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INFLAMMATORY AND STRESS OXIDATIVE IMPROVING POTENTIAL OF CHROMIUM SUPPLEMENTATION: PROTOCOL FOR A SYSTEMATIC REVIEW AND META ANALYSIS OF RANDOMIZED CLINICAL TRIALS

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Abstract

In modern and machinery life, it has been established that inflammatory reactions and oxidative stress play an important role in the onset and progression of numerous common metabolic diseases. Environmental factors such as dietary factors are underlying these modern diseases.

In this systematic review and meta analysis, clinical randomized trials of effect of chromium supplementation on inflammatory and stress oxidative indices will be searched by the prespecified search strategy in PubMed, Scopus, International Scientific Indexing, Proquest, Cochrane, clinical trial.gov and Google Scholar. Quality (risk of bias) of relevant articles will be assessed by Cochrane software. Design ,disease type, sample size, supplement dose, study duration, before and after intervention mean ± standard deviation of outcomes (inflammatory cytokines and stress oxidative mediators) will be extracted from included studies. The overall effect size of intervention will be expressed as weighted mean differences in the Random Effect Model. Subgroup analyses will be based on the dosage and duration of chromium supplementation, health condition of the participants, study location and sample size. The comprehensive meta-analysis software will be used for data analysis. P values <0.05 will be considered as statistically significant.

Keywords:*chromium, inflammation, stress oxidative, systematic review, meta analysis, protocol.*

Introduction

Inflammation, immune system reaction to maintain the body function against hemostatic imbalance, is often associated with acute inflammatory and increase of inflammation-mediated cytokines due to infection or tissue damage [*Chung H et al., 2009*]. Low-grade, chronic inflammation is less well known. While this inflammation, evidence suggests that plays a major role in the development of many current non-communicable diseases, including cardiovascular dis-

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ease [*Pearson T et al., 2003*], type 2 diabetes [*Sarangi R et al., 2012*], cancers [*Shivappa N et al., 2016*], Crohn's disease [*Strober W et al., 2010*] asthma and chronic obstructive pulmonary disease [*Thomas M, Taylor D, 2011*] and even depression [*Leighton S et al., 2018; Eyre H et al., 2016*]. Systematic review and meta-analyze studies have also shown the association of increase of inflammatory cytokines including tumor necrosis factor-alfa (TNF-α), interleukin 1 and 6 (IL-1, 6) and C-reactive protein (CRP) with pathological mechanisms of mentioned diseases, in practice [*Pearson TA., 2003; Il'yasova D et al., 2005; Liu C et al., 2016*]. It should be noted that not all cytokines are inflammatory, such as Adiponectin, but, is anti-inflammatory [*Liu C et al., 2016*].

Oxidative stress is a condition of physiological status in which production and accumulation of active oxygen species and free radicals exceed from the neutralizing capacity of enzymatic and non-enzymatic anti oxidative defense system of the body [*Forcados G et al., 2016; Sies H et al., 2017*]. Some of antioxidant defenses are included of glutathione peroxidase, superoxide dismutase, catalase, albumin, some vitamins and minerals [*Namazi N et al., 2017; Heshmati J et al., 2018; Slominski A et al., 2017*]. Although a fraction of active oxygen species are needed to activate the signaling pathways and regulate the physiological and biological processes such as cell proliferation and host defense mechanisms [*Zuo L et al.,2015; Hasani M et al., 2019*], its high amounts, degrades proteins, carbohydrates and lipids biomolecules and even Dinucleic acid of cells. This condition eventually leads to a variety of cancers, including breast, colon, liver, lung, ovarian, prostate and brain cancer [*Oh B et al., 2016; Saijo H et al., 2016; Wang Z et al., 2016; Jaroonwitchawan T et al., 2017; Lee J et al., 2017; Saed G et al., 2017; Zhang L et al., 2017*]. Genetic, exposure to radiation, environmental toxins, inactivity and nutrition affect the balance of oxidant and antioxidant capacity of the body [*Schieber M, Chandel N, 2014*]. Therefore, from role of food and nutritional factors in controlling the inflammation and oxidative stress in the body, some components of the our diet are considered as antioxidants and some as pre-oxidant. Excessive intake of fats and carbohydrates and to a lesser extent, proteins and amino acids gradually exceeds of the mitochondrial oxidative phosphorylation capacity of cells and inevitably electron-carrying oxygen molecules enter the bloodstream, increasing the oxidative state of the blood. Thus, increasing of the oxidative stress and inflammation in conditions of overnutrition and overweight and obesity is quite justifiable. In addition, Excess macro nutrient intake, also leads to increased production of active oxygen species and free radicals by lipid peroxidation and carboxylation of proteins in leukocytes [*Dandona P et al., 2001; Ceriello A et al., 2004; Wallace J et al., 2010*].

