Effect of Chromium on Glucose and Lipid Profiles in Patients with Type 2 Diabetes; A Meta-analysis Review of Randomized Trials

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Abstract – Purpose. Chromium (Cr) as an essential trace element in metabolism of carbohydrate, lipid and protein is currently prescribed to control diabetes mellitus (DM). The objective of this meta-analysis was to compare the effect of Cr versus placebo (Pl) on glucose and lipid profiles in patients with type 2 DM. **Methods.** Literature searches in PubMed, Scopus, Scirus, Google Scholar and IranMedex was made by use of related terms during the period of 2000-2012. Eligible studies were randomized clinical trials (RCTs) with intake of Cr higher than 250 µg at least for three months in type 2 DM. Glycated hemoglobin (HbA1c), fasting blood sugar (FBS), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglyceride (TG), and body mass index (BMI) were the main outcomes. **Results.** Seven out of 13 relevant studies met the criteria and were included in the meta-analysis. HbA1c change in diabetic patients in Cr supplement therapy comparing to Pl was -0.33 with 95%CI= -0.72 to 0.06 (P= 0.1). Change of FBG in Cr therapy vs. Pl was -0.95 with 95%CI= -1.42 to -0.49 (P< 0.0001). TC change in Cr therapy vs. Pl was 0.07 with 95%CI= -0.16 to 0.31 (P= 0.54). TG change in diabetic patients in Cr supplement therapy comparing to Pl was -0.15 with 95%CI= -0.36 to 0.07 (P= 0.18). **Conclusions.** Cr lowers FBS but does not affect HbA1c, lipids and BMI.

INTRODUCTION

Diabetes mellitus (DM) is a serious health problem with the high financial and societal impression on health systems (1). A significant increase in costs of long-term treatment of diabetes and its complications is felt (2). Change in lifestyle, use of proper safe diets, cost of drugs, use or not use of supplements and adjuvant therapies are among current concerns, and thus strategies are being designed to control DM (3). In the recent years, many natural products or antioxidants have been proposed for management of DM (4) but cost-effectiveness of most of them is under debate. Some experts believe that use of antioxidant supplementary regimens help synthetic drugs to better work in the way to reduce total treatment cost (5).

Trivalent chromium (Cr) as an essential trace element in metabolism of carbohydrate, lipid and protein is currently prescribed by some clinicians in an aim to control DM (6,7). Previous studies have shown that Cr could light up insulin receptors, stimulate the liver enzyme glucokinase, and enhance pancreatic B islets (8). It is proposed that Cr can complex to Glucose Tolerance Factor (GTF) in the yeast and in low molecular weight Cr-like substance (LMWCr) in animal cells (9). In 1959, it was shown that Cr III as an active component of

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GTF could control the impaired glucose tolerance in rats fed diets with Cr. In 1977, for the first time in human studies, it was shown that severe diabetic symptoms in a female patient could be relieved with Cr III in parenteral nutrition (10). From 1977 up to now, many articles have noticed some positive effects of Cr on human and animals. Despite the presence of reviews on Cr, the net effect of Cr has not been clarified yet because of lots of reasons, including studies which did not exclusively examine type 2 DM, differences in the outcomes or study population, low quality, and duration of treatment. In addition, some studies were non-randomized. Regarding these deficits and in the line of our idea (11), we aimed to conduct this meta-analysis to clarify the effect of Cr versus Pl on the glucose and lipid profiles among type 2 DM patients.

METHODS

Literature searches in electronic databases such as PubMed, Scopus, Scirus, Google Scholar and IranMedex was made using terms such as diabetes, type 2 diabetes, insulin, insulin sensitivity, chromium, chromium picolinate, yeast, glycemic control, lipid profile, supplementary, hemoglobin A1C (HbA1c) and randomized clinical trial (RCT) during the period of 2000-2012. Eligible studies were RCTs of Cr with intake of $\geq$ 250 µg at least for three months among type 2 DM. Two reviewers independently screened abstracts and full papers. Primary outcomes of interest were HbA1c and fasting blood sugar (FBS). Secondary outcomes were total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglyceride (TG), and body mass index (BMI). All duplicated articles and any paper, which did not meet our inclusion criteria, were excluded.

Assessment of trial quality

Jadad score, which indicates the quality of the studies based on their description of randomization, blinding, and dropouts (withdrawals) was used to assess the methodological quality of trials (12). The quality scale ranged from 0 to 5 points with a low quality report of score 2 or less and a high quality report of score at least 3. (Table 1).

