zinc complexes. An exception has been for fortification of bread and other wheat products where zinc oxide is reported to be equal to zinc sulfate. However, in this study, both zinc complexes gave a relatively low percent absorption.

Zinc sulfate is a standard form of zinc in experimental animal studies, and it has been used in the past as a standalone zinc supplement. However, current human use is limited mostly to just a few multi-vitamin–mineral supplements. Based on animal studies, absorption of zinc sulfate appears to be superior to zinc oxide.

There are reports of GI tract upset in some people who take zinc sulfate. Zinc gluconate is the most common standalone zinc supplement and is used in zinc lozenges, which are discussed later. In one study, the use of a zinc tolerance test shows zinc gluconate to be better absorbed than zinc sulfate. It can also be noted that zinc gluconate has given positive results in a number of supplementation studies, including some done for malnutrition situations. On the other hand, in a small unpublished study from this author, zinc gluconate was very ineffective at raising plasma zinc, while a zinc amino acid chelate raised plasma zinc in all subjects tested (Figure 5.1). In addition, in a rat supplementation study, neither zinc gluconate nor zinc sulfate was as effective as a zinc–amino acid chelate in protecting against chemically induced oxidant damage. Thus, zinc gluconate seems to be a good source of zinc for many purposes, though in some applications, it may not be the absolute best source.

As just noted, zinc–amino acid chelates are also used as zinc supplements. At present, there is not a lot of data comparing the stability and biological effectiveness of such chelates from different suppliers. Thus, data on one zinc–amino acid chelate may or may not be applicable to a zinc–amino acid chelate from a different source. This author’s laboratory has completed two studies where zinc glycinate from Albion Laboratories has produced positive results, but these studies did not make comparisons with other zinc preparations. On the other hand, the data in Figure 5.1 involves comparison of zinc glycinate with zinc gluconate, where the glycinate shows better activity, though based only on plasma zinc readings. A number of animal studies have shown good effects of one type of zinc–amino acid chelate or another, which, in some cases, have been better than what is obtained from other forms of zinc such as oxide or sulfate. However, in other studies, differences between
FIGURE 5.1 Plasma zinc response to zinc supplementation as gluconate (GLUC) or glycinate chelate (CHE). Young adult females were given 60 mg zinc/day for six weeks. Post-treatment values for the glycinate but not the gluconate were significantly different from pretreatment (p < 0.001, paired t-test).
certain amino acid chelates and zinc sulfate have not been seen. Future research should be done on various zinc–amino acid chelates from different suppliers in regard to absorption and other bioactivities.

Another form of zinc supplement is zinc picolinate. Although zinc picolinate is not used as much as chromium picolinate, this form of zinc has been shown to raise serum zinc and improve taste abnormalities. In an old study, 50 mg of zinc as zinc picolinate, but not as zinc gluconate or citrate, raises urine, erythrocyte, and hair zinc in adult men. However, this study is a little hard to interpret, since none of the three supplements raised plasma zinc, which normally would rise with 50 mg zinc.

Zinc citrate is sometimes used in food fortifications and has been shown to be reasonably well absorbed.

In summary, zinc oxide appears to be the least desirable choice for a zinc supplement. A number of other zinc complexes have been used effectively, though some complexes may be more active in some applications. This last area could use more research.

TYPICAL INTAKES VERSUS NEEDS

Severe zinc deficiency on a large scale in humans was first reported in areas of the Middle East. Although multiple factors may have played a role, a major influence was consumption of unleavened bread, which is high in phytate, which impairs zinc absorption.

Besides dietary causes of severe zinc deficiency, this state can also be produced by a genetic condition where zinc absorption is impaired. This disease, acrodermatitis enteropathica, is recognizable by a skin condition that develops at a very early age. The condition can be treated with supplemental zinc.

Marginal zinc deficiency may occur in many people, though there are still many questions here. One obvious theoretical reason why marginal zinc deficiency could occur would be moderately low zinc intake. Many surveys have found moderately low zinc in different groups. For example, in the U.S., analysis of the third National Health and Nutrition Examination Studies indicates that a substantial number of people in the U.S. do not eat the recommended amounts of zinc. At particular risk are children aged 1 to 3 years, adolescents who eat a lot of low-nutrient-density foods, adolescent females in general, and the elderly, especially but not exclusively in low-income situations. There is also some doubt as to whether the zinc RDA is even accurate (11 mg for adult men, 8 mg for adult women). The RDA has been lowered over the years from the 15 mg that is used for the recommended intake on food and supplement labels. The zinc RDA is based on balance studies (amount of zinc needed to balance losses) rather than on functional indications. The balance approach can be somewhat justified in that there is no clear choice for what to use for zinc functional indicators. Even so, the balance approach to determining the zinc RDA has drawn some questions for a long time.

Besides zinc intake, other factors could also contribute to marginal zinc deficiency. These include impaired zinc absorption, high zinc excretion, abnormal body distribution of zinc (i.e., high levels of one zinc protein pool drains zinc from other
pools), and high needs for certain zinc functions. One or more of these factors are suspected to produce marginal zinc deficiencies in a variety of types of people. Table 5.2 gives a list of some types of people where at least one study has shown this group to be prone to marginal zinc deficiency based on dietary survey or biochemical assessments. The listing of children with Down’s syndrome provides an example where abnormal zinc pool distribution may be a key factor. In this case, such children have an extra copy of a gene that codes for the enzyme copper–zinc superoxide dismutase. Copper–zinc superoxide dismutase can account for a substantial portion of a cell’s content of the metals contained in the enzyme. This is not typical for most metalloenzymes in relation to a cell’s metal distribution, but it is true for copper–zinc superoxide dismutase and these two minerals. The increase in this enzyme in Down’s syndrome may draw zinc away from other functions unless extra zinc is consumed. The same rationale could be applied to copper, but this has not been tested.

Table 5.2 is not meant to be comprehensive but is meant to illustrate the range of people who may be vulnerable. A complete list may grow in the future as more people groups are studied for marginal zinc status.

Table 5.2 lists vegetarians since vegetarian diets are often lower in zinc than are diets that contain meat. In addition, vegetarian diets can be high in factors that reduce zinc absorption. There are also studies showing lower serum zinc values in subjects consuming vegetarian diets. In contrast, there have been some propositions that vegetarians can adapt to the low zinc intake and low zinc bioavailability of some vegetarian diets by reducing zinc excretion and increasing zinc absorption. This could turn a negative zinc balance (zinc losses exceed zinc gains) into a zero balance (losses equal gains). There is evidence that this type of balancing can go on to some extent with variations in zinc intake, but there is not extensive

<table>
<thead>
<tr>
<th>TABLE 5.2</th>
<th>Examples of People Groups Prone to Biochemical Signs or Dietary Zinc Intake Patterns Consistent with Marginal Zinc Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s disease patients</td>
<td>Sickle cell anemia patients</td>
</tr>
<tr>
<td>Renal dialysis patients</td>
<td>Children with Down’s syndrome</td>
</tr>
<tr>
<td>Diabetic individuals</td>
<td>Vegetarians</td>
</tr>
<tr>
<td>Alcoholics</td>
<td>People with hepatitis</td>
</tr>
<tr>
<td>Rheumatoid arthritis patients</td>
<td>Some types of young children</td>
</tr>
<tr>
<td>Young adult females</td>
<td>Middle-aged adult females</td>
</tr>
<tr>
<td>Adolescent/preadolescent girls</td>
<td>The elderly (both genders)</td>
</tr>
<tr>
<td>Some cancer patients</td>
<td>People with AIDS</td>
</tr>
</tbody>
</table>

This listing of people types is meant to provide examples and not be complete. The same is true of references listed for each people type.

* DiSilvestro, R.A., unpublished results based on plasma zinc and 5′-nucleotidase activities in over 80 subjects
characterization of how well it works for different types of vegetarian diets. Even
if overall zinc balance can be maintained in terms of zinc in vs. zinc out, it can be
asked: Are zinc functions maintained adequately during this process of balancing?
Since this question has not yet been answered, it seems wise to this author that
vegetarians should strive to eat the best non-meat sources of zinc (e.g., legumes
and certain grain products) or consider zinc supplementation.

In almost every one of the situations listed in Table 5.2, there is still uncertainty
about how frequently marginal deficiency really occurs. This uncertainty arises
mainly because large groups of people have not been tested thoroughly. There is
also uncertainty about what symptoms, if any, result from marginal zinc deficiency.
The symptoms may vary depending on what else is happening simultaneously. For
example, in someone with diabetes plus marginal zinc deficiency, there may be
increased risk of developing side complications, whereas in children with marginal
zinc deficiency, the most pronounced symptom may be poor growth. The whole area
of marginal zinc deficiency occurrence and consequences sorely needs more
research.

CURRENT RESEARCH ON SUPPLEMENT USE

This section is among the longest in the book because so many different uses have
been considered for zinc supplements. In general, these applications have been given
research attention, though some applications have been given much more than others.
There is still a lot of question as to who should get zinc supplements and what
benefits they would have. Another issue is the dose to use. The doses have varied
considerably in different studies, and dose response curves are virtually non-existent.

OVERT DEFICIENCY CORRECTION IN CHILDREN

This book emphasizes supplement uses other than correcting overt deficiencies.
Nonetheless, it can be stated here that in certain parts of the world, where economics
limit food choices, the effects of zinc deficiency can be clearly seen in children.³
Zinc supplementation has been used successfully to treat zinc deficiency in a number
of settings. One example is protection against diarrhea in children.⁵ Six The possible
uses of zinc supplements for treating severe zinc deficiency requires more research
as to where supplementation is most needed, identification of the full range of
benefits of zinc supplementation, as well as the pros and cons of supplementation
vs. diet changes or food fortification.

CORRECTION OF MARGINAL ZINC DEFICIENCY IN YOUNG CHILDREN

Some classic examples of documented marginal zinc deficiency involve studies done
some time ago by Krebs and Hambidge on children in Colorado, U.S. These studies
are summarized below:

• Children are identified who have low values for hair zinc who also have
  anorexia, poor growth, and poor taste sensitivity.⁹³
• In young children with evidence of mild zinc deficiency, zinc supplementation improves food intake.81
• In children with low growth percentiles, zinc supplementation improves growth.82
• Intake of a zinc-fortified food product increases plasma and hair zinc values.94
• In children with pica, a rapid improvement follows zinc supplementation.95

There have also been studies by other investigators suggesting that zinc supplementation can improve growth in short children with marginal zinc deficiency.96,97,98
In one of these studies, the effect is most pronounced when treatment includes iron supplementation.96

Other work concerning marginal zinc deficiency and zinc supplementation in children has concerned possible connections to physical activity maturation, motor development, and cognitive function development, particularly in the area of neuropsychological processes. These studies have not been extremely extensive yet, and the results have been conflicting.99,100 This inconsistency is not terribly surprising considering all the potential nutritional and non-nutritional variables that can influence these health effects. In addition, in these studies, there can be variations in assessment methodology, the choice of zinc complex and dose, subject age range, and other variations. In this author’s opinion, it is safe to say that some children would probably be helped in these areas by increasing their zinc intake via diet or supplementation. However, there is just no good clinical practice yardstick to say who these children are and how much zinc they should get. Even so, this author feels that clinicians and community public health specialists should be more aware of the possibility of marginal zinc deficiency in children. This author recommends the use of hair and serum zinc monitoring in individual patients or in populations that show poor growth. Despite the limitations of these methods in diagnosing marginal zinc deficiency, more often than not, low values would likely be informative about children who have no other severe health problems.

**Selected Breast-Fed Infants**

Some infants who are exclusively breast fed can develop symptomatic zinc deficiency. In these situations, the deficiency seems to result due to a defect in transfer of zinc from maternal serum to breast milk.101,102 Supplementation with zinc is a practical means for addressing this problem. In addition, an appropriate solid food introduction strategy should be adopted.

**Premature Infants**

Premature infants can show biochemical signs of zinc deficiency such as low serum zinc values both right after birth and during growth spurts in the first year post-birth.103–107 The cause may be similar to that which may occur for premature infants with iron and copper deficiencies. Specifically, premature birth cuts out the latter
stages of pregnancy where the inborn baby stores substantial amounts of zinc. These stores are supposed to meet much of the zinc need for the first six months or more past birth. If a child is born prematurely, the time to build these stores is eliminated or minimized, which can result in some degree of zinc deficiency. Although signs of some degree of zinc deficiency are found in premature infants, there are two major questions connected with this issue. One, what percent of premature-born children actually have substantial problems with zinc deficiency? Two, what physiological consequences are associated with this deficiency? Unfortunately, not enough research has been directed toward these questions. One exception is a recent study reporting a zinc-induced increase in linear growth at six months corrected postnatal age, along with higher serum zinc and serum alkaline phosphatase activities.\textsuperscript{108}

**IMMUNE FUNCTION**

Immune function can affect resistance to classical infectious diseases as well as resistance to other problems such as cancer and stroke.\textsuperscript{109,110} In rats and mice, immune function seems to be especially sensitive to marginal zinc deficiency.\textsuperscript{3} Therefore, one could expect that indices of immune function would be among the easiest measures to change with zinc supplementation. Consistent with this idea, a number of studies of zinc supplementation have shown improvements in one aspect or another of laboratory assessments of immune function. These are summarized in Table 5.3. It should be noted that many of the measurements in these studies are biochemical or cellular, such as changes in readings for immune regulatory molecules, cell populations, antibody titers, short-term vaccine responses, and blood cell secretion rates of specific molecules \textit{ex vivo} (rates assessed after blood removal from the zinc-supplemented subjects). These measurements, though very important, cannot always be translated into a quantitative assessment of how zinc supplements would affect more practical outcomes such as infection incidence, protection against cancer onset or reoccurrence, impact on stroke risk, and so on.

**TABLE 5.3**

Subject Types where Zinc Supplementation has Improved Measures of Immune Function

<table>
<thead>
<tr>
<th>Down's syndrome children\textsuperscript{114,115}</th>
<th>Renal dialysis patients\textsuperscript{10,117}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burn patients\textsuperscript{112}</td>
<td>The elderly\textsuperscript{106,118}</td>
</tr>
<tr>
<td>Cancer patients\textsuperscript{62,119}</td>
<td>Sickle cell patients\textsuperscript{71,111}</td>
</tr>
<tr>
<td>People with AIDS\textsuperscript{45}</td>
<td>Rheumatoid arthritis patients\textsuperscript{120}</td>
</tr>
<tr>
<td>Preschool children\textsuperscript{55}</td>
<td>Low birth weight infants\textsuperscript{135}</td>
</tr>
<tr>
<td>Alcoholics\textsuperscript{121}</td>
<td></td>
</tr>
<tr>
<td>Men with experimentally induced marginal zinc deficiency\textsuperscript{122}</td>
<td></td>
</tr>
</tbody>
</table>

People groups listed and references used are representative and not exhaustive.
However, there are a number of studies that do look at practical consequences. In one such study, which involved sickle cell anemia patients, zinc supplementation has practical impacts on immune health including decreased incidence of documented bacteriologically positive infections. Although the number of subjects was not tremendously large, these results merit follow-up. In another study, zinc supplementation of burn patients produced a significant decrease in the number of bronchopneumonia infections. In yet another study, low-birth-weight infants in Brazil showed a reduction in the prevalence of cough in response to zinc supplementation. More on zinc and Down’s syndrome is presented in the Down’s Syndrome subsection.

Thus, these studies suggest that zinc supplements can have good effects on immune function in a variety of people. Nonetheless, research in an area like this normally has to become very extensive before a general consensus is reached that a given intervention should be a standard procedure. It should also be noted that not all studies of zinc supplementation have shown effects on immune function, even in subjects that seem to overlap those of Table 5.3. Three reasons for the inconsistency could be the starting zinc status of the subjects, the dose used (high doses of zinc can be immunosuppressive; see the Toxicity section), and the type of immune parameter measured. In the latter regard, some aspects of immune response should be more apt to respond to zinc than others. As far as starting zinc status goes, it is noteworthy that the subject types listed in Table 5.3 are generally also listed in Table 5.2 as groups prone to marginal zinc deficiency. Therefore, it would be simple to conclude that zinc supplements tend to help with immunity when there is a degree of zinc deficiency, and do not help when there is not any deficiency.

However, there are two problems with this simple conclusion. One, not all studies of zinc supplements and immunity have monitored overall zinc nutritional status. Therefore, to state that starting zinc status affects response to zinc supplements is an assumption, not a confirmed conclusion. Moreover, there is at least one study reporting that zinc-replete subjects can respond to zinc supplementation with boosted immunity based on vaccine response. However, this study must be interpreted cautiously in terms of “zinc replete,” since the study makes that assertion based solely on normal range serum zinc values. Serum zinc is not always an infallible indicator of marginal zinc deficiency.

The studies showing zinc supplementation and improved immune function in cancer patients are still extremely limited in scope. One study was done in China on a group of subjects whose zinc status is very uncertain in comparison to other parts of the world. Another study involves a small group of lung cancer patients, which may or may not have applicability to a broader cancer patient population. Whether or not zinc supplements can safely improve immunocompetence in a large percentage of cancer patients, undergoing various types of treatments, is still a very underdeveloped research area.

The benefits of zinc supplementation on immune function, or on other aspects of health in alcoholics, has not been studied extensively. An old, small study does
report an improvement in one parameter of immune function with high-dose zinc supplementation. One problem with studying alcoholics and zinc is that cytokine metabolism can be abnormal in alcoholics, which can alter serum zinc values. This could explain why low serum zinc values do not always respond to zinc supplementation.

**Down’s Syndrome**

As noted above, Down’s syndrome is associated with an extra copy of a gene that codes for a protein that can account for a good deal of a cell’s zinc. This could rob other zinc pools of this metal unless moderately high zinc levels are consumed. There may be other zinc metabolism abnormalities as well in this population.

Quite a few studies report a beneficial effect of zinc supplementation in people with Down’s syndrome. These benefits are not a cure of the disease, but include the above-noted improved immune function, as well as enhanced DNA repair, and desirable hormonal changes, especially for thyroid hormones. It can be pointed out that trials with larger numbers of subjects would be useful. However, some would argue that there is already enough data to justify clinical use of low-dose, long-term zinc supplements in Down’s syndrome. On the other hand, there has been a letter to the editor in one journal cautioning that zinc supplements in Down’s syndrome could increase the risk of later Alzheimer’s disease. However, the link between zinc and this problem is still very debatable from a physiology standpoint, and not studied at all from a nutrition standpoint (see the Toxicity section). In addition, the above-mentioned letter drew a response letter that argues that zinc may help people with Down’s syndrome lower Alzheimer’s disease risk.

One drawback of routine use of zinc supplements in Down’s syndrome could be an antagonism of copper absorption. Although low doses of zinc should not bother copper function in copper-adequate people, much less is known about the effects in people with marginal copper deficiency. Down’s syndrome patients probably fall into this category, though this has not been checked by research. However, the theoretical reason to expect copper deficiency is strong. The zinc protein that is over-expressed in Down’s syndrome is superoxide dismutase 1, which also contains a high percent of a cell’s copper content. One objection to the Down’s syndrome–copper deficiency hypothesis is that serum copper values are high in some studies of Down’s syndrome. However, it should be noted that under some circumstances, serum copper can be high despite some degree of copper deficiency. Thus, the best mineral treatment for Down’s syndrome may be a modest dose of zinc plus a modest dose of copper, with both minerals given as well-absorbed complexes. However, before this can be recommended, the copper status and metabolism of Down’s syndrome patients needs to be evaluated to determine that copper supplements would do no harm.

**Macular Degeneration**

A number of years back, a pilot study was presented suggesting that zinc supplementation could slow macular degeneration, the leading cause of blindness in the
Although the study design may have had some limitations, as pilot studies often do, the study drew considerable attention to the possible relationship of zinc and eyesight loss. One difficulty in studying macular degeneration is the slow progression of eyesight loss. A lengthy research project, known as the AREDS study (Age-Related Eye Disease Study), finished recently. In this work, subjects were given either placebo, zinc plus copper, an antioxidant vitamin cocktail, or zinc/copper + the cocktail for five years. Modest effects on eyesight protection are reported for either the zinc or antioxidant treatments in a study subpopulation, with a little better response with the combination treatment. Possibly, the effect would have been better with an even longer study, but obviously, the length previously used already required a large commitment of funds and professional time. Another concern about the AREDS study is the use of a high dose of zinc oxide rather than a lower dose of a better absorbed form of zinc. In addition, the antioxidant cocktail used in conjunction with zinc may not have been the optimal preparation. It would be interesting to see the results of an upgraded study, but due to the time and money needed, we may not ever see such a study.

Acne

Zinc has been tried both orally and topically for treatment of acne. One might assume that the oral zinc would treat acne by correcting a marginal zinc deficiency. This assumption would derive from the fact that the genetic zinc deficiency noted earlier is characterized by a dermatitis-like condition. However, there is not a lot of direct evidence that more moderate forms of zinc deficiency can produce skin problems such as acne. In one study, subjects with the most advanced acne in the study group had lower mean serum zinc than other subjects in the study. However, this could be as much a marker of inflammation as of zinc status. Thus, any effectiveness of zinc against acne may or may not be limited to correction of a deficiency. An alternative basis for zinc in acne treatment could be an anti-inflammatory effect due to an above-adequate zinc intake.

A number of studies have found that zinc supplements can reduce acne, particularly inflammatory acne. In most cases, the zinc doses are high, which is consistent with an anti-inflammatory effect. This approach has drawn some concern because high-dose zinc can cause copper deficiency. Indeed, a number of the case studies of high-dose zinc supplements causing copper deficiency involve people who were trying to treat acne. However, the idea that zinc doses must be extremely high to treat acne may be flawed. At least one study reports effectiveness with just a moderately high zinc gluconate dose (30 mg zinc/day). Despite some observations suggesting that zinc can treat acne, it is still debatable as to whether the effect is better than, or even equal to, alternative treatments. In addition, since many of the studies with positive results for zinc tend to emphasize inflammatory acne, zinc’s effectiveness on acne may not be as good with other types of acne.

