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DIABETES EPIDEMIOLOGY (NM MARUTHUR, SECTION EDITOR)

Does Zinc Really "Metal" with Diabetes? The Epidemiologic Evidence

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Abstract Zinc (Zn) is important in a number of processes related to insulin secretion and insulin activity in peripheral tissues, making this element an interesting potential co-adjuvant in the treatment of patients with type 2 diabetes (T2D). This issue has been matter of interest in recent years. The available evidence is analyzed in this review. Information from epidemiologic studies evaluating the relationship between Zn and T2D is inconsistent. Furthermore, few studies examined the association between Zn status and insulin action and/or glucose homeostasis. In terms of usefulness of Zn as a preventive agent for T2D development, information is insufficient to reach firm conclusions. Results from Zn supplementation trials found some positive effects only in those with initial sub normal Zn status in a significant proportion of individuals. In conclusion, the effect of Zn on patients with type 2 diabetes is still an open question, and better study designs are needed to clarify the real impact and characteristics of the Zn–diabetes interaction.

Keywords Zinc · Type 2 diabetes · Supplementation · Humans

Introduction

Diabetes mellitus is a complex entity; it includes a number of syndromes with distinct etiologies having hyperglycemia as a common feature. The consequences of diabetes mellitus can be severe affecting several organs. Two major types of diabetes are recognized, type 1 diabetes (T1D, previously known as insulin-dependent diabetes mellitus (IDDM)) and type 2 diabetes (T2D, previously known as non-insulin-dependent diabetes mellitus (NIDDM)). Type 1 diabetes appears in childhood and adolescence, and it has a major autoimmune component leading to destruction of pancreatic insulin-producing cells. Five to ten percent or less of diabetes cases are thought to be due to type 1 diabetes, with the remaining 90–95 % attributed to type 2 diabetes [1]. This form is often associated with obesity, and it is characterized by insulin resistance in early stages, and β-cell exhaustion in its later stages [2].

In the last decade, interesting advancements have been made regarding the role of zinc (Zn) in insulin secretion and action; perhaps, the most relevant was the identification of the Zn transporter ZnT8 as a key element in β-cell function [3, 4], and later, the findings obtained from genome-wide association studies focused on of genetic variant of this transporter and its association with risk of diabetes [5, 6]. This review focuses on the recent epidemiologic evidence between Zn and type 2 diabetes risk/course.

Zinc in Biology

Zinc is an essential element in key aspects of mammalian cell metabolism. Zn is required for the function of more than 300 enzymes [7, 8], and for a long time, this was thought to be the principal role of zinc in mammalian biology. It is now clear that regulatory roles of Zn are also highly relevant. For instance, Zn is crucial to form Zn fingers, which allow protein–DNA interactions. A significant number of transcription factors and nuclear receptors contain zinc fingers. Thus, Zn participates in the regulation of expression of a large number

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of genes and activity of selected hormone and vitamins. Zinc participates in DNA synthesis and DNA transcription, translation of mRNA into proteins, and also in the structure and stabilization of proteins [9]. Even though Zn is redox-inert, it presents relevant antioxidant effects [10]. Free or loosely bound zinc is able to take part in cell signaling processes [11]. As a result, Zn is involved in growth, immunity, cell and tissue repair, hormone (including insulin) action, vitamin A metabolism, and neuropsychological functions, among others.

Zn homeostasis is highly complex and requires the compartmentalization of this element into cellular organelles. Twenty-four proteins (Zn transporters) have been identified, and knowledge of their roles is incomplete. There are 14 members of the family gene solute-linked carrier SLC39 family that encodes for Zn transporters ZIP 1–14. They are mainly importers of Zn into the cytoplasm. There are ten members of the family gene solute-linked carrier SLC30 that encode for Zn transporters ZnT1–10. They are mainly exporters of Zn from the cytoplasm to organelles and to the extracellular space. Zn transporter expression is regulated by cytokines, hormones, and Zn itself, among others [12]. In the context of Zn and diabetes, there are interesting data on the role of ZnT8.

