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Review Article

Zinc Supplementation Might Not Affect Serum Leptin and Adiponectin Levels in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials

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Abstract

Background: Zinc as one of the important trace elements in human health has been suggested to be a supplement for modifying the level of adipokines, whereas findings from studies have been inconsistent. This study aimed to systematically review the evidence provided by randomized controlled trials (RCTs) regarding the effect of zinc supplementation on serum adipokines levels.

Methods: PubMed, Google Scholar, Web of Science, and Scopus were systematically searched up to June 2019. The mean differences and their corresponding standard deviations (SDs) of changes in serum adipokines levels were used as effect size.

Results: Eight eligible RCTs (leptin n=6, adiponectin n=3) were included in the current study. There were no significant changes in serum leptin levels [weighted mean difference (WMD) =0.60 ng/ml, 95% confidence interval (CI): -1.78, 2.99; I-squared (I^2) = 64.3%] and adiponectin levels (WMD = 1.09 ng/ml, 95% CI: -0.76, 3.18, I^2 = 78.8%) following zinc supplementation compared to placebo group. These findings did not change after considering several subgroups including gender, study duration, health status, body weight and the type of zinc used for supplementation.

Conclusion: No evidence was found to support the efficacy of dietary zinc supplements on serum levels of adipokines. Further, high-quality, long-term controlled clinical trials are warranted to confirm these findings.

Keywords: Zinc; Adipokines; Leptin; Adiponectin; Meta-analysis

Introduction

Obesity is one of the most common nutritional problems that lead to other life-threatening chronic disorders, such as hypertension (1), diabetes (2, 3), dyslipidemia (4), cardiovascular diseases (5), and some types of cancer (6-8). Based on WHO reports, more than 650 million and 1.9 billion people are obese and overweight around the world, respectively (9).

Adipose tissue is a dynamic endocrine organ owning to secretes a series of bioactive peptides so-called adipokines, such as adiponectin and leptin

(10) which regulating energy balance and creating a balance between food intake and energy expenditure as the major contributors to obesity (11). Leptin through changing the neuropeptide concentration in the hypothalamus, not only leads to a reduced appetite but also increases energy expenditure (12-17), thus the anti-obesity properties has been attributed to leptin (18). Adiponectin is another adipokines demonstrated to be negatively correlated with body fat and weight (19). Adiponectin has a remarkable role in glucose and lipid homeostasis (20).

The trace elements like zinc are proposed to be associated with the regulations of adipokines homeostasis (21). Zinc has an important role in many metabolic pathways including fat metabolism, controlled enzymatic system like adipokines and insulin (22-24), and some chronic situations like obesity, diabetes, and kidney disease (25-27). The lower levels of micronutrients like zinc was reported in overweight and obese individuals and also hemodialysis patients when compared to the rest of the population (27, 28). Zinc deficiency is associated with decreased appetite (29, 30) and alterations in circulating or local neurotransmitters concentrations in the hypothalamus (31). Zinc deficiency was linked to lower serum levels of adiponectin (32). Zinc directly affect serum leptin and adiponectin levels by increasing activation of PPAR-ϒ in both mRNA and protein levels, cytokine production (IL-2, TNF-α) (33-35) and hypothalamic leptin receptor (Ob-R) mRNA expression; and also indirect stimulation of leptin synthesis by increasing the consumption of glucose in the adipose tissue (29, 36, 37).

The findings from RCTs showed controversial results about the effect of zinc supplementation on serum levels of adipokines. For example, zinc supplementation led to reduced serum leptin levels (27, 38), and rest of them did not found any significant change in serum adipokines levels (26, 39-41).

A recent meta-analysis included only studies that evaluated the effect of zinc supplementation on serum leptin levels and did not investigate the effect of zinc supplementation on serum level of adiponectin (42).

The present meta-analysis was conducted to gather the maximum number of controlled clinical trials that considered the effect of zinc supplementation on serum levels of adipokines, summarized their results and if possible explored the possible sources of heterogeneity between the studies published in this regard.

Materials and Methods

The present study followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (43).

The study protocol has been registered in the international prospective register of systematic reviews (PROSPERO); the registration code is CRD42018089735.

