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Effects of chromium supplementation on blood pressure, body mass index, liver function enzymes and malondialdehyde in patients with type 2 diabetes: A systematic review and dose-response meta-analysis of randomized controlled trials

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ABSTRACT

Background: Several studies reported beneficial effects of chromium supplementation for management of type 2 diabetes mellitus (T2DM). The present study aimed to provide a systematic review and meta-analysis of randomized controlled trials (RCTs) examining the effects of chromium supplementation on blood pressure, body mass index (BMI), liver function enzymes and malondialdehyde (MDA) in patients with T2DM.

Methods: PubMed, Scopus, and Embase were searched up to 15 November 2020 with no language and time restriction. RCTs that reported the effects of chromium supplementation on blood pressure, BMI, liver function enzymes and MDA in patients with T2DM were included. A random-effects model was used to compute weighted mean differences (WMDs) with 95 % confidence intervals (CIs). Between-study heterogeneity was assessed by Cochran's Q test and quantified by I^2 statistic.

Results: Of 3586 publications, 15 RCTs were included for the meta-analysis. Pooled effect sizes indicated that chromium significantly reduced diastolic blood pressure (DBP) (WMD): -2.36 mmHg, 95 % CI: −4.14, −0.60; P = 0.008), and MDA (WMD: −0.55 umol/l, 95 % CI: −0.96, −0.14; P = 0.008). However, chromium supplementation did not significantly affect BMI, systolic blood pressure (SBP), alanine aminotransferase (ALT), aspartate aminotransferase (AST). Meta-regression analysis did not show significant linear relationship between dose of chromium and change in BMI (p = 0.412), SBP (p = 0. 319), DBP (p = 0.102), ALT (p = 0.923), AST (p = 0.986) and MDA (p = 0.055).

Conclusion: The present systematic review and meta-analysis shows that supplementation with chromium at dose of 200–1000 μg/day may reduce DBP and MDA in T2DM patients.

Abbreviations: RCTs, randomized controlled trials; SBP, systolic blood pressure; DBP, diastolic blood pressure; MDA, malondialdehyde; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WMD, Weighted Mean Difference; T2DM, type 2 diabetes mellitus; PTP1B, protein tyrosine phosphatase 1B; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; MeSH, medical subject heading; CI, confidence interval.

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1. Introduction

Diabetes mellitus is a metabolic disease with a high financial and social burden on the health care system.[1] The prevalence of type 2 diabetes mellitus (T2DM) have been steadily increasing over the past few decades. Chronic hyperglycemia is associated with the risk of cardiovascular complications and induces a wide range of acute negative effects such as blindness, ketoacidosis, and renal failure.[2] There are also some negative chronic effects such as liver abnormalities.[3] In order to fight T2DM complications have been suggested, various methods such as diet, physical activity, and dietary supplements.[4,5] It has been hypothesized that dietary supplements have led to noted results in improvement of T2DM.[6–10]

Chromium is a trace element widely distributed in the earth's crust which participates in carbohydrate and lipid metabolism and could have a beneficial effect on body composition.[11] Recently, our meta-analysis of 23 randomized controlled trials (RCTs) showed that chromium supplementation significantly improved fasting plasma glucose (FPG), insulin, hemoglobin A1C (HbA1C) and homeostatic model assessment for insulin resistance (HOMA-IR) in patients with T2DM.[6] Since chronic hyperglycemia is the primary cause of various diabetic complications, hypoglycemic supplements such as chromium may improve T2DM complications. However, the effects of chromium supplementation in these complications such as hypertension, oxidative stress and liver function are unclear.

Hypertension is common among patients with T2DM [12] and is associated with a higher risk of mortality in these populations.[13] There are some controversies about the effects of chromium supplementation on blood pressure. It has been reported that low plasma chromium was connected with high blood pressure in patients with T2DM.[14] Furthermore, some studies have reported that chromium supplementation may improve blood pressure levels.[15,16] For instance, Farrokhian et al. exposed that a 12-week supplementation of chromium in diabetic patients had beneficial effects on diastolic blood pressure (DBP).[17] However, some studies failed to demonstrate such effects.[18,19]

It is thought that oxidative stress plays important role in the development of vascular complications in T2DM.[20] Malondialdehyde (MDA) assay is the most widely used lipid peroxidation technique [21] which can be used as an indicator for oxidative stress in patients with T2DM.[22] Moreover, a significant positive correlation has been reported between plasma MDA levels and FPG in T2DM.[23]

It is well established that patients with T2DM have a high prevalence of liver disease.[24–26] Diabetic patients have a higher incidence of liver function abnormalities than individuals who do not have diabetes.[3] Since, the literature has emerged that offers contradictory findings about the effects of chromium supplementation on liver function, it seems necessary to evaluate dietary intake changes following chromium supplementation. Therefore, the aim of this study was to conduct a systematic review and meta-analysis of the pooled data from controlled trials to evaluate the effect of chromium supplementation on blood pressure, oxidative stress, liver enzymes and body mass index (BMI) in T2DM patients.

2. Methods

2.1. Literature search and selection

This systematic review and meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline.[27] Relevant studies published up to 15 November 2020 were searched through PubMed, Scopus and Embase databases using the following terms: ("chromium", "chromium picolinate" and "chromium nicotinate") and ("Type 2 diabetes mellitus", "T2DM", "diabetes","insulin-independent diabetes", "insulin resistance", "diabetic patients") and ("metabolic", "oxidative stress" and "malondialdehyde", "blood pressure", "diastolic blood pressure" and "systolic blood pressure", "weight", "body mass" and "body mass index", "BMI", and "body composition"). A first decision was made based on titles and abstracts. For studies that appear to meet the inclusion criteria, or in cases when a definite decision cannot be made based on the title and/or abstract alone, the full paper should be obtained for detailed assessment against the inclusion criteria. No limitations of language or time of publication were used. To avoid missing any publication, electronic database systematic searches were completed along with reference lists and citation hand searches. If the amount of information reported about a study was insufficient to make a decision about inclusion, and we contacted study authors to ask for more details. Unpublished data and grey kinds of literature, including dissertations, congresss abstracts, and patents, were not included in this meta-analysis. Besides, we removed duplicate citations. PRISMA diagnostic test accuracy guideline [28] were mentioned in supplementary file 1.

