Zinc as a potential coadjuvant in therapy for type 2 diabetes

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Abstract

***Background**: Type 2 diabetes is highly prevalent in populations having high rates of overweight and obesity. It is a chronic condition responsible for long-term severe dysfunction of several organs, including the kidneys, heart, blood vessels, and eyes. Although there are a number of pharmacologic products in the market to treat insulin resistance and impaired insulin secretion—the most prominent features of this disease—interventions directed at preserving the integrity and function of β-cells in the long term are less available. The use of some nutrients with important cellular protective roles that may lead to a preservation of β-cells has not been fully tested; among these, zinc may be an interesting candidate.*

***Objective**: To assess the potential of zinc supplementation as coadjuvant to diabetes therapy.*

***Methods**: This article reviews the available information on the use of zinc as part of diabetes therapy.*

***Results**: Cellular and animal models provide information on the insulin mimetic action of zinc, as well as its role as a regulator of oxidative stress, inflammation, apoptosis, and insulin secretion. Zinc supplementation studies in humans are limited, although some positive effects have been reported; mainly, a modest but significant reduction in fasting glucose and a trend to decreased glycated hemoglobin (HbA1c).*

***Conclusions**: Zinc supplementation may have beneficial effects on glycemic control. Nevertheless, among the studies considered, the vast majority lasted for 6 months or less, suggesting the importance of conducting long-duration studies given the characteristics of type 2 diabetes as a chronic disease.*

Key words: Diabetes, insulin, pancreas, zinc

Introduction

Type 2 diabetes affects a significant proportion of the adult population worldwide. It is a chronic condition responsible for long-term severe dysfunction of several organs. In addition, it is a heavy burden to the healthcare system because of the continuous care and treatment these patients need. Although there are pharmacological options to treat some of the main features of this disease (insulin resistance and impaired insulin secretion), alternatives directed to preserving the integrity and function of β-cells in the long term are less available. This review will analyze the evidence for a potential role of zinc in the treatment of diabetes.

Diabetes mellitus

General characteristics

Diabetes mellitus comprises a variety of syndromes with distinct etiologies characterized mainly by hyperglycemia. This feature results from impairment of insulin secretion and alteration of hormone activity at the target tissues. The consequences of diabetes mellitus include long-term damage, dysfunction, and failure of several organs, especially the eyes, kidneys, heart, and blood vessels. Less than 10% of cases fall into the category of insulin-dependent diabetes mellitus (IDDM or type 1 diabetes), which generally appears in childhood and adolescence and results from autoimmune destruction of insulin-producing cells in the pancreas.

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Far more common is non-insulin-dependent diabetes mellitus (NIDDM or type 2 diabetes), which, at least in its early stages, is mainly characterized by the failure of the hormone to act efficiently in target tissues such as muscle, liver, and adipose tissue rather than insulin deficiency. Unlike type 1 diabetes, type 2 diabetes is often associated with obesity [1]. Type 2 diabetes affects about 285 million people worldwide, and by the year 2030 this figure will reach 366 million [2]. In countries with rapid epidemiological transition, such as Chile, in which the aged, overweight and obese, and physically inactive population has been increasing at high rates, a dramatic increase in diabetes prevalence has also been noted. For instance, according to the latest National Health Survey, the prevalence of type 2 diabetes in Chile increased from 6.3% in 2003 to 9.4% in 2009 [3].

Metabolic and molecular aspects

Insulin resistance along with compensatory hyperinsulinemia is the earliest stage of type 2 diabetes [4, 5]. Later, insulin secretion is impaired leading to hyperglycemia [6, 7]. Regarding β-cell function, a distinctive defect in type 2 diabetes is the loss of the first phase of glucose-induced insulin secretion [8]. Additionally, the normal 11- to 14-minute insulin secretion oscillation is lost in diabetic patients. Such anomaly is suggested to contribute to impaired insulin-dependent suppression of hepatic glucose production [9]. Also, the serum proinsulin-to-insulin ratio increases as a result of a hypermobilization of granules, leading to a rapid transit time and incomplete processing to fully mature insulin [10].

Insulin resistance and β-cell dysfunction are complex processes, and a host of molecular mechanisms are involved. Tripathy and Chavez reviewed this issue elsewhere [11]. Among the factors related to insulin action at the skeletal muscle are impaired insulin signaling mediated by reduced IRS-1 tyrosine phosphorylation and PI3-kinase activity, lipotoxicity, mitochondrial dysfunction, and increased inflammation mediated by increased lkB-β/NF-kB pathway activity. Insulin signaling is also affected in the liver, brain, and hypothalamus. Adipose tissue also participates in insulin resistance through secretion of adipokines; for example, adiponectin has a positive effect on insulin sensitivity, in contrast to TNF-α, resistin, and interleukin-6, which have the opposite effect. Insulin secretion-related mechanisms involve decreased β-cell mass, lipotoxicity as result of chronic exposure to free fatty acids, endoplasmic reticulum stress, decreased glucagon-like peptide-1 (GLP-1) secretion and increased glucose-dependent insulinotropic peptide (GIP) resistance, and dysregulation of β-cell apoptosis. Dysregulation of apoptosis seems to be a key determinant of reduction of β-cell mass [12–14].