Search strategy

The online databases including PubMed, Google Scholar, Web of Science, and Scopus were searched up to Jun 2019 without any limitation in time or language to obtain all relevant articles. Medical subject headings (MeSH) and text words were both used. The keywords were: "Zinc" AND "Adipokines" OR "Leptin" OR "Adiponectin" OR "Resistin" OR "Visfatin" OR "Vaspin" OR "Apelin" OR "Chemerin" OR "Omentin" AND "clinical trials" OR "randomized". A Robust search strategy was designed to identify all RCTs examining the effect of zinc supplementation on serum adipokines irrespective of considering adipokines as a primary or secondary outcome.

Eligibility criteria

The studies were included in the present study if: They reported the effect of zinc supplementation on serum adipokines levels, were published as the original article, their designs were randomized controlled clinical trial (RCT) and compared only zinc supplement without any other vitamins or food, had a control group, were conducted in adult population (aged >18 yr), and dietary zinc supplement was consumed. Any limitation in terms of follow-up duration and serum zinc level was con-

sidered. The studies in children, pregnant and lactating women; and the review and duplicate studies were excluded.

Study selection process and quality assessment

The titles and abstracts of all records identified through database and searching were screened by two authors (MT, SS) independently to retrieve relevant studies based on eligibility criteria. The quality of included articles was assessed using the Cochrane collaboration's tools for clinical trials (44). The following domains were assessed in each study: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective reporting). Studies unknown risk for one domain or more were regarded as unclear and those with at least one high-risk domain were categorized as high risk. Any disagreement was solved after discussion by ASA.

Data Extraction

The following data were extracted and recorded from the eligible articles: the first author's last name, publication year, study location, study design (parallel/crossover), participants' health status (healthy/ diabetic/ obesity/ kidney disease), the type and the dose of zinc supplementation, the method used for zinc-supplementation (single dose, daily, weekly, and monthly doses), participants' gender, total number of the participants, duration of the study, mean and standard deviation of adipokines at baseline and after study period in the intervention and control groups.

Statistical analysis

The difference in mean change of serum adipokines between the zinc supplemented and the control groups were used as effect size for the meta-analysis. In the studies that the mean difference in serum adipokines was not reported, this value was calculated according to the Cochrane Handbook for Systematic Review (45); also we computed standard deviations (SDs) for mean changes by using correlation r between the baseline and after intervention values [for leptin r=0.536 (39, 40) and for adiponectin r=0.631 (40)]. The weighted mean difference (WMD) was estimated following DerSimonian and Laird random-effects model which considers the between-study variability (46). The heterogeneity between studies results was evaluated using I-squared and Cochran's Q test. I-squared > 50% was indicates substantial heterogeneity (44). Subgroup analysis based on the following variables were undertaken to investigate the possible sources of between-study variations: 1) gender, 2) study duration, 3) participants' health status, and 4) the type of zinc (zinc sulfate/zinc gluconate/zinc amino chelate/zinc elemental) used for supplementation. The publication bias was evaluated by visual inspection of the Begg's funnel plots (47) and by using Egger's regression test (48). The influence analysis was carried out to test the robustness of the overall analysis by removing the eligible studies one by one from the meta-analyses. Statistical analyses were performed by using STATA software (version 11; StataCorp, College station. TX). *P*-values <0.05 were considered as statistically significant.

Results

Included studies

Implementing the search strategy in different databases retrieved 2,311 articles; after removing duplicate articles, and screening titles and abstracts, 105 articles were identified for full-text assessment. Of these, 97 articles were excluded after applying the inclusion and exclusion criteria. Eight randomized controlled clinical trials with 362 participants were included in the systematic review and meta-analysis [leptin (n=6) (26, 27, 39-41, 49), adiponectin (n=3) (25, 40, 50)] (Fig. 1).

The main characteristics of RCTs included in the systematic review are presented in Table 1.

