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SYSTEMATIC REVIEWS AND META-ANALYSES

Effects of zinc supplementation on lipid profile in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials

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Abstract *Background and aim:* Findings on the effects of zinc supplementation on the lipid profile in patients with type 2 diabetes mellitus (T2DM) are conflicting. The current comprehensive systematic review and meta-analysis aimed to summarize available evidence in this regard.
Methods and results: After a systematic search in the online databases, we included the randomized controlled trials (RCTs) investigating the effect of zinc supplementation on lipid profile [total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG)] in patients with T2DM. Altogether, 9 studies with a total sample size of 424 patients with T2DM were included in the analysis. Combining 9 effect sizes from 9 RCTs, we found a significant lowering effect of zinc supplementation on serum levels of TG (weighted mean difference (WMD): −17.08, 95% CI: −30.59, −3.58 mg/dL, $P = 0.01$) and TC (WMD: −26.16, 95% CI: −49.69, −2.62 mg/dL, $P = 0.02$). Although the overall effect of zinc supplementation on LDL-C levels was not significant, a beneficial effect was seen in studies that administered <100 mg/d zinc. Based on the non-linear dose−response analysis, a greater reduction in serum levels of TC and LDL-C following zinc supplementation was seen at <12 weeks' duration of intervention. Unlike the overall effect size, we found a significant increasing effect of zinc supplementation on serum HDL-C concentrations in most subgroups of RCTs according to the subgroup analyses.

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Conclusion: We found that zinc supplementation may beneficially influence lipid profile in patients with T2DM.

Background

Diabetes is a public health problem that is growing worldwide and is associated with a great deal of morbidity and economic cost [1]. The total number of people with diabetes is estimated to rise from 171 million in 2000 to 300 million by 2025 and 366 million by 2030 [2]. Type 2 diabetes mellitus (T2DM) is the most prevalent form of diabetes accounting for over 90% of people with diabetes [3]. According to the International Diabetes Federation (IDF), almost 75–80% of patients with diabetes die from cardiovascular complications [4]. Several risk factors contribute to diabetes-induced cardiovascular diseases including hyperglycemia, insulin resistance, and dyslipidemia [5]. Dyslipidemia is a common feature of T2DM characterized by increased serum levels of triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and decreased serum levels of high-density lipoprotein cholesterol (HDL-C) [6,7].

Zinc is an essential trace element involved in multiple physiological processes [8]. Assembling insulin hexamers in secretory vesicles, zinc has an important role in the biosynthesis and storage of insulin [9]. Increased urinary excretion of zinc and decreased total body zinc have been frequently reported in patients with T2DM [10]. Therefore, zinc intake may have a benefit for T2DM patients. However, there are conflicting data on the effect of zinc supplementation on metabolic measures in these patients [11–20]. Zinc supplementation resulted in a significant reduction in serum concentrations of TG, LDL-C and total cholesterol (TC) in some clinical trials [12,13,15], while it had no significant effect in some others [14,20]. A previous meta-analysis of randomized controlled trials (RCTs), performed by Jayawardena et al. showed no significant effect of zinc supplements on lipid measures in patients with T2DM [21]. Moreover, in a recent meta-analysis, Jafarnejad et al. concluded that zinc supplementation alone or with multi-nutrient significantly decreased serum levels of TC and LDL-C, and increased serum levels of HDL-C [22]. It should be considered that several methodological limitations were detected from both meta-analyses. The authors in the meta-analysis of Jafarnejad et al. missed 2 relevant studies [14,18] and inadvertently included duplicate publications more than once [23–25] which can induce a significant bias. In addition, authors in both meta-analyses included RCTs that administered supplements containing zinc in combination with other nutrients such as chromium which the effect of zinc could not be separated [26,27]. Overall, it seems that the conclusion obtained from the previous meta-analyses might be misleading and therefore, a more comprehensive meta-analysis is needed to reveal the effect of zinc supplementation on lipid profile in patients with T2DM. Therefore, we aimed to conduct a comprehensive systematic review and meta-analysis of RCTs to summarize available findings on the effect of zinc supplementation alone on lipid profiles in patients with T2DM.

Methods

This systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [28].

Search strategy

A comprehensive literature search was conducted using the online databases of PubMed, Scopus, Web of Science and Cochrane up to September 2019. We did not perform any language and time restriction. We searched for randomized, placebo-controlled, human trials that investigated the effect of zinc supplementation on lipid concentrations in patients with T2DM. The search terms and strategies were constructed based on the PICOS model which includes questions about patient (individual with T2DM), intervention (zinc supplementation), comparator (placebo), outcome (reduction in TG, TC, LDL-C levels, and increase in HDL-C levels) and study design (parallel and cross-over clinical trials). The following terms were used in the search strategy: Zinc AND ("Type 2 diabetes" OR T2DM OR diabetes) AND (Triglyceride OR Triacylglycerol OR TG OR cholesterol OR lipoprotein OR "very low-density lipoprotein" OR VLDL OR "low-density lipoprotein" OR LDL OR LDL-C OR "high-density lipoprotein" OR HDL-C OR HDL OR "lipid profile")

Inclusion criteria

The title and abstract of all identified articles were screened for study eligibility. Studies were included in the current meta-analysis if they: 1) were randomized controlled trials or placebo-controlled trials 2) performed on adult subjects (≥18 years old) with T2DM, 3) administered oral zinc alone (not in combination with other nutrients), 4) had an intervention duration of at least 4 weeks, 5) reported the mean and standard deviation (SD)

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of serum lipid profile (TC, LDL-C, HDL-C, TG) at baseline and end of trial for both intervention and control groups.

