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Mineral Absorption and Deficiency

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SUMMARY CONCLUSIONS:

A wide range of minerals is essential for human health. The recommended dietary allowances (RDAs) serve as guidelines for daily intakes of nutrients that population groups in the United States should have in their diets. Dietary Reference Intakes (DRIs) have been established for the following essential minerals: calcium, phosphorus, and magnesium. In addition, DRIs have been set for other trace elements, which have been identified to have important—if not essential roles in maintaining health. These include: iron, zinc, copper, manganese, selenium, boron, chromium, cobalt, molybdenum, vanadium, nickel, lithium, iodine and fluoride.[1]

There is evidence that the need for mineral intake is not being met, especially in certain subpopulations. It is difficult for most individuals to ingest enough calcium from foods available in a cereal-based economy without liberal consumption of dairy products, for example.[2] Supplementation with minerals is recommended to complement dietary intake and avoid deficiencies.[3]

Mineral supplements are associated with different absorptive capacities. The absorption of minerals depends on a number of physiological, biochemical, and hormonal characteristics of the consumer and the form of the mineral consumed. Potential mineral sources are not all alike and should be evaluated for bioavailability.[4]

Factors that enhance mineral absorption include the form of the mineral ingested, maintenance of chemical stability, presence of a specific transporter, small particle size, solubility, ascorbic acid, and low intestinal motility. Factors that inhibit absorption include oxalic acid, phytic acid, [5] fiber[6], sodium, tannins[7], caffeine, protein, fat, antacids, rapid transit time, malabsorption syndromes, precipitation by alkalinization, other minerals[8], hormones and nutritional status.[9]

Colloidal minerals exhibit properties that enhance absorption. Principles of biochemistry support the view that colloidal minerals may be more bioavailable than minerals in solid supplement or food forms.

A number of diseases are associated with mineral deficiencies or impaired metabolism of minerals. Supplementation with minerals has improved the nutritional status and lowered disease risk and progression factors among patients with arthritis, diabetes, cancer, anorexia, and hypertension.

I. INTRODUCTION

There is no doubt that nutrient deficiencies and excesses can influence disease states. Despite advances in the development of therapeutic agents, nutritional balance is crucial for prevention and resolution of disease. To expect the human body to function properly in the face of nutrient deficiency neglects current knowledge of the physiological needs of metabolically active tissues. While there are extensive studies on how nutrient deficiencies and supplementation affect diseases, there are considerably fewer direct studies available on the mechanisms of action of nutrient supplementation. This report applies generally accepted principles of chemistry and biological systems to mineral supplementation and their absorbability. This report addresses factors affecting the differences in the body's absorption of minerals with particular attention to

colloidal minerals and the role of mineral deficiencies in disease. Specific issues addressed include:

- Mineral Requirements
- Mineral Absorption and Bioavailability
- Mechanisms of absorption
- Essential Minerals and their specific absorption
- Physiologic factors affecting absorption
- Food and Non-Food Sources and Absorption
- Diseases Associated with Mineral Deficiencies
- Cancer
- Arthritis
- Diabetes
- Anorexia
- Hypertension

A. Mineral Requirements

Throughout the life span, the human body requires new supplies of nutrients and adequate and appropriate reserves of nutrients for proper metabolic and structural function. There is evidence that nutritional need for mineral intakes are not being met, especially in certain age-sex groups and populations.[10] Supplementation with minerals is recommended to prevent deficiencies.[11] Vitamins and minerals are generally dispensed in solid (tablet or capsule form). However some mineral supplementation is available in colloidal form. Mineral absorption is complicated and dependent upon a number of factors related to mineral solubility and absorbability.

II. MINERAL ABSORPTION: A COMPLEX PROCESS

A. Absorption

Absorption is the rate at which and the process by which molecules and atoms from the environment enter the interior of the organism via passage across (or around) the lining cells of the gastro-intestinal tract. Absorption can occur all the way from the stomach to the rectum, although the small intestine is the organ most importantly involved in absorption.[12]

Absorptive efficiency for many nutrients, notably iron, calcium and zinc, is governed by homeostatic feedback regulation. When the body stores are too low, the intestine up-regulates the avidity with which the intestine takes up the nutrient. When the body reserves are adequate or increased, the gut down-regulates the nutrient's uptake. At a molecular level, this regulation can be expressed by the control of intraluminal binding ligands, cell surface receptors, intracellular carrier proteins, intracellular storage proteins, or the energetics of the transmembrane transport.