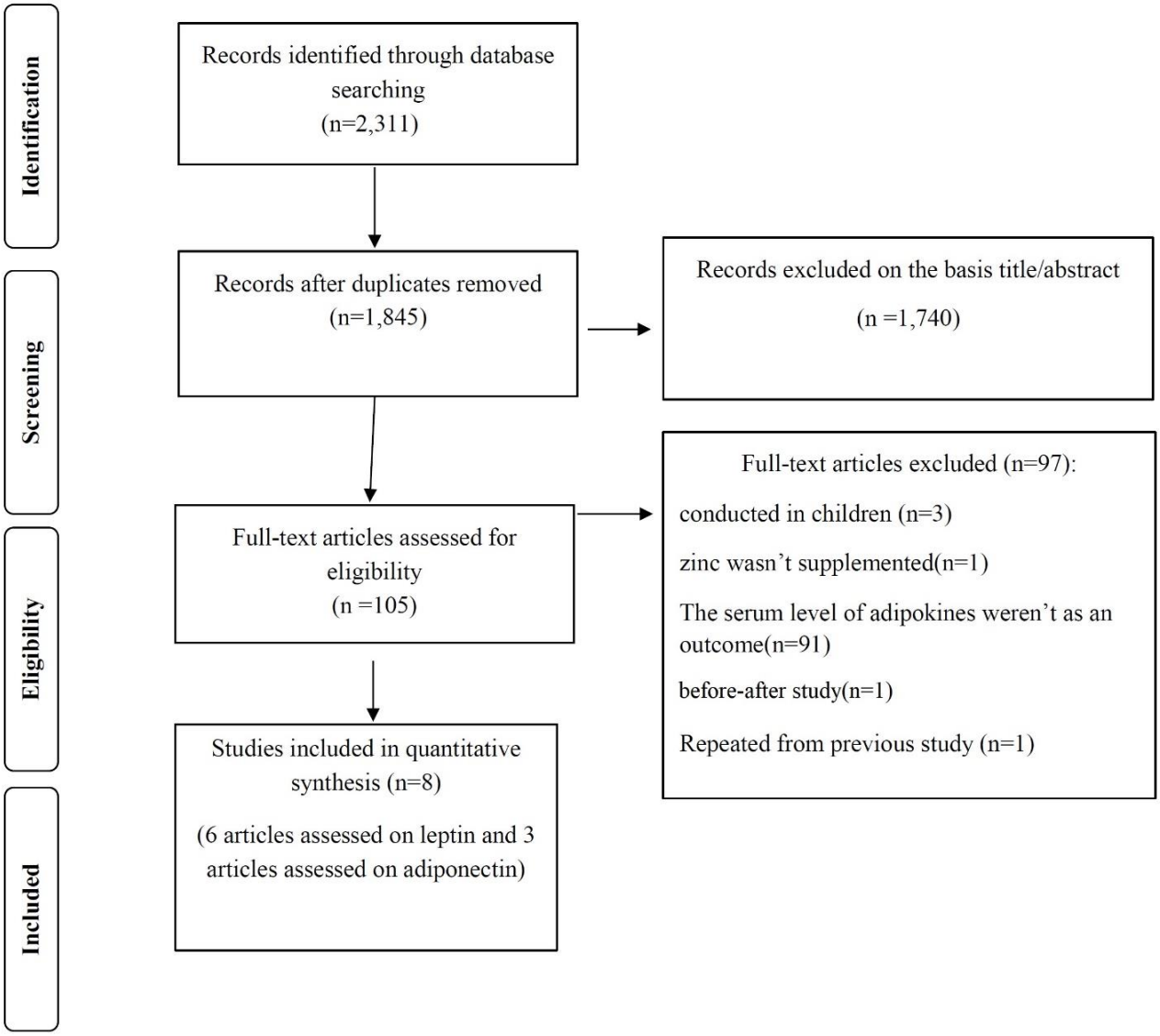

Fig. 1: Flow diagram for study selection process

Briefly, most of the studies were conducted in Asia (n=5)(25-27, 40, 50), and others were conducted in South America (n=2)(39, 41), and Europe (n=1)(49). All studies had a parallel design. Of 8 articles; 2 were conducted only in males (39, 49), two were conducted in females (40, 41) and the remaining studies included both genders. Only in three studies, the participants had zinc deficiency (27, 41, 49) and the other studies did not mention the zinc status level at baseline. The studies were conducted in participants with different health status: obese (n=4), diabetic (n=2), healthy (n=1) and kidney disease (n=1). The study duration in these RCTs ranged between 1-12 weeks. Zinc supplementation ranged from 30 to 100 mg/day and different types of zinc-supplemented were used: zinc gluconate (n=4), zinc sulfate (n=3), and elemental zinc (n=1). The type of intervention which used for the control groups were placebo (n=7), and no intervention (n=1).

