Nutritional Regulation of Blood Glucose

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ABSTRACT: The effect of various micronutrients on blood glucose regulation is reviewed. Based on this information, it is possible to develop a nutritional supplement program which may be of value for individuals suffering from diabetes or hypoglycemia.

Introduction

Effective regulation of blood glucose has important implications for health and disease. Glucose dysregulation can be life-threatening at the extremes (diabetic coma or hypoglycemic shock). Milder disruptions of glucose homeostasis can also have adverse consequences. Thus, chronic diabetes may result in cardiovascular disease, neuropathy, blindness, or renal failure. Hypoglycemia (also called reactive hypoglycemia or dysinsulinism), though not generally associated with the organ damage seen in diabetes, can be responsible for a number of troublesome physical and psychological symptoms.

The human body possesses a complex set of checks and balances with which to maintain blood glucose concentrations within a narrow range. Blood sugar control is influenced by the pituitary, thyroid, and adrenal glands, as well as by the pancreas, liver, and skeletal muscle.

Glucose homeostasis also depends on a wide range of micronutrients. Many of these nutrients are in short supply in they typical refined, processed American diet. In addition, some individuals with blood sugar disorders may have a higher-than-normal requirement for one or more micronutrients. Supplementation with appropriate vitamins and minerals may therefore be of value in the treatment of diabetes and hypoglycemia.

It might seem that nutrients used to treat hyperglycemia would not also be indicated for the treatment of hypoglycemia. However, these two conditions frequently have certain path physiologic similarities, such as delayed postprandial insulin release and tissue resistance to insulin. In addition, the presence of dysinsulinism, as determined by glucose-insulin tolerance testing, is associated with an increased risk of developing diabetes.[1] Controlled studies and clinical experience have demonstrated that nutrients which are of value in the treatment of type II diabetes can also be used successfully to treat hypoglycemia.

Nutrients which may be useful in the treatment of blood sugar disorders are reviewed below. Based on this information, it is possible to develop a nutritional supplement program which may be of value for individuals suffering from diabetes or hypoglycemia.

Chromium

Rats fed a chromium (Cr)-deficient diet developed hyperglycemia and glycosuria.[2] Monkeys maintained on a low Cr diet had abnormal glucose metabolism, which was corrected by Cr supplementation.[3] Cr also protected guinea pigs against streptozotocin-induced pancreatic beta-cell destruction[4] and reduced insulin resistance in genetically obese mice.[5]

The effect of Cr on glucose metabolism apparently requires conversion to glucose tolerance factor (GTF), a low-molecular-weight compound that contains Cr. Niacin (nicotinic acid), glycine, glutamic acid, and cysteine. GTF, which occurs naturally in brewer's yeast and to a lesser extent in other foods, has been shown to potentiate the action of insulin at the cellular level.[6]

Cr deficiency is known to occur in man. Individuals maintained on parenteral nutrition developed a complex metabolic disorder including impaired glucose tolerance, which was reversed by Cr supplementation.[7,8] Less severe forms of C deficiency may be common in the United States. Because of farming techniques which fail to replenish trace minerals in the soil, the Cr content of food is most likely far lower than it was at the turn of the century. Tissue Cr levels were found to decline with age in Americans, but not in individuals living in other countries.[9] One dietary survey revealed that 90% of American diets contained less than the minimum suggested daily intake for Cr.[10]

Cr supplementation has produced encouraging results. In a double-blind trial, daily administration of 200 µg of Cr resulted in a significant reduction in 2-hour postprandial glucose in elderly women with borderline glucose tolerance.[11] In another study of elderly patients, Cr significantly reduced mean plasma glucose during a glucose tolerance test and significantly improved glucose utilization.[12] Treatment with 150 µg/day of Cr for four months normalized glucose tolerance in four of ten elderly individuals with abnormal glucose tolerance.[13] Administration of 150 to 1,000 µg/day of Cr improved glucose tolerance in three of six diabetics. The larger doses were more effective than the smaller doses.[14]