Besides oral zinc use for acne, topical use has been considered. This use, since it is not a supplement issue, is not covered here.
WOUND HEALING

There is no question that severe zinc deficiency impairs wound healing, possibly via multiple mechanisms. However, it is less clear if oral zinc supplements can help wound healing by correcting marginal zinc deficiency, or if zinc can have benefits beyond correcting deficiency. Much of the support for recommending zinc supplements for wound healing have come from topical zinc applications, which may not be relevant to oral supplementation. Some other support has been derived from an old study on young men with wounds caused by excision of pilonidal sinuses. This study reports that zinc helps subjects who have low serum zinc. In addition, there are some studies on zinc and certain types of ulcerations. A meta-analysis concludes that while oral zinc sulfate does not appear to aid healing of leg ulcers, it might be beneficial in those with venous leg ulcers and low serum zinc. These two considerations have led to the attitude that zinc supplements help with wound healing, but only in people with some degree of zinc deficiency. Unfortunately, this conclusion has been built on relatively little data. For one thing, the venous ulcer data may not be relevant to other types of wound healing. Moreover, the older study has not had confirmation. Furthermore, even if zinc is effective for wound healing when there is low serum zinc, this could reflect that effectiveness is tied not to poor zinc status, but rather the presence of inflammation, which can also depress serum zinc.

In this author’s opinion, we still know very little about any of the following:

- The degree of zinc deficiency necessary to impair wound healing
- Whether zinc supplements can help with wound healing in the absence of any deficiency
- What range of wound types might be helped by zinc supplements

This sort of uncertainty is echoed in an opinion article that appeared awhile ago in the journal Lancet. Although a number of years have passed since that article appeared, not much new research has occurred in this area.

In this author’s opinion, since low-dose zinc supplementation probably won’t hurt healing, such supplementation is reasonable in people recovering from wounds. On the other hand, high-dose zinc supplements would not be a good idea because of possible antagonism of the absorption of copper, which is also needed for wound healing.

ZINC–CARNOSINE AND ULCERS

This particular zinc complex has been proposed for use in the healing of gastric ulcers. The strategy is that complexing zinc with carnosine delays exit of zinc from the stomach and also sticks zinc to the ulcer. This retained zinc, being anti-inflammatory, can promote healing of the ulcer (the carnosine itself may also have anti-inflammatory effects). The anti-ulcer activity has been tested in experimental animals and in a whole series of clinical trials in Japan, though finding the publications can be challenging. Some of the results are mentioned in a review.
This author has read reports of these studies. In his opinion, the design of these studies for zinc–carnosine and ulcers is not always spelled out well in the reports, and some have questionable aspects of design. Nonetheless, the sheer number of subjects, the impressiveness of the reported efficacies, and the multi-site nature of the studies all suggest that the potential anti-ulcer efficacy of zinc–carnosine should be taken very seriously. Even so, a new, well-controlled clinical study would be useful to see if the anti-ulcer use of zinc–carnosine can be confirmed.

RHEUMATOID ARTHRITIS/CROHN’S DISEASE

Although zinc can stimulate immune function, it can also suppress some aspects of the immune system relevant to oxidant stress and inflammation. In addition, zinc could conceivably help with inflammation via the other indirect antioxidant effects of zinc (Table 5.1). This leads to the logical question: Are zinc anti-inflammatory actions of any value in arthritis or Crohn’s disease, either for correction of marginal zinc deficiencies or for pharmacological purposes? The answer is that we don’t know. As far as correction of a marginal deficiency in arthritis, there is some limited evidence that marginal zinc deficiency may be common in people with rheumatoid arthritis. First, low-serum zinc has been reported for people with rheumatoid arthritis, though this could just be due to cytokine release, which can lower plasma zinc via regulatory mechanisms. In fact, in one study of human arthritis, serum zinc correlates inversely with serum values for two cytokines.

On the other hand, there is a study that, based on a zinc tolerance test and urinary zinc, implies that rheumatoid arthritis patients may be prone to marginal zinc deficiency. However, as noted above, these methods are not overly confirmed means of assessing zinc status. On the other hand, based on zinc metabolism and inflammation in rats, one could make a theoretical argument that inflammation, as occurs in arthritis, raises dietary zinc requirements. In rats, inflammation greatly increases the amount of the zinc-binding protein metallothionein in the liver and other tissues. It can be reasoned that since this increased metallothionein becomes the largest zinc pool in tissues, zinc will be pulled from other pools unless dietary zinc is moderately high. Although this idea makes sense, it has not been confirmed directly, even in rats.

If zinc needs are raised by arthritis, this could be especially problematic if zinc intake is also moderately low. Indeed, one paper finds that rheumatoid arthritis patients in New Zealand tend not to eat even the amount of zinc recommended for healthy people. The same is true for a study of similar subjects in the U.S.

If marginal zinc deficiency is common in people with rheumatoid arthritis, then what would be the benefits of correcting it? One possibility is that the primary symptoms of arthritis may diminish, particularly if combined with other therapy. Another possibility is that other aspects of health would be improved. Unfortunately, neither of these possibilities has been tested very much. For the second possibility, two studies have been done. In a very small study (five subjects), which is not placebo controlled, supplementation with beta-alanyl-L-histidinato zinc improves some, but not other, parameters of bone health. In another study, zinc supplementation improves one measure of cellular immune function, though in the authors’
own words, the clinical importance of this effect is unknown. Therefore, in people with rheumatoid arthritis, the possibility that zinc supplementation correction of marginal zinc deficiency helps with primary or secondary symptoms is interesting, but very much untested.

In addition to correcting marginal zinc deficiency, zinc supplements may also have a benefit for arthritis from a pharmacological perspective. This case could be made by noting the following:

- High doses of zinc can certainly be anti-inflammatory in animals. 50,14
- Topical zinc has been anti-inflammatory for ulcers in humans. 148
- Oral zinc–carnosine appears to have anti-ulcer activity, 155 which is a type of anti-inflammatory effect.
- An old pilot study reports that very high-dose zinc supplementation can cause some clinical improvement in rheumatoid arthritis patients. 163

The last study is counter-balanced by a small study with zinc sulfate, which does not show long-term improvement in rheumatoid arthritis patients. 52 Thus, at present, despite some background rationale, the following question still remains: Can high-dose zinc supplementation provide a safe treatment that can exceed or extend what is already accomplished by current therapies? This question has simply not been answered yet.

The same questions about zinc supplementation and arthritis can also be asked about Crohn’s disease. However, compared to the situation with rheumatoid arthritis, marginal zinc deficiency seems to be a little more established for Crohn’s disease. 164–167 In Crohn’s disease, zinc status would not only be influenced by inflammation effects on body zinc distribution, but in some subjects, there is also impaired zinc absorption. 158,169 Even so, not all reports on zinc status in Crohn’s disease consistently find evidence of marginal zinc deficiency in all patients. 170,172,173 Studies on zinc supplementation in people with Crohn’s disease are limited. One study shows a supplementation-induced rise in two markers of zinc status. 171,175 In addition, a project is nearing completion in this author’s laboratory on zinc supplementation in Crohn’s disease.

In conclusion, there is a basis to suspect that marginal zinc deficiency occurs in some people with rheumatoid arthritis or Crohn’s disease. The possible benefits of correcting these marginal deficiencies is not yet well tested, nor is the possible value of zinc pharmacological treatments.

CANCER PREVENTION

Two zinc actions, antioxidant effects and immunostimulation, are consistent with cancer risk reduction. Furthermore, epidemiologic studies and some experimental animal work suggest that some degrees of zinc deficiency may be associated with increased risk of some types of cancer. 172 Of particular interest are two epidemiology studies showing an inverse relationship between zinc intake and skin cancer. 173,174 What makes these studies particularly interesting is that they cover two different countries, do not involve overt malnutrition, and do not show a relationship for most
other nutrients tested. However, these results are somewhat confusing in light of a paper reporting high serum zinc values in melanoma patients.\textsuperscript{175}

Unfortunately, further consideration of zinc–cancer risk via supplement studies has not yet developed. The few zinc supplement intervention studies in this area have used zinc in combination with other micronutrients, which makes the results difficult to interpret.

**Exercise**

Strenuous exercise alters zinc metabolism,\textsuperscript{176} but this does not necessarily mean that strenuous exercise raises zinc nutritional needs. For example, serum zinc can be depressed by strenuous endurance exercise, but such depressions can simply be an inflammatory response.\textsuperscript{6} There are various reports saying that zinc nutritional status may or may not be compromised in a number of types of endurance athletes or other people who engage in strenuous exercise.\textsuperscript{176} However, most of these studies are based on serum, sweat, or urine zinc, which are not always a reliable means of assessing zinc nutritional status. Also, some of the studies\textsuperscript{176} focus on very specific types of people, where the results may or may not apply to other circumstances. Thus, at present, it is hard to say whether exercise influences zinc needs.

There are a lot of functional reasons why good zinc status or extra zinc might influence exercise performance. These include antioxidant and anti-inflammatory actions (which can enhance muscle recovery), hormonal effects, energy substrate utilization, cell signaling, and others. There has also been speculation that poor zinc status combined with habitual strenuous exercise has particularly negative effects on immune function and bone health. However, at present, we simply don’t know whether zinc supplements can actually be of major help for exercise performance, or help with immune function or bone health in exercisers. There is one study of acute supplementation with zinc before exhaustive running.\textsuperscript{177} There is no effect noted for some metabolic and endocrine responses. In contrast, short-term zinc supplementation does show some effects on blood flow properties and exercise tolerance in submaximal evidence in 10 men.\textsuperscript{178} In another small study (five subjects), zinc plus copper supplementation lowers postexercise activation of phagocytes, a process that leads to oxidant stress.\textsuperscript{179} Even so, a lot more subjects, types of settings, and measures need to be done before making any big conclusions on zinc supplements and exercise.

A current popular supplement for exercise is “ZMA,” which contains zinc, magnesium, and vitamin B\textsubscript{6}. A meeting abstract reports some benefits for ZMA in exercise performance,\textsuperscript{180} but more detailed reports will be needed to evaluate these findings. Some Internet sites claim that other research backs up this product, but the research cited is not specific to ZMA. Rather, the research deals with zinc function in general or zinc supplements in contexts that may not be relevant to the people most apt to use ZMA.
Hepatitis

Mild zinc deficiency makes rats highly vulnerable to chemically induced liver injury,\textsuperscript{159,181} while pharmacological zinc injections have the opposite effect.\textsuperscript{182} The relevance of the latter to human hepatitis situations has never been tested. As far as marginal zinc deficiency, there is evidence that it may occur frequently in at least some forms of hepatitis. This evidence for marginal zinc deficiency is low serum zinc in hepatitis patients,\textsuperscript{183,184} low serum 5'-nucleotidase activities in subjects with fulminant hepatitis,\textsuperscript{185} low values for zinc tolerance test in one category of liver damage (though not in another),\textsuperscript{186} elimination of a skin lesion with zinc supplementation in a few patients with hepatitis C (not a controlled study),\textsuperscript{187} hepatic liver content that decreases as severity of hepatitis increases,\textsuperscript{188} and low polymorphonuclear cell zinc contents in certain hepatitis patients.\textsuperscript{189}

Although this seems like an impressive list, the evidence is not all that tight. Many of the studies use small subject numbers, the serum zinc results can be explained by regulatory factors unrelated to zinc nutritional status, and the designs are not always ideal. Nonetheless, the range of the studies noted in the previous paragraph at least raise the possibility that many people with some forms of hepatitis have a degree of zinc deficiency. This idea is reinforced by a very interesting study in hepatitis C patients.\textsuperscript{190} A group of responders and non-responders to interferon therapy are examined for serum zinc and liver metallothionein. The responders have higher serum zinc and most show therapy-induced increases in liver immunoreactive staining for metallothionein (non-responders show a decrease). Since in rats, metallothionein induction by several agents can be inhibited by even moderate zinc deficiency,\textsuperscript{159,181} the work in humans on interferon therapy\textsuperscript{190} suggests that responders have better zinc status than non-responders. In fact, interferon induction of metallothionein could possibly be a mechanism by which this therapy works. If that is the case, then adequate zinc status would be needed for the therapy to be effective. This idea is supported by a study in which zinc supplementation enhances the response to interferon therapy in certain patients with intractable chronic hepatitis C.\textsuperscript{191} The effect of zinc supplementation by itself is not reported.

In summary, zinc status may be compromised in many people with hepatitis (though the data is not airtight), zinc supplementation helps some hepatitis C patients respond to interferon therapy (at least based on limited study), and mild zinc deficiency and pharmacological zinc affect hepatitis in rat models (but similar studies have not been done in humans).

Osteoporosis Prevention

In principle, zinc can affect bone via multiple mechanisms, which include:

- Enzymatic roles in bone matrix structure\textsuperscript{192}
- Regulatory stimulation of bone formation and inhibition of bone resorption\textsuperscript{3}
- Cofactor role in alkaline phosphatase, a key enzyme in bone synthesis\textsuperscript{3}
• Stimulation of the production of hormones like IGF, which influence bone health

• Antioxidant actions (Table 5.1) (bone resorption is stimulated by certain oxidant stress)

Although this is an interesting area for future research, there are just a few studies as to how much variations in zinc intake or zinc supplementation affect osteoporosis risk. In one such study, dietary zinc supplementation correlates with IGF values in postmenopausal women, and IGF increases with zinc supplementation. In other work, in healthy adult males in Belgium, zinc supplementation increases blood activities of alkaline phosphatase as well as bone-specific alkaline phosphatase, which is involved in bone synthesis. However, this study is hard to interpret for the following reasons:

• Values for a urine marker of bone resorption are unaffected.
• Young adult men in meat-eating communities tend to be in good zinc status.
• Bone metabolism tends to be problematic in fewer young adult men than women.
• The changes in blood readings for bone-specific alkaline phosphatase are hard to interpret because blood activities should go up with better zinc activation but down with better bone synthesis (less release into the blood).

There are a couple of other positive studies for zinc on bone-related measures, but neither presents a totally clear picture. In one case, as noted earlier, a particular zinc complex, usually used for ulcers, had beneficial effects on some but not other measures of bone health in a group of arthritis patients. However, the subject number is very small, there is no placebo control, and the zinc complex used may have specific pharmacological actions beyond zinc status impact. In the other study, bone loss in healthy older postmenopausal women is reduced by calcium plus a zinc-inclusive trace element cocktail. Although this is interesting, it is hard to know what role is played by any of the individual minerals.

There is also at least one study with a negative finding for zinc supplementation and bone health. In pubertal girls, supplementation with 15 mg of zinc as citrate has no effect on serum IGF nor on a urinary measure of bone resorption.

Therefore, at present, although zinc has a possible theoretical role in preventing osteoporosis, practical research in this area has barely begun.

RENSAL DIAIYSIS PATIENTS

Renal dialysis patients seem prone to some degree of deficiency for a number of nutrients due to low intakes or high needs. Low serum zinc values have been reported for dialysis patients in a number of studies. This could indicate a tendency toward marginal zinc deficiency, but it could also just indicate inflammation, which can lower serum zinc independently of zinc nutritional status. The former explanation is supported by the results of zinc tolerance tests in renal dialysis patients.
There have been papers reporting an inverse correlation between serum zinc and some other factor such as antibody response to immunization. The papers typically interpret this to mean that zinc status is a major factor in determining health in dialysis patients. However, subjects with the lowest serum zinc may simply be those with the most inflammation, which could mean those with the worst overall health. Thus, at this point it is hard to say if zinc status has a major impact on health in dialysis patients. Nonetheless, there are some supplementation studies that lend credibility to the idea that zinc status is a problem in many dialysis patients.

In one such study, zinc is administered to a small group of patients in the lowest 30th percentile for serum zinc among a group of dialysis patients. The administered zinc raises serum alkaline phosphatase, which can be an indicator of zinc status in some situations. In other work with hemodialysis patients, zinc supplementation decreases osmotic fragility and lipid peroxidation, which are two symptoms of zinc deficiency in rats. In still another study of renal dialysis patients, zinc supplementation increases the protein catabolic rate. There are also studies in this same type of subjects showing that zinc supplementation can increase serum thyroid hormone levels and have various positive effects on immune function. For example, zinc administration improves lymphocyte function in a way that seems to be mediated by increased intracellular ATP. In addition, an old study finds that zinc supplementation can improve gonadal function in dialysis patients. Furthermore, zinc supplementation in dialysis patients improves food intake and serum cholesterol readings.

In light of the above studies, zinc supplementation would appear to be beneficial for at least some dialysis patients, but that conclusion is not totally clear. Some of the above-mentioned studies do not have a large number of subjects, and there are other studies where zinc supplementation does not show an intended benefit. In some of the negative studies, questions can be raised about design. For example, one study looks for an increase of zinc in the leukocytes and an enhanced response to a vaccination. However, leukocyte zinc in people with health problems is not always very informative since there are frequent variations in leukocyte subpopulations, which vary greatly in their zinc concentrations. In addition, the subject number is low in this study. Furthermore, the zinc administration protocol consists of adding zinc chloride to the dialysate. Zinc chloride may not be an ideal complex for this means of zinc delivery. In fact, in this study, serum zinc is not elevated, which would be expected if the administered zinc was retained well. Nonetheless, one cannot simply dismiss the negative findings of this or some other studies without further new studies.

In this author’s opinion, there needs to be a study that evaluates different types of dialysis patients (varying ages, dialysis treatment type, medications, other complications, dietary practices, etc.). This study should include various indicators of zinc status before and after zinc supplementation. If such a study demonstrates marginal zinc deficiency in a high percentage of the patients, then various doses of zinc supplementation should be tested for effects on health parameters such as immune function and hormonal make-up. This examination should be done in both the subjects that appear to be zinc deficient and in subjects with the best zinc status.
This will determine what benefits are associated with correcting zinc deficiency, and if zinc can have any benefits apart from such correction.

In the meantime, in the absence of such a study, it seems that a low-dose zinc supplement may help some people on dialysis without posing a risk. The one red flag here is that one study finds high erythrocyte zinc in dialysis patients. If this is some sort of toxic reaction, then zinc supplementation may be problematic. On the other hand, the high erythrocyte zinc may just reflect abnormal blood cell metabolism. There could be a high number of erythrocytes at a cell age where they accumulate more zinc. Alternatively, some abnormal physiology in dialysis patients may elevate erythrocyte levels of a zinc-accumulating protein such as metallothionein. In that case, increasing zinc intake may help fill non-erythrocyte zinc pools depleted by zinc movement into the erythrocyte. Based on general trends in zinc metabolism, this author feels that the high erythrocyte zinc contents in dialysis patients is not a good reason to avoid low-dose zinc supplementation. Even so, this author would like to see some study of erythrocyte zinc metabolism in dialysis patients.

**CARDIOVASCULAR DISEASE**

In terms of the two most common evaluators of cardiovascular disease risk, blood pressure and blood lipid profiles, zinc has not been given much attention as a cause of problems. On the other hand, there is a little bit of work suggesting that some drugs given for hypertension may tend to compromise zinc status. However, this is not the same as saying low dietary zinc can cause or aggravate hypertension (though there is one recent study in rats along these lines). If zinc does affect risk of cardiovascular disease, most of the effect is likely to be due to actions other than lowering blood pressure or serum lipid values. Alternative actions could include the indirect antioxidant actions of zinc (Table 5.1), which can restrict inflammation, which is thought to contribute to atherosclerosis. Certain immunosuppressive actions, such as restricting cytokine actions, could also work against cardiovascular-relevant inflammation. These anti-inflammatory actions may be especially useful for protecting against endothelial integrity and for inhibiting lipoprotein oxidation, an initiator of atherosclerosis. A zinc effect on the former has been demonstrated in cell culture work, which the latter has been shown to be dramatically affected by mild zinc deficiency in rats. Zinc function may also be important to maintaining cardiac muscle integrity. Along these lines, one study suggests that zinc status is poor in subjects with dilated or hypertrophic cardiomyopathies. Unfortunately, the subject number in this study is small and bases zinc status on zinc in the urine, plasma, and erythrocytes, none of which are among the best ways to identify marginal zinc deficiency (see Nutritional Status Assessment). Nonetheless, the study is interesting and merits follow-up.

There have been two studies on zinc supplementation and lipoprotein oxidation, neither of which finds any effect. However, neither study holds the last word on the subject. In one study, which is from this author’s laboratory, the zinc supplementation period (three weeks) may have been too short to see an effect. The subjects are type 2 diabetic women in poor glucose control, which show very bad
zinc status based on plasma zinc and 5′-nucleotidase activities. The supplementation treatment does not fully restore adequate zinc status based on the latter parameter (which increases but does not normalize) in the subjects. Thus, the lack of effect on lipoprotein oxidation may require a better improvement in zinc status. In the other study, young healthy men are examined, which may mean that zinc status was already good before supplementation.

In summary, zinc status may affect risk of cardiovascular disease primarily via mechanisms that don’t involve lowering blood pressure or serum lipid values. However, the extent to which zinc status typically affects risk is still very uncertain.

**Diabetes**

Type 1 and type 2 diabetes increase urinary zinc losses. In addition, based on a rat study, diabetes pushes relatively large amounts of zinc into certain pools, which may increase the amount of zinc needed to fill other pools. These effects of diabetes would be expected to make people very vulnerable to some degree of zinc deficiency. Indeed, there are signs of marginal zinc deficiency in diabetic subjects. However, the work in this area cannot be called exhaustive nor 100% consistent. Some questions that are not completely answered are:

- What percentage of people with diabetes have some degree of zinc deficiency?
- Does glucose control affect the tendency toward zinc deficiency?
- Do factors such as gender and disease treatment affect the tendency toward zinc deficiency?
- What health consequences accompany marginal zinc deficiency in diabetes?

One way of answering the last question is to see what happens when marginal zinc deficiency is reversed by zinc supplementation. As noted earlier, this author’s laboratory has done one such study. Three weeks supplementation with 30 mg of zinc as glycinate, but not placebo, raises plasma zinc and plasma activities of the zinc enzyme 5′-nucleotidase in 20 type 2 diabetic, postmenopausal women. However, the latter increase, though substantial, does not bring activities back to normal. As noted earlier, the zinc supplementation in these subjects does not affect lipoprotein oxidation, but this could be due to the short supplementation duration, which may not have normalized zinc status. An interesting effect is noted for insulin-like growth factor values, which are compressed by zinc treatment (low values increase and high values decrease).