B. Bioavailability

Bioavailability refers to the extent to which a nutrient reaches its site of pharmacologic action. For practical purposes, this definition includes the extent to which the nutrient reaches a fluid

(e.g. blood) that bathes the site of action and via which the nutrient can readily reach the site of action. The bioavailability of a mineral depends directly on the extent to which the mineral is absorbed and distributed to the site of action and depends inversely on the extent to which it is metabolized and excreted prior to arriving at the site of action. (1620). It is necessary to consider the factors that affect absorption in order to determine the relative bioavailability of nutrients in different forms.

C. Factors Affecting Absorption

Current knowledge on intestinal absorption of nutrients includes multiple factors that can affect absorption. Physiochemical processes that influence both the extent and the rate at which minerals cross the mucosal barrier and enter the bloodstream influence absorption. The following table lists factors that specifically enhance absorption of an orally administered nutrient:

Factors That Enhance the Extent and Rate of Absorption of an Orally Administered Nutrient[13]

Lack of complex formation with diet ingredients
Maintenance of chemical stability at stomach/small intestine pH
Presence of a specific transporter
Small size for transportation with bulk water flow
Lipid solubility—nonionized at local pH
High circulation to the site of absorption, to maintain concentration gradient
Appropriate stomach-emptying rate
Low small intestinal motility

Moreover, the clinical study of absorption is complex and potentially misleading. For example, absorption data derived from giving pulse doses of a miniscule quantity of an element in fasting subjects may not accurately reflect the real life situation in which individuals consume larger amounts in diets full of inhibitory and/or accelerating factors (i.e., phytates[14], fiber[15], ascorbic acid[16], tannins[17], and other minerals[18]).[a] In contrast, mineral absorption may be understood through basic principles of biochemistry and physical chemistry. [19]

D. Mechanisms of Absorption

The vast bulk of mineral absorption occurs in the small intestine. The best-studied mechanisms of absorption are clearly for calcium and iron, deficiencies of which are significant health problems throughout the world. Intestinal absorption is a key regulatory step in mineral homeostasis. Mineral homeostasis is the body's physiologic efficiency in absorbing the level of minerals the body requires from those minerals that are available to it.

Active transport of minerals is an important mechanism of homeostatic control. The minerals in foods are normally present at low concentrations. Active transport mechanisms have evolved to

[a] Absorption of one mineral can decrease absorption of another. For example, there are absorptive interactions between calcium and magnesium and between iron, zinc, and copper. These interactions can be used therapeutically; oral zinc supplementation inhibits copper absorption in patients with Wilson's disease, who have excessive tissue copper loads.

ensure their absorption. In general, there is an inverse relationship between mineral availability and absorption. Active transport of minerals increases in response to a mineral deficiency or decreases if a mineral is in excess. [20]Thus, the more of an actively transported nutrient is supplied, the less that is absorbed. For example, feeding a diet low in calcium results in an increase in intestinal calcium absorption. This adaptive mechanism is caused by a PTH-mediated stimulation of 1,25-dihydroxyvitamin D synthesis, the active vitamin D metabolite that increases the rate of transcellular active calcium transport in the intestine.[21]

III. EVIDENCE THAT MINERALS IN COLLOIDAL FORM ARE MORE ABSORBABLE THAN MINERALS IN SOLID FORMS

A. Colloidal Minerals

Liquid preparations of minerals are known as "colloidal minerals." A "colloid" is a substance dispersed in particle size large enough to prevent or delay passage through a semipermeable membrane, but small enough to remain in suspension in a liquid or gas.[22] Colloids consist of very tiny particles that are usually between 1 nanometer and 1000 nanometers in diameter and that are suspended in a continuous medium, such as a liquid, a solid, or a gaseous substance.[23]
The surface area of colloidal particles is very large. Particles may be electrically charged and have stabilizing agents added to prevent precipitation. Most are negatively charged but this varies between different colloid types.[b] The charges are particularly important for attracting water molecules and cations. The enormous surface area and charged sites on colloids attract and bind many biologically active substances. Another advantage of minerals in colloidal form is that the bound substances are able to withstand enzymatic attack.[24]