2.2. Eligibility criteria

The following data were extracted by two independent reviewers (OA and EE). The Participant, Intervention, Comparison, Outcomes, and Studies (PICOS) framework was used for this systematic review and meta-analysis. Briefly, included studies involved patients with T2DM. The interventions included RCTs that had a pre-post design and reported outcomes of a chromium supplementation intervention greater than two weeks. Comparison groups consisted of patients with T2DM receiving placebo. The primary outcomes specified for the meta-analysis were MDA, BP and liver enzymes. Secondary outcomes were BMI. In the case of many publications with the same data set, we considered only the most complete one. we have excluded Studies that: (1) were conducted on animal models, pregnant or lactating women, (2) did not have a random allocation, (3) did not have any comparing control group. Controversies about the study selection process were solved by discussion.

According to the eligibility criteria, we included studies that had well-defined RCTs which reported at least one of the following primary outcome measures: MDA and BP; or secondary outcomes: liver enzymes and BMI.

2.3. Quality assessment of studies

The risk of bias for the considered studies was examined using the Cochrane quality assessment tool for RCTs.[29] Two investigators (EE and BN) partly evaluated the methods and the quality of the included studies through Cochrane Collaboration's tools. Cochrane Collaboration's tools for quality evaluation of studies including the following seven criteria: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting, and 7) other sources of bias. To assess the quality of studies, each study was assigned a label (yes, no or unclear) demonstrating it was considered low risk, high risk or unknown risk of bias, respectively.[29]

2.4. Data extraction

Standardized data extraction forms provided for reducing bias and improving validity and reliability. The following data were gathered from each study: first author's name, year of publication, study location, study duration, mean age and gender of participants partly by intervention and control groups, study design, health status of the population, type of diet, number of participants in each group, Dose of chromium, and mean and SD of mentioned variables at baseline, end of study and/or changes between baseline and post-intervention. In cases of lack of pertinent data, we notified the corresponding authors to receive their help. Data extraction of eligible studies was performed independently by EE and BN using a pre-determined extraction form. Any discrepancies were resolved by consensus or by consultation with a

third reviewer (OA).

2.5. Meta-analysis of data

To analyze the effect size for BMI, blood pressure, oxidative stress and, liver enzymes the mean change and its standard deviation for intervention and non-intervention groups as comparison groups were extracted. A random-effects model was used to compute weighted mean differences (WMDs) with 95 % confidence intervals (CIs). Between-study heterogeneity was assessed by Cochran's Q test and quantified by I^2 statistic. Between subgroup, heterogeneity was examined using a fixed-effect model. Sensitivity analysis was performed by eliminating each study one by one and recalculating the pooled assessments. Egger's regression asymmetry tests were conducted for identifying potential publication bias. Any publication bias was identified by the 'trim and fill' test.[30] Meta-regression analysis was conducted to evaluate the association between pooled effect size and chromium dose (μg /day).[31] Statistical analysis was performed using STATA, version 11.2 (Stata Corp, College Station, TX). The statistical significant value was explained as P values <0.05.

3. Results

3.1. Study selection

We found 3586 publications in our initial search; 1448 duplicates were identified and removed. Out of the remaining 2138 articles, 1382 were identified as unrelated after reviewing for titles and abstracts. Additional 365 papers were excluded due to animal studies and 370 papers due to review studies. When investigating full texts of articles, 6 papers were excluded due to a lack of reporting of desire data. Finally, 15 trials [15,16,32–44] were included in this meta-analysis (Fig. 1). From these 15 trials, 6 studies evaluate the effects of chromium supplementation on BP, 9 studies determined the effect of chromium on BMI. Moreover, 3 and 7 studies evaluate the effects of chromium intake on liver enzymes and MDA respectively.

3.2. Feature of studies

Overall, 15 RCTs, published between 2001 and 2020, were included in our Meta-analysis, characteristics of the 15 randomized clinical trials,[15,16,32–43,45] are reported in Table 1. These studies included a total of 806 participants (428 intervention and 378 control) aged ≥18 years.