In another study, short-term zinc administration IV decreases cortisol levels in type 1 diabetic subjects, but does not change blood glucose readings. In a different study of type 1 diabetic subjects, zinc supplementation decreases lipid peroxidation readings, an indicator of oxidant stress. A similar effect is noted for zinc supplementation in type 2 diabetic subjects in Tunisia. In that study, zinc does not change glucose homeostasis.
Obviously, these studies are just the start of what could be done in the way of trials of zinc supplementation in diabetes. The very early work suggests that zinc supplementation does improve zinc status, does not affect the primary glucose defect, has antioxidant effects, and may normalize some hormone abnormalities. Much more research can be used in this area.

**Pregnancy**

In experimental animals, adequate zinc is known to be essential for the normal growth and development of the fetus. On the other hand, studies of zinc supplementation in women living in industrialized countries have yielded mixed results. For example, a pair of studies by Tamura's group examines supplementation with 25 mg zinc in the second half of pregnancy in women of low socioeconomic status with low plasma zinc concentrations. In the offspring, supplementation increases birth weight and head circumference, but not neurologic development at age 5. In another study, in urban poor women in the U.S., low intake of dietary zinc in early pregnancy is associated with over a threefold increase in the risk of very preterm delivery.

In less-developed countries, the degree of marginal zinc deficiency may be greater on average than that seen in more industrialized countries. A recent review discusses preliminary findings of eight randomized, controlled intervention trials performed in less-developed countries. These studies indicate maternal zinc supplementation has a beneficial effect on neonatal immune status, early neonatal morbidity, and infant infections. The results are more conflicting for labor and delivery complications, gestational age at birth, and fetal neurobehavioral development. In another study, prenatal supplementation with zinc in poor women from Bangladesh does not confer benefits on infants’ mental development. In contrast, in a study of Nepalese pregnant women with low serum zinc, zinc supplementation enhances the effect of vitamin A in reducing night blindness. However, the presence of night blindness suggests that there is more than marginal problems with zinc deficiency and nutrition in general. There has also been a study in India showing a beneficial effect of zinc supplementation on hematological indexes in pregnant women. Again, these studies may involve women with fairly substantial zinc deficiencies.

Unfortunately, these studies do not present a clear picture of which pregnant women would benefit from zinc supplementation and the potential benefits. Another issue is that in some situations, zinc supplements might only produce benefits in conjunction with increased intake of other nutrients. Thus, clinicians and public health professionals are not left with a clear mission in terms of zinc supplementation and pregnancy. In countries like the U.S., a clinician can prescribe a prenatal supplement that includes zinc, but the zinc is usually the poorly absorbed zinc oxide.

**Zinc Lozenges and Colds**

Exactly why a zinc lozenge should be effective for treating or preventing colds is not clear. At first glance, the rationale for zinc and colds may seem to be an
improvement of immune function by correction of marginal zinc deficiency. However, in that case, a lozenge would not be an improvement over a zinc pill. Alternatively, a lozenge might seem to be good at generating a high local concentration of zinc at the site of potential nasal infection. However, this does not seem to actually happen with currently used zinc lozenges. Other explanations for how the lozenges might work also have problems. Thus, there is not yet a known reason why the zinc lozenges should work. Nonetheless, it can still be asked: Do the lozenges work, even if we don’t know how they work? The answer here seems to be that we don’t know.

Two types of studies have been done concerning zinc lozenges and the common cold. In one type, a cold is induced experimentally. In the other type, “naturally occurring” colds are monitored. In the former design, zinc lozenges have generally not been shown to be effective. For the “naturally occurring” colds, a revised meta-analysis has been applied. The analysis only examined cold duration, which means it may not be applicable to other assessments such as symptom severity or number of colds. In this meta-analysis, the zinc lozenge effect is not statistically significant. There has also been the concern that some studies showing a positive result may not have been blinded well (e.g., the participants could taste the difference between the zinc and the placebo). On the other hand, there have been comments made that the studies giving negative results have not given the lozenges with the most effective timing nor used the best lozenge composition. However, the relevance of the latter has been disputed, though some make-ups may be better than others at releasing zinc from the lozenge and binding it to the mouth.

After the revised meta-analysis was done, three new studies have appeared. In one, zinc acetate is used rather than the zinc gluconate used more often in these studies. Benefits are reported as superior to placebo. The number of subjects that completed the study, though large for some types of studies, is not large for this type of a study. Nonetheless, the strong separation of values between zinc and placebo for some of the parameters is attention catching. Even so, it should be noticed that cold severity and durations, though reduced, are still very detectable in the zinc group. Thus, at best, this study suggests that zinc cuts down on cold severity and duration, but does not do this instantly, or at 100% symptom elimination. In contrast to the positive results of this study, mostly negative results are obtained in another recent study comparing zinc gluconate, zinc acetate, and placebo. Both naturally occurring and experimentally induced colds are considered. The number of subjects is substantial. The only positive result is a small change in cold duration for the induced colds. All other results are negative. The study makes an attempt to eliminate blinding problems.

In the third more recent study, there is an examination of children enrolled at a school where zinc lozenges were introduced. Medical chart review is done for periods before and after lozenge introduction for students who did or did not take the lozenges. Statistically significant decreases are reported for three parameters: cold duration (though the mean difference is small), the median number of colds per year (also a small mean difference), and concomitant antibiotic use to manage colds (a substantial mean difference). One issue with this study is that there is no placebo control. Also, the number of colds per year is reported as 0 for the treatment...
group, and 1.3 for the non-treatment group. These low mean numbers make quantitative interpretations of the benefits of zinc lozenges difficult.

At present, it is hard to say if zinc lozenges are very effective, a little bit effective, or not effective for preventing and treating common colds. Also, when used for long-term prevention, there are unresolved safety issues. The doses used are typically well above the zinc Upper Levels, which could conceivably produce problems with copper status, cholesterol profiles, and suppression of some aspects of immunity (see the next section).

**TOXICITY**

**Copper Deficiency**

Historically, the single biggest concern about high-dose zinc supplementation has been the possibility of inducing copper deficiency. Indeed, there are case histories of copper deficiency, characterized by anemia and low neutrophil counts, due to high-dose zinc supplementation (usually over 100 mg/day). In addition, moderately high-dose zinc supplementation has been seen to lower HDL cholesterol, possibly via compromised copper status.

The lowest supplement dose at which problems occur for copper status is not actually known and may vary depending on the person’s dietary zinc and copper intake. One study reports no adverse effects of 30 mg zinc/day on certain white blood cell counts or on indicators of copper status. Another study finds that 50 mg per day of zinc for just 12 days can produce a 20% decrease in erythrocyte activities of the copper enzyme superoxide dismutase. A similar effect is seen for 60 mg/day of zinc as gluconate. In contrast, in college-aged women, this author’s laboratory does not find any effect of that same zinc dose as either gluconate or glycinate on that same copper enzyme activity (unpublished data).

At this point, there has not been a zinc supplement vs. copper status dose response curve done. This would be useful, especially for different dietary copper and zinc background intakes. For present, the Upper Level has been set at 40 mg, with the assumption that this dose won’t bother copper status in most people. This seems to be a good safety cap for adults, though this author is not convinced that higher doses will always affect copper status, or that lower doses always will not.

**Immunosuppression**

This effect of zinc can occur due to copper deficiency, but there may be other causes as well. The exact zinc dose at which this becomes a problem has not been well defined. In some situations, this effect may be helpful (e.g., in arthritis), though long-term consequences could often be detrimental. Again, the dose at which this becomes problematic is unknown.

**Prostate Cancer**

This concern derives in part from an epidemiological study showing increased risk in men taking over 100 mg of supplemental zinc, which is about nine times the
adult male RDA. This risk increase is not seen for lower doses. The increased risk associated with the high-dose supplements could be coincidental and not actually involve the zinc supplements themselves. However, even if the zinc relationship is cause and effect, the risk can be avoided simply by not taking such a high zinc dose. On the other hand, poor zinc intake may increase prostate cancer risk based on the following:

- Prostate contains the highest zinc concentration of any tissue in the body, but these concentrations fall with prostate cancer.\textsuperscript{242}
- Zinc function affects citrate levels, which are thought to affect prostate cancer risk.\textsuperscript{243}
- Zinc can inhibit growth of cultured prostate cancer cells.\textsuperscript{244}
- Some epidemiological studies show an inverse relationship between zinc and prostate cancer risk.\textsuperscript{242,250}

**ALZHEIMER’S DISEASE**

The evidence for detrimental effects of zinc is as follows:

A. Zinc interacts with amyloid proteins \textit{in vitro} in a way that induces changes resembling those that occur during Alzheimer’s disease.\textsuperscript{246}
B. There is a news report, which is not published as a journal article, that zinc supplements can adversely affect Alzheimer’s disease patients.
C. Some studies show high accumulations of zinc, or metallothionein, a protein induced by high levels of zinc, in certain sites in Alzheimer’s disease patients.\textsuperscript{246}
D. An antibiotic with metal chelating properties (clioquinol) has positive effects on transgenic mice with some Alzheimer’s disease traits;\textsuperscript{247} also, a short-term clinical trial of clioquinol in Alzheimer’s disease shows modest cognitive function improvement.\textsuperscript{248}

Each of these evidences is thought provoking but none is conclusive. An objection to evidence A is that in these studies, the other brain molecules that would bind zinc are not typically included. Thus, there is no competition for zinc binding with the amyloid proteins. Also, the zinc concentrations used are very high. This statement is made based not on total zinc in a tissue or fluid, but based on the concentrations of this mineral \textit{in vivo}, which might be free to bind to amyloid proteins. It can also be mentioned that zinc can have actions \textit{in vitro} that may be protective against Alzheimer’s disease development.\textsuperscript{249} For evidence B, two major objections are that the subject number is low and technical details are not available. For example, the zinc dose is not given (which could be toxic), nor is the zinc complex identified (the metal binder, rather than the zinc, could have produced the adverse effects). In addition, according to a newspaper report and comments made at a zinc meeting (National Institute of Health conference: “Zinc and Health: Current Status–Future Directions,” November 1998), there is lack of Alzheimer’s disease specificity for the negative effects that the zinc produced (i.e., stomach discomfort and mental
stress). Such effects could have been triggered by something as simple as an upset stomach, a symptom that can result from some zinc supplements.

A problem with evidence C is that local elevations in zinc may be a response to Alzheimer’s disease inflammation rather than a cause. An objection to the human subjects trial in evidence D is that it is not a well-controlled trial. In addition, for both this study and the related one in mice,\textsuperscript{247} it cannot be said that the benefits were due to lowering the negative effects of zinc. The chelator given has a range of biological effects.\textsuperscript{250,251}

In contrast to the assertions that zinc promotes Alzheimer’s disease, there are evidences for beneficial effects of zinc:

A. In the so-called “Nun study” of Alzheimer’s disease, serum zinc values in nuns are inversely correlated with progression time of dementia symptoms.\textsuperscript{252}

B. Low concentrations of zinc can interact with amyloid proteins \textit{in vitro} in a way that could restrict Alzheimer’s disease symptoms.\textsuperscript{249}

C. A modest improvement in Alzheimer’s disease symptoms has been noted for a few Alzheimer’s disease patients treated with zinc supplements.\textsuperscript{253}

D. In this author’s laboratory, eight Alzheimer’s disease patients show lower values for zinc status indicators than their spouses (unpublished data).

As with the detriment scenario, each evidence of benefit is interesting but inconclusive. An objection to A could be that serum zinc values are just being depressed by inflammation.\textsuperscript{6} A problem with B is that there are papers showing the opposite effect.\textsuperscript{240} A limitation of C and D is the low subject number.

In summary, there are reasons to suspect that zinc could aggravate or inhibit Alzheimer’s disease symptom progression. However, at present, there are no clear indications of whether either is true. It should also be noted that even if zinc–amyloid protein binding is a problem in Alzheimer’s disease, there is no real evidence that

**TABLE 5.4**

**Zinc Supplements at a Glance**

- **Adult RDA:** 11 mg (male), 8 mg (female) (based on balance studies, not function indexes)
- **Typical dose in supplement studies:** very variable (dose response curves not available)
- **Best supplement complex:** oxide least desirable; a number of others are well absorbed, though some complexes may have advantages in certain applications (not well studied)
- **Applications:** correction of overt deficiency seems well established; use in Down’s syndrome and renal dialysis is likely helpful, but not fully confirmed; use in diabetes or small-for-age children is possibly useful for some subjects; several other uses (e.g., osteoporosis prevention) are interesting but not fully confirmed; lozenge use for the common cold (still under debate); some other uses questionable (e.g., acne treatment)
- **Upper Level:** 40 mg (not well established)
- **Safety issues:** copper deficiency risk is well established but minimum safe dose is not; other toxicity issues are unresolved
dietary zinc has any effect on the problem. By analogy, although calcification occurs in atherosclerotic plaques, low calcium intake is not being recommended to protect against atherosclerosis. Therefore, in this author’s opinion, fear of Alzheimer’s disease is not currently a known reason for avoiding zinc supplements.

SUMMARY AND CONCLUSIONS

A large volume of research has been done in relation to zinc and various health concerns. Despite all this research, there are few practical guidelines for who would benefit from zinc supplements, and how much should be given. Nonetheless, it is very likely that some people will benefit from zinc supplements, especially where health problems make adequate intake of zinc difficult due to high needs or low food intake. Toxicity issues for zinc supplementation have not been fully clarified.

REFERENCES


For the last 25 years or so, a number of copper researchers have pointed to marginal copper deficiency as a possible problem in many people. However, this message has not spread extensively to most of the nutrition field, nor to the rest of the biomedical community. Although the message is supported by some research, the copper nutrition field needs a blockbuster, large-scale, broad-scope, copper supplementation intervention study to either spread the alarm or calm down the alarm sounders.

OVERVIEW OF FUNCTION
Copper functions in certain metalloenzymes by cycling between +2 and +1 charges to donate electrons to a substrate. Some of the known copper enzymes and their functions are listed in Table 6.1. Ceruloplasmin is unusual in that it is thought to both possess enzyme function and contribute to serum copper transport. There are some symptoms of copper deficiency that have not yet been matched to depressed activity of a specific copper metalloenzyme. Examples of such symptoms include impairments of immune function and abnormal cholesterol metabolism. In the latter case, part of the story could be superoxide dismutase 1, which eliminates superoxide. Superoxide is known to alter activity of an enzyme involved in cholesterol synthesis.

OVERVIEW OF METABOLISM
Copper is absorbed mostly in the upper intestine. The main interference with this process is high intake of oral zinc. In the past, the mechanism for zinc antagonism of copper absorption was assumed to involve the protein metallothionein. Recent work with metallothionein knock out mice have shown that this is not the main mechanism.

Once copper is absorbed, its metabolism seems to be geared toward restricting free movement of copper. This would seem beneficial because the redox properties of free copper, like those of iron, can cause damaging oxidant reactions. Based on laboratory animal work, when copper enters the body, via diet or injection, it is cleared rapidly from the blood and enters the liver and kidney, the two main copper storage sites. The liver can place copper into metalloenzymes, eliminate copper via the bile, store this mineral bound to the protein metallothionein (which also occurs in the kidney and, to some extent, in other tissues), or secrete copper back into the
In the latter case, the copper is tightly incorporated into the protein ceruloplasmin. The protein ceruloplasmin has enzymatic activity plus it transports copper to other tissues. Receptors for ceruloplasmin have been found on tissue samples and cultured cells. These receptors release copper from ceruloplasmin, which is reminiscent of iron uptake from transferrin, but the copper uptake process has some differences from iron. Despite these findings on ceruloplasmin receptors, copper transport independent of ceruloplasmin can also be demonstrated. Thus, ceruloplasmin may not be essential for copper transport, though it may be the primary means in most circumstances. Once inside extra-hepatic cells, copper binds to chaperone proteins via a process that is garnering substantial research attention.

**NUTRITIONAL STATUS ASSESSMENT**

Severe copper deficiency can be spotted by low values for serum copper or enzyme activity of ceruloplasmin, which contains most of the copper in serum. Ceruloplasmin protein levels can also be affected by copper status, since copper-poor ceruloplasmin degrades faster than normal. However, during deficiency, ceruloplasmin protein values decline a little less than does ceruloplasmin activity. One problem with identifying severe copper deficiency using serum copper or ceruloplasmin values is that Wilson’s disease, a genetic disorder of copper toxicity, also causes low values for serum copper and ceruloplasmin. The two states can be distinguished by other evaluations. For example, in severe copper deficiency, anemia and low neutrophil counts often occur.

A method for identification of marginal copper deficiency has not been given any consensus among copper researchers, though a number of candidates have some support. This lack of consensus has restricted efforts to identify the frequency and consequences of marginal copper deficiency. The use of serum copper or ceruloplasmin values is not

<table>
<thead>
<tr>
<th>Name</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceruloplasmin</td>
<td>Iron transport, antioxidant actions (e.g., restrict iron catalyzed radical creation)</td>
</tr>
<tr>
<td>Superoxide dismutase 1</td>
<td>Eliminate superoxide radicals in cells</td>
</tr>
<tr>
<td>Extracellular superoxide dismutase</td>
<td>Eliminate superoxide radicals outside cells</td>
</tr>
<tr>
<td>Cytochrome c oxidase</td>
<td>Aerobic energy release in electron transport chain</td>
</tr>
<tr>
<td>Dopamine–hydroxylase</td>
<td>Make norepinephrine (hormone and neurotransmitter)</td>
</tr>
<tr>
<td>Diamine oxidase</td>
<td>Degradation of polyphenols</td>
</tr>
<tr>
<td>Lysyl Oxidase</td>
<td>Crosslink collagen and elastin in connective tissue</td>
</tr>
<tr>
<td>Tyrosinase</td>
<td>Melanin formation</td>
</tr>
<tr>
<td>Peptidylglycine alpha-amidating</td>
<td>Neuropeptide activation</td>
</tr>
<tr>
<td>Monoxygenase</td>
<td>Copper is likely part of some other enzymes</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from References 1 and 5.
ideal because values do not always fall quickly or consistently with marginal copper deficiency. Moreover, values can be influenced by other factors such as inflammation, other physiological stress, oral contraceptive use, menstrual state, and pregnancy. A number of other measurements have been proposed as alternates for assessing marginal copper deficiency (Table 6.2). Each has some data to support its use, but none has the full support of the copper research community.

Part of the problem is that each of these parameters seem to “work” in some studies but not others. Another issue is that not one of these measures seems impervious to all influences other than copper status. Despite these problems, in this author’s opinion, these measures can be used right now to study marginal copper deficiency if two criteria are met. One, the studies involve measures taken before and after copper supplementation. In these circumstances, even if there is some variation in baseline values, if copper is a limiting factor in values, copper supplementation should affect the values. The other criterion is that the measure or measures used should be chosen with the study population in mind. For example, diamine oxidase activities should not be used during pregnancy nor in subjects with renal problems, because both situations greatly affect serum diamine oxidase activity values. On the other hand, these values can work well for healthy, non-pregnant subjects given copper supplements.

TABLE 6.2
Parameters Proposed for Assessment of Moderate Copper Deficiency

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell copper</td>
<td>19</td>
</tr>
<tr>
<td>Erythrocyte superoxide dismutase activity</td>
<td>17,20</td>
</tr>
<tr>
<td>Platelet cytochrome c oxidase activity</td>
<td>21</td>
</tr>
<tr>
<td>Plasma or serum diamine oxidase activity</td>
<td>17,18</td>
</tr>
<tr>
<td>Ceruloplasmin activity to protein ratios</td>
<td>22</td>
</tr>
</tbody>
</table>

BIOAVAILABILITY FROM FOODS AND SUPPLEMENTS

Copper absorption from foods has not been studied as extensively as has iron or zinc. Copper absorption from foods does not seem to be as inhibited by phytate as are some other minerals. Animal proteins may promote copper absorption even though foods like beef and dairy products don’t provide real high percents of the copper RDA. In the U.S., vegetarian diets often contain more copper than meat-inclusive diets, but the absorption of the copper appears to be lower in the meatless diets. An exception to this pattern may be diets that are very high in soy products. Soy protein contains a good amount of copper that seems to be well absorbed, but substantial amounts must be eaten to have a major impact on daily copper intake. In this author’s work, subjects eating 40 g of soy protein per day for three to four weeks showed an increase in activities for the copper enzyme diamine oxidase (unpublished results).
High-dose vitamin C is often claimed to reduce copper absorption. This does seem to be true in experimental animals given very high vitamin C doses, but these doses greatly exceed what people typically take, even as so-called megadoses. In human studies, vitamin C supplements can reduce ceruloplasmin activity. However, in at least some of these cases, this may be a direct effect of vitamin C on ceruloplasmin enzyme activity, rather than reduced copper absorption. Thus, whether vitamin C supplements typically pose a major threat to copper absorption is still debatable. We also don’t know if vitamin C ever directly inhibits ceruloplasmin activity in vivo enough to cause problems. One paper contends that the inhibition effect, though it may take place during an assay, does not occur for normal situations in vivo. In contrast, there has been speculation that this inhibition does take place in some premature infants.

The biggest known influence on copper absorption from foods is zinc supplementation. High-dose zinc supplements have been known to cause severe copper deficiency. High-dose iron supplements could also be a problem, though this has not been given as much study as zinc. To complicate matters, some doses of iron, in some circumstances, may promote good copper status.

The copper in most multi-vitamin–mineral pills and food fortifications is oxide, though sulfate is sometimes used. The latter is a common copper complex in animal feeds. Copper is not typically added to cereal products intended for human consumption because of negative effects on the product during storage. The most common form of copper in standalone human supplements is copper gluconate. Copper chelated to amino acids or hydrolyzed protein has been used in some human and livestock research studies. These copper chelates can also be applied to food fortification and supplement capsules or pills, though this has not been done as often as with copper oxide or gluconate. Comparisons of these different types of copper complexes in human studies are pretty much non-existent. However, some inferences can be drawn from animal studies. One inference is that copper oxide is generally poorly absorbed. In a number of studies in experimental animals and farm animals, copper oxide has shown very low bioavailability.

