Nutrition

Zinc and glycemic control: A meta-analysis of randomised placebo controlled supplementation trials in humans

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\textbf{ABSTRACT}

\textbf{Background:} Impaired zinc metabolism is prominent in chronic disorders including cardiovascular disease and diabetes. Zinc has the potential to affect glucose homeostasis in animals and humans and hence impact the risk of type 2 diabetes mellitus.

\textbf{Methods:} A systematic review and meta-analysis of randomised placebo controlled trials was conducted to determine the effect of zinc supplementation on fasting blood glucose, HbA1c, serum insulin and serum zinc concentrations. Relevant studies for inclusion were identified from a literature search of electronic databases up to July 2011.

\textbf{Results:} Fourteen reports (n=3978 subjects) were included in the meta-analysis. In the overall analysis, a small but statistically significant reduction in fasting glucose concentrations was observed (\(-0.19 \pm 0.08 \text{ mmol/L, } P = 0.013\)) after zinc supplementation. HbA1c tended to decrease in zinc-supplemented individuals (\(-0.64 \pm 0.36\% , P = 0.072\)). No significant effect was observed for serum insulin concentrations. Plasma zinc concentrations increased significantly following supplementation (\(+4.03 \pm 0.81 \mu \text{mol/L, } P = 0.001\)). In secondary analyses of participants with chronic metabolic disease (types 1 and 2 diabetes mellitus, metabolic syndrome and obesity), zinc supplementation produced a greater reduction in glucose concentrations (\(-0.49 \pm 0.11 \text{ mmol/L, } P = 0.001\)) compared to the effect that was observed in healthy participants.

\textbf{Conclusion:} The significant albeit modest reduction in glucose concentrations and tendency for a decrease in HbA1c following zinc supplementation suggest that zinc may contribute to the management of hyperglycemia in individuals with chronic metabolic disease.

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\textbf{Introduction}

Zinc is a component of numerous enzymes that function in a wide range of biological processes, including growth and development, intermediary metabolism and immunity \cite{1,2}. Zinc deficiency is associated with a multitude of clinical manifestations \cite{1,2}, and may play a role in chronic diseases such as cardiovascular disease (CVD) \cite{3} and type 2 diabetes mellitus (DM) \cite{4}.

Zinc is implicated in glucose metabolism through its participation in insulin crystallisation and signalling \cite{5,6}. Under physiological conditions zinc is abundant throughout the pancreas, but is concentrated in the secretory vesicles of the β-cells where it forms an integral component of the insulin structure \cite{7}, serving to stabilise it and minimise its susceptibility to oxidative damage \cite{8,9}. Recent evidence has demonstrated a role for zinc in insulin sensitivity via the induction of the PI3K/Akt cascade that mediates insulin signalling and subsequent glucose disposal \cite{6}. A defect in zinc homeostasis is reported in DM patients, including higher urinary zinc excretion in some studies \cite{10}, and lower serum zinc concentrations \cite{11} as compared to healthy controls. Low zinc status in DM is associated with a decrease in insulin sensitivity \cite{12} and impaired glucose utilisation \cite{13}.

Zinc supplementation has been investigated as a potential adjunct therapy in the management of DM, however the outcomes of such interventions are conflicting \cite{14}. The aims of the present study are to systematically evaluate the effects of zinc supplementation on markers of glycemic control (glucose, insulin and HbA1c) in humans and to conduct a meta-analysis of eligible controlled trials to quantify the magnitude of the response to zinc supplementation.

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Methods and materials

Search strategy

A literature search was conducted of Medline, PubMed and Web of Science electronic databases from 1950 up to July 2011. The search term ‘zinc’ was combined with each of the terms ‘insulin’*, ‘glucose’, ‘glycemic’, ‘HbA1c’, ‘diabetes’ and ‘glycated’. Studies were restricted to human, clinical trials, published in English. Reference lists of retrieved studies were inspected for additional relevant articles.

Study selection

Of the research articles identified by the three database searches, duplicate records were discarded. The titles and abstracts of the remaining articles were screened to determine their eligibility for full review. The full report was retrieved if the study was a controlled clinical trial in humans that included supplementation with zinc, and at least one of the following outcomes: HbA1c, glucose or insulin concentrations. At least two investigators independently reviewed each full report to determine if the study met the inclusion criteria.