The ionic form of minerals is important for mineral absorbability. Colloidal minerals from humic shale extracts predominantly contain sulfates of iron and aluminum and traces of metal hydroxides. Many of the minerals in humic shale extracts are present in ionic forms. This may make it easier for them to cross cellular membranes. Mineral bioavailability is facilitated by the way in which metals cross the intestinal mucosa. A variety of conditions may affect metal transport across the intestinal mucosa. These factors can act at the brush border membrane, within the cytosol, and at the basolateral membrane. Metal ions, probably bound to intracellular ligands, cross the cytosol and are extruded across the basolateral membrane into the portal circulation. Once a metal ion enters the enterocyte, it may be used by the cell for its own metabolic needs or released in the circulation for the metabolic needs of other tissues. Because colloidal minerals do not have to undergo disintegration and dissolution, in contrast with minerals taken in the form of tablets and capsules, under applicable principles of biochemistry they are said to have enhanced-absorption capability, i.e. absorbability.[25]

This absorbability is evident in solubility. For example, small-molecular weight ligands, such as amino acids and other organic acids, can increase solubility and facilitate absorption; In liquid supplements, minerals are already dissolved and therefore are immediately bioavailable. Furthermore, the liquid supplements usually are acidic; specifically, they are formulated to contain citric acid, ascorbic acid, and other substances that increase the bioavailability of minerals,[26] such as carbohydrates (glucose,[27] lactose[28]), polyols (sorbitol), amino acids (arginine, lysine), vegetable gums, peptides, and emulsifying agents. Solid vitamin-mineral preparations instead contain inert excipients and are usually buffered so as not to cause gastric discomfort on ingestion, although this may reduce mineral bioavailability.[29]

[b] Surface charges of colloidal minerals may be affected by pH.

The bioavailability of a mineral in the body is governed by multiple factors, including body stores, hormonal regulation, the chemical form of the nutrient, and concomitant nutrient intake. There are few controlled clinical studies that examine the composition, efficacy, absorbability, or other properties of mineral supplements. There are, however, biochemical reviews of the properties of colloidal minerals that conclude that they are more bioavailable than minerals in other forms. [30] That conclusion is consistent with the applicable principles of biochemistry discussed above.

B. The Form of a Mineral Affects Absorption

The chemical form of a mineral is an important factor in its absorption. Although few studies have been done comparing absorption differences among mineral supplements, there is biologically plausible evidence that the form in which minerals are ingested affects absorption.[c] [31]For example, in one study of bioavailability, when glucose polymer was perfused on a 30-cm segment of jejunum for 60 minutes, net calcium absorption increased by fourfold (95 vs. 488 mumol/30 cm/h), and net jejunal uptake of magnesium (393 mumol/30 cm/h) was observed. In addition, co administration of glucose polymer doubled net zinc absorption (13 vs 29 mumol/30 cm/h). These results suggest that glucose polymer may have potential as an agent to significantly enhance mineral absorption.[32]

In contrast, the properties of minerals in solid forms have an impact on their bioavailability. For example, the particle size, surface area and solubility of a substance affect its dissolution rate.[33] A number of studies involving solid dosage forms of drugs have demonstrated that the gastrointestinal absorption of these forms is often dissolution rate limited.[34] Thus, the dissolution rate is important for measuring the absorbability of a mineral. There are a number of manufacturing variables that may also affect the release characteristics of minerals in a tablet, including tablet compression force, the type and amount of excipients, and coating materials.[35] Thus, the availability of a mineral in a solid dosage form is a function of its dissolution in the body into a liquid form.[36] Once dissolved, the minerals from a solid dosage are only then available for absorption. Thus, the liquid form is in this sense superior.

The bioavailability and absorbability of minerals in foods is similarly complicated as minerals in solid dosage form. The composition of foods and beverages determines the chemical form of a mineral component. In many solid foods, elements are not free, but firmly bound in the food matrix. They can be in covalent association with a protein, as in metalloenzymes, or in electrochemical chelation arrangements to a non-specific binder. Chelated forms of minerals may interact with other minerals to reduce absorbability.[37] For example, metallic iron in food is poorly assimilated because it must be oxidized to Fe (III) and then reduced to Fe (II) while still in the upper small intestine, before it is absorbed. Whatever fraction of the metallic iron becomes oxidized, at any level of the intestinal tract, is likely to be chelated by phytate in cereal and thus be rendered nonabsorbable.[38]

Absorption of supplements is improved when they are taken with food, perhaps by slowing gastric emptying and thereby extending the time in which the mineral-containing chyme is in

[c] Biological plausibility is one of the criteria by which scientists evaluate studies.

contact with the absorptive surface. However, some foods may actually diminish the bioavailability or absorption of nutrients. For example, several plant constituents form indigestible salts with calcium, thereby decreasing absorption of calcium. In addition, long-chain fatty acids from ingestion of lipids form insoluble calcium and magnesium salts, which are poorly absorbed. Protein rich foods also contain phosphorus, which reduces calcium absorption.