Table 1: Randomized controlled trials which were eligible to be included in the systematic review and meta-analysis

Author (yr)	Participants, Gender	Mean age	Country	Design	Health status	Zinc dose (mg /day)	Duration (weeks)	Control groups	Results
Bribiescas 2003 (39)	14, Male	47.2 (int) 31.3 (cont)	Paraguay	Parallel	Healthy	Zinc gluconate (50)	1	Placebo	Leptin level was not changed in the intervention and control groups
Garcia 2006 (49)	14, Male	21.8 (int)	France	Parallel	Obesity	Zinc sulfate (100)	4	Placebo	Serum leptin level increased after the intervention
Marreiro 2006 (41)	56, Female	25.1 (cont)	Brazil	Parallel	Obesity	Zinc amino-chelate (30)	4	Placebo	Leptin level did not change in the intervention and control groups
Asghari 2011(50)	60, Both	35.5 (int) 33.9 (cont)	Iran	Parallel	Diabetes	Zinc gluconate (30 mg elemental zinc)	12	Placebo	The level of adiponectin increased significantly in the intervention group
Soheilykhah 2012 (25)	58, Both	45.8 (int) 45.8 (con)	Iran	Parallel	Diabetes	220mg Zinc sulfate (50 mg elemental zinc)	12	No intervention	The level of adiponectin was significantly increased in the intervention group
Kim 2014 (40)	40, Female	37.6 (int) 37.6 (cont)	South Korea	Parallel	Obesity	Zinc gluconate (30 mg elemental zinc)	8	Placebo	Serum leptin and plasma adiponectin were not changed significantly in the intervention and control groups.
Argani 2014 (27)	60, Both	20.8 (int) 20.8 (cont)	Iran	Parallel	Kidney disease	440 mg Zinc sulfate (100 mg elemental zinc)	8	Placebo	Serum leptin level decreased after the intervention in women significantly.
Payahoo 2014 (26)	60, Both	55.6 (int) 55.6 (cont) 31 (int) 33 (cont)	Iran	Parallel	Obesity	Zinc (30)	4	Placebo	Serum leptin level was significantly increased in the intervention group

Assessment of the risk of bias in included studies

Overall, all studies were categorized as unknown risk of bias. Seven studies did not mention enough information regarding the random sequence generation (25, 27, 39-41, 49, 50). One study only represented complete outcome information to conceal the allocation of participants (49) and was considered as low risk for this domain. Blinding of participants and personnel and outcome assessment was unclear in two studies (25, 39) (Table 2).

Meta-analysis

Overall result (244 participants) indicated no significant effect of zinc supplementation on serum leptin levels (WMD=0.60, 95% CI: -1.78, 2.99, P effect=0.620, number of studies=6). The heterogeneity was evident and significant between the included studies reported data for serum leptin (Q statistic=14.02, P for heterogeneity=0.015, I^2 = 64.3%) (Fig. 2).

Table 2: Study quality and risk of bias assessment by Cochrane Collaboration's tool

First author (year)	*Random sequence generation*	*Allocation concealment*	*Blinding of participants and personal*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective reporting*	*Quality score*	*Overall quality*
Bribieacas (2003) (39)	?[1]	?	?	?	+	+	2	Unclear
Garcia (2006) (49)	?	+	+	+	+	+	5	Unclear
Marreiro (2006) (41)	?	?	+	+	+	+	4	Unclear
Asghari (2011) (50)	?	?	+	+	+	+	4	Unclear
SoheilyKhah (2012) (25)	?	?	?	?	+	+	2	Unclear
Kim (2014) (40)	?	?	+	+	+	+	4	Unclear
Argani (2014) (27)	?	?	+	+	+	+	4	Unclear
Payaho (2014) (26)	+[2]	?	+	+	+	+	5	Unclear

