Review

Effects of chromium supplementation on oxidative stress biomarkers

A systematic review and meta-analysis of randomized clinical trials

Mohammad Reza Amini[1], Fatemeh Sheikhhossein[1], Farhang Djafari[2], Alireza Jafari[2], Kurosh Djafarian[1], and Sakineh Shab-Bidar[2]

[1] Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Tehran, Iran

[2] Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Tehran, Iran

Abstract: *Aim:* This systematic review and meta-analysis aimed to evaluate the effects of chromium supplementation on oxidative stress biomarkers such as superoxide dismutase (SOD), glutathione (GSH), glutathione peroxidase (GPX), malondialdehyde (MDA), total antioxidant status (TAS), thiobarbituric acid reactive substances (TBARS), catalase (CAT), nitric oxide (NO), total antioxidant capacity (TAC) and protein carbonyl. *Methods:* Relevant studies, published from inception until July 2019, were searched through PubMed/Medline, Scopus, ISI Web of Science, Embase, and Google Scholar. All randomized clinical trials investigating the effect of chromium supplementation on oxidative stress were included. *Results:* Out of 252 citations, 10 trials that enrolled 595 subjects were included. Chromium supplementation resulted in a significant increase in GSH (WMD: 64.79 mg/dl, 95% CI: 22.43 to 107.15; P=0.003) but no significant change in MDA, TAS, TBARS levels, SOD, CAT levels and GPX. Chromium picolinate supplementation resulted in a significant increase in TAC while failing to have a significant effect on NO. Moreover, both chromium picolinate and chromium dinicocysteinate supplementation reduced protein carbonyl levels. *Conclusion:* Overall, this meta-analysis demonstrated that chromium supplementation increased GSH without any significant changes in the mean of GPX, MDA, TAS, TBARS, CAT and SOD.

Keywords: meta-analysis, oxidative markers, chromium

Introduction

Chromium (Cr) is one of the well-known trace elements, that has important oxidant states such as Cr (III) and Cr (VI) [1]. Compared to Cr (III), Cr (VI) passes through the cell membranes more easily due to ion carriers. Thus, Cr (VI) is more toxic [2–4]. Cr (III) is considered an important mineral, which is involved in biochemical reactions in human metabolic pathways [5, 6].

Cr (III) as a candidate for improving metabolic disorders containing insulin resistance, impaired glucose metabolism, and homeostasis.

Since Cr (III) is the source of Cr used in mining, accordingly, it is considered as an essential trace element for the human diet and found naturally in barley, fruits, vegetables, meat, fish, and especially brewer's yeast as a rich source [7, 8]. The recommended dose of Cr for all adults is 30 micrograms per day. Slight harmful effects such as developmental issues, damage to the skin, respiratory, reproductive, and digestive systems, and cancer have been associated with high Cr intakes. Therefore, there is no established tolerable upper intake level for this mineral [9, 10]. Oxidative stress is a process in which the accumulation and production of reactive oxygen species (ROS) or oxidative capacity increases compared to antioxidant capacity [11–14].

Cr intake can reduce oxidative stress markers by inhibiting epinephrine due to its insulinotropic effect and activation of glutathione reductase or other enzymes that detoxify free radicals and ROS [15, 16]. Findings demonstrated that in patients with impaired glucose tolerance (IGT), diabetes, and some lipid disorders, there is a relative

Cr deficiency and Cr supplementation in these patients has a beneficial effect such as improving insulin resistance and other related disorders [17]. Cr niacinate supplementation (400 μg/kg body weight) for 7 weeks decreased blood levels of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-alpha), interleukin 6 (IL-6), C-reactive protein (CRP), and biomarkers of oxidative stress by preventing nuclear factor kappa B (NF-kB) activation in diabetic fatty rats [18].

Additionally, serum superoxide dismutase (SOD) levels and total antioxidant capacity (TAC) were also observed after intake of Cr at 400 μg/kg in growing pigs [19]. The beneficial effects of Cr supplementation on enhanced endocrinal status, inflammatory markers, and oxidative stress level might be attributed to the activation of glutathione reductase or some other enzymes, the improvement of insulin resistance, and the prevention of protein glycosylation [16]. Although Several human surveys have shown that daily supplementation of Cr (III) had positive impacts on antioxidant enzymes such as glutathione (GSH), glutathione peroxidase (GSHPx), thiobarbituric acid reactive substances (TBAR), malondialdehyde (MDA), and TAC, in type 2 diabetes patients and women with polycystic ovarian syndrome [20–27], the results are still inconclusive and some studies have revealed that Cr administration had no significant effect on antioxidative capacity [28, 29]. Therefore, we conducted a comprehensive systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate whether Cr supplementation could ameliorate stress oxidative status in adults.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines were followed in conducting this systematic review and meta-analysis [30].