The assessment of Zn status remains a difficult task because despite the large number of indices proposed, all have problems affecting their validity [13, 14]. Zinc presents very effective homeostatic mechanisms that respond to modifications in Zn intake; in addition, there are no specific Zn stores in mammals, including humans. Lowe et al. [14] carried out a systematic analysis of 32 methods to assess Zn status in humans. Their main conclusions were that plasma Zn may be a useful indicator but with many limitations. Similar conclusions have been reached by King et al. [8, 15]. This issue is highly relevant because, with few exceptions, most epidemiologic studies have used plasma/serum Zn as the only Zn status parameter.

Biological Basis for the Interaction Zn–Type 2 Diabetes

Zn is important for a number of processes related to insulin secretion and insulin activity in peripheral tissues, making this element an interesting potential co-adjuvant in the treatment of type 2 diabetes patients. This issue has been reviewed by Ruz et al. [16]. Briefly, Zn is essential for the correct processing (formation of insulin hexamers), storage, and secretion of insulin by β-cells [17]. Zn is co-secreted along with insulin and is involved in the paracrine regulation of glucagon secretion by α-cells [18, 19]. In addition, Zn that reaches the liver through the portal circulation suppresses hepatic insulin clearance by a clathrin-dependent mechanism [20]. Studies in animal models have shown that Zn can reduce both fasting glucose and insulin in *db/db* mice [21], and lessen oxidative changes in the retinas of diabetic rats [22].

Among the mechanisms explaining the effects of Zn on diabetes, the seminal work by Chimienti and colleagues [3, 4] clarifying the role of Zn transporter ZnT8 was crucial. This work showed that ZnT8, a zinc transporter, is responsible for the transport of Zn into insulin granules in beta cells. In cellular and animal models, it was observed that overexpression of ZnT8 was associated with increased intracellular Zn [23], and that deletion of this Zn transporter altered insulin secretion [24]. In addition, Zn has been shown to inhibit release of inflammatory cytokines involved in β-cell destruction [25], has anti-apoptotic effects in a number of cells and tissues [26], and presents antioxidant functions that are protective to β-cells [27]. More recently, participation of Zn in cell signaling processes has been described [11], suggesting Zn insulin-mimetic roles: Zn may be involved in the activation of the insulin receptor by increasing its β subunit phosphorylation and activation of several key components of insulin pathways, which include the extracellular signal-regulated kinase 1/2 (ERK1/2) and phosphoinositide 3-kinase (PI3K)/Akt signaling pathways [26, 28••].

This biology linking Zn to glucose homeostasis has raised much interest in the possible role of Zn in the development of diabetes and as a therapeutic agent in diabetes. In this review, we synthesize the current evidence from epidemiologic and supplementation studies in humans on the association between zinc and diabetes mellitus.

Analysis Strategy

Using the Pubmed electronic database (search dates: June 2011–2016), we identified 798 articles using the string "Zinc OR Zn" AND "diabetes." After we restricted to studies in humans with type 2 diabetes and epidemiologic studies and clinical trials, we identified 26 publications for this review. We synthesized the evidence from epidemiologic (non-intervention) studies separately from Zn supplementation trials. Of the epidemiologic studies, we discuss studies evaluating zinc status (i.e., measured zinc levels) separate from those evaluating zinc intake. We included additional key/landmark studies outside of the search dates based on expert opinion to provide additional support to available evidence.

Non-Supplementation Studies in Type 2 Diabetes

Twelve observational studies evaluating the relationship between Zn status by a measured Zn level and T2D were analyzed (Table 1). Among these, 11 studies evaluated plasma/serum Zn concentration as Zn status parameter, 3

Table 1 Summary of observational studies on the relationship between zinc status/intake and type 2 diabetes (T2D) and related traits in the last 5 years

