Micronutrients as Nutriceutical Interventions in Diabetes Mellitus

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Hyperglycemia portends chronic complications in insulin-dependent diabetes mellitus (IDDM) and substantial benefits are associated with “tight” glycemic control. Other interventions should either enhance glycemic control per se or add benefit to an established degree of glycemic control. Several micronutrients enhance insulin action and others offer promise in countering the untoward consequences of hyperglycemia. Supplements of micronutrients including the vitamins niacin (as niacinamide), C and E and the minerals zinc, chromium, and vanadium have been studied. For the purpose of this review, the term “nutriceutic” refers to supplementation on the order of 2 to 10 times the RDA for which a benefit is linked to a mechanism of action. Benefits associated with “nutriceutic” supplementation are reported in small trials for vitamins C and E and these supplements are safe and affordable from food or tablet sources. A dietary strategy adding 200–600 mg of vitamin C and 100 IU of vitamin E to a healthy dietary pattern is worthy of consideration as an intervention for individuals with IDDM.

Key teaching points:

• “Tight” glycemic control is effective in decreasing the complications of diabetes mellitus.
• Niacinamide is under clinical trial for efficacy in delaying or preventing the onset of type I diabetes.
• Several micronutrients enhance insulin action and others effectively counter the pathologic consequences of hyperglycemia.
• Vitamins C and E offer promise for diminishing protein glycoxidations.

INTRODUCTION

Dr. Grace Goldsmith’s legacy to the American College of Nutrition includes high standards for education at our annual meetings and scholarship in our nutrition research [1]. Her bench work on vitamin biochemistry clarified interactions between folic acid and vitamin B12. Furthermore, she transitioned to a public health emphasis and documented the need for, and the benefit from, micronutrient enrichment of foods to overcome dietary insufficiencies. These interests of Dr. Goldsmith mesh well with contemporary work seeking to identify nutrient functions beyond the prevention of classic deficiency symptoms and supplementing micronutrient intakes of individuals at high risk. This presentation briefly overviews emerging possibilities for micronutrient efficacy in one such arena, that of insulin-dependent diabetes mellitus (IDDM).

Micronutrients are a subset of the larger group of known dietary essential nutrients for man that are recognized in scientific publications such as the Recommended Dietary Allowances (RDA) [2]. The RDA or an estimated safe and adequate daily dietary intake (ESADDI) for an individual micronutrient is less than 100 mg. This category encompasses all of the vitamins and many of the minerals, including those sometimes referred to as “trace” minerals.

The term “nutr-i-ceutical” is coined for the present context to differ from the widely (mis)used and less precisely characterized term “nutr-a-ceutical.” The point is well made that neither of these has a legal or scientific definition at present. Nutriceutical is a convenient descriptor for a supplemental nutrient intake that is associated with a specific therapeutic effect. Firstly, “nutri” conveys that a known essential nutrient is under consideration, whereas the more generally used “nutra”
has no such implication and could be used in the context of numerous chemical supplements that may, or may not, be nutrients. Secondly, the level of supplementation is grounded in an established specific effect on a biochemical pathway or a physiologic process rather than reflecting nonspecific effects that may occur at higher pharmacologic doses. Thirdly, “nutriceutic” emphasizes the documentation of a healing benefit for an individual who is ill. This sets the discussion apart from the RDA conceptual framework where good health is presumed and health maintenance is the endpoint [2]. A nutriceutic intervention will raise total dietary intake above the RDA, but not beyond a 2 to 10 fold factor. Beyond that level of intake, terms prefixed by “pharma” would generally apply. For non-nutrients being touted as “nutraceutic” there is no recommended intake level upon which to set a parallel division.