Data extraction

Data from included studies were extracted independently by at least two investigators and any differences were resolved by discussion. The data extraction worksheet included information such as, study design, participant details, the duration of supplementation, dose of elemental zinc, corresponding anion, and whether zinc was administered alone or combined with other nutrients. The methodology of each trial was assessed [15] and data were extracted that related to the outcome measures: concentrations of glucose, insulin, zinc, and HbA1c at baseline and post intervention.

Statistical analysis

Meta-analyses were carried out using the Comprehensive Meta-Analysis package, version 2 (Biostat, 2005, Englewood, NJ, www.meta-analysis.com). Results were generated using endpoint values for supplement minus control group, and are summarised in the form of Forest plots. The random effects model was utilised rather than the fixed-effects approach as differences in study design among included studies precluded the assumption of a common effect size. All results are expressed as mean difference ± SE, with the standard error of difference calculated using the independence of supplement and control groups. Secondary analyses were conducted for the effects of zinc supplements on glucose concentration by health status (healthy subjects compared to those with conditions that impair glucose metabolism, including obesity), and type of supplement (zinc alone or in combination with other micronutrients). Sensitivity analyses and Funnel plots of SE by mean were generated for each outcome to assess the influence of each report on the overall outcome and publication bias, respectively.

Results

Study designs

Several studies [16–29] were excluded from further evaluation and reasons for their exclusion are shown in Table 1. Fourteen articles [30–43] qualified for inclusion in the present analysis (Fig. 1). Some of the articles reported on more than one intervention study and therefore the total number of zinc interventions was 18. Characteristics of the included interventions are presented in Table 2. The outcome measures were fasting plasma, serum or blood glucose concentrations (18 interventions, n = 3978) [30–43], HbA1c (7 interventions, n = 385) [31,34,38–40], plasma or serum insulin concentrations (9 interventions, n = 546) [30–36] and plasma or serum zinc concentrations (11 interventions, n = 508) [30–32,36,38–40,42,43]. The median number of participants was 55 and the duration of the trials was in the range 1.5–390 weeks.

Participants’ characteristics

Interventions were undertaken in males (3 interventions, n = 1353), females (2 interventions, n = 1917) and both males and females (13 interventions, n = 708). The effects of zinc supplementation on biomarkers of glycemic control were examined in type 2 DM (8 interventions, n = 408), type 1 DM (n = 48), 1 study with both types 1 and 2 DM patients (n = 48), metabolic syndrome (2 interventions, n = 120), and 1 study in obese subjects (n = 56). There were 4 interventions (n = 3298) in healthy subjects (Table 2).

Zinc supplements

The effects of supplementation were investigated in trials that utilised zinc as the sole intervention (11 interventions, n = 581) or combined with other micronutrients (7 interventions, n = 3397) (Table 2). The dose of elemental zinc ranged from 3 mg/d to 240 mg/d (median: 30 mg/d). The median zinc dose in combination with other supplements (20 mg/d) tended to be lower than the dose when zinc was administered alone (50 mg/d). The corresponding anions were: sulphate, gluconate or amino chelate (Table 2). Serum zinc concentrations increased significantly (+4.03 ± 0.81 μmol/L, P = 0.000) following zinc supplementation.

Table 1

<table>
<thead>
<tr>
<th>Reasons for exclusion</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not a randomised controlled trial</td>
<td>[16–20]</td>
</tr>
<tr>
<td>Glucose data not provided</td>
<td>[16,18,19,21,22]</td>
</tr>
<tr>
<td>Possible confounding factors</td>
<td>[23–25]</td>
</tr>
<tr>
<td>No oral zinc supplementation</td>
<td>[26]</td>
</tr>
<tr>
<td>Insufficient data provided</td>
<td>[27,28]</td>
</tr>
<tr>
<td>Repeated information</td>
<td>[29]</td>
</tr>
</tbody>
</table>

Fig. 1. PRISMA flow diagram of study selection.
**Table 2**  
Characteristics of randomized controlled trials (RCT).