Search strategy

Online medical databases, including MEDLINE, Cochrane library, EMBASE, and Web of Science searched from launch since July 2019. The search algorithm included all possible MESH and non-MESH terms: (chromium[tiab] OR chromium[MeSH]) AND (Oxidative[tiab] OR "nitric oxide"[tiab] OR NO[tiab] OR "total antioxidant capacity" [tiab] OR TAC[tiab] OR "total antioxidant status"[tiab] OR TAS[tiab] OR "protein carbonyl"[tiab] OR glutathione [tiab] OR GSH[tiab] OR malondialdehyde[tiab] OR MDA [tiab] OR "Superoxide dismutase"[tiab] OR SOD[tiab] OR catalase[tiab] OR CAT[tiab] OR "glutathione peroxidase"[tiab] OR GPx[tiab] OR "Oxidative Stress"[Mesh] OR "Nitric Oxide"[Mesh] OR "Protein Carbonylation"[Mesh] OR "Glutathione"[Mesh] OR "Glutathione Peroxidase"[Mesh] OR "Malondialdehyde"[Mesh] OR "Superoxide Dismutase"[Mesh] OR "Superoxide Dismutase-1"[Mesh] OR "Catalase"[Mesh]) AND (intervention [tiab] OR "controlled trial"[tiab] OR randomized[tiab] OR random[tiab] OR Randomly[tiab] OR Placebo[tiab] OR Assignment[tiab] OR "clinical trial"[tiab] OR trial[tiab] OR randomised[tiab] OR "Methods"[Mesh] OR "Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "Placebos"[Mesh] OR "Placebo Effect"[Mesh] OR "Clinical Trial"[Publication Type] OR "Clinical Trials as Topic"[Mesh]). The search was not restricted by language or time. Moreover, to avoid losing any relevant study, we performed all the references of the included articles hand searched.

Inclusion and exclusion criteria

The search terms and strategies were based on the PICOS model [31]. Potentially relevant studies were included if they met the following inclusion criteria: (adults aged 18 years old or more), intervention (Cr supplementation), comparator (placebo), outcome (SOD, GSH, GPX, MDA, TBARS, total antioxidant status (TAS), catalase (CAT), nitric oxide (NO), Protein carbonyl and TAC) and study design (parallel). Studies were excluded if they were; letters, comments, conference papers, reviews, meta-analyses, and ecologic studies, or if they were conducted on animals, children, or were not placebo-controlled groups and assessed the effects of supplementation along with other interventions. Also, unpublished and grey literature, like patents, congress abstracts, and dissertations were excluded.

Data extraction

Two researchers (MRA, FS) independently extracted data for this meta-analysis, evaluated the quality of eligible studies, and performed double-check. Any disagreements and differences were resolved by a third independent investigator (SS-b), if necessary. The following data were extracted in the standardized form: studies' characteristics, including authors, year, design, country, trial duration, and intervention arms; subjects' information, including inclusion criteria, age, sex, and health status; outcomes assessed, including baseline and final values of outcomes of interest (SOD, GSH, GPX, MDA, TAS, TBARS, CAT, NO, Protein carbonyl and TAC). If additional details were needed, we contacted the authors of the studies.

Quality assessment

The quality of all included studies was assessed using a quality assessment checklist adapted from the updated Consolidated Standard of Reporting Trials guidelines containing the following items [32]: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants, personnel, and outcomes; 4) incomplete outcome data; 5) selective outcome reporting; 6) other potential sources of bias. The risk of bias was stratified as low, high, and unclear. The final score of discrepancies was resolved by discussion.

