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Complementary Therapies for Diabetes: The Case for Chromium, Magnesium, and Antioxidants

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A growing body of interest on the possible beneficial role of chromium, magnesium, and antioxidant supplements in the treatment of diabetes has contributed to debate about their value for reaching metabolic control and to prevent chronic complications in diabetic subjects. In this article we use a systematic approach focused on clinically based evidence from clinical trials regarding the benefits of chromium, magnesium, and antioxidant supplements as complementary therapies in type 2 diabetes.

Chromium, magnesium, and antioxidants are essential elements involved in the action of insulin and energetic metabolism, without serious adverse effects. However, at present there is insufficient clinically based evidence and its routine use in the treatment of type 2 diabetes is still controversial.

Because the most frequent origin of deficiencies in micronutrients is an inadequate diet, health care providers should invest more effort on nutrition counseling rather than focusing on micronutrient supplementation in order to reach metabolic control of their patients.

Results from long-term trials are needed in order to assess the safety and beneficial role of chromium, magnesium, and antioxidant supplements as complementary therapies in the management of type 2 diabetes.

Key Words: Chromium, Magnesium, Vitamin E, α-Tocopherol, Lipoic acid, Antioxidants, Micronutrients, Type 2 diabetes.

Introduction

As dietary supplements are widely used not only by the general public but also by diabetic patients (1–3), a growing interest in its beneficial role has contributed to debate regarding the value of "alternative therapeutics" in the treatment of diabetes (4). Use of "alternative therapies" closely mirrors cultural preferences and individual circumstances that must be taken into account by health care providers in order to attain the best metabolic control for their patients. In this regard, the American Diabetes Association (ADA) issued a Position Statement regarding the "Unproven Therapies" that might be provided to patients (5). Among these, trace elements such as chromium and magnesium, as well as the antioxidants, are the most widely used.

Because the background of micronutrient deficiencies is an inappropriate diet, more than an alternative therapy, the adequate intake of foods rich in chromium, magnesium, and antioxidants should be considered as part of the nutritional support that must be counseled to diabetic patients. Because these essential micronutrients are enhanced by insulin action (6), it should be expected that an adequate daily dietary intake exerts a beneficial role in the metabolic control of subjects with type 2 diabetes. Because the long-term success of dietary intervention usually is poor (7), strategies for reaching the required micronutrient intake, such as oral supplementation, are of particular interest in the management of diabetes.

According to the ADA Position Statement (5) that recommends that the use of adjuvant therapies must be based on evidence emerged from clinical research, in this article we

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will present a systematic approach regarding the benefits of chromium, magnesium, and antioxidant supplements, focusing on clinical trial-based evidence, in the management of type 2 diabetes.

Chromium

Trivalent chromium (Cr^{3+}) is an essential trace element (1) required for the maintenance of normal glucose (8) and fat metabolism (9). Because chromium potentiates the action of insulin, it was named from its recognition in the late 1950s (10) as the glucose tolerance factor term that emphasizes its importance in glucose metabolism.

Chromium is present in many foods, especially in liver, Brewer's yeast, American cheese, wheat germ, vegetables such as carrots, potatoes, broccoli, and spinach, and is also present in alfalfa, brown sugar, molasses, dried beans, nuts, seeds, mushrooms, and animal fats (1,11).

In general, it is accepted that a chromium intake of 30–40 μg/day is sufficient for achieving the daily requirements (12), and that healthy people usually reach it in their customary diet. However, because some foods, particularly those high in simple sugars, negatively affect the absorption of chromium (12,13), in the absence of well-balanced diets, chromium deficiency frequently appears. Furthermore, because chromium metabolism is altered in diabetic subjects by increased loss, decreased absorption (14), and an inadequate dietary intake (15), little is known about the daily chromium requirements for those subjects.

Tyrosine kinase, the enzyme required for phosphorylation, is chromium dependent, and phosphotyrosine phosphatase, an enzyme that inactivates the insulin receptor, is inhibited by chromium (12). Thus, in addition to the increase in the number of insulin receptors (12), chromium improves the action of insulin by improving tyrosine kinase activity on the insulin receptor (15–17). Finally, it has been reported that Cr^{3+} also exerts a powerful cellular antioxidant action (18) and decreases the hepatic extraction of plasma insulin (19). Deficiency of chromium may result in similar clinical manifestations to those observed in insulin resistance and type 2 diabetes, and supplementation with chromium could improve insulin sensitivity, leading to a more efficient peripheral glucose uptake.

A great body of conflicting data (9,12,18,20–27) regarding the benefits of chromium supplements in type 2 diabetes has been accumulated in past decades (Table 1). Although lack of agreement among these studies may be explained by both type of chromium and dose used (28), there are other variables that may contribute to the inconsistent results such as differences in glycemic control, background of targeted populations, lack of control for dietary contribution of chromium, and biochemical assays used for analysis (11,12). Furthermore, it is necessary to keep in mind that beneficial effects of supplementation will be seen in those subjects with chromium deficiency, a variable not measured in the clinical assays (9,12,18,20–27), and that chromium has no effects on glucose and insulin concentrations in non-diabetic individuals. Because a significant number of confounding variables have not been adequately controlled, chromium status has not been evaluated in baseline conditions and follow-up of supplementation. Benefits of chromium supplements in type 2 diabetes have not been conclusively demonstrated (29).

In this regard, there is no accurate and simple method for measurement of chromium status making clinical chromium deficiency difficult to demonstrate. Currently, the best method for diagnosing chromium deficiency is retrospective, demonstrating reduction of insulin resistance after chromium supplementation and reappearance of resistance after the supplement is withdrawn (8,27,30). Furthermore, the mechanisms of absorption and transport of chromium also are still unclear (30,31). As a consequence, the multitude of confounding variables and unresolved biochemical procedures contribute to the unreliability of the results of studies on chromium.

Finally, although the toxicity of chromium is low, high doses of chromium have been related to chromosomal damage (32) and in some cases related to renal and hepatic toxicity, rhabdomyolysis, and psychiatric disturbances (11). Thus, the use of chromium for long periods may result in a toxic risk.

As chromium seems to exert a positive effect on glucose and insulin levels of type 2 diabetic subjects, chromium supplements could be indicated for short periods of time, only in those patients in whom the deficiency of chromium is suspected, based on dietary questionnaires. Because there is insufficient clinical evidence, it is still controversial whether chromium supplements should be routinely recommended in the management of diabetes (31).

Magnesium

Magnesium, the second most abundant intracellular cation (33), is an essential cofactor of high-energy phosphate-bound enzymatic pathways (34,35) involved in the energetic metabolism, synthesis of protein, and modulation of glucose transport across cell membranes.

Hypomagnesemia, commonly due to insufficient magnesium intake and/or increased magnesium loss (36), is strongly related to metabolic syndrome (37) and has been associated with the development of type 2 diabetes (38), high blood pressure, (39) atherogenic alterations (39,40), and micro- and macrovascular diabetic complications (41–44).

The main dietary sources for magnesium are whole grains, leafy green vegetables, legumes, nuts, and fish (11,45). The most important risk factors associated with magnesium deficiency are aging (46), alcohol intake (47), and diuretics (48). In addition, hypomagnesemia is one of the more