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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

Table 1. Clinical trials of chromium supplements in subjects with and without type 2 diabetes

	n	Study population	Supplement	Dose (μg)	Results
Anderson (12)	180	Type 2 diabetes	Chromium picolinate	200	Both doses decrease fasting and postprandial insulin
				1000	High doses decrease fasting and postprandial glucose
Anderson (18)	110	Type 2 diabetes	Chromium pidolate	400	No effects on glucose and insulin levels
Abraham (9)	25	Type 2 diabetes	Chromium chloride	250	Decrease triglycerides
Ravina (20)	114	Type 2 diabetes	Chromium picolinate	200	Decrease glucose and insulin levels
Lee (21)	30	Type 2 diabetes	Chromium picolinate	200	Reduce triglycerides
Thomas (22)	5	Type 2 diabetes	Chromium nicotinate	200	No effects on glucose and insulin levels
	14	Healthy			
Uusitupa (23)	26	Elderly with IGT	Chromium-rich yeast	160	No effects on glucose and insulin levels
Anderson (24)	17	IGT	Chromium chloride	200	Decrease insulin levels. Improve glucose tolerance
Lefavi (25)	34	Male athletes	Chromium nicotinate	200	Decrease total cholesterol
Wilson (26)	26	Healthy non-obese	Chromium picolinate	200	Decrease fasting insulin
Volpe (27)	44	Obese women	Chromium picolinate	400	No effects on glucose and insulin levels

IGT = impaired glucose tolerance.

common electrolytic alterations in subjects with diabetes, especially in those with poorly controlled diabetes (41) with increased urinary loss (45).

Because magnesium is predominantly an intracellular ion, its serum concentrations do not necessarily reflect the magnesium status or intracellular pool, and intracellular magnesium depletion can be seen with normal serum concentrations (49). Significant magnesium deficiency is required before its serum levels decrease, but once serum magnesium declines, it shows a high correlation with intracellular magnesium concentration (50,51). Thus, serum magnesium measurement is a specific, but not sensitive, marker of magnesium deficiency (11).

Magnesium deficiency may result in disorders of tyrosine kinase activity on the insulin receptor and increased intracellular calcium concentration (34,52), events related to the development of insulin resistance. We found that low serum magnesium levels are strongly related to elevated serum concentrations of both tumor necrosis factor alpha (53) and C-reactive protein (53), suggesting that magnesium deficiency may also be involved in the development of low-grade chronic inflammation syndrome and through this pathway, with the development of glucose metabolic disorders. Based on recent studies that report a significant increase of pro-inflammatory markers in magnesium-deficient animals (55–60) and obese subjects (53,54), and the fact that release of substance P, one of the earliest events in the chronic inflammation response (61), is linked to hypomagnesemia (55,57,59), we have hypothesized that magnesium deficiency could be involved in the triggering of low-grade inflammatory response (52,53).

Similar to the findings with chromium, effects of magnesium supplements on the metabolic profile of type 2 diabetic subjects also are controversial (Table 2). Recently, we conducted a clinical trial among type 2 diabetic subjects with low serum magnesium levels. We showed a beneficial effect of oral supplementation with magnesium chloride on fasting and postprandial glucose levels and insulin sensitivity (62), a finding in accordance with some (63–65) but not all studies (66–69). As we have previously noted (62), differences in magnesium salt and doses used, as well as baseline magnesium status, may explain the divergence among these studies. In this regard, we have found that magnesium chloride solution has excellent bioavailability improving the serum magnesium concentrations within the first month of supplementation (62,70).

Other beneficial effects of magnesium supplements in type 2 diabetic patients are related to the improvement of lipid profile (40), atherosclerosis, and high blood pressure (39). In addition, Barragan et al. (from our group), found that magnesium supplements improve symptoms of depression in elderly type 2 diabetic subjects with low serum magnesium levels (unpublished data).

Among apparently healthy subjects, the beneficial effects of magnesium supplements are scarce (70,71) but show a consistent significant increase in insulin sensitivity among non-diabetic subjects who received magnesium supplements. Thus, taking into account that low serum magnesium is a risk factor strongly associated with development of type 2 diabetes (38), the use of magnesium supplements could be an alternative tool for the prevention of type 2 diabetes, a hypothesis that requires confirmation.

Magnesium is relatively non-toxic in those people with conserved renal function. The most frequent side effects due to magnesium supplementation are headache, nausea, hypotension, and nonspecific slight abdominal and bone pain that usually do not require specific treatment or discontinuation of magnesium salt (67,70).