Statistical analysis

Data analysis was performed using STATA 12.0 (Stata Corp., College Station, TX, USA). A significant difference was considered as P<0.05. Mean and standard deviation (*SD*) were collected in a similar unit to estimate the pooled effects. If SD was not reported, we calculated it [33] (from *SD*=*SE*×square root of the number of subjects; or *SD*=IQR/1.35 (symmetric data distribution), where n is the sample size, SEM is the standard error of the mean, and IQR is interquartile range, consecutively). Finally, we extracted data from the diagrams and charts via plot digitizer software. The mean difference *SD*s were calculated as follows:

$$SD_{\text{Change}} = \sqrt{((SD_{\text{Baseline}})^2+(SD_{\text{Final}})^2)-(2\times R\times SD_{\text{Baseline}}\times SD_{\text{Final}})}$$

Initially, a fixed-effect model was performed to determine the relationship with a forest plot. The degree of heterogeneity was defined based on the I-squared statistic. The heterogeneity was substantially significant when the Cochrane test showed I^2 more than 50% with a p-value <0.1. Data with significant heterogeneity were analyzed using DerSimonian and Laird random-effects model.

Results

Selected studies

We identified 1,634 studies in our initial search. In the next step, we identified 101 duplication records, 221 animal models, 71 review articles, and 1229 unrelated studies. After excluding these papers, 12 studies remained for full-text review. Finally, 10 papers [20, 34–42] were eligible for this systematic review and meta-analysis. Figure 1 demonstrates the process by which articles were selected.

Study characteristic

Study characteristics listed in Table 1. We found eleven studies that evaluated the effect of Cr supplementation on oxidative stress. They were published between 2004 and 2019. Also, three studies have been conducted in Iran [22, 24, 36], two studies in Taiwan [21, 25], two cases in Denmark [26, 35], two studies in the United States [23, 34] and one in Tunisia [20]. The design of all experiments was parallel. The total number of participants ranged from 22 to 70 in the age range of 29 to 58 years. Half of the participants had type 2 diabetes mellitus, three studies included women with polycystic ovary syndrome [24, 36] and the other studies included patients with metabolic syndrome [35]. Three studies included only women [24, 36] and others enrolled both genders. Different Cr forms were used: chromium picolinate [20, 22, 35], chromium dinicocysteinate [23, 34], and yeast Cr [21, 25, 26] with a dose ranging from 200 to 1000ug/day and an intervention period of 8 to 24 weeks. Control groups in all studies used a placebo.

Quality assessment

The quality of all included studies was assessed using a quality assessment checklist adapted from the Cochrane quality assessment tool for RCTs listed in Table 2. All studies presented little or no information on sequence generation and allocation concealment also used a blinding method. Three studies [21, 23, 34] reported incomplete outcome data while three of those cases reported selective outcome with a low risk of bias.

Systematic review

We did not have enough studies for TAC, NO, and carbonyl protein to conduct a meta-analysis. Therefore, we explained their results here. Jamilian et al. recruited 40 women with polycystic ovary syndrome that 20 of them took 200μg Cr picolinate, and 20 received placebo for 8 weeks. The use of Cr picolinate resulted in a significant increase in TAC (P<0.001) [24]. In the study of Farrokhian et al, 64 participants with diabetes and coronary heart disease were divided into two groups of 32 subjects. The intervention group consumed 200μg Cr picolinate and the control group received a placebo. The use of Cr picolinate resulted in a significant increase in TAC (P=0.002). In the study of Siavashani et al, 40 women with polycystic