Exclusion criteria

Studies with the following criteria were excluded:1) *in vitro* and animal studies, 2) studies with cohort, cross-sectional and case−control designs, 3) review articles, 3) trials without a placebo or control group, 4) trials that used other nutrients in combination with zinc, and 5) those trials that enrolled subjects without T2DM.

Data extraction

The following information was extracted from each eligible study by two independent reviewers: 1) author's name; 2) year of publication; 3) country 4) number, gender, and age of participants, 5) study design, 6) type and dosage of zinc, 7) baseline levels of hemoglobin A1c (HbA1c), 8) duration of trial, 9) mean and SD of changes in serum lipid profile between pre- and post-intervention. When data on lipid measures were reported in different units, we converted them to the most frequently used unit.

Risk of bias assessment

We used the Cochrane quality assessment tool to assess the risk of bias for each study included in the current meta-analysis. This tool contained seven domains including random sequence generation, allocation concealment, reporting bias, performance bias, detection bias, attrition bias, and other sources of bias. Each domain was given a "high risk" score if the RCT comprised methodological defects that may have distorted the results, a "low risk" score if the defect was considered ineffectual and an "unclear risk" score if the information was not sufficient to determine the impact. If an RCT had a "low risk" score for all domains, it was labeled as a high-quality study with a totally low risk of bias [29]. The risk of bias assessment was done independently by two reviewers. Any disagreement was resolved by consensus.

Statistical analysis

The meta-analysis was carried out using the Stata, version 11.2 (StataCorp). Mean changes (SD) of the outcome measures (TG, TC, LDL-C, and HDL-C) reported for the intervention and control groups were used to obtain the overall estimates. When mean changes were not reported, we computed them by considering changes in each lipid measure during the intervention. If outcome variables (TG, TC, LDL-C, and HDL-C) were reported in mmol/L, we converted them to mg/dL through available suitable formulas. We also converted standard errors (SEs), 95% confidence intervals (CIs), and interquartile ranges (IQRs) to SDs using relevant formulas [30−32]. A random-effects model, which takes between-study variations into account, was used to obtain the overall effect size. Heterogeneity was determined using I^2 statistics and the Cochrane Q test. I^2 value >50% or *P*-value <0.05 was considered as significant between-study heterogeneity [33,34]. To find probable sources of heterogeneity, subgroup analyses were performed according to predefined criteria including intervention duration (≥12 vs. <12 weeks), zinc dosage (≥100 vs. <100 mg/d), baseline levels of lipid profile (abnormal vs. normal levels), and HbA1c (≥8 vs. <8%; based on median value across the included RCTs) using the fixed-effects models. To determine the non-linear potential effects of zinc dosage (mg/d) and intervention duration (week) on lipid profile, the fractional polynomial modeling was executed. Sensitivity analysis was used to explore the extent to which inferences might depend on a particular study. The possibility of publication bias was evaluated by the visual inspection of funnel plots and the formal test of Begg. *P*-value < 0.05 was considered as significant level.

Results

Findings from the systematic review

We found a total of 1282 papers from our initial search. After screening title and abstract, 1268 articles were excluded because they were duplicate publications (n = 185), animal studies (n = 218), review articles (n = 165) and irrelevant studies (n = 700). Among the remaining 14 articles, we excluded 3 RCTs that assessed the effects of zinc supplementation on glycemic indices, but not on lipid profile [35−37]. Two other RCTs were also excluded because they investigated the combined effect of zinc and other nutrients such as chromium [26,27]. Overall, a total of 9 RCTs were eligible for inclusion in the current meta-analysis [12−20]. Supplemental Fig. 1 shows a summary of the study selection.

Characteristics of the 9 studies included in the current meta-analysis are illustrated in Table 1. These studies included a total of 427 patients with T2DM including 214 patients in the control group and 210 patients in the intervention group. Studies were published between 2006 and 2019, and were conducted in USA (n = 1), Mexico (n = 1), Iran (n = 4), Singapore (n = 1), Saudi Arabia (n = 1), and Australia (n = 1). The dosage of zinc was between 30 and 660 mg/day. The intervention duration varied from 6 to 52 weeks. All of the selected studies used oral zinc supplementation in patients with T2DM. The mean age of participants was between 48.2 and 65.9. Two studies were conducted on Men [17,19], one was performed on women [38], and six studies were on both genders [12−16,18]. In addition, two trials used zinc gluconate [15,19], one study used elemental zinc [38], and others administered zinc sulfate for intervention [12−14,16−18]. Out of 9 selected RCTs, two were crossover [16,17] and others had a parallel design [12−15,18,19,38]. According to the Cochrane Risk of Bias

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Table 1 Characteristics of included RCTs investigating the effects of zinc supplementation on lipid profile in patients with T2DM.