Commercial supplements of minerals are available in a wide variety of forms. The time required for absorption affects their absorbability. These include isolated compounds such as inorganic salts, organic salts, amino acid chelates and a yeast form. Bioavailability of trace elements has been studied in long-term animal supplementation (3-4 weeks) studies by measuring the trace element in liver, blood, serum or plasma and comparing the slope of the dose-concentration plots. A preliminary depletion is usually performed using trace element deficient food. In short-term experiments, the area under the blood, serum or plasma concentration-time curve is used to compare bioavailabilities after a single dose of the test substance is given. In laboratory studies, examination of the blood concentration-time curves for short-term human experiments involving selenium, zinc and copper revealed that the yeast form was more slowly absorbed, i.e., took longer to reach its maximum concentration, and was thus more bioavailable.[39]

This is analogous to the situation of trace elements in foods that have been shown to be more slowly absorbed than the isolated salts of the trace elements. Thus, because minerals in colloidal form are at lower concentration than isolated salts of trace elements, they may be more slowly absorbed. Since low concentration and slower absorption rates enhance absorption, the bioavailablity of colloidal minerals can be expected to be superior to that of minerals in other forms.

Furthermore, because minerals in colloidal form do not have to go through dissolution or disintegration as solid tablets do, and have particles that are small in size with a large surface area, the colloidal mineral ingested can be expected to be more available for absorption.

C. Clinical Evidence That Mineral Supplementation in Colloidal or Liquid Form Are More Absorbable Than Minerals in Solid Form

Further evidence that a liquid medium may be a superior vehicle for mineral absorption comes from clinical studies of calcium and magnesium supplementation and their deficiency.

The efficacy of commercially available brands of calcium carbonate tablets on mineral metabolism has been studied.[40] Formal investigation of the bioavailability of this product revealed it to have impaired disintegration and dissolution and a lack of clinical efficacy.[41] Solubility of minerals is an important consideration in absorption. Most people absorb calcium better from calcium citrate than from carbonate because calcium citrate is soluble in water. The citrate form is also considered safer and better tolerated.

Preparing salt forms with improved water solubility can enhance the bioavailability of calcium.[42] Presumably this occurs because the dissolution and ultimately the rate and/or extent of absorption are increased. Because calcium is reported to be absorbed in its ionic form the potential impact of the salt form on bioavailability is obvious. [43] The problem of absorbability has led to the development of other forms of mineral supplements that seek to avoid the disadvantages associated with solid tablets.

Therapies to correct calcium deficiency recommend a liquid medium for greater absorbability. Of the therapies approved for the prevention or treatment of postmenopausal osteoporosis in the United States (which include hormone-replacement therapy, the selective estrogen-receptor modulator raloxifene, calcitonin, and the oral bisphosphonates alendronate and risedronate), the bisphosphonates are the only medications that have been shown in large randomized trials to reduce the risk of hip fracture. Bisphosphonates have low oral bioavailability and can cause esophageal inflammation or, rarely, ulceration. Thus, when taking alendronate or risedronate, the patient must be upright, have an empty stomach, drink a full glass of water, and remain sitting or standing and eat nothing for 30 minutes.[44] This therapy recommends that oral ingestion of a liquid medium, as in colloidal minerals, increases absorbability of minerals.