Trivalent chromium, a trace element, there is in various food sources such as meats, grains, fruits, seeds and nuts and brewer's yeast [*Hadaegh F et al., 2009*]. Its absorption rate is 0.4 to 2.5%, while the daily required is up to 35$^{\mu g}$. It's absorption through high dose supplement is almost similar to the absorption from foods. Because of well tolerable of this micronutrient and no any case has been reported from the side effects of high dose intake, upper limit of its intake has not been set [*Mahdi G,1995; Vincent J, 2019*]. Chromium supplementation is believed to be effective in improving the glucose metabolism, insulin sensitivity , lipid profile, weight loss, body composition and inflammation, but there is no conclusive scientific evidence [*Cheng H et al., 2004; Farrokhian A et al., 2020; Kooshki F et al., 2021*]. Some clinical trials showed the effect of chromium supplementation on the reduction of oxidative stress and inflammation markers [*Anderson R et al., 2001; Racek J et al., 2006; Lai M, 2008; Jain S et al., 2012; Chen Y et al., 2014; Saiyed Z, Lugo J, 2016; Jamilian M et al., 2018; Pingali U et al., 2021*], while in other clinical trial studies, its effect was not confirmed [*Jamilian M et al., 2016; Amiri Siavashani M et al., 2018*]. According to a recent systematic review and meta-analysis study, chromium supplementation reduced significantly the inflammatory mediators C-reactive protein and tumor necrosis factor-alfa and not interleukin-6 as one of the major inflammatory mediators [*Zhang X et al., 2021*]. Also, in another systematic review and meta-analysis, chromium supplementation increased total antioxidant capacity, glutathione as the antioxidant enzymes , but not other antioxidant defense enzymes including superoxide dismutase, catalase, glutathi-

one peroxidase, as well as malondialdeide, total antioxidant status and thiobarbituric acid reactive substances as end products of lipid peroxidation [*Amini M et al.,2021*].

One of the latest systematic review study and meta-analysis of clinical trial studies, showed that chromium supplementation has an effect only on malondialdeide and total antioxidant capacity, but not on catalase, glutathione peroxidase, glutathione, superoxide dismutase and thiobarbituric acid reactive substances [*Morvaridzadeh M et al., 2022*].

Although, the effect of chromium supplementation on inflammation indices and oxidative stress has been evaluated in systematic review studies separately , but to our best knowledge, no study has evaluated the effect of chromium on biomarkers of oxidative stress and inflammatory cytokines together, so this systematic review and meta analysis will asess the anti inflammatory anti stress oxidative effects of chromium supplementation in randomized clinical trials.

Materal and methods

Research Objective:

Primary aim of this systematic review and meta analysis is evaluating the effect of oral chromium supplementation on blood concentration of inflammatory cytokines including interleukins, tumor necrosis factor-alfa, C-Reactive Protein, monocyte chemo attractant protein-1, intercellular adhesion molecule-1, adipocytokines, nuclear factor kappa-light-chain-enhancer of activated B cells and oxidative stress indicators including malondialdehyde, catalase, glutathione, glutathione peroxidase, superoxide dismutase, total antioxidant capacity, total antioxidant status, thiobarbituric acid reactive substances, 8-hydroxy deoxy guanosine. It should be noted that if new relevant variables are identified during the review of eligible randomized clinical trial studies, will be added to the list of primary outcomes.

Types of studies: According to the title of our manuscript, only randomized clinical trials with a placebo group can be included to minimize possible study biases. Considering that in this systematic review and meta-analysis, the effect of chromium supplementation on inflammation mediators and oxidative stress indices will be investigated and for each of these indicators, systematic review and meta-analysis has been done in the past, separately, so finding the relevant articles will not be difficult.

Search strategy: A comprehensive search of text words of “chromium” as independent variable and inflammatory cytokines and oxidative stress indexes as dependent keywords “inflammat*” OR “cytokine” OR “interleukin-*” OR “tumor necrosis factor-alfa” OR “TNF-*” OR “IL-*” OR “C-reactive protein” OR “CRP” OR “hs- CRP” OR “monocyte chemo attractant protein-1” OR “monocyte chemo attractant protein-1” OR “intercellular adhesion molecule-1” OR “intercellular adhesion molecule-1” OR “adipocytokine” OR “adipokine” OR “nuclear factor kappa-light-chain-enhancer of activated B cells” OR “ nuclear factor kappa-light-chain-enhancer of activated B” OR “oxidative stress” OR “malondialdehyde” OR “malondialdeide” OR “glutathione” OR “glutathione” OR “glutathione peroxidase” OR “glutathione peroxidase” OR “nitric oxide” OR “NO” OR “total antioxidant capacity” OR “total antioxidant capacity” OR “total antioxidant status” OR “total antioxidant status” OR “thiobarbituric acid reactive substances” OR “TBARS” OR “superoxide dismutase” OR “superoxide dismutase” OR “catalase” OR “catalase” OR “8-hydroxy deoxy guanosine” OR “8-HDG”) only in randomized controlled trials not in animal or histological calture studies without limitation of language and date of publication will be done in valid scientific databases including PubMed, Scopus, International Scientific Indexing, Proquest,Cochrane and Google Scholar. Clinical trial.gov will be also searched for inclusion of unpublished studies. The search strategy is shown in supplemental table.