Author, year	Country	Design	Participants, n	Age, year[a]	Intervention		Duration (week)	Outcomes (changes, mg/dL)[a]		Adjust/matching
					Treatment group	Control group		Treatment group	Control group	
Hernandez et al., 2006	Mexico	RA/DB/ crossover	Zinc:27 PbO: 27	51.7 ± 7.1	100 mg/d zinc sulfate	Placebo	12	TG: −29.67 ± 54.74 TC: −18.77 ± 28.58 LDL-C: 3.08 ± 23.92 HDL-C: 18.45 ± 8.23	TG: 1.41 ± 37.49 TC: 2.04 ± 25.62 LDL-C: 6.42 ± 18.24 HDL-C: −7.48 ± 8.17	No
Afkhami et al., 2008	Iran	RA	Zinc:20 PbO: 20	52.6 ± 8.6	660 mg/d zinc sulfate	Placebo	6	TG: −89.55 ± 83.57 TC: −34.65 ± 29.12 LDL-C: −29.3 ± 24.96 HDL-C: 7.3 ± 15.01	TG: −8.85 ± 62.03 TC: 96.95 ± 24.59 LDL-C: −3.25 ± 18.57 HDL-C: 0.21 ± 12.18	No
Parham et al., 2008	Iran	RA/DB/ crossover	Zinc:42 PbO: 39	Zinc: 52.0 ± 9.3, PbO: 54.5 ± 9.2	132 mg/d zinc sulfate	Placebo	12	TG: −16 ± 45.71 TC: −8.93 ± 20.16 LDL-C: 0.77 ± 17.67 HDL-C: −3.07 ± 5.52	TG: −16.31 ± 43.47 TC: −13.2 ± 18.62 LDL-C: −6.46 ± 16.42 HDL-C: −2.93 ± 5.91	No
Seet et al., 2011	Singapore	RA	Zinc:20 PbO: 20	Zinc: 57.0 ± 9.0, PbO: 55.0 ± 8.0	240 mg/d zinc gluconate	Placebo	12	TG: 7.96 ± 30.04 TC: −1.16 ± 21.77 LDL-C: 9.67 ± 23.67 HDL-C: −2.71 ± 6.32	TG: 0 ± 77.15 TC: 5.41 ± 35 ± 27 LDL-C: 17.79 ± 35.01 HDL-C: 0.39 ± 4.94	Age
Ashmony et al., 2012	Saudi Arabia	RA/SB	Zinc:26 PbO: 30	Zinc: 48.46 ± 4.61, PbO: 48.2 ± 4.09	40 mg/d zinc sulfate	Placebo	8	TG: −21.85 ± 20.26 TC: −35.69 ± 9.90 LDL-C: −33.77 ± 8.53 HDL-C: 10.53 ± 4.10	TG: 14.5 ± 28.11 TC: 16.73 ± 22.48 LDL-C: 5.35 ± 9.27 HDL-C: −2.27 ± 7.00	No
Heravi et al., 2017	Iran	RA/DB	Zinc:30 PbO: 30	Zinc: 58.3 ± 8.6, PbO: 60.0 ± 10.0	220 mg/d zinc sulfate	Placebo	12	TG: −10.9 ± 30.67 TC: −9.6 ± 25.19 LDL-C: −12.1 ± 24.09 HDL-C:4.1 ± 4.9	TG: −2.1 ± 30.67 TC: −1.7 ± 25.19 LDL-C: −1.8 ± 24.09 HDL-C: 1.1 ± 4.9	Sex, age, BMI, medication, DM duration, baseline measurements
Perez et al., 2018	USA	RA/DB	Zinc:13 PbO: 15	Zinc: 56.2 ± 5.3, PbO: 56.3 ± 8.9	30 mg/d zinc sulfate	Placebo	52	TG: −2.4 ± 24.12 TC: 2.2 ± 20.58 LDL-C: 9.2 ± 21.25 HDL-C: −9.4 ± 9.30	TG: 15.1 ± 25.78 TC: 15.2 ± 19.38 LDL-C: 13.8 ± 17.99 HDL-C: −0.4 ± 6.59	Sex, DM duration
Foster et al., 2013	Australia	RA/DB	Zinc:12 PbO: 10	Zinc: 65.9 ± 10.8, PbO: 64.6 ± 5.8	173 mg/d zinc sulfate	Placebo	12	TG: 17.69 ± 30.62 TC: 0 ± 13.37 LDL-C: 0 ± 13.37 HDL-C: −3.86 ± 5.33	TG: 0 ± 27.95 TC: 0 ± 24.41 LDL-C: 3.83 ± 24.41 HDL-C: −3.86 ± 12.2	No
Nazem et al., 2019	Iran	RA/DB	Zinc:35 PbO: 35	Zinc: 53.28 ± 7.3, PbO: 54.34 ± 7.1	50 mg/d zinc gluconate	Placebo	8	TG: −6.38 ± 29.86 TC: −11.85 ± 19.63 LDL-C: −5.65 ± 13.51 HDL-C: 4.6 ± 4.97	TG: 17.35 ± 32.80 TC: 0 ± 24.41 LDL-C: 5.12 ± 10.38 HDL-C: 1.2 ± 5.60	DM duration, medication

Abbreviations: RCTs: randomized clinical trials, RA: randomized, DB: double-blinded; SB: single-blinded; PbO: placebo; TG: triglycerides, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, BMI: body mass index, T2DM: type 2 diabetes mellitus.

[a] Values are mean ± SD.

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Assessment tool, some studies had a low risk of bias in the most domains of this tool (Supplemental Table 1).

Findings from the meta-analysis

The effect of zinc supplementation on serum TG concentrations

Combining 9 effect sizes from 9 RCTs, we found a significant lowering effect of zinc supplementation on serum TG concentrations in patients with T2DM compared with the control group (WMD: −17.08, 95% CI: −30.59, −3.58 mg/dL, $P = 0.01$) (Fig. 1). However, between-study heterogeneity was significant (I^2: 74.7, $P < 0.001$). To detect probable sources of heterogeneity, we did subgroup analysis based on intervention duration (≥12 vs. <12 weeks), zinc dosage (≥100 vs. <100 mg/d), baseline levels of TG (≥150 vs. <150 mg/dL), and HbA1c (≥8 vs. <8%; based on median value across the included RCTs). Subgroup analysis based on these variables could explain the between-study heterogeneity. In these analyses, we found that zinc supplementation resulted in a significant reduction in serum TG concentrations in studies conducted on patients with elevated serum levels of TG (>150 mg/dL), those with an intervention duration of <12 weeks, and RCTs that administered <100 mg/d zinc. Also, zinc supplementation had a beneficial effect on individuals with normal and elevated levels of HbA1c (Table 2).