Progression to type 2 diabetes is determined by β-cell failure leading to impaired insulin secretion [6]. β-Cell dysfunction is exacerbated by insulin resistance, whereas the development of the disease is delayed by improvement of insulin sensitivity [15]. Common features observed in type 2 diabetic patients are obesity, increased hepatic glucose output, hyperglycemia, and glycosuria. Additionally, decreased plasma adiponectin and increased plasma free fatty acid levels are also reported, even in comparison with levels in nondiabetic obese counterparts [16]. Another crucial factor involved in the pathophysiology of diabetes is the presence of an oxidative stress condition. Hyperglycemia is associated with increased production of reactive oxygen species, as well as depletion of antioxidant defense system components, with the concomitant accumulation of oxidative end products [17, 18]. Oxidative stress has been implicated in a number of consequences of diabetes, such as increased risks of cardiovascular disease, nephropathy, cataract, retinopathy, and neuropathy, among others [19, 20].

Clinical features

Diabetic patients can have hyperglycemia over long periods of time, leading to functional defects in a variety of organs, with no obvious manifestations [1]. In fact, β-cell function can be impaired by 50% at the moment of diagnosis [21]. It is estimated that β-cells become affected 10 to 12 years before diagnosis [22]. Diabetes is associated with increased morbidity and mortality from its associated complications, which are mainly related to the accumulation of advanced glycation end products [23, 24]. Among the complications are retinopathy, angiopathy, neuropathy, arthropathy, and nephropathy. Diabetic patients usually present hypertension, altered lipoproteins, and increased risks of cerebrovascular and cardiovascular disease [1].

Treatment

The treatment of type 2 diabetes is oriented to correcting hyperglycemia by enhancing insulin secretion and/or insulin sensitivity. The treatment includes changes in feeding patterns and lifestyle, as well as pharmacologic therapy, including administration of exogenous insulin (or insulin analogues) when there is minimal or no insulin secretion [25]. Pharmacologic treatment includes insulin-sensitizing drugs (biguanides, thiazolidinediones), insulin secretagogues (sulfonylureas, meglitinides), inhibitors of carbohydrate digestion and intestinal absorption (α-glucosidase inhibitors), GLP-1 analogues, dipeptidyl peptidase-4 (DPP-4) inhibitors, amylin agonists, and insulin therapy. When diabetes is diagnosed, it is recommended that pharmacologic treatment with metformin be initiated along with diet and lifestyle modifications; use of additional pharmacologic preparations will depend on the observed

metabolic control of the patient [25, 26].

Regardless of the pharmacologic treatment, the patients suffer a progressive alteration of glycemic control, mainly as a result of the increasing impairment of pancreatic β-cell function with time [21, 27, 28]. The rate of decline of β-cell function was reported to be 38% in metformin-treated and 52% in sulfonylurea-treated patients during 6 years of observation [21]. In the ADOPT (A Diabetes Outcome Progression Trial) study, the loss of β-cell function was between 8% and 13% per year [28]. Thus, a major challenge is to identify a product directed to preserving β-cell functionally. There have been some attempts that, for a number of reasons, have not gone beyond promising results in animal models, such as treatment with GLP-1 infusion, which inhibited apoptosis of pancreas β-cells [29].

An interesting approach in diabetes treatment has been the use of micronutrients as coadjuvants. Chromium has been the most studied, and although there are some animal data supporting positive effects on some indices of diabetes control, the effects in humans have been controversial [19, 30]. In fact, many studies failed to observe improvements [19, 31, 32]. Since some complications of diabetes are related to oxidative stress, a focus of attention has been the use of antioxidant nutrients. Golbidi et al. [33] reviewed the information published during the last 10 years on this issue and concluded that there was no benefit of routine antioxidant supplementation in diabetes management. Kataja-Tuomola et al. [34] did not find any association between dietary antioxidants and decreased risk of diabetes in a cohort of 29,133 smokers. A systematic review of micronutrients and diabetic retinopathy concluded that vitamins C and E and magnesium intakes do not seem to be associated with this pathology [35]. Chehade and colleagues [36] concluded that antioxidant micronutrient supplementation in diabetic patients without underlying deficiency does not have enough support; furthermore, some data showed potential adverse effects of vitamins E, C, and A and selenium, making it advisable not to use them.

