Selected Vitamins and Minerals in Diabetes

ARSHAG D. MOORADIAN, MD, WRITING COMMITTEE CHAIR
MARK FAILLA, PHD
BYRON HOOGWERF, MD
MELINDA MARYNIUK, MED, RD
JUDITH WYLIE-ROSETT, EDD, RD

The interrelationship between diabetes and various vitamins and minerals is characterized by a high degree of reciprocity. Chronic uncontrolled hyperglycemia can cause significant alterations in the status of these nutrients, and conversely, some of these substances, especially those that have been characterized as micronutrients, can directly modulate glucose homeostasis (1). Differences in patient populations studied and methodological uncertainties account for the discrepancies in most reported studies. Certain subgroups of individuals with diabetes, such as elderly patients, vegans (who consume no animal products), and pregnant and lactating women, are at particular risk for deficiencies for such nutrients. Additionally, caloric restriction for obese patients and the effects of a high fiber diet and a host of drugs on the metabolism of vitamins and minerals are of concern (2,3).

Here we review the current status of our knowledge about the interrelationship between diabetes and several important vitamins and minerals and provide a balanced perspective on what is known about this topic. Some of these concepts have been discussed in previous publications (1,4). In some cases, support for specific recommendations for how to deal with abnormalities that exist in patients with diabetes is not readily available.

Accurate assessment of vitamin/mineral status has proved difficult, with the notable exception of iron. A traditional assumption has been that the levels of such nutrients in body fluids, such as plasma, reflected tissue pools, and therefore, decreased levels of the nutrient were indicative of suboptimal status. Although the assumption may be valid in cases of deficiency or excess that can be readily established in experimental animals, the correlation between plasma levels and tissue status in marginal deficiency is not always apparent. Note that metabolism and use of many nutrients is homeostatically regulated and subject to factors such as hormones and other physiological influences (5). Thus, alterations in levels of these substances in tissues and body fluids may actually represent highly integrated and necessary adaptive responses of the host to specific physiological conditions rather than depleted tissue pools.

In addition, early work on the effect of some micronutrient deficiencies, notably chromium, was fraught with problems because a deficient state was rare and could not be easily assessed. Most of these problems have been surmounted. Nevertheless, the interpretation of reported studies or reconciliation between inconsistent experimental outcomes is still problematic.

Here we review the available literature on micronutrient status of individuals with diabetes, discuss the effect of various nutrients on carbohydrate tolerance, and suggest guidelines for evaluation of nutrient status and management of possible deficiencies. Because of the limitations of the literature and paucity of studies after the 1960s and 1970s, intervention should be approached with caution.

Magnesium was the subject of a 1992 Consensus Development Conference sponsored by the American Diabetes Association (6); therefore, it will be covered only briefly in this technical review.

TRACE MINERALS

Chromium

Chromium (Cr) is found in tissues throughout the body. Glucose tolerance factor (GTF) is the Cr-containing compound related to glucose homeostasis (7–10). GTF is a complex that contains nicotinic acid, elemental Cr, and amino acids such as glutamic acid, glycine, and cysteine. Brewer's yeast, liver, and kidney are rich sources of GTF. Previous studies, however, have concluded that nicotinic acid is not a component of GTF in bovine colostrum (11). The precise biochemical basis for the effect of Cr on glucose homeostasis is not known, although some evidence suggests that GTF enhances the binding of insulin to its receptors (7,8). However, the 4-h lag period between administration of GTF and enhancement of

Accepted for publication 10 October 1993.

From the St. Louis University Medical Center (A.D.M.), St. Louis, Missouri; the University of North Carolina (M.F.), Greensboro, North Carolina; Cleveland Clinic Foundation (B. H.), Cleveland, Ohio; the Joslin Diabetes Center (M.M.), Boston, Massachusetts; and the Albert Einstein Institute (J.W.-R.), Bronx, New York.

GTF, glucose tolerance factor; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; RDA, Recommended Dietary Allowance; NIH, National Institutes of Health.

insulin action suggests that a complex cascade of events are involved in Cr-induced potentiation of insulin action (12). Cr also alters lipid metabolism, although this may be secondary to its effect on glucose metabolism; other unrelated mechanisms cannot be excluded at this time. Results from controlled human studies have been reviewed recently, and factors requiring further investigation have been recommended.

Dietary deficiency of Cr in laboratory animals is associated with elevated blood glucose, cholesterol, and triglyceride levels (13,14). GTF administration in diabetic mice reduces elevated plasma glucose concentration by 14–29% and lowers elevated plasma cholesterol and triglyceride levels by 35 and 45%, respectively (12). In two patients on prolonged total parenteral nutrition during a 6-month to 5-year period, Cr deficiency was implicated in the emergence of glucose intolerance that was reversed with Cr supplementation (15,16). For one of these patients, Cr supplementation not only reversed glucose intolerance but also ameliorated the neuropathy, high free fatty acid levels, and low respiratory quotient. These symptoms had not responded to the improved glucose tolerance with insulin therapy (15). However, Cr supplementation has not resulted in improved glucose tolerance in healthy adults (17–20). In a subgroup of elderly subjects (21–23) and those with blood glucose values >100 mg/dl at 90 min post glucose challenge, Cr supplementation has been shown to improve glucose tolerance (24). A 28-day study in 12 healthy elderly volunteers found that the combination of Cr and nicotinic acid improved glucose tolerance when Cr or nicotinic acid administered alone was ineffective (25). In a well-controlled study, Cr supplementation (4 μmol/day) for 4 weeks improved glucose tolerance of middle-aged male and female subjects exhibiting impaired glucose tolerance after consumption of a low-Cr diet (<0.4 μmol/day) for 4 weeks (26).

In individuals with diabetes, three double-blind crossover studies on Cr supplementation did not result in any improvement of blood glucose control (27–29). All three studies evaluated elemental Cr, and one evaluated brewer's yeast as well. In another study, however, 1.6 g of brewer's yeast per day (equivalent to 30 μg of elemental Cr) resulted in a 17% decrease in glycosylated hemoglobin levels and a 36% increase in high-density lipoprotein (HDL) cholesterol levels (30).

A similar controversy exists regarding the effect of Cr on plasma lipid profiles of diabetic and nondiabetic subjects. Several studies have indicated that supplementation of 200 μg Cr (as elemental Cr or brewer's yeast) per day may reduce total cholesterol by 5–12% and increase HDL cholesterol by 8–36% without altering the level of serum triglycerides (17,18,28–30). It is possible that Cr supplementation may improve plasma lipid profile and enhance insulin action only in patients with frank Cr deficiency. However, prevalence of Cr deficiency in diabetic patients is not known. No reliable methods exist to evaluate marginal Cr deficiency. Plasma Cr concentration in non-insulin-dependent diabetes mellitus (NIDDM) patients is not significantly different from that in healthy control subjects (28). Insulin-dependent diabetes mellitus (IDDM) patients, however, exhibit an elevated basal plasma Cr concentration (28). In contrast, hair Cr content of diabetic children (31) and, possibly, IDDM women (32) is reduced. Mean levels of Cr in hair or erythrocytes in adult male IDDM or NIDDM patients were not significantly different from those of control subjects (33), although the range of Cr levels was lower in the diabetic patients. These observations suggest that there might be a subgroup of diabetic patients with Cr deficiency, but hair analysis and erythrocyte concentration are not appropriate clinical tools for assessing Cr status.

Some suggest that plasma Cr response to an oral glucose load is a potential test for estimating the status of tissue Cr stores. Using this criterion, male subjects with IDDM or NIDDM appeared to have adequate Cr stores (33). Conversely, a group of women with glucose intolerance showed a decline in plasma Cr levels in response to an oral glucose load, which suggests inadequate stores or possibly a Cr deficiency (18). Dietary supplementation with brewer's yeast resulted in elevation of plasma Cr after glucose ingestion (18). The plasma Cr response to oral glucose administration increased more in NIDDM subjects than in normal control subjects, but this difference was not found when IDDM subjects were compared with control subjects. Among the normal control subjects, obese subjects had a significantly greater increase in plasma Cr levels compared with lean subjects (34). Of interest is the finding that carbohydrates that cause increased insulin release also stimulated urinary loss of Cr (35). Plasma measurements of elemental Cr level may not be the best assay of functional Cr status. Whether bioassay for GTF activity would yield more physiologically relevant information remains to be seen. Sensitive tools for the assessment of Cr status are needed.

Most individuals with diabetes apparently are not Cr deficient. Although severe Cr deficiency can lead to glucose intolerance, its role in the pathogenesis of overt diabetes does not appear to be significant.

Zinc

Zinc (Zn) is an essential constituent of enzymes in many major metabolic pathways and is found in nucleic acids and bone. The role of Zn in carbohydrate metabolism has been the subject of considerable interest. Approximately 0.5% of crystalline insulin is Zn. Zn deficiency in some studies has been associated with reduced insulin secretion and increased tissue resistance to insulin action (36–39). Zn enhances the binding of insulin to hepatocyte membranes (40) and potentiates the lipogenic effect of insulin in rat adipocytes (41). The effect of Zn on insulin secretion is biphasic. Very high or very low Zn plasma concentrations impair insulin se-

cretion (42–44). As with Cr deficiency, severe Zn deficiency may cause glucose intolerance, but its role in the pathogenesis of diabetes is not proven.

Much of our knowledge of the effect of diabetes on tissue Zn stores has been based on animal model studies. In genetically obese diabetic mice (*db/db*), decreased concentrations of tissue Zn have been reported (45). In contrast, Zn deficiency has not been seen in streptozocin- or alloxan-induced diabetic mice. The true prevalence of Zn deficiency among diabetic patients is unknown. In one study, 9% of patients with NIDDM had low serum Zn levels (<70 μg/dl). The serum Zn levels in the nondiabetic comparison group in this study ranged from 70 to 120 μg/dl. Although the serum Zn levels could not be related to blood glucose levels, the lower serum Zn levels in the diabetic patients is probably the result of diabetes-related hyperzincuria and impaired intestinal Zn absorption (46–47). Walter et al. (48) found reduced serum plasma Zn concentrations in a group of NIDDM and IDDM subjects. Lower content of Zn in lymphocytes, granulocytes, and platelets has also been found in diabetic subjects (49). In addition, IDDM subjects have reduced levels of thymulin, a biomarker of Zn biological activity (50). However, evaluation of streptozocin-induced diabetic rats has shown that absorption of Zn may be altered, but not necessarily impaired (47). In diabetes, absorption (influx) appears to be normal, and endogenous secretion from the pancreas may be decreased, which compensates for urinary excretion (5). This homeostatic control would facilitate maintenance of normal tissue stores even when urinary losses are elevated. Thus, secretion of endogenous Zn via the gut normally appears to be the primary means of regulating whole body Zn status (5). Total body clearance values for Zn in IDDM boys and girls with zincuria and glycosuria were markedly higher than in control subjects (24.6 ± 0.6 ml · $kg^{-1} \cdot h^{-1}$).