<table>
<thead>
<tr>
<th>Study and reference</th>
<th>Duration (week)</th>
<th>N. control/supplement</th>
<th>Gender (M/F)</th>
<th>Age control/supplement (year)</th>
<th>Trial type</th>
<th>Health status</th>
<th>Co-supplements</th>
<th>Trial type</th>
<th>Health status</th>
<th>Co-supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seet et al. [38]</td>
<td>28/28</td>
<td>30/30</td>
<td>M/F</td>
<td>28</td>
<td>T2DM</td>
<td>Metabolic syndrome</td>
<td>Vitamins A, B1, B5, B6, B7, C</td>
<td>T2DM</td>
<td>Healthy</td>
<td>Vitamins A, C, β-carotene, Se</td>
</tr>
<tr>
<td>Yoon et al. [39]</td>
<td>27/27</td>
<td>52</td>
<td>M/F</td>
<td>52</td>
<td>T2DM</td>
<td>Healthy</td>
<td>Sulphate, Vitamins A, Mg, Co, Se</td>
<td>T2DM/T2D M and neuropathy</td>
<td>Healthy</td>
<td>Vitamins C, E, Mg</td>
</tr>
</tbody>
</table>

**Effects of zinc supplementation on biomarkers of glycemic control**

A significant reduction in glucose concentration was observed after zinc supplementation in the overall, ungrouped analysis (−0.19 ± 0.08 mmol/L, P=0.013, Fig. 2). When grouped by health status, patients with DM (types 1 and 2), metabolic syndrome and obesity displayed a greater reduction in fasting glucose concentrations after zinc supplementation (−0.49 ± 0.11 mmol/L, P=0.001, Fig. 3) than those classified as healthy. Overall, zinc supplementation produced a decrease in HbA1c (−0.64 ± 0.36%) that reached borderline statistical significance (P=0.072). No significant effect of zinc supplementation on insulin concentrations was observed.

**Effects of individual trials**

One study removed sensitivity analyses revealed no single study that had a disproportionate effect on the results. Funnel plots gave no indication of publication bias, though in some of the sub-analyses the number of studies included was small.

**Discussion**

The present meta-analysis of clinical trials shows that zinc supplementation produces a modest but significant reduction in glucose concentrations, with the effect being more pronounced in subjects who are classified as diabetic or obese. In a sub-set of trials HbA1c tended to decrease following zinc supplementation but insulin concentrations were not significantly affected.

In addition to the RCTs included in the present report, a number of other studies have investigated the effects of zinc supplementation on glycemia. A combination of zinc, melatonin and metformin in type 2 DM patients resulted in a significant decrease in HbA1c in the intervention group compared to the control group [23]. Similarly, supplementation with zinc combined with bovine prostate extract resulted in a decrease in HbA1c in type 1 DM patients [24]. Cohort studies have reported inverse associations between total zinc intakes and serum glucose concentration [44] and risk of type 2 DM [45]. Zinc is inversely associated with cardiovascular risk in subjects with type 2 DM, as indicated by an increase in HDL cholesterol concentrations following zinc supplementation [46]. Taken together with the result of the present meta-analysis, these observations suggest that an increase in zinc intake has modest but favourable effects on cardiometabolic risk factors in DM.

The response in healthy individuals is less clear. The SUVIMAX study is the largest of the trials that was included in the present meta-analysis. The trial was carried out in healthy men and women, and showed no significant effect of zinc (20 mg) together with a mixture of micronutrients (vitamins C and E, β-carotene and Se) on plasma glucose concentrations. The participants were consuming a diet that was classified as good quality, and the dietary intakes of β-carotene and plasma vitamin C concentrations at baseline were inversely associated with plasma glucose concentrations [37]. Thus it is possible that under these circumstances any effect of zinc in healthy subjects is overshadowed by other dietary factors.