[1] Unknown risk for each domain
[2] Low risk for each domain

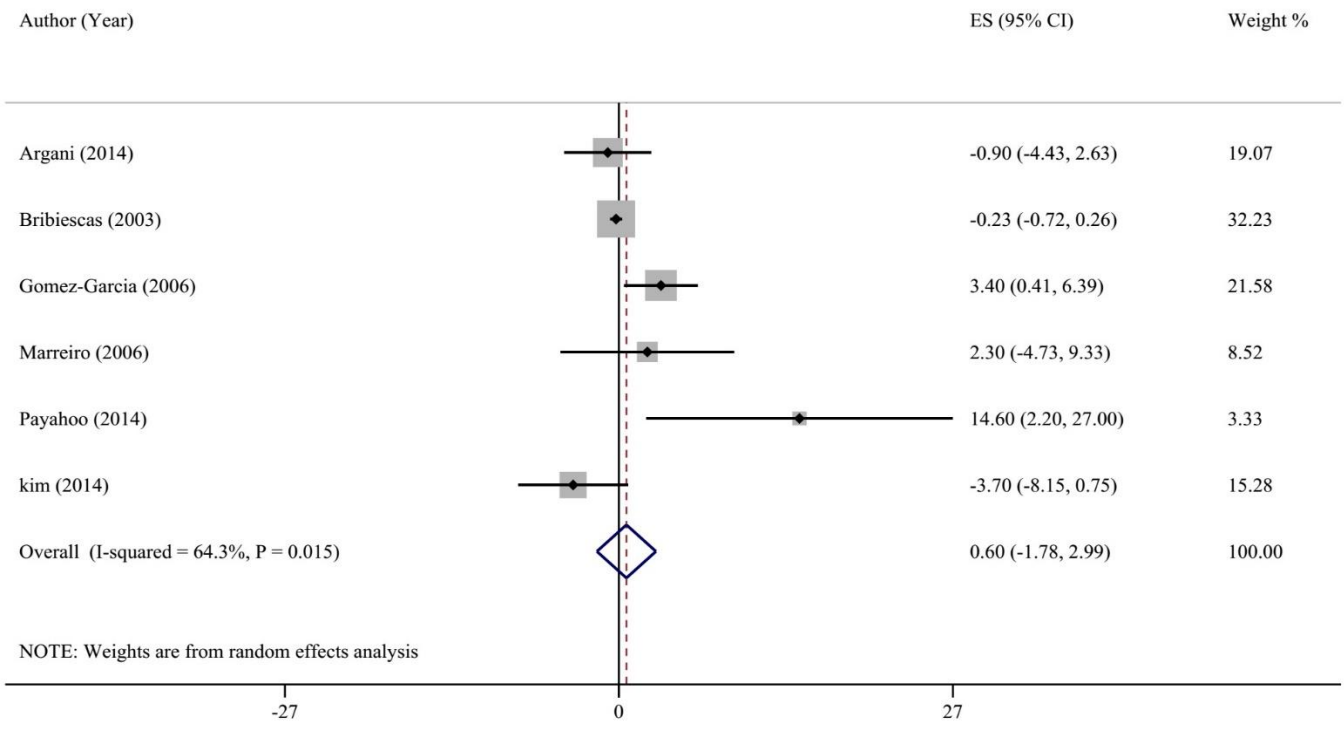

Fig. 2: Forest plot illustrating the weighted mean difference in leptin change between the zinc-supplemented and control groups

The meta-analysis on serum adiponectin levels included 158 participants. Overall result showed no significant effect (WMD=1.09, 95% CI: -0.76, 2.94, P effect = 0.246, number of studies=3); moreover, high heterogeneity for serum adiponectin was found (Q statistic =9.45, P for heterogeneity=0.009, I^2 = 78.8%) (Fig. 3).

The findings of analysis did not change based on different subgroups: gender, duration of intervention, healthy status (health, obese, diabetes, kidney disease) and the types of zinc supplementation; significant heterogeneity between included studies was associated with the zinc type used for supplementation (Table 3).

Table 3: Meta-analysis showing the effect of zinc supplementation on the serum leptin level based on several subgroups

Study group	***Number of studies***	***Number of participants***	***Meta-analysis***		***Heterogeneity***			
			WMD (95% CI)	*P* effect	Q statistic	*P* within group	I^2(%)	*P* between group
Overall	6	244	0.60(-1.78,2.99)	0.620	14.02	0.015	64.3	
Gender								0.613
Female	3	150	-1.58(-4.607,1.46)	0.309	2.10	0.350	4.6	
Male	3	94	0.69(-1.69,3.05)	0.571	5.61	0.061	64.3	
Both	2	60	5.66(-9.35,20.68)	0.460	5.55	0.018	82.0	
Duration								0.190
Short period(≤ 4 weeks)	4	144	2.48(-1.18,6.13)	0.184	11.37	0.010	73.6	
Long period(> 4 weeks)	2	100	-1.98(-4.75,0.79)	0.161	0.93	0.334	0.00	
Disease status								0.677
Patients on hemodialysis	1	60	-0.90 (-4.43,2.63)	0.617	0.00	--	--	
No hemodialysis	5	184	1.13 (-1.96,4.22)	0.475	13.85	0.008	71.1	
Obesity								0.093
Obesity	4	170	2.407(-2.96,7.77)	0.38	11.07	0.011	72.9	
Non-obesity	2	74	-0.24(-0.725,0.24)	0.324	0.14	0.712	0.0	
Zinc type								0.083
Zinc gluconate	3	110	-1.23(-4.31,1.85)	0.434	2.30	0.129	56.6	
Zinc sulfate	2	74	1.356(-2.85,5.56)	0.528	3.32	0.068	69.9	
Zinc elemental	1	60	14.6 (2.196, 27.0)	0.021	0.00	--	--	