Pharmacological doses of supplemental Zn had no effect on glycated hemoglobin levels in diabetic patients (49). However, Zn supplementation may have other effects. In a subgroup of NIDDM patients with Zn deficiency, Zn supplementation improved T-cell response to phytohemagglutinin stimulation without enhancing natural killer cell activity (52). Although Zn status is important for the functional integrity of the immune system, additional factors peculiar to the diabetic state are involved in the changes of the immune system in diabetes (53). Zn status can influence cardiac β-adrenergic responsiveness, but diabetes-related changes in cardiac adrenergic receptor activity seem to be independent of Zn status (54). Studies also have shown that the incidence of pregnancy-related complications was higher in marginally Zn deficient diabetic rats than in those with adequate or high Zn status (55). Last, the observation by Begin-Heick et al. (56) that Zn supplementation attenuated hypersecretion of insulin in *ob/ob* mice provides another argument that either the dietary Zn requirement of the diabetic rodent is increased and/or chronic changes in micronutrient metabolism are associated with abnormal function.

A beneficial effect of Zn supplementation on healing venous leg ulcers has been suggested in uncontrolled studies of elderly subjects (57,58). Venous leg ulcers in patients with serum Zn levels >110 μg/dl, either at baseline or after Zn supplementation, healed faster than did those in patients with lower serum Zn levels (58). A pharmacological dose of Zn (>250 mg of elemental Zn daily) has resulted in increased levels of low-density lipoprotein (LDL) cholesterol and decreased levels of HDL cholesterol (59). This effect appears to be related to impaired copper metabolism associated with high Zn intake. Double-blind studies on the effects of Zn supplements on diabetic foot ulcers are needed. Although Zn is involved in testicular steroidogenesis, its role in diabetic patients with sexual dysfunction is still unknown (60). No current evidence supports Zn supplementation for treating diabetes-related impotence.

Zn exemplifies the difficulty of accurate assessment of micronutrient status. Plasma levels of this trace metal have been shown to be significantly lower during pregnancy and inflammatory episodes of animals and humans with adequate Zn nutriture. In addition, sampling factors, such as time of day, fasting versus fed state, and collection of either plasma or serum, may influence levels of Zn even when analytical methods of the highest quality are employed. Hair analysis does not reliably determine Zn status, and results can be affected by hair-care products. Thus, moderate reduction of Zn in plasma and serum is not necessarily indicative of lower Zn status, and differences between studies assessing similar parameters may appear contradictory because of failure to account for physiological influences and procedural details. It is important to recognize that a change in the level of Zn (or any other trace metal) needs to be correlated with abnormal biochemical and, more importantly, physiological functions to demonstrate that altered metal status reflects deficiency or excess.

Although individuals with diabetes, especially those with poor blood glucose control, are at high risk of Zn deficiency, at present, no clear guidelines exist for diagnosis and treatment of marginal Zn status in these patients.

Copper

Copper (Cu) is an essential nutrient for all mammals and is a constituent of tyrosinase, cytochrome oxidase, ceruloplasmin, and other ferroxidases. High concentrations of Cu are found in the brain, liver, heart, and kidney.

Although Cu deficiency is associated with impaired glucose tolerance in experimental animals (61), Cu deficiency is usually not a problem in diabetes. Most studies in individuals with diabetes or in animal models of diabetes have found that serum and tissue Cu concentrations are either normal or increased compared

with nondiabetic control subjects (48,62–71). Elevated serum Cu concentration also has been found in association with arteriosclerosis (72–73). The pathogenetic implications of these observations are not clear because Cu deficiency, not excess, is associated with elevated serum cholesterol levels (74). Sjogren et al. (75) found that skeletal muscle content of Cu in IDDM subjects may be reduced even when plasma Cu concentrations are elevated. This is in contrast with much of the data available on tissue content of Cu in diabetic humans and rats (62–70) and needs to be further evaluated. Streptozocin-induced diabetic rats have increased intestinal Cu absorption and increased urinary excretion of Cu reversed with insulin treatment (76,77). In one study of patients with NIDDM, serum Cu and ceruloplasmin levels were elevated, and older individuals with diabetes or those with diabetes complications appear to have higher (>150 μg/dl) levels of serum Cu (62). When excess Cu accumulates in tissues, especially in the kidney, it may be toxic.

Magnesium

Although more than half of the body's magnesium (Mg) is in bone, it also is concentrated in soft tissue. Mg is an essential component of many enzymes and is second only to potassium in cellular concentration. It is important in maintaining the electrical potential in nerve and muscle membranes and is also involved in glucose homeostasis. Mg modulates glucose transport across cell membranes and is a cofactor in various enzymatic pathways involved in glucose oxidation (78–81).

Individuals with diabetes, especially those with glycosuria and ketoacidosis, may have excessive urinary losses of Mg (82–86). Hypomagnesemia is common in these patients and can potentially cause insulin resistance (87). One study found that serum Mg levels correlated inversely with duration of diabetes in children (88).

The effect of diabetes on tissue content of Mg is variable (88–92). IDDM patients have been reported to have normal levels of Mg in erythrocytes, leukocytes, and muscle (89–92), but in one of these studies, the Mg content in trabecular bone of iliac crest biopsies was reduced by 30% (92). In another study, NIDDM patients also had reduced Mg content of skeletal muscles, which could not be predicted from the serum Mg measurements (93).

Although biological sequelae of modest Mg deficiency in individuals with diabetes are not proven, Mg deficiency may possibly contribute to the insulin insensitivity in patients with NIDDM. For example, one study showed that the insulin secretory capacity improved with dietary Mg supplementation for 4 weeks (94). These patients did not have clinical or biochemical evidence of Mg deficiency before the study. Epidemiologically, Mg deficiency also has been associated with diabetic retinopathy (95) and ischemic heart disease in some but not all studies (48,96,97). Although no evidence indicates that Mg supplementation can alter these two diabetes-related complications, the Mg status of individuals with diabetes in poor blood glucose control or at risk for Mg depletion, such as with thiazide diuretic use (98), should be assessed. Mg supplementation may be warranted using Mg-containing antacids for those patients with modest deficiency. However, monitoring is problematic, and dose and duration of treatment are not well established.

Manganese

Manganese (Mn) is concentrated in the pituitary, liver, pancreas, and mammary glands and is an essential element for normal bone structure, reproduction, and central nervous system function. Pyruvate carboxylase contains Mn, and Mn is involved in the enzyme systems responsible for polysaccharide elongation and mucopolysaccharide synthesis.

Alterations in Mn metabolism also have been implicated in glucose intolerance. Mn deficiency in laboratory animals causes impaired glucose tolerance, which is readily normalized after Mn supplementation (99). The Mn status in diabetes is controversial. The hepatic tissue content of Mn in diabetic animals is increased (68,100,101). In one study reported 30 years ago, the majority of individuals with diabetes (62%) had elevated serum Mn levels (>1.6 μg/dl), and 7% had reduced serum levels (<1.0 μg/dl) (63). Mn supplementation in NIDDM subjects did not have glucose-lowering effects (102), although an earlier study had found Mn-induced lowering of plasma glucose (103). The biological significance of the reported association between elevated serum Mn levels and myocardial infarction (104) or atherosclerosis (105) is not known at this time.

Iron

Iron (Fe) is a constituent of hemoglobin, myoglobin, and several enzymes. In contrast to other essential minerals, excretion of Fe occurs only through the loss of Fe-containing tissues and erythrocytes. Fe excess found in hemochromatosis is commonly associated with glucose intolerance. An intriguing report of diabetic individuals with elevated ferritin levels (but without classical hemochromatosis) suggested improved glycemic control after therapy with deferoxamine and corresponding reduction in Fe levels (106). This observation has not been made by others (107). Further analyses are necessary before instituting routine therapy with deferoxamine. The role of Fe in glucose homeostasis appears to be relatively minor (108), although Fe metabolism may be altered in diabetes (109). Nevertheless, individuals with diabetes do not appear at special risk of Fe deficiency unless diabetes is complicated by renal failure or gastrointestinal neuropathy with malabsorption. Experimental animal models of diabetes tend to have increased tissue Fe content in liver, kidney, and femur (70). Whether similar changes are found in diabetic individuals is not known.

Selenium

Selenium (Se) is an antioxidant nutrient and parallels many of the functions of vitamin E. The interrelationship between vitamin E and Se is not well understood. Se deficiency in rats is associated with reduced insulin secretory capacity. In one study, glucose intolerance developed when Se deficiency was coupled with vitamin E deficiency (110). Se deficiency in humans has been associated with reduced glutathione peroxidase activity, an enzyme that has a protective role against tissue damage caused by free radical–induced lipid peroxidation (111). Several case reports have found Se deficiency to be associated with certain forms of cardiomyopathy (112–114). The Se status of individuals with diabetes is not well studied. In one study, the serum Se level of children with diabetes was higher than that of normoglycemic control subjects. These higher levels were independent of either fasting plasma glucose or glycated hemoglobin levels (115). Additional observations related to the impact of diabetes on Se, vitamin E, and antioxidant status have been reviewed (116).

At present, there is no reason to believe that individuals with diabetes are at risk for Se deficiency unless they live in Se-deficient areas.

VITAMINS

Vitamin A

Vitamin A exists in animal tissue in several forms, but largely occurs as retinol. It is stored in the liver in combination with fatty acids as retinol esters. The carotenoid beta-carotene, a precursor of vitamin A, is found in plants. Beta-carotene is converted to vitamin A in the intestinal mucosa, but can enter the lymphatic system intact. Both vitamin A and beta-carotene appear to have a role in immunity and may be important in wound healing.

Vitamin A has an important role in the regulation of insulin secretion by cultured islet cells (117). At low concentrations, retinol stimulated insulin secretion, and high concentrations of the vitamin inhibited secretion. The clinical significance of these observations are not clear at the present time. Vitamin A supplementation in diabetic rats did not alter glucose levels in the blood or in the urine (118). Diabetic individuals reportedly have normal serum levels of beta-carotene and retinol, and they do not appear to have any impairment in the absorption or conversion of beta-carotene to retinol (119). However, in some patients with increased serum beta-lipoprotein levels, the serum level of retinol was reported to be elevated (119). In another study, young IDDM patients were found to have low serum retinol and retinol-binding protein concentrations (120).

The majority of individuals with diabetes are not likely to be vitamin A-deficient. Megadoses of vitamin A have serious potential toxicity and teratogenic effects. No toxicity has been associated with beta-carotene, but hyperpigmentation of the skin on the palm of the hand and the sole of the foot is common.