In contrast, in these same studies, copper sulfate has shown considerably better bioavailability than copper oxide. In a few studies, an amino acid–copper complex shows better bioavailability by various indices than does copper sulfate. On the other hand, in a cattle study, a copper–amino acid chelate and copper sulfate give the same results. The last study is difficult to evaluate for two reasons. One, the evaluation method is limited (plasma copper response by initially copper-deficient animals). Two, little is known about the copper chelate complex used. Although many mineral–amino acid mixtures are called chelates, different preparations may have different chemical interactions and stability. Interestingly, copper gluconate, the most common standalone human copper supplement, has not been tested to any great extent for bioavailability.

**TYPICAL INTAKES VERSUS NEEDS**

The best sources of copper are not typically eaten often, or are eaten in small amounts. These sources include liver, shellfish, nuts, seeds, soy protein products,
and cocoa. In regard to the last food, cocoa, foods concentrated in cocoa, such as dark chocolate candy, are high in copper. On the other hand, products that contain less cocoa, such as milk chocolate candy, are not as high, though they can make a contribution to copper intake. For many people, much of the copper intake is a cumulative effect from different food sources, as well as from a substantial intake of one given food source. For the latter situation, a case in point is beef. Beef will not provide as high a percent of the copper RDA per serving as it would for iron or zinc. Even so, if beef is eaten in substantial quantities, it can provide some of a day's copper needs. In addition, as discussed above, meat may help promote copper absorption from other foods.

Copper intakes have been reported many times as often falling below former recommendations. However, the recent RDAs are more in line with lower copper intakes. There are no obvious symptoms associated with such lower intakes, though this does not rule out unrecognized symptoms. Along these lines, a section heading in a past Annual Review of Nutrition asked: “Is mild chronic copper deficiency a significant health problem in humans?” The first sentence in this section stated: “This is the important practical question for the future.” It is now many years later, and the question still remains. Controlled human feeding trials in USDA laboratories have highlighted potential issues, but there is little work with “naturally occurring” marginal copper deficiency in free-living subjects. One reason for this lack of work has been the lack of consensus noted above about how to identify who has marginal copper deficiency.

Another issue in this area is the effect of various health problems on needs. In rats and humans, copper needs are increased by inflammatory stress, at least based on copper enzyme activities. If this translates into impact on various aspects of health, then inflammation, and possibly other physiological stress, could make people especially prone to problems related to marginal copper deficiency. However, this issue requires considerably more research.

One argument that many people eat insufficient copper is that submaximal values for copper-related parameters can be found in both apparently healthy people and in subjects with some health problems. Examples include:

- Diamine oxidase activities in normal adults and in some men with moderately high cholesterol
- Erythrocyte superoxide dismutase activities in rheumatoid arthritis patients, apparently healthy adults, and young adult women
- White blood cell copper in people with atherosclerosis
- Superoxide dismutase activities (and low activity to immunoreactive protein ratios) in aortic samples removed during surgery for aneurysms or coronary bypass
- Serum copper in certain women who subsequently developed breast cancer
- Ceruloplasmin and superoxide dismutase activities in premature infants
• Three blood copper enzymes, including blood cell cytochrome c oxidase, in a large number of cystic fibrosis patients

• Ceruloplasmin activity to immunoreactive protein ratios in a large number of renal dialysis patients and DiSilvestro, R.A., unpublished results

One problem in interpreting these studies is that it is not certain whether factors other than copper status are causing the abnormalities in copper-related parameters. For instance, ceruloplasmin and superoxide dismutase could be inactivated by copper-independent mechanisms. Nonetheless, copper status would seem to be the most likely explanation in studies where multiple copper parameters are measured. Even so, in these and other studies, further clarification would be helpful. For example, determining the copper content of the enzymes being studied would be helpful. This would say whether there is a low amount of copper per enzyme molecule. However, this is rarely done due to time concerns and technical requirements.

If human copper intake often fails to maximize values for copper-related parameters, then what are the practical health consequences, if any? One consideration is that in experimental animals, copper deficiency, sometimes including marginal deficiency, can produce negative effects relevant to human health problems. These effects include compromised immune function, poor resistance to chemically induced acute tissue injury, high vulnerability to chemical carcinogenesis, various negative effects on cardiovascular-related parameters including elevated serum cholesterol, and some hormonal abnormalities. Some of these same effects can also occur in studies where small numbers of healthy human volunteers are fed low copper levels. Nonetheless, an important question remains largely unanswered: Does “naturally” occurring marginal copper deficiency in free-living people cause any real problems? This question can be subdivided into three questions:

1. Does moderate copper deficiency cause undetected health defects in apparently healthy people (i.e., compromised immune function)?
2. Can moderate copper deficiency increase the risk of developing health problems that are not strictly copper deficiency diseases (e.g., cancer)?
3. Will moderate copper deficiency aggravate primary or secondary symptoms of existing diseases (e.g., rheumatoid arthritis)?

One way to answer any of these questions is intervention studies where moderate copper deficiency is diagnosed and is then treated with increased copper intake. For example, subjects at risk for certain diseases can be screened for moderate copper deficiency, then given copper or placebo supplements, and then evaluated for either disease onset or measures that assess risk for the disease. This has not yet been done to any great extent. One reason has been the lack of consensus about diagnosing marginal copper deficiency. However, as noted above, this author feels that the currently available diagnostic tools can be used if the right tool is selected for the people being studied.
CURRENT RESEARCH ON SUPPLEMENT USE

Despite the various studies claiming that copper intake is often below optimal levels, and despite the speculations that such moderate deficiencies could have negative health effects, there are just a few copper supplementation studies. The main existing studies are summarized in Table 6.3. It should be noted that many of these studies have focused just on effects on copper metalloenzyme activities, rather than on parameters directly related to specific health problems. This is because most copper supplement studies are trying to justify that marginal copper deficiency occurs in a given situation, or verify that a given copper enzyme is a good indicator of marginal deficiency. Both goals are supported by finding submaximal values for copper metalloenzyme activities, which increase in response to copper supplementation.

A number of the studies cited in Table 6.3 show that copper supplementation can raise copper enzyme activities. This supports the view that marginal copper deficiency does occur in some people, at least based on copper enzyme activities. An alternative interpretation is that copper enzymes can keep increasing as copper intake increases beyond adequate levels. This latter contention is weakened by one study where split analysis is done by dividing subjects into two groups based on a median split in copper enzyme activities. In that case, copper supplementation produces an increase in copper enzyme activities when starting values are below the median split, but not when values are above the split.

TABLE 6.3
Copper (Cu) Supplementation Trials

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Complex</th>
<th>Outcome*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young adult women</td>
<td>Glycinate</td>
<td>2 Cu enzymes up, oxidant stress markers down49</td>
</tr>
<tr>
<td>Normal adults</td>
<td>Glycinate</td>
<td>Various Cu enzymes up50</td>
</tr>
<tr>
<td>Normal adults</td>
<td>Glycinate</td>
<td>Erythrocyte superoxide dismutase up50</td>
</tr>
<tr>
<td>Rheumatoid arthritis adults</td>
<td>Glycinate</td>
<td>Erythrocyte superoxide dismutase up50</td>
</tr>
<tr>
<td>Cystic fibrosis patients</td>
<td>Glycinate</td>
<td>No effect: 3 Cu enzymes51</td>
</tr>
<tr>
<td>Adults (high cholesterol)</td>
<td>Not stated</td>
<td>Reduce serum cholesterol52</td>
</tr>
<tr>
<td>Males (high cholesterol)</td>
<td>Glycinate</td>
<td>No effect: cholesterol; varied effect with split analysis on 2 Cu enzymes, lipoprotein oxidation52,53</td>
</tr>
<tr>
<td>Young adult men</td>
<td>Sulfate</td>
<td>No depression in total serum cholesterol53</td>
</tr>
<tr>
<td>Young adult women</td>
<td>Glycinate</td>
<td>Erythrocyte superoxide dismutase up; no effect: on sulfate bone markers52</td>
</tr>
<tr>
<td>Young adult women</td>
<td>Glycinate</td>
<td>Erythrocyte superoxide dismutase up; bone markers ratio up (Figure 6.1)</td>
</tr>
<tr>
<td>Postmenopause women</td>
<td>Gluconate</td>
<td>Bone loss down53</td>
</tr>
</tbody>
</table>

* Enzyme effects refer to changes in activities

b See text for details on split analysis
The next logical question is whether an improvement in copper enzyme activities translates to any practical health improvements. The median split study gives one indication along those lines. In subjects below the median split, copper supplementation depresses lipoprotein oxidation, a measure related to atherosclerosis development.

In experimental animals, a large number of studies find high serum cholesterol readings with copper deficiency. That observation is duplicated in a few humans intentionally fed a low-copper diet. Unfortunately, little is known about how well copper supplementation can affect cholesterol readings in free-living people. None of the three cholesterol studies noted in Table 6.3 is ideal, including the one by this author. One study shows no copper-induced decrease in cholesterol parameters, but this study shows high variability in the placebo groups. In addition, the study examines young adult men with low starting cholesterol. Thus, this group may not easily show improvement in cholesterol readings. The study by this author, which showed no effect on plasma total cholesterol, does examine subjects with moderately high cholesterol. However, this study uses only a four-week supplementation period, which may be too short to lower cholesterol by copper supplementation. The one study that does show copper depression of serum cholesterol examines a very small subject number who are not screened for starting copper status. Despite these limitations, the area of copper and cholesterol should be given more study in human subjects, especially since correction of marginal copper deficiency in livestock can reduce cholesterol values.

The practical consequences of copper supplementation for bone health in women is still very unsettled. A review article provides a good theoretical basis for copper’s importance for bone. In theory, copper status influences bone structure via lysyl oxidase, which affects the collagen in bone. Copper also is needed for antioxidant superoxide dismutase enzymes, which eliminate superoxide, which can stimulate bone resorption. Still, these functional considerations do not necessarily mean that typical variations in copper intake affect bone health. This can only be determined via human intervention trials. One such study has shown that copper slows bone loss in postmenopausal women, but the results are difficult to interpret. For one thing, copper is given with a group of minerals. This means that we don’t know how much the copper contributed to the results. In addition, there is a lot of overlap in results between study groups, and a lot of variation within groups. Along these lines, a group getting just calcium has a slightly better mean value than a group getting calcium plus trace minerals. Yet, only the latter differs statistically from the placebo group.

For young adult women, two studies each give negative results for copper supplementation effects on blood and urine markers for bone metabolism. However, a meeting abstract by this author shows that if the bone marker results are expressed a certain way, then a statistically significant effect can be observed. In this study, copper has no effect on two urinary markers of collagen degradation: deoxypyridinoline (DPD), a crosslink in collagen, and type I collagen helical peptide. However, if a ratio of DPD to type I collagen helical peptide is examined, copper increases this ratio (Figure 6.1). This ratio may be a more accurate reflection of copper effects on bone health than either of the two parameters individually. The reasoning is as follows. Marginal copper deficiency could restrict lysyl oxidase
activity, which can limit DPD crosslink formation in collagen. This could cause low values for the DPD crosslinks in urine. At the same time, this low crosslinking can cause collagen degradation to increase, which will increase urinary DPD values. Collagen degradation could also be increased by marginal copper deficiency due to high superoxide stimulation of bone resorption. Thus, marginal copper deficiency could simultaneously produce opposite effects on urinary DPD values, which could essentially cancel each other out. However, a ratio of DPD crosslinks to another marker of collagen, such as that used in Figure 6.1, should reflect how well the crosslinking process is occurring. These results merit follow up research.

The lack of copper effect in cystic fibrosis is disappointing. These people seem to be prone to a more severe marginal copper deficiency than is typical. One reason for the negative results may be that cellular copper uptake processes are impaired in these subjects. Possibly, a novel copper complex could be designed to remedy this situation.

Clearly, there is a need for more copper supplementation studies where starting copper status is considered, and where effects on copper enzyme activities are examined in concert with other health-related effects. This should be done both for healthy people and for people with health problems that might raise copper needs. One of the biggest barriers to such studies has simply been a lack of funding for such work.

All of the discussion of copper supplementation thus far has revolved around correcting marginal deficiency. Could there be benefits to copper intake beyond that needed to prevent or correct deficiencies? At present, the idea of health benefits for an above-adequate copper intake has not been studied to any great degree in humans. However, there is one study that raises the possibility. Administration of copper sulfate or glycinate increases erythrocyte resistance to lysis in vitro. Since there is no accompanying increase in erythrocyte superoxide dismutase activities, this action may not work via correction of a deficiency. Another justification of copper benefits beyond correcting deficiencies could be found in a series of studies in copper-adequate rats and mice. In this work, specific copper complexes have anti-inflammatory and other protective actions. However, these effects may be limited to just these complexes acting as drugs.

TOXICITY

According to present knowledge, copper supplementation at doses typically used by the public seem to be safe unless they cause GI tract upsets. The current adult Upper Level for copper is 10 mg, which is well beyond what is found in any typical copper supplement. Even this dose may not be terribly dangerous except for GI problems. In a 12-week study, a 10 mg daily dose of copper produces no obvious physical or clinical chemistry symptoms. Nonetheless, there is the possibility that some copper toxicity effects are not recognized yet. Along these lines, in hypercholesterolemic postmenopausal women, 12 weeks of supplementation of 3 mg copper/day suppresses lymphocyte proliferation when the cells are removed from the body (the type of copper complex used is not stated). The general applicability of this study is not yet known since the population studied is not a generic population.
FIGURE 6.1 Ratios of deoxypyridinoline (DPD), a crosslink in collagen, and type I collagen helical peptide (a measure of excreted total collagen protein) in response to copper glycinate (Cu) or placebo. Young adult females (N = 8 per group) were given copper glycinate (2 mg copper/day) or placebo for six weeks. Values are means ± SD for arbitrary ratio units. Copper, but not placebo, produced a statistically significant effect (p < 0.05, paired t-test).
Also, the practical health implications of the effect on lymphocytes are also not known yet.

Nausea or other GI tract discomforts can be an early symptom in many people with copper poisoning.\textsuperscript{1} In fact, this author has noted from his own experience that some people get nauseated even from a 2 or 3 mg copper dose if taken on an empty stomach. Thus, there is some built-in protection against oral copper supplementation toxicity. Even so, this is not necessarily a foolproof protection, since the study of 10 mg copper/day as gluconate reports no more GI problems than placebo.\textsuperscript{82}

Most medical reports on copper toxicity involve environmental and occupational exposures, or the genetic condition Wilson’s disease, rather than dietary copper intake or high-dose supplementation.\textsuperscript{1} There has been some speculation at mineral meetings that some mild, undiagnosed forms of Wilson’s disease may exist, and that some people may have other genetic sensitivities to copper toxicity. However, at present, there is little documentation for these ideas, though they can’t be ruled out.

There has also been some speculation that moderately high copper intake can promote breast cancer and cardiovascular disease. One argument for the latter arises from an epidemiological linking of high serum copper with cardiovascular disease in Finland.\textsuperscript{84} However, these high serum copper values likely just mark physiologic stress. Serum levels of ceruloplasmin, which contains nearly all serum copper, tend to rise with most any stress.\textsuperscript{14} This author has shown that in rats, stress produces high serum copper or ceruloplasmin levels even with marginal copper deficiency.\textsuperscript{48,85} Another reason that copper is sometimes thought to promote cardiovascular disease is that copper ions, and the copper protein ceruloplasmin, can oxidize lipoproteins \textit{in vitro}.\textsuperscript{74,86} Oxidized lipoproteins are thought to promote atherosclerosis.\textsuperscript{74} However, catalytically active, low molecular weight copper ion is generally absent from serum.\textsuperscript{87} Moreover, this author notes that elevation of ceruloplasmin levels in rats does not increase lipoprotein vulnerability to oxidation.\textsuperscript{88} Also, ceruloplasmin promotion of LDL oxidation \textit{in vitro} requires a loosely bound copper.\textsuperscript{86} This author and others note that such loose copper is not considered part of native ceruloplasmin and can be easily removed by serum albumin.\textsuperscript{86,88,89} This removal should occur readily in the blood during real-life situations.\textsuperscript{89} It should also be noted that in humans, a fairly high dose of copper (6 mg/day) does not increase lipoprotein oxidation.\textsuperscript{90} Plus, in one study, copper supplementation at lower levels actually reduces lipoprotein oxidation in some people.\textsuperscript{17}

The breast cancer issue is similar to the cardiovascular issue in that there is an epidemiological linking of high serum copper with high risk of breast cancer.\textsuperscript{51} Once again, this likely has more to do with stress elevation of serum ceruloplasmin levels than with high copper intake. Interestingly, the same epidemiological study\textsuperscript{51} also found that low serum copper readings are associated with a high breast cancer risk. Thus, low copper intake could be a problem in this regard.

In this author’s opinion, the most common copper supplement doses (1 to 3 mg/day) do not pose any known dangers. Nonetheless, research should be done to see if there are unidentified dangers of moderately high copper doses, and to identify who, if anyone, is overly sensitive to copper toxicity.
SUMMARY AND CONCLUSIONS

There are reasons to believe that marginal copper deficiency is a problem in many people and that correction, including that by supplementation, can have various health benefits. However, this concept is still missing too many pieces of the research puzzle to make definitive conclusions. Copper toxicity of supplements requires more research, though at present no major dangers have been clearly identified for typical doses.

REFERENCES


### TABLE 6.4

**Copper Supplements at a Glance**

- **Adult RDA:** 0.9 mg (controversial; may be too low)
- **Typical dose in supplement studies:** 2–5 mg (2 mg is probably effective in most cases)
- **Best supplement complex:** glycinate or sulfate is used in most research; gluconate may be good, though largely untested; oxide is commonly used, but has very low bioavailability in animal studies
- **Applications:** increases copper enzyme activities in some people; several health promotion effects possible, but not well confirmed
- **Upper Level:** 10 mg
- **Safety issues:** supplement uses have been well below the Upper Limit


7 Selenium

Selenium functions in certain enzymes, but the way selenium is incorporated into these enzymes is quite different from the processes for other minerals. Selenium has drawn interest for its roles in antioxidant defense and thyroid hormone production, as well as for possible applications in cancer prevention. The latter may be independent of selenium’s enzyme functions and may require intake well beyond the levels needed to prevent deficiency. This last area will be a prominent research interest for selenium for quite some time. Some other applications of selenium supplements also have some data to support usefulness. In contrast, for still other claims, despite some Internet sites making very definitive claims, the current evidence is not very definitive.

OVERVIEW OF FUNCTION

Selenium is a component of a number of proteins. Selenium can exist as an anion at biological pH, which makes it able to both give and accept electrons. The best understood physiological functions of selenium are two enzyme functions. One of these functions is done as part of a family of proteins named glutathione peroxidase (one is found inside of cells, another is outside cells in places like the plasma). Glutathione peroxidase is part of the body’s antioxidant defense network by eliminating peroxides, including hydrogen peroxide, which can be both precursors and products of free radicals. Selenium also functions in an enzyme that is part thyroid hormone synthesis.

A more recently discovered selenium enzyme is known as thioredoxin reductase, which seems to have a number of regulatory roles within cells, and seems to affect antioxidant defense by influencing electron flow in some reactions. One interesting point about this enzyme is that in rats, the enzyme activities can be increased by elevating selenium intake above those normally considered adequate.

Selenoproteins can also have non-enzymatic functions. Sperm capsule selenoprotein is a structural protein found in the midpiece region of the sperm tail. In selenium deficiency, morphological anomalies in this region give rise to spermatozoa with impaired motility. There are also several other selenoproteins in the male gonads that may contribute to male reproductive function. In addition, selenium is needed for normal testosterone metabolism and testicular morphology.

A protein called selenoprotein P has been studied from a regulatory perspective, but the functional importance of this protein is still not fully understood.
There are other proteins in the body that have been found to contain selenium, but their function is not yet known. Selenium may also exert some enzyme-independent actions relevant to cancer prevention (see Cancer subsection), but it is gray as to whether to call these actions selenium functions or selenium pharmacological effects. The latter would be based on processes that can be affected by selenium, but that are not essential roles for this element.

Selenium deficiency can also affect immune function, though the mechanisms are not completely clear. Both the antioxidant and thyroid modulating actions of selenium could be involved, though there may be other mechanisms as well. One unusual interaction between selenium status and immune function is the impact on viral virulence. This is discussed further in the Human Immunodeficiency Virus (HIV) subsection. Selenium interactions with viral virulence also extend to other virus classes. For example, in mice, selenium deficiency increases the pathology of an influenza virus infection.

OVERVIEW OF METABOLISM

Selenium from foods is absorbed well by mechanisms that overlap amino acid absorption. Selenium absorption is not controlled by homeostatic mechanisms such as those that exist for minerals like iron and calcium.

Most minerals that exist in metalloproteins are inserted into the protein by attaching to selected amino acids, or in the case of some iron proteins, by insertion into a heme or cytochrome structure, which can be inserted into a protein. Selenium is different in that it is substituted for a sulfur in amino acids, typically cysteine. This selenocysteine amino acid becomes a part of certain proteins during protein synthesis. Selenocysteine has its own codon and specific biosynthetic and insertion machinery. In the presence of a downstream stem-loop structure, the UGA codon in mRNA, instead of behaving as a stop codon, specifies the insertion of a selenocysteine into an expanding peptide chain.

NUTRITIONAL STATUS ASSESSMENT

Unlike the case for a lot of minerals, selenium has some well-established methods for status assessment. Plasma selenium is proportional to selenium intake at both high and low levels. Whole blood or red blood cell selenium can also be useful for marking long-term selenium status. Plasma glutathione peroxidase activities are proportional to selenium intake, but do plateau at certain intakes. In fact, these plateaus are used to establish the selenium RDAs. For this application, one under-addressed issue is how well the plasma value plateaus compare to tissue plateaus for glutathione peroxidase activities.

Erythrocyte glutathione peroxidase activity is also sometimes used to assess selenium status, though the values may be affected to a small degree by some influences other than selenium status. The combination of glutathione peroxidase activities and plasma selenium can provide information on the response to selenium supplementation in subjects who are barely deficient, or in adequate status, before treatment. For example, if the supplementation raises plasma selenium but not
glutathione peroxidase, the subjects are likely in adequate status but the selenium supplement did add to body selenium. This type of analysis is important in cancer prevention studies (see Cancer subsection) where the goal is not always just to correct deficiency, but to provide an above-adequate intake.

A number of large-scale studies use toenail selenium for status assessment. There is data showing higher values with long-term selenium supplementation, and a small degree of association with dietary selenium intake. Values seem to rise very slowly with increased selenium intake, which means the main use of this parameter would be for long-term assessments.