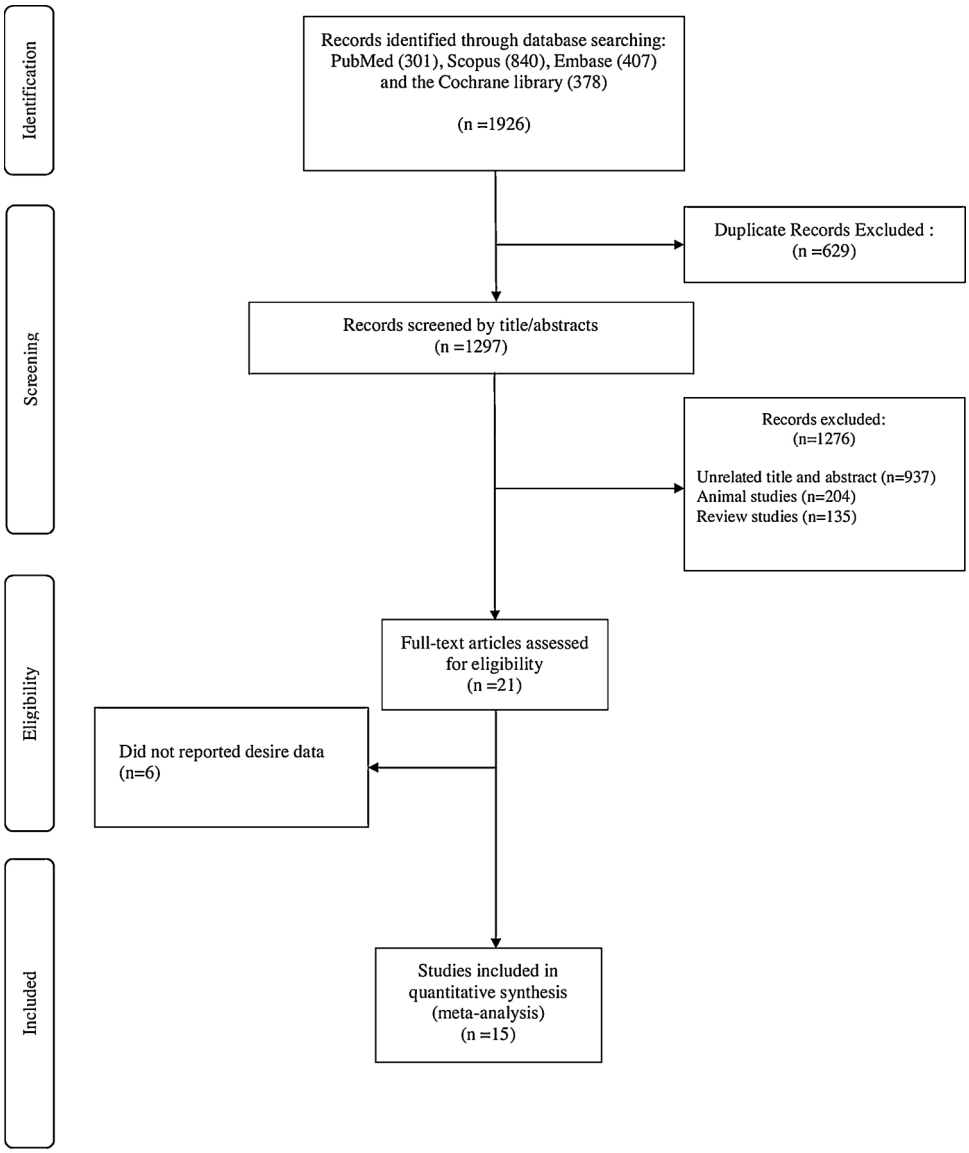

Fig. 1. Flowchart of study selection for inclusion trials in the systematic review.

Table 1
Characterist ic of included studies in meta-analysis.

Author	Publication years	Country	Study Design	Sample (Sex)	Trial Duration (Week)	Means Age		Means BMI		Intervention			Sample Size		Study results	
						IG	CG	IG	CG	Treatment group	Chromium dose (μg)	control	IG	CG	IG	CG
RA Anderson	2001	USA	parallel	56: M/F	25	52 ± 8.2	55.5 ± 7.7	29.5 ± 0.83	29.6 ± 0.8	chromium pidolate	400	Placebo	27	29	MDA: -0.45 ± 0.37	MDA: -0.14 ± 0.33
HH Cheng	2004	Taiwan	parallel	G1: 20: 14 M, 6F G2: 21: 9 M, 12 F	25	IG1: 52.5 ± 6.63 IG2: 53.1 ± 6.63	CG1: 50.8 ± 6.9 CG2: 50.5 ± 6	IG1: 27.3 ± 2.32 IG2: 25.9 ± 2.32	CG1: 26.8 ± 3 CG2: 27.8 ± 2.52	chromium yeast	1000	Placebo	IG1: 11 IG2: 11	CG1: 9 CG2: 10	IG1: MDA: -0.29 ± 0.44 IG2: MDA: -0.98 ± 0.38	CG1: MDA: 0.08 ± 0.37 CG2: MDA: 0.15 ± 0.43
M Vrtovec	2005	USA	Cross-over	60: M/F	12	NR	NR	29.9 ± 3.6	30.9 ± 5.2	chromium picolinate	1000	Placebo	30	30	BMI: -0.4 ± 3.45 SBP: -4 ± 22.64 DBP: -4 ± 11	BMI: -0.3 ± 5.01 SBP: -1 ± 23.06 DBP:-6 ± 7
J Racek	2006	Denmark	parallel	36: 9 M, 27F	12	60.8 ± 7.5	61.8 ± 10.7	33.59 ± 5.6	35.16 ± 6.55	chromium yeast	400	Placebo	19	17	BMI: -0.45 ± 6.07 MDA: 0.05 ± 0.36	BMI: -0.05 ± 8.36 MDA: 0.04 ± 0.48
N Kleefstra	2006	Netherlands	parallel	IG1: 31: 14 M, 17F IG2: 32: 15 M, 17F	25	IG1: 60 ± 8.8 IG2: 59 ± 6.4	62 ± 7.5	IG1: 35 ± 7.2 IG2: 33 ± 4.2	34 ± 4.3	chromium picolinate	IG1: 500 IG2: 1000	Placebo	IG1: 14 IG2: 15	CG1: 9 CG2: 8	IG1: BMI: 0.2 ± 1.1 SBP: -7 ± 15 DBP: -4 ± 11 IG2: BMI: 0.2 ± 1 SBP: -1 ± 21 DBP: 0 ± 11	BMI:0 ± 0.7 SBP: -7 ± 19 DBP: -6 ± 7
N Kleefstra	2007	Netherlands	parallel	57: 35 M, 22 F	25	68 ± 8.2	66 ± 8.6	30 ± 5.9	30 ± 5.6	chromium yeast	400	Placebo	29	28	BMI: 0.1 ± 0.85 SBP: 6 ± 17 DBP: 0 ± 9	BMI: 0.4 ± 0.9 SBP: 9 ± 15 DBP: 3 ± 8
MH Lai	2008	Taiwan	parallel	20: 9 M, 11F	25	53.2 ± 2	50.5 ± 1.9	25.7 ± 0.9	25.8 ± 0.8	chramium yeast	1000	Placebo	10	10	BMI: -0.1 ± 0.85 ALT: 0.8 ± 3.84 AST: -0.7 ± 2.95 MDA: -1.01 ± 0.10	BMI: -0.1 ± 0.75 ALT: 0.9 ± 3.14 AST: -0.3 ± 2.81 MDA: 0.15 ± 0.13
S Sharma	2011	India	parallel	40: M/F	12	35–67	35–67	25.09 ± 8.58	26.12 ± 3.89	chromium yeast	378	Placebo	20	20	BMI: -0.63 ± 7.93 SBP: -20 ± 23.13 DBP: -2 ± 14.35	BMI: 2.05 ± 7.40 SBP: -8 ± 22.35 DBP: 2 ± 12.01
E Król	2011	Poland	Cross-over	20: 11 M, 9F	8	54.7 ± 9.4	54.7 ± 9.4	35.3 ± 9.2	35.3 ± 9.2	chromium yeast	500	Placebo	20	20	BMI: 0.01 ± 0.69	BMI: -0.34 ± 0.54
SK Jain	2012	USA	parallel	IG1: 50: 9 M, 41F IG2: 49: 10 M, 39F	12	IG1: 51.12 ± 10.15 IG2: 48.79 ± 8.91	48.64 ± 9.95	IG1: 35.44 ± 10.3 IG2: 36.85 ± 10.77	38 ± 8.55	IG1: chromium picolinate IG2: Chromium Dinicocysteinate	400	Placebo	G1: 25 G2: 24	CG1 13 CG2 12	IG1: ALT: 1.6 ± 1.9 AST: -0.7 ± 1.55 IG2: ALT: 2.5 ±	ALT: -2.1 ± 3.17 AST: 0.2 ± 2.38