On the other hand, the multiple roles of zinc in a number of relevant cellular and systemic functions, some of them closely related to features of diabetes, have called attention to zinc as a potential natural adjuvant in the management of this pathology. Human studies of this question are very limited.

Zinc

Zinc is essential for all forms of life. Zinc is required for virtually all aspects of cell metabolism, including DNA synthesis and transcription, translation of mRNA into proteins, and the structure and stabilization of proteins. It participates in metabolism through its catalytic, structural, and regulatory roles [37, 38]. Zinc is required for the function of more than 300 enzymes of all classes [39, 40], and it is involved in the regulation of a large number of genes [41]. Zinc participates in some hormone–receptor interactions [42] and also in intracellular signaling [38]. Although zinc is redox-inert, it has a number of relevant indirect antioxidant effects [43, 44]. Thus, zinc is involved in growth and a number of relevant functions, such as immunity, cellular signaling, tissue repair, protection against oxidative damage, apoptosis, vitamin A metabolism, neuropsychological functions, and the action of hormones, including insulin [45–47]. Zinc is also involved in both endocrine and exocrine functions of the pancreas [38].

Roles of zinc in diabetes

There is a significant body of evidence indicating the involvement of zinc in diabetes. In 1938, Scott and Fisher first reported that pancreatic zinc levels in cadavers of diabetic patients were approximately 50% of those in nondiabetic persons, suggesting an association between zinc and this pathology [48]. Increased urinary zinc is commonly seen in diabetes [49–52]. Decreased plasma zinc levels have been observed in patients with type 2 diabetes, which have been interpreted as indicating impaired zinc status [51, 53]. In type 1 diabetes, in contrast, plasma zinc tends to increase, probably as a result of destruction of pancreatic β-cells that release this mineral into the bloodstream [54, 55].

As mentioned earlier, diabetes is a complex entity presenting with insulin resistance along with decreased insulin secretion capacity [1]. Zinc participates in a number of processes related to such conditions. Zinc is highly concentrated in the pancreas, especially within the islets [56]. Conversion of proinsulin to insulin in combination with the acidic medium allows for crystallization of insulin within the mature granule. Insulin can associate into dimers that can further associate to form hexamers in the presence of zinc. The zinc hexamers can then be packed together to form a stable structure. The hexamers dissociate upon secretion, enabling the hormone to function in the bloodstream. Thus, zinc is essential for the correct processing, storage, and secretion of insulin [57]. Zinc is cosecreted along with insulin. Indeed, insulin oversecretion can deplete the β-cells of zinc [58]. Zinc actions in the pancreas are not limited to the β-cell; zinc also regulates the α-cell response to hypoglycemia [59]. Zinc was able to reduce both fasting glucose and insulin and increase pancreatic zinc in db/db mice [60]. Zinc impaired oxidative changes in the retina of diabetic rats [61]. Zinc supplementation in rats before treatment with the pancreatic toxic agents alloxan or dithiozone prevented hyperglycemia and destruction of islets [62].

The mechanisms of the effects of zinc on diabetes are only partially known. Given the importance of zinc in insulin storage and secretion, one of the most relevant findings has been the identification of the role of the

zinc transporter ZnT8 by Chimienti and colleagues [63]. ZnT8 was initially described as pancreatic β-cell specific. Subsequent studies showed it can also be expressed in subcutaneous fat tissue, pancreatic α-cells, and peripheral blood mononuclear cells [41, 64, 65]. ZnT8 is targeted by autoantibodies in 60% to 80% of new cases of type 1 diabetes, compared with less than 3% in type 2 diabetic patients [66]. Overexpression of ZnT8 in cultured cells is associated with increased intracellular zinc [67, 68]. Interestingly, this ZnT8 overexpression protected cells from zinc depletion-induced death but did not induce zinc toxicity as a result of increased zinc content [68]. In addition, ZnT8 decreased glucagon secretion by 50% [67]. On the other hand, deletion of ZnT8 caused dramatic defects in insulin processing and secretion at the β-cell [69]. A single nucleotide polymorphism in the ZnT8-encoding gene has been shown to increase the risk of type 2 diabetes [70, 71].