Another study found that the mineral form with the greater solubility had the greater bioavailability. This study compared magnesium oxide and magnesium citrate with respect to in vitro solubility and in vivo gastrointestinal absorbability. The solubility of 25 mmol magnesium citrate and magnesium oxide was examined in vitro in solutions containing varying amounts of hydrochloric acid (0-24.2 mEq) in 300 ml distilled water intended to mimic achlorhydric to peak acid secretory states found in the small intestine. Magnesium oxide was virtually insoluble in water and only 43% soluble in simulated peak acid secretion (24.2 mEq hydrochloric acid/300 ml). Magnesium citrate had high solubility even in water (55%) and was substantially more soluble than magnesium oxide in all states of acid secretion. Reprecipitation of magnesium citrate and magnesium oxide did not occur when the filtrates from the solubility studies were titrated to pH 6 and 7 to stimulate pancreatic bicarbonate secretion. Approximately 65% of magnesium citrate was complexed as soluble magnesium citrate, whereas magnesium complexation was not present in the magnesium oxide system. Magnesium absorption from the two magnesium salts was measured in vivo in normal volunteers by assessing the rise in urinary magnesium following oral magnesium load. The increment in urinary magnesium following magnesium citrate load (25 mmol) was significantly higher than that obtained from magnesium oxide load (during 4 hours post-load, 0.22 vs 0.006 mg/mg creatinine, $p < 0.05$; during second 2 hours post-load, 0.035 vs 0.008 mg/mg creatinine, p less than 0.05). Thus, magnesium citrate was more soluble and bioavailable than magnesium oxide. [45]

D. Conclusion

While the ultimate absorption of minerals by the human body is dependent upon numerous factors including homeostasis, body stores, and hormonal regulation, the absorbability of minerals (their availability for absorption) is also affected by the form in which the minerals are ingested. Minerals in solid forms such as in solid dosage supplements and in foods must be dissolved and disintegrated prior to being available for absorption. Principles of biochemistry show that minerals in a liquid medium, or in soluble acids, i.e. colloidal minerals, can be expected to be more absorbable due to their smaller size, larger surface area and relative charge. The solubility of a mineral has been shown to enhance its bioavailability. Thus, there is scientific evidence that colloidal minerals may be more efficient, a preferred vehicle for absorption, than minerals in solid forms.

IV. MINERAL DEFICIENCIES CONTRIBUTE TO DISEASES

There is evidence that mineral deficiencies contribute to disease. For example, iron deficiency is a frequent finding in Rheumatoid Arthritis. Deficiencies of other minerals, such as potassium and magnesium, and possibly zinc and chromium, may predispose a person to carbohydrate intolerance. Intakes of selenium above those needed to maximize selenoproteins have been shown to have an anticancer effect in humans. Zinc deficiency has been linked to anorexia. Calcium and magnesium supplementation has been shown to reduce blood pressure in clinical studies. These findings indicate that there is a therapeutic role for supplementation with minerals that may improve the prognosis, reduce risk, or prevent diseases such as arthritis, diabetes, cancer, anorexia and hypertension.

A. Arthritis

Iron Deficiency in Rheumatoid Arthritis

Iron deficiency anemia due to poor dietary intake or gastrointestinal blood loss secondary to medication may occur in rheumatoid arthritis (RA) patients. Anemia is a frequent finding in patients with chronic inflammatory rheumatic diseases and may arise from different mechanisms. It is believed to be caused by a cytokine-mediated failure of the bone marrow to increase red blood cell production in response to erythropoietin and an impaired release of iron from the reticuloendothelial system are the most likely underlying mechanisms.[46]

The anti-inflammatory and immunomodulatory properties of selenium have also been investigated in RA. In most of the studies of RA [47,48] plasma levels of selenium were significantly lower than those of healthy controls. Trials with selenium have been conducted in rheumatoid arthritis to correct impaired selenium status and increase defenses against deleterious oxidant species. In a double blind multi-centric placebo-controlled study the effects of selenium supplementation in RA was observed on fifty-five patients with moderate RA. The visual analog scale, the Ritchie index, the number of swollen and painful joints, and morning stiffness significantly decreased with time in both groups ($p<0.001$), but no difference between groups could be identified. When examining the quality of life a significant ($p<0.01$) improvement in arm movements and health feeling was evidenced in selenium-treated patients.[49]

Altered selenium metabolism has been implicated in the low levels of selenium in patients with RA. While selenium supplementation (250 mg/day) significantly increased selenium concentration in serum and red blood cells of both RA and control subjects [50,51] it did not increase selenium levels in PMN leukocytes from patients with RA as it did in PMNs from control subjects.[52]