STATISTICAL ANALYSIS

Data from selected studies were extracted in the form of 2×2 tables by study characteristics. Included studies were weighted by effect size and pooled. Data were analyzed using StatsDirect version 2.7.9. Standardized effect size and 95% confidence intervals (95%CI) were calculated using Mulrow-Oxman (for fixed effects) or Der Simonian-Laird (for random effects) methods. The Cochran Q test was used to test heterogeneity and $P<0.05$ was considered significant. In case of heterogeneity, the random effects model was used. Funnel plot was used as publication bias indicator.

RESULTS

According to related key words for Cr clinical studies, there were 230 studies cited in PubMed, Scopus, Scirus, Google Scholar and IranMedex. (Figure 1). Two hundred and seventeen studies were excluded because of the following reasons; studies which did not exclusively studied type 2 DM, different outcome measures, improper study population, and non-randomization. (Table 2). Of the 13 related studies, 6 were rejected because of short duration of treatment (less than 3 months) and one because of low quality in scale of Jadad score. Finally seven studies were included in the meta-analysis. (Table 3).

Effect of Cr on HbA1c in diabetic patients

The summary for effect size of weighted mean differences of HbA1c change "ΔHbA1c" in diabetic patients in Cr supplement therapy for seven included trials comparing to Pl (13-19) was -0.33 with 95% CI= -0.72 to 0.06 (P= 0.1, Figure 2-a). The Cochrane Q test for heterogeneity indicated that the studies are heterogeneous (P= 0.01) and could not be combined, thus the random effects for individual and summary of effect size for weighted mean differences was applied. For evaluation of publication, Egger bias regression of normalized effect vs. precision for all included studies for "ΔHbA1c" in diabetic patients among Cr supplement vs. Pl therapy was -1.9 (95% CI= -4.3 to 0.45, P= 0.1) and Begg-Mazumdar Kendall's test on standardized effect vs. variance indicated tau= -0.29, P= 0.28 (Figure 2-b, unbiased meta-analysis).

Table 1. Quality score of randomized controlled trial included in the meta-analysis

Study	Factors and Jadad scores			
	Randomization	Blinding	Withdrawals and dropouts	Total Jadad score
Cefalu et al., (13)	2	2	1	5
Lai, (17)	2	2	1	5
Kleefstra et al., (15)	2	2	1	5
Martin et al., (18)	2	2	1	5
Kleefstra et al., (16)	2	2	1	5
Racek et al., (19)	2	2	0	4
Ghosh et al., (14)	2	2	1	5

