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The Effect of Zinc Supplementation on Serum Leptin Levels: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Recently, obesity has become a common worldwide concern. Leptin, as an adipocytokine, plays a major role in the etiology of obesity. Prior studies have demonstrated that zinc potentially affects serum leptin levels. However, clinical trials carried out in this regard are not consistent. Therefore, current meta-analysis was conducted to ascertain the actual effect of zinc supplementation on serum leptin levels in adults. Databases of PubMed, SCOPUS, and Google Scholar were methodically searched to identify relevant articles up to April 2018. Clinical trials that examined the effect of zinc supplementation on serum leptin concentrations as outcome variables in human adults were included. The mean difference (SD) of leptin changes in the intervention and placebo groups were used to calculate the overall effect size. Totally, 663 articles were identified, of which 6 studies were eligible randomized controlled trials (RCTs) with 7 treatment arms. The analysis suggested that zinc supplementation exerts no significant effect on overall serum leptin (WMD: 0.74 ng/ml; 95 % CI: − 1.39 to 2.87, p = 0.49). Nevertheless, sex and duration of intervention seemed to impact the extent of zinc's influence. In trials with female subjects, zinc consumption led to a significant decrease in serum leptin level (WMD: − 1.93 ng/ml; 95 % CI: − 3.72 to − 0.14, p = 0.03) as well as trials that lasted for more than 6 weeks (WMD: − 1.71 ng/ml; 95 % CI: − 3.07 to − 0.35, p = 0.01), in comparison to the control group. Zinc supplementation did not significantly improve leptin concentrations, but it may result in a decreased circulating leptin level in studies with a duration of more than 6 weeks especially among females.

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Introduction

Obesity is a pathological condition characterized by an imbalance between receiving and consuming energy. In 2016, World Health Organization reported that 650 million adults throughout the world were obese [1]. It has been established that obesity is a major contributor to mortality in developed countries [2]. Moreover, obesity is deemed as a risk factor for cardiovascular diseases, hypertension, diabetes mellitus and some cancers [3–5].

Several biological agents such as leptin and zinc-α_2-glycoprotein are implicated in body weight regulation and metabolic homeostasis [6–8]. For example, zinc-α_2-glycoprotein is involved in the regulation of adipose tissue metabolism [9, 10]. Leptin is a known adipokine that is implicated to have biological functions in inflammation, reproduction, angiogenesis and bone formation [11–14]. Leptin, as an indicator of adipose tissue mass, affects the hypothalamus through negative feedback, thus promotes satiety and subsequently reduces food intake [15, 16]. Moreover, high serum leptin level is associated with renal impairment [17]. Recently, the association between serum leptin level and several other elements such as zinc, has been extensively studied.

Zinc is a trace element and is required for the optimal activity of multitudinous proteins including enzymes, gene expression regulatory proteins, receptors, and membrane proteins. Thus, zinc participates in almost all the metabolic pathways [18]. Moreover, zinc affects insulin function and consequently carbohydrate metabolism [19, 20]. In some studies, low dietary intake and low serum level of zinc are associated with higher incidence of diabetes, insulin resistance, cardiac diseases, hypertension, and some cancers [21, 22]. Unlike some other elements, zinc is generally not stored in body, therefore, it should be received via food or supplement [23].

According to previous studies, zinc supplementation has a controversial effect on serum leptin levels. Zinc is connected to insulin signaling and in some situations like obesity and end-stage renal disease [24–28]. So far, zinc has been widely studied for its therapeutic and preventive features and its association with serum leptin level is investigated in several studies. Some of these trials found a direct association between zinc intake and leptin level [25, 29–31], while others, among which a study conducted on Ache males of eastern Paraguay, did not find such an association [26, 32, 33]. Serum leptin levels in patients with renal failure are higher than normal subjects due to renal filtration defects, and this leads to decreased appetite and protein-energy malnutrition in these patients. The study of Argani et al. showed that zinc supplementation decrease serum leptin levels [25]. According to Payahoo et al., leptin plays a key role in regulating body weight and fat mass by influencing appetite and fuel utilization, and zinc supplementation seems to increase serum leptin levels in obese individuals [28].