Reference and location	Design	Subjects	Criteria inclusion/exclusion	Main glucose control or diabetes status-related findings	Limitations/notes
Vashum et al. 2014 [35] Australia	Cross-sectional study The Hunter Community Study	452; 238 males and 205 females Random sample of older community-dwelling individuals 152 normoglycemic; age 65.6 ± 7.3 years 151 prediabetes; age 66.3 ± 7.0 years 149 diabetes; age 67.9 ± 7.7 years	Inclusion criteria; age 55–85 years.	Serum zinc was not different among normoglycemic, prediabetic, and diabetic subjects. Greater serum zinc concentrations were associated with increased insulin sensitivity (by using the Homeostasis Model Assessment HOMA2 calculator) only in the prediabetic group.	Not specified time since diagnosis of diabetes. Not recorded supplement use Not considered other trace elements or drugs that may influence participant's zinc status.
Foster et al. 2012. [66] Australia	Cross-sectional study	40 females 20 control group; age 39.4 ± 13.8 years 20 T2D group; age 63.8 ± 8.8 years Time since diagnosis diabetes 6.5 ± 5.2 years	Inclusion criteria: age 21–79 years. Exclusion criteria: T2D group: current major illness; abnormal glomerular filtration rate or microalbumin/creatinine ratio; use of medications known to interact with zinc; taking oral hypoglycemic medications >7 years; insulin therapy; smoking. Control group: current major illness; use of medication known to interact with zinc; smoking; pregnancy or breastfeeding.	Plasma zinc concentration, zinc intake, and phytic acid/zinc molar ratio were not significantly different between diabetic and non-diabetic groups. Compared to the healthy group, the mRNA ratio of ZnT1 (zinc export transporter) to ZIP 1 (zinc import transporter) in blood mononuclear cells was lower in participants with T2D, which may indicate perturbed zinc homeostasis.	Small sample size. Significant difference in age and BMI of the two groups, but the results were adjusted for these variables.
Lima et al. 2011 [67] Brazil	Case–control study	73; 22 males and 51 premenopausal females 37 control group; age 37.2 ± 8.6 years 36 T2D group; age 46.0 ± 7.4 years Time since diagnosis diabetes: 4.0 ± 2.4 years	Inclusion criteria: age 25–59 years; T2D group: only oral hypoglycemic agents; absence of complications from diabetes; Both groups: without vitamin–mineral supplementation or medicines that could interfere with zinc. Control group: no family history of diabetes.	Plasma zinc concentrations, erythrocyte zinc concentration, and superoxide dismutase activity were significantly increased in T2D group versus control group. Zinc intake was above the recommendation in both males and females from both groups.	
Islam et al. 2013 [34] Bangladesh	Case–control study	280; 151 males and 129 females 143 normoglycemic (control group); age 45.5 ± 10.7 years 36 prediabetes; age 46.7 ± 10.6 years 101 T2D age 47.4 ± 11.5 years	Age older than 30 years.	Mean serum zinc was lowest in prediabetic compared with control and diabetic individuals. A significant interaction between dichotomized serum zinc and BMI for insulin resistance in multivariate analysis was observed. At similar BMI, participants with low serum zinc levels were more likely to have higher insulin resistance than those with high serum zinc.	Not specified time since diagnosis of diabetes. Not recorded supplement use. Not consider other trace elements or drugs that may influence participant's zinc status.

Table 1 (continued)