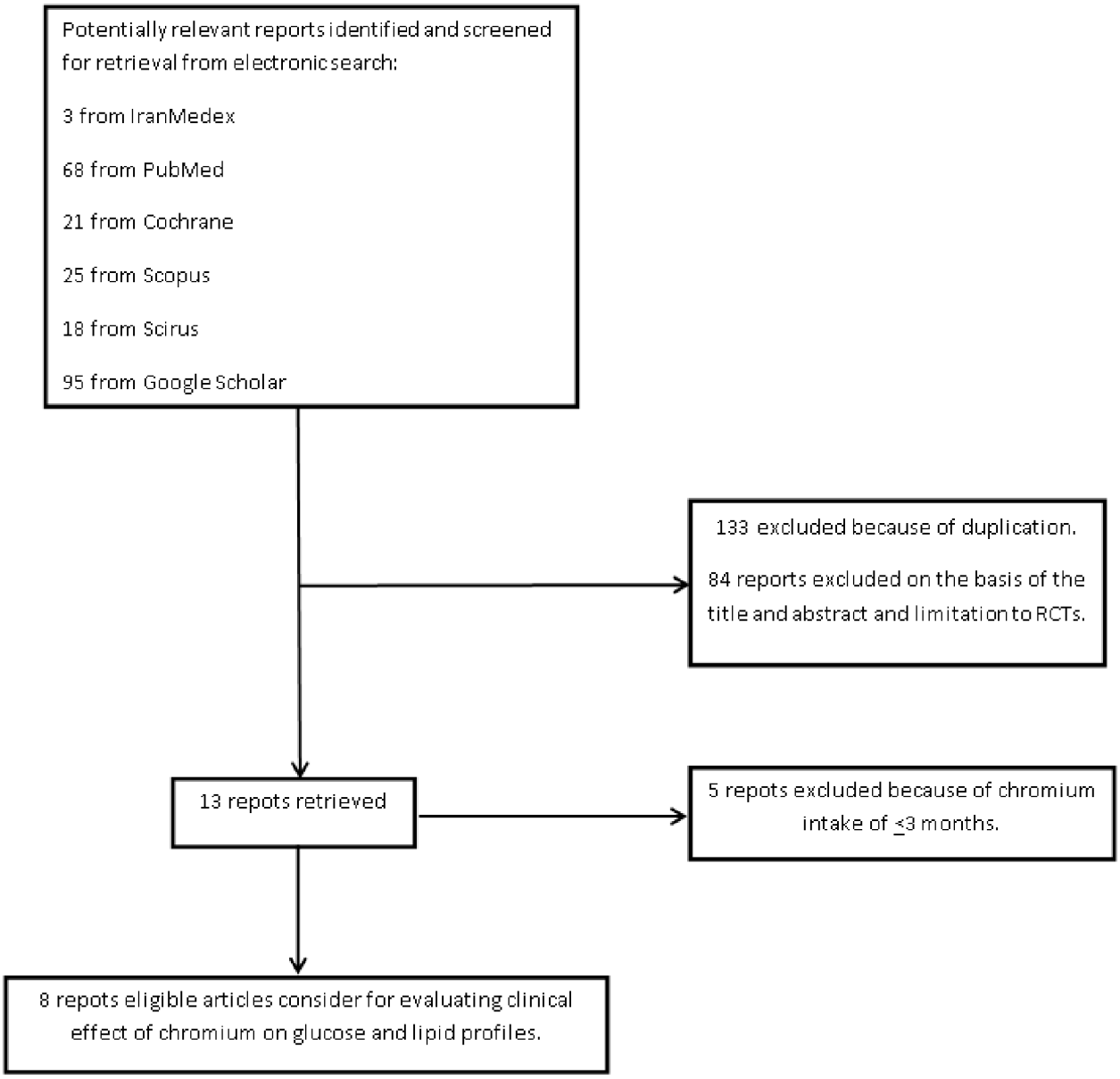

Figure 1. Flow diagram of the study selection process.

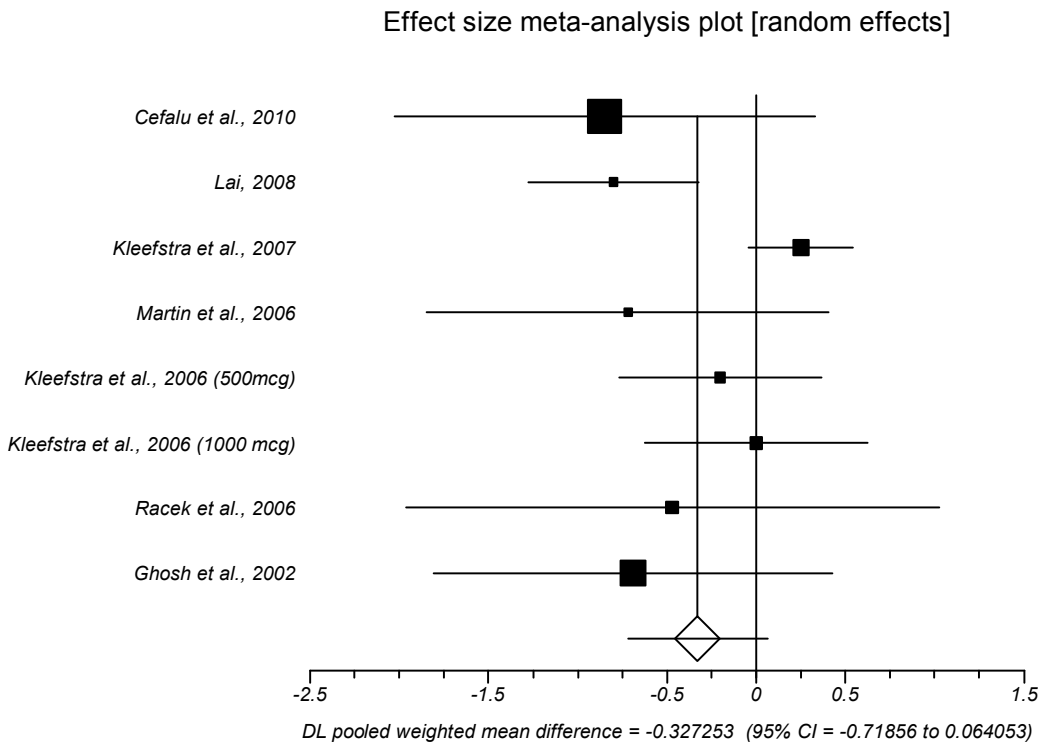

Figure 2-a. Individual and pooled effect size for weighted mean differences for the outcome of "ΔHbA1c" in the studies considering chromium supplement comparing to placebo therapy for diabetic patients