Cr was also effective in the treatment of reactive hypoglycemia. Eight women, aged 33-69 years, with symptoms of reactive hypoglycemia received 200 µg of Cr or a placebo, each for 12 weeks, in a double-blind crossover trial. Cr alleviated the hypoglycemic symptoms, including an improvement in blurred vision in some cases, and significantly raised the minimum serum glucose values at two to four hours following a glucose load.[15] In another study, 76 healthy

volunteers received 200 µg/day of Cr or a placebo, each for 90 days, in a double-blind crossover trial. Among those with glucose levels greater than 100 mg/dl at 90 minutes after a glucose load, Cr supplementation significantly reduced the mean 90-minute glucose concentration from 135 to 166 mg/dl. Among those whose 90-minute glucose level was less than the fasting level, Cr significantly increased the mean 90-minute glucose level from 71 to 81 mg/dl.[16] Thus, Cr is capable of lowering blood sugar when it is too high and raising it when it is too low.

Other studies have produced negative results. In two double-blind studies, supplementation with 150 or 200 µg. day of Cr failed to improve glucose tolerance in diabetic patients.[17,18]

These conflicting results may be due to several factors. First, in all of the studies described above, Cr chloride was used. Because only 0.5% of this form of chromium is absorbed, the dosage may have been inadequate. Second, in order to be effective, inorganic Cr must be converted into GTF, its biologically active form. Biosynthesis of GTF requires, among other things, an adequate supply of niacin, a nutrient which may be in short supply in many individuals (see below).

In our experience, Cr aspartate is a well-utilized form of supplemental Cr which appears to be more effective than Cr chloride. Cr picolinate and Cr polynicotinate also seems to have a high degree of bioavailability. The doses of Cr used in most clinical trials (150 to 200 µg/day) are apparently inadequate for some patients, even when more effective CR compounds are used. Larger amounts of Cr, such as 500 to 1000 µg/day have often resulted in greater symptom relief and more effective blood sugar control than the lower doses.

So-called "GTF-Cr" has been widely touted as the preferred Cr supplement. It is true that GTF extracted from food is absorbed to a greater extent and has greater biologic activity than inorganic Cr. However, the precise molecular structure of GTF is still unknown, and GTF has never been successfully synthesized in the laboratory. According to Mertz, who originally discovered GTF, analysis of one of the so-called "GTF-Cr" products revealed no GTF activity.[19]

Niacin and Niacinamide

As a component of glucose tolerance factor, niacin plays an important role in carbohydrate metabolism. Many refined foods consumed by Americans are depleted of niacin. Grains and other foods that are "enriched" usually contain added niacinamide, which cannot apparently be converted by the human body into niacin. In addition, most vitamin supplements contain niacinamide, rather than niacin. Although niacinamide is capable of performing most of the functions of vitamin B_3, a small amount of niacin seems to be necessary for synthesis of GTF.

Sixteen healthy elderly individuals received either 200 µg of chromium, 100 mg of niacin, or both, daily for 28 days. Fasting plasma glucose levels and glucose tolerance were unaffected by either chromium or niacin alone. However, the combination caused a significant 14.8% decrease in the area under the glucose curve and a significant 6.8% reduction in fasting glucose.[20]

Both niacin and niacinamide may be of additional value to diabetics through a mechanism unrelated to glucose tolerance factor. In animal studies, niacinamide protected against streptozotocin-induced diabetes[21,22] and inhibited the development of experimental autoimmune diabetes.[23] Niacin administration also prevented the diabetogenic effect of alloxan in rabbits and rats.[24] There is evidence that both experimental diabetes and type I (insulin-dependent) diabetes in humans are related to a depletion of NAD within pancreatic ß-cells, resulting in failure of oxidative metabolism and subsequent cell death. As precursors to NAD, niacin and naicinamide are apparently capable of preventing the apparently capable of preventing the depletion of NAD in pancreatic ß-cells.