Because serum magnesium levels are easy to determine and provide specific data on magnesium deficiency, and magnesium supplements have a low rate of non-serious side effects, it seems to be rational that diabetic patients should be routinely tested in order to demonstrate the presence of low serum magnesium levels and, if there are no specific

Table 2. Clinical trials of magnesium supplements in subjects with and without type 2 diabetes

	n	Study population	Supplement	Dose	Results
Rodriguez-Morán (62)	63	Type 2 diabetes	Magnesium chloride	2.5 g	Decrease fasting glucose and improve insulin sensitivity
Paolisso (63)	12	Type 2 diabetes	Magnesium pidolate	4.5 g	Decrease fasting glucose, increase posprandial insulin
Yokota (64)	9	Type 2 diabetic controlled subjects	Natural magnesium	300 mg	Decrease insulin and triglycerides levels, improve insulin sensitivity
Paolisso (65)	9	Type 2 diabetes	Magnesium pidolate		No effects on glucose levels, improve insulin sensitivity
Eibl (66)	40	Type 2 diabetes	Magnesium citrate	30 mmol	No effects on glucose and insulin levels
De Valk (67)	50	Type 2 diabetes	Magnesium aspartate	15 mmol	No effects on glucose and insulin levels
Lima (68)	128	Type 2 diabetes	Magnesium oxide	20.7 mmol	No effects on glucose levels
Gullestad (69)	56	Type 2 diabetes	Magnesium citrate	15 mmol	No effects on glucose and insulin levels
Guerrero-Romero (70)	60	Insulin resistance	Magnesium chloride	2.5 g	Improve insulin sensitivity

contraindications, to indicate short-term periods of oral magnesium supplements.

Antioxidants

There is a great body of evidence showing that hyperglycemia is the primary risk factor associated with development of both micro- and macrovascular complications (72,73). Among the biochemical pathways through which hyperglycemia produces its deleterious effects is the production of free reactive oxygen species (ROS) (74–76). Thus, oxidative stress, defined as a persistent imbalance between the excessive production of ROS and/or defects in antioxidant defense, has been implicated in the pathogenesis of diabetic complications.

Recently, it has been recognized that the mitochondrial process involved in the glucose-mediated insulin secretion is particularly affected by oxidative stress (77). Increase in mitochondrial ROS, a consequence of increased glucose levels (78), could be the proximal defect leading to pathological consequences of hyperglycemia (75), contributing to progression of disease through a positive feedback in which hyperglycemia increases mitochondrial ROS in pancreatic β-cells, disturbing their capacity of response to elevation of glucose concentrations which in turn produces further hyperglycemia (75,79,80).

These observations support the hypothesis that antioxidants, by decreasing the damage produced by hyperglycemia, could be useful in the prevention and management of chronic diabetic complications. Vitamin E (α-tocopherol) and α-lipoic acid (thioctic acid) are the most widely used antioxidants as adjuvant in the treatment of diabetic patients.

Among the group of fat-soluble vitamins, vitamin E (α-tocopherol) is the most abundant and biologically active (11). Recommended dietary allowance for men and women is 9.6 and 7.0 mg/day, respectively, which can be obtained from a balanced diet of fruits and vegetables and fats and oils (81), mainly from cereals, eggs, green vegetables, margarine, meat, wheat germ, seeds, and nuts (82).

Vitamin E, the most efficient chain-breaking and potent lipophilic antioxidant with a redox potential $E_0{}^+$ of +370 mV (83), scavenges the peroxyl radical, neutralizing free radical species produced during normal cellular metabolism, and suppressing lipid peroxidation in cell membranes (84). It also interacts with water-soluble antioxidants such as glutathiones (11), for decreasing protein glycation, lipid oxidation, and inhibiting platelet aggregation (85,86).

Clinical trials evaluating the beneficial role of vitamin E supplements on glucose levels and incidence of vascular diabetic complications revealed conflicting results (87–92) (Table 3). What these studies show is that antioxidant supplementation with vitamin E in type 2 diabetic subjects may have a greater effect in protection of LDL from oxidation (91) and, in this way, from development of cardiovascular disease. But there have been no consistent effects on decreasing fasting glucose and HbA1c levels. The lack of action of vitamin E on glucose metabolism may be related to the fact that α-tocopherol acts on the plasma membranes but not on mitochondrial respiratory chain, the major site of ROS production within the cell, or other intracellular events involved in apoptosis and gene transcription (84). In this regard, it has been reported that pancreatic beta-cell mitochondrial function is particularly susceptible to oxidative damage leading to decreased mitochondrial function and induction of mitochondrial permeability that predispose cells to necrosis and apoptosis (93). Therefore, α-tocopherol successfully inhibits LDL oxidation, but it is not able to improve beta-cell function.

Recently, an early released article by Miller et al. (94), who performed a meta-analysis of the dose response relationship between vitamin E supplementation and total mortality using data from clinical trials reported between 1993 and 2004, showed that high doses (≥400 IU/day) of vitamin E increase all-cause mortality. Although in the analysis by Miller et al. (94) the effects of vitamin E were not isolated from those of other supplements present in 52.3% of the 19 trials included in the meta-analysis, this finding emphasizes the need to discourage the use of high doses of vitamin E for long periods, until evidence of efficacy is appropriately documented.