Due to the conflicting results, we performed a systematic review and meta-analysis of published randomized control trials (RCTs) to clarify the nature of the association between zinc supplementation and serum leptin level.

Materials and Methods

Search strategy

SCOPUS (http://www.scopus.com), Medline (http://www.ncbi.nlm.nih.gov/PubMed), and Google Scholar were searched to find all the relevant clinical trials up to April 2018. We used the following search terms in our search in the aforementioned databases: ("zinc [MeSH]" OR "zinc" OR "zn") AND ("leptin [MeSH]" OR leptin OR "leptin level" OR "adipokines"). Additionally, we also performed a hand-search of the reference lists of retrieved articles and previous reviews to include other potentially eligible trials. Language restrictions were not applied. Cochrane handbook for systematic reviews of interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed through all steps of the study [34, 35].

Selection criteria

Human trials were included in the meta-analysis if they fulfilled the following inclusion criteria: (I) were randomized clinical trials with either parallel or crossover designs in human adults; (II) reported corresponding serum leptin levels before and after intervention in each group; (III) compared oral zinc supplementation with the placebo group. Studies were excluded if they: (I) experimented other agents along with zinc; (II) were non-clinical trials; (III) did not provide sufficient information on leptin levels before and after the trial in placebo and intervention groups.

Data extraction and quality assessment

First author's last name, country of origin, publication date, study population, gender, sample size, zinc dose, treatment duration and means ± SD of leptin for intervention, and placebo groups before and after the trial were extracted from included studies. A first reviewer (MKh) performed the data extraction and numerical calculations, results were double-checked by a second reviewer (MZ). Discrepancies were resolved through discussion with a third reviewer (SMM). In trials with crossover design, only data from the first part of the study (before washout period) were considered for analysis.

The quality of eligible articles was assessed using the Jadad scale based on the description of randomization, allocation concealment, blinding, drop-outs and the presentation of an intention-to-treat analysis [36]; trials with 3 or more points and 2 or fewer points were considered as a "high" and "low" quality studies, respectively.

Statistical analysis

The effect size of meta-analysis was calculated based on mean differences and their corresponding standard deviations (SDs) of changes in leptin levels for both intervention and control groups [37]. In studies that reported the standard error of means (SEM), SD was calculated via multiplying SEM by the square root of the sample size: $SD = SEM \times \sqrt{n}$. The statistical and between-study heterogeneity was evaluated using the Cochran's Q-test and the I^2 index. Subgroup analysis was done to identify potential sources of heterogeneity; subgroups were based on the dose, trial duration, baseline BMI, gender, and mean age of participants. To investigate the influence of an individual study on the overall weight mean differences, a sensitivity analysis was performed. Meta-regression test

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using the unrestricted maximum likelihood method was used to assess the relation between pooled effect size and zinc supplementation dose and duration of treatment. Funnel plot and Egger's weighted regression tests were done to examine publication bias [38]. All statistical analyses were carried out via STATA software, version 14.0 (Stata Corporation, College Station, TX, USA). p-Values less than 0.05 were considered statistically significant.