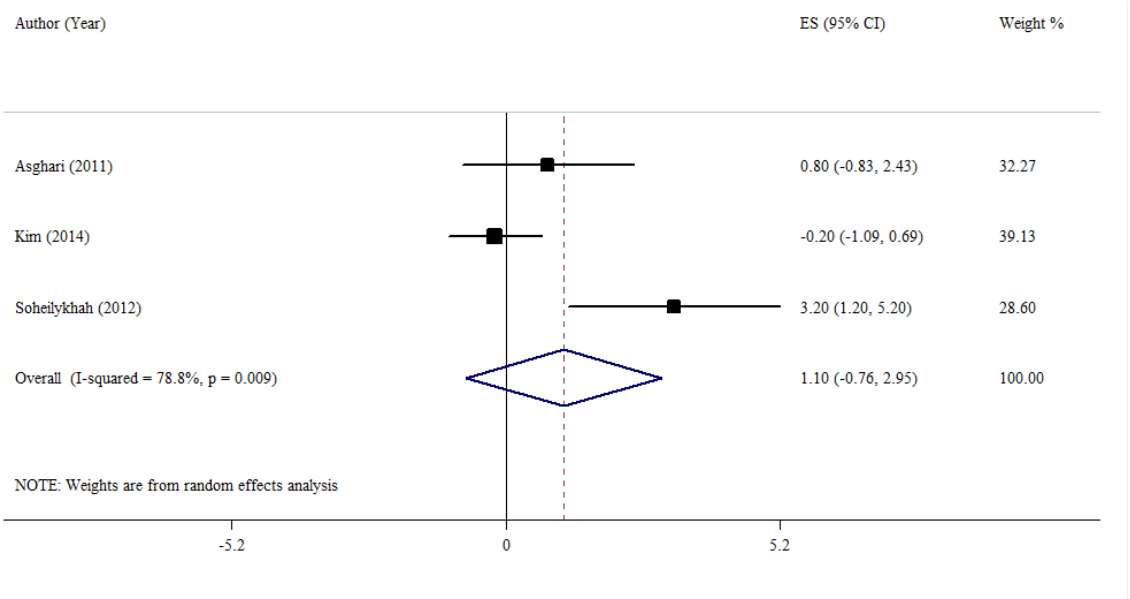

Fig. 3: Forest plot illustrating the weighted mean difference in adiponectin change between the zinc-supplemented and control groups

Sensitivity analysis and publication bias

Sensitivity analysis showed that excluding a certain study might not alter the effect of zinc supplementation on serum leptin or adiponectin levels. There was no evidence for publication bias in the included studies after checking this point by using funnel plots and asymmetry tests (Begg's test=0.707, Egger's test=0.406) (Fig. 4).