Reference and location	Design	Subjects	Criteria inclusion/exclusion	Main glucose control or diabetes status-related findings	Limitations/notes
Ferdousi et al. 2010 [68] Bangladesh	Case–control study	120 (gender not specified) 60 control group (apparently healthy non-diabetic) 60 newly diagnosed T2D	Age 50–60 years. Case and control having no current medication, intercurrent illness, macro- or microvascular complications, or history of renal failure.	Plasma zinc concentrations are significantly decreased in T2D group when compared with control group.	Small sample size. Not specified time since diagnosis of diabetes. Not recorded supplement use. Not specified gender and age of each group. Not considered other trace elements or drugs that may influence participant's zinc status
Xu et al. 2013 [69] China	Case–control study	239; 141 males and 98 females 50 healthy controls; 12 IFG group; 15 IGT group; 25 T1D group; 137 T2D group Patients with diabetes complications were: 24 nephropathy; 34 retinopathy; 50 peripheral neuropathy	Age 20–65 years.	Serum zinc was significantly reduced and urinary zinc increased in T2D compared to the controls. Serum zinc and urinary zinc were not different among IFG, IGT, and controls.	Not specified time since diagnosis of diabetes. Not recorded supplement use. Not considered drugs that may influence participant's zinc status.
Shan et al. 2014 [39] China	Case–control study	1796; 932 males and 864 females 793 NGT 218 IGR 785 newly diagnosed T2D	Chinese Han ethnicity. Age older than 30 years Inclusion criteria for IGR and newly diagnosed T2D: age $\geq$ 30 years, BMI < 40 kg/m^2, no history of medications for hyperlipidemia, or hypertension. Exclusion criteria: Significant neurological, endocrine, or other systemic diseases; acute illness and chronic inflammatory; or infectious diseases. Inclusion criteria for control group: the same as those for patients, except age $\geq$25 years	Odd ratio of T2D and IGR associated with 10 μg/dL increased plasma zinc was 0.87. The inverse association between plasma zinc and T2D was modified by SLC30A8 rs13266634 genotypes. C allele of SLC30A8 rs13266634 was associated with increased ORs for newly detected IGR and T2D. CC genotype was associated with a 72.8 % higher risk of IGR and a 52.5 % higher risk of T2D than the TT genotype.	Not specified time since diagnosis of diabetes. Not recorded supplement use.
Feng et al. 2015 [30] China	Cross-sectional study	2242; 779 males and 1463 females 1765 NGT 259 IFG 218 T2D	Chinese adults in Wuhan. Age 18–80 years.	After adjusting for confounders, the adjusted OR of diabetes comparing extreme quartiles for urinary zinc was 4.055 (95 % CIs 2.429, 6.768). Such association was not significant with respect to IFG.	Not specified time since diagnosis of diabetes. Not recorded supplement use. In addition to zinc, the study analyzed urinary aluminum, titanium, vanadium, chromium, manganese, iron, cobalt, nickel, copper, arsenic, selenium, rubidium, strontium,

Table 1 (continued)

Reference and location	Design	Subjects	Criteria inclusion/exclusion	Main glucose control or diabetes status-related findings	Limitations/notes
					molybdenum, cadmium, tin, antimony, barium, tungsten, thallium, lead, and uranium.
Basaki et al. 2012 [31] Iran	Case–control study	40 females 20 control group; age 25 ± 5.3 years 20 T2D group; age 27 ± 6.2 years	Age 18–40 years. Inclusion criteria case: T2D without vitamin and mineral supplements, insulin, or drugs that influence the glucose metabolism in the last 4 weeks; no history of recent acute illness or kidney, liver, or endocrine diseases; without chronic diabetic complications.	Serum zinc in T2D was reduced compared with non-diabetic controls.	Small sample size. Not specified time since diagnosis of diabetes. Copper and chromium but not iron were also reduced in T2D patients.
Forte et al. 2013 [32] Italy	Case–control study	319 male and female 59 controls; age 57.2 ± 18.0 years 192 T1D; age 48.8 ± 16.4 years 68 T2D; age 68.4 ± 11.2 years Time since diabetes diagnosis: T1D: 20.6 years and T2D 10.2 years	Age 18–80 years. Inclusion criteria for T2D: no treatment with vitamin and mineral supplements, thyroid hormones, estrogen, progesterone, diuretics, or antihypertensive agents; no history of recent acute illness or kidney, liver, or endocrine diseases; absence of chronic diabetic complications; non-smokers and non-drinkers patients. Control subjects: history of diabetes and any other disease, no alcohol, smoke, or drugs use. Not occupationally exposed to metals not carrying artificial metallic parts in the body.	Whole blood zinc is reduced in T2D patients, with no clear influence of duration of disease.	Whole blood zinc is reduced in T1D patients.
Rahim and Iqbal 2011 [70] Pakistan	Case–control study	40 males and females 20 without T2D with senile cataract 20 T2D with cataracts Time since diagnosis diabetes 11.8 ± 6.8 years	Exclusion criteria: T2D group: any systemic disease other than diabetes; pregnancy with pre eclamptic subjects; smoking; use of vitamin supplements; history of age-related cataract with any other ophthalmologic disease; or any past history of ophthalmic surgery. Control group: history of antibiotic therapy within 6 months prior to	Significant decrease in zinc levels in diabetic patients with cataract when compared to individuals with senile cataract.	Small sample size. Not specified how many male and female by groups. Not specified age of each group. Not specified diabetes treatment.