Sensitivity analysis showed that leaving out the study of Ashmony et al. [13] would attenuate the significant effect of zinc supplementation on serum TG concentrations. However, the effect remained marginally significant (WMD: −13.75, 95% CI: −27.60, 0.09 mg/dL, $P = 0.05$). In addition, visual inspection of funnel plots and results from the Begg test ($P = 0.80$) revealed no evidence of substantial publication bias.

When we did the non-linear dose−response meta-analysis, we failed to find a significant effect of zinc dosage on serum TG concentrations in patients with T2DM ($P_{\text{non-linearity}} = 0.16$) (Supplemental Fig. 2.A). Besides, the duration of intervention had no significant non-linear relationship with serum TG concentrations ($P_{\text{non-linearity}} = 0.15$) (Supplemental Fig. 3.A).

The effect of zinc supplementation on serum TC concentrations

Nine effect sizes from 9 RCTs included in this meta-analysis. Overall, the quantitative meta-analysis revealed that zinc supplementation resulted in a significant reduction in serum TC levels, compared with the control group, in patients with T2DM (WMD: −26.16, 95% CI: −49.69, −2.62 mg/dL, $P = 0.02$) (Fig. 2). There was significant heterogeneity among studies ($I^2 = 97.0\%$, $P < 0.001$). Subgroup analysis based on the duration of intervention and baseline levels of HbA1c could decrease the between-study heterogeneity. Also, we found a significant reducing effect of zinc supplementation on serum TC levels in RCTs with <12 weeks' intervention duration, those trials that administered either ≥100 or <100 mg/d zinc, and those that enrolled subjects with normal or elevated levels of TC and HbA1c (Table 2). Based on findings from the sensitivity analysis, exclusion of Ashmony et al. study [13] could attenuate the significant reducing effect of zinc supplementation on serum TC concentrations; however, it was still marginally significant (WMD: −22.79, 95% CI: −47.88, 2.29, P = 0.07). The funnel plot and results from the Begg test showed no evidence of significant publication bias ($P = 0.80$).

In the non-linear dose−response analysis, we did not find a significant effect of zinc dosage on serum TC levels ($P_{\text{non-linearity}} = 0.20$) (Supplemental Fig. 2.B). However, the relationship between the duration of intervention and serum levels of TC was in a non-linear fashion ($P_{\text{non-linearity}} = 0.04$) (Supplemental Fig. 3.B).

The effect of zinc supplementation on serum LDL-C concentrations

We combined 9 effect sizes from 9 RCTs presented the effect size for the effect of zinc supplementation on serum levels of LDL-C. The quantitative meta-analysis showed a non-significant effect of zinc supplementation on serum LDL-C concentrations in patients with T2DM compared with the control group (WMD: −11.21, 95% CI: −24.37, 1.94 mg/dL, $P = 0.09$). There was significant between-study heterogeneity in this regard ($I^2 = 94.5\%$; $P < 0.001$) (Fig. 3). Findings from the subgroup analysis showed that dividing studies based on baseline serum levels of LDL-C and HbA1c as well as the duration of intervention could explain the heterogeneity among studies. Moreover, a significant reduction in LDL-C concentrations following zinc supplementation was seen in studies with an intervention duration of <12 weeks, those trials that administered <100 mg/d zinc, and individuals with either normal or elevated levels of baseline LDL-C or HbA1c (Table 2). Based on the sensitivity analysis, leaving out the study of Parham et al. [16] resulted in a significant reducing effect of zinc supplementation on serum LDL-C levels (WMD: −13.79, 95% CI: −26.37, −1.22 mg/dL, $P = 0.03$). Based on the funnel plot and the formal test of Begg, no evidence of publication bias was seen ($P = 0.62$).

When we did the non-linear dose−response analysis, no significant effect of zinc dosage on serum LDL-C levels was observed ($P_{\text{non-linearity}} = 0.23$) (Supplemental Fig. 2.C). Nevertheless, intervention duration showed a significant non-linear association with serum levels of LDL-C ($P_{\text{non-linearity}} = 0.01$) (Supplemental Fig. 3.C).

The effect of zinc supplementation on serum HDL-C concentration

Combining 9 estimates from 9 studies, no significant effect of zinc supplementation on serum HDL-C was seen compared with the control group (WMD: 4.54, 95% CI: −1.03, 10.10 mg/dL, $P = 0.11$) (Fig. 4). The heterogeneity among studies was significant, as indicated by $I^2 = 95.5$ ($P < 0.001$). In the subgroup analysis, baseline levels of HbA1c could somewhat explain the between-study heterogeneity. Moreover, zinc supplementation could significantly increase serum levels of HDL-C in studies with ≥12 and < 12 weeks' intervention

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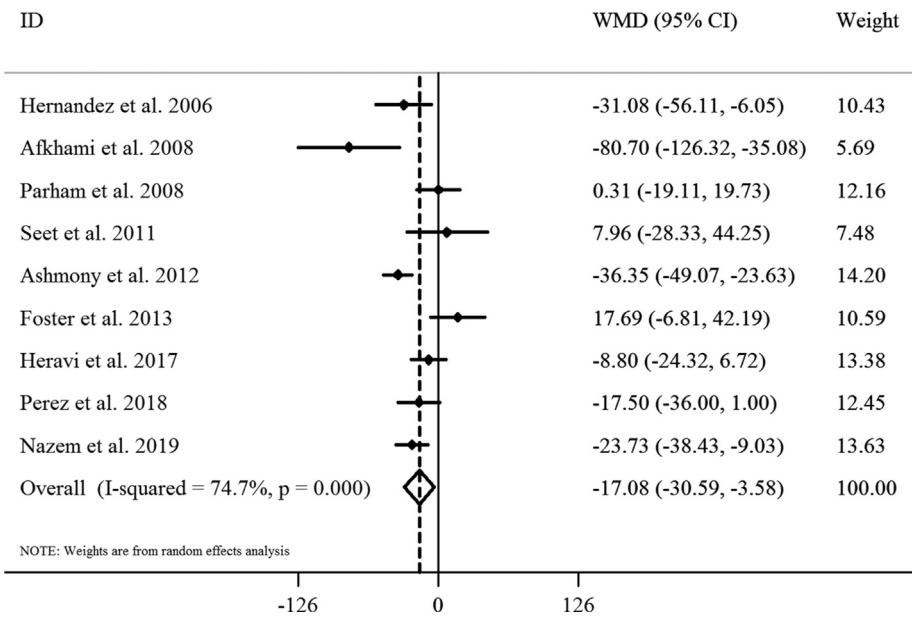