**BIOAVAILABILITY FROM FOODS AND SUPPLEMENTS**

Selenium in foods is generally part of selenocysteine and selenomethionine. Since these compounds are absorbed similarly to the common amino acids, the percent absorptions for selenium are very high compared to other trace minerals. One exception, at least based on a rat study, is the selenium in tuna. The bioavailability, though not terrible, is not as high as most other types of foods or even other seafoods. One other food with low selenium bioavailability, based on a study in Finnish women, is mushrooms.

There are four main selenium supplements: sodium selenate, sodium selenite, L-selenomethionine, and high selenium yeast, which contains protein-bound L-selenomethionine, which is liberated during digestion. Selenium supplements are absorbed relatively well. However, in some, but not all, comparisons between supplement types, there are differences found for various bioactivities. The “winner” in these comparisons varies for different end points, and sometimes for the same end points in different circumstances. L-selenomethionine, in yeast or in the free form, is the “winner” more often than the inorganic forms (though there are also a number of “ties”). Examples of those studies where L-selenomethionine shows an advantage are summarized in Table 7.1. However, it should be noted that in some

<table>
<thead>
<tr>
<th><strong>TABLE 7.1</strong></th>
<th><strong>Examples of Better Activity of L-Selenomethionine (Free or in Yeast) vs. Selenite</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subject Type</strong></td>
<td><strong>Key Finding</strong></td>
</tr>
<tr>
<td>Dairy cows</td>
<td>Higher blood and milk Se*, blood GPx**</td>
</tr>
<tr>
<td>Humans, low-Se area of China</td>
<td>Better increases in plasma and erythrocyte Se**</td>
</tr>
<tr>
<td>Young adult women in New Zealand</td>
<td>Higher blood Se**</td>
</tr>
<tr>
<td>Cattle</td>
<td>Higher Se in milk and some tissues**</td>
</tr>
<tr>
<td>Lactating women</td>
<td>Higher Se absorption**</td>
</tr>
<tr>
<td>Pigs</td>
<td>Higher muscle Se**</td>
</tr>
<tr>
<td>Rats</td>
<td>Higher Se in some tissues**</td>
</tr>
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</table>

* Se = selenium; **GPx = glutathione peroxidase
of the studies cited, L-selenomethionine is not better at some parameters that are not noted in the table. Moreover, for certain circumstances in some of the studies, L-selenomethionine is not better at even the parameters listed. In fact, for some measures in some circumstances, sodium selenite or selenate works better. For example, in one study, the yeast works better for blood selenium, but selenate has a bigger effect on glutathione peroxidase activities in the platelets.\textsuperscript{21}

To make matters more complicated, in rats given a chemical that induces colon cancer, supplemental selenite or selenate, but not L-selenomethionine, reduces values for precancer indicators.\textsuperscript{27} The protective effect of selenite and selenate is not due to better elevation of tissue selenium contents or glutathione peroxidase activity. In fact, selenomethionine gives better results in those regards. The mechanisms responsible for the protective effects on the inorganic selenium are unclear. They may involve breakdown and elimination of the cancer-producing chemicals given to the rats. Such an action may or may not be relevant to human cancer situations that are not necessarily initiated by the same chemicals used in rat experiments. Thus, we don’t know if selenite and selenate would have an advantage over L-selenomethione in preventing human cancers. It is noteworthy that in the most publicized study of human cancer prevention by selenium, selenomethionine in yeast is used.\textsuperscript{28}

Selenate and selenite seem to have both similarities and differences in terms of bioactivity. For example, when relatively low doses are given to human subjects, selenate absorption and urinary excretion are faster than that of selenite, though retention is about the same.\textsuperscript{29}

One disturbing result is found in a study in selenium-replete humans.\textsuperscript{30} In this work, one commercial yeast selenium supplement is far superior to another commercial yeast selenium supplement. This study is from a number of years ago. It would be interesting to see if today’s high-yeast selenium supplement products show differences in bioavailability.

In conclusion, all of the major selenium supplement forms are capable of impacting selenium function, but for certain effects, differences have been seen between supplement forms. Unfortunately, the differences do not present a clear picture of the advantages of one form over another.

**TYPICAL INTAKES VERSUS NEEDS**

Selenium intake is very much tied to the soil selenium content or bioavailability where plants are grown or livestock is grazed.\textsuperscript{11} Among commonly eaten foods, two of the best sources are wheat products, especially whole grains, and meat, in the broad sense to include poultry and fish.\textsuperscript{31} For the latter category, though all meat products are respectable selenium sources, some products are better than others. As far as wheat products, the selenium content can vary greatly depending on the soil where the wheat was grown. In the U.S., pasta is an especially good selenium source because it is made from durum wheat that comes from the Dakotas, where soil selenium is high.\textsuperscript{31} Another food, Brazil nuts, can be extremely high in selenium, though the content may vary depending on the origin of the product.\textsuperscript{32}

There are a substantial number of records of selenium deficiency in livestock in areas where there is low soil selenium or low selenium bioavailability to the plants.\textsuperscript{11}
In some of these same areas, marked selenium deficiency can also be seen in humans (see Geographical Populations with Severe Selenium Deficiency). On the other hand, in some of these areas, there are not many cases of severe human selenium deficiencies. Possibly, the selenium in the soil may be good enough to prevent severe human deficiency. In addition, not all human food in these areas is derived from local sources. Furthermore, as discussed immediately below, the worst cases of human selenium deficiency seem to involve not just low selenium intake, but also additional factors that worsen the consequences of low selenium intake.

The first report of a large-scale selenium deficiency was for a section of China where a condition called Keshan disease was observed. The disease appears to result from a combination of low selenium intake plus a susceptibility to a strain of virus known as the coxsackievirus. The cause of the low selenium intake appears to be that the selenium in the soil is largely unavailable to the plants grown in the region. Keshan disease has a number of symptoms including cardiomyopathy. Once the disease is established, selenium administration is unable to cure it. On the other hand, increased oral intake of selenium is very protective against Keshan disease.

Another seemingly selenium-related disease, known as Kaschin-Beck disease, has been detected in children in parts of Asia. The most prominent symptoms are joint necrosis related. As with Keshan disease, Kaschin-Beck disease also occurs in areas where the availability of soil selenium for plant growth is low. Kaschin-Beck disease is thought to be caused by a combination of selenium deficiency plus other factors such as mycotoxins in grains grown in the region.

There are some other areas, such as Turkey, where iodine deficiency plus some degree of selenium deficiency combine to disrupt thyroid function. Supplementation with both iodine and selenium help with thyroid function.

Somewhat low soil selenium has been identified in other areas of the world, such as in parts of Australia, Finland, and New Zealand. In Australia, selenium intake is considered moderately low, but no obvious symptoms of widespread, overt selenium deficiency have been noted. In Finland, there has been a conscious effort to keep selenium intake adequate by measures such as adding selenium to fertilizers for agricultural crops. In New Zealand, there are reports of moderately low intake, low blood selenium values, and low blood glutathione peroxidase activities. However, what, if any, health symptoms are associated with these findings are not well characterized. Several attempts at elucidating the symptoms have not produced clear examples. For example, selenium supplementation has no obvious effects on outcome in low-birth-weight infants. In other work, since degeneration of the cardiac and skeletal muscle is associated with selenium deficiency in livestock and experimental animals, a study was done to see if similar problems occurred in New Zealand. In subjects who complained of muscle problems like pain and tenderness, both selenium supplementation and placebo improved subjective symptoms in about half the subjects tested. In still other work, an analysis of whole blood selenium in a small number of people with dilated cardiomyopathy is similar to controls (lower values in the patients but not statistically significant).

Selenium deficiency also occurs with some medical states such as total parenteral nutrition (though this is usually treated or prevented now). Another example is GI tract problems such as Crohn’s disease and surgical intestinal
removal, which can impair selenium absorption.\textsuperscript{43,44} There may also be some degree of selenium deficiency in other types of inflammation, though this issue is not settled. Serum selenium falls with inflammation,\textsuperscript{45,46} though how this affects overall body selenium functional status is still unclear. For example, in rats, endotoxin injection drastically lowers serum and liver selenium, but produces small increases of selenium in some other tissues.\textsuperscript{46} It is not clear if the inflammation-induced fall in serum and liver selenium produces a degree of selenium deficiency, though that seems to be the assumption that many researchers are making. More research is needed to confirm or refute this idea, though some has started (see the Arthritis and HIV subsections).

The consequences of marginal selenium deficiency in otherwise healthy people are poorly characterized. There are indications that this research area will be given more attention in the next few years. One reason is that concern has been expressed about falling selenium intake in the U.K.\textsuperscript{48} Among the causes for this trend is the decline in import of high selenium wheat products. There has also been some speculation that bioavailability of selenium may have fallen in certain areas due to acid rain or excessive artificial fertilization of soils, both of which reduce plant selenium absorption. The average selenium intakes in the U.K. are now below recommendations of both the U.K. and U.S.\textsuperscript{48} A pilot study of low-dose selenium supplements in U.K. residents show improved selenium enzyme activities, though the effect varied a lot between subjects.\textsuperscript{49}

Selenium intake in the U.S. and some other industrialized countries generally exceeds the RDA,\textsuperscript{50} but there are reasons why selenium intake may still be a concern there:

1. The RDA is based on blood glutathione peroxidase activities, but it is unclear how well these activities relate to tissue activities.
2. There may a substantial number of people who are the exception to the rule that selenium intake exceeds the RDA, though this has not been checked extensively.
3. Based on blood selenium values, certain health conditions, such as critical illnesses, premature birth, alcoholism, and HIV infection, produce some degree of deficiency in some people (see the next section).
4. Optimal selenium intake for cancer prevention may be considerably greater than the RDA (see the Cancer subsection).

**CURRENT RESEARCH ON SUPPLEMENT USE**

**Geographical Populations with Severe Selenium Deficiency**

Applications of selenium supplementation to geographical pockets of severe selenium deficiency, or suspected severe selenium deficiency, can be efficacious.\textsuperscript{11} These applications, in some cases, can include treatment of the combination of selenium and iodine deficiencies.\textsuperscript{33}
CANCER

The idea that selenium intake and cancer could be connected is not new. The first big impetus for this connection was a series of epidemiological observations and rodent carcinogenesis studies. The rodent studies show differences between high and low selenium intake in terms of resistance to chemically induced carcinogenesis. The main problem with many of the early studies is that the high selenium intake levels are too high to have practical human applications.

Some of the emphasis on research examining the relationship of selenium to cancer has focused on deficiency, severe or marginal. In principle, selenium deficiency could compromise immune function, which could also affect cancer risk. In addition, selenium deficiency could produce low glutathione peroxidase activities, which could produce high oxidant stress, which is a factor in cancer onset. Despite this rationale, a lot of the work on selenium and cancer has considered selenium supplementation for purposes other than correcting a deficiency. The supplementation levels (usually 200 g/day) are generally well above the RDA. At those intakes, glutathione peroxidase activities would not be expected to increase beyond those produced by RDA level intakes. Possible anti-cancer mechanisms for the high selenium intakes include immunostimulation, which selenium could conceivably do even when intake is increased from RDA levels to above-adequate levels. Another possibility is that thioredoxin reductase activity is involved. More dietary selenium may be needed to saturate this enzyme activity compared to glutathione peroxidase. Other proposed mechanisms involve moderately high concentration of selenium compound metabolites, such as methyl selenol, causing apoptosis of cancer cells (programmed cell death) and having other regulatory effects. It may be relevant to these latter mechanisms that oral selenium supplementation increases prostate selenium levels in non-selenium-deficient men.

This author also proposes another possible anti-cancer mechanism for a moderately high selenium intake. This mechanism involves glutathione peroxidase. Although erythrocyte glutathione peroxidase activities normally plateau at RDA intake levels, this enzyme activity may not plateau as easily at some potential cancer sites, particularly if precancer processes affect selenium distribution. Thus, high selenium intake may be needed to maximize glutathione activities at certain sites in certain circumstances.

A number of lines of evidence have been used to link selenium and cancer. Examples are summarized in Table 7.2. Note that a prospective study is where some type of reading is taken (e.g., serum selenium) for samples obtained before testing for an outcome (in this case, a cancer-related measure). For example, serum selenium readings are done for cancer-free subjects who are then monitored for cancer onset.

It is noteworthy that the prospective studies listed in Table 7.2 are just a few examples of many studies. These studies have surveyed literally tens of thousands of people. For example, in a study of Taiwanese men with chronic hepatitis–virus infection, a noted risk factor for liver cancer, over 7000 men are studied. In this study, an inverse association is seen between selenium levels in stored plasma and later development of hepatocellular carcinoma. One question about the serum or toenail selenium studies is whether they are suggestive of a detrimental effect of...
some degree of selenium deficiency, or whether they are suggesting a protective effect of high selenium intake.

The observations of Table 7.2 that have gotten the biggest recent attention are those of the last listing. Some of the results that have garnered the most attention are not the original primary focus of the project, which had to do with skin cancer. The most attention-catching results include a lower prostate cancer risk in the selenium supplement users. Unfortunately, some of the initial excitement has been tempered by new analysis of the subjects for the years following the initial published report. 28,65,66 Although some positive effects still remain, some became less general, some others were eliminated, plus some detrimental results appeared. These negative observations, plus examples of other observations not supporting a selenium-cancer prevention relationship, are summarized in Table 7.3.

Many speculations can be made about the supportive and non-supportive studies for selenium intake and cancer prevention. The bottom line seems to be that the picture is not yet clear. One point that can be made for the positive results is that the prospective studies (predictive studies) with positive results cover many more people than those of prospective studies with negative results. Also, the negative

TABLE 7.2
Examples of Evidences Linking Selenium to Cancer Risk

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<th>Table 7.2</th>
<th>Examples of Evidences Linking Selenium to Cancer Risk</th>
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<tr>
<td>Prospective studies: serum or toenail selenium predict risk of cancer incidence or mortality 53-57</td>
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<tr>
<td>Chinese hepatitis carriers: liver cancer cases, selenium supplement vs. placebo, 7 vs 0 58</td>
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<tr>
<td>Selenium in salt in China: 35% reduction in liver cancer incidence vs. control towns 59</td>
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<td>Selenium supplements (3 and 9 months) gives a small but significant decrease in PSA* 60</td>
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<tr>
<td>Supplementation with selenium plus other factors lowers cancer mortality, especially for stomach cancer, in a high-cancer section of China 61</td>
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<tr>
<td>Long-term selenium supplementation in U.S. in subjects with a history of non-melanoma skin cancer: lower cancer mortality and lower total cancer incidence; lower prostate, lung, and colorectal cancer incidence 62-65</td>
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<td>* Prostate-specific antigen levels, which are correlated with prostate cancer risk 64</td>
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TABLE 7.3
Examples of Negative Results for Studies on Selenium and Cancer Risk

<table>
<thead>
<tr>
<th>Table 7.3</th>
<th>Examples of Negative Results for Studies on Selenium and Cancer Risk</th>
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<tr>
<td>Lack of association of toenail selenium and some cancers 67</td>
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<tr>
<td>No association is seen for serum selenium and later lung cancer in Chinese tin miners 68</td>
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<tr>
<td>Serum selenium shows no predictive value for later colon cancer incidence 69</td>
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<tr>
<td>Update of the study on long-term selenium supplementation in the U.S. in subjects with a history of non-melanoma skin cancer: total cancer incidence effect now found to be significant just for men, biggest change for prostate cancer seen only in certain subgroups, former report of reduced risk of colon and lung cancer are not seen in longer time frame; higher rates seen for some forms of skin cancer and some other body site cancers, all-site cancer higher in men with the highest serum selenium values 28,65,66</td>
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study with Chinese miners\textsuperscript{68} may not have wide-range applicability since the environmental stress is very high, and the selenium supplement levels may have been too low.

Some of the concerns brought out in the reevaluation of the large U.S. selenium supplementation study (last line, Table 7.3) may not be all that serious. For example, the increase in cancer risk seen for skin cancer may not indicate a real increased risk. As noted in one of the papers,\textsuperscript{66} for certain skin cancers, if one eliminates cancers diagnosed in the first year of supplementation or placebo, then the increase is no longer statistically significant. This elimination may be justified under the grounds that the cancer process may have already begun before the selenium supplementation started. In addition, it is often forgotten that the increases seen for some other body sites in the supplemented group, such as breast cancer, are not statistically significant.\textsuperscript{28} The same is true for the increase in all site cancer in men with the highest serum selenium values.\textsuperscript{28} In addition, for many body sites, the total number of cases is not overly large, especially considering the size of the total study population, and considering that this population is a high cancer risk group. Therefore, this work raises the possibility, but does not prove, that selenium supplementation can raise the rate of some cancers.

Another issue that is perhaps overrated is that overall cancer incidence effects are statistically significant only for men.\textsuperscript{28} This is not that surprising considering two facts. One, there are about three times more men in the study than women. Two, the biggest effect is on prostate cancer, which is limited to men.

It also needs to be remembered that this study is done on only one type of subject: people with a past history of certain types of skin cancer. Thus, any results found here may or may not be applicable to other populations. Along similar lines, it should be recalled that certain subgroups of men in this project show better responses than others (e.g., PSA levels and starting serum selenium levels). Although some people view this as a negative finding, this should not be overly unexpected. For many supplementation therapies, some people are more apt to be helped than others. Thus, selenium has not yet been ruled out for value in some types of cancer prevention.

On the other hand, it should be noted that for the positive results obtained in the large supplementation project,\textsuperscript{28,63,65,66} the selenium supplementation does not eliminate cancer. Thus, at best, selenium supplementation should only be part of a cancer prevention plan. That should be obvious, given that cancer is a complex disease. Even so, this idea is often forgotten when discussing one specific intervention. Similarly, the fact that selenium does not lower cancer rates in all sites should be expected. Many preventive agents may be better at certain site cancers than others.

In conclusion, there is data on both sides of the issue as to whether selenium supplementation can reduce cancer risk, but there are still many research directions left to explore. There is the possibility that selenium supplementation can sometimes increase cancer risk, but this is very uncertain. Ultimately, we may find that selenium supplementation is more appropriate for some people than others, but that may be the case for many applications of mineral supplements.
CARDIOVASCULAR DISEASE

Severe selenium deficiency, particularly when combined with viral infection, can cause cardiovascular problems including cardiomyopathy. However, much of the current interest in selenium and cardiovascular health centers around two different questions. One, can marginal selenium deficiency raise the risk of common cardiovascular disease? Two, can above-adequate selenium intake lower the risk of common cardiovascular disease?

There is some theoretical reason to think that selenium may help prevent common cardiovascular disease. One idea is that selenium has antioxidant roles and oxidant stress contributes to cardiovascular disease. However, there may also be other possible mechanisms such as inhibition of platelet aggregation, which is an action of selenium.

Although this issue has drawn some attention, there is not much recently published new research on the subject. Older epidemiological studies have provided some evidence for a possible role of selenium intake in cardiovascular disease. On the other hand, studies on serum selenium patterns within populations are conflicting (some show a relationship, others do not). An interesting perspective can be found in a recent review article. Although this article centers on the possible need for many people to increase selenium intake, the cardiovascular disease connection is not presented as a strong argument. Instead, the review presents this area mostly in light of the conflicting epidemiological evidence. The review also states that even if low serum selenium is associated with some cases of cardiovascular disease, it may just be a regulatory reaction to inflammation.

There is a need for supplementation studies to settle the issue. Many studies of nutrient supplements and cardiovascular disease use markers of risk such as cholesterol or LDL oxidation. However, in the case of selenium, the main mechanisms of protection against cardiovascular disease may not affect these measurements. Therefore, studies on selenium supplementation may have to use actual cardiovascular disease events as the end points. This would be quite lengthy and require a lot of research subjects. This may explain why there has not been a lot of recent research in this area.

In summary, despite the hype in the popular press and on the Internet about selenium supplements and cardiovascular disease, there are no direct demonstrations of this concept, and indirect evidence is not clear.

ARTHRITIS

As noted earlier, serum selenium values drop in humans with inflammation such as arthritis, but it is not known whether or not this is a sign of selenium deficiency. One argument for marginal selenium deficiency contributing to arthritis risk is a large case-control study in Finland. This study examines serum selenium in people who initially do not have arthritis. Although no relationship is seen for development of rheumatoid-factor-positive arthritis, the group with the lowest serum selenium values has the highest incidence rate for rheumatoid factor-negative rheumatoid arthritis. Since these results assess serum selenium prior to arthritis onset, the results argue against the idea that low serum selenium in arthritis is only due to disease-
induced regulatory responses. On the other hand, the study does not completely rule out the possibility that low serum selenium is just a coincidental marker of other factors that predispose to arthritis.

One German study supports the idea that selenium status may often be marginal in arthritis patients. This study reports a substantial difference between controls and arthritis patients in erythrocyte selenium contents. Selenium supplementation does not normalize these values, but does improve certain indices of disease severity.

The results for glutathione peroxidase activities in rheumatoid arthritis patients are mixed (reports range from low values to high values). There is also some diversity in reports on selenium supplementation effect on glutathione peroxidase activities in rheumatoid arthritis. For example, selenium supplementation can increase activities in erythrocytes without fully normalizing activity in a white blood cell population.

Clinical trials of selenium supplementation in rheumatoid arthritis have not been exhaustive. One study in Germany was mentioned earlier. The other few that exist have not been as encouraging as hoped. The most positive result came in a double-blind, randomized controlled trial in a very small group of people. Supplementation with 200 g selenium as selenium-enriched yeast for three months shows a significant reduction in pain and joint involvement. However, a later similar study by the same group was not as positive. Both the placebo group and the selenium group show the same degree of reduction in a number of symptoms of discomfort. The authors themselves state that the placebo effect is strong in the results. The selenium group does show some improvement in arm movements and health perception. However, this may be related to selenium effects on mood, which though still tentative, are possibly true (see the Mood subsection).

Another study examines six months of selenium supplementation versus placebo in 40 rheumatoid arthritis patients. The patients in the selenium group are given daily supplements of 256 g selenium as selenium-enriched yeast. Although concentrations of selenium in serum and erythrocytes increase considerably, no significant anti-rheumatic effects of selenium are demonstrated.

