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Review

The effect of zinc supplementation on plasma C-reactive protein concentrations: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Previous studies have shown zinc has potential anti-inflammatory and anti-oxidative effects. However, findings from clinical trials about the effect of zinc on plasma C-reactive protein (CRP) appeared inconsistent and uncertain. Therefore, the aim of this meta-analysis was to summarize the effect of zinc supplementation on plasma CRP concentrations in adults. The literature search through PubMed, SCOPUS, and Google Scholar were done to find published studies up to October 2017. Random or fixed-effects model depending on the results of heterogeneity tests were used to estimate the pooled effect size. Between-study heterogeneity was assessed using Cochran's Q test and I^2 index. Funnel plot and Egger's regression test were used to assess publication bias. Our search found 1505 publications, of which 8 randomized controlled trials (RCTs) were eligible to be included in the analysis. The results of the meta-analysis displayed a significant reduction in circulating CRP levels (WMD: − 1.68 mg/l; 95% CI: − 2.4 to − 0.9, P = < 0.001) following zinc supplementation. In the subgroup analysis, supplementation dosage, study quality, study population, and baseline CRP level were the potential sources of heterogeneity. Participants took equal to 50 mg/d zinc (WMD: − 1.97 mg/l; 95% CI: − 2.28 to − 1.67, P = < 0.001), low quality studies (WMD: − 2.9 mg/l; 95% CI: − 3.68 to − 2.12, P = < 0.001) and those with renal dysfunction (WMD: − 7.43 mg/l; 95% CI: − 12.57 to −2.29, P = 0.005) showed greater improvement in CRP levels. In conclusion, zinc supplementation may have a beneficial effect on the serum CRP, especially at doses equal to 50 mg/d and in renal insufficiency patients compared with healthy subjects.

1. Introduction

Inflammation which characterized by the innate response to harmful stimuli like pathogens, injury, and metabolic stress, plays an important role in innate immunity (HogenEsch et al., 2017). Even though inflammation is an indispensable part of the host defense system, it has been proved that low-grade inflammation might trigger a wide range of chronic diseases such as cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM) and other metabolic illnesses (Esser et al., 2015; Shukla et al., 2016). Cardiovascular disease is one of the leading causes of mortality and morbidity worldwide (Kovacic et al., 2012). According to the recent WHO report, CVDs are accountable for 31% of all global deaths (Mensah, 2017). C-reactive protein (CRP), secreted by the liver in response to factors released by macrophages and adipocytes, is a protein that increases in the blood with inflammation and infection as well as following a heart attack, surgery, or trauma (Koenig et al., 1999; Lau et al., 2005; Póvoa, 2002). Hence, it is one of the several proteins that are often mentioned as acute phase reactants (Steel and Whitehead, 1994). The high-sensitivity CRP test measures low levels of CRP in the blood to identify low levels of inflammation that are linked to the risk of developing cardiovascular disease (Ridker, 2001). CRP is a systemic marker of inflammation and a strong predictor of CVDs risk compared with other inflammatory markers (Ridker et al., 2000; Xu et al., 2003). Kaptoge et al. (2013) in a recent meta-analysis noted that increased serum of CRP was strongly and positively correlated with CVD risk.

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Zinc is an essential micronutrient which has anti-inflammatory and anti-oxidative properties in the human body (Bozalioğlu et al., 2005; Prasad, 2008). It expresses molecular signal for immune cells and many transcription factors that involved in gene expression of inflammatory cytokines (Prasad, 2014b). Moreover, several studies have shown that zinc deficiency causes an increase in the concentrations of inflammatory cytokines, oxidative stress and immune dysfunction (Prasad, 2014a; Wong et al., 2013). Zinc supplementation studies have shown decreased oxidative stress and decreased generation of inflammatory cytokines in a different group of the population (Bao et al., 2010a; Kim and Ahn, 2014; Tabrizi et al., 2011). In contrast, some other studies revealed that zinc supplement has not changed serum CRP levels (Jamilian et al., 2016; Rashidi et al., 2009).

Differences among studies in supplementation dosage, length of intervention, and health status of the participant may yield an inconsistency in the actual effect of zinc supplementation in reducing CRP level. In the present study, we performed a systematic review and meta-analysis of published RCTs to evaluate the quantitative effect of zinc supplementation on CRP level.

2. Materials and methods

The Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) statement guideline was followed to perform and report this systematic review meta-analysis (Moher et al., 2009).