The effects of zinc on glycemia are mediated by varied mechanisms, including interactions between zinc and the insulin receptor, structural integrity of insulin, and insulin signalling pathways [4–6]. Zinc supplementation has been shown to increase the rate of glucose disposal and improve glucose tolerance in healthy subjects [18]. In rodent models, it is well recognised that zinc deficiency decreases insulin secretion and exacerbates glucose intolerance [47,48]. Conversely, animals supplemented with zinc exhibit improved glucose homeostasis compared to controls [49–51]. Zinc exerts insulin-like effects by stimulating phosphorylation of the IR β-subunit. Further, zinc can induce the PI3K/Akt insulin-signalling...
Fig. 2. Random effects model of the overall change in glucose concentrations associated with zinc supplementation. Data obtained from mean-adjusted endpoints and expressed as differences in means. The sizes of the symbols are proportional to study variability (studies with lower SE are shown as the larger symbol).

pathway by impacting molecular targets such as protein tyrosine phosphatases and lipid phosphatases [4–6]. Recent evidence from studies in cell culture (HuT-78 cells) has shown that zinc enhances the insulin-induced phosphorylation of Akt [52]. The authors propose that zinc supplementation may improve glucose homeostasis in people with impaired glucose metabolism by providing zinc to insulin-responsive cells, a suggestion that is supported by the present findings. However, despite the rationale for the cellular effect of zinc on insulin signalling, no significant effects of zinc supplementation on insulin concentrations were observed in the trials that were included in the present meta-analysis, possibly due to the small number of studies that report insulin results.

Impaired zinc homeostasis is reported often in people with DM [4,10,11]. Serum zinc concentrations increased significantly in response to zinc supplementation in the present meta-analysis; the serum zinc response has been shown previously to be greater in type 2 DM than in healthy subjects [46], which is suggestive of perturbed zinc homeostasis in the disorder. Two classes of zinc transporters are integral to the maintenance of intracellular zinc homeostasis: the ZnT (SLC30) and Zip (SLC39) transporter families. ZnTs promote cellular zinc efflux or the sequestration of zinc into intracellular organelles; conversely, Zip transporters traffic extraacellular or organellar zinc into the cytoplasm [53]. Single nucleotide polymorphisms in the ZnT8 gene are associated with impaired

Fig. 3. Random effects model of the change in glucose concentrations in subjects classified as healthy (N) or reported to have chronic metabolic disease (Y). Includes types 1 and 2 diabetes mellitus, metabolic syndrome, obesity. Data obtained from mean-adjusted endpoints and expressed as differences in means. The sizes of the symbols are proportional to study variability (studies with lower SE are shown as the larger symbol).

### Table

<table>
<thead>
<tr>
<th>Study name</th>
<th>Difference in means</th>
<th>Standard error</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seet et al (2011)</td>
<td>-0.10</td>
<td>0.86</td>
<td>-1.78</td>
<td>1.58</td>
<td>0.907</td>
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<td>Gunasekara et al (2011)</td>
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<td>0.30</td>
<td>-1.14</td>
<td>0.04</td>
<td>0.066</td>
</tr>
<tr>
<td>Hashemipour et al (2009) (supp first)</td>
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<td>0.10</td>
<td>-0.79</td>
<td>-0.39</td>
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<tr>
<td>Hashemipour et al (2009) (placebo first)</td>
<td>-0.48</td>
<td>0.10</td>
<td>-0.68</td>
<td>-0.28</td>
<td>0.000</td>
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<td>Shidfar et al (2010)</td>
<td>0.14</td>
<td>1.55</td>
<td>-2.90</td>
<td>3.18</td>
<td>0.928</td>
</tr>
<tr>
<td>Oh &amp; Yoon (2008) (Diabetics)</td>
<td>0.12</td>
<td>0.56</td>
<td>-0.98</td>
<td>1.22</td>
<td>0.830</td>
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<tr>
<td>Oh &amp; Yoon (2008) (Non diabetics)</td>
<td>0.45</td>
<td>0.19</td>
<td>0.08</td>
<td>0.82</td>
<td>0.017</td>
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<td>Arsenault et al (2007)</td>
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<td>0.08</td>
<td>-0.14</td>
<td>0.16</td>
<td>0.895</td>
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<tr>
<td>Marreiro et al (2006)</td>
<td>-0.01</td>
<td>0.19</td>
<td>-0.38</td>
<td>0.36</td>
<td>0.958</td>
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<tr>
<td>Czernichow &amp; al (2006) (men)</td>
<td>0.04</td>
<td>0.04</td>
<td>-0.03</td>
<td>0.11</td>
<td>0.262</td>
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<tr>
<td>Czernichow &amp; al (2006) (women)</td>
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<td>0.02</td>
<td>-0.05</td>
<td>0.03</td>
<td>0.646</td>
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<td>2.76</td>
<td>3.16</td>
<td>0.995</td>
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<td>-3.28</td>
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<td>0.145</td>
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<td>0.90</td>
<td>-2.19</td>
<td>1.33</td>
<td>0.632</td>
</tr>
<tr>
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<td>-3.02</td>
<td>0.44</td>
<td>0.144</td>
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<td>-1.34</td>
<td>2.78</td>
<td>0.494</td>
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<td>Gupta et al (1998)</td>
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<td>-1.60</td>
<td>-0.46</td>
<td>0.000</td>
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<td>Kajanachumpol et al (1995)</td>
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<td>1.36</td>
<td>-6.16</td>
<td>-0.80</td>
<td>0.011</td>
</tr>
<tr>
<td>Overall</td>
<td>-0.19</td>
<td>0.08</td>
<td>-0.34</td>
<td>-0.04</td>
<td>0.013</td>
</tr>
</tbody>
</table>
proinsulin conversion [54] and increased risk of developing type 2 DM [55]. Individuals with a variant (rs11558471) in ZnT8 exhibit higher glucose concentrations that are attenuated by an increase in the total intake of zinc from diet and supplemets [44]. ZnT8 co-localizes with insulin in human pancreatic islets and appears to be involved in both zinc accumulation and regulation of insulin secretion in β-cells [56]. Recently ZnT8 expression was observed also in α-cells [57], suggesting that defects in zinc transport potentially affect both α- and β-cell function. The RCTs that are included in the present meta-analysis do not report on polymorphisms of ZnT8 and thus the potential impact of SNPs on glucose metabolism in the context of a zinc supplementation trial remains unknown.