The relevance of these findings to humans has recently been demonstrated.[25] Sixteen type I diabetics received, in double-blind fashion, either niacinamide (n = 7; 3 g/day) or a placebo (n = 9), beginning one week after the start of insulin therapy. Insulin was successfully discontinued in 85.7% of the patients taking niacinamide, compared to 55.6% of those taking placebo ($p < 0.05$). Three patients treated with niacinamide for 18 months remained in remission for more than 2 years. Remissions of such a long duration are extremely rate in type I diabetes. These results suggest that niacinamide reduces destruction of ß-cells or enhances their regeneration, thereby extending remission time.

Although extremely large doses of niacin may occasionally make diabetes worse,[26] the evidence above indicates that a low dose of niacin, combined with a moderate dose of niacinamide, may have therapeutic value.

Biotin

The initial step in glucose utilization by the cell is its phosphorylation, mediated by the biotin-dependent enzyme glucokinase. Hepatic glucokinase activity was decreased in biotin-deficient rats, and was restored to normal by biotin supplementation.[27] The effect of biotin on glucokinase activity was similar to that of insulin. Administration of biotin (2 to 4 mg/kg of body weight/day) to genetically diabetic mice improved glucose tolerance and lowered insulin resistance.[28]

Biotin has also shown promise in the treatment of diabetes in humans. Seven insulin-dependent diabetics were removed from insulin therapy and treated with biotin (16 mg/day) or a placebo for one week. Fasting blood glucose rose significantly in patients given placebo, but decreased significantly in those treated with biotin.[29]

Pyridoxine (vitamin B_6)

Serum vitamin B_6 levels were below normal in 25% of a series of 518 diabetics.[30] Pyridoxine supplementation of diabetic patients improved glucose tolerance in some studies,[31,32] but was without effect in others.[33]

Administration of pyridoxine (50 mg, three times a day) to ten patients with diabetic neuropathy completely eliminated the neuropathic symptoms in all cases.[34]

Copper

Rats fed a copper-deficient diet had increased plasma glucose levels after a glucose load and a delayed insulin response to glucose administration.[35] Copper-deficient rats also had impaired insulin binding in vitro[36] and increased concentrations of glycosylated hemoglobin, indicative of chronic hyperglycemia.3[7]

Because the typical American diet contains only about half of the RDA (2 mg/day) for copper,[38] deficiency of this mineral may be common. Two male volunteers fed a controlled intake of 0.7-0.8 mg of copper per day for 5-6 months had increased glucose levels during a glucose tolerance test which returned toward normal after copper repletion.[39] In two other volunteers, administration of 6 mg/day of copper improved glucose tolerance, suggesting that their usual diet was deficient in copper.[40]

Magnesium

Serum magnesium (Mg) concentrations were significantly lower in a group of 56 diabetics than in controls.[41] Hypomagnesaemia was more pronounced in individuals with diabetic retinopathy[42] or cardiac complications than in diabetics without such complications.[43] The Mg content of trabecular bone was also significantly lower in type I diabetics and insulin-treated type II diabetics than in non-diabetic controls.[44] Poor control of diabetes was often associated with low serum magnesium.[45] Urinary Mg excretion was significantly greater in diabetics than in controls, possibly indicative of a specific disorder of Mg renal tubular transport in diabetes.[46] Mg deficiency is thought to play a role in the development of insulin resistance.[47]

Mg has also been found to be a factor in hypoglycemia.[48] Twenty-two individuals with reactive hypoglycemia documented by glucose tolerance tests were studied. Hair Mg levels were significantly lower in female hypoglycemics and nonsignificantly lower in male hypoglycemics ($p < 0.10$) than in controls. Erythrocyte and plasma Mg levels were significantly reduced in female hypoglycemics but not in males. These 22 individuals were treated with 340 mg/day of Mg (sulfate) or a placebo, for 6 weeks. Of those taking Mg, 57% reported feeling better, compared to 25% of those taking placebo. In some individuals receiving Mg, the glucose nadir during a glucose tolerance test increased. Lack of response to Mg supplementation was associated with a failure of urinary Mg excretion to increase. Nonresponders may have therefore had poor gastrointestinal Mg absorption or a relatively large tissue Mg deficit which was not fully corrected during the study period.