Group B vitamins

This group of vitamins, particularly thiamine (B_1), riboflavin (B_2), nicotinic acid (B_3), pyridoxine (B_6), and vitamin B_{12}, have important roles in glucose metabolism. The B vitamins are water soluble. Poor diabetes control can result in excess excretion, which could potentially alter nutrient requirement. These vitamins will be discussed in detail because they have been extensively evaluated in clinical studies.

Thiamine (B_1). Thiamine pyrophosphate functions as a coenzyme in the metabolism of α-keto acids and 2-keto sugars. Thiamine is essential for the oxidative decarboxylation of pyruvic acid.

Thiamine status of diabetic individuals is highly controversial. IDDM patients typically have low blood thiamine levels, and older NIDDM patients usually have normal blood levels of thiamine (1,121). One Japanese study, however, found elevated plasma thiamine levels in individuals with diabetes of unspecified type, which they attributed to impaired tissue transport of thiamine (122). Note that erythrocyte transketolase activity has been reported to be reduced in diabetic individuals independent of thiamine status (123). It is possible, therefore, that borderline thiamine status may further impair the activity of this key enzyme.

Although the occasional patient with diabetic neuropathy may respond to pharmacological doses of thiamine, there is no justification for routine thiamine supplementation in diabetes management at the present time.

Niacin (B_3). The term "niacin" is used to refer to nicotinamide and nicotinic acid. Nicotinamide functions as a component of coenzymes involved in glycolysis, fat synthesis, and tissue repair. Nicotinic acid, in relatively large doses, is used pharmacologically in the treatment of hyperlipidemia, but it can result in deterioration of carbohydrate tolerance. On the other hand, one study in healthy elderly volunteers found that the combination of nicotinic acid and Cr improves glucose tolerance (24). Several uncontrolled studies have suggested that nicotinamide may protect the pancreatic β-cell function in newly diagnosed diabetic patients and improve their metabolic control (124–126). The precise mechanisms of the β-cell protective effect of nicotinamide is not known. However, a recent double-blind randomized clinical trial failed to show any beneficial effect of nicotinamide in inducing remission of early-onset IDDM (127).

Pyridoxine (B_6). Vitamin B_6 functions as a coenzyme for many of the enzymes involved in amino acid metabolism. Vitamin B_6 deficiency has been commonly reported to occur among individuals with diabetes (128–130). In one study, patients treated with insulin typically had lower plasma levels of pyridoxine compared with those using oral agents (128). Patients with poor diabetes control also may have lower plasma levels of pyridoxine.

Pyridoxine has an important role in carbohydrate metabolism. Pyridoxine deficiency in experimental animals and humans is associated with glucose intolerance and impaired secretion of insulin and glucagon (131–133). Although the mechanism of the pyridoxine effect on carbohydrate metabolism is not clear, it may be related to the regulatory effect of pyridoxine on tryptophan metabolism. Indeed, certain catabolic metabolites of tryptophan, such as quinolinic acid and hydroxyanthranilic acid, can impair carbohydrate metabolism (134,135). Individuals with diabetes also may have abnormalities in tryptophan metabolism with accumulation of xanthurenic acid and hydroxykynurenine. The former of these metabolites has been shown to bind insulin and to reduce its biological activity (136). However, abnormalities of tryptophan metabolism may be an epiphenomenon rather than a direct cause of carbohydrate intolerance.

In a study of women with glucose intolerance related to contraceptive steroid use, pyridoxine administration normalized tryptophan metabolism but improved glucose tolerance only in those with frank pyridoxine deficiency (137). In addition, pyridoxine administration has not been shown to affect blood glucose levels in women with gestational diabetes (138,139). Similarly, supplementation of pyridoxine in diabetic individuals with pyridoxine deficiency did not improve blood glucose control (140). In one study of patients with NIDDM and normal pyridoxine status, administration of pyridoxine for 6 weeks resulted in decreased glycosylated hemoglobin levels without a change in fasting blood glucose levels (141). This may have been the result of either a modification in nonenzymatic glycosylation of hemoglobin or improved postprandial blood glucose values.

Overall, it appears that individuals with diabetes, especially those requiring insulin therapy and those with poor blood glucose control, may likely have low plasma pyridoxine levels. Individuals with diabetes also may have biochemical abnormalities related to pyridoxine deficiency, such as altered tryptophan metabolism. However, pyridoxine supplementation in these patients does not appear to be beneficial. Nevertheless, some benefit has been noted in some patients with diabetic neuropathy (142), but the clinical efficacy of this treatment is not proven. Administration of megadoses of B_6, in fact, may be associated with toxic effects, including neuropathy (143).

Vitamin B_{12}. Vitamin B_{12} is a cobalt-containing compound found in all cells. It is a component of various coenzymes and is involved in nucleic acid synthesis. A deficiency of either Vitamin B_{12} or folic acid can cause megaloblastic anemia, but B_{12} deficiency also results in neuronal cell dysfunction. Vitamin B_{12} absorption is largely regulated by gastric secretion of intrinsic factor.

Vitamin B_{12} deficiency is usually associated with IDDM in the context of polyglandular autoimmune diseases (144). On the other hand, the prevalence of NIDDM and pernicious anemia increases independently with age (145). Thus, finding these two diseases concurrently in the same individual is not uncommon. No evidence, however, indicates any causal relationship between diabetes and vitamin B_{12} deficiency. A possible relationship between vitamin B_{12} and diabetic neuropathy was suggested by the demonstration that leg parasthesias improved after intrathecal injection of high-dose methylcobalamin (146). Randomized controlled studies are needed to confirm this observation.

Ascorbic acid (Vitamin C)

Vitamin C is involved in the synthesis of collagen and generally functions as a reducing agent. It is involved in immunity and wound healing. Ascorbic acid is the most common dietary supplement used by patients. Experimental data in animals suggest that very high doses of dehydroascorbic acid, an oxidative metabolite of ascorbic acid, is a neurotoxic and diabetogenic agent (147,148). The clinical implication of this observation is unclear. One study in India reported that individuals with diabetes exhibited plasma ascorbate levels that were lower and plasma dehydroascorbic acid concentrations that were higher than those of matched control subjects (149). Diabetic individuals in England and the U.S. reportedly have normal plasma levels of ascorbic acid (150–152). Ascorbate and glucose have a common transport mechanism (153,154), and the depletion of tissue stores of ascorbic acid by chronic hyperglycemia in streptozocin-induced diabetes has been reported (155). Ascorbic acid content of white blood cells and platelets has been found to be low in diabetic patients (153,156). Whether these low levels account for some of the abnormalities in the functions of white blood cells and platelets in diabetic individuals is not clear. One study has also suggested that vitamin C deficiency may be clinically associated with microangiopathy (157).

Vitamin C supplementation at a dose of 500 mg/dl for 15 days did not affect blood glucose levels in unselected NIDDM patients (158). In patients with low dietary ascorbic acid intake, supplementation therapy (500–1,000 mg/day) has reportedly reduced hypercholesterolemia (159) and cutaneous vascular fragility (160). However, one study in an unselected population found that ascorbic acid supplementation (500 mg/day) had no effect on hyperlipidemia (161). The effect of supplemental ascorbic acid on polyol metabolism is of interest. Both in vivo and in vitro administration of ascorbic acid reduced sorbitol accumulation in human erythrocytes (162). Plasma level of ascorbic acid in diabetic rats was normalized with dietary *myo*-inositol supplementation or treatment with an aldose reductase inhibitor (163). The clinical significance of these observations is yet to be proven.

A higher turnover of ascorbic acid was found in patients with NIDDM (164), which may indicate the need for higher dietary requirements. Therefore, on theo-

retical grounds, a case can be made that the current Recommended Dietary Allowances (RDAs) for ascorbic acid may need to be increased for diabetic individuals to 100 mg/day as was recommended for cigarette smokers (165). However, for most patients, dietary supplementation of ascorbic acid is not justifiable. Potential drawbacks of using large doses of ascorbic acid supplements include interference with blood glucose monitoring, possible precipitation of oxalate stones, and rebound scurvy in the occasional patient (166).

Vitamin E

Vitamin E is a potent antioxidant preventing oxidation of vitamin A, unsaturated fatty acids, and other nutrients. Although vitamin E deficiency is not a feature of diabetes, recent evidence indicates diabetes is a state of increased free radical activity and diabetic patients may have higher requirements for antioxidants such as vitamin E. Several clinical studies have indicated that diabetic patients, with IDDM or NIDDM, may have elevated plasma and tissue levels of total vitamin E and α-tocopherol (167–171). Whether these changes are compensatory in nature or are secondary to a defect in vitamin E metabolism is not clear. The inverse correlation between α-tocopherol content of the platelets and adenosine diphosphate–induced platelet aggregability (172) suggests that higher α-tocopherol levels in the platelets of individuals with diabetes may have a protective role. Platelet α-tocopherol content, however, may be relatively insufficient (173). In double-blind trials, vitamin E supplementation of IDDM and NIDDM patients normalized platelet thromboxane production and platelet aggregability (174–177).

More recently reported data suggest that vitamin E administration may reduce glycosylation of glycohemoglobin in both rats and human diabetic subjects (178,179). Vitamin E supplementation (900 mg/dl for 4 months) improved insulin action in 15 subjects with NIDDM and in healthy control subjects (180). There are no data supporting the concept that this will reduce the risk for any complications of diabetes that may be mediated through glycosylation of proteins.

Additional studies are needed before recommending widespread supplementation of the diabetic diet with α-tocopherol. Note that plasma α-tocopherol levels are positively correlated with plasma cholesterol and apolipoprotein B–containing lipoproteins, especially LDL cholesterol levels (181,182). Thus, the plasma lipid levels should be taken into consideration when plasma α-tocopherol levels are being evaluated. Whether sufficient levels of vitamin E could be administered to human subjects to affect oxidized lipoprotein levels and reduce their atherogenic potential remains to be seen (183).

Vitamin D

Vitamin D functions principally as a regulator of calcium and phosphate metabolism. In IDDM patients, significant changes in vitamin D and calcium metabolism have been found along with reduced bone mass. These changes include low serum 1,25-dihydroxy-cholecalciferol (calcitriol), normal or increased levels of 24,25-dihydroxy-cholecalciferol, low serum Mg and ionized calcium, and low serum immunoreactive parathyroid hormone. Because vitamin D-binding protein in the serum is unaltered in individuals with diabetes, the low level of serum 1,25 $(OH)_2D$ cannot be attributed to decreased transport capacity (184). These biochemical changes have not been consistent features of IDDM patients. The status of renal function is an important determinant of vitamin D and calcium metabolism. This may account for some of the variability in the reported studies. The changes in bone mass and vitamin D metabolism are more pronounced in pubertal children with diabetes (184–186). No association is found between the severity of bone loss and the severity or duration of diabetes (187). Unlike prepubertal children with diabetes who appear to have normal parameters of calcium metabolism (188), pubertal diabetic adolescents and some IDDM adults (189) and pregnant patients with diabetes are at risk of bone loss. Plasma concentrations of 25 hydroxycholecalciferol (calcidiol) and 1,25 $(OH)_2D$ are lower in pregnant women with diabetes compared with pregnant women without diabetes (190,191). Adult NIDDM patients have minimal changes in bone mass and calcitriol metabolism (192), but some people with NIDDM, especially women, may have reduced bone mineral content (193–195). Epidemiological studies, however, have failed to show increased incidence of fractures in individuals with diabetes. Children and elderly individuals with diabetes, as well as pregnant or lactating mothers with diabetes, who are at risk of developing metabolic bone disease, should be evaluated for possible supplementation with calcium and vitamin D. Although the RDA for calcium in adults is 800 mg, the National Institutes of Health (NIH) Consensus Development Conference on Osteoporosis recommended that elderly individuals receive at least 1,000 mg of elemental calcium a day. It should be acknowledged, however, that there still are no conclusive data to support this recommendation of the NIH Consensus Development Conference (196).