Results

Study selection

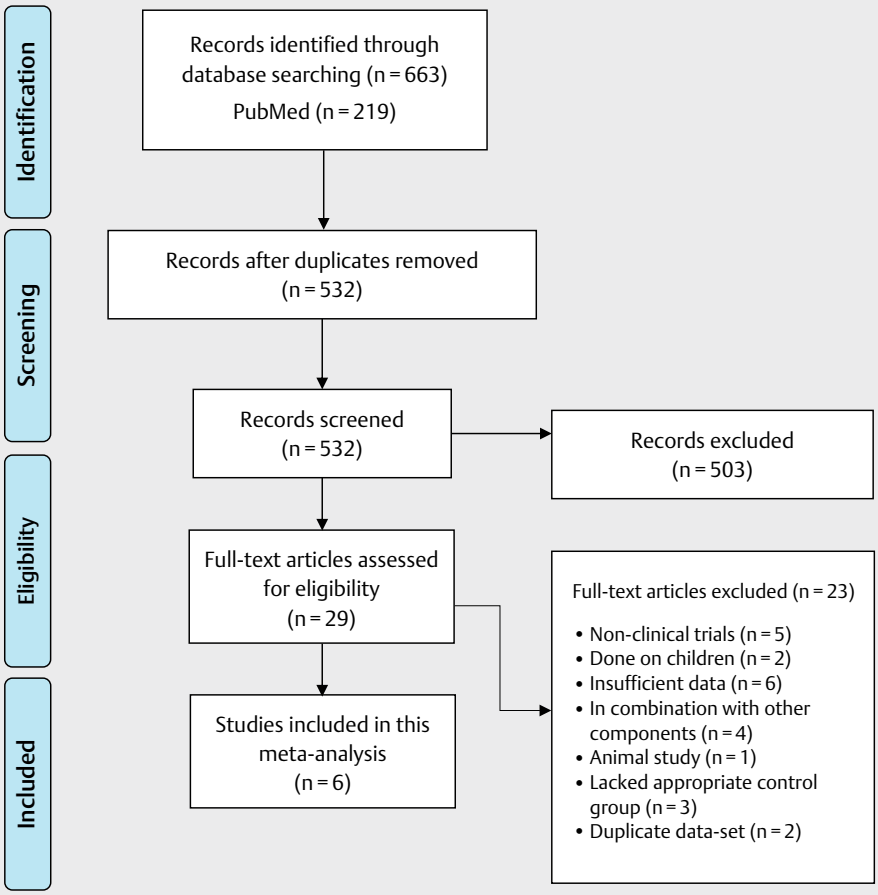
A total of 663 records including 219 from PubMed and 444 from the Scopus was identified following the initial literature search. The process of study selection is shown in ▶ **Fig. 1**. After removing 131 duplicate records, 532 articles were assessed based on title and abstract. Subsequently, after the title and abstract screening, 29 articles were retrieved for full-text assessment. Among these remaining records, 23 articles were excluded for the following reasons: were not clinical trials (n = 5), were animal studies (n = 1) or done on children (n = 2), not reporting sufficient data for baseline and/or final leptin levels (n = 6), done in combination with other components (n = 4), without placebo group (n = 3) and same population data set (n = 2). Finally, 6 eligible RCTs with 7 treatment arms were included in this meta-analysis.

Study characteristics

The demographic characteristics of eligible studies are outlined in ▶ **Table 1**. Overall 244 subjects were enrolled in these trials (67 % women). The mean age of the subjects ranged from 23–56.6 years old and the BMI was between 21.6 and 34.7 kg/m^2. Among these trials, 2 studies were carried out exclusively on women [39, 40], 2 on men [26, 31], one on both genders [28], and one study provided separate data for men and women, thus this study was counted as two studies [25]. The studies were published from 2003 to 2014; they were conducted in various countries including Paraguay [26], Mexico [31], Brazil [39], South Korea [40], and Iran [25, 28]. Included papers were randomized clinical trials, all with double-blinded design except one [26]. Four studies enrolled obese subjects [28, 31, 39, 40], one Ache males [26], and another one was done on hemodialysis patients [25]. Supplementation dose varied from 25–100 mg/d and intervention duration ranged from 10 days to 8 weeks.

The effect of zinc supplementation on serum leptin

Forest plot of the effectiveness of zinc supplementation on serum leptin is demonstrated in ▶ **Fig. 2**. The pooled estimate from the random-effect model which was performed on 7 studies with 121



▶ **Fig. 1** PRISMA flow chart of study selection process.

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cases and 123 controls, did not imply a significant change in serum leptin levels after zinc supplementation (WMD: 0.74 ng/ml; 95 % CI: − 1.39 to 2.87, p = 0.49). The effect size was unaltered after sensitivity analysis. Also, a significant between-study heterogeneity was found among studies (I^2 = 81.7 %, p = < 0.001).