Table 1 (continued)

Reference and location	Design	Subjects	Criteria inclusion/exclusion	Main glucose control or diabetes status-related findings	Limitations/notes
			study, history of any systemic disease		
Doşa et al. 2011 [36] Romania	Case–control and prospective study (3-month follow-up)	47; 26 males and 21 females 17 control group 30 T2D	Age 30–60 years. Inclusion criteria: T2D patients: Exclusive use of metformin as antidiabetic drug (1000 mg/day as intervention); No micronutrients supplementation Exclusion criteria: pregnancy, breast feeding, renal disorders, malabsorption syndrome, psychiatric disorders, hepatic cirrhosis, and diuretic medication	Inverse correlation between plasma zinc and glycemia ($r = -0.399$, $p = 0.029$). Plasma zinc concentration was significantly decreased and urinary zinc increased in T2D group, before metformin, versus control group.	Small sample size. Not specified time since diagnosis of diabetes. Metformin after 3 months did not modify significantly plasma or urinary zinc concentrations.

Data are presented as number, mean (SD), or median (interquartile range)

IFG impaired fasting glucose, *IGR* impaired glucose regulation, *IGT* impaired glucose tolerance, *MetS* metabolic syndrome, *NGT* normal glucose tolerance, *T1D* type 1 diabetes, *T2D* type 2 diabetes, *NIDDM* non-insulin-dependent diabetes mellitus, *OR* odd ratio, *CI* confidence interval, *BMI* body mass index

used urinary Zn excretion, 1 whole blood Zn, and 1 evaluated erythrocyte Zn concentration and erythrocyte superoxide dismutase (SOD) activity. It is often indicated that plasma Zn is reduced in T2D as consequence of increased urinary losses [29]. Nevertheless, available evidence analyzed here only partially supports this conclusion because of the 11 studies that evaluated plasma/serum Zn, only 6 found significantly reduced concentrations in T2D patients compared to controls, 4 did not find significant differences, and 1 reported increased levels. In terms of urinary Zn, two studies reported increased values in T2D compared to controls. In addition, a cross-sectional analysis found an association between higher urinary Zn and increased prevalence of T2D [30]. Of note, in 5 of the 12 studies, participants with diabetes had a baseline mean plasma/serum Zn in the Zn deficiency range (below 70 μg/dL or 10.7 μmol/L). We identified several issues with quality in these studies: For instance, one of the studies that reported significant differences between groups did not provide the units of plasma/serum Zn used [31], and in another study, authors used whole blood Zn, which is not an appropriate index of Zn status [32].

Few studies have evaluated the association between Zn status and insulin action (e.g., HOMA-IR) and/or glucose homeostasis (e.g., fasting glucose). Yerlikaya [33•] in Turkey evaluated the relationship between plasma/serum Zn values and insulin resistance by HOMA-IR in non-diabetic obese and T2D obese subjects and found an inverse association between Zn status and insulin resistance in both groups, although such association was stronger in diabetic individuals. A similar result was found by Islam [34] in a group of glucose-intolerant patients. Vashum [35] reported a positive association between Zn status and insulin sensitivity in persons with prediabetes. In terms of glucose homeostasis, as shown in Table 1, only two studies provided information in this regard [33•, 36].

Gender may be a confounding variable when evaluating Zn status and some metabolic outcomes (e.g., positive correlation between serum Zn and insulin in men but not in women) [37, 38]. The relevance of gender in the context of the association between Zn and T2D has not been evaluated. Among the studies in Table 1, only three considered this potential confounder [30, 32, 39].

Similarly, another relevant biologic variable that is not always considered in the designs is body weight/composition (e.g., BMI). Among the studies evaluated here, it is worthy to mention the findings of Yerlikaya et al. [33•], which showed no differences in plasma/serum Zn between obese subjects with and without diabetes, but both obese groups showed reduced plasma Zn relative to non-obese non-diabetic subjects. Likewise, Islam et al. [34] found a significant interaction between plasma/serum Zn and BMI for insulin resistance.