Folic acid

Folic acid is involved in the transport of single carbon groups such as formyl, formaldehyde, and methanol. Folic acid deficiency presents primarily as megaloblastic anemia. Folate deficiency is not a common problem in diabetes (129,197). In one large survey, only 3% of individuals with diabetes were found to have folate deficiency (129). However, elderly individuals with diabetes, especially those of low socioeconomic class, are at high risk of folate deficiency. Such patients and those on drugs known to alter folate metabolism, such as phenytoin, should be given appropriate supplementation.

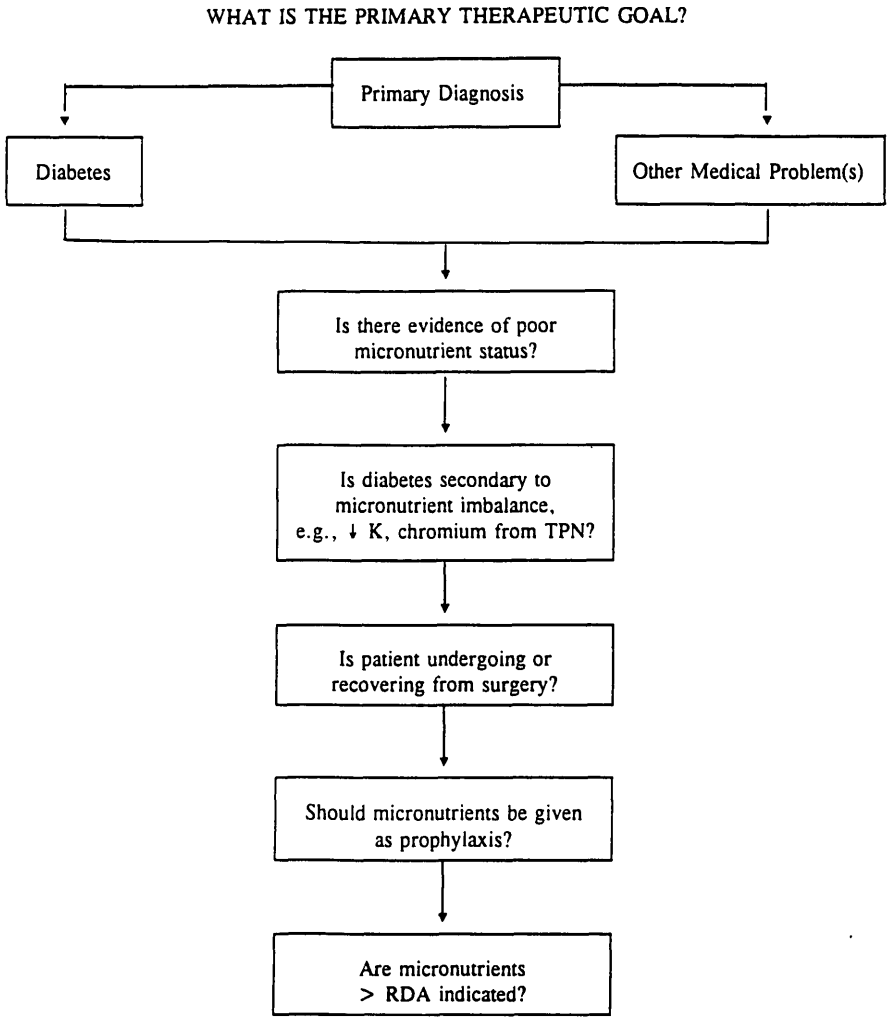

Figure 1—*Schematic presentation of the relative priorities in assessing micronutrient status of diabetic patients.*

ASSESSMENT OF SELECTED VITAMIN AND MINERAL NEEDS

— The vitamin and mineral needs of individuals with diabetes can vary widely. The care needs for patients with diabetes are often complex, and care providers may have difficulty setting priorities. Figure 1 illustrates the establishment of relative priorities when assessing micronutrient status. This decision process can guide recommendations regarding the potential role of micronutrients in the overall health needs of the individual, while focusing on diabetes. When diabetes is not the primary diagnosis, the nutritional intervention may need to be modified to address micronutrient requirements related to other health problems.

The RDAs are designed to ensure adequate nutrients for healthy people. Diabetic individuals who are in good health appear to have nutritional needs that are addressed by the RDAs. However, many acute and chronic medical problems associated with diabetes can affect nutritional needs. Diabetes itself can be secondary to a deficiency of a micronutrient such as Cr or Zn. When total parenteral nutrition is used for longer than a month, assessment of trace element status and supplementation may be needed. This may be needed sooner if a patient's nutritional status was greatly compromised before starting total parenteral nutrition.

Micronutrients can play an important role in the overall status of the patient. Acute and chronic complications of diabetes may be associated with micronutrient imbalance or deficiency. Poorly controlled diabetes may result in excessive loss of water-soluble vitamins and minerals. Improving metabolic control alone may not achieve normal levels of nutrients in patients with multiple medical problems.

The role of supplementation with micronutrients such as Zn in wound healing may be a priority in the management of individuals with diabetes. For patients with critical medical problems or metabolic stress, vitamin and mineral requirements can be altered and may exceed the RDAs. When patients with diabetes are at risk of developing marginal and moderate vitamin and mineral deficiencies, rigorous dietary monitoring is indicated and nutrient supplementation may be indicated.

More sensitive methods for diagnosing marginally deficient micronutrient levels in individuals are needed. Recent studies have suggested that assessment of serum thymulin activity, lymphocyte and granulocyte Zn, mitogen-induced secretion of interleukin-2 by cultured peripheral blood mononuclear cells, and erythrocyte metallothionein (intracellular Zn binding protein) may all be useful indicators of Zn status (198–200). The assessment methods need to target nutrient function rather than quantifying the level of mineral per se.

GENERAL RECOMMENDATIONS

— For the general population who eat a wide variety of foods, inadequate intake of micronutrients is rare. The underlying principle behind the Exchange Lists for Meal Plan-

Table 1—*Recommended Dietary Allowances and food sources of selected micronutrients*

	Recommended daily intake	Food Sources	Comments on possible excess
Chromium	50–200 μg*	Brewer's yeast, liver, kidney, wheat germ, American cheese	Substantial margin of safety. No adverse effects seen in rats given up to 100 mg/kg in diet
Zinc	15 mg (men)† 12 mg (women)	Meat and other animal foods, whole grains	Impaired Cu status has been noted with intakes of 18.5 or 25 mg/day; GI irritation and vomiting with intakes of 2 g or more in sulfate form
Copper	1.5–3 mg*	Organ meats, seafood, nuts, seeds	No deleterious effects can be expected in humans whose intake is 0.5 mg/kg per day
Magnesium	350 mg (men)† 280 mg (women)	Widely distributed; nuts, legumes, unmilled grains	May be of concern in patients with impaired renal function who take large doses of Mg-containing drugs
Manganese	2.0–5.0 mg*	Whole grains, vegetables, fruits	Low toxicity; occasional intake of 10 mg/day by adults can be considered safe
Iron	10 mg (men)† 15 mg (women)	Meats, eggs, fortified cereals	Deleterious effects of daily intakes between 25 and 75 mg are unlikely in healthy persons; may be toxic for children who ingest adult medicinal iron supplements
Selenium	70 μg (men)† 55 μg (women)	Seafood, organ meats, whole grains	Some reports of selenium intoxication when large doses of supplements were taken (>5 mg/day)
Vitamin A	1000 μg RE (men)† 800 μg RE (women)	Liver, fish liver oils, milk, eggs, carrots, spinach	Signs of toxicity (headache, vomiting, diplopia, liver damage) may occur in adults with sustained daily intakes >15,000 μg retinol (50,000 IU)
Vitamin B_1	1.5 mg (men)† 1.0 mg (women)	Cereal grains, brewer's yeast, organ meats, pork	Easily cleared by kidneys; oral doses of 500 mg daily for 1 month showed no toxicity
Vitamin B_6	2.0 mg (men)† 1.6 mg (women)	Chicken, fish, unmilled rice, soy, eggs	Neurological symptoms (ataxia, sensory neuropathy) were seen in 103 women who took 117 ± 93 mg for >6 mo to 5 years
Vitamin B_{12}	2.0 μg (men)† 20 μg (women)	Meats and other animal products	No clear toxicity has been reported from daily oral intake up to 100 μg
Vitamin C	60 mg†	Citrus fruits, green peppers, broccoli, strawberries	Although many people habitually ingest 1 g/day with no side effects, others have reported adverse effects; risks of sustained high intake are not known and, therefore, high intake is not recommended
Vitamin E	10 mg (men) TE† 8 mg (women) TE	Vegetable oils, wheat germ, nuts	Appears nontoxic by mouth, no deleterious signs when ingested up to 100–800 mg/day
Vitamin D	5 μg†	Fortified milk, eggs, butter, margarine	May be toxic in some at levels of 5 times the RDA (45 μg in children)
Folate	200 μg (men)† 180 μg (women)	Widely distributed; liver, yeast, leafy vegetables	Avoid large doses, especially in those with epilepsy controlled by phenytoin

*1989 Estimated Safe and Adequate Daily Dietary Intake (ESASSI). †1989 Recommended Dietary Allowance (RDA). The RDA figures given are for adults (age 25–50) and the ESADDI given are for adults (no age definition). Adapted from National Research Council: *Recommended Dietary Allowances*. 10th ed. Washington, D.C., National Academy Press, 1989.

ning (201) or other food grouping systems is to ensure consumption of foods from each of the different food groups to provide minimum required levels of micronutrients. However, certain subgroups of the population may be at risk for consuming less than adequate levels of micronutrients because of limited food choices or tolerance. The diabetes healthcare team should pay particular attention to the nutritional history of people in these subgroups and assess the adequacy of their intake. Those who appear to be more at risk for micronutrient deficiencies include the following subgroups:

1. Dieters: Adults who consume <1,200 calories a day have difficulty consuming adequate levels of all micronutrients, especially Fe and folic acid.
2. Vegans: People who omit the consumption of animal foods will have difficulty obtaining adequate vitamin B_{12}, calcium, riboflavin, Fe, and Zn.
3. Elderly: The elderly may have more

difficulty meeting the RDAs because of physical or other factors that limit the variety of foods eaten.
4. Pregnant and lactating women: Fe, Zn, calcium, and folic acid requirements are increased.
5. Women who have very heavy menstrual bleeding: Increased Fe to replace losses may be needed.
6. People taking medications that affect vitamin or mineral status or who have other complicating factors: Both drug-induced diuresis and chronic renal disease can lead to Mg deficiency.