Although most of the work on selenium and arthritis has focused on the rheumatoid variety, one supplementation study has considered osteoarthritis. In this work, a commercial supplement of selenium plus three vitamins fails to demonstrate significant efficacy versus placebo at three or six months.

In conclusion, rheumatoid arthritis might make people prone to marginal selenium deficiency, which might worsen the arthritis. In addition, marginal selenium deficiency in non-arthritic subjects may increase the risk of later arthritis. However, none of these statements has been confirmed satisfactorily. Selenium supplement studies, though not extensive, have not given a clear indication of efficacy. Possibly, future work with different study designs might show benefits in at least some people with arthritis, but this is still speculative.

**Pancreatitis**

Another disease of inflammation is pancreatitis. Selenium supplementation has been considered as part of the therapy and prevention of this problem, but usually, this
consideration has come as part of a combination antioxidant therapy, not selenium administration alone. A recent review\textsuperscript{79} concludes that there is evidence that patients with chronic pancreatitis have enhanced levels of free radical production and antioxidant deficiencies, especially for selenium. The review further concludes that limited published research suggests that dietary antioxidant supplementation may ameliorate the pain associated with chronic pancreatitis, diminish the frequency of acute exacerbations, and reduce the requirement for pancreatic surgery.

Exactly why there would be deficiencies of selenium and other antioxidant nutrients during chronic pancreatitis is not totally settled. Various reasons have been proposed, though not all data supports these propositions.

The best-known study of selenium and chronic pancreatitis is from the Manchester Royal Infirmary, Manchester, U.K.\textsuperscript{80} In fact, the connection between chronic pancreatitis and antioxidant therapy is sometimes called the Manchester Oxidant Stress Hypothesis.\textsuperscript{80} The treatment of the combination of selenium (600 µg/day) plus other antioxidants, in patients with chronic and recurrent pancreatitis, significantly reduces pain and number of days spent in the hospital. The treatment also seems to greatly reduce the need for surgery. If this success can be duplicated in other settings, then this therapy could become a standard treatment.

In contrast to the work on chronic pancreatitis, the work on acute pancreatitis in relation to selenium and other antioxidants has not been as encouraging. On the positive side, in animal models for severe acute pancreatitis, a seleno-compound, which has a glutathione peroxidase-like activity, has protective action.\textsuperscript{81} In contrast, a review\textsuperscript{82} notes that human clinical trials of selenium therapy have not been successful for acute pancreatitis. One reason for the difference in human and animal work could be in the form of selenium given. The selenium supplements used in the human trials can only increase glutathione peroxidase activity within the limits of synthesis of the proteins. On the other hand, the animal studies use a specific compound that could have glutathione peroxidase-like activity independently of the glutathione peroxidase enzymes. Whether this same compound, or one like it, could be used for human therapies remains to be seen.

In contrast to these results, there is a small study in Germany where intravenous selenium, in patients suffering from acute necrotising pancreatitis, shows a mortality of 89% in controls vs. 0% in treated.\textsuperscript{83} This observation should be given follow-up.

In summary, there are indications that chronic pancreatitis can be helped by supplementation with selenium plus other antioxidants, though a large-scale demonstration is needed for confirmation. The case for selenium with acute pancreatitis has been less promising, though there may be some selenium-related approaches that can be tested more.

**Human Immunodeficiency Virus (HIV)**

There is a precedent for tying selenium status to progression of a viral disease. As noted earlier, the classic selenium deficiency known as Keshan disease involves enhanced virulence of a virus.\textsuperscript{11} Thus, progression of another viral problem, HIV infection, could be affected by selenium status. This would be especially true if the
viral infection predisposes a person to selenium deficiency. This may happen even in the early stages of HIV infection, as evidenced by a decline in plasma selenium.84 During the development of acquired immune deficiency syndrome (AIDS), selenium deficiency can be substantial, though a degree of malnutrition can exist for a number of nutrients.84 However, the decline in selenium status has predictive value for the rate of AIDS progression and mortality,84,85,86 though this may be coincidental to macronutrient depletion.84 In a mouse model for AIDS, selenium supplementation produces higher glutathione peroxidase activities and lower lipid peroxide values, an indication of decreased oxidant stress.87 Some immunological effects are also noted.

There have been a few studies of selenium supplementation in HIV positive people, though none has shown a major, large-scale physiological effect. One study has reported improvements in mood-related parameters.88 Another study reports inconsistent results.89 An additional study of selenium supplementation has been carried out in 186 HIV positive men and women.90 A significant decrease is seen in hospitalization parameters (e.g., number of hospitalizations). There are two limitations to the study. First, a substantial effect is seen in the placebo group. Second, the placebo and selenium groups are not identical in regard to conventional HIV therapy drug use. Nonetheless, this study, along with the other considerations noted above, justifies further research on selenium supplementation in HIV positive people. On the other hand, to say that selenium supplementation is a major benefit for AIDS patients, as is claimed on some Internet sites, is premature.

**MALE INFERTILITY**

As noted above in the Overview of Function section, selenium has specific roles in male reproduction. In addition, there is a form of glutathione peroxidase that seems to be especially involved in protecting the fertility of spermatozoa.88 In one study of infertile men, the sperm protein activity of this enzyme in infertile men is just half that of fertile men.91 It would be interesting to see if selenium supplementation can raise these activities in infertile men, or if the low activities are just a regulatory reaction or a metabolic defect that cannot be overcome with high selenium intake. If supplementation could raise activities, then this could mean that some infertile men do not consume an RDA level of selenium. On the other hand, it could also mean that some infertile men need moderately high amounts of selenium to get normal activation of this form of glutathione peroxidase. However, all of this is speculative at this time.

Another argument for a selenium–infertility connection is that in animals consuming selenium-deficient diets, structural abnormalities in the sperm midpiece occur that are linked to poor motility and frequent tail breakage.92,93 Therefore, selenium nutritional status could be a factor in human male infertility. Even so, this does not automatically mean that selenium deficiency is a usual contributor to this problem in humans. One reason is that in the animal studies, the degree of selenium deficiency likely greatly exceeds what would be seen in most infertile males (many of which may not even be selenium deficient at all).
One argument for a selenium–human infertility connection is that seminal fluid selenium concentrations correlate positively with sperm count, as well as with total sperm concentration, in a group of subfertile Norwegian men.\(^9^4\) However, it should be noted that high sperm selenium concentrations are also reported to have a negative influence on the number of spermatozoa, sperm motility, partner abortion rate, and signs of partner ovarian dysfunction.\(^9^5\) Thus, too much or too little selenium in semen could be detrimental. It should also be considered that in another study, selenium concentration in 211 semen samples from normozoospermic, oligozoospermic, asthenozoospermic, and azoospermic men finds no correlation with sperm count or motility.\(^9^6\)

A few studies have been done on selenium supplementation and fertility-related parameters. For example, supplementation of subfertile men with 100 g selenium/day for three months significantly increases sperm motility.\(^9^7\) This study is done with subjects from the U.K., where mean selenium intake has become marginal in recent years.\(^4^8\) Of the men receiving the selenium, 11% (five men) achieve paternity compared to none in the placebo group. On the other hand, it should be noted that for sperm motility, the study had a high number of non-responders. In fact, a statistically significant effect is only achieved if the selenium group is pooled with a selenium-plus-vitamins group. It is also noteworthy that in a study of subfertile Polish men, administration of 200 g selenium/day shows no benefit for sperm motility.\(^9^8\) In another study,\(^9^9\) nine oligoasthenoteratozoospermic men are supplemented for a period of four months with both selenium and vitamin E. Statistically significant increases are observed for selenium and vitamin E levels, sperm motility, and percent live or percent normal spermatozoa. All of the parameters return to baseline values during the posttreatment period. Even so, none of the couples report a pregnancy during the supplementation period. Furthermore, this study is not placebo controlled. Finally, in a recent study, vitamin E plus selenium supplementation produces a significant decrease in a measure of lipid oxidant stress and an improvement of sperm motility.\(^1^0^0\) However, the study seems to suffer from poor compliance, as less than half the original subjects completed the study.

In conclusion, there is only weak or inconsistent evidence that selenium supplementation could help many men with infertility. One possible need for future studies is to look for subpopulations of infertile men who may be selenium responsive. There may also be an optimal level of selenium supplementation that has not been identified. Too much as well as too little seminal selenium could be detrimental.

**Pregnancy Miscarriages**

This issue in relation to selenium gets some strong endorsements on the Internet. One line of reasoning is that selenium supplementation has sometimes been used to prevent miscarriages in veterinary practice.\(^7^1\) Despite these endorsements, the current data linking selenium supplementation to human risk for miscarriage is weak. First of all, there are no direct studies of the subject. Moreover, the evidence for marginal selenium deficiency associated with miscarriage is not very strong because the number of studies is low, most of the studies focus on just serum selenium, and the
studies give mixed results (some studies find depressed serum selenium in women with recurring miscarriage, while others do not).\textsuperscript{101,102,103} One of the studies with a negative finding has been criticized for including women who have had one miscarriage,\textsuperscript{103} but there are other studies with negative findings where that is not the case.\textsuperscript{102} One study in India has evaluated selenium content of red blood cells and found the values low in women with recurring miscarriage.\textsuperscript{104} However, the mean value is not that low (80\% of normal). In addition, the values are taken after the miscarriages, when the women are not pregnant. This means that any selenium depletion could be due to a practice or body reaction that has resulted from the women’s response to the miscarriages.

Even if serum or blood cell selenium is low in women with recurring miscarriage, it does not necessarily mean that marginal selenium deficiency contributes heavily to miscarriage. Possibly, the low blood selenium level is a reaction to the processes behind the miscarriage, rather than a cause of the processes. Also, poor selenium status, if it is really occurring, could just be a marker of some aspects of poor nutrition, or some physiological tendency, either of which could be the real contributor to the miscarriages.

Conspicuously absent from most studies on selenium and miscarriage is measurement of glutathione peroxidase. In one exception, red blood cell and plasma glutathione peroxidase activities of women who had a miscarriage are significantly lower than in normal pregnancies.\textsuperscript{105} However, the measurements are taken right after pregnancy termination. This lowering of glutathione peroxidase could be a recovery reaction rather than a cause of what happened. Also, it is unclear that the lower enzyme activities are due to a selenium problem. In support of this concept, plasma selenium contents are normal in these women.

Despite all the concerns just expressed about existing data, it is still possible that selenium status does play a major role in a substantial number of miscarriages. The existing data do not rule that out. However, the data also do not rule it in, given the small amount of ambiguous data currently available.

**Mood**

During selenium deficiency, the brain retains this mineral better than other tissues.\textsuperscript{106} This suggests that some selenium functions in the brain are of high priority. One possible function is mood maintenance. The mechanisms that could be involved are unknown, though speculations include the involvement of thyroid hormone.\textsuperscript{107} Several studies have reported that a low selenium intake is associated with poorer mood.\textsuperscript{71} One example is a study where 11 healthy men are given diets to deplete, then replete, selenium.\textsuperscript{108} The men are tested by a criterion known as the Profile of Mood States–Bipolar Form. No significant effects are reported for selenium intake, but the lower the starting selenium, the lower the scores fall with selenium depletion. Thus, this study does not in itself provide a direct link between mood and selenium intake, but does offer the possibility that other study designs might provide the link.

In a study of selenium supplementation, 50 subjects are given either a placebo or selenium, plus they have their background diet analyzed for dietary selenium.\textsuperscript{109} On three occasions, these subjects fill out the Profile of Moods States form. Selenium
intake is reported as associated with a general elevation of mood, and in particular, a decrease in anxiety when taking selenium. In addition, the lower the level of selenium in the diet, the more reports of anxiety, depression, and tiredness, which also decrease following five weeks of selenium therapy. The strength of this study is that it is a double-blind crossover design. There is variation in the background diet, though the study tries to examine diet and supplementation simultaneously.

If selenium does affect mood, it is not known whether the connection concerns detriments of marginal deficiency, benefits of above-adequate intake, or both. One argument against the marginal deficiency is that if the brain resists depletion of selenium, then marginal selenium deficiency should not impact brain function (including mood regulation). On the other hand, a marginal selenium defect that does not occur directly in the brain may still affect the brain. For example, an effect on thyroid hormone metabolism could affect brain functioning.

This area is far from settled, but in this author’s opinion, there is enough pilot data to consider the matter with further research.

**Immune Function**

In addition to effects on viral virulence (see the HIV subsection), selenium can have other effects on immune function. This can be seen in selenium-deficient animals, though as noted earlier, the mechanisms are not completely clear. A number of human studies have been done with selenium supplementation and immune function. However, many are hard to interpret in terms of practical consequences. Some studies give multiple nutrients, not just selenium. In another study, although just selenium is tested, and improvement is shown for some of the parameters, the subject size is very small. This is especially true for the population studied, which is renal dialysis patients. In such subjects, there can be tremendous variations in secondary health problems, drug prescriptions, compliance tendencies, and dietary practices. In some other studies, the starting selenium status of the subjects is not well characterized, or only high selenium doses are tested. In some of the high-dose studies, certain laboratory parameters of immune function, such as natural killer cell activity, do increase. In one of these studies, the subjects are declared to be selenium replete, which raises the possibility of a stimulating effect on immune function of above-adequate selenium intakes. Even so, this concept would require considerably more verification before it would be accepted.

Despite these issues, there are enough positive results that it would seem worthwhile to expand studies on selenium supplementation and immune function.

**Asthma**

Some Internet sites and alternative medicine writings are declaring that selenium prevents and treats asthma. There may be some truth in this claim, but at this point, the claim is still speculative. Several studies show that values for some selenium status assessment tools are low in asthmatics vs. controls, and low for atopic vs. non-atopic subjects. However, these differences are generally not very large. Conceivably, the differences in selenium function could be bigger in certain tissues,
such as the lung, but that is pure speculation. It is also possible that the small differences in selenium-related blood measures are just a relatively benign effect of asthma or the drugs given to treat this problem.

A few small selenium supplementation studies have been tried with asthmatic subjects. In one, anti-inflammatory regulatory actions are seen when cells are challenged outside the body. This work is interesting, but it needs follow-up in other study designs. A different study, which examines 17 corticoid-dependent asthmatics in Slovakia, reports the selenium brings about reduced consumption of inhaled corticosteroids. However, the study is small, plus, it is not placebo controlled despite involving a patient-controlled end point. In an additional study, a significant improvement is reported for assembled clinical evaluations in 12 selenium-supplemented Swedish asthmatics compared to a placebo group. However, this improvement did not translate to significant changes in the separate clinical parameters of lung function and airway hyperresponsiveness.

In conclusion, there is some data connecting selenium status with asthma prevention or treatment, but the case is not compelling yet.

**KETOGENIC DIET IN EPILEPSY PATIENTS**

The so-called ketogenic diet is often applied to intractable epilepsy, even though the diet is deficient in a number of nutrients. A very recent study reports a patient on this diet who had no detectable whole blood selenium plus cardiomyopathy, the classic symptom of Keshan disease. In further work in this same study, 10 of 39 children show low blood selenium values, which improves upon selenium supplementation. This study is interesting and potentially important for children on the ketogenic diet. Follow-up studies should include other measures of selenium status (e.g., glutathione peroxidase) and more parameters indicative of potential health consequences of selenium deficiency.

**MISCELLANEOUS HEALTH PROBLEMS**

There are a number of other health problems where some type of blood selenium measures are reported as low. At present, there is not a tremendous amount of information on the benefits of selenium supplementation in these states. In this author’s opinion, if low serum selenium combined with low erythrocyte glutathione peroxidase values appear in the literature for a condition, then low-dose supplementation of selenium shouldn’t hurt and may help. In some extreme cases, more aggressive supplementation may be warranted, but that can’t be said until more information is gathered.

An example where more study is needed is for critical care patients. In one study of some types of these patients, low serum selenium remains low despite some degree of selenium supplementation. In other work, a study in Germany considers high-dose selenium supplementation in critical care patients at risk for septic shock. The supplementation improves serum selenium readings, as well as a few measures of oxidant stress and thyroid hormone metabolism. It would be good to
know if, in critical care settings, high selenium doses actually confer any benefits or pose any risks.

**GENERAL ANTIOXIDANT EFFECTS**

In this author’s opinion, there is a need for a general characterization of various markers of antioxidant function and oxidant stress in people with differing starting selenium status and health states. This has been done only to a minimal degree with varying results, and in some of the studies selenium is given only as part of an antioxidant mixture. At present, we don’t know enough about how much variations in selenium status actually affect antioxidant capacities and in whom. Unfortunately, a comprehensive version of such a study is unlikely to get funded by U.S. government grant agencies because it would be labeled as a “loser descriptive study.”

**TOXICITY**

The biggest known case of selenium toxicity from foods or supplements occurred in certain areas of China, the same country that has shown the biggest population group for selenium deficiency. The toxicity cause was eating food grown in high-selenium soil, the exact opposite of the case for Keshan disease in another part of China.

<table>
<thead>
<tr>
<th>TABLE 7.4</th>
<th>Selenium Supplements at a Glance</th>
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<tbody>
<tr>
<td><strong>Adult RDA:</strong> 55 g (may cover basic function without maximizing protective actions against health problems that are not strictly selenium deficiencies)</td>
<td></td>
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<tr>
<td><strong>Typical dose in supplement studies:</strong> RDA levels for selenium deficiency prevention, 200 g for health problem treatment or prevention</td>
<td></td>
</tr>
<tr>
<td><strong>Best supplement complex:</strong> selenite, selenate, L-selenomethionine (free or in yeast) all have high absorption compared to most trace mineral supplements; in comparison studies for various bioactivities, the different forms have shown the same activity in some cases, but differences in others (all three forms have been “winners” in comparisons, but L-selenomethionine has more “wins” than the others)</td>
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<tr>
<td><strong>Applications:</strong> there is supportive, but not conclusive, data for prevention of some cancers, for chronic pancreatitis treatment, and for nutritional support for epileptic children on the ketogenic diet; for other applications, there is less supporting data, but more research is justified; these applications include miscellaneous immune and antioxidant effects, as well as nutritional support for people with HIV; for many other applications, there is a theoretical basis, but just a little supporting data (e.g., treatment/prevention of arthritis and therapy for reproductive problems)</td>
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<tr>
<td><strong>Upper Level:</strong> 400 g (below an intake that will cause early physical signs of toxicity)</td>
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</tr>
<tr>
<td><strong>Safety issues:</strong> supplements usually not a concern since most doses are well below 400 g; the idea that supplements raise the risk of certain cancers is very speculative</td>
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</table>
The adult Upper Level is based on the intake from food plus supplements that should stay below the total intake that cause an early toxic reaction observed in China.\textsuperscript{11} This reaction is marked by hair loss and nail sloughing.

Selenium toxicity due to supplements has not been commonly reported, probably because the doses being considered for cancer prevention, though higher than the RDA, are still below the Upper Level for adults. There has been one prominent report of severe selenium supplement toxicity, but this was due to a manufacturing error that produced toxic levels of selenium in the supplements.\textsuperscript{11}

**SUMMARY AND CONCLUSIONS**

For parts of the world with low soil selenium, or low bioavailability of the soil selenium, it seems useful to promote either selenium supplementation, selenium food fortification, high-selenium fertilizers for food plant growing, or the importing of grain foods from high-selenium soil regions. Selenium supplementation for the prevention of cancer, as part of the treatment of chronic pancreatitis, and as a nutritional support for epileptic children on the ketogenic diet all may have some merit, though these applications are not confirmed. The use of selenium supplements to treat or prevent other health problems have various degrees of support, but all still remain fairly speculative. Toxicity risks from common selenium supplement doses are low.

**REFERENCES**


Manganese could be poised to garner major attention from both researchers and the public, or it could continue to generate limited attention. The potential interest burst would likely involve this element as a contributor to antioxidant function, as a builder of bone structure, or as a regulator of blood sugar. On the other hand, the relative obscurity of manganese could continue due to limited information in three areas:

1. Typical intakes vs. needs
2. Bioavailability from different food and supplement sources
3. Sensitivity of various functions to small changes in nutritional status

In other words, we still don’t know if moderate changes in manganese intake from various sources really impacts health in many people. If we can gain more insight on these issues, manganese could prove to be a very interesting mineral in human nutrition.

OVERVIEW OF FUNCTION

Manganese has two general categories of biochemical function. One, which is like magnesium, is that manganese is needed to activate certain enzymes that utilize ATP. It appears that the number of enzymes with an absolute requirement for manganese over magnesium is far less than those that work better with magnesium. Nonetheless, the manganese enzymes are very important. Among these enzymes are phosphoenolpyruvate carboxykinase, a component of gluconeogenesis, and an enzyme family known as the glycosyl transferases. The latter enzymes are involved in producing connective tissue structural carbohydrate, which are especially important in bone formation and maintenance. These carbohydrates, including chondroitin sulfate, are also involved in other connective tissue aspects, most notably joint health.

The other major biochemical function of manganese is to be a component of some metalloenzymes. The best known of these is manganese superoxide dismutase (Mn SOD), which eliminates superoxide radicals in the mitochondria. This enzyme has been the topic of literally hundreds of research papers, though a relatively low percentage of these papers have a nutrition focus. Instead, most of these papers consider biochemical or physiological aspects of Mn SOD. Other manganese metalloenzymes include arginase, the terminal enzyme in the urea cycle, and pyruvate carboxylase, an important enzyme in liver synthesis of glucose.
A substantial amount of a cell’s manganese is found in the nucleus, which has led to speculation that manganese can play enzymatic and non-enzymatic roles in gene expression.\textsuperscript{1,2} More study is needed to sort out this issue.