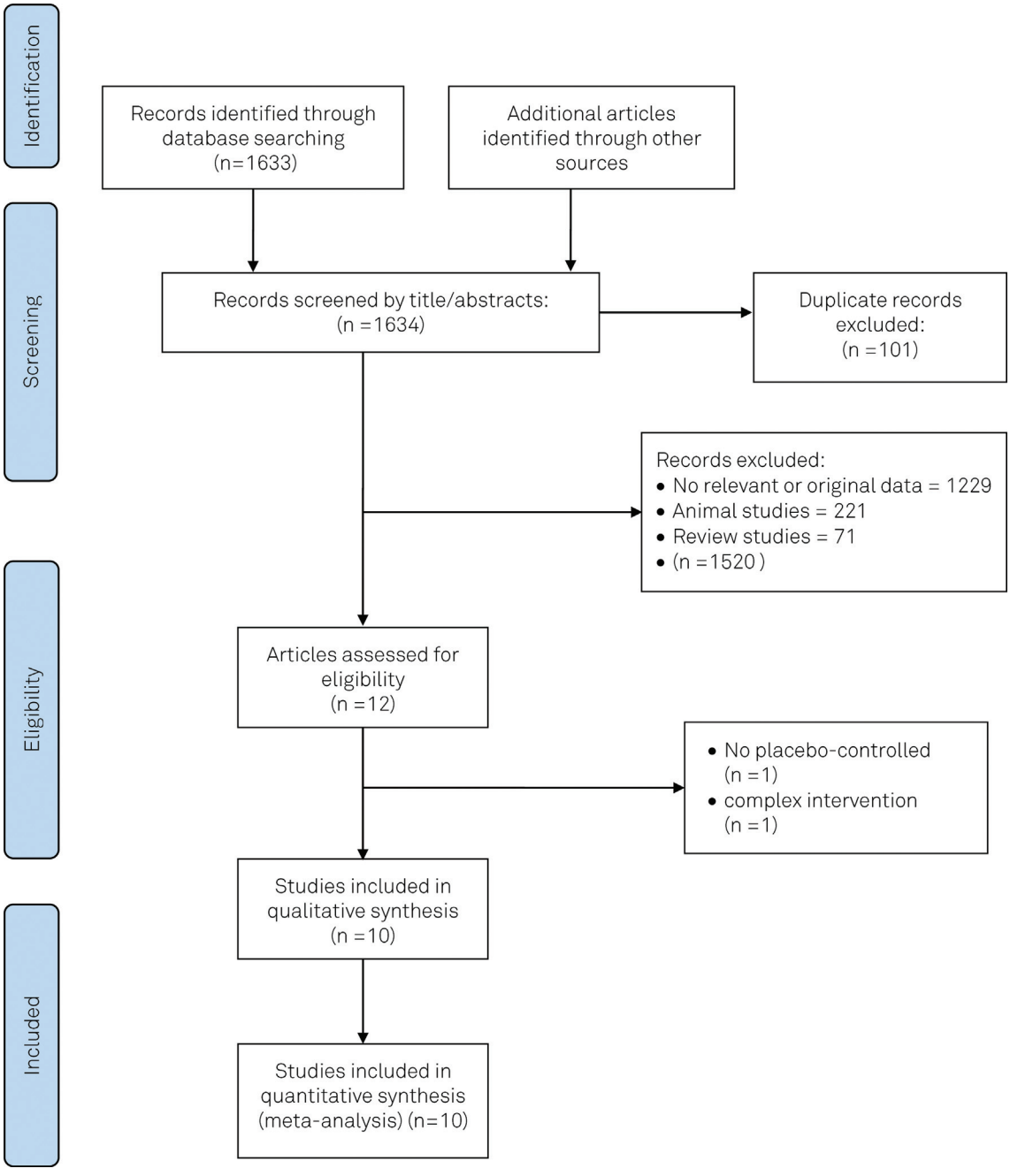

Figure 1. Flow chart of the number of studies identified and selected into the meta-analysis.

ovary syndrome were divided into two groups each containing 20 subjects. The intervention group consumed 200 µg Cr picolinate, which did not show a significant effect on NO levels [36]. Jain et al included 25 individuals with type 2 diabetes mellitus who took 400µg Cr picolinate compared to 25 subjects in the placebo group. There was a significant decrease in protein carbonyl level (P=0.005) [22]. Also, Saiyed et al. showed that 12 weeks 400µg Cr picolinate as well as Cr dinicocysteinate supplementation reduced the protein carbonyl levels (P=0.03) in comparison to placebo in 43 subjects [34].

Meta-analysis

The effect of chromium supplementation on GSH

Collecting the effect size of four studies [22, 24, 26, 29, 35] showed that Cr supplementation had a significant effect on GSH (WMD: 64.79 mg/dl, 95% CI: 22.43 to 107.15,