Subgroup analysis

Considering that the supplementation dose, intervention duration, participants' gender, body mass index (BMI), and age may influence the net changes of leptin, we performed subgroup analysis on the basis of these variables to identify heterogeneity sources. Findings from subgroup analysis are displayed in ▶ **Table 2**. The subgroup analysis showed that the dose of zinc supplementation (≥ 50 mg/d: I^2 = 0.0 %, p = 0.75), intervention duration (≥ 6 weeks: I^2 = 43.8 %, p = 0.16), participants' gender (males: I^2 = 28.4 %, p = 0.24), mean age of subjects (≥ 45 years: I^2 = 0.0 %, p = 0.75), and baseline BMI (< 25 kg/m^2: I^2 = 0.0 %, p = 0.75) were the potential sources of heterogeneity. Among these, a treatment duration of greater than 6 weeks (WMD-1.71 ng/ml; 95 % CI: − 3.07 to − 0.35, p = 0.01) significantly reduced leptin concentration compared with shorter duration (WMD: − 0.16 ng/ml; 95 % CI: − 0.47 to 0.13, p = 0.27). In patients with female gender, also a significant reduction in leptin was observed (WMD: − 1.93 ng/ml; 95 % CI: − 3.72 to − 0.14, p = 0.03).

Meta-regression

Meta-regression analysis was used to investigate the relationship between changes in serum leptin levels and potential moderator variables. The results revealed that the pooled estimate is independent of zinc dose (slope: − 0.0601; 95 % CI: − 0.23, 0.11; p = 0.41) and treatment duration (slope: − 0.8642; 95 % CI: − 2.99, 1.26; p = 0.34; ▶ **Fig. 3**).

Publication bias

Visual inspection of funnel plot was not indicative of a significant publication bias in this meta-analysis (▶ **Fig. 4**). This observation was also upheld by the Egger's linear regression (p = 0.53).

Discussion

The present meta-analysis was conducted on 6 eligible studies (with 7 treatment arms) to determine the direction and magnitude of zinc's influence on serum leptin. To the best of our knowledge, this is the first meta-analysis of RCTs on this topic. Results showed no significant association between oral zinc supplementation and serum leptin level. Nevertheless, in subgroup analyses based on intervention duration and gender, there was a statistically significant reduction in serum leptin in studies lasted for more than 6 weeks and carried out on women.

Nowadays, obesity has become one of the most challenging issues in health-care field. Complications of obesity such as hypertension, hyperlipidemia, diabetes, etc. are themselves risk factors for many conditions and thus may lead to substantial mortality [41]. Leptin serves as a biomarker of overweight and obesity and is secreted from adipose tissue. At the cellular level, it seems to regulate food intake and energy expenditure via different signaling pathways [42]. Moreover, leptin affects the function of other organs in pulmonary, circulatory, reproductive, and nervous systems

▶ **Table 1** General characteristics of the included studies.

First author (year) [Ref.]	Location	Study design	Gender	Mean age (year)	Baseline BMI	Patient features	Sample size	Duration (week)	Dose (mg/d)	Baseline leptin levels (ng/ml)	Jaded score
Bribiescas et al. (2003) [26]	Paraguay	Randomized, clinical trial	Males	47.2	22.8	Ache males	14	1.5	50	1.34	2
Gomez-Garcia et al. (2006) [31]	Mexico	Randomized, double-blinded, placebo-controlled	Males	25.5	30.7	Obese males	14	4	25	16.4	3
Marreiro et al. (2006) [39]	Brazil	Randomized, double-blinded, placebo-controlled	Females	35.5	35.8	Obese Women	56	4	30	23.6	3
Kim et al. (2012) [40]	South Korea	Randomized, double-blinded, placebo-controlled	Females	23	28.25	Obese Women	40	8	30	19.22	4
Argani et al. (2014) [25]	Iran	Randomized, double-blinded, placebo-controlled	Males	55.6	22.5	Hemodialysis patients	36	8	100	6.4	3
Argani et al. (2014) [25]	Iran	Randomized, double-blinded, placebo-controlled	Females	55.6	21.6	Hemodialysis patients	24	8	100	9	3
Payahoo et al. (2014) [28]	Iran	Randomized, double-blinded, placebo-controlled	Both	31.8	34.7	Obese subjects	60	4	30	35.8	3