It is generally accepted that hyperglycemia portends chronic diabetic complications. The benefits expected from “close” or “tight” glycemic control are highly salutary as shown by the Diabetes Control and Complications Trial (DCCT) [3]. The rationales for other interventions should be consistent with either enhancing glycemic control per se or adding benefit to an established degree of glycemic control. Since “tight” control achieves less than “pancreatic” control of glycemia, i.e., glycemia at 6 mM rather than 5 mM and glycated hemoglobin at 7% rather than 5%, additional benefits are likely to be achievable. Furthermore, the practice of tight control, though recommended, does involve compliance and monitoring that many individuals with IDDM are unwilling to follow. Several micronutrients enhance insulin action and others effectively counter the untoward consequences of hyperglycemia. While this review focuses on IDDM, with the exception of primary prevention, the benefits from micronutrients are expected for individuals with either IDDM or non-insulin dependent diabetes mellitus (NIDDM). Indeed, for vitamins E and C and for chromium and vanadium there is literature for efficacy in NIDDM that is not presented herein.

NIACINAMIDE AND PRIMARY PREVENTION

An impressive case for efficacy from niacinamide in pharmacologic daily dose has been made by Elliott and co-workers [4]. The delay of onset of IDDM among treated high risk individuals, defined as a high islet cell antibody (ICA) titer and family relationship, is striking. For extremely high risk individuals, those with ICA >80 units with a diminution of first phase insulin release already evident, IDDM onset incidence during 2 years was totally prevented vs. a 90% onset for controls; at 4 years the incidence was only 40%. Similarly, for children younger than 10 years with ICA mildly elevated at >10 units, incidence of IDDM during 5 years was 20% vs. 80% for controls and for those with ICA >20 at any age onset was 15% vs. 40% over that period. Recruitment is underway for an international multi-center trial called ENDIT (European Niacinamide Diabetes Intervention Trial), including eight centers in Canada (CanENDIT) and one in the USA. Most of over 500 at risk (ICA + on two occasions, at least 20 units on one) subjects have been enrolled. All will be followed to endpoints of IDDM or 5 years free of frank disease with a prediction of 50% efficacy. Niacinamide appears to be nontoxic at the chosen dose of 1200 mg per square meter body surface area up to 3000 mg daily.

The dose, as in Elliott’s trials, exceeds the RDA or Canadian equivalent on the order of 80 to 100 fold. To qualify as a “nutriceutical” therapy a titration to an efficacious lower dose would need to follow any demonstration of benefit at the pharmacologic level under study. Secondly, to meet the test of “nutriceutical”, a mechanistic explanation would also be needed. In this regard, animal studies suggest that the role for niacinamide may reside in DNA damage/repair processes or in protection from free radical damage [5].

ANTIOXIDANT VITAMINS AS NUTRICEUTIC INTERVENTIONS

As noted, the complications of IDDM including blindness, kidney disease and neuropathy are attributed to be consequences of hyperglycemia. The DCCT results support this notion. Two operational mechanisms are considered possible which are not mutually exclusive: the glycoxidation (glycation) of proteins leading to crosslinking and altering physiologic function [6]; and the accumulation of sorbitol in cells causing a cascade of biochemical abnormalities [7]. The antioxidant vitamins C and E appear effective as nutriceuticals in the prevention of glycation. Furthermore, vitamin C shows efficacy in the normalization of intracellular sorbitol concentrations. The J Am Coll Nutr has published an important demonstration of efficacy for each of these vitamins at nutriceutical levels [8,9].

The most recent work [8] shows that supplemental vitamin E at 100 IU daily significantly lowers glycated hemoglobin. An improvement in glycemia may signal that the mechanism of action involves improved insulin action or increased nonoxidative glucose disposal as has been reported for pharmacologic vitamin E in individuals with NIDDM. Earlier work by this group showed that erythrocyte membrane lipid peroxidation, a known vitamin E responsive index, is positively correlated with the glycHb level [10] and that the 100 IU daily supplement corrected this abnormality [11]. This suggests that nutriceutical vitamin E supplementation will impart at least two benefits to individuals with IDDM. Improvement in circulating triglycerides is an additional salutatory effects of this regimen [9].