Table 1. General demographic characteristics of the included studies

Author	Year	Country	Study design	Participants	Sex	Mean age (intervention/control)	Intervention	Duration (week)	Dose (μg)	Sample size (intervention/control)
Anderson	2001	Tunisia	Parallel	Adults with T2DM	F/M	42.5	Chromium picolinate	12	400	27/27
Cheng	2004	Taiwan	Parallel	Adults with T2DM	F/M	52.5	Yeast Chromium	16	1000	12/12
Cheng	2004	Taiwan	Parallel	Adults with T2DM and midly hyperglycemic	F/M	52.5	Yeast Chromium	16	1000	11/11
Cheng	2004	Taiwan	Parallel	Adults with T2DM and severely hyperglycemic	F/M	52.5	Yeast Chromium	16	1000	11/11
Racek	2006	Denmark	Parallel	Adults with T2DM	F/M	61.5	Yeast Chromium	12	400	19/17
Lai	2008	Taiwan	Parallel	Adults with T2DM	F/M	46.5	Yeast Chromium	16	1000	10/20
Jain	2012	USA	Parallel	Adults with T2DM	F/M	51.1	Chromium picolinate	12	400	25/25
Jain	2012	USA	Parallel	Adults with T2DM	F/M	48.8	Chromium dinicocysteinate	12	400	25/24
Saiyed	2016	USA	Parallel	Adults with T2DM	F/M	50.6	Chromium picolinate	12	400	12/13
Saiyed	2016	USA	Parallel	Adults with T2DM	F/M	49.3	Chromium dinicocysteinate	12	400	18/13
Nussbaumerova	2018	Denmark	Parallel	Metabolic syndrome and impaired glucose	F/M	58	Chromium picolinate	24	300	35/35
Jamilian	2018	Iran	Parallel	Polycystic ovary syndrome	F	29	Chromium picolinate	8	200	20/20
Amiri Siavashani	2018	Iran	Parallel	Polycystic ovary syndrome	F	33.3	Chromium picolinate	8	200	20/20
Farrokhian	2019	Iran	Parallel	Adults with DM, Metabolic syndrome and CHD	F/M	62.5	Chromium picolinate	12	200	32/32

Notes: F: Female; M: Male; T2DM: Type 2 Diabetes Mellitus; DM: Diabetes Mellitus; CHD: Coronary heart disease.

Table 2. Risk of bias for the included studies, assessed according to the Cochrane risk of bias tool

Study	Random sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other bias
Anderson (2001)	L	L	L	H	U	L
Cheng (2004)	L	U	L	H	U	L
Racek (2006)	L	L	L	L	L	L
Lai (2008)	L	L	L	L	U	L
Jain (2012)	U	U	L	H	U	L
Saiyed (2016)	U	U	L	H	U	L
Nussbaumerova (2018)	L	L	L	L	L	L
Jamilian (2018)	L	L	L	H	L	L
Amiri Siavashani (2018)	L	L	L	L	L	L
Farrokhian (2019)	L	L	L	L	L	L

Notes: L: low risk of bias; H: high risk of bias; U: unclear risk of bias.

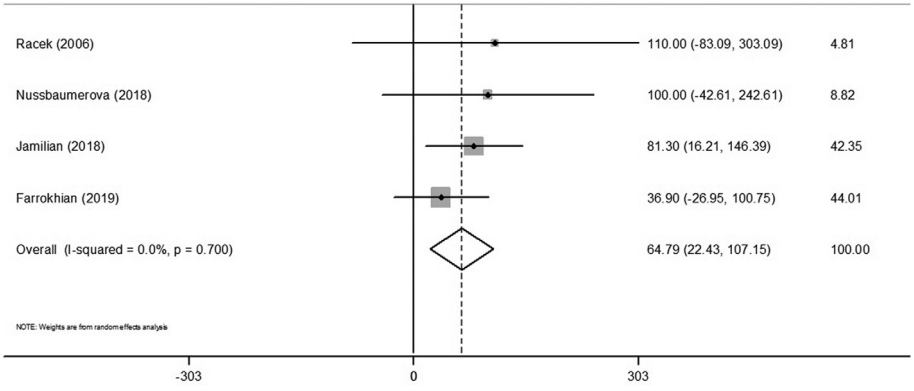

Figure 2. The effect of chromium supplementation on GSH.

P=0.003) with no heterogeneity (I^2=0.0%, P=0.7) (Figure 2).

The effect of chromium supplementation on MDA

The meta-analysis of three studies [22, 24, 26, 29] revealed no significant effect on MDA compared with placebo (WMD: −0.22 mg/dl, 95% CI: −0.59 to 0.15, P=0.495) with significant heterogeneity (I^2=89.6%, P<0.001) (Figure 3).

The effect of chromium supplementation on TAS

Cr supplementation had no significant effect on TAS in three studies (WMD: 0.03 mg/dl, 95% CI: −0.09 to 0.15, P=0.242) [21, 25, 26]. There was significant heterogeneity among the included studies (I^2=79.7%, P<0.001) (Figure 4).

The effect of chromium supplementation on TBARS

TBARS levels did not change significantly with the Cr supplementation intervention [20, 21, 25, 35] (WMD: −0.36 mg/dl, 95% CI: −0.96 to 0.24, P=0.242), however heterogeneity between studies was significant (I^2=79.7%, P<0.001) (Figure 5).