A nutrition assessment should be completed for all people with diabetes, and a brief annual dietary history will help determine adherence with their meal plan. A nutrition history is important, especially for individuals in the subgroups named above. The history usually includes a 24-h recall or food record and the food frequency assessment. The 24-h recall and the description of a typical day's intake alone may not reflect the overall variety of foods consumed. The food record reflects an intake for a slightly longer period. Assessing the frequency of foods consumed can provide additional information about target nutrient intake. Drinking water can be a source of trace minerals that can potentially affect total intake. When the interviewer is focusing on vitamin and mineral status, particular attention should be paid to the following:

1. A balance of all food groups—To best assure that nutritional requirements are met, adults should consume a minimum of 2 cups of low-fat milk or yogurt per day; 4–5 ounces of lean meat or protein alternate; 6–11 servings of whole grain breads, cereals, and starches; and at least 5 servings of fruit and vegetables, including a good source of ascorbic acid and vitamin A.
2. Use of whole-grain products—Whole-grain breads and cereals are preferred more than enriched products because they contain more Mg, Zn, folate, vitamin B_6, Cr, vitamin E, fiber, and many other nutrients. These nutrients will be present in breads made from a whole-grain flour as the first ingredient (whole wheat) but will not be replaced in enriched wheat (white or refined) flour that has been colored with molasses or caramel coloring to appear brown.
3. Food preparation methods—Water-soluble vitamins (such as ascorbic acid) tend to be leached out when vegetables and other foods are cooked in excess water.
4. Nutritional supplements—Establish whether any supplements are taken on a regular basis. Many people fail to mention supplements as part of a food history or as part of their medications unless specifically asked. The dose of nutrient supplements should generally be limited to the RDA or to the level therapeutically indicated for the special circumstances reviewed above.

The RDA and the common dietary sources of some micronutrients are summarized in Table 1.

CONCLUSIONS — For patients with diabetes, micronutrient supplementation should be individualized based on dietary history, clinical findings, and laboratory evaluation of nutritional status.

The literature on micronutrient status of individuals with diabetes is replete with controversial reports. Future studies should focus on clarifying various methodological uncertainties in assessing status. Specific biomarkers that characterize the nutrient function should be identified and used in screening. Serum thymulin and erythrocyte metallothionein appear to be good markers of Zn status. Serum ferritin concentration is a good index of Fe status. Similar markers for other micronutrients should be sought. At the present time, routine vitamin and mineral supplementation in diabetes management does not appear to be justified. Patients on weight-reducing diets of ≤1,200 calories, vegans, elderly individuals, pregnant or lactating women, and those taking medications known to alter micronutrient metabolism need a comprehensive nutritional assessment. When a deficiency is diagnosed by the clinical and laboratory evaluation, appropriate diet counseling and/or supplementation should be instituted.

Reports suggest that for patients with leg ulcers or poor wound healing, a 3-month trial of Zn supplementation may be warranted. Doses of 70 mg of elemental Zn three times daily with meals have been suggested, but dose, duration, and monitoring of therapy still are problematic. For those with marginal vitamin C intake and vascular fragility, vitamin C supplementation (500 mg–1 g/day) may be considered as a trial. Older patients, including those with diabetes, should be encouraged to take at least 1,000 mg of elemental calcium per day, which is consistent with the NIH Osteoporosis Consensus Conference (196). For patients with diabetic neuropathy, a 2-month trial of thiamine, vitamin B_1 (50 mg/day), or vitamin B_6 (50 mg/day) may be considered. However, the efficacy of these supplements is not proven. Further studies and clinical trials are needed to develop appropriate recommendations regarding potential use of these vitamins and mineral supplements in treating neuropathy.

References

1. Mooradian AD, Morley JE: Micronutrient status in diabetes mellitus. *Am J Clin Nutr* 45:877–895, 1987
2. Jenkins DJA: Dietary fibre, diabetes and hyperlipidemia. *Lancet* 2:1287–1290, 1979
3. Anderson JW, Ferguson SK, Karounos D, O'Malley L, Seiling B, Clen WJL: Mineral and vitamin status on high-fiber diets: long-term studies of diabetic patients. *Diabetes Care* 3:38–40, 1980
4. Reed LR, Mooradian AD: Nutritional status and dietary management of elderly diabetic patients. *Clin Ger Med* 6:883–901, 1990
5. Cousins RJ: Absorption, transport, and

hepatic metabolism of copper and zinc: special reference to metallothionein and ceruloplasmin. *Physiol Rev* 238–244, 1985
6. American Diabetes Association: Consensus Statement: Magnesium supplementation in the treatment of diabetes. *Diabetes Care* 15:1065–1067, 1992
7. Mertz W: Chromium occurrence and function in biological systems. *Physiol Rev* 49:163–239, 1969
8. Mertz W, Toepfer EW, Roginski EE, Polansky MM: Present knowledge of a role of chromium. *Fed Proc* 33:2275–2280, 1974
9. Mertz W: Chromium in human nutrition: a review. *J Nutr* 123:626–633, 1993
10. Wallach S: Clinical and biochemical aspects of chromium deficiency. *J Am Coll Nutr* 4:107–120, 1985
11. Yamamoto A, Wada O, Suzuki H: Purification and properties of biologically active chromium complex from bovine colostrum. *J Nutr* 118:39–45, 1988
12. Tuman RW, Doisy RJ: Metabolic effects of the glucose tolerance factor (GRF) in normal and genetically diabetic mice. *Diabetes* 26:820–826, 1977
13. Schroeder HA: Chromium deficiency in rats: a syndrome simulating diabetes mellitus with retarded growth. *J Nutr* 88: 439–445, 1966
14. Wolliscroft J, Barbosa J: Analysis of chromium-induced carbohydrate intolerance in the rat. *J Nutr* 107:1702–1706, 1977
15. Jeejeeboy KN, Chu RC, Marliss EB, Greenberg GR, Bruce-Robertson A: Chromium deficiency, glucose intolerance, and neuropathy reversed by chromium supplementation, in a patient receiving long-term total parenteral nutrition. *Am J Clin Nutr* 30:531–538, 1977
16. Freund H, Atamian S, Fischer JE: Chromium deficiency during total parenteral nutrition. *JAMA* 241:496–498, 1979
17. Riales R, Albrink MJ: Effects of chromium chloride supplementation on glucose tolerance and serum lipids including high-density lipoproteins of adult men. *Am J Clin Nutr* 34:2670–2678, 1981
18. Liu VJK, Morris JS: Relative chromium response as an indicator of chromium status. *Am J Clin Nutr* 31:972–976, 1978
19. Polansky MM, Anderson RA, Bryden NA, Roginski EE, Mertz W, Glinsmann WH: Chromium supplementation of free living subjects: effect on glucose tolerance and insulin (Abstract). *Fed Proc* 40:885, 1981
20. Polansky MM, Anderson RA, Bryden NA, Glinsmann WH: Chromium (Cr) and brewer's yeast supplementation of human subjects: effect on glucose tolerance, serum glucose, insulin, and lipid parameters (Abstract). *Fed Proc* 41:391, 1982
21. Glinsmann WH, Mertz W: Effect of trivalent chromium on glucose tolerance. *Metab Clin Exp* 15:510–520, 1966
22. Levine RA, Streeten DHP, Doisy RS: Effect of oral chromium supplementation on the glucose tolerance of elderly subjects. *Metab Clin Exp* 17:114–125, 1968
23. Offenbacker EG, Rinko CJ, Pi-Sunyer FX: The effects of inorganic chromium and brewer's yeast on glucose tolerance, plasma lipids, and plasma chromium in elderly subjects. *Am J Clin Nutr* 42:454–461, 1985
24. Anderson RA, Polansky MM, Bryden NA, Roginski EE, Mertz W, Glinsmann WH: Chromium supplementation of human subjects: effects on glucose insulin and lipid variables. *Metabolism* 32: 894–899, 1983
25. Anderson RA, Polansky MM, Bryden NA, Canary JJ: Supplemental chromium effects on glucose, insulin, glucagon and urinary chromium losses in subjects consuming low-chromium diets. *Am J Clin Nutr* 54:909–916, 1991
26. Urberg M, Parent M, Hill D, Zemel M: Evidence for synergism between chromium and nicotinic acid in normalizing glucose tolerance (Abstract). *Diabetes* 34 (Suppl. 1):147A, 1986
27. Sherman L, Glennon JA, Brech WJ, Klomberg GH, Gordon ES: Failure of trivalent chromium to improve hyperglycemia in diabetes mellitus. *Metabolism* 17:439–442, 1968
28. Rabinowitz MB, Gonick HC, Levin SR, Davidson MB: Effect of chromium and yeast supplements on carbohydrate and lipid metabolism in diabetic men. *Diabetes Care* 6:319–327, 1983
29. Uusitupa MI, Kumpulainen JT, Voutilainen E, Hersio K, Sarlund H, Pyorala KP, Koivistoinen PE, Lehto JT: Effect of inorganic chromium supplementation on glucose tolerance, insulin response and serum lipids in non-insulin-dependent diabetics. *Am J Clin Nutr* 38:404–410, 1983
30. Grant AP, McMullen JK: The effect of brewer's yeast containing glucose tolerance factor on the response to treatment in type II diabetics: a short controlled study. *Ulster Med J* 51:110–114, 1982
31. Hambidge KM, Rodgerson DO, O'Brien D: Concentration of chromium in the hair of normal children and children with juvenile diabetes mellitus. *Diabetes* 17:517–519, 1968
32. Rosson JW, Foster KJ, Walton RJ, Monro PP, Taylor TG, Alberti KGMM: Hair chromium concentrations in adult insulin-treated diabetics. *Clin Chem Acta* 93: 299–304, 1979
33. Rabinowitz MB, Levin SR, Gonick HC: Comparisons of chromium status in diabetic and normal men. *Metabolism* 29: 355–364, 1980
34. Earle KE, Archer AG, Baillie JE: Circulating and excreted levels of chromium, body mass index, hypoglycemic drugs, and presence and absence of diabetes mellitus. *Am J Clin Nutr* 49:685–689, 1989
35. Anderson RA, Bryden NA, Polansky MM, Reiser S: Urinary chromium excretion and insulinogenic properties of carbohydrates. *Am J Clin Nutr* 51:864–868, 1990
36. Quarterman J, Mills CF, Humphries WR: The reduced secretion of and sensitivity to insulin in zinc deficient rats. *Biochem Biophys Res Commun* 25:356–358, 1966
37. Hendricks DG, Mahoney AW: Glucose tolerance in zinc deficient rats. *J Nutr* 102:1079–1084, 1972
38. Huber AM, Gershoff SN: Effect of zinc deficiency in rats on insulin release from the pancreas. *J Nutr* 103:1739–1744, 1973
39. Kirchgessner M, Roth HP, Weigand E: Biochemical changes in zinc deficiency. In *Trace Elements in Human Health and*