Zinc Intake and Risk of Type 2 Diabetes

Of the studies that we identified evaluating the association between Zn intake and risk of type 2 diabetes, two cohorts found an inverse association: Compared to the lowest quintile of Zn intake, the highest Zn intake quintile was associated with lower risk of type 2 diabetes in the Australian Longitudinal Study [40] and the Nurses Health Study [41]. However, in a third cohort, the Multi-Ethnic Study of Atherosclerosis (MESA) study in the USA, there was no association between dietary Zn or supplements use at baseline and risk of T2D in the results of the 10-year follow-up [42, 43].

Another factor related to risk of T2D development, currently under intense study, is the genetic component, particularly, the presence of genetic variants in *SLC30A8*, the gene encoding ZnT8 [44–46, 47•]. While these studies suggest an interaction between zinc status or intake and glucose homeostasis, these studies have either between cross-sectional or small studies of brief duration and are unable to address the clinical relevance of *SLC30A8* variation and zinc status to diabetes risk at this time.

Zinc Supplementation Studies in Type 2 Diabetes

A valuable tool to assess translation of mechanisms associated to Zn action is response to Zn supplementation.

Prevention of Type 2 Diabetes

El Dib et al. [48] carried out a systematic review on Zn supplementation for the prevention of T2D in adults with insulin resistance. They were able to identify three trials with a total of 128 subjects. Duration of intervention was from 4 to 12 weeks. Nevertheless, none of the studies reported on key outcome measures (incidence of type 2 diabetes mellitus, adverse events, health-related quality of life, all-cause mortality, diabetic complications, and socioeconomic effects). Thus, there is no enough evidence to properly assess usefulness of such intervention as a preventive action.

Effects of Zn Supplementation among Persons with Type 2 Diabetes

During the past 5 years, the number of Zn supplementation studies carried out in diabetic populations is very limited, although two meta-analyses were available in this period. In our analysis of studies evaluating the effect of Zn supplementation on diabetes, we considered not only the recent supplementation trials but also those included in the meta-analyses.

The meta-analysis conducted by Jayawardena et al. [49] included studies in which Zn was supplemented, alone or combined with other vitamins and minerals, in patients with T2D (22 studies), and 3 studies in patients with T1D. The second meta-analysis developed by Capdor et al. [50••] reviewed nine studies on T2D, one trial in T1D, another trial with both types of diabetes, and seven trials in non-diabetic populations including metabolic syndrome patients or healthy subjects.

In the meta-analysis of Jayawardena et al. [49], 12 studies in T2D considered as outcomes the change in fasting blood glucose levels [51–62], and 8 of them also evaluated changes in HbA1C [54–56, 58–62]. Among other observed results were the effects on plasma lipids, antioxidant effects, and neuro-physiological parameters and symptoms of neuropathy. Eight of the 12 trials were randomized, double-blind and controlled [51, 52, 54–56, 58, 60, 61], 3 studies were single-blind [57, 59, 62], and 1 was a case–control study [53]. Intervention periods in these 12 studies, ranged from 3 weeks to 6 months, with supplementation doses of elemental Zn between 20 and 240 mg/day. In seven of these trials, with a mean time of intervention of 2.5 months, a significant reduction of fasting glucose concentration (FG) compared with the control group was observed [51–54, 58, 59, 62]. In the other five trials, with a mean of 3.9 months of intervention, no significant effect of supplementation was detected [55–57, 60, 61]. In studies with positive results of Zn supplementation, cumulative Zn dose was 4170 mg per patient, and in studies with negative results was 4463 mg per patient.

Changes in HbA1C were analyzed only in studies with at least 3 months of intervention, four of them had a significant reduction in the Zn arm [54, 58, 59, 62] and the remaining four studies showing no significant change [55, 56, 60, 61]. The cumulative Zn doses were 4059 and 3125 mg per patient, respectively.

In the meta-analysis by Capdor et al. [50••], most of the studies in T2D considered by Jayawardena et al. were also included, and they added the study by Oh et al. [63], which was a 4-week intervention with 50 mg of Zn, in which a reduction in fasting glucose and increase in C peptide was observed only in diabetic patients with Zn deficiency. Another study, added in the meta-analysis by Capdor et al., conducted by Kajanachumpol et al. [64], was a randomized, controlled trial in 25 T2D patients with Zn deficiency, which showed a significant reduction in fasting glucose after 12 weeks of intervention.