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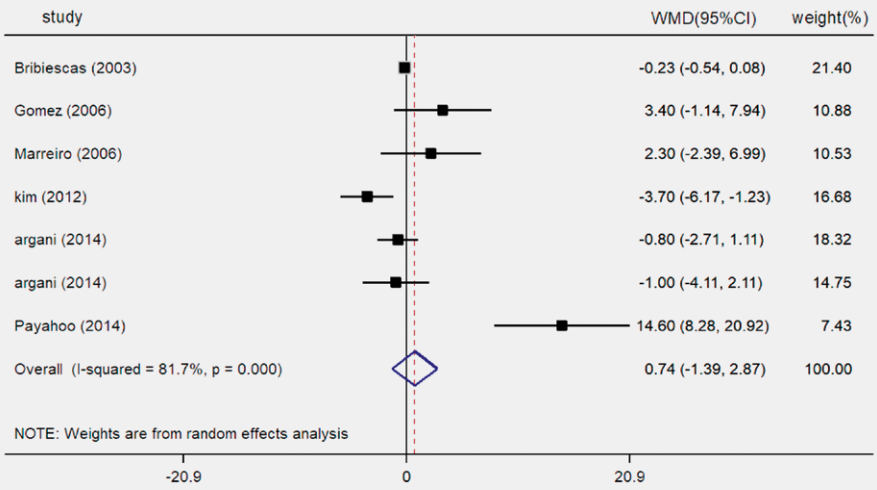

▶ **Fig. 2** Forest plot detailing weighted mean difference and 95 % confidence intervals for the impact of supplementation with zinc on serum leptin levels.

▶ **Table 2** Pooled estimates of effects on leptin within different subgroups.

Group	No of comparisons	WMD (95 % CI)	p-Value	p-Heterogeneity	I^2 (%)
Total	7	0.737 (−1.395, 2.869)	0.498	<0.001	81.7
Zinc dosage (mg)					
<50	4	0.102 (−1.779, 1.983)	0.915	<0.001	90.7
≥50	3	−0.251 (−0.551, 0.049)	0.101	0.757	0.0
Intervention duration (week)					
<6	4	−0.169 (−0.472, 0.134)	0.275	<0.001	87.8
≥6	3	−1.718 (−3.079, −0.356)	0.013	0.169	43.8
Gender					
Male	3	−0.228 (−0.529, 0.072)	0.137	0.247	28.4
Female	3	−1.934 (−3.723, −0.145)	0.034	0.066	63.2
Mean age					
<45	4	0.102 (−1.779, 1.983)	0.915	<0.001	90.7
≥45	3	−0.251 (−0.551, 0.049)	0.101	0.757	0.0
Baseline BMI					
<25	3	−0.251 (−0.551, 0.049)	0.101	0.757	0.0
≥25	4	0.102 (−1.779, 1.983)	0.915	<0.001	90.7

[43]. In obese individuals, leptin is elevated as a result of low sensitivity to circulating leptin. This low sensitivity might account for the decreased efficacy of leptin in suppressing food intake in these patients [44]. It has been suggested that leptin and insulin are biologically linked and affect each other and they both are implicated in the pathophysiology of obesity [45]. As a trace element, Zinc serves several important functions in the body; its role has been established in metabolism, appetite, taste, skin and hair health, the function of various enzymes and above all, insulin performance [46–48]. It has been shown that zinc impacts insulin's production, storage, and release and seems to decrease insulin sensitivity [49]. Accordingly, an association between zinc itself and leptin might exist which may consequently affect obesity.

In vitro and in vivo studies indicated that zinc deficiency seems to decrease expression of leptin gene. In an animal study, zinc deficiency caused a decrease in leptin gene expression, synthesis, and secretion corresponding to adipose tissue mass in rats [50]. Also, Kwun et al. showed that mRNA of leptin significantly decreased following zinc deficiency in rats [51].