(*continued on next page*)

Table 1 (*continued*)

Author	Publication years	Country	Study Design	Sample (Sex)	Trial Duration (Week)	Means Age		Means BMI		Intervention			Sample Size		Study results	
						IG	CG	IG	CG	Treatment group	Chromium dose (μg)	control	IG	CG	IG	CG
YL Chen	2013	Taiwan	parallel	66: 43 M, 23f	16	53.3 ± 10.1	54.2 ± 8.5	28.2 ± 4.2	26.8 ± 3.9	chromium chloride	400	Placebo	38	28	2.04 AST: 0.34 ± 2.00 BMI: 0 ± 4.30 ALT: 2.5 ± 2.04	BMI: -0.5 ± 3.85 ALT: -2.1 ± 3.17
S Kalbasi	2013	Iran	parallel	60: M/F	12	NR	Nr	NR	NR	chromium picolinate	200	Placebo	30	30	SBP: -1.07 ± 4.97 DBP: -3.03 ± 6.57	SBP: 0.44 ± 5.36 DBP: 0.18 ± 4.03
N Parsaeyan	2013	Iran	parallel	100: 58 M, 42f	12	53.15 ± 11.9	52.7 ± 12.5	24 ± 4.1	23.8 ± 3.2	chromium picolinate	400	Placebo	50	50	MDA: -0.1 ± 5.00	MDA: -0.1 ± 4.00
A Farrokhian	2019	Iran	parallel	64: 32 M, 32 F	12	58 ± 8	60.9 ± 7.7	30.4 ± 4.3	29.9 ± 3.8	chromium picolinate	200	Placebo	32	32	BMI: -0.4 ± 4.20 SBP: -1 ± 14.06 DBP: -3.3 ± 7.30 MDA: -0.2 ± 0.26	BMI: 0 ± 3.8 SBP: 1.4 ± 18.95 DBP: 0.7 ± 10.41 MDA: 0 ± 0.55
F Imanparast	2020	Iran	parallel	46	16	NR	NR	NR	NR	chromium picolinate	500	Placebo	23	23	MDA: -0.6 ± 0.71	MDA: 0.3 ± 0.91

Abbreviations: IG, intervention group; CG, control group; NR, not reported; F, Female; M, Male; NR, not reported.

Table 2
Quality assessment.

Study	Random sequence generation	Allocation concealment	Selective reporting	Other sources of bias	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data
RA Anderson	L	U	H	H	L	H	L
HH Cheng	L	H	L	H	L	H	L
M Vrtovec	L	H	L	H	L	U	L
J Racek	L	U	L	H	L	U	L
N Kleefstra	L	L	L	H	L	U	L
N Kleefstra	L	U	L	H	L	U	L
MH Lai	L	U	H	L	L	U	L
S Sharma	L	L	L	H	L	H	L
E Król	L	L	L	H	L	U	L
SK Jain	L	L	L	L	L	H	L
YL Chen	L	H	L	H	L	H	L
S Kalbasi	L	U	L	H	L	U	L
N Parsaeyan	L	U	L	H	L	U	L
A Farrokhian	L	L	L	H	L	U	L
F Imanparast	L	U	L	H	L	U	L

Abbreviations: L, low-risk of bias; H, high-risk of bias; U, unclear-risk of bias.

All studies were done on both genders. Three studies were performed in the United States,[32,34,40] three in Taiwan,[15,33,37] four in Iran,[41–43,45] two in Netherlands,[16,36] one in Denmark,[35] one in Poland [38] and one in India.[39] 12 studies had parallel design,[15,16,32,33,35–37,39–44] and 2 were crossover studies.[34,38] The intervention period in the included RCTs varied from 8 [38] to 25 [16,32,33,36,37] weeks. All studies have been conducted on people with type 2 diabetes, the study population of Farrokhian et al., in addition to type 2 diabetes, also had Coronary Heart Disease.[43] In terms of supplement type, in 6 studies chromium yeast,[33,35–39] 7 studies chromium picolinate,[16,34,40–44] one study chromium chloride,[15] one study chromium pidolate [32] and in one arm of Jain et al., study chromium dinicocysteinate [40] have been prescribed. Daily recommended dosage of chromium in the included RCTs varied between 200 and 1000 μg/day.

3.3. Quality assessment

All included RCTs mentioned random sequence generation. In related with allocation concealment, 3 trials [15,33,34] had high-risk of bias, 6 trials,[16,36,38–40,43] had low-risk of bias and other studies [32,35,37,41,42,44] had unclear-risk of bias. Most of included trials showed low risk of bias regarding selective reporting.[15,16,33–36,38–44] However, two studies [32,37] showed high-risk of bias. All of the included studies were mentioned blinding of participants.[15,16,32–44] However, in related with blinding of outcome assessment was unclear in 9 studies.[16,34–38,41–43] The risks of bias assessment were illustrated in Table 2.

3.4. Effect of Chromium supplementation on blood pressure

Totally, 6 eligible studies with 7 effect sizes, including a total of 327 participants (intervention = 170, control = 157), examined the effect of chromium intake on blood pressure.[34,36,39,42,43,46] Combining their findings based on random-effects model, we found that chromium supplementation had no significant effect on SBP (Weighted Mean Differences (WMD): -1.83 mmHg, 95 % CI: -4.09, 0.42; P = 0.111) compared to the control group, with no significant between-study heterogeneity (I^2 = 0.0 %, P = 0.793) (Fig. 2A, Table 3). Pooled effect sizes indicated that chromium significantly reduced DBP (WMD: -2.36 mmHg, 95 % CI: -4.13, -0.60; P = 0.008) compared to placebo and without significant heterogeneity (I^2: 21.1 %, p = 0.268) (Fig. 2B, Table 3).