**OVERVIEW OF METABOLISM**

There are many knowledge gaps concerning the metabolic biochemistry of manganese. However, there are assorted observations and speculations. For instance, little is known about manganese absorption into intestinal cells, but there are hints that regulation occurs to work against excess uptake.\textsuperscript{3,4} Manganese absorption appears to have some overlap with iron mechanisms.\textsuperscript{2} After manganese is absorbed from the intestine, much of it binds to albumin and rapidly enters the liver.\textsuperscript{1,2} From there it can be excreted in the bile, go into liver enzymes, or be transported to other tissues. Manganese excretion via the bile seems to be regulated by body manganese content.\textsuperscript{3} Manganese transport from the liver to other tissues seems to involve transferrin, the protein that transports iron, but some manganese also binds to alpha-2-macroglobulin, a protein that contains tightly bound zinc.\textsuperscript{1,2} The metabolic importance of the latter is unknown. It is not certain how manganese enters extrahepatic tissue cells.\textsuperscript{1,2} There is the thought that this mineral rides in with transferrin in a process that overlaps iron absorption.\textsuperscript{1} Manganese does not seem to have a specific storage protein as does iron or zinc, but quite a bit passively accumulates in bone.\textsuperscript{1}

**NUTRITIONAL STATUS ASSESSMENT**

There has not been a lot of work in this area simply because there has not been a lot of demand for it. Serum or plasma total manganese is the most commonly used tool, but urinary manganese as well as activities of serum arginase or lymphocyte manganese SOD have also been used.\textsuperscript{3}

**BIOAVAILABILITY FROM FOODS AND SUPPLEMENTS**

This area sorely needs more research. Among the foods with the most manganese are nuts, tea, and whole grains.\textsuperscript{5} The bioavailability from these foods is largely unknown, though a rat study suggests that manganese absorption from tea is good.\textsuperscript{6} Indirect evidence suggests that manganese absorption, at least in some circumstances, is inhibited by iron supplements.\textsuperscript{2,7}

Supplement forms include sulfate, gluconate, ascorbate (found in one prominent joint health product), and amino acid chelates. As with food sources of manganese, little is known about the absorption properties of different manganese supplements. The Internet has various sites warning that calcium supplements will impair absorption of manganese supplements. This claim has some support, but the importance is far from clear cut. In a human study, acute absorption of manganese is lowered by adding calcium to human milk but not to other test meals.\textsuperscript{8} In a rat study with a perfusion \textit{in vivo}, calcium inhibits manganese absorption in one section of the intestine, but increases it in another section.\textsuperscript{9} In a study in chickens, feeding high
calcium levels does not affect manganese absorption. Thus, the practical importance of the calcium–manganese interaction remains unknown. Unresolved questions include:

- How high does the calcium-to-manganese ratio have to be to produce a major impairment in manganese absorption?
- Will different calcium complexes have more, less, or the same tendencies to inhibit manganese absorption?
- How is the inhibition enhanced or restricted by foods eaten at the same time as the supplements?

Some Internet sites state that manganese supplements should be taken on an empty stomach. The rationale for this recommendation is unclear. As with most minerals, there are some dietary components known to increase, decrease, or have no effect on manganese absorption.

TYPICAL INTAKES VERSUS NEEDS

Severe manganese deficiency in humans is considered rare or nonexistent short of overall malnutrition. The idea of more marginal deficiencies has received little attention, partly because there is not a good handle on what constitutes adequate manganese intake. In fact, no RDA has been established for manganese. Some consideration of the occurrence of marginal manganese deficiency may eventually be motivated by four considerations:

1. In a balance study, university students do not show particularly high stores of manganese.
2. One supplement study suggests that lymphocyte Mn SOD activities are not maximized by typical intakes by a group of male university students (though this interpretation of this study is controversial; see below).
3. There may be some situations that raise manganese requirements to the point where needs are not easily met by most diets; the data for the practical importance of this concern is not yet compelling, but may become that way with more research; situations that could raise manganese requirements include epilepsy, rheumatoid arthritis, hemodialysis, and states associated with fat malabsorption.
4. Scattered observations say that calcium can interfere with manganese absorption.

The practical consequences of this interference is poorly characterized, but in light of the increasing popularity of calcium supplementation, this issue merits attention.

These considerations indicate that there is the possibility that marginal manganese deficiency may occur in various types of people. However, this issue remains unsettled and is often met with indifference by both researchers and the general public.
CURRENT RESEARCH ON SUPPLEMENT USE

There are relatively few supplementation studies on manganese compared to a number of other minerals. The main studies are summarized in Table 8.1. The study that has drawn the most attention is number 1, a study where manganese chelate supplements increase lymphocyte Mn SOD activities in a group of university male students. There are four possible interpretations of this result:

1. Typical intakes in such subjects are insufficient to saturate Mn SOD protein, which indicates a moderate manganese deficiency is common in these subjects.
2. Typical intakes in such subjects is insufficient to saturate Mn SOD protein, but this and other manganese functions are still good enough to maintain good health.
3. Lymphocyte Mn SOD activity does not max out easily with increasing manganese intake, possibly because Mn SOD gene expression is regulated by dietary manganese.
4. Manganese supplementation at 12 mg/day, which is above the Upper Level (UL), induces a toxic reaction; this elevates Mn SOD gene expression, which is known to be increased by physiological stress.\textsuperscript{16,17}

At present, it is hard to distinguish between these possible interpretations of this very interesting study. Some would argue against the last of the interpretations by saying that there is no direct evidence that the study’s manganese dose and duration can cause a toxic reaction. Although the dose exceeds the Upper Level, the basis for the Upper Level value is somewhat vague (see the Toxicity section).

The casual observer might assume that multiple follow-up studies would immediately follow Study number 1 of Table 8.1. Yet, that has not been the case. Possibly, the reason is simply that manganese is not a big funding priority of nutrition agencies.

Study number 2 of Table 8.1 may give the impression that supplementation with manganese gluconate plus calcium carbonate may aid body weight management. However, the percent increase in fecal fat loss is very small. Moreover, this percent is per total fecal fat, not percent of total ingested fat. The latter would represent a bigger impact on fat balance. Therefore, the impact on absorbed calories is very small.

Studies number 3 and 4 from Table 8.1 are interesting, but manganese supplementation was not tested by itself, only in combination with other products. Thus, it is hard to determine to what extent, if any, the manganese promotes bone and joint health in these studies. Possibly, the non-manganese portion of the products accounted for the full effect. Moreover, if the manganese did play a role, it is not known if the role was correction of some degree of deficiency, or an effect of elevating manganese intake beyond that needed for maintenance of basic functions (an above-adequate intake effect).

There is a rationale for manganese to affect bone and joint health. Manganese function, via the glycosyl transferases, affects production of structural carbohydrates needed for the connective tissue found in bones and joints.\textsuperscript{1} This function is
apparently important for both growth and maintenance. In addition, it is within the realm of possibility that Mn SOD also affects bone health. Superoxide is thought to stimulate bone and joint degeneration.

These connections between manganese and bone or joint health are based heavily on data from severe manganese deficiency in animals. Since severe deficiency is considered very rare in humans, three questions arise concerning manganese and bone or joint health:

1. Can a marginal manganese deficiency affect bone or joint health?
2. If so, how often does this marginal deficiency occur?
3. Would bone health be promoted by eating manganese at levels beyond the minimum needed to prevent marginal deficiency?

At present, each of these questions remains largely unanswered.

Study number 5 from Table 8.1 was likely motivated by three observations. One, severe manganese deficiency in rats produces poor glucose tolerance. Two, some diabetic subjects show high urinary manganese values, which could mean that such subjects lose a lot of manganese. Three, there is an anecdotal report of manganese supplementation helping blood sugar control in a diabetic subject. Despite this background, Study number 5 did not produce a consistent lowering of blood sugar in subjects with or without type 1 diabetes. This may not be extremely surprising upon closer inspection of the blood sugar abnormality in manganese-deficient rats. The effect appears to be due to low concentrations of insulin mRNA. This condition is not considered a typical cause of high blood sugar in type 2 diabetes or in most human high blood sugar states. Type 1 diabetes is characterized by impaired insulin secretion, but the cause is likely completely independent of manganese function. Therefore, unless a new connection is established between manganese deficiency and high blood sugar, manganese supplementation would seem inappropriate for depressing blood sugar in most human situations.

Ironically, it might be interesting to consider an opposite manganese effect, restriction of blood sugar depression. As noted above, two enzymes that need manganese for function are components of gluconeogenesis.

Conspicuously absent from manganese research is work on interactions between dietary manganese and agents that can elevate Mn SOD gene expression. Mn SOD

### TABLE 8.1
Human Manganese (Mn) Supplementation Studies

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Effect</th>
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<tbody>
<tr>
<td>1. College-aged males</td>
<td>Increases lymphocyte Mn SOD activity</td>
</tr>
<tr>
<td>2. Adults</td>
<td>When given + Ca Carbonate, increases fecal fat, decreases fecal nitrogen</td>
</tr>
<tr>
<td>3. Postmenopausal women</td>
<td>When given + copper/zinc, slows bone turnover</td>
</tr>
<tr>
<td>4. Osteoarthritis adults</td>
<td>When given + chondroitin sulfate/glucosamine, reduces symptoms</td>
</tr>
<tr>
<td>5. Adults ± type 2 diabetes</td>
<td>No consistent effects</td>
</tr>
</tbody>
</table>
gene expression appears to be heavily regulated by a variety of factors. In many situations, increasing Mn SOD gene expression could be beneficial as evidenced by work in transgenic mice that over- or under-express Mn SOD. These mice show resistance to a variety of induced maladies. Thus, induction of high gene expression of Mn SOD in some human situations may produce above-normal resistance to some health problems. However, this effect may require that manganese intake is sufficient to fully activate the enzyme being produced. This may not be the case where a marginal deficiency exists. Moreover, in some cases, “extra” intake of manganese may be needed to fully saturate Mn SOD when “extra” Mn SOD protein is being produced. However, we currently know next to nothing about interactions between manganese intake and states that elevate Mn SOD gene expression.

This author has done an unpublished study along these lines in rats. A marginal manganese deficiency produces low Mn SOD activities in liver and lungs, plus it prevents cytokine-induced increases in Mn SOD activities (lung data shown in Figure 8.1). In addition, marginally manganese-deficient rats die from a normally sublethal dose of injected endotoxin (unpublished results), a model for septic shock. One problem with this unpublished study is that we don’t know if the degree of manganese deficiency induced in the rats is common in humans.

**MANGANESE AND EPILEPSY**

There have been rumblings on the Internet that people with epilepsy may benefit from manganese supplementation. Manganese-deficient rats show vulnerability to seizures, and rats that are genetically prone to epilepsy have low brain and blood manganese levels. Patients with some types of epilepsy show low values for whole blood manganese. However, the relationship of whole blood manganese to overall manganese functional status is poorly defined. Even if there is a strong relationship, it is not known if the low manganese values are a cause or effect of the neurological problems. In addition, there are no established human trials demonstrating the utility of manganese supplementation in epilepsy.

**TOXICITY**

Manganese toxicity is known to occur due to occupational or environmental exposure. Symptoms include neurological problems, some of which can show a resemblance to Parkinson’s disease. The manganese toxicity in itself should not actually cause Parkinson’s disease, because the manganese toxicity affects a different aspect of neurochemistry than does the primary defect of Parkinson’s disease. In any case, an association of Parkinson’s-like symptoms with typical oral manganese supplement doses is not well established. On the other hand, in rats with a pre-Parkinson’s disease-like state, symptoms can be accelerated by high-dose manganese toxicity. Thus, at least in theory, manganese overexposure, in a person with a tendency toward Parkinson’s disease, may impact time of onset and severity of neurological symptoms. The logical question is: How much manganese exposure is necessary to enhance Parkinson’s disease symptoms? This question is not yet
FIGURE 8.1 Cytokine treatment (Cyto) effect on lung manganese superoxide dismutase activities in growing rats fed adequate or marginal manganese levels. Values are means ± SD for enzyme activity units/g lung tissue. Cytokine treatment and manganese intake had significant effects (ANOVA, p < 0.01), with all groups significantly different from each other except that marginal versus marginal/cytokine (p < 0.01, LSD).
answered, especially for oral exposure, which could require higher doses for toxicity than with skin or inhalation exposure. However, some experts have opted for the safety-first approach and urged caution for manganese supplementation.

This caution can be seen in the setting of the adult Upper Level for manganese at 10 mg/day. There are some diets that can give that type of intake even without supplements. In addition, two supplement studies have given manganese at well above the UL without observing any adverse effects. It is not known yet whether this UL is excessively cautious or realistic.

Two special areas of concern for manganese toxicity are for people with blocked bile flow and for fortification of soy-based infant formulas. In the former case, since manganese excretion is largely via the bile, in principle, a blockage there could make one prone to manganese toxicity. Direct human studies of this issue have not yet occurred. In the case of soy and infant formula, since manganese is so well absorbed when mixed with soy protein, manganese toxicity may occur at unusually low intakes. Although there is not yet data showing that infants have been manganese poisoned from soy-based infant formulas, caution here would seem prudent.

**SUMMARY AND CONCLUSIONS**

Manganese research will not move forward until we firm up a basis for an RDA for manganese, more fully characterize what situations raise manganese requirements, know more about typical dietary levels of manganese, and characterize how well different food sources and supplements of manganese are absorbed. We also need to know if there is any value to eating manganese at levels above those needed to maintain basic function, particularly for bone and joint health. In addition, nothing has been done on interactions between manganese intake and factors that can elevate Mn SOD gene expression. In contrast to these research needs, it is currently hard to justify further research on manganese supplements as a means of lowering blood sugar. If manganese supplementation does increase in popularity, then toxicity issues need to be better defined. At present, some concerns about toxicity may be an overreaction, but others may be justified, especially as more research comes forward.

**TABLE 8.2**

**Manganese Supplements at a Glance**

**RDA:** none  
**Typical dose in supplement studies:** 5–15 mg (minimal effective dose unknown)  
**Best supplement complex:** not enough studies to classify a best complex  
**Applications:** bone and joint applications are possible, but only slightly researched; various antioxidant uses are possible, but not researched directly yet  
**Upper Level:** 10 mg (controversial; may be low for most people)  
**Safety issues:** dose needed to produce neurological problems in sensitive individuals is not yet well defined
REFERENCES


In terms of nutrition, chromium received little attention prior to the last 40 years. In contrast, in the last 25 years, chromium supplements have grabbed considerable public attention for various perceived health benefits. Nutrition researchers and the medical community, though accepting that chromium is an essential nutrient, have been hesitant to accept the validity of supplement claims. Some of the hesitancy has been justified by gaps in available research data. One reason for the gaps has been the technical problems in studying this mineral. Nonetheless, research is slowly clarifying what chromium supplements can and can’t do.

**OVERVIEW OF FUNCTION**

Much of the impetus to declare chromium as an essential nutrient arose when type 2 diabetes-like symptoms were reversed in subjects on total parenteral nutrition. Subsequently, chromium deficiency in experimental animals was found to cause high blood sugar due to poor insulin utilization. Upon further study, it was decided that chromium plays a role in cellular utilization of insulin. The mechanism for this chromium function is still not settled. At one time, it was thought that a serum chromium-containing glucose tolerance factor aids insulin utilization. At times, it looked like this factor had been identified via isolation techniques. Instead, many isolation attempts produced chromium complex “artifacts” (complexes that formed during the isolation procedure). It is now thought that chromium mediation of insulin utilization may involve, at least in part, a low molecular weight-binding molecule in cell membranes.

Some other functions have been ascribed to chromium, including effects on lipid metabolism and indirect antioxidant actions. These actions may result in whole or in part from chromium’s actions on insulin utilization. There are also some poorly defined interactions of chromium with nucleic acids. These interactions may include regulating a gene that affects certain cells’ response to insulin, which may be one of the ways that chromium affects insulin utilization.

**OVERVIEW OF METABOLISM**

Chromium metabolism has not been studied extensively. One thing that is known is that absorption is very low (under 2.5% in some studies). It is also known that chromium in the serum can bind to a number of molecules, but much of it locates...
in transferrin, the protein that transports iron. In theory, chromium binding to transferrin can compete with iron, but this has little impact on iron metabolism. The reason is that serum contains much more iron than chromium.

**NUTRITIONAL STATUS ASSESSMENT**

The lack of a routine means of assessing marginal chromium deficiency has been a major stumbling block to chromium research. Chromium in blood and urine are very low. Until recently, the instrumentation needed to measure these levels was not available to most nutrition researchers. Now, instrumentation has been developed that allows more researchers to make such measures. However, these measures still require specialized equipment and considerable effort to deal with problems such as chromium contamination of samples. Even if the measures are made, serum or plasma chromium values are not considered ideal means of assessing moderate chromium deficiency. Although values can rise with chromium supplementation, values do not reflect tissue levels all that well.

Another approach is to consider the effects of a chromium supplement intervention on glucose tolerance, but obviously, this strategy is not an easy approach to this task. In addition, glucose tolerance response to chromium supplementation may be overshadowed in some individuals by other factors that affect glucose tolerance. Thus, many studies on chromium supplementation simply don’t test for chromium status. Others just use urinary chromium as an assumed indicator that some of the administered chromium is absorbed from the intestine.

These considerations have greatly limited the amount of research on human chromium status. As a result, there is still need for more development of means to assess moderate deficiencies of chromium.

**BIOAVAILABILITY FROM FOODS AND SUPPLEMENTS**

Chromium absorption from foods has been given little research. In terms of supplements, inorganic chromium shows a very low percent absorption. As a result, chromium picolinate and chromium nicotinate have been advertised as better means of obtaining supplemental chromium, a claim backed by some research on radioactive chromium absorption by rats. A high chromium yeast product has also been used as a chromium supplement, though this use has declined.

There have been some claims that chromium nicotinate is superior to chromium picolinate. In contrast, both chromium picolinate and chromium nicotinate are effective at restricting blood pressure in spontaneously hypertensive rats. Some of the claim that nicotinate is the better chromium source is based on a rat study examining radiolabeled chromium. By one type of assessment, chromium nicotinate shows better tissue retention than chromium picolinate. Even so, this study, though interesting, should be interpreted carefully. For example, it should be noted that the results varied with tissue and time point, that the total chromium intake was not overly high (which may influence relative absorption), and that the retentions were based on fractional absorptions, not absolute labeling. Although this approach has
certain advantages for error corrections, there are also limits to how the data can be applied. For example, total chromium retention in a tissue for one type complex could exceed the other, but still have a lower fractional retention.

**TYPICAL INTAKES VERSUS NEEDS**

There are claims that chromium intake in the U.S. is often inadequate enough to produce a marginal deficiency. It has been difficult to verify this contention due to the above-noted technical barriers to identifying marginal deficiency. In addition, it has often been hard to figure out chromium contents of various diets. This is because development of a broad data base for food chromium has been hampered by the need for specialized equipment and problems with chromium contamination of samples. Based on present knowledge, the best food sources of chromium include whole grain products, some animal products, and a few vegetable products, such as mushrooms.¹

Despite the difficulties in evaluating chromium intake and status, there is work that raises the possibility that typical U.S. chromium intakes fall well below adequate levels.⁸

Despite these lines of evidence, there is not a wide range of studies demonstrating that poor chromium status is a major health concern for a majority of people in the U.S.. However, in fairness, it has to be said that this lack of demonstration may simply result from there just not being enough data. Data have been slow in coming due to technical difficulties, limitations in the funds made available to study chromium, and the low number of researchers committed to studying chromium.

**CURRENT RESEARCH ON SUPPLEMENT USE**

Claims for chromium supplements mainly fall into the categories noted in Table 9.1. Each of these may have considerable overlap. For example, if the first two effects occur (fat loss, lean body mass gain), then this could promote total body weight loss (since lean body mass stimulates basal metabolic rate more than does fat mass). Two other potentially overlapping areas are improved glucose tolerance and altered blood lipid profiles. In principle, the former can produce the latter. Possibly, all of the possible claims of Table 9.1 could derive from chromium’s function of enhancing insulin sensitivity, which in turn can reduce the amount of insulin released over time.

**TABLE 9.1**

<table>
<thead>
<tr>
<th>Claims for Chromium Supplementation</th>
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<tbody>
<tr>
<td>Promotion of fat loss</td>
</tr>
<tr>
<td>Promotion of lean body mass gain</td>
</tr>
<tr>
<td>Stimulation of body weight loss</td>
</tr>
<tr>
<td>Improved glucose tolerance</td>
</tr>
<tr>
<td>Beneficial alterations in blood lipid profiles</td>
</tr>
<tr>
<td>Indirect antioxidant actions</td>
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Are any of the claims of Table 9.1 true? At times, the majority of the biomedical research community has considered some of these claims dead and buried, but then they have resurfaced again for another look. Each claim is considered in more detail below.

**Body Weight and Composition Alterations**

Research on the claim for an effect on total weight loss and on fat loss is currently in the dormant stage. Most studies on chromium supplementation have not shown a large impact on body weight or fat loss. However, it should be noted that many of the studies that report a negative finding were not designed with total body weight loss as the main focus. Another issue here is that any pronounced effect of chromium on body weight loss may take a very long time to see. This long time exceeds the time used by most studies done so far. The reason for the need for a long-time intervention has to do with a proposed mechanism by which chromium would affect weight loss. Under this mechanism, chromium plus exercise would follow the following sequence:

1. Lean body mass increases and body fat decreases.
2. This change elevates basal metabolic rate (BMR).
3. This increase in BMR is sustained for a long enough period to affect body weight.

The last step would take considerable time. Increases in BMR due to altered body composition are usually not big enough to have a large short-term effect, though they may have a substantial effect over a long period. Most, if not all, studies on chromium and weight loss have not considered long time periods such as one year or more. This limitation in research arises for very practical reasons. A weight loss study where the intervention lasts one to two years is expensive and consumes a lot of effort on the part of both the researchers and subjects.

This author concludes, at least for now, that if chromium can affect weight loss (and fat loss), it will be a small, and often undetectable, effect over short periods of time. Even so, the effect might be noticeable over a long period of time. Note that the words “if” and “might” are used to describe an effect of chromium on weight loss. The first step to strengthening this very speculative conclusion is to demonstrate that chromium can impact lean body mass (essentially the same as saying impact muscle mass). This effect could be useful not only where total body weight loss is an issue, but also for other considerations. For example, athletes often desire to add muscle weight while maintaining or increasing total body weight. Another case where muscle gain would be desirable is in elderly subjects, where muscle weight loss can contribute to a decline in quality of life. So, for considerations of both weight loss and other concerns, it has to be asked: Can chromium supplementation, particularly when combined with exercise, increase lean body mass? Unfortunately, the answer is: It depends on what study is cited.

There has been great inconsistency as to whether chromium does or does not enhance exercise-induced increases in lean body mass. Part of the problem may be
that there are a large number of variables that can affect whether or not a given nutritional–exercise intervention can affect lean body mass gain. These variables include the type of subjects, the type of exercise, background diet, study duration, and other considerations.