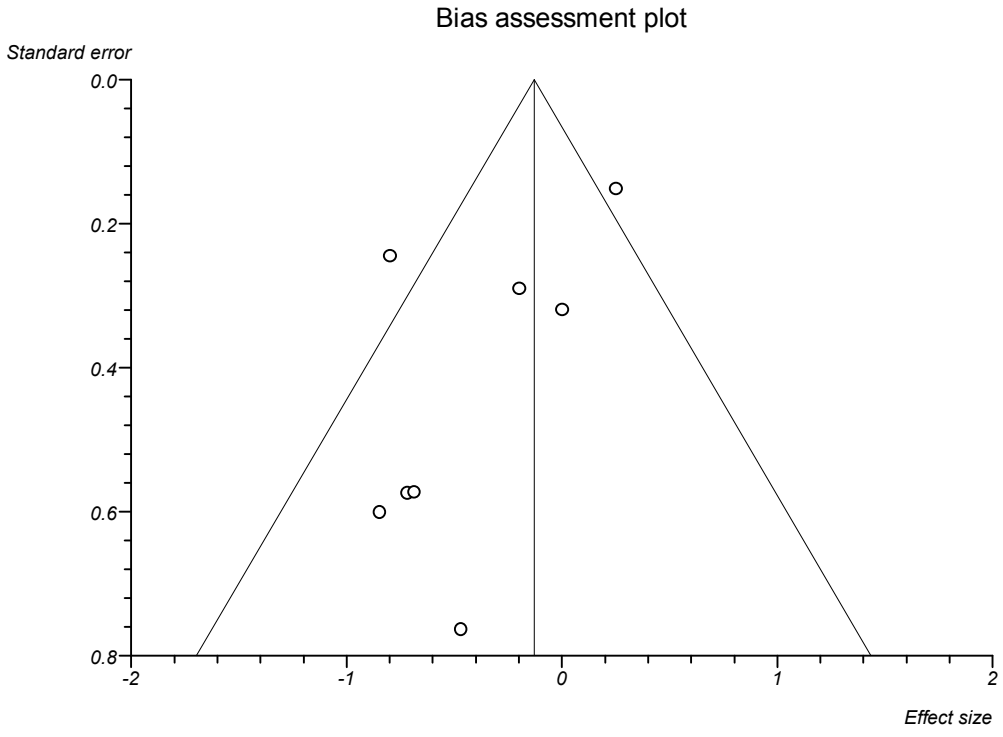

Figure 2-b. Publication bias indicators for the outcome of "ΔHbA1c" in the studies considering chromium supplement comparing to placebo therapy for diabetic patients

Effect of Cr on FBG in diabetic patients

The summary for effect size of weighted mean differences of FBG change "ΔFBG" in diabetic patients in Cr supplement therapy for six included trials comparing to Pl (13-15, 17-19) was -0.95 with 95% CI= -1.42 to -0.49 (P< 0.0001, Figure 3-a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (P= 0.3) and could be combined, thus the fixed effects for individual and summary of effect size for weighted mean differences was applied. For evaluation of publication Egger bias regression of normalized effect vs. precision for all included studies for "ΔFBG" in diabetic patients among Cr supplement vs. Pl therapy was= 0.43 (95% CI= -0.04 to 4.9, P= 0.81) and Begg-Mazumdar Kendall's test on standardized effect vs. variance indicated tau= 0.2, P= 0.72 (Figure 3-b, unbiased meta-analysis).

Effect of Cr on TC in diabetic patients

The summary for effect size of weighted mean differences of TC change "ΔTC" in diabetic patients in Cr supplement therapy for four included trials comparing to Pl retrieved from three studies (14-16) was 0.07 with 95%CI= -0.16 to 0.31 (P= 0.54, Figure 4-a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (P= 0.24) and could be combined, thus the fixed effects for individual and summary of effect size for weighted mean differences was applied. For evaluation of publication, Egger bias regression of normalized effect vs. precision for all included studies for "ΔTC" in diabetic patients among Cr supplement vs. Pl therapy was= -2.11 (95% CI= -3.73 to -0.5, P= 0.03) and Begg-Mazumdar Kendall's test on standardized effect vs. variance indicated tau= -0.67, P= 0.08 (Figure 4-b, unbiased meta-analysis).