3.5. Effect of chromium supplementation on BMI

The impact of Chromium supplementation on BMI was assessed in 9 trials with 10 treatment arms including 429 participants (intervention = 227, control = 202). The pooled estimates demonstrate that supplementation with Chromium did not cause a significant decrease in BMI (WMD: 0.08 kg/m2, 95 % CI: -0.15, 0.31; P: 0.498), with no evidence of significant between-study heterogeneity (I^2: 0.0 %, P = 0.662) (Fig. 2C, Table 3).

3.6. Effect of Chromium supplementation on liver enzymes

Combining 4 effect sizes from 3 studies for ALT [37,40,47] including 160 participants (intervention = 227, control = 203) and 3 effect sizes from 2 studies for AST[37,40] including 94 participants (intervention = 59, control = 35), show that supplementation with Chromium did not have a significant effect on plasma levels of ALT (WMD: 2.11 u/l, 95 % CI: -0.69, 4.91; P: 0.141) with a significant between-study heterogeneity (I^2: 74.3 %, P = 0.009) (Fig. 2D, Table 3) and AST (WMD: -0.42 u/l, 95 % CI: -1.39, 0.55; P: 0.395) without any between-study heterogeneity (I^2: 0.0 %, P = 0.630) (Fig. 2E, Table 3).

3.7. Effect of Chromium supplementation on malondialdehyde

In total, 7 trials [33,35,37,41,43,45,48] including 8 effect sizes including

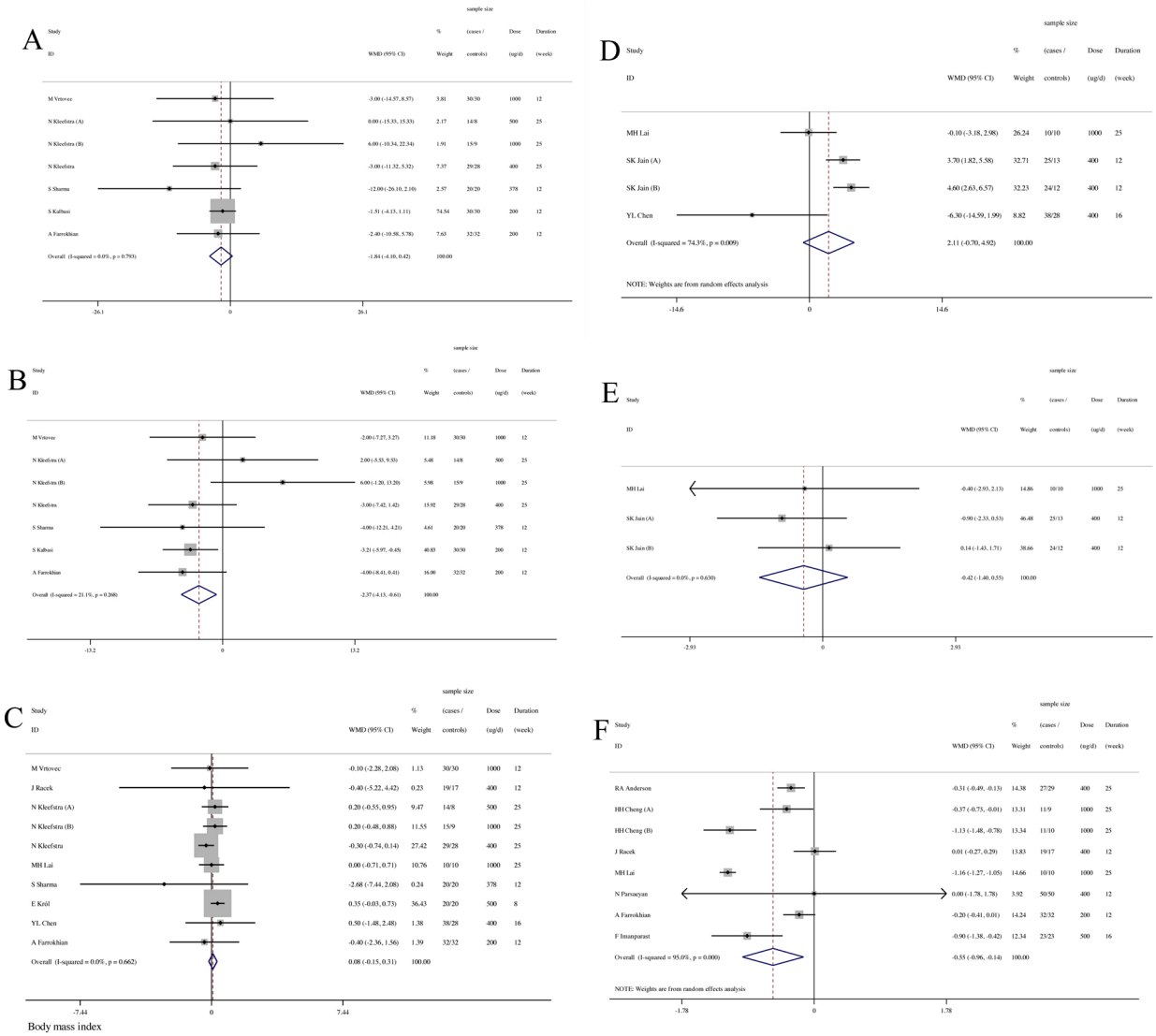

Fig. 2. A. Forest plot detailing WMDs and 95 % CIs for the effect of chromium supplementation on systolic blood pressure compared with control groups. **B.** Forest plot detailing WMDs and 95 % CIs for the effect of chromium supplementation on diastolic blood pressure compared with control groups. **C.** Forest plot detailing WMDs and 95 % CIs for the effect of chromium supplementation on body mass index compared with control groups. **D.** Forest plot detailing WMDs and 95 % CIs for the effect of chromium supplementation on alanine aminotransferase compared with control groups. **E.** Forest plot detailing WMDs and 95 % CIs for the effect of chromium supplementation on aspartate aminotransferase compared with control groups. **F.** Forest plot detailing WMDs and 95 % CIs for the effect of chromium supplementation on malondialdehyde compared with control groups.

363 patients (intervention = 183, control = 180) provided data on the effects of chromium on MDA, based on findings, significant changes were observed in MDA following the chromium supplementation (WMD: -0.55 umol/l, 95 % CI: -0.96, -0.14; P = 0.008) with significant between-study heterogeneity (I^2:95.0 %, p < 0.001) (Fig. 2F, Table 3).