A number of years ago, Richard Anderson of the USDA wrote a review trying to make sense of diverse results for studies on chromium supplementation and lean body mass.\textsuperscript{10} Anderson cites 13 human studies that examine effects on lean body mass of chromium supplementation, mostly in conjunction with exercise. Some studies show an effect, while others do not. He also notes a number of studies in pigs that support a role for chromium in promoting lean body mass gain. For the human studies, Anderson proposes that the negative results are caused by one or more of the following factors:

1. The subjects had adequate chromium intake without supplementation.
2. The study’s exercise plan, in the time frame used, could not promote lean body mass gain for the given subjects’ fitness level.
3. The amount of chromium administered was insufficient to have the desired effect.

The explanations offered could explain some of the diversity of the results, and in this author’s opinion, present excellent starting points for examining the diversity of results. Even so, these explanations may not cover all the differences in results. For example, the first proposition assumes that chromium administration will only help with lean body mass gain if the subjects have some degree of chromium deficiency. This is not an automatic assumption. Theoretically, chromium supplementation could increase lean body mass by increasing chromium intake beyond that needed for basic function. Unfortunately, some speculation is involved in this area because, for reasons discussed earlier, chromium status has not been checked in most studies on chromium supplementation.

Another issue is the chromium dose. If chromium will only produce an effect where there is a pre-existing moderate deficiency, it can be asked: Why would the chromium dose for any of these studies be insufficient to correct this deficiency? Each of the studies cited use at least 200 $\mu$g chromium, which is much higher than what is currently considered an adequate intake. It could be said that current recommendations are wrong, but such a contention would be highly speculative. If current recommendations are correct, it can be asked: Shouldn’t 200 $\mu$g chromium be enough to correct a moderate deficiency? The answer could be no, but there is no direct evidence yet for such an answer. Moreover, some studies cited show positive results with 200 $\mu$g. Therefore, it can be asked why would this dose work in some studies but not others? Therefore, there is still gray as to the role of initial chromium status or chromium dose in determining the outcome of chromium supplement studies.

Since the time of Dr. Anderson’s review article, four more studies have appeared on chromium supplementation and lean body mass.\textsuperscript{10–14} All four produce negative results (no effect of chromium). Two of the studies examine moderately overweight older subjects, one examines elite athletes, and one considers moderately obese
women participating in an exercise program. In two studies, the chromium dose is over 900 µg, but in the athletes, 500 µg is employed. In one of the studies in the older subjects, the subjects did not appear to be chromium deficient based on chromium supplement effects on insulin sensitivity. In the other studies, chromium status is uncertain. Therefore, these studies add to the list of negative results, but don’t clarify the reason for conflict with the studies showing positive results.

There are two other considerations that can be offered as to why conflicting results have been obtained. First, in some of the positive results studies, some of the methodology, especially for lean body mass assessment, has been criticized. Even so, methodology concerns don’t explain all the conflicting results. Alternatively, another source of variability could be background diet. Perhaps chromium works best in conjunction with good intake of some other nutrients or phytochemicals. Possibly, in some of the chromium studies showing positive results, the subjects’ diets were superior in some unidentified way to the diets in the studies showing negative results. In support of this concept, one study reports that chromium in combination with other supplements promotes desirable changes in body composition. Unfortunately, in this study, chromium was not examined by itself. Even so, this study at least raises the possibility that perhaps chromium works best when combined with good intake of other dietary factors.

In light of these conflicting reports, it is still uncertain as to whether chromium supplementation can consistently affect lean body mass gain. If it does affect lean body mass gain in some circumstances, the exact definitions of those circumstances have not been identified yet.

**Improved Glucose Tolerance**

The following sequence of reasoning has taken place in some people’s minds:

1. Chromium deficiency impairs glucose tolerance via poor insulin utilization.
2. Type 2 diabetes as well as other conditions, such as obesity without diabetes, impairs glucose tolerance via poor insulin utilization.
3. Therefore, chromium supplementation will help glucose tolerance in people with poor insulin utilization (insulin resistance).

However, this line of reasoning is not necessarily valid because the cause of poor insulin utilization in type 2 diabetes and certain other situations is not chromium deficiency. Therefore, claims that chromium supplements can eliminate the root cause of type 2 diabetes and some other problems of blood sugar regulation are clearly wrong. Nonetheless, one or more of the following possibilities could be true:

1. If some degree of diet-induced chromium deficiency is superimposed over other causes of insulin resistance, then blood sugar problems will be heightened; correcting the deficiency will help with glucose tolerance.
2. Type 2 diabetes, and perhaps other conditions, produce very high chromium needs that cannot typically be met by dietary chromium intake; high-dose chromium supplementation can meet the high needs and help with glucose tolerance.

3. Even if a person with type 2 diabetes or a related problem has no chromium deficiency, high-dose chromium supplementation can have an “above-adequate intake effect” or a drug-like effect, which helps with glucose tolerance.

Unfortunately most studies of chromium supplementation have not directly addressed these different possibilities, but have just looked at the overall effects of the supplementation. One reason for this more general approach is that, as noted earlier, it has not been easy to determine chromium nutritional status.

Compared to a lot of other mineral supplement issues, the issue of chromium supplementation and glucose tolerance has been the subject of quite a few studies. However, as is often true of nutrient supplement studies, there is a mixture of positive or negative results. One recent critical review of the various studies\(^{16}\) concludes that chromium supplementation does not appear to reduce glucose levels in people with normal blood glucose, but that chromium supplementation may reduce glucose levels in people with high blood sugar. Another recent paper\(^ {17}\) applies meta-analysis to randomized controlled studies of chromium supplementation studies in regard to blood sugar control. This study also finds no effect in non-diabetic studies but, unlike the other paper, this study concludes that the data for diabetic subjects is inconclusive. This paper drew three letters to the editor that questioned the criteria for inclusion and exclusion of various studies for analysis.

From this author’s perspective, the meta-analysis\(^ {17}\) follows the principles that statisticians should follow for inclusion and exclusion. On the other hand, this author can also see the critics’ points about the meta-analysis not accounting for the following:

1. A large study in China shows a beneficial effect of chromium\(^ {18}\) (excluded from the meta-analysis because the population is different from those of the other studies).
2. A number of studies with a beneficial effect are excluded (a reasonable decision in terms of randomized design standards, but these excluded studies collectively do make some case for chromium).
3. Some negative results included in the meta-analysis use chromium doses or chromium supplement forms that may not be ideal.
4. Some people with diabetes may respond to chromium better than others; the meta-analysis cannot account for this because there is no established criteria for screening who is most apt to respond.

Therefore, in this author’s opinion, the proposition that chromium supplementation can improve glucose tolerance in people with type 2 diabetes or other insulin resistance has support, but the support is not airtight. Furthermore, we may not yet
know the ideal conditions where chromium might be maximally effective (e.g., dose, adjuvant therapy, types of subjects, etc.). An ideal study, which would also be very expensive and time consuming, should consider variations in supplement forms, time frames, co-existing therapies, initial chromium status, doses, and stages of diabetes or insulin resistance. The last few variables may be related, as the dose may need to be adjusted to the degree of glucose tolerance impairment.

So far, most of the studies done on chromium have used large doses relative to the normal chromium requirement. This suggests that if chromium helps those with type 2 diabetes, either the help is a non-nutritional pharmacological effect, or these subjects have a very abnormally high chromium requirement. However, one could also argue that until lower doses are thoroughly studied, we cannot reach any conclusions about dose.

**Beneficial Alterations in Blood Lipid Profiles**

If chromium improves glucose tolerance, then that action can produce beneficial actions on blood lipid profiles. However, there have also been human studies, though some are small, plus studies in experimental animals, where chromium supplementation alters some serum lipid parameters in the absence of diabetes. It is possible that a subtle effect of chromium on insulin metabolism could be responsible for an effect.

Pretty much everything that was just said about chromium and glucose tolerance could also be said about chromium and blood lipids, except that there are not as many studies for the latter. Thus, in this author’s opinion, there is some reason to believe that chromium supplementation can alter blood lipids in some people, though it is still debatable as to how often, how much, and in whom the effect can occur. It is also up for debate as to whether the effect, if and when it occurs, is due to correction of a deficiency or a pharmacological effect (or both could occur).

**Indirect Antioxidant Actions**

This claim is based primarily on a study in Tunisian subjects with type 2 diabetes. Supplementation with chromium, plus or minus zinc, lowers values for a marker of oxidant stress. The mechanism is speculated to involve an indirect hormonal effect.

**Toxicity**

The movie *Erin Brockovich* made many people aware of the toxicity of hexavalent chromium. The chromium in nutritional supplements is trivalent, which is much less toxic, though as with any metal, toxicity can occur. Even so, there is no Upper Level (UL) set for chromium because trivalent chromium has not shown obvious toxicity in the many studies in which supplements have been studied. Thus, we are not yet sure at what dose and duration trivalent chromium becomes toxic. There is one case study where a woman shows renal impairment after consuming chromium picolinate at 1200 to 2400 g/day for four to five months. The impairment reverses with therapy, which includes eliminating chromium supplements. It is not known if this subject...
was overly sensitive to chromium. It is also not known if the chromium actually caused the problems, since therapy was not limited to discontinuing chromium supplementation.

There has been a suggestion that chromium picolinate can exert toxicity beyond that of other chromium complexes. This toxicity includes generation of hydroxyl radicals, which can damage DNA and other biological molecules. Much of this contention is based on cell culture work where non-physiologically large concentrations of chromium picolinate are studied. There is also a study where chromium picolinate produces deleterious effects in fruit flies, but this effect may have been due more to the picolinate than the chromium. In addition, the relevance of this study to humans taking chromium picolinate is not known.

In contrast to the negative cell culture studies on chromium picolinate, no toxic effects are reported for rats fed chromium picolinate at doses many times higher than typically used in human supplementation. However, the rat toxicology assessments do not directly check for signs of hydroxyl radical-induced damage. In contrast, a study in humans does report a lack of DNA damage due to chromium picolinate supplementation. Unfortunately, the dose (400 µg chromium) and dosing time (four or eight weeks) are less than those used in many chromium studies. In addition, the method used to assess DNA damage, antibody titers to 5-hydroxymethyl uracil, is not heavily used, especially for the time frame of this study. Therefore, in this author’s opinion, doubts remain about the practical importance of chromium picolinate as a stimulator of DNA damage due to hydroxyl radicals, though this area certainly could use more study.

SUMMARY AND CONCLUSIONS

Chromium supplementation continues to be interesting, though consensus about applications has not been forthcoming. Part of the reason for the uncertainty seems to be the current difficulties in studying chromium, plus the difficulties in studying the health applications being considered. A big unanswered question is whether chromium supplementation is effective only for correcting deficiencies, or if there are pharmacological benefits.

TABLE 9.2

<table>
<thead>
<tr>
<th>Chromium Supplements at a Glance</th>
</tr>
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<tbody>
<tr>
<td><strong>Adult RDA:</strong> none; adequate intake is 35 µg (male), 25 µg (female)</td>
</tr>
<tr>
<td><strong>Typical dose in supplement studies:</strong> 200–1000 µg (effective dose debatable, could sometimes be &lt; 200 µg)</td>
</tr>
<tr>
<td><strong>Best supplement complex:</strong> picolinate or nicotinate (controversial between the two)</td>
</tr>
<tr>
<td><strong>Applications:</strong> none settled; blood sugar and lipids best current candidates for utility</td>
</tr>
<tr>
<td><strong>Upper Level:</strong> none set</td>
</tr>
<tr>
<td><strong>Safety issues:</strong> debatable accusations against picolinate form</td>
</tr>
</tbody>
</table>
REFERENCES


10 Other Minerals

Most of the current interest in mineral supplements revolves around the minerals that have been given their own chapter in this book. Even so, there is some interest in certain other minerals. These are covered below.

PHOSPHORUS

Unlike most nutritionally essential minerals, phosphorus is not a metal. Rather, phosphorus exists in the body primarily bound to oxygen as a negatively charged phosphate ion. Phosphorus intake is usually adequate in most people without malnutrition because good food sources are found in almost any diet. Compared to most other essential minerals, there are not a lot of cases of documented phosphorus deficiency, though a few causes do exist in unusual circumstances. Supplement suppliers have not done much advertising for standalone phosphorus supplements, though there can be a fair amount of phosphorus in some protein and creatine supplement powders. Similarly, calcium supplements, when in the form of calcium phosphate, also can supply a good amount of phosphorus. One paper has proposed that the phosphate portion of this type of supplement is important. The reasoning is that high calcium intake decreases phosphorus absorption, which can be offset by a calcium supplement being at least partly phosphate. A counter-argument is that most diets are so high in phosphorus that calcium effects on absorption are not overly important. Thus, ensuring the inclusion of some calcium phosphate in calcium supplement regimens is not overly important. So far, the first view has not drawn too much attention.

One other area of attention for phosphorus supplementation is for a procedure known as phosphate loading. For a period such as three days, high doses of phosphate are ingested to improve competitive performance in sports of high exertion, especially cycling. A number of possible mechanisms can be evoked for a performance-enhancing effect of high-dose phosphate. These include a buffering effect, enhanced synthesis of a molecule that affects oxygen transport dynamics, and increased ATP production. Actual studies of phosphate loading do not show unanimous results, but there are a number of studies that show apparent benefits on factors such as perceived exertion, VO\textsubscript{2} max (a measure relevant to aerobic exercise capacity), acute recovery of peak power, and anaerobic threshold. No obvious safety problems have emerged yet with infrequent use of phosphate loading, other than GI tract irritations in some people. However, it should be noted that more safety studies could be done. Repeated use of phosphate loading could be problematic.
since the loading plus diet could produce a very high total phosphorus intake. However, the exact risks of excess phosphorus intake in most types of people other than renal dialysis patients are poorly characterized.

**IODINE**

In a sense, iodine is the most heavily used mineral supplement in the world because so many people use iodized salt. However, in a more narrow definition of supplement (i.e., in a pill or capsule), iodine is not widely used.

Iodine is another mineral that is not a metal. Rather, in the body, this element exists as iodide, a negatively charged ion. Iodide is an essential component of thyroid hormones $T_3$ and $T_4$. Iodine deficiency impairs the functions of these thyroid hormones, which has deleterious effects on various body processes. In severe cases, this deficiency can produce a goiter, which is an enlarged thyroid gland.

Iodine intake can be tied to the soil levels. As a result, iodine deficiency has often occurred in geographical areas where soil iodine is low, especially if combined with low intake of saltwater fish, a good iodine source. In many countries, iodine deficiency has been largely eliminated by adding iodine to salt, or in some cases, to vegetable oils. In the U.S., salt is typically iodized, including much of the salt that finds its way into processed foods. Many multi-vitamin–mineral supplements also contain iodine. Even so, iodine deficiency is still a major problem in some parts of the world where iodine-fortified products are not widely available or are not consumed.

In contrast to the parts of the world where iodine deficiency abounds, in other parts of the world, including the U.S., iodine nutrure gets little attention compared to other nutritional issues. Even so, a few people in industrialized countries like the U.S. and Australia still become iodine deficient. There is also some question as to whether mild forms of iodine deficiency occur with some regularity in a number of industrialized countries. Although this issue hasn't drawn large amounts of attention yet, this may change. A mild deficiency would be a problem, since it could produce serious effects, such as impairment of mental and physical development in children pre- and postbirth. If this mild deficiency does occur with some regularity, then in some of these cases iodine supplementation may prove to be a viable response. Nonetheless, it does not seem that the nutrition community thinks that mild iodine deficiency represents a major threat in countries such as the U.S.

For the most part, few claims for iodine supplementation have appeared in popular nutrition advertising. Occasionally, there have been scattered claims that iodine supplementation could help obese people lose weight. The rationale is that there can be a connection between poor thyroid function and obesity, and that iodine deficiency can cause poor thyroid function. Although at face value these ideas are true, there is no evidence that most obesity is caused by poor thyroid function due to iodine deficiency. In fact, in one study of a large number of obese German children with abnormal serum thyroid hormone profiles, iodine nutritional status appeared to be normal.
There has also been some attention given to the idea that iodine supplementation could help women with fibrocystic breast disease. The Internet contains many sites reporting this use, and often the claim is made that the purpose of the iodine supplements is the correction of an iodine deficiency. However, such sites neglect to point out that the work that examines this effect of iodine uses doses that are huge compared to the iodine RDA. This means that iodine is being used as a drug, not as a means to correct a deficiency. The adult RDA for iodine is 150 µg but 80 µg/kg body weight is a typical dose tested for treatment of fibrocystic breast disease.

The main rationale for this use of iodine is a paper published in 1993, which evaluates three previous studies. It is noteworthy that different forms of iodine are used among the studies and even within the studies. Each of the three reviewed studies report subjective or objective improvement in some but not all of the women. In one trial, there are reports of side effects with sodium iodide. The review concludes that molecular iodine works better than sodium iodide or protein-bound iodide. Whether or not these studies constitute enough data to say that relevant women can be safely and effectively treated with molecular iodine is debatable.

**ULTRATRACE MINERALS**

Very small amounts of a number of minerals find their way into the human body. These are sometimes termed “ultratrace minerals.” It is not known if these minerals are required for normal body function, or if they are just body “contaminants” from the environment. Most likely, some of these ultratrace minerals will ultimately be recognized as essential nutrients, and some already seem to be on their way. Besides the possible roles as essential nutrients, some of these ultratrace minerals may have drug applications. In fact, one could say that this has already happened with the use of lithium to treat depression.

Some supplement companies are including certain ultratrace minerals in their products. One possible motivation could be just to say that their products contain something lacking in a competitor’s product. On the other hand, some of the inclusions may have some more noble motivations. The three ultratrace elements that have gotten the most attention are vanadium, boron, and silicon.

Vanadium could be essential in humans, but that is based mainly on some properties in vitro, a vanadium requirement for some enzymes in lower life forms, and a few studies of supplementation in experimental animals. There have also been some studies attempting to demonstrate that a vanadium deficiency can occur in animals, though interpretation of those studies has been gray.

The vanadium action that has drawn the most attention may be more of a drug effect than a reflection of an essential function. This effect is to lower blood sugar. This effect has been shown in diabetic rats, plus in a small number of humans with or without diabetes. The typical vanadium complex used for this purpose has been vanadyl sulfate. However, other complexes are being considered for better qualities in terms of oral absorption, safety, and anti-diabetes properties. The mechanism behind the blood sugar-lowering effects of vanadium complexes is still not known, though some ideas exist.
This author is classifying the anti-diabetic effects as a drug action rather than a nutrient effect because of the doses involved. The tests of vanadium complexes in humans have given 100 mg or more per day.\textsuperscript{19,20} Even at this dose, the effect on blood glucose is not enormous, and in one small, short-term study of non-diabetic subjects, there is no effect.\textsuperscript{22} In rats, the doses giving strong anti-diabetic actions of vanadium complexes, if scaled up to human body weights, would be even much higher than what has been tried in the human studies. On the other hand, from a nutritional standpoint, if animal growth studies are extrapolated to humans, the vanadium requirement, if any, could be as low as 10 µg.\textsuperscript{17}

The long-term safety of vanadium doses for treating diabetic humans raises concerns. There is evidence that vanadium toxicity can begin at under 20 mg/day.\textsuperscript{23} As noted above, some research groups are trying to cope with this issue by searching for a particular vanadium complex that, in a safe dose, can substantially lower blood sugar in people with diabetes.\textsuperscript{21} If this occurs, then vanadium complexes may become a means of treating diabetes. However, at present, given the possible risks of taking vanadium at thousands times higher than what may be considered nutritional, this author cannot recommend that diabetic people treat themselves with vanadium complexes.

Vanadium has also been touted for improving exercise performance but this has no real research rationale at present.

Silicon appears to stimulate connective tissue health in experimental animals, especially in regard to extracellular matrix glycoprotein metabolism.\textsuperscript{17} This has led to consideration of silicon as a promoter of bone health in humans, and possibly as a promoter of cartilage maintenance. In regard to the bone issue, there is a small study reporting that silicon can improve femoral bone density in women with osteoporosis.\textsuperscript{24} It has also been speculated that silicon effects on connective tissue promote cardiovascular health. Some of this speculation arises because silicon supplementation can inhibit atherosclerosis in rabbits.\textsuperscript{25} In humans, an old study notes that silicon in blood vessel declines with age as cardiovascular disease incidence increases.\textsuperscript{26} Silicon supplements are appearing on the market, but human research on the effectiveness of such supplements is nonexistent. Eventually, such research may prove interesting.

Boron is gaining increasing interest as a possibly essential nutrient. This mineral influences the activities of a variety of enzymes, impacts plasma steroid hormone metabolism, and affects the metabolism of other micronutrients including calcium, magnesium, copper, and vitamin D.\textsuperscript{17} A lot of this information comes from animal studies, but there has also been some human work concerning boron interactions with other minerals. For example, effects on the status of other minerals has been shown in small controlled feeding studies in humans.\textsuperscript{27,28} In this work, boron-restricted diets are fed followed by boron repletion. In addition, in two small human studies of postmenopausal women, boron supplementation has influenced calcium, vitamin D, and magnesium measures.\textsuperscript{29,30}

Since the nutrients proposed to be influenced by boron intake are all involved in bone health, boron has a potential tie with bone health. Along these lines, manipulation of dietary boron in experimental animals affects bone health.\textsuperscript{17} In contrast, in an initial study of young adult females, boron supplementation did not influence...
bone mineral density, though dietary intake of other minerals may have been a factor in this study. Additional studies may be needed to see if boron intake can play a major role in bone health.

A number of other possible beneficial actions have been proposed for boron, including enhancement of lean body mass gain, beneficial effects on plasma lipid profiles, stimulation of brain cognitive functions, and improvement in the somatic and psychological symptoms of menopause. These propositions are based on possible boron functions derived from animal studies, plus anecdotal reports. A few small pilot human studies have not given dramatic support to these claims, though there has been some interesting data. However, these studies may not be optimally designed because we do not yet know the best circumstances to see any possible benefits of increased boron intake.

In summary, boron is an interesting mineral, may be essential, and supplements may have benefits in certain circumstances, but these circumstances have not been clarified greatly in initial human supplement studies.

**REFERENCES**