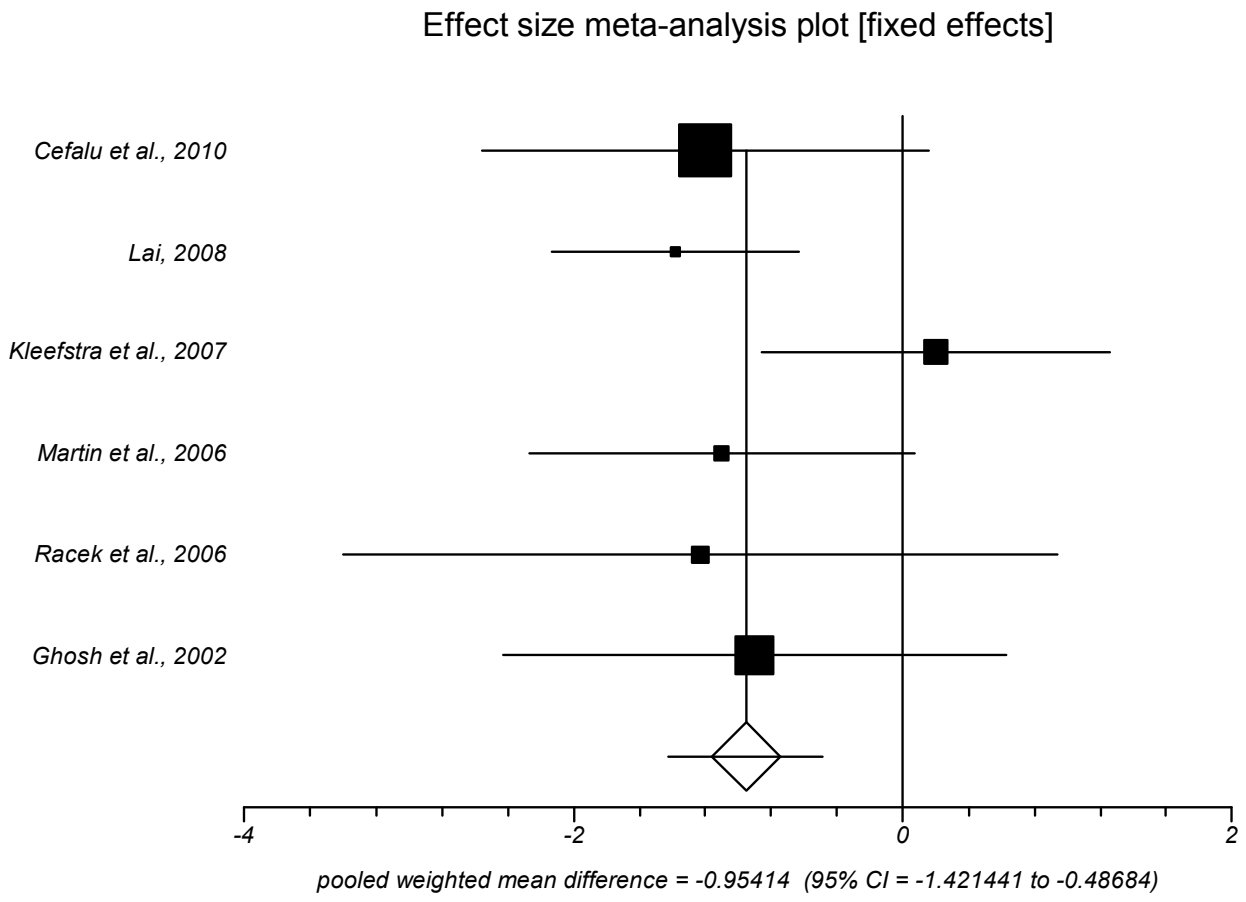

Figure 3-a. Individual and pooled effect size for weighted mean differences for the outcome of "ΔFG" in the studies considering chromium supplement comparing to placebo therapy for diabetic patients