More recently, Foster et al. [65] published the results of a controlled trial in 43 postmenopausal T2D women without Zn deficiency, observing no significant effects on glucose metabolism after 12 weeks of intervention with 40 mg of Zn alone or associated with alpha-linolenic acid.

It is intriguing that despite diabetes is a chronic condition, Zn supplementation studies have been rather short-term duration, of just a few months. Our group in Chile is finishing a 2-year Zn supplementation trial in T2D individuals; results should be available shortly.

Table 2 Summary of glycemic control outcomes and presence of zinc deficiency at the beginning of zinc supplementation

Reference	Location	Fasting glucose[a]	HbA1C[a]	Zinc deficiency[b]
Al-Maroof et al. 2006 [59]	Iran	Improved	Improved	☑
Gunasekara et al. 2011 [62]	Sri Lanka	Improved	Improved	☑
Gupta et al. 1998 [51]	India	Improved	NA	☑
Hayee et al. 2005 [52]	Bangladesh	Improved	NA	☑
Kajanachumpol et al. 1995 [64]	Thailand	improved	NA	☑
Farvid et al. 2005 [60]	Iran	No change	No change	☒
Farvid et al. 2011 [61]	Iran	No change	No change	☒
Parham et al. 2008 [55]	Iran	No change	No change	☒
Partida-Hernández et al. 2006 [56]	Mexico	No change	No change	☒
Seet et al. 2011 [57]	Singapore	No change	NA	☒
Foster et al. 2014 [65]	Australia	No change	No change	☒
Oh et al. 2008 [63][c]	Korea	No change	NA	☒
Oh et al. 2008 [63][c]	Korea	Improved	NA	☑

NA Not available

[a] Significant change respect to control group

[b] Serum zinc levels below <70 μg/dL or < 10.7 μmol/L, in all or a significant proportion of individuals

[c] The study conducted an analysis stratified between patients with and without zinc deficiency

Examining changes in fasting blood glucose levels, and/or HbA1C, beyond the point of view of Zn supplemented/dose, but also considering initial Zn status, 12 of 15 trials available provided such information (Table 2). In five studies, which observed metabolic improvement, a significant proportion of T2D patients had Zn deficiency at the beginning of intervention [51, 52, 59, 62, 64]. Instead, six trials in which there was no improvement in fasting blood glucose levels or HbA1C were conducted in patients with T2D with absence of Zn deficiency [55–57, 60, 61, 65]. The case of the study of Oh et al. [63] is illustrative, showing metabolic improvement only in the subgroup of T2D patients with Zn deficiency.

Conclusions

Despite the host of mechanisms through which Zn may have beneficial effects on prevention and/or therapy of T2D, results of human studies are not consistent. While some positive results have been reported in some, in others such effects have not been observed. Potential causes of such discrepancy are varied. Diabetes is a complex disease, with a number of factors involved in its development and evolution; therefore, elements such as stage of the disease, degree of metabolic disturbance, co-morbidities, type and duration of medication, among others, have to be considered when developing study protocols. On the Zn side, despite the limitations plasma/serum zinc may present, it is a useful tool to assess Zn status. Moreover, it was noteworthy that only supplementation trials with a significant proportion of subjects with subnormal Zn status showed positive responses in terms of glucose control outcomes. Certainly, including better Zn indices, such as the size of the rapidly exchangeable Zn pool, in addition to plasma/serum Zn, would strengthen this literature. Longer supplementation periods are also needed for conclusive evidence. We hope to make soon available the results of a 2-year Zn supplementation study that recently completed its data collection phase. Also, genetic factors, such as variation in *SLC30A8*, should not be overlooked. In conclusion, the effect of Zn on type 2 diabetes remains an open question, and better study designs are needed to clarify the real impact and characteristics of this interaction.

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Compliance with Ethical Standards

Conflict of Interest Manuel Ruz, Fernando Carrasco, Andrés Sánchez, Alvaro Perez, and Pamela Rojas declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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