The evidence for vitamin C’s ability to diminish protein glycations is less clear despite its widespread use in food preservation to protect against just this “browning” reaction between sugar and proteins. The extant literature is based largely on observations of glycated hemoglobin per se for
which there are mixed results as reviewed in another symposium at these meetings [12]. On balance, the data are promising. In addition, there is convincing evidence for the efficacy of vitamin C in normalizing erythrocyte sorbitol concentrations [9,13,14]. This is, perhaps, not surprising given the wide spectrum of chemicals with at least some aldose reductase inhibitor (ARI) activity [15]. We have demonstrated that an ARI mechanism as operational using an in vitro system [9,12]. Reasonable nutriceutic doses of vitamin C, ranging between 250 and 600 mg daily, can be expected to normalize erythrocyte sorbitol and likely will also positively influence protein glycations.

**MICROMINERAL SUPPLEMENTATION AND INSULIN ACTION**

Little evidence exists to support a role for micromineral supplements in directly diminishing protein glycations or sorbitol accumulation in anyone not otherwise deficient in the specific mineral. A rise in glycated hemoglobin is reported as a manifestation of copper deficiency in rats [16,17]. The elevation is linked to an increase in peroxidation products and it is responsive to treatment with the free radical scavenger DMSO. Copper status, as evidenced by plasma ceruloplasmin concentration, may be altered in individuals with IDDM, but this is a variable finding [18]. Another distinct observation is that patients who were treated for either iron deficiency anemia or vitamin B₁₂ deficiency responded with a fall in glycated hemoglobin [19], but from a normal level in disease. IDDM patients with any of these deficiencies would benefit from correction while no supplement role appears to exist otherwise.

Many individuals with IDDM routinely supplement with zinc at levels 2 to 3 times the RDA. While this is a nutriceutical practice that can be grounded in the knowledge that hyperzincuria is a hallmark of diabetes [20], our data suggest that supplementation is not beneficial. We found normal plasma and leukocyte Zn in IDDM at baseline as well as an increased “throughput” of zinc in both IDDMs and nondiabetics during supplementation. This suggests either that no deficiency existed or that a Zn deficiency was refractory to supplementation. We, however, did not examine indices of functional improvement and other workers do report positive results from zinc supplementation as reviewed at these meetings [21]. The issue remains unsettled while supplementation continues to be widely practiced.

Chromium and vanadium are trace minerals offering great promise as nutriceutic supplements to enhance insulin action in diabetes. The role of chromium in insulin action and glucose transport is well documented, but the potential benefits from supplementation pertain primarily to individuals with impaired glucose tolerance or NIDDM and are not presented here. Vanadium is a known essential nutrient but has no RDA or ESADDI at present. Animal studies as well as short term studies with IDDM show promise for this insulinomimetic agent as reviewed in a symposium at this meeting [22]. The oral doses used to date in human trials are much lower than for animal studies but an appreciable rise in serum vanadium is achieved. Sodium vanadate supplementation at 125 mg daily for 2 weeks lowered the insulin requirement of five IDDMs and also lowered their plasma cholesterol [23]. A concern for mild nausea and gastrointestinal upset may be overcome by the use of vanadyl sulfate [24].

**CONCLUSION**

The ability of pharmacologic supplementation with niacinamide to delay the onset of IDDM is under multi-center trial that will be completed in approximately 5 years. If efficacy for a substantial delay of onset of IDDM among high risk individuals is established, a titration of the effective dose may reach the nutriceutical range. Supplements of either vitamin E or vanadium appear to improve insulin action. Other micronutrients including zinc, copper, and chromium are candidates for imparting a benefit beyond that gained from tight glycemic control for individuals with IDDM, but substantial evidence of a specific benefit is presently lacking. Benefits from nutriceutic supplementation are reported in small trials for vitamins C [25] and E [8] and these supplements are safe and affordable from food or tablet sources. A dietary strategy that adds 200 to 600 mg of vitamin C and 100 IU of vitamin E to a dietary pattern providing approximately the RDAs for these nutrients is worthy of consideration as an intervention for individuals with IDDM.

**REFERENCES**

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