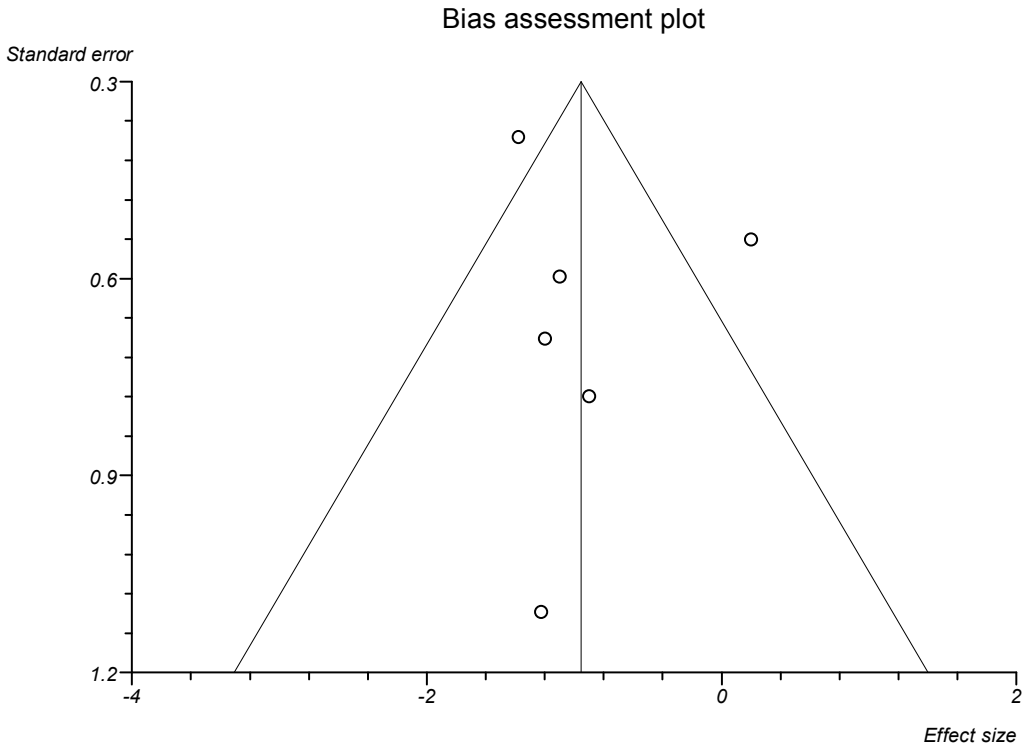

Figure 3-b. Publication bias indicators for the outcome of "ΔFG" in the studies considering chromium supplement comparing to placebo therapy for diabetic patients

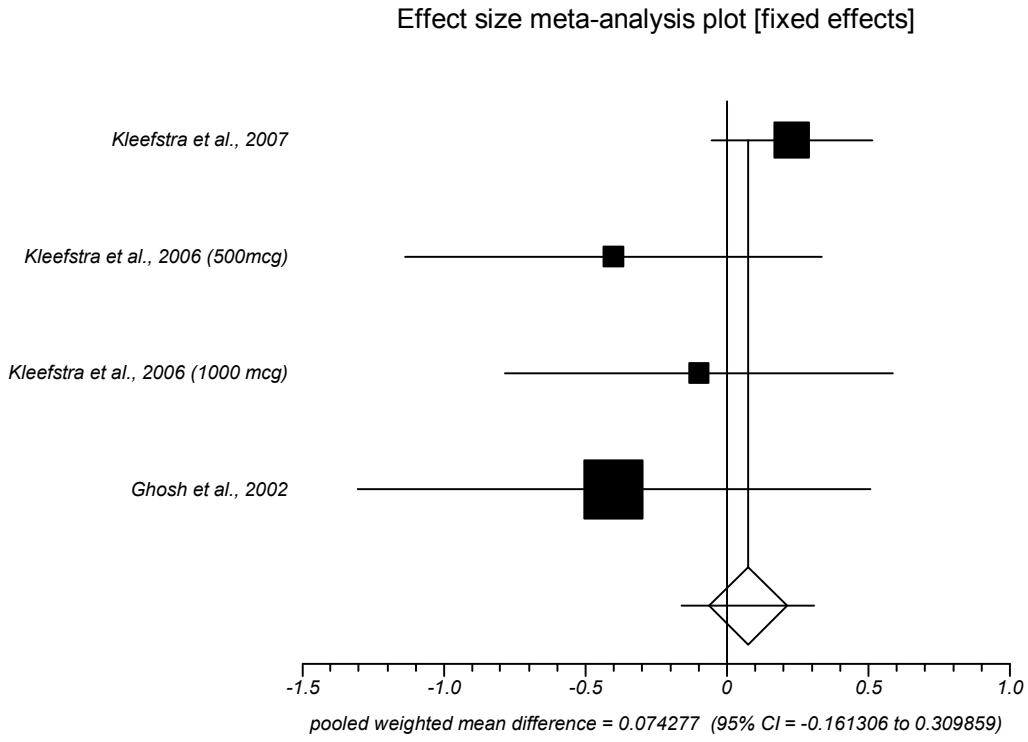

Figure 4-a. Individual and pooled effect size for weighted mean differences for the outcome of "ΔTC" in the studies considering chromium supplement comparing to placebo therapy for diabetic patients