Disease: Zinc and Copper. Vol 1. Prasad AS, Oberleas D, Eds. New York, Academic Press, 1976, p. 189–266
40. Arquilla ER, Packer S, Tarmas W, Miyamoto S: The effect of zinc on insulin metabolism. *Endocrinology* 103:1440–1449, 1978
41. Coulston L, Dandona P: Insulin-like effect of zinc on adipocytes. *Diabetes* 29: 665–667, 1980
42. Ghalghazi T, Ludvigsen CW, McDaniel ML, Lacy PE: The inhibitory effect of zinc on insulin secretion. *IRCS J Med Sci* 7:122, 1979
43. Figlewicz DP, Formby B, Hodgson AT, Schmid FG, Grodsky GM: Kinetics of zinc uptake and distribution in fractions from cultured rat islets of Langerhans. *Diabetes* 29:767–773, 1979
44. Figlewicz DP, Heldt A, Forhan SE, Grodsky GM: Effect of exogenous zinc on insulin secretion in vivo. *Endocrinology* 108:730–732, 1980
45. Levine AS, McClain CJ, Handwerger BS, Brown DM, Morley JE: Tissue zinc status of genetically diabetic and streptozotocin-induced diabetic mice. *Am J Clin Nutr* 37:382–386, 1983
46. Kinlaw WB, Levine AS, Morley HE, Silvis SE, McClain CJ: Abnormal zinc metabolism in type II diabetes mellitus. *Am J Med* 75:273–277, 1983
47. Song MK, Mooradian AD: Intestinal zinc transport: influence of streptozotocin-induced diabetes, insulin and arachidonic acid. *Life Sci* 42:687–694, 1988
48. Walter RM Jr, Uriu-Hare JY, Olin KL, Oster MH, Anawalt BD, Critchfield JW, Keen CL: Cooper, zinc, manganese, and magnesium status and complications of diabetes mellitus. *Diabetes Care* 14:1050–1056, 1991
49. Pai LH, Prasad AS: Cellular zinc in patients with diabetes mellitus. *Nutr Res* 8:889–897, 1988
50. Mocchegiani E, Boemi M, Fumelli P, Fabris N: Zinc-dependent low thymic hormone level in type I diabetes. *Diabetes* 38:932–937, 1989
51. Nakamura T, Higashi A, Nishiyama S, Fujimoto S, Matsuda I: Kinetics of zinc status in children with IDDM. *Diabetes Care* 14:553–557, 1991
52. Niewoehner CB, Allen JI, Boosalis M, Levine AS, Morley JE: The role of zinc supplementation in type II diabetes mellitus. *Am J Med* 81:63–68, 1986
53. Mooradian AD, Norman DC, Morley JE: The effect of zinc status on the immune function of diabetic rats. *Diabetologia* 31: 703–707, 1988
54. Mooradian AD, Morley JE, Scarpace PJ: The role of zinc status in altered cardiac adenylate cyclase activity in diabetic rats. *Acta Endocrinol* 119:174–180, 1988
55. Uriu-Hare JY, Stern JS, Keen CL: Influence of maternal dietary Zn intake on expression of diabetes-induced teratogenicity in rats. *Diabetes* 38:1282–1290, 1989
56. Begin-Heick N, Dalpe-Scott M, Rowe J, Heick HMC: Zinc supplementation attenuates insulin secretory activity in pancreatic islets of the *ob/ob* mouse. *Diabetes* 34:179–184, 1985
57. Haeger K, Lanner E, Magnusson PO: Oral zinc sulfate in the treatment of venous leg ulcer. In *Clinical Applications of Zinc Metabolism*. Pories WJ, Strain WH, Hsu JM, Woosley RL, Eds. Springfield, IL, Thomas, 1974, p. 158–67
58. Hallbook T, Lanner E: Serum-zinc and healing of venous leg ulcers. *Lancet* 2:780–782, 1972
59. Hooper PL, Visconti L, Garry PJ, Johnson GE: Zinc lowers high-density lipoprotein cholesterol levels. *JAMA* 244: 1960–1961, 1980
60. Morley JE, Korenman SG, Mooradian AD, Kaiser FE: Male sexual dysfunction in the elderly. *J Am Geriatr Soc* 34:1014–1022, 1987
61. Cohen AM, Teitelbaum A, Miller E, Ben-Tor V, Hirt R, Fields M: The effect of copper on carbohydrate metabolism. *Isr J Med Sci* 18:840–844, 1982
62. Noto R, Alicata R, Sfogliano L, Neris S, Bifarella M: A study of cupremia in a group of elderly diabetics. *Acta Diabetol Lat* 20:81–85, 1983
63. Lisun-Lobanova VP: Trace elements (manganese, copper, and zinc) in patients with diabetes mellitus. *Zdravookhr Beloruss* 9:49–54, 1963
64. Kanabrocki EL, Case LF, Graham L, Fields T, Miller EB, Dester YT, Kaplan E: Non-dialyzable manganese and copper levels in serum of patients with various diseases. *J Nucl Med* 8:166–172, 1967
65. Martin Mateo MC, Bustamante Bustamante J, Gonzalez Cantalapiedra MA: Serum zinc, copper, and insulin in diabetes mellitus. *Biomedicine* 29:56–58, 1978
66. Lahey ME, Gubler CJ, Cartwright GE, Wintrobe MM: Studies on copper metabolism. VI. Blood copper in normal human subjects. *J Clin Invest* 32:322–328, 1953
67. Pidduck BS, Wren MD: Plasma zinc and copper in diabetes mellitus. *Diabetes* 19: 234–239, 1970
68. Failla ML, Kiser RA: Altered tissue content and cytosol distribution of trace metals in experimental diabetes. *J Nutr* 111:1900–1909, 1981
69. Failla ML, Kiser RA: Hepatic and renal metabolism of copper and zinc in the diabetic rat. *Am J Physiol* 244:E115-E121, 1983
70. Johnson WT, Evans GW: Effects of the interrelationship between dietary protein and minerals on tissue content of trace metals in streptozotocin-diabetic rats. *J Nutr* 114:180–190, 1984
71. Carnes WH: Copper and connective tissue metabolism. *Int Rev Connect Tissue Res* 4:197–232, 1968
72. Schroeder HA: The role of trace elements in cardiovascular diseases. *Med Clin North Am* 58:381–396, 1974
73. Jarrett RJ, Keen H: Diabetes and atherosclerosis. In *Complications of Diabetes*. Jarrett RJ, Keen H, Eds. London, Arnold, 1975, p. 179–204
74. Klevay LM, Inman L, Johnson LK, Lawler M, Mahalko JR, Milne DB, Lukask HS, Bolenchek W, Sandsherd HH: Increased cholesterol in plasma in a young man during experimental copper depletion. *Metabolism* 33:1112–1118, 1984
75. Sjogren A, Edvinsson L, Floren C-H, Abdulla M: Zinc and copper in straited muscle and body fluids from subjects with diabetes mellitus type I. *Nutr Res* 6:147–154, 1986
76. Craft NE, Failla ML: Zinc, iron, and copper absorption in the streptozotocin-diabetic rat. *Am J Physiol* 244:E122-E128, 1983
77. Lau AL, Failla ML: Urinary excretion of