Inclusion criteria: In this systematic review and meta analysis, title and abstract of all randomized controlled, double-blind trials of any form of dietary chromium^{+3} supplement including chromium picolinate, chromium nicotinate, chromium polynicotinate, chromium chloride, chromium histidinate and brewer’s yeast, on patients or healthy subjects such as athletes with intervention duration at least 2 weeks and with any publication language will be screened by two authors (Mozaffari-Khosravi H.and Ebrahimzadeh kour B.) independently. Articles with language other than English , will be

translated into English and if have other inclusion criteria of our study, the required data will be extracted. The reference lists of all included, similar and review articles will be screened to achieve maximum qualified papers.

Exclusion criteria: In this systematic review and meta-analysis study, all animal studies, case reports/series, observational studies and clinical studies with no randomization and with no placebo group and intervention duration less than 2 weeks will be excluded.

Study screening: Using above mentioned pre-prepared search strategy, the relevant articles will be extracted from each of the above databases and article information including title, authors, abstract, publication year and journal specifications including volume and number and print pages of all articles extracted from all databases will be entered in Endnote software and due to the possibility of definitive over lap of databases, in the first stage, duplicate articles will be removed and then by carefully reading the abstracts by three authors, the qualified articles for our study will be extracted. Quality of relevant papers, will be assessed based on Cochrane criteria [*Higgins J et al., 2011; Mansournia M et al., 2017*]. According to this guideline, any source of bias is included the selection bias, performance bias, detection bias, attrition bias, and reporting bias. In simple terms, based on this tool, the validity of clinical trials will be measured based on the following seven criteria of randomization generation, allocation concealment, blinding of outcome assessors, blinding patients/study personnel, incomplete outcome data (that is, lost to follow-up, selective outcome reporting,and other risks of bias. Quality evaluation team will be 2 independent reviewers (Jambarsang S. and Ebrahimzadeh kour B.). When the two researchers' opinion differed about the quality of an article, the third researcher (Mozaffari-Khosravi H.) will judge between them. If randomized controlled trial containing > 1 intervention group, each of them were deemed independent datasets. According to the guidelines of the Cochrane tool, screened articles will be divided into three groups in terms of risk bias: low risk, high risk andor unclear risk (when it neither fits the low or high risk of bias category). Details on how to assess the bias risk and how to segment and interpret the results have already been detailed ,elsewhere[*Moher D et al., 2009*].

Data Extraction: The data including first author's name, participants characteristics (age, gender,race), year and country of publication, study design, ,disease type, sample size, supplement dose, study duration, before and after intervention mean± standard deviation (SD) of studied outcomes (inflammatory cytokines and stress oxidative mediators) will be extracted . Mean change of outcomes will be calculated by following formula:

(after intervention amount of variable − before intervention amount of variable in the supplement group) − (after intervention amount of variable − before intervention amount of variable in the placebo group)

If standard deviation of the mean difference do not be reported , will be calculated by following formula:

$$SD^2 = ((SD_{besline})^2+(SD_{final})^2 - (2R\times SD_{besline}\times SD_{final}).$$

A crrelation coefficient of 0.8 will be considered as R-value in this formula. The Standard Errors (SEs), interquartile ranges (IQR) and 95% confidence intervals were converted to SDs.

$IQR=Q_3 - Q_1$

$SD=IQR/1.35$

$SD=SE\times\sqrt{n}$

(n = the number of individuals in each group).

$SD=\sqrt{n}(Upper\ limit- Lower\ limit)/3.92$

For large sample size>100 in each group, in 90% confidence intervals 3.92 should be replaced by 3.29, and for 99% confidence intervals it should be replaced by 5.15. If the sample size is small, 4.128 must be considered as the divisor [*Higgins J et al., 2011*].

Analysis plan: The preferred reporting items for systematic reviews and meta-analysis guidelines [*Moher D et al., 2009*] will be used to show the flow of included and excluded articles based on the search strategy and inclusion and exclusion criteria. The mean change and standard deviation for each outcome will be used to estimate the over-

all effect size of the intervention , and will be expressed as weighted mean differences in the random effect model. Statistical heterogeneity between studies will be examined using the Cochran's Q-test and I^2 static. The proportion of each study in the overall effect will be assessed by sensitivity analysis. Subgroup analyses will be based on the dosage and duration of chromium supplementation, the health condition of the participants, study location and sample size. Publication bias will be assessed by visual inspection of funnel plots as well as Egger's test. Data analysis was performed using comprehensive meta-analysis software (Version 3) . p- values <0.05 was considered as statistically significant.

Discussion

Given to the best our knowledge, no systematic review and meta-analysis has been conducted on the effect of trivalent chromium supplementation on both inflammation and oxidative stress, simultaneously, we hope that this study provides a better insight about the effects of chromium supplementation on the body. Also in this study, we will examine the effect of chromium supplementation in combination with other nutrients in a subgroup analysis, which can also be interesting in this regard because the effect of nutrients are always in combination and in interaction with other nutrients.

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