The effect of chromium supplementation on SOD

Combining the results of four studies [20, 21, 25, 26], it was found that Cr supplementation did not alter SOD (WMD: 0.10 mg/dl, 95% CI: −0.19 to 0.40, P=0.495) with no significant heterogeneity between studies (I^2=0.0%, P=0.772) (Figure 6).

The effect of chromium supplementation on CAT

Meta-analysis of two studies [38, 42] showed no significant difference in Cr supplementation and placebo (WMD: 0.23 mg/dl, 95% CI: −0.51 to 0.97, P=0.547) with no significance homogeneity concerning the studies (I^2=0.0%, P=0.987) (Figure 7).

The effect of chromium supplementation on GPX

The effect size of the five studies [20, 21, 25, 26] showed no statistically significant difference in GPX, Cr supplementation with placebo (WMD: 0.28 mg/dl, 95%

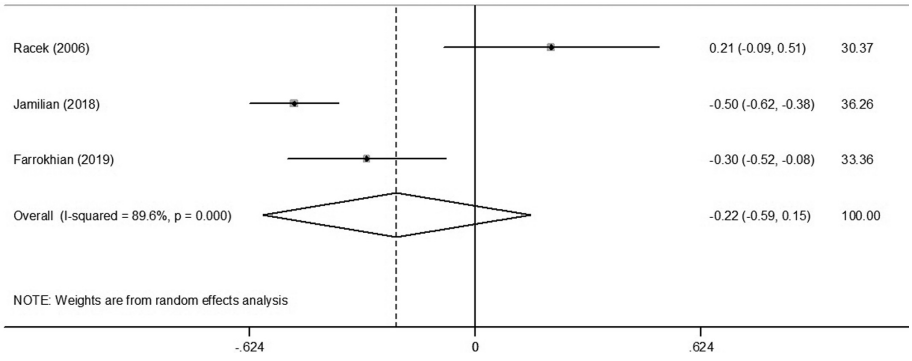

Figure 3. The effect of chromium supplementation on MDA.

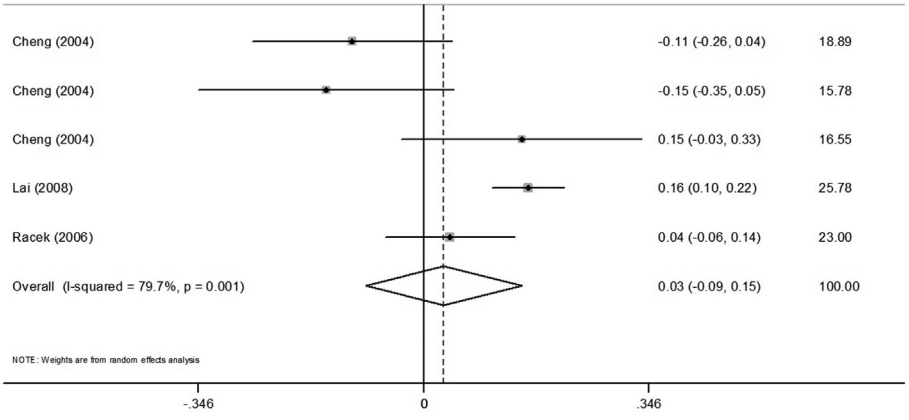

Figure 4. The effect of chromium supplementation on TAS.

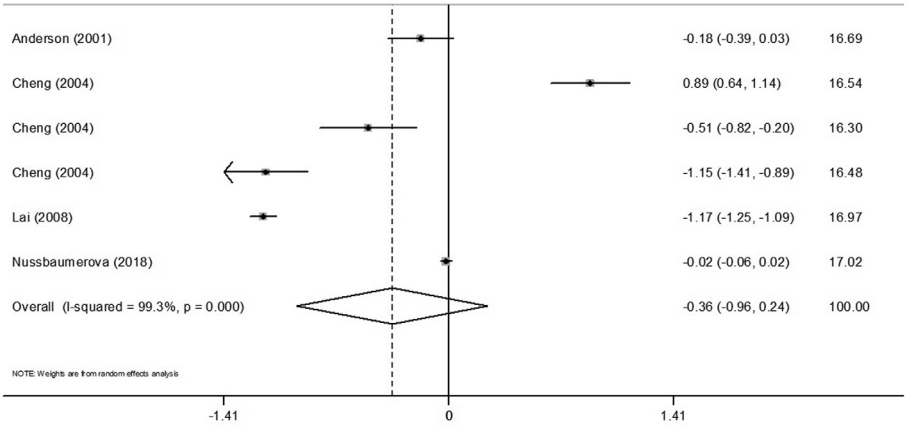

Figure 5. The effect of chromium supplementation on TBARS.