zinc, copper and iron in the streptozotocin-diabetic rat. *J Nutr* 114:224–233, 1984
78. Lehninger AS: Role of metal ions in enzyme systems. *Physiol Rev* 30:393–429, 1950
79. Aikawa JK: *Magnesium: Its Biologic Significance*. Fort Lauderdale, CRC, 1981
80. Goldman J, Fisher V: Magnesium is required in addition to calcium for insulin stimulation of glucose transport (Abstract). *Endocrinology* 112 (Suppl.):271, 1983
81. Yajnik CS, Smith RF, Hockaday TDR, Ward NI: Fasting plasma magnesium concentrations and glucose disposal in diabetes. *Br Med J* 288:1032–1034, 1984
82. Fujii S, Takemura T, Wada M, Akai T, Okuda K: Magnesium levels in plasma, erythrocyte and urine in patients with diabetes mellitus. *Horm Metab Res* 14: 161–162, 1982
83. McNair P, Christensen MS, Christiansen C, Madsbad S, Transbol IB: Renal hypomagnesaemia in human diabetes mellitus: its relation to glucose homeostasis. *Eur J Clin Invest* 12:81–85, 1982
84. Butler AM: Diabetic coma. *N Engl J Med* 1243:648–659, 1950
85. Fort P, Lifshitz F, Wapnir IL, Wapnir RA: Magnesium metabolism in experimental diabetes mellitus. *Diabetes* 26: 882–886, 1977
86. Schneider LE, Schedl HP: Effects of alloxan diabetes on magnesium metabolism in the rat. *Proc Soc Exp Biol Med* 147: 494–497, 1974
87. Jain AP, Gupta NN, Kumar A: Some metabolic effects of magnesium in diabetes mellitus. *J Assoc Physicians India* 24: 827–831, 1976
88. Ewald U, Gebre-Medhin M, Tuvemo T: Hypomagnesemia in diabetic children. *Acta Paediatr Scand* 72:367–371, 1983
89. Rosner F, Gorfien PC: Zinc and magnesium levels in diabetes. *JAMA* 211:2156, 1970
90. Milewicz A, Stepien-Dobrowlska M, Szklarz E, Glebowska H, Gladysz A, Czarnowska J: Behaviour of the magnesium level in the serum, whole blood and erythrocytes in juvenile diabetes. *Wiad Lek* 29:599–601, 1976
91. Levine GE, Mather HM, Pilkington TRE: Tissue magnesium status in diabetes mellitus. *Diabetologia* 21:131–134, 1981
92. DeLeeuw I, Vertommen J, Abs R: The magnesium content of the trabecular bone in diabetic subjects. *Biomedicine* 29:16–17, 1978
93. Sjogren A, Floren CH, Nilsson A: Magnesium, potassium, and zinc deficiency in subjects with type II diabetes mellitus. *Acta Med Scand* 224:461–466, 1988
94. Paolisso G, Passariello N, Pizza G, Marrazzo G, Giunta R, Sgambato S, Varricchio M, D'Onofrio F: Dietary magnesium supplements improve β-cell response to glucose and arginine in elderly non-insulin-dependent diabetic subjects. *Acta Endocrinol* 121:16–20, 1989
95. McNair P, Christiansen C, Madsbad S, Lauritzen E, Faber O, Binder C, Transbøl I: Hypomagnesaemia, a risk factor in diabetic retinopathy. *Diabetes* 27:1075–1077, 1978
96. Seelig MS, Heggtveit HA: Magnesium interrelationships in ischemic heart disease: a review. *Am J Clin Nutr* 27:59–79, 1974
97. Marier JR: Cardio-protective contribution of hard waters to magnesium intake. *Rev Can Biol* 37:115–125, 1978
98. American Diabetes Association: Magnesium supplementation in the treatment of diabetes. *Diabetes Care* 16: (Suppl. 2): 79–81, 1993
99. Everson GJ, Shrader RE: Abnormal glucose tolerance in manganese deficient guinea pigs. *J Nutr* 94:89–94, 1968
100. Bond JS, Failla ML, Unger DF: Elevated manganese concentration and arginase activity in livers of streptozotocin-induced diabetic rats. *J Biol Chem* 258: 8004–8009, 1983
101. Eriksson UJ: Diabetes in pregnancy: retarded fetal growth, congenital malformations, and feto maternal concentrations of zinc, copper, and manganese in the rat. *J Nutr* 114:447–484, 1984
102. Walter RM, Aoki T, Keen CL: Acute oral manganese does not consistently affect glucose tolerance in nondiabetic and type II diabetic humans. *J Trace El Exp Med* 4:73–79, 1991
103. Rubenstein AH, Levin NW, Elliott GA: Manganese-induced hypoglycemia. *Lancet* 2:1348–1351, 1962
104. Hegde B, Griffith GC, Butt EM: Tissue and serum manganese levels in evaluation of heart muscle damage: a comparison with SGOT. *Proc Soc Exp Biol Med* 107:734–737, 1961
105. Volkov NF: Cobalt, manganese, and zinc content in the blood of atherosclerosis patients. *Fed Proc* 22:897–899, 1963
106. Cutler P: Deferoxamine therapy in high ferritin diabetes. *Diabetes* 38:1207–1210, 1989
107. Redman JB, Pyzdrowski KL, Robertson P: No effect of deferoxamine therapy on glucose homeostasis and insulin secretion in individuals with NIDDM and elevated serum ferritin. *Diabetes* 42:544–549, 1993
108. Dandona P, Hussain MA, Varghese Z, Politis D, Flynn DM, Hoffbrand AV: Insulin resistance and iron overload. *Ann Clin Biochem* 20:77–79, 1983
109. Bern MM, Busick EJ: Disorders of blood and diabetes. In *Joslin's Diabetes Mellitus*. Marble A, Krall LP, Bradley RF, Christlieb AR, Soeldner JS, Eds. Philadelphia, PA, Lea and Febiger, 1985, p. 748–752
110. Asayama K, Kooy NW, Burr IM: Effect of vitamin E deficiency and selenium deficiency on insulin secretory reserve and free radical scavenging systems in islets: decrease of islet manganosuperoxide dismutase. *J Lab Clin Med* 107:459–464, 1986
111. Sunde RA, Hoekstra WG: Structure, synthesis and functions of glutathione peroxidase. *Nutr Rev* 38:265–273, 1980
112. Van Rij AM, Thomson CD, McKenzie JM, Robinson MF: Selenium deficiency in total parenteral nutrition. *Am J Clin Nutr* 32:2076–2085, 1979
113. Chen X, Yang G, Chen J, Chen X, Wen Z, Ge K: Studies on the relations of selenium and Keshan disease. *Biol Trace Elem Res* 2:91–107, 1980
114. Johnson RA, Baker SS, Fallon JT, Maynard EP, Ruskin JN, Wen Z, Ge K, Cohen HJ: An occidental case of cardiomyopathy and selenium defficiency. *N Engl J Med* 304:1210–1212, 1981
115. Gebre-Medhin M, Ewald V, Plantin LO, Tuvemo T: Elevated serum selenium in

diabetic children. *Acta Paediatr Scand* 73:109–114, 1984
116. Strain JJ: Disturbances of micronutrient and antioxidant status in diabetes. *Proc Nutr Soc* 50:591–604, 1991
117. Chertow BS, Baker GR: The effects of vitamin A on insulin release and glucose oxidation in isolated rat islets. *Endocrinology* 103:1562–1572, 1979
118. Seifter E, Readawer J, Stratford F, Kambosos D, Levenson SM: Impaired wound healing in streptozotocin diabetes: prevention by supplemental vitamin A. *Ann Surg* 194:42–50, 1981
119. Ramachandran K: Beta caro levels in diabetes mellitus. *J Pharmacol* 31:1098–1100, 1981
120. Basu TK, Tze WJ, Leichter J: Serum vitamin A and retinol-binding protein in patients with insulin-dependent diabetes mellitus. *Am J Clin Nutr* 50:329–333, 1989
121. Saito N, Kimura M, Kuchiba A, Itokawa Y: Blood thiamine levels in outpatients with diabetes mellitus. *J Nutr Sci Vitaminol* 33:421–430, 1987
122. Hobara R, Ozawa K, Okazaki M, Yasuhara H: Relationship between thiamine and glucose levels in diabetes mellitus. *J Pharmacol* 31:1098–1100, 1981
123. Kjosen MS, Seim SH: The transketolase assay of thiamine in some diseases. *Am J Clin Nutr* 30:1591–1596, 1977
124. Vague P, Picq R, Bernal M, Lassmann-Vague V, Vialettes B: Effect of nicotinamide treatment on the residual insulin secretion in type I (insulin-dependent) diabetic patients. *Diabetologia* 32:316–321, 1989
125. Mendola G, Casamitjana R, Gomis R: Effect of nicotinamide therapy upon β-cell function in newly diagnosed type I (insulin-dependent) diabetic patients. *Diabetologia* 32:160–162, 1989
126. Pozzilli P, Visalli N, Ghirlanda G, Manna R, Andreani D: Nicotinamide increases C-peptide secretion in patients with recent onset type I diabetes. *Diabetic Med* 6:568–572, 1989
127. Lewis CM, Canafax DM, Sprafka JM, Barbosa JJ: Double-blind randomized trial of nicotinamide on early-onset diabetes. *Diabetes Care* 15:121–123, 1992
128. Sebastian HM, de Castro Del Pozo S, De La Fuente, Gomez L, Caro-Paton Gomez T: Estudio sobre carencia de piridoximia en los diabeticos. *Rev Clin Esp* 91:99–103, 1963
129. Davis RE, Calder JS, Curhow DH: Serum pyridoxal and folate concentrations in diabetics. *Pathology* 8:151–159, 1976
130. Wilson RG, David RE: Serum pyridoxal concentrations in children with diabetes mellitus. *Pathology* 9:95–98, 1977
131. Toyota T, Kai Y, Kakizaki M, Ohtsuka H, Shibata Y, Goto Y: The endocrine pancreas in pyridoxine deficient rats. *Tohuku J Exp Med* 134:331–336, 1981
132. Tezuka I, Makino K: Hyperglycemia in pyridoxine deficient rats. *J Vitaminol* (Kyoto) 5:304–306, 1959
133. Emerson GA, Kishi HS, Morril BJ, Snipes JW, Walker JB: Effects of low intakes of vitamin B_6 upon diabetic and control rats. *Vitam Horm* 22:643–653, 1964
134. Quagliariello E, Papa S, Saccone C, Alifano A: Effect of 3-hydroxyanthranilic acid on the mitochondrial respiratory system. *Biochem J* 91:137–146, 1964
135. Veneziale CM, Walter P Kneer N, Lardy HA: Influence of L-tryptophan and its metabolites on gluconeogenesis in the isolated perfused liver. *Biochemistry* 6:2129–2138, 1967
136. Kotake Y, Sotokawa T, Murakami E, Hisatake A, Abe M, Ideka Y: Studies on the xanthurenic acid-insulin complex. II. Physiological activities. *J Biochem* (Tokyo) 63:578–581, 1968
137. Adams PW, Wynn V, Folkard J, Seed M: Influence of oral contraceptives, pyridoxine (vitamin B_6), and tryptophan on carbohydrate metabolism. *Lancet* 1:759–764, 1976
138. Perkins RP: Failure of pyridoxine to improve glucose tolerance in gestational diabetes mellitus. *Obstet Gynecol* 50: 370–372, 1977
139. Gillmer MDG, Mazibuku D: Pyridoxine treatment of chemical diabetes in pregnancy. *Am J Obstet Gynecol* 133:499–502, 1979
140. Rao RH, Vigg BL, Jaya Rao KS: Failure of pyridoxine to improve glucose tolerance in diabetics. *J Clin Endocrinol Metab* 50: 198–200, 1980
141. Solomon LR, Cohen K: Erythrocyte O_2 transport and metabolism and effects of vitamin B_6 therapy in type II diabetes mellitus. *Diabetes* 38:881–886, 1989
142. Kaplan WE, Abourizk NN: Diabetic peripheral neuropathies affecting the lower extremity. *J Am Podiatry Assoc* 71:356–362, 1981
143. Schamberg H, Kaplan J, Windebank A, Vick N, Rasmus S, Pleasure D, Brown MJ: Sensory neuropathy from pyridoxine abuse: a new megavitamin syndrome. *N Engl J Med* 309:445–448, 1983
144. Trence DL, Morley JE, Handwerger BS: Polyglandular autoimmune syndromes. *Am J Med* 77:107–116, 1984
145. Reed RL, Mooradian AD: Nutritional status and dietary management of elderly diabetic patients. *Clin Geriatr Med* 6:883–901, 1990
146. Ide H, Fujiya S, Asanuma Y, Tsuji M, Sakai H, Agishi Y: Clinical usefulness of intrathecal injection of methylcobalamin in patients with diabetic neuropathy. *Clin Ther* 9:183–192, 1987
147. Patterson JW: The diabetogenic effect of dehydroascorbic and dehydroisoascorbic acid. *J Biol Chem* 183:81–88, 1950
148. Sjostrand SE: Pharmacological properties of dehydroascorbic acid and ascorbic acid: effects on the central and peripheral nervous systems in experimental animals. *Acta Physiol Scand* 358 (Suppl.):1–79, 1970
149. Som S, Basu S, Mukherjee D, Deb S, Choudhury PR, Mukherjee S, Chatterjee SN, Chatterjee IB: Ascorbic acid metabolism in diabetes mellitus. *Metabolism* 30:572–577, 1981
150. Newill A, Habibzadeh N, Bishop N, Schorah CJ: Plasma levels of vitamin C components in normal and diabetic subjects. *Ann Clin Biochem* 21:488–490, 1984
151. Stankova L, Riddle M, Larned J, Burry K, Meneshe D, Hart J, Bigley R: Plasma ascorbate concentrations and blood cell dehydroascorbate transport in patients with diabetes mellitus. *Metabolism* 33: 347–353, 1984
152. Schorah CJ, Bishop N, Wales JK, Hansbro PM, Habibzadeh N: Blood vitamin C concentrations in patients with diabetes mellitus. *Int J Vitam Nutr Res* 58:312–318, 1988