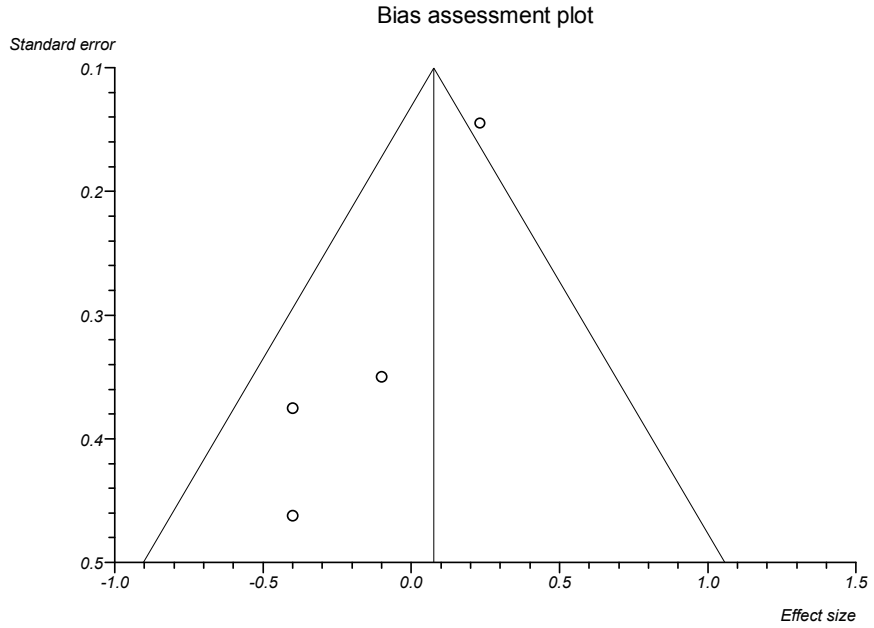

Figure 4-b. Publication bias indicators for the outcome of "ΔTC" in the studies considering chromium supplement comparing to placebo therapy for diabetic patients

Effect of Cr on HDL-C in diabetic patients

The summary for effect size of weighted mean differences of HDL-C change "ΔHDL-C" in diabetic patients in Cr supplement therapy for five included trials comparing to Pl retrieved from four studies (14-16, 19) was -0.01 with 95% CI= -0.07 to 0.05 (P= 0.67, Figure 5-a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (P= 0.19) and could be combined, thus the fixed effects for individual and summary of effect size for weighted mean differences was applied. For evaluation of publication Egger bias regression of normalized effect vs. precision for all included studies for "ΔHDL-C" in diabetic patients among Cr supplement vs. Pl therapy was= -1.08 (95% CI= -5.39 to 3.24, P= 0.49) and Begg-Mazumdar Kendall's test on standardized effect vs. variance indicated tau= -0.6, P= 0.08 (Figure 5-b, unbiased meta-analysis).

Effect of Cr on LDL-C in diabetic patients

The summary for effect size of weighted mean differences of LDL-C change "ΔLDL-C" in diabetic patients in Cr supplement therapy for five included trials comparing to Pl retrieved from four studies (14-16, 19) was -0.02 with 95% CI= -0.19 to 0.15 (P= 0.84, Figure 6-a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (P= 0.06) and could be combined, thus the fixed effects for individual and summary of effect size for weighted mean differences was applied. For evaluation of publication Egger bias regression of normalized effect vs. precision for all included studies for "ΔLDL-C" in diabetic patients among Cr supplement vs. Pl therapy was= -2.48 (95% CI= -7.71 to 0.76, P= 0.08) and Begg-Mazumdar Kendall's test on standardized effect vs. variance indicated tau= -0.6, P= 0.08 (Figure 6-b, unbiased meta-analysis).

Effect of Cr on VLDL-C in diabetic patients

The summary for effect size of weighted mean differences of VLDL-C change "ΔVLDL-C" in diabetic patients in Cr supplement therapy for two included trials comparing to Pl (13, 19) was -0.51 with 95% CI= -0.93 to 1.95 (P= 0.49, Figure 7). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (P= 0.15) and could be combined, but because of few included studies the random effects for individual and summary of effect size for weighted mean differences was applied. Evaluation of publication bias of all included studies for "ΔVLDL-C" in diabetic patients among Cr supplement vs. Pl therapy could not be calculated because of too few strata.