Figure 1 Forest plot detailing weighted mean difference and 95% CI for the effect of zinc supplementation on serum levels of triglyceride in patients with type 2 diabetes mellitus, WMD: weighted mean difference, CI: confidence interval.

duration, those that administered ≥100 and < 100 mg/d zinc, RCTs that conducted on patients with normal levels of HDL-C (>40 mg/dL), and those that enrolled subjects with elevated levels of HbA1c (≥8%) (Table 2). Based on the sensitivity analysis, when we excluded the study of Perez et al. [18], the overall effect size of zinc supplementation on serum HDL-C concentrations became significant (WMD: 6.14, 95% CI: 0.43, 11.85 mg/dL, $P = 0.03$). Visual inspection of the funnel plot and findings from the Begg test showed no evidence of publication bias ($P = 0.62$).

In the non-linear dose–response analysis, we failed to detect significant effects of zinc dosage ($P_{non\text{-}linearity} = 0.14$) (Supplemental Fig. 2.D) and intervention duration ($P_{non\text{-}linearity} = 0.32$) (Supplemental Fig. 3.D) on serum concentrations of HDL-C.

Discussion

Overall, we found that supplementation with zinc alone may produce a favorable effect on serum levels of TG and TC, but not on serum LDL-C and HDL-C, in patients with T2DM. Although the overall effect of zinc supplementation on serum concentrations of LDL-C and HDL-C was not significant, a beneficial effect was seen in most subgroups of RCTs. To the best of our knowledge, this study is the first comprehensive meta-analysis that summarizes prior studies on the effects of zinc supplementation on lipid profile in patients with T2DM. Of note, two recent meta-analyses in this regard had several methodological flaws that made their findings misleading [21,22].

In patients with T2DM, abnormal levels of the lipid profile are a common complication associated with increased risk of cardiovascular diseases and mortality [39–41]. Several therapeutic approaches including pharmaceutical and non-pharmaceutical interventions have been proposed to control lipid profile in patients with T2DM [42,43]. Recent studies provide conflicting evidence regarding the efficacy of zinc supplementation on blood lipids in these patients [11–20]. Based on the current meta-analysis, zinc supplementation resulted in a significant reduction in serum levels of TG and TC. Our findings were in line with the results from two recent meta-analyses in which zinc supplementation had a significant lowering effect on serum TC levels [21,22]. However, unlike our findings, they did not find any significant effect of zinc supplementation on serum TG concentrations. Some methodological limitations in these meta-analyses might explain the discrepant findings. For instance, Jafarnejad et al. [22] did not include two relevant RCTs in which a beneficial effect of zinc supplementation on TG levels was reported [14,18]. Also, in both meta-analyses, authors included trials that assessed the combined effect of zinc and other nutrients in which the independent effect of zinc cannot be obtained [21,22]. Moreover, a review on 3 RCTs concluded that zinc supplementation has a neutral effect on lipid profile in patients with insulin resistance [44].

In the current study, zinc supplementation had no significant effect on serum levels of LDL-C and HDL-C in patients with T2DM. In line with our findings, a clinical trial, performed on healthy adults, showed that zinc supplementation could not affect serum levels of LDL-C and HDL-C [45]. Such finding was also reported in a meta-analysis in which the effects of zinc intake on metabolic indices in hemodialysis patients were investigated [46]. However, our findings appeared to be in contrast with the previous meta-analysis by Jafarnejad et al. [22] in which zinc supplementation had a beneficial effect on serum levels of LDL-C and HDL-C. The observed discrepancy might be due

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Table 2 Subgroup analysis on the effects of zinc supplementation on lipid profile in patients with T2DM.