3.8. Publication bias

Egger's regression test indicated no publication bias for BMI (p = 0.282), SBP (p = 0.390), DBP (p = 0.057), AST (p = 0.764), However, there was significant publication bias for ALT (P = 0.044) and MDA (P = 0.013). Due to, significant publication bias, we conducted the trim and fill sensitivity analysis, which was calculated from hypothesized negative unpublished studies. Therefore, results would not be changed if 4 new trials were published regarding chromium supplementation effects on ALT (WMD: 2.11 u/l, 95 % CI: -0.69, 4.91; P = 0.141). However, MDA values could be changed if an additional 3 unpublished studies were added; the trim and fill analysis findings changed results to (−0.84 umol/l, 95 % CI: -1.24, -0.44, p < 0.001).

3.9. Sensitivity analysis

The results of the sensitivity analysis showed that, after the omission of each study, the overall results for SBP, BMI, AST, and MDA did not change. However, by removing study of Kalbasi et al. the overall results for DBP was significantly changed (WMD): -1.78 mmHg, 95 % CI: -4.07, 0.50), and also, by removing studies by Lai et al. (WMD: 3.09 u/l, 95 % CI: 0.20, 5.99) and Chen et al. (WMD: 3.01 u/l, 95 % CI: 0.68, 5.35) the overall results for ALT was significantly changed.

3.10. Meta-regression analysis

We performed a meta-regression analysis to investigate the potential association between a decrease in BMI, SBP, DBP, AST, ALT, and MDA

Table 3
Overall effects of chromium supplementation on blood pressure, body mass index, liver function enzymes and malondialdehyde.

	Number of studies	WMD (95 %CI)	P within group	P heterogeneity	I^2
BMI	10	0.08 (−0.15, 0.31)	0.498	0.662	0.0 %
SBP	7	−1.83 (−4.09, 0.42)	0.111	0.793	0.0 %
DBP	7	−2.36 (−4.13, −0.60)	**0.008**	0.268	21.1 %
ALT	4	2.11 (−0.69, 4.91)	0.14	0.009	74.3 %
AST	3	−0.42 (−1.39, 0.55)	0.395	0.630	0.0 %
MDA	8	−0.55 (−0.96, −0.14)	**0.008**	<0.001	95.0 %

Abbreviations: CI, confidence interval; WMD, weighted mean differences; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MDA, malondialdehyde.

and dose of chromium supplementation (μg/day). Meta-regression analysis did not show significant linear relationship between dose of chromium and change in BMI (p = 0.412), SBP (p = 0. 319), DBP (p = 0.102), ALT (p = 0.923), AST (p = 0.986) and MDA (p = 0.055) (Fig. 3A-F).

3.11. Certainty assessment

The overall certainty of evidence across the studies was graded according to the guidelines of the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) Working Group. The quality of evidence could be classifed into four categories according to the corresponding evaluation criteria: high, moderate, low, and very low.

4. Discussion

In this meta-analysis, we evaluated the effects of chromium supplementation on blood pressure, BMI, liver function enzymes and MDA in patients with T2DM. According to the results derived from this study, chromium supplementation may reduce DBP and MDA. However, chromium supplementation failed to affect SBP, BMI and liver function enzymes. Hypotensive effects of chromium seemed larger in studies supplementing higher doses of chromium. Surprisingly, our results showed potential beneficial antioxidant effects of chromium in studies supplementing lower doses of chromium in patients with T2DM. To the best of our knowledge, this is the first systematic review and meta-analysis evaluating the effects of chromium supplementation on blood pressure, MDA, liver function enzymes and BMI in patients with T2DM.

Increased blood pressure is a leading risk factor for death and disability in patients with T2DM.[13,49] Scientific organizations recommend initiating treatment for hypertension in patients with T2DM whose blood pressure is more than 140/90 mmHg with a treatment goal of SBP less than 140 mmHg and DBP less than 90 mmHg.[50,51] Epidemiological studies suggest that consumption of chromium and plasma levels of chromium may play a major role in regulating blood pressure.[14,50,52] Our results supported this contention by demonstrating that chromium supplementation, especially for higher dose improved blood pressure levels by decreasing DBP. Moreover, the present meta-regression suggesting that higher chromium dose may associated with a better response to SBP. However, potential side effects of high-dose of chromium supplementation should be carefully monitored. In line with our results, some clinical trial indicated a significant reduction in DBP after chromium supplementation.[39,43] Moreover, a clinical trial of 60 patients with T2DM which examined the impacts of chromium supplementation on QTc interval, found no significant changes in SBP levels.[34] The possible mechanism for hypotensive effects of chromium is unclear. It has been shown that low plasma chromium is associated with high blood pressure.[14] Recently, our meta-analysis of 23 RCTs showed that chromium supplementation significantly improved glycemic profile by decreasing FPG, insulin, HbA1C and HOMA-IR in patients with T2DM. Moreover, Rajendran et al. showed that the mean serum chromium levels were lower in patients with uncontrolled diabetes.[53] On the other hand, previous findings suggested that proper control of glycemic profile in patients with T2DM may improve blood pressure.[54,55] Therefore, since chronic hyperglycemia is the primary cause of various diabetic complications such as hypertension, hypoglycemic supplements such as chromium may improve blood pressure in this population. However, animal studies suggested that these effects may be related to lower renin-angiotensin system activity, reduced angiotensin converting enzyme activity, and increased nitric oxide system activity following chromium supplementation.[56,57] Moreover, chromium can induce its hypotensive effects in patient with T2DM by its the potential beneficial antioxidant effects.[58,59] It has been suggested that oxidative status and intensity of the oxidative stress in diabetic patients are higher compared to non-diabetic populations.[60] High levels of reactive oxygen and nitrogen species are induced in patients with diabetes.[61] Therefore, the strong implication of reactive oxygen and nitrogen species in the etiology of hypertension suggest that antioxidants such as chromium may be effective in the treatment of hypertension.[62] However, future mechanistic studies are needed to revealed the possible mechanism of the effects of chromium on blood pressure in patient with T2DM.