CI: −0.29 to 0.86, P=0.332) but a considerable heterogeneity was shown (I^2=77.5%, P<0.001) (Figure 8).

Publication bias and sensitivity analysis

Sensitivity analysis showed that removing any of the studies could not substantially change the effect of Cr supplementation on GSH, MDA, TAS, TBARS, SOD, CAT, and GPX. Egger's weighted regression tests were performed to explore the publication bias. The results of Egger's test showed no publication bias for GSH (P=0.393), MDA (P=0.197), TAS (P=0.125), TBARS (P=0.567), SOD (P=0.999), CAT (P=0.276) and GPX (P=0.881).

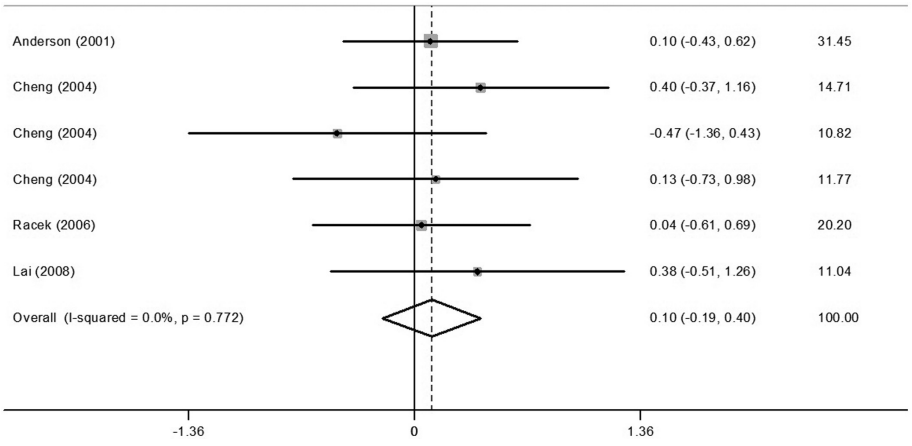

Figure 6. The effect of chromium supplementation on SOD.

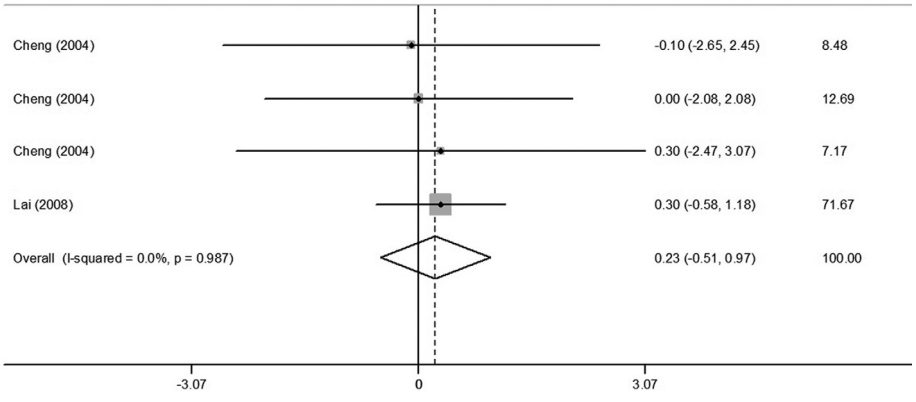

Figure 7. The effect of chromium supplementation on CAT.

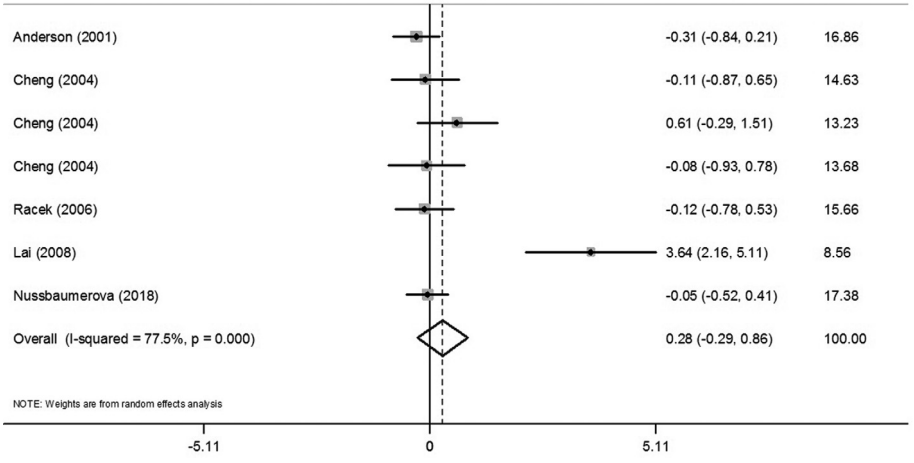

Figure 8. The effect of chromium supplementation on GPX.