2.1. Search strategy

We systematically searched online medical search engines including PubMed, SCOPUS, and Google Scholar until 11 October 2017. There were no language or calendar date restrictions. In our searched strategy, we used a combination of Medical subject headings (MeSH) and non-MeSH terms by following keywords: (("Zinc"[Mesh]) OR zn [Title/Abstract])) AND (("C-Reactive Protein"[Mesh]) OR ("high-sensitivity CRP"[Title/Abstract]) OR ("hs-CRP"[Title/Abstract]) OR ("CRP"[Title/Abstract])). In addition, we manually reviewed reference lists from the retrieved articles, systematic reviews, and meta-analyses to avoid missing any pertinent articles. Unpublished articles and grey literature such as conference papers, theses, and patents were not included in the study.

2.2. Eligibility criteria

We included studies that met our inclusion criteria, which were as follow; 1) randomized controlled trial studies (either parallel or cross-over design) 2) Intervention with zinc as supplement (we considered studies that the supplement adjunct to another supplement/drug in both treatment and placebo groups) 3) reported sufficient information about serum CRP at baseline and end of the intervention in zinc and the placebo groups 4) done on adult subjects (> 18 years) 5) were published in English. We excluded publications that had the following criteria: 1) non-RCTs studies 2) done on children, pregnant women, or animals 3) investigated the effect of other interventions along with zinc in cases but not in placebo group 4) studies without placebo group 5) did not report CRP concentrations at baseline and end of the intervention. 6) were performed on patients with severe inflammation (CRP ≥ 20 mg/l).

2.3. Data extraction

Two investigators (SMM and AM) independently abstracted articles for eligibility and resolved discrepancies by consensus. Any controversy among authors was discussed and eventually resolved and confirmed by a third reviewer (SS-b). The relevant data were extracted from each study including: general characteristics of the study and population (the first author's name, country, publication's year, study design, type of study population, number of cases and controls, participants' mean age and gender, intervention duration and dosage of zinc supplements) and results (means and standard deviations (S.D) of CRP before and after intervention and/or the changes between pre- and post-intervention). The reported concentration of CRP in all studies were converted into the usual unit (mg/l).

2.4. Quality assessment

The quality of studies was evaluated by using Jadad scoring system (Jadad et al., 1996). This scale consists of 5 questions in which 0 or 1 points were given for each of the following questions: 1) randomization 2) the of use proper method for randomization 3) double-blinding 4) the use of proper method for double-blinding 5) description of withdrawals and dropouts with suitable reason (Jadad et al., 1996). Scores ≥ 3 and < 3 were considered as high-quality and low-quality studies, respectively (Moher et al., 1999).

2.5. Data synthesis and statistical analysis

The mean change (S.D) for CRP concentration, were used to estimate the overall effect size of the intervention. If S.D was not reported in each of individual study; it was calculated using following formula: $S.D_{change}$ = square root $[(S.D_{baseline}^2 + S.D_{final}^2)-(2 \times R \times S.D_{baseline} \times S.D_{final})]$. A correlation coefficient of 0.8 was considered as R-value of the above-mentioned formula (Borenstein et al., 2009). Where standard error of mean (S.E.M) was only reported, standard deviation (S.D) was calculated by $S.D = S.E.M \times \sqrt{n}$ (n is the number of participants in each group). Finally, in studies which only reported outcome measure in graphic form, data extraction was performed by using GetData Graph Digitizer 2.24 (Fedorov, 2002).

Estimates of effect sizes were expressed based on weighted mean difference (WMD) and 95% CI from the random-effects model. Assessment of between-study heterogeneity was carried out using Q test and I-square (I^2) test (Higgins et al., 2003). Pre-defined subgroup analysis based on zinc dosage, duration of intervention, baseline CRP level, mean age, gender, study population, and study quality was conducted to detect potential sources of heterogeneity. The sensitivity analysis was conducted by the one-study remove (leave-one-out) approach, to explore the impact of each study on the pooled effect size. Publication bias was evaluated using visual assessment of funnel plots and Egger's weighted regression tests. All statistical analyses were performed using Stata software version 12 (StataCorp. College Station, Texas, USA). $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Study selection

Of 1505 articles which found in our primary search, after removing 327 duplicates, 1178 publications remained. On the basis of title and abstract screening, 1140 irrelevant articles were excluded. Finally, 38 potentially relevant articles were selected for full-text review. 30 studies were removed for the following reasons: were done on children (n = 9) and pregnant women (n = 1), did not report CRP concentration (n = 5), zinc supplementation was done in combination with other components (n = 4), lack of the placebo group (n = 2), did not provide sufficient data at the end of the intervention (n = 2), non-trials in design (n = 4), and studies were done on patient with severe conditions (n = 3). Therefore, 8 eligible RCTs were included in this meta-analysis. The flow diagram of study selection is displayed in Fig. 1.

3.2. Study characteristics

The general characteristics of the included studies are shown in Table 1. Data were pooled from 8 eligible studies including 417 subjects

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