Previous studies have shown that oxidative stress plays a pivotal role in the development of diabetes complications.[63] Oxidative stress levels are positively associated with an increase in insulin resistance and inflammation.[64–66] Some studies showed the potential beneficial antioxidant effects of chromium in patients with T2DM. A systematic review of 12 studies in 2016 which aimed to evaluate the impacts of chromium picolinate supplementation on control of metabolic variables, found that chromium supplementation had beneficial effects on oxidative stress and inflammatory response in patients with a pathologic status established.[67] Our finding also showed that chromium supplementation may improving oxidative stress by decreasing circulating levels of MDA. The possible mechanism for improving MDA levels is unclear. However, animal studies showed that MDA-lowering effects of chromium supplementation may be related to its antioxidant features.[68,69] As is characteristic of diabetic condition, chronic hyperglycemia was linked with an increase in oxidative stress. Sundaram et al. revealed that chromium picolinate may attenuate hyperglycemia-induced oxidative stress in diabetic rat.[70] A recently published systematic review of 33 studies showed that chromium supplementation leads to reducing oxidative stress indices such as MDA in diabetes patients.[71] Moreover, the authors revealed that chromium supplementation markedly increases antioxidant enzymes' activity and improves levels of antioxidant indices in both human and animal studies. Furthermore, it has been revealed that chromium decreases oxidative stress by decreasing the nitrite serum levels, leading to suppressing the reaction of superoxide with nitrite and then reducing peroxynitrite generation.[50,72] In addition, MDA-lowering effects after chromium intake might be related to the inhibition of epinephrine because of the insulinotropic effect of chromium.[73] Moreover, chromium supplementation may decrease oxidative stress by the activation of glutathione reductase or some other enzymes that detoxifies reactive oxygen and nitrogen species.[74] Surprisingly, our analysis showed that potential beneficial antioxidant effects of chromium have seen in studies supplementing lower doses of chromium in patients with T2DM. Regarding optimal dose, further clinical trials studies with different dose are needed to confirm our findings. Moreover, the findings of the study should be interpreted with caution

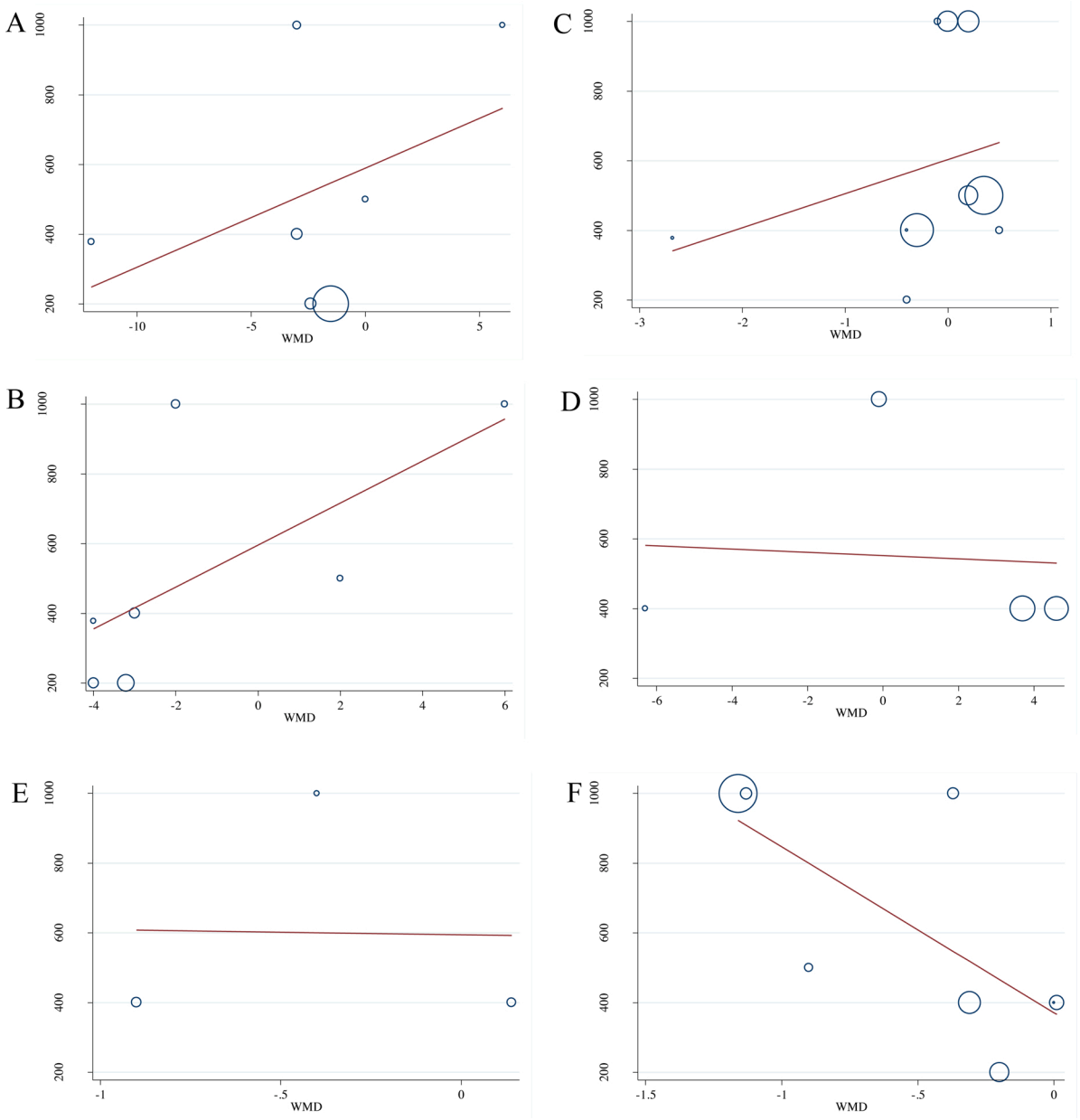

Fig. 3. **A.** meta-regression plots of the association between dose of chromium supplementation (μg/day) and weighted mean difference of systolic blood pressure. **B.** meta-regression plots of the association between dose of chromium supplementation (μg/day) and weighted mean difference of diastolic blood pressure. **C.** meta-regression plots of the association between dose of chromium supplementation (μg/day) and weighted mean difference of body mass index. **D.** meta-regression plots of the association between dose of chromium supplementation (μg/day) and weighted mean difference of alanine aminotransferase. **E.** meta-regression plots of the association between dose of chromium supplementation (μg/day) and weighted mean difference of aspartate aminotransferase. **F.** meta-regression plots of the association between dose of chromium supplementation (μg/day) and weighted mean difference of malondialdehyde.

because of significant heterogeneity. It seems that, the heterogeneity is because of clinical baseline heterogeneity, including differences between sample characteristics of the studies, dissimilar dosages and different types of chromium used in the included studies.