Discussion

The current systematic review and meta-analysis showed that the Cr supplementation increased GSH. However, the results showed no significant alterations of GPX, MDA, TAS, TBARS, CAT, and SOD activities. To the best of our knowledge, the present study is the first systematic review and meta-analysis on the effect of Cr supplementation on oxidative stress biomarkers.

Oxidative stress due to the production of free radicals is associated with diabetes and cardiovascular diseases [45]. High free radicals production triggers auto-oxidation of blood glucose, lipid peroxidation, the activation of leucocytes, and elevated transition metal bioavailability [46, 47]. Recently, trace elements are a new insight to decrease oxidative damage [48–50]. One of the important trace elements is Cr that may act as a potent antioxidant to balance glucose and lipid metabolism [5]. It could lower oxidative stress by activating glutathione reductase or other enzymes that participate to detoxify free radicals and ROS [16]. Additionally, it has been hypothesized that serious Cr deficiency is related to insulin resistance and diabetes [51]. Our findings are in line with the studies that found no significant effect of Cr supplementation on markers of oxidative stress, except GSH. In the study conducted by Tan et al. [52] supplementation with Cr picolinate in pigs for 80 days did not change the oxidative stress markers. Furthermore, the results of Thomas et al. study [53] were consistent with us, showing that 200 mcg Cr along with 1.8 mg nicotinic acid supplement had no favourable effects on glucose and lipid metabolism. Moreover, in Trow et al. research [54], supplementation with 100 mcg Cr during 8 weeks showed no significant changes in insulin and lipoprotein levels. Although these results differed from those of other published studies [19, 55], Jamilian et al. [29] showed that Cr consumption (200 mcg/day) during 8 weeks by women with PCOS could increase TAC and decrease MDA levels, but did not affect GSH concentration. A 13.6% decrease in the level of TBARS was found in diabetic patients with 200 mcg/day Cr picolinate supplementation after 6 months [20]. The mechanisms that Cr acts as an antioxidant are not quite transparent [56]. Cr, which lessens circulating insulin, might reduce lipid peroxidation via the glucose/insulin system. Also, it preserves rats from oxidative impairment concerning carbon tetrachloride [57]. As well, in a study by Duman et al. [58] Cr improved the insulin function in adipocytes by the increment of intracellular triglyceride synthesis and reducing extracellular lipid. Therefore, it lessens the tendency to peroxidation of extracellular lipids and leads to an increased tendency to plasma TAS [59]. Moreover, reduced markers of oxidative stress after Cr ingestion might be related to the epinephrine inhibition through the insulinotropic effect of Cr [15].

Weaknesses

The results of our study might be affected by some limitations. For instance, one of the factors influencing the effect of Cr supplementation on the test variables is the baseline Cr status. In the majority of included studies of Cr supplementation in diabetics and healthy participants, the Cr status has not been determined. Therefore, it is not clear whether the findings of such studies demonstrate the nutritional effects of supplementation with Cr on Cr-deficient persons or pharmacological influences on Cr-replete patients [26]. Also, the change in the dose and the period of Cr supplementation can affect the outcome. The small number of studies for each biomarker is also another limitation.

Conclusion

In general, the evidence from our meta-analysis showed that there was no significant effect of Cr supplementation on oxidative stress markers, except for GSH. More research should focus on the establishment of a standard to evaluate Cr status since there is no method to determine Cr deficiency properly. Moreover, well-designed RCTs with sufficient sample size are needed to determine the effect of Cr supplementation on oxidative stress.

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History
Received March 31, 2021
Accepted March 31, 2021
Published online May 20, 2021

Conflict of interest
The authors declare that there are no conflicts of interest.

Sakineh Shab-Bidar
Department of Community Nutrition
School of Nutritional Sciences and Dietetics
Tehran University of Medical Sciences
No 44, Hojjat-dost Alley, Naderi St.
Keshavarz Blvd
Tehran
Iran
s_shabbidar@tums.ac.ir