153. Chen MS, Hutchinson ML, Pecoraro RE, Lee WYL, Labbe RF: Hyperglycemia-induced intracellular depletion of ascorbic acid in human mononuclear leukocytes. *Diabetes* 32:1078–1081, 1983
154. Mooradian AD: The effect of ascorbate and dehydroascorbate on tissue uptake of glucose. *Diabetes* 36:1001–1004, 1987
155. Yew MS: Effect of streptozotocin diabetes on tissue ascorbic acid and dehydroascorbic acid. *Horm Metab Res* 15: 158, 1983
156. Sarji KE, Kleinfelder J, Brewington P, Gonzalez J, Hempling H, Colwell JA: Decreased platelet vitamin C in diabetes mellitus: possible role in hyperaggregation. *Thromb Res* 15:639–650, 1979
157. Jennings PE, Chirico S, Jones AF, Lunec J, Barnett AH: Vitamin C metabolites and microangiopathy in diabetes mellitus. *Diabetes Res* 6:151–154, 1987
158. Stankova L, Riddle M, Larned J, Burry K, Meneshe D, Hart J, Bigley R: Plasma ascorbate concentrations and blood cell dehydroascorbate transport in patients with diabetes mellitus. *Metabolism* 33: 347–353, 1984
159. Ginter E, Zdichynec B, Holzerova O, Ticha E, Kobza R, Koziakova M, Cerra O, Ozdin L, Hruba F, Novakova V, Sasko E, Gaber M: Hypocholesterolemic effect of ascorbic acid in maturity-onset diabetes mellitus. *Int J Vitam Nutr Res* 48:368–373, 1978
160. Cox BD, Butterfield WJH: Vitamin C supplements and diabetic cutaneous capillary fragility. *Br Med J* 3:205, 1975
161. Bishop N, Schorah CJ, Wales JK: The effect of vitamin C supplementation on diabetic hyperlipidemia: a double blind, crossover study. *Diabetic Med* 2:121–124, 1985
162. Vinson JA, Staratz ME, Bose P, Kassm HM, Basalyga BS: In vitro and in vivo reduction of erythrocyte sorbitol by ascorbic acid. *Diabetes* 38:1036–1041, 1989
163. Yue DK, McLennan S, Fisher E, Heffernan S, Capogreco C, Ross GR, Turtle JR: Ascorbic acid metabolism and polyol pathway in diabetes. *Diabetes* 38:257–261, 1989
164. Som S, Basu S, Mukherjee D, Deb S, Choudhury PR, Mukherjee S, Chatterjee SN, Chatterjee IB: Ascorbic acid metabolism in diabetes mellitus. *Metabolism* 30:572–577, 1981
165. National Research Council (U.S.) Committee on Dietary Allowances: *Recommended Dietary Allowances*. 10th ed. Washington, D.C., National Academy Press, 1989
166. Alhadeff L, Guaitieri CT, Lipton M: Toxic effects of water-soluble vitamins. *Nutr Rev* 42:33–40, 1984
167. Darby WJ, Ferguson ME, Furman RH, Lemley JM, Ball CT, Meneely GR: Plasma tocopherols in health and disease. *Ann NY Acad Sci* 52:328–388, 1949
168. Vatassery GT, Morley HE, Kuskowski MA: Vitamin E in plasma and platelets of human diabetic patients and control subjects. *Am J Clin Nutr* 37:641–644, 1983
169. McMasters V, Howard T, Kinsell LW, Van Der Veen J, Olcott MS: Tocopherol storage and depletion in adipose tissue and plasma of normal and diabetic human subjects. *Am J Clin Nutr* 20:622–666, 1967
170. Caye-Vaugien C, Krempf M, Lamarche P, Charbonnel B, Peiri J: Determination of alpha-tocopherol in plasma, platelets, and erythrocytes of type I and type II diabetic patients by high-performance liquid chromatography. *Int J Vitam Nutr Res* 60:324–330, 1990
171. Gisinger C, Wantanabe J, Colwell JA: Vitamin E and platelet eicosanoids in diabetes mellitus. *Prostaglandins Leukotrienes Essent Fatty Acids* 40:169–179, 1990
172. Watanabe J, Umeda F, Wakasugi H, Ibayashi H: Effect of vitamin E on platelet aggregation in diabetes mellitus. *Thromb Haemost* 51:313–316, 1984
173. Karpen CW, Cataland S, O'Dorisio TM, Panganamala RV: Production of 12-hydroxy eicosatetraenoic acid and vitamin E status in platelets from type I human diabetic subjects. *Diabetes* 34: 526–531, 1985
174. Gisinger C, Jeremy J, Speiser P, Mikhailidis D, Dandona P, Schernthaner G: Effect of vitamin E supplementation on platelet thromboxane A2 production in type I diabetic patients: double-blind crossover trial. *Diabetes* 37:1260–1264, 1988
175. Colette C, Pares-Herbute N, Monnier LH, Cartry E: Platelet function in type I diabetes: effects of supplementation with large doses of vitamin E. *Am J Clin Nutr* 47:256–261, 1988
176. Kunisaki M, Umeda F, Inoguchi T, Wantanabe J, Nawata H: Effects of vitamin E administration on platelet function in diabetes mellitus. *Diabetes Res* 14:37–42, 1990
177. Wu HP, Tai TY, Chuang LM, Lin BJ, Wnag JD, Teng CM: Effect of tocopherol on platelet aggregation in non-insulin-dependent diabetes mellitus: ex vivo and in vitro studies. *Taiwan I-Hsueh-Hui Tsa-Chih* 91:270–275, 1992
178. Ozden I, Deniz G, Tasali E, Ulusarac A, Altug T, Buyukdevrim S: The effect of vitamin E on glycosylated hemoglobin levels in diabetic rats: a preliminary report. *Diabetes Res* 12:123–124, 1989
179. Ceriello A, Giugliano D, Quatraro A, Donzella C, Dipalo G, Lefebvre PJ: Vitamin E reduction of protein glycosylation in diabetes: new prospect for prevention of diabetic complications? *Diabetes Care* 14:68–72, 1991
180. Paolisso G, D'Amore A, Giugliano D, Ceriello A, Varricchio M, D'Onofrio F: Pharmacologic doses of vitamin E improve insulin action in healthy subjects and non-insulin-dependent diabetic patients. *Am J Clin Nutr* 57:650–656, 1993
181. Vandewoude MG, VanGaar LF, Vandewoude MF, De-Leeuw IH: Vitamin E status in normocholesterolemic and hypercholesterolemic diabetic patients. *Acta Diabetol Lat* 24:133–139, 1987
182. Krempf M, Rangnathan S, Ritz P, Morin M, Charbonnel B: Plasma vitamin A and E in type I (insulin-dependent) and type II (non-insulin-dependent) adult diabetic patients. *Int J Vitam Nutr Res* 61: 38–42, 1991
183. Morel DW, Chisolm GM: Antioxidant treatment of diabetic rats inhibits lipoprotein oxidation and cytotoxicity. *J Lipid Res* 30:1827–1834, 1989
184. Rodland O, Markestad T, Aksnes L, Aarskog D: Plasma concentrations of vitamin D metabolites during puberty of diabetic children. *Diabetologia* 28:663–

666, 1985
185. McNair P: Bone mineral metabolism in human type I (insulin dependent) diabetes mellitus. *Dan Med Bull* 32:109–121, 1988
186. Hui SL, Epstein S, Johnston CC Jr: A prospective study of bone mass in patients with type I diabetes. *J Clin Endocrinol Metab* 60:74–80, 1985
187. Leon M, Larrodera L, Lledo G, Hawkins F: Study of bone loss in diabetes mellitus type I. *Diabetes Res Clin Pract* 6:237–242, 1989
188. Verrotti A, Blasetti A, Tumini S, Chiarelli F, Morgese G: Calcium homeostasis in prepubertal diabetic children. *Acta Diabetol Lat* 25:173–177, 1988
189. Auwerx J, Dequeker J, Bouillon R, Geusens P, Nijs J: Mineral metabolism and bone mass at peripheral and axial skeleton in diabetes mellitus. *Diabetes* 37:8–12, 1988
190. Kuoppala T: Alterations in vitamin D metabolites in diabetic pregnancy. *Gynecol Obstet Invest* 25:99–105, 1988
191. Mimouni F, Tsang RC, Hertzberg VS, Neumann-V, Ellis K: Parathyroid hormone and calcitriol changes in normal and insulin-dependent diabetic pregnancies. *Obstet Gynecol* 74:49–51, 1989
192. Levin ME, Boisseau VC, Avioli LV: Effects of diabetes mellitus on bone mass in juvenile and adult-onset diabetes. *N Engl J Med* 294:241–245, 1976
193. Weinstock RS, Goland RS, Shane E, Clemens TL, Lindsay R, Bilezikian JP: Bone mineral density in women with type II diabetes mellitus. *J Bone Miner Res* 4:97–101, 1989
194. Isaia-G, Bodrato L, Carlevatto V, Mussetta M, Salamano G, Molinatti GM: Osteoporosis in type II diabetes. *Acta Diabetol Lat* 24:305–310, 1987
195. Ishida H, Seino Y, Matsukura S, Ikeda M, Yawata M, Yamashita G: Diabetic osteopenia and circulating levels of vitamin D metabolites in type II (non-insulin-dependent) diabetes. *Metabolism* 34: 797–801, 1985
196. National Insitutes of Health Consensus Conference: Osteoporosis. *JAMA* 252: 799–802, 1984
197. Carpentier JL, Bury J, Luyckx A, Lefebvre P: Vitamin B_{12} and folic acid serum levels in diabetics under various therapeutic regimens. *Diabete Metab* 2:187–192, 1976
198. Kaplan J, Hess JW, Prasad AS: Impaired interleukin-2 production in the elderly: association with mild zinc deficiency. *J Trace Elem Exp Med* 1:3–8, 1988
199. Prasad AS, Meflah S, Abdallah J, Daplan J, Brewer GJ, Back JF, Dardenne M: Serum thymulin in human zinc deficiency. *J Clin Invest* 82:1202–1210, 1988
200. Grider A, Bailey LB, Cousins RJ: Erythrocyte metallothionein as an index of zinc status in humans. *Proc Pak Acad Sci* 87:1259–1262, 1990
201. American Diabetes Association: *Exchange Lists for Meal Planning*. Alexandria, VA, American Diabetes Association, 1989