Despite the popularity of chromium as a weight loss supplement, there are some controversies about the effects of chromium on decreasing body weight and BMI. Some previous studies have been suggested that chromium may reduce BMI and increasing insulin sensitivity,[75] potentiation of the actions of insulin at its receptor [76] reducing food craving,[77] and increasing metabolic rate.[78] A meta-analyses of 7 RCTs showed that chromium supplementation results in statistically significant reductions in body weight and percentage body fat without any reduction in BMI, waist circumference or waist to hip ratio.[79] The results from our analysis find no evidence to support that chromium supplementation reduces BMI in patients with T2DM. Body mass and BMI loss is not primarily determined by consuming dietary supplements, but instead by the number of calories ingested.[80] Previous investigations did not report any significant changes in calorie intake following chromium supplementation, therefore, in agreements with the "calories in, calories out" theory, the unchanged caloric intake following chromium supplementation corresponded to no changes in BMI. In contrast with our findings, a systematic review of 7 RCTs in 2017 which assessed the impacts of chromium supplementation in polycystic ovary syndrome patients exhibited beneficial effects on reducing BMI.[81] It should be noted that the findings of the study should be interpreted with caution because of low number of included studies and clinically insignificant results. Moreover, recent meta-analysis of 19 studies published in 2019 showed that chromium supplementation improved

anthropometric indices in subjects with overweight or obesity.[82] However, the effect size was medium and therefore, results remain uncertain. These controversies about the effects of chromium supplementation on body weight and BMI, may be because of different dose of chromium in previous studies. Moreover, the controversies also can be because of the different from disease of subjects (polycystic ovary syndrome patients, T2DM patients, and subjects with overweight and/or obesity). Based on findings of present meta-regression, higher chromium dose may associated with better response to obesity in patients with T2DM.

It is well established that patients with T2DM have a high prevalence of liver disease [24–26] and a higher incidence of liver function test abnormalities than individuals who do not have diabetes.[3] Chen et al. exhibited that chromium supplementation inhibited progression of NAFLD and improved liver enzymes levels by suppression of inflammation and oxidative stress.[83] Furthermore, a clinical trial included 66 patients suggested a significant decrease in ALT levels in patients with type 2 diabetes after chromium supplementation.[15] The results from our analysis in people with T2DM failed to show efficacy of chromium supplementation on improving serum levels of AST and ALT. These findings on the effects of chromium supplementation on liver enzymes should be interpreted with caution because of low numbers of included studies. Further studies are needed to allow for additional evaluation of the influence of chromium supplementation on liver function tests in patients with T2DM.

Our current study has important strengths. First, all studies that included in our review were high quality, well-designed, randomized, double-blinded trials. Second, using Egger's regression, we did not observe any publication bias for studies evaluating the impact of chromium supplementation on BMI, SBP, DBP, and AST. Third, since most of the trials lasted $\geq$ 3 months, our analysis is able to show the long-term effects of chromium supplementation on BMI, blood pressure, oxidative stress and liver enzymes in patients with T2DM. However, our present analysis is not without its limitations. Chromium supplementation was used in dissimilar dosages and different types. Moreover, until now, the reference range of serum chromium levels are still worthy of discussion, especially for patients with T2DM. Furthermore, most included articles did not report baseline levels of serum chromium. Therefore, it may be difficult to determine which studies investigate the effects of chromium in subjects with chromium deficiency. Moreover, chromium adequate intake (AI) is 35 μg/day and 25 μg/day for young men and women, respectively. In addition, the AI for chromium for ages 51 and older is 0.2 μg/day 30 μg/day and 20 μg/day for men and women, respectively. From all included studies, only 1 studies by Paiva et al. [84] reported the dietary intakes of chromium. Therefore, at the present time, it is not possible to determine which patients had low serum chromium levels and how much of these effects of chromium on blood pressure and MDA are attributable to chromium deficiency. Moreover, a significant heterogeneity was encountered perhaps due to various regimens, doses, duration, center settings, populations enrolled. Calling for cautious interpretation of the results.

This is a serious limitation and should be included because it may significantly undermine the validity of results. In terms of publication bias, there was significant bias for ALT and MDA. This is a serious limitation and should be included because it may significantly undermine the validity of results. In terms of publication bias, there was significant bias for ALT and MDA.[85,86] Previous investigations showed that measurement of isoprostanes is far superior to measurement of MDA as an index of lipid peroxidation and oxidative stress in vivo.[87,88] Therefore, in terms of evaluating the effects of chromium supplementation on lipid peroxidation and oxidative stress, further studies are needed to determine the effects of chromium on isoprostanes levels. Finally, in most of the included studies, blood pressure, BMI, liver function enzymes and oxidative stress biomarkers had announced as secondary outcomes. Moreover, present study has not been registered in the PROSPERO, this could be considered as a limitation as well.

5. Conclusion

In conclusion, present systematic review and meta-analysis of all available published RCTs up to February 2020 showed that chromium supplementation at dose of 200–1000 μg/day may reduce DBP and MDA in T2DM patients. However, chromium had no significant effect on SBP, BMI and liver function enzymes. Moreover, hypotensive effects of chromium seemed larger in higher doses of chromium while antioxidative effects are larger in lower dose. Although our finding suggests chromium as a possible therapeutic agent in improving blood pressure and MDA, results from long-term trials are needed in order to assess the safety of chromium supplements as complementary therapies in the management of type 2 diabetes. Therefore, additional long-term and high-quality RCTs conducted in individuals with different serum concentrations and dietary intakes of chromium are needed to further evaluate and confirm these findings.

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Availability of data and material

The primary data for this study is available from the authors on direct request.

Author contributions

OA contributed in conception, data collection and manuscript drafting. DAL, FN, EE, SM, EM and MRK contributed in conception, data collection and manuscript drafting. All authors read and approved the final version of the paper. MK and AAN revised the manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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