The assessment of zinc status is challenging particularly in the absence of robust biomarkers [58]. Factors that affect the concentration of zinc in biopsy samples include technical aspects of the analysis, the clinical protocol of blood collection, as well as physiological factors [59–61]. More recently, chronic systemic inflammation has been identified as a condition that can influence zinc concentrations significantly [62]. The latter is well recognised in a variety of chronic conditions, such as diabetes, hypertension, obesity and cardiovascular disease [4].

The zinc dose in many of the trials exceeded the recommended upper limit of 40 mg/d. Such high doses of zinc may induce copper deficiency and adversely impact antioxidant enzymes such as superoxide dismutase [63]. In addition, zinc supplementation of healthy individuals may result in a decrease in HDL cholesterol concentrations [46]. In women, low-dose zinc supplementation has been shown to decrease biomarkers of iron status [64,65], particularly in those with low iron reserves [65]. Thus despite the apparent benefit of zinc supplementation in individuals with DM, further information is required before any broader public recommendations can be made regarding zinc supplementation.

A number of limitations of the present report should be acknowledged. These include the possibility that relevant articles were omitted because they were written in a language other than English, not retrieved by the keys words that we used, or published in a source that is not indexed in the electronic databases that we accessed. Although all the trials included in the current analysis reported fasting glucose concentrations, the measurements were carried out on a range of different sample sources such as plasma, serum or whole blood. Fewer studies provided data on the concentrations of zinc, HbA1c or insulin. In the present analyses we did not evaluate the specific analytical aspects of the trials, such as the laboratory procedures and instrumentation. There is limited availability of published data to investigate a dose–response and potential confounders including concomitant pharmacotherapy, the impact of specific chronic diseases(s), age and gender. Despite these limitations, the present meta-analysis has notable strengths including the large number of subjects, the use of the random effects model of meta-analysis that allows for heterogeneity among studies, and no evidence of bias as determined by the sensitivity analyses and funnel plot tests.

Conclusion

Impaired zinc homeostasis is prominent in chronic disorders including atherosclerosis, hypertension, insulin resistance, and dyslipidemia. The present meta-analysis shows that there is a significant albeit modest reduction in the circulating glucose concentration following zinc supplementation, particularly in subjects with DM. While lifestyle modification, dietary and pharmacological therapy remain a priority in the management of DM, our findings suggest that zinc status is worthy of consideration in the management of hyperglycemia.

References

multimineral diabetes. in immunity zinck. KH.