Similarly, deficiencies in other minerals have been found in patients with Rheumatoid Arthritis. To determine the adequacy of calcium, folic acid, vitamin E, zinc, and selenium intake in patients with RA, an observational study on 48 patients (13 men, 35 women; mean age, 64.5 years) with RA attending a specialty clinic in New Zealand was conducted. This study compared their dietary intake as measured by a 5-day dietary survey with recommended dietary intake (RDI) guidelines. Information on disease activity, functional ability, and drug therapy also was obtained. The percentage of patients who achieved the RDI was 23% for calcium, 46% for folic acid, 29% for vitamin E, 10% for zinc, and only 6% for selenium. In contrast, dietary intake of iron and protein was largely adequate and unrelated to anemia. The recommendations of studies like this have been to provide dietary education or supplementation to bring patient's intake of calcium, folic acid, vitamin E, zinc, and selenium up to the RDI.[53]

B. Diabetes

Deficiencies of certain minerals, such as potassium and magnesium, and possibly zinc and chromium, may predispose a person to carbohydrate intolerance. Whereas the need for potassium or magnesium replacement is relatively easy to detect based on low serum levels of these minerals, the need for zinc or chromium supplementation is more difficult to detect.[54]

Magnesium Deficiency in Diabetes

Diabetes mellitus is probably the most common disorder associated with magnesium depletion.[55] More than 30% of ambulatory diabetic patients without renal insufficiency were hypomagnesemic on a multifactorial basis.[56] A significant negative correlation was noted between serum/plasma magnesium and blood glycohemoglobin levels in insulin-dependent pregnant women, with significant relationships to the rates of spontaneous abortion and malformation.[57] About one-third of infants born to diabetic mothers were hypomagnesemic during the first 3 days of life. Similar negative correlations were noted between plasma and muscle magnesium and glycohemoglobin levels in adult insulin-dependent diabetes mellitus (IDDM).[58] In one group of children with IDDM, serum magnesium, calcium, PTH, calcitriol, and osteocalcin levels were lower than in age-and sex-matched controls;[59] in another series, magnesium and potassium were low in skeletal muscle.[60] Following oral magnesium supplementaion, these values increased significantly. Supplementation also decreased the insulin requirement.[61] When very elderly patients with normal serum magnesium and glucose levels but subnormal erythrocyte magnesium concentrations were given oral daily magnesium supplements, their erythrocyte magnesium levels rose, accompanied by net increases in insulin secretion and action.[62]

Magnesium depletion in diabetic ketoacidosis occurs in part because of acidosis-induced cellular loss. Many such patients have normal or elevated serum magnesium (because of decreased glomerular filtration with volume contraction), but administration of fluid and insulin (particularly with intermittent relatively large amounts of the latter) without supplementary magnesium soon induces low serum levels indicating low tissue levels.[63]

Intracellular magnesium concentration is reduced in muscle and in various blood cells of type II diabetics.[64] One cause of depletion appears to be increased urinary losses accompanying glycosuria-induced osmotic diuresis. Because insulin normally increases intracellular magnesium concentration, the insulin lack or resistance of the two types of diabetics has been suggested as a cause of reduced intracellular magnesium. Magnesium-deficient type II diabetics with decreased red cell magnesium had increased sensitivity to platelet aggregation, which was reduced by magnesium supplements.[65]

Chromium Supplementation in Diabetes

There have been two randomized, placebo-controlled studies in Chinese diabetic subjects where chromium supplementation has had beneficial effects on glycemia.[66] However, the study populations may have had marginal baseline chromium status. In the first study,[67] the chromium status was not evaluated either at baseline or after supplementation. Other smaller studies have also suggested a role for chromium supplementation in the management of diabetes,[68,69]. Results from these studies indicate that the dosage and formulation of chromium used significantly influences the outcome. In one study of patients with diabetes,[70] 1,000 µg/day of chromium

picolinate was more effective than 200 µg/day. Similarly, in gestational diabetes, 8 µg · kg^{-1} · day^{-1} of chromium was more effective than 4 µg · kg^{-1} · day^{-1}.[71] In contrast, two well-designed studies in the U.S.[72,73] and two in Finland[74,75] failed to demonstrate any significant benefit of chromium supplementation in patients with diabetes. The latter studies used chromium chloride, which may not be as bioavailable as chromium picolinate. At the present time, benefit from chromium supplementation in diabetic individuals requires further study with more bioavailable forms.