	Effect size, n	WMD[a]	95% CI	P-value[b]	Heterogeneity	
					I[b] (%)[c]	P-heterogeneity[d]
Zinc supplementation on serum levels of TG						
Intervention duration (week)						
≥12	6	−7.34	−15.87, 1.19	0.09	49.7	0.07
<12	3	−33.06	−42.48, −23.65	<0.001	66.6	0.05
Zinc dosage (mg/d)						
≥100	6	−7.84	−17.24, 1.57	0.102	73.3	0.002
<100	3	−28.08	−36.62, −19.55	<0.001	37.8	0.20
Baseline serum TG (mg/dL)						
≥150	5	−27.16	−35.19, −19.14	<0.001	73.8	0.004
<150	4	−5.49	−15.75, 4.77	0.294	47.9	0.12
Baseline HbA1c (%)						
≥8	4	−28.62	−38.20, −19.05	<0.001	80.0	0.002
<8	5	−11.47	−19.88, −3.05	0.008	58.9	0.045
Zinc supplementation on serum levels of TC						
Intervention duration (week)						
≥12	7	−4.63	−9.90, 0.64	0.08	54.0	0.05
<12	3	−43.48	−49.40, −37.56	<0.001	98.8	<0.001
Zinc dosage (mg/d)						
≥100	6	−16.54	−21.88, −11.19	<0.001	97.6	<0.001
<100	3	−28.10	−33.92, −22.27	<0.001	96.0	<0.001
Baseline serum TC (mg/dL)						
>200	2	−43.75	−51.33, −36.17	<0.001	92.5	<0.001
<200	7	−13.72	−18.33, −9.12	<0.001	97.2	<0.001
Baseline HbA1c (%)						
≥8	4	−33.51	−38.86, −28.17	<0.001	98.7	<0.001
<8	5	−7.96	−13.78, −2.14	0.007	0	0.854
Zinc supplementation on serum levels of LDL-C						
Intervention duration (week)						
≥12	7	−0.51	−5.30, 4.27	0.83	37.4	0.15
<12	3	−27.51	−30.99, −24.03	<0.001	96.5	<0.001
Zinc dosage (mg/d)						
≥100	6	−3.18	−7.93, 1.57	0.189	74.9	0.001
<100	3	−26.31	−29.81, −22.82	<0.001	97.0	<0.001
Baseline serum LDL-C (mg/dL)						
>100	4	−22.95	−26.61, −19.29	<0.001	97.6	<0.001
<100	5	−11.28	−15.68, −6.88	<0.001	34.4	0.19
Baseline HbA1c (%)						
≥8	4	−23.73	−21.00, −15.37	<0.001	97.5	<0.001
<8	5	−9.47	−13.99, −4.96	<0.001	0	0.896
Zinc supplementation on serum levels of HDL-C						
Intervention duration (week)						
≥12	6	2.65	1.24, 4.07	<0.001	96.4	<0.001
<12	3	7.27	5.41, 9.13	<0.001	91.2	<0.001
Zinc dosage (mg/d)						
≥100	6	3.43	2.00, 4.87	<0.001	96.0	<0.001
<100	3	5.82	4.00, 7.63	<0.001	95.8	<0.001
Baseline serum HDL-C (mg/dL)						
>40	7	5.33	4.03, 6.62	<0.001	96.1	<0.001
<40	2	1.28	−1.02, 3.57	0.274	92.2	<0.001
Baseline HbA1c (%)						
≥8	4	8.48	6.77, 10.19	<0.001	97.4	<0.001
<8	5	1.21	−0.28, 2.71	0.11	81.6	<0.001

Abbreviation: WMD: weighted mean difference, TG: triglycerides, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, HbA1c: hemoglobin A1c, CI: confidence interval, T2DM: type 2 diabetes mellitus.

[a] Obtained from the fixed-effects model.

[b] Refers to the mean (95% CI).

[c] Inconsistency, percentage of variation across studies due to heterogeneity.

[d] Obtained from the Q-test.

to the methodological limitations of that meta-analysis in which two eligible RCTs were not included [14,18] and authors inadvertently included duplicate publications more than once [23–25]. In the current meta-analysis, unlike the overall analysis, subgroup analyses showed a beneficial effect of zinc supplementation on serum levels of LDL-C in trials that administered <100 mg/d zinc and studies conducted on patients with either normal or

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elevated levels of baseline LDL-C or HbA1c. Moreover, zinc supplementation had an increasing effect on HDL-C levels in most subgroups of RCTs.

We observed significant heterogeneity across the included studies. One of the most important factors explaining the heterogeneity is variation in the baseline levels of lipid profile among the included RCTs. As seen in the current study, when we performed subgroup analysis based on baseline values of lipid profile (abnormal vs. normal levels), the between-study heterogeneity was reduced in RCTs that were conducted on individuals with normal levels of lipid indices. Moreover, the observed heterogeneity in the other subgroups including RCTs with a short duration of intervention (<12 weeks) or those trials that administered a high dosage of zinc (≥100 mg/d) might be due to the presence of studies performed on individuals with elevated levels of baseline lipid profile.

Based on our subgroup analysis, zinc supplementation significantly reduced serum levels of TG, TC, and LDL-C in RCTs with <12 weeks' intervention duration, but not in those trials with a duration of ≥12 weeks. Serum levels of HDL-C were also significantly increased in both trials with ≥12 and < 12 weeks' intervention duration. Since baseline levels of these outcome variables influenced most of the heterogeneity seen in the subgroup analyses, we tested whether the mean baseline levels are equal in the studies with the duration of ≥12 vs. <12 weeks (Supplemental Table 2). Interestingly, all studies on serum TG and HDL-C with a duration of <12 weeks were included patients with high baseline levels of these outcome variables. Moreover, in studies with long-term duration (≥12 weeks), significant improvement in serum HDL-C was only observed in trials with high baseline values. Therefore, the difference in duration of treatment was most likely not the reason for differences in TG and HDL-C reduction but was a consequence of different baseline levels of these biomarkers. However, considering serum TC and LDL-C, the observed beneficial effect of zinc supplementation in studies with <12 weeks' duration of intervention was seen in both normal and elevated levels of these biomarkers. Therefore, it seems that the differences in the effects of zinc on TC and LDL-C levels between the two subgroups of intervention duration were not due to different baseline levels of these biomarkers. Also, the significant non-linear inverse association between intervention duration and serum levels of TC and LDL-C reinforces the fact that these biomarkers may benefit from a short duration of zinc supplementation. Nevertheless, the lack of beneficial effects in interventions with long-term duration might be due to the lack of controlling for some confounders such as dietary intakes and physical activity that are hard to be controlled in these trials.