Inflammatory cytokines play a major role in β-cell destruction in both type 1 and type 2 diabetes. Interleukin 1β (IL-1β) is involved in alteration of insulin secretion and islet destruction; apparently these effects are mediated by the activation of NF-kB [62]. Zinc has relevant effects on cytokine synthesis and activity. For instance, zinc supplementation inhibits the release of some inflammatory cytokines [72]. On the other hand, zinc restriction in HL-60 cells increased IL-1β, as pointed out by Jansen et al., who also concluded that zinc may have protective effects in diabetics by suppressing IL-1β release and inhibiting NF-kB activation [62]. Egefjord et al. [73] observed that zinc transport, particularly that mediated by ZnT8 in β-cells, is highly cytokine sensitive. Although these authors explored some effects in two apoptosis genes (Bax and Bcl2), there are a number of unanswered questions in this regard. In type 2 diabetes, loss of β-cell mass can reach 60%. Increased apoptosis seems to be a crucial process determining the course of the disease. For instance, obese diabetic patients can present apoptosis rates three times greater than those of obese nondiabetic patients. This difference is even more marked when nonobese diabetics and nondiabetics are compared: the apoptosis rates are 10 times as great in diabetics [74].

Type 2 diabetes is associated with increased oxidative stress [20]. Although zinc cannot undergo direct redox reactions, it has several antioxidant functions. Zinc can induce synthesis of metallothionein and glutathione, which have protective roles against the effects of reactive oxygen species. Zinc is part of the enzyme superoxide dismutase (SOD), which acts on the superoxide radical to convert it into hydrogen peroxide. It competes with Fenton's catalytic agents, such as copper and iron, and stabilizes disulfide bridges in proteins [43, 44]. Overexpression of metallothionein and SOD is β-cell protective [75, 76]. Overexpression of metallothionein is also protective against cardiomyopathy, one of many complications of diabetes [77]. On the other hand, some polymorphisms of different isoforms of metallothionein lead to lower plasma zinc and greater glycated hemoglobin (HbA1c) and an increased rate of ischemic cardiomyopathy [78]. In addition to the roles described above, zinc is able to modulate protein–protein interactions of redox-sensitive proteins that are part of signaling processes. Some authors have regarded zinc as a signaling ion itself. It has been suggested that zinc is involved in the regulation of NF-kB, phosphorylation of protein kinase C (PKC), and activation of the phosphoinositide 3'-kinase (PI3K)/Akt signaling pathway, among others [44, 62].

Zinc supplementation and diabetes in human studies

Although there are a number of reports in the literature of processes in which zinc may have a beneficial effect on the course of diabetes (discussed above) and of promising results in animal models [60, 79], well-designed, randomized zinc supplementation trials carried out in humans are very limited. Thus, Beletate et al. in 2007 carried out the first systematic analysis of randomized zinc supplementation studies for the prevention of type 2 diabetes [80]. Only one study met minimal methodological requirements. This study was only 4 weeks in duration, and no major changes were observed except for a decrease of the homeostatic model assessment (HOMA) index in the supplemented group, while no modifications were noted in the placebo group [81].

Recently, two meta-analyses have been made available [82, 83]. Both studies concluded that zinc supplementation (mostly in physiological amounts) may have beneficial effects on glycemic control, as indicated by a modest but significant reduction of fasting glucose and a trend toward decreased glycated hemoglobin. It is worth mentioning that among the studies considered, the vast majority lasted for 6 months or less, suggesting the importance of implementing long-duration studies. Also, a number of them included other micronutrients as cosupplements, making it difficult to identify the exact cause of the effects observed. Further studies are needed to identify the exact biological mechanisms responsible for these results. Although it is not a supplementation study, it is also worth mentioning the work by Sun et al., who analyzed data from the Nurses' Health Study. After 24 years of follow-up of the initial 82,297 participants, 6,030 developed diabetes, and the authors concluded that higher zinc intakes may be associated with a slightly lower risk of type 2 diabetes [84].

There are few studies using supraphysiological amounts of zinc (150 mg/d) for shorter periods of time (6 to 8 weeks). The study by Niewoehner et al. [85] did not find improvements in diabetes control, in contrast to Gupta et al. [86], who reported improvement in fasting glucose as well as in peripheral neuropathy.

Research gaps and agenda

The knowledge of functions of zinc related to diabetes is far from complete. Its involvement in intracellular signaling, which in part may explain its insulin-mimetic action, as well as its role as a regulator of oxidative stress, inflammation, apoptosis, and insulin secretion, makes this element an interesting candidate as a coadjuvant to diabetes therapy. Although there are promising results in cultured cells and animal models suggesting a potential beneficial effect of increasing intracellular zinc bioavailability in both pancreatic β-cells and insulin target tissues, information from human studies is very limited.

In order to address the identified research gaps, our research efforts are focused on two kinds of study. A two-year, double-blind placebo-controlled trial of the effect of zinc supplementation on diabetic subjects is currently under way in Santiago, Chile. Since our main hypothesis is that zinc may preserve β-cell function, the study is conducted in individuals with mild forms of type 2 diabetes (non-insulin-dependent with less than 10 years since diagnosis and HbA1c < 9%). In parallel with the human study, a series of studies in cultured cell models is being carried out to elucidate the participation of zinc in α and β pancreatic cells, as well as in muscle cells.

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