In another study of chromium supplementation in patients with and without non-insulin dependent diabetes, serum triglycerides were lower in the chromium-treated patients than in the patients who received placebo, and serum high-density lipoprotein (HDL) increased in the patients who received chromium.[76]

Zinc Supplementation in Diabetes

Another area of current interest in micronutrient supplementation is the role of zinc in diabetic individuals. Small studies in older subjects with diabetes have suggested some benefit from zinc supplementation in healing skin ulcerations.[77,78] A more recent placebo-controlled trial with a formulation of zinc and rabbit prostatic extracts found a significant reduction in HbA_{1c}[d] in subjects randomized to the active treatment arm.[79] However, in that study, those randomized to the active treatment had higher baseline HbA_{1c} levels than those randomized to placebo.

Calcium Supplementation in Diabetes

The rationale for recommending daily intakes of 1,000-1,500 mg of calcium, especially in older subjects with diabetes,[80] is based on the recommendations of the Institute of Medicine Food and Nutrition Board[81] and the National Institutes of Health Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy.[82] This recommendation appears to be safe and likely to reduce the incidence of osteoporosis in older individuals with diabetes. Vitamin D is also required for optimal calcium absorption, and a recommended vitamin D intake of 400-600 IU/day has been established for adults.[83]

C. Cancer

Calcium Supplementation in Colon Cancer

The effect of dietary calcium in reducing the risk for colonic tumors has been suggested in a number of studies. Dietary calcium may protect against abnormal epithelial growth.[84] One proposed mechanism is that Ca2+ precipitates bile acids and fatty acids that can otherwise stimulate colon cell proliferation. Intakes of 1800 mg/day for men and 1500/day for women have been recommended to reduce the incidence of colon cancer.[85] Data supporting the hypothesis that dietary vitamin D and/or calcium could prevent cancer came from the observation of a gradient of increasing colon cancer mortality rates with increasing latitude north.[86] Such an association could be due to the impact of ultraviolet light on synthesis of vitamin D in the skin and, subsequently, on absorption of dietary calcium. A 19-year prospective study in Chicago demonstrated a 50% reduction in colon cancer risk in men with a daily intake of 3.75 ug vitamin D and 75% reduction in men with a daily intake above 1200 mg calcium.[87] A prospective study on women in Iowa further supported the hypothesis that vitamin D and/or calcium protect against colon cancer.[88]

[d] Hemoglobin A1c is an indicator of glycemic control.

Selenium Supplementation to prevent cancer

Selenium has been studied as an anticarcinogenic agent for more than 25 years. Correlations between selenium status and tumorigenesis are derived from studies demonstrating an increase in cancer risk with decreased blood, tissue, or intake levels of this micronutrient.[89] Clark et al[90] found an inverse correlation between forage selenium level and cancer mortality. An important consideration in determintion of biologic/anticarcinogenic activity of selenium is its chemical form. Although the predominant form of selenium in the human diet is selenomethionine, other forms, particularly selenite, have greater anticarcinogenic effect.[91]

Clinical trials testing the anticarcinogenic effects of selenium obtained from foods or supplements have been carried out in areas of the world where nutrient deprivation is common, as in parts of China and India. Blot et al.[92] conducted supplementation trials that included combinations of micronutrients. These studies found that selenium in combination with other nutrients, particularly vitamins A and E, had an inhibitory effect on esophageal and stomach cancers.[93] In a study of micronutrient supplementation, including selenium, on tobacco chewers and smokers in India, significantly fewer in the supplemented group developed oral lesions or ulcers than in the placebo group. [94] Biochemical assessment of study participants showed that formation of DNA adducts, an indicator of carcinogenicity, was significantly lower in the supplemented subjects than in those receiving placebo.[95]

D. Anorexia

There is evidence that zinc deficiency is associated with anorexia. Mild zinc deficiency is difficult to detect because of the lack of definitive indicators of zinc status. Behavioral changes can occur with Zn deficiency. Administration of large doses of histidine to induce zincuria caused anorexia and dysfunction of smell and taste in adult subjects.[96] The subjects then became irritable depressed, easy to anger, lethargic, and sleepy. Some developed a fine tremor, ataxic gait, and slurred speech. Supplementation with 0.8 mmol (50 mg) of Zn quickly reversed these symptoms.