Also, zinc supplementation resulted in a significant change in serum levels of TG and LDL-C in RCTs that administered <100 mg/d of zinc, but not in those with zinc dosage of ≥100 mg/d. This disparity might be explained by the different quality of the included RCTs. For example, in two [15,18] from three RCTs [13,15,18] with zinc dosage of <100 mg/d, participants in zinc and placebo groups were matched for the duration of diabetes mellitus and also were blinded for the allocated interventions. In contrast, out of six RCTs that administered ≥100 mg/d zinc [12,14,16,17,19,38], four trials did not match zinc and placebo groups for any potential confounders [12,16,17,38] and in two studies, participants were not blinded to the interventions received [12,19].

Our meta-analysis showed a favorable effect of zinc on serum concentrations of TG and HDL-C in patients with elevated baseline levels of these biomarkers. It has been shown that zinc levels are enhanced in patients with hyperlipidemia [47]. Therefore, the favorable effect of zinc in patients with elevated baseline levels of lipid profile

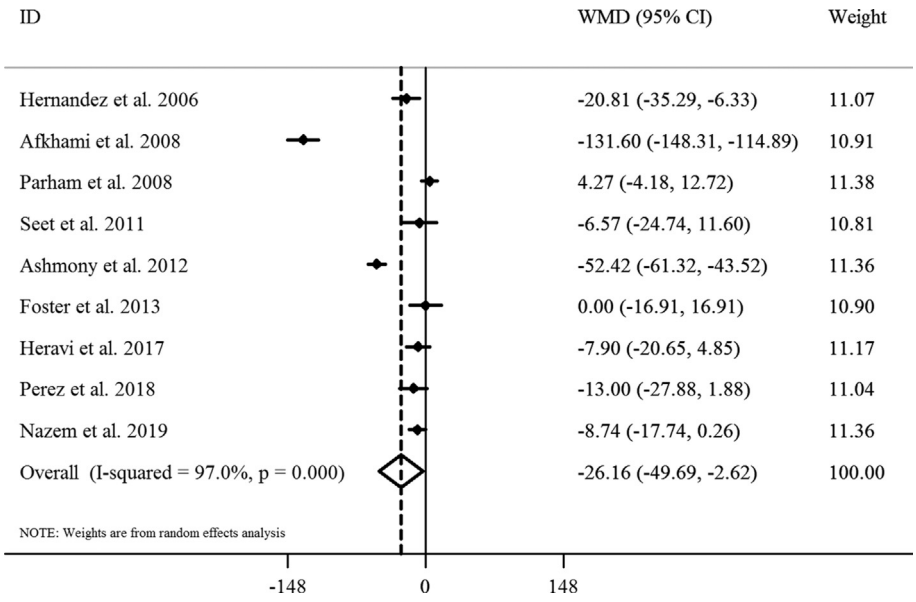

Figure 2 Forest plot detailing weighted mean difference and 95% CI for the effect of zinc supplementation on serum levels of total cholesterol in patients with type 2 diabetes mellitus, WMD: weighted mean difference, CI: confidence interval.

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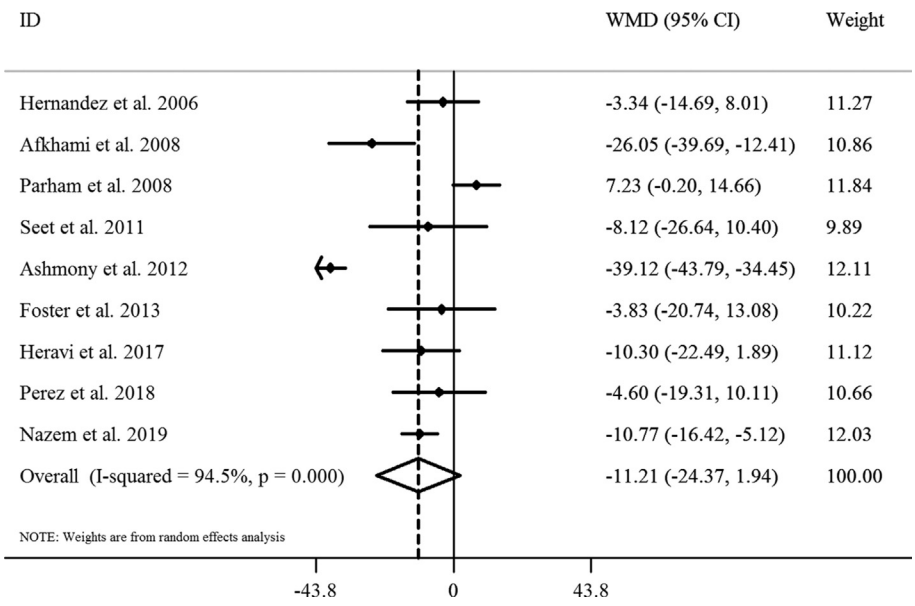

Figure 3 Forest plot detailing weighted mean difference and 95% CI for the effect of zinc supplementation on serum levels of LDL-C in patients with type 2 diabetes mellitus, LDL-C: low-density lipoprotein cholesterol, WMD: weighted mean difference, CI: confidence interval.

might be explained by elevated levels of zinc in these patients leading to an increase in the lipid-lowering effect of zinc.