The American diet is often low in Mg. Dietary surveys have shown that 80-85% of American women consume less than the RDA for this mineral.49 Daily Mg intake in two other studies was only about two-thirds of the RDA.[50,51] Mg supplementation may therefore be indicated for the majority of Americans.

Potassium

Potassium-deficient rats had elevated blood glucose levels and a reduced insulin response to a glucose load.[52] Obese patients undergoing a protein-sparing modified fast without potassium supplementation had a striking reduction in peripheral glucose utilization and insulin levels. These changes were reversed by potassium supplementation.[53] Administration of potassium to children with protein-calorie malnutrition resulted in rapid improvement in the insulin response to an intravenous glucose load.[54] Potassium supplementation also prevented impaired glucose tolerance resulting from treatment with thiazide diuretics.[55]

Zinc

Plasma zinc concentration was reduced and urinary zinc excretion was elevated in diabetic humans[56-59] and animals.[60] Zinc enhanced insulin synthesis by pancreatic ß-cells in vitro,[61] and increased insulin binding to liver and adipose tissue cells.[62,63] Patients with zinc deficiency resulting from gastrointestinal diseases had significantly higher glucose levels and significantly lower insulin levels than similar patients without zinc deficiency. Zinc repletion increased plasma insulin levels in these patients.[64] Healthy male volunteers consuming a low-zinc diet had a significant increase in fasting blood glucose levels.[65] Impaired glucose tolerance also developed in rats fed a zinc-deficient diet.[66] Administration of zinc to diabetic patients increased the T lymphocyte response to phytohemagglutinin in those with initially low responses.[67]

The typical American diet is low in zinc. In one dietary survey, 68% of adults consumed less than two-thirds of the RDA for zinc.[68] These data suggest that zinc deficiency is common in the United States and may adversely affect glucose tolerance.

Ascorbic acid (vitamin C)

Ascorbic acid (AA)-deficient guinea pigs had diabetic glucose tolerance curves, glycosuria, and decreased pancreatic insulin content.[69] Diabetic blood sugar curves were also seen in patients with AA deficiency; these values returned to normal after AA supplementation.[70] In diabetic patients, plasma[71] and platelet[72] AA concentrations were lower than in healthy controls.

Administration of AA (1 g/kg of diet) reduced mean plasma glucose by 34% in streptozotocin-diabetic rats.[73] Treatment of human diabetics with AA has produced conflicting results. A man with insulin-dependent diabetes was able to reduce his insulin requirement by 59% by ingesting AA every hour while awake.[74] In other studies, supplementation with 300 to 1,200 mg/day of AA failed to improve glucose tolerance of diabetics.[75,76]

However, the potential benefit of AA in diabetics may extend beyond any possible effect on glucose metabolism. Because of the structural similarity of AA to glucose, AA transport across cell membranes appears to be enhanced by insulin[77] and inhibited by hyperglycemia.[78] In diabetes, uptake of AA into certain tissues may therefore be impaired, producing a kind of "local scurvy," which might result in accelerated atherosclerosis, basement membrane thickening, cataracts, and other pathologic changes seen in diabetes. These effects would presumably be preventable by AA supplementation. In addition, supplementation with 2,000 mg/day of AA has been shown to reduce erythrocyte sorbitol accumulation by 56.1% and 44.5% in healthy individuals and diabetics, respectively.[79] Intracellular accumulation of sorbitol is believed to be involved in the pathogenesis of diabetic end-organ damage. These studies therefore suggest that a large intake of AA may prevent some of the complications of diabetes.