Argani et al. showed that 100 mg daily oral zinc supplementation for 8 weeks significantly decreased mean leptin level in hemodialytic women [25], however, in another study, daily supplemen-

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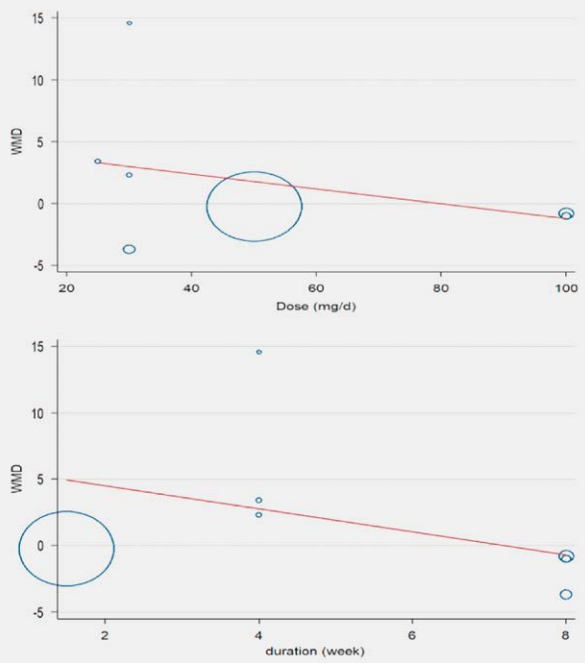
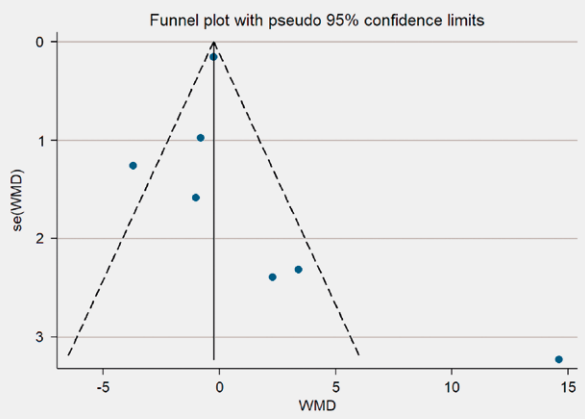


▶ **Fig. 3** Meta-regression plots of the association of mean changes in serum leptin levels with dose and duration of zinc supplementation.



▶ **Fig. 4** Funnel plot displaying publication bias in the studies reporting the impact of zinc on serum leptin levels.

tation with 30 mg of zinc for 4 weeks did not change leptin levels significantly in obese women [39]. Moreover, zinc supplementation did not change leptin levels in Ache males [26]. On the contrary, Payahoo et al. showed that daily supplementation with 30 mg of zinc significantly increased leptin level in obese subjects [28].

According to the results of subgroup analysis based on gender, zinc supplementation significantly decreased leptin levels in women. Physiologically, leptin levels are higher in women than in males due to the higher fat mass in women. Considering that women had a higher baseline of leptin [52], the amount of reduction in leptin was statistically significant in comparison to that in men. Also, in studies that lasted for more than 6 weeks, zinc supplementation led to a significant decrease in leptin level. Zinc reduces leptin through gene expression of involved enzymes or proteins, this possibly explains the significance of results with longer duration. These results also indicate that zinc supplementation may be beneficial for patients with renal insufficiency, because of the impairment in glomerular filtration, the level of leptin in these patients increases, which can reduce appetite and subsequently increase protein-energy malnutrition [53].

The current study has some limitations that should be noted. The included RCTs possessed relatively small sample sizes (only one study had 60 patients), which resulted in poor statistical power to detect meaningful effects in individual trials and in the overall analysis. In addition, the eligible trials were heterogeneous due to the sample size, dose, and duration of intervention, gender and age of participants. Also, various chemical forms of zinc have been used in included studies including gluconate, acetate, and sulfate, which have different oral absorption, and bioavailability. According to the WHO, zinc sulfate (23 % zinc), zinc acetate (30 % zinc), and zinc gluconate (14 % zinc) have similar bioavailibilities. [54].

Conclusion

Results from this meta-analysis did not support the notion that zinc supplementation may tend to decrease serum leptin level. However, zinc supplementation may significantly reduce leptin in females and in interventions with duration of more than 6 weeks. Additional studies with larger sample sizes, different doses, and duration should be performed to approve our findings.

Author Contributions

MKh designed and SMM supervised the study. MZ, AS, and JR conducted literature searches, data extraction, and independent search and reviewing. AT, NA, and HKV performed the statistical analysis and composed the initial draft of the manuscript. All authors read and approved the final version of the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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