It seems that the beneficial effect of zinc supplementation on the lipid profile is mediated by an improvement in glycemic control. In a recent meta-analysis on 32 trials including the selected RCTs in our study, Wang et al. reported that zinc supplementation improved glycemic indicators including fasting glucose, 2-h postprandial glucose, fasting insulin, HbA1c, and homeostasis model assessment for insulin resistance (HOMA-IR) [48]. Zinc activates signal transduction and improves insulin sensitivity through phosphorylation of insulin receptors [49]. Blood sugar-controlling effects of zinc can reduce the production and release of free fatty acids from adipose tissue and consequently reduce the production of blood lipids including very-low-density lipoprotein (VLDL) and TG [50]. Furthermore, zinc is an essential mediator of the storage and secretion of insulin from pancreatic beta-cells [51]. Zinc is also involved in the activation of insulin through the conversion of monomeric insulin to dimeric form (the active form of insulin) [52]. Insulin has an

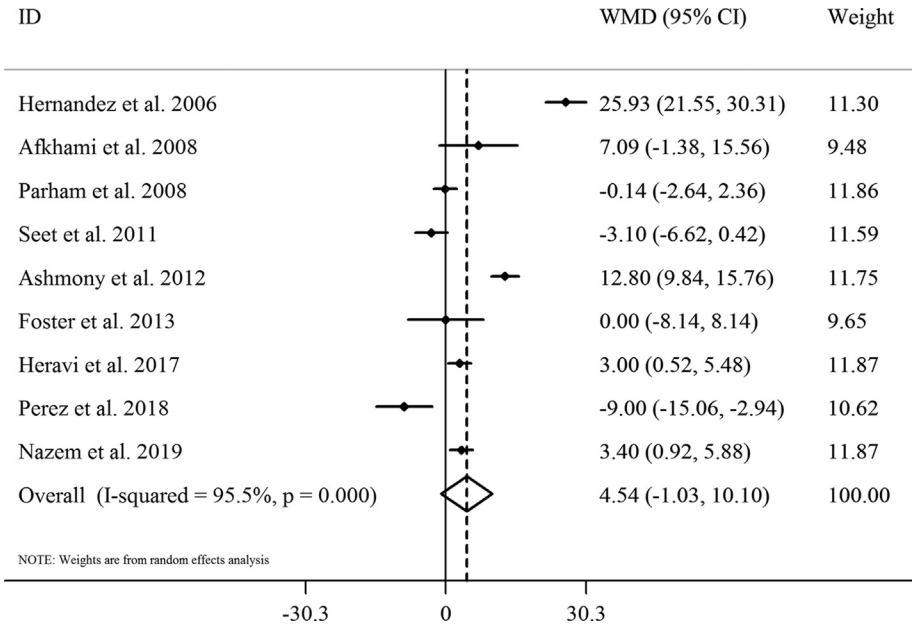

Figure 4 Forest plot detailing weighted mean difference and 95% CI for the effect of zinc supplementation on serum levels of HDL-C in patients with type 2 diabetes mellitus, HDL-C: high-density lipoprotein cholesterol, WMD: weighted mean difference, CI: confidence interval.

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important role in the transmission of blood lipids to adipose tissue. High serum levels of zinc can improve superoxide dismutase (SOD) activity resulting in an increase in serum antioxidant capacity [53,54]. It has been shown that the high serum total antioxidant capacity and increased antioxidant–enzyme activity can beneficially affect the lipid profile [55].

As the strengths of the current meta-analysis, we included all available RCTs investigating the effects of zinc supplementation on lipid profile in patients with T2DM. There was significant heterogeneity among the included studies; however, we found potential sources of this heterogeneity in our analyses. In addition, we performed the meta-analysis by using a random-effects model which takes between-study heterogeneity into account. Some limitations should also be considered when interpreting the present results. The RCTs used different types of zinc supplements which might affect our findings. Future studies are recommended to focus on the most effective type of zinc supplement. Moreover, the lack of controlling for baseline measures in some studies and different study designs must be considered in the interpretation of our findings.

Conclusion

Overall, unlike the previous review articles and meta-analyses, we found a beneficial effect of zinc supplementation on serum levels of TG and TC in patients with T2DM. While the overall effect size of zinc supplementation on LDL-C concentrations was not significant, we found a favorable effect of zinc supplementation in RCTs that administered $<$100 mg/d zinc and studies conducted on patients with normal or elevated levels of LDL-C and HbA1c. Moreover, unlike the overall effect size, zinc supplementation resulted in a significant increase in serum HDL-C concentrations in RCTs with that administered $\geq$100 and $<$ 100 mg/d zinc, studies conducted on patients with normal levels of HDL-C, and those with elevated levels of HbA1c. Although we found significant improvement in serum HDL-C and TG following zinc supplementation in studies with short duration of intervention, the effect may be confounded by differences in baseline levels of these biomarkers. In the meanwhile, short duration of intervention may be more effective in reducing serum levels of LDL-C and TC.

Implications for clinical practice

Based on our consideration of the best, the current meta-analysis revealed that zinc supplementation provides a benefit for the management of lipid abnormalities in patients with T2DM. However, our findings showed that supplementation with $<$100 mg/d zinc is more effective than higher dosages. Moreover, a short duration of supplementation may be effective in the improvement of serum LDL-C and TC but not HDL-C and TG. Whether our findings are generalizable to other types of diabetes remains unclear due to the lack of studies investigating the effects of zinc supplementation in patients with type 1 diabetes and gestational diabetes mellitus. Since data on long-term safety are not available, the safety of long-term supplementation with zinc is unknown.

Implications for future research

Future well-designed interventional studies recruiting a homogenous group of patients are required in this area. Moreover, since high dosages of zinc (range 100–300 mg/day) far higher than the recommended dietary allowance (RDA) (15 mg/d) induce symptoms of toxicity such as copper deficiency, neutropenia and impaired immune function [56], conducting future studies with high dosage should be done with caution.

Authors' contribution statement

OA, MS, FF, BP, OS, AP: study conception and design, study search, data extraction, data interpretation and analysis, and critical revision of the manuscript; MN and AS: study search, data extraction, data interpretation, and preparation and revision of the manuscript; MK: data interpretation and analysis, and critical revision of the manuscript. All authors approved the final manuscript for submission.

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Declaration of Competing Interest

The authors declared no personal or financial conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2020.03.021.

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