Zinc deficiency has been shown to adversely affect brain growth, learning and activity.[97] Generally, hypozincaemic individuals have a poor appetite, do not enjoy eating and complain of food, particularly protein, as being disagreeable. Reduced food consumption is a major consequece of these alterations in taste, but subchronic low protein intake worsens zinc availability. Hypogeusia and loss of appetite exacerbate zinc deficiency. Anorexia nervosa, frequently found in young females, especially in athletes, has a number of symptoms in common with zinc deficiency: body weight loss, depression and amenorrhoea. Zinc supplementation of anorexia nervosa patients has been reported to increase their weight gain in open trials.[98]

In athletes, zinc deficiency can lead to anorexia, significant loss in bodyweight, latent fatigue with decreased endurance and a risk of osteoporosis.[99]

Magnesium deficiency has also been implicated in a controlled study of anorexia in rats. Animals received a diet providing only approximately 25 per cent of the Mg requirement; controls received drinking water fortified with Mg (16 mmol/L). During 125 days ad libitum feeding, Mg-deficient obese rats consumed nearly 50 per cent less feed pellets and gained 50 per

cent less body weight than their obese counterparts. In addition, Mg was decreased and Ca increased in Mg-deficient rats indicating increased cardiac risk.[100]

A study of patients with anorexia nervosa treated with parenteral nutrition or overzealously with a normal diet has shown that hypophosphatemia and phosphorus deficiency play major roles in their metabolic complications.[101]

E. Hypertension

The role of calcium in ameliorating hypertension is less well documented than for osteoporosis but has been extensively studied in the last decade. A recent metaanalysis [102] of randomized, controlled intervention trials showed that calcium supplementaion has a small lowering effect on systolic blood pressure (-1.27 mm Hg) but not on diastolic blood pressure. However, a metaanalysis specifically confined to calcium supplementation trials with pregnant women showed a much more dramatic effect of calcium.[103] Other groups that may be vulnerable to calcium deficiency –related hypertension include African Americans and the elderly.[104]

The inverse association between blood pressure and magnesium nutriture has also been examined by a number of approaches. In epidemiological studies in which hypertension was correlated with dietary food records, higher magnesium intake was associated with decreased diastolic pressure.[105] In a 4-year follow-up of 1248 male health professionals, the same relationship was noted; namely, hypertension was inversely related to the intakes of magnesium and dietary fiber. Only dietary fiber, however, had an independent inverse association. [106]
With adult females in a similar type of study, dietary magnesium (and calcium) was independently inversely related to hypertension.[107]

The results of intervention studies using magnesium supplements are much more relevant. Hypertensive patients on thiazide diuretics given magnesium supplements exhibited a subsequent drop in blood pressure.[108,109] Hypertensive patients with left ventricular hypertrophy (LVH) – a prognostic factor for congestive heart failure and a risk factor for myocardial infarction and sudden death – had lower erythrocyte magnesium levels significantly over those of patients without LVH.[110]

Epidemiological evidence is also emerging for the beneficial effects of selenium supplementation in hypertension. Researchers have demonstrated that these compounds exhibited dose-dependent antihypertensive activity in spontaneously hypertensive rats.[111] Selenium's antioxidant and hypolipemic properties may explain results of a study of selenium yeast as a powerful in vitro and in vivo antioxidant as well as a hypolipemic agent.[112] These two actions could explain the benefit of selenium seen in epidemiological studies.

V. CONCLUSIONS

1. **A wide range of minerals is essential for human health.**

2. **There is evidence that nutritional need for mineral intake is not being met, especially in certain subpopulations. Supplementation with minerals is recommended to complement dietary intake and avoid deficiencies.**

3. **Mineral supplements are associated with different absorptive capacities.**

4. **The absorption of minerals depends on a number of physiological, biochemical, and hormonal characteristics of the consumer and the form of the mineral consumed.**

5. **Factors that enhance mineral absorption include maintenance of chemical stability, presence of a specific transporter, small particle size, solubility, large surface area and low intestinal motility.**

6. **Colloidal minerals exhibit properties that enhance absorption. Principles of biochemistry support the view that colloidal minerals may be more bioavailable than minerals in solid supplement or food forms.**

7. **A number of diseases are associated with mineral deficiencies or impaired metabolism of minerals.**

8. **Supplementation with minerals has been shown to improve the nutritional status and/or lower risk factors among patients with arthritis, diabetes, cancer, anorexia, and hypertension.**

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A copy of my curriculum vitae is attached as Exhibit A

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