On the other hand, lipoic acid (thioctic acid), a disulfide compound soluble in both lipid and water (95), is an essential

Table 3. Clinical trials of antioxidants supplements in subjects with type 2 diabetes

	n	Study population	Supplement	Dose	Results
Gomez-Perez (87)	53	Non-controlled type 2 diabetes	D-α-Tocopherol	400 mg	No effects on fasting glucose, HbA1c, nor lipid profile
Paolisso (88)	25	Elderly type 2 diabetes	D-α-Tocopherol	900 mg	Decrease fasting glucose, HbA1c, and triglycerides, no changes in insulin
Paolisso (89)	15	Controlled type 2 diabetes	D-α-Tocopheryl acetate	900 mg	Decrease fasting glucose, HbA1c, no changes in insulin, hepatic glucose output, nor glucose oxidation
Reaven (90)	21	Type 2 diabetes	D-α-Tocopherol	1600 IU	No effects on fasting glucose, HbA1c, decrease susceptibility of LDL to oxidation
Skrha (91)	11	Obese type 2 diabetes	D-α-Tocopherol	600 mg	Decrease glucose disposal rate, and malondialdehyde
		Type 2 diabetes	α-Tocopherol	800 IU	Decreased risk for coronary heart disease. No effects on fasting glucose nor HbA1c
Anderson (92)	40	Non-diabetic men	β-Carotene	24 mg	
			Ascorbate	1000 mg	
Jacob (100)	74	Type 2 diabetes	α-lipoic acid	600 mg	Increase insulin sensitivity and glucose uptake
				1200 mg	No effects on fasting glucose
				1800 mg	
Ziegler (102)	73	Type 2 diabetes and CAN[a]	α-lipoic acid	800 mg	Slight improve in cardiac autonomic neuropathy
				1200 mg	
Ziegler (103)	328	Type 2 diabetes and PN[b]	α-lipoic acid	600 mg	Reduce symptoms of diabetic peripheral neuropathy
				100 mg	
Ziegler (104)	509	Type 2 diabetes and SPN[c]	α-lipoic acid	600 mg[d]	Favorable effects on neuropathy deficits
				1800 mg[d]	No effects on neuropathic symptoms
Ametov (105)	120	Type 2 diabetes with SPN[c]	α-lipoic acid	600 mg[e]	Improve neuropathic sensory symptoms

[a]Cardiac Autonomic Neuropathy; [b]Peripheral Neuropathy; [c]Symmetrical Distal Peripheral Neuropathy; [d]600 mg IV for 3 weeks followed by 600 mg t.i.d. for 6 months; [e]IV.

cofactor in multienzyme complex such as α-oxoacid-dehydrogenase and mitochondrial enzymes, and a potent lipophilic free radical scavenger with a redox potential of E_0^+ −290 mV (83). It is synthesized in the liver and controls glucose oxidation (83) by increasing both oxidative and non-oxidative glucose metabolism, enhancing insulin sensitivity (96) and preventing glucose-induced protein modifications (3).

In vitro, lipoic acid increases glucose transport by stimulating translocation of GLUT4 from internal pools to plasmatic membrane and protects against the impairment in insulin-stimulated protein-kinase B activation (95). In addition, it protects the insulin receptor from oxidative damage (95,97). The bioactivity of lipoic acid has been attributed to its capacity to directly react with various reactive oxygen species and to its ability to interfere with the oxidation process in the lipid and aqueous cellular compartments (93,98).

In experimental and cross-sectional studies, treatment with lipoic acid improves both oxidative stress (99) and insulin sensitivity (100,101). However, as lipoic acid is essentially a potent free radical scavenger of peripheral nerves, it is of particular interest to elucidate its clinical applications in the prevention and treatment of diabetic neuropathy (102–105) (Table 3). Some studies show that lipoic acid is useful for the treatment of neuropathy (103,105) and that its toxicity is extremely low (106,107). Nonetheless, inconsistencies among the studies, as well as the high placebo response, particularly in the ALADIN studies (103,104) that enrolled 837 type 2 diabetic subjects with peripheral neuropathy, imply the necessity for future clinical trials based on specific primary end points able to be measured in a precise way, in order to convincingly demonstrate the beneficial effect of lipoic acid on peripheral neuropathy. Because clinical trials showing the beneficial role of lipoic acid on glucose metabolism are scarce, an evidence direction cannot be established. Nonetheless, several lines of evidence suggest that oxidative stress is increased in type 2 diabetic subjects and could play a role in the development of micro- and macrovascular complications, clinical evidence is still controversial. Although vitamin E and lipoic acid appear to be safe and well tolerated, currently there is insufficient evidence for supporting its regular use in clinical practice.

Conclusions

Although chromium, magnesium, and antioxidants are essential elements involved in the action of insulin and energetic metabolism, without serious adverse effects, there is insufficient clinically based evidence. Its routine use in the treatment of type 2 diabetes is still controversial. In general, dietary supplements are inexpensive and easily accessible to the public and because of this, they are frequently used inappropriately.

The most frequent origin of micronutrient deficiencies is an inadequate diet and persons with diabetes should receive appropriate nutritional counseling in order to consume an adequate quantity of foods rich in essential micronutrients for

achieving their daily dietary requirements. The advantage of this diet over pharmacological supplements is the combined action of the several micronutrients that an appropriate diet contains. Health care providers should invest more effort in diet changes rather than focusing on micronutrient supplementation to reach metabolic control of their patients.

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

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