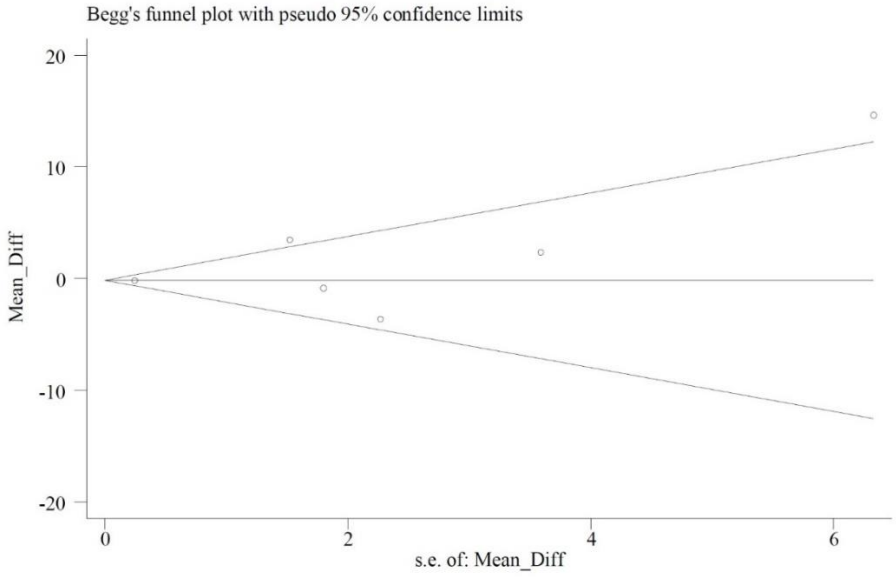

Fig. 4: Begg's funnel plot (with pseudo 95% Cis) depicting the difference in means versus the standard error of the mean differences for studies that assessed the effect of zinc supplementation on serum level of leptin. The historical line shows the weighted mean difference calculated using the DerSimonian and Laird random-effects model

Discussion

The present systematic review and meta-analysis of 8 RCTs demonstrated that zinc supplementation has no significant effect on serum leptin and adiponectin levels. This finding was consistent across several subgroups such as gender, obesity status, study duration, kidney disease, and the type of zinc supplementation.

These results are consistent with the findings from recent meta-analysis that the serum leptin level did not influence by zinc supplementation (42). The significant decrease in the serum leptin level following zinc supplementation when their analyses were restricted to female participants (42). This discrepancy is probably attributed to difference in method of calculating effect size. Present meta-analysis estimating mean difference and its SE using coefficient r retrieved from studies that reported baseline, after intervention and change values (39, 40); however, the previous meta-analysis did not mention any method for estimating effect size when eligible original studies did not provide change values. Moreover, zinc supplementation led to a decrease in the serum leptin levels in RCTs longer than 6 wk duration. It is not clear why 6 wk was considered as a cut-off to categorize studies based on their duration.

There are some reasonable explanations for the null effect of zinc supplementation on serum adipokines in the present study. First, the effect of zinc supplementation on serum levels of adipokines might be influenced by the serum zinc status. Zinc supplementation could be influenced on serum level of leptin in zinc deficiency status including hemodialysis or diabetes (23, 27, 50). However, all of the included trials did not describe the baseline zinc status of their participants.

Second, the effect of zinc supplementation on serum adipokines has been shown in a time-dependent manner. The dietary zinc supplementation (30 mg/day) showed its clinical effects on serum adipokines in studies extended more than 8 wk (40), while the effect of pharmacological zinc doses (more than 40 mg/day) might become apparent in 4 weeks (29). Third, the serum level of adipokines was not considered as a primary outcome for the estimation of the sample size. The sample size was small to detect the effect of zinc supplementation on serum level of adipokines.

The present study has some strong points. To the best of our knowledge, this study is the first meta-analysis on the effect of zinc supplementation on serum adiponectin levels. A robust search strategy was adopted to find all RCTs examining the effect of zinc supplementation on serum adipokines irrespective of considering adipokines as a primary or secondary outcome. The meta-analysis was conducted on RCTs that are considered as a gold standard study design to identify the clinical effectiveness of dietary supplementations. However, some limitations should be noted. A major concern is the small number of included trials that their quality was unknown based on Cochrane collaboration's tool; therefore, the present findings should be interpreted with caution. Moreover, there was significant heterogeneity across the studies that were not disappeared after several subgroup analyses; this suggests unmeasured confounders including zinc bioavailability, medications, and physical activity. Most of trials included in present meta-analysis used only zinc tablet counting to measure the adherence, while the serum zinc level as reliable surrogate biomarkers of zinc status was not chacked at the end of the follow-up. Future RCTs should use validated markers to demonstrate the participants' compliance to the intervention. In addition, the difference in the intake of zinc absorption inhibitors like dietary phytate and oxalate at least partly reduce the zinc bioavailability; however, this was not addressed in all trials.

Conclusion

Zinc supplementation has no significant effect on the serum level of leptin and adiponectin in the adults' population. However, several methodological limitations do not allow us to provide definite conclusion about the effect of zinc supplementation on the serum levels of adipokines. Further; high-quality, long-term, large-scale, randomized

clinical trials are warranted to provide a more decisive document of the effect of zinc supplementation on serum adipokines.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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