Manganese

Manganese is a cofactor for certain enzymes involved in the intermediary metabolism of carbohydrates. In addition, the concentration of manganese in the pancreas is approximately ten times higher than in other organs.[80] Manganese-deficient animals developed histologic abnormalities of pancreatic ß-cells[81] and diabetic glucose tolerance curves.[82] Supplementation with manganese improved both the histologic findings and the glucose intolerance. Administration of oral manganese to an insulin-dependent diabetic resulted in a dramatic reduction in the glucose response to an oral glucose load. However, glucose tolerance of seven other diabetics was not affected by manganese.[83]

The optimal intake of manganese is not known, but at least half of the manganese in a typical diet is lost when whole grains are replaced by refined flour.[84] The American diet may therefore be low in manganese.

Selenium

Selenium-deficient rats had decreased insulin secretory reserve. When combined with vitamin E deficiency, selenium deficiency results in glucose intolerance.[85] Dietary selenium protected against early-stage retinopathy in rats.[86] In a group of insulin-dependent diabetic pregnant women, there was an inverse association between serum selenium concentration and the degree of visual impairment.[86]

Vitamin B_{12}

Vitamin B_{12} is involved in a number of different steps in carbohydrate metabolism. Prolonged treatment of rats with cortisone or ACTH caused hyperglycemia, which was corrected by injection of vitamin B_{12}.[87] The incidence of vitamin B_{12} deficiency (pernicious anemia) was significantly greater in a series of diabetics than in the general population.[88] Parenteral administration of vitamin B_{12} was followed by improvement of retinopathy in the majority of a group of young insulin-dependent diabetics.[89,90]

Folic acid

Supplementation of rats with large doses of folic acid prevented fasting-induced hypoglycemia, apparently by increasing gluconeogenesis through stimulation of key enzymes in the liver and small intestine.[91]

Thiamine

Experimental thiamine deficiency in animals caused a rise in blood sugar.[92] Administration of thiamine resulted in prolonged survival in alloxan-diabetic mice.[93] Blood thiamine concentrations were significantly lower in insulin-dependent diabetics than in controls.[94] Administration of 10 mg of thiamine per day for 4 weeks reduced hyperglycemia and glycosuria in 6 (54.6%) of 11 diabetics.[95]

Calcium

Administration of 3 g of calcium lactate along with an oral glucose load augmented glucose-induced insulin secretion in diabetics, but not in non-diabetics.[96] An intravenous infusion of calcium (35 mEq over 5 hours) during a glucose tolerance test minimized the fall in blood glucose and eliminated the symptoms of hypoglycemia in 12 patients with reactive hypoglycemia.[97]

Carnitine

Urinary carnitine excretion was significantly greater in streptozotocin-diabetic rats than in controls.[98] Marked decreases in muscle carnitine concentrations and carnitine body pools were observed in alloxan-diabetic rats. However, muscle carnitine concentrations did not differ between human diabetics and controls.[99] Carnitine stimulated gluconeogenesis by rabbit liver and kidney slices in vitro, an effect which might help prevent hypoglycemia during fasting.[100] Hypoglycemia has been described as part of the clinical picture of carnitine deficiency.[101]

Vanadium

Vanadate, an oxidized form of vanadium, appears to have an insulin-like action.[102] Vanadate also increased insulin sensitivity of isolated rat muscle[103] and stimulated insulin secretion from rat pancreatic islets in vitro.[104]

Vitamin E

Rats treated with vitamin E had increased resistance to the diabetogenic effect of streptozotocin or alloxan.[105] Shute reported that vitamin E supplementation will reduce blood sugar levels in some diabetics.[106] This observation was confirmed in one study,[107] but vitamin E was without benefit in others.[108,109]

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