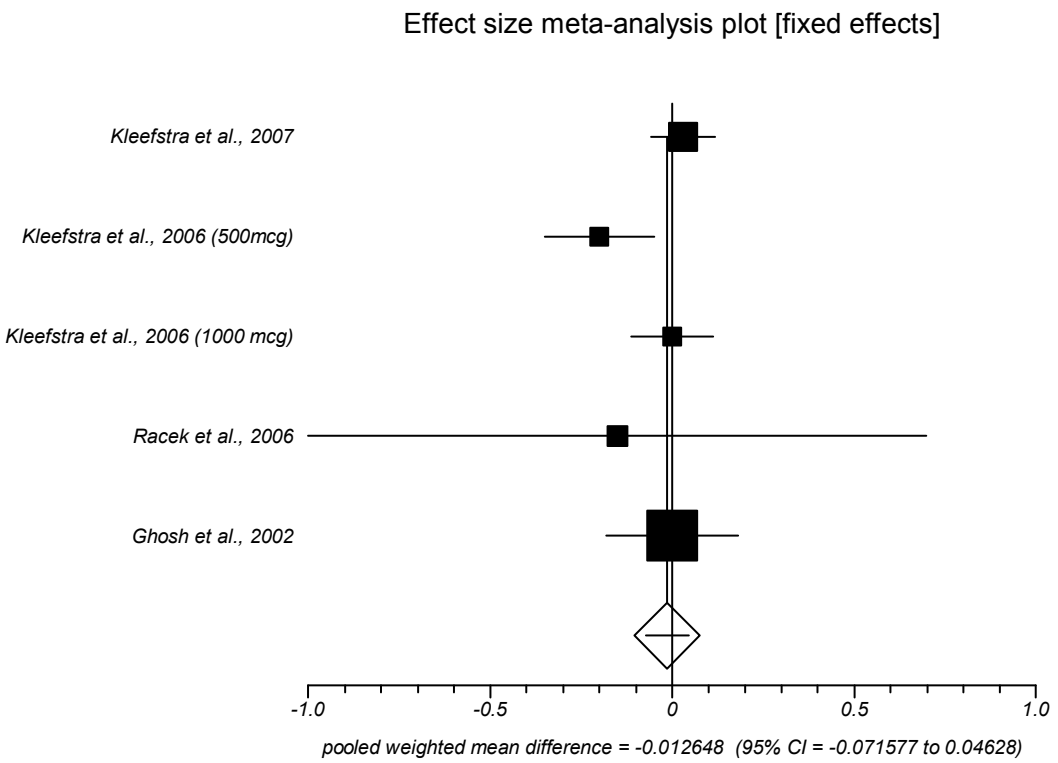

Figure 5-a. Individual and pooled effect size for weighted mean differences for the outcome of "ΔHDL-C" in the studies considering chromium supplement comparing to placebo therapy for diabetic patients

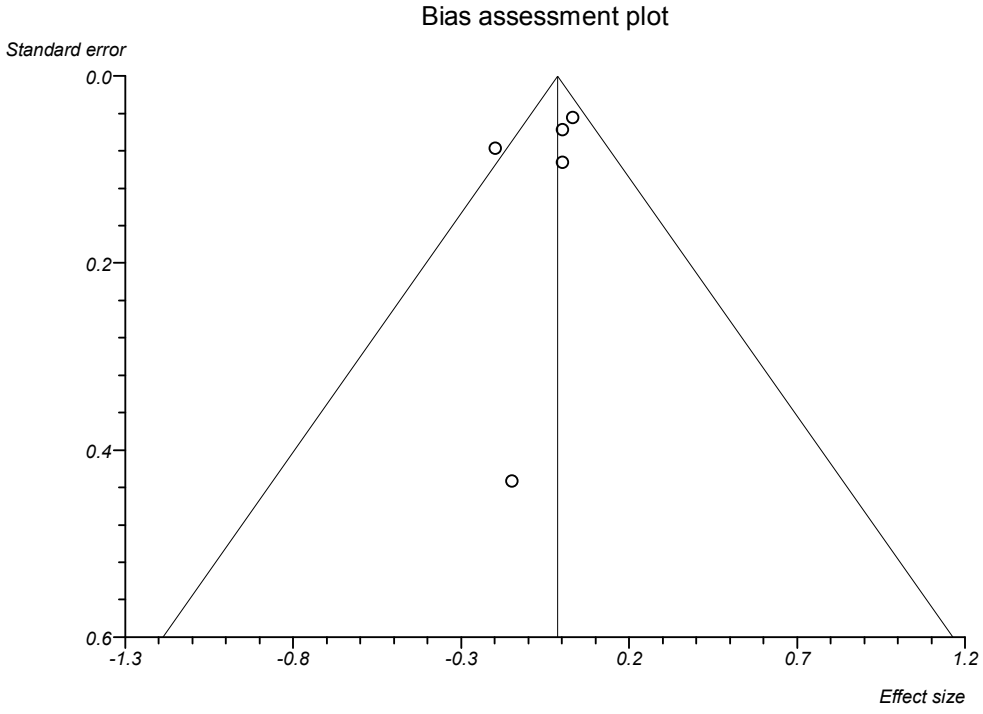

Figure 5-b. Publication bias indicators for the outcome of "ΔHDL-C" in the studies considering chromium supplement comparing to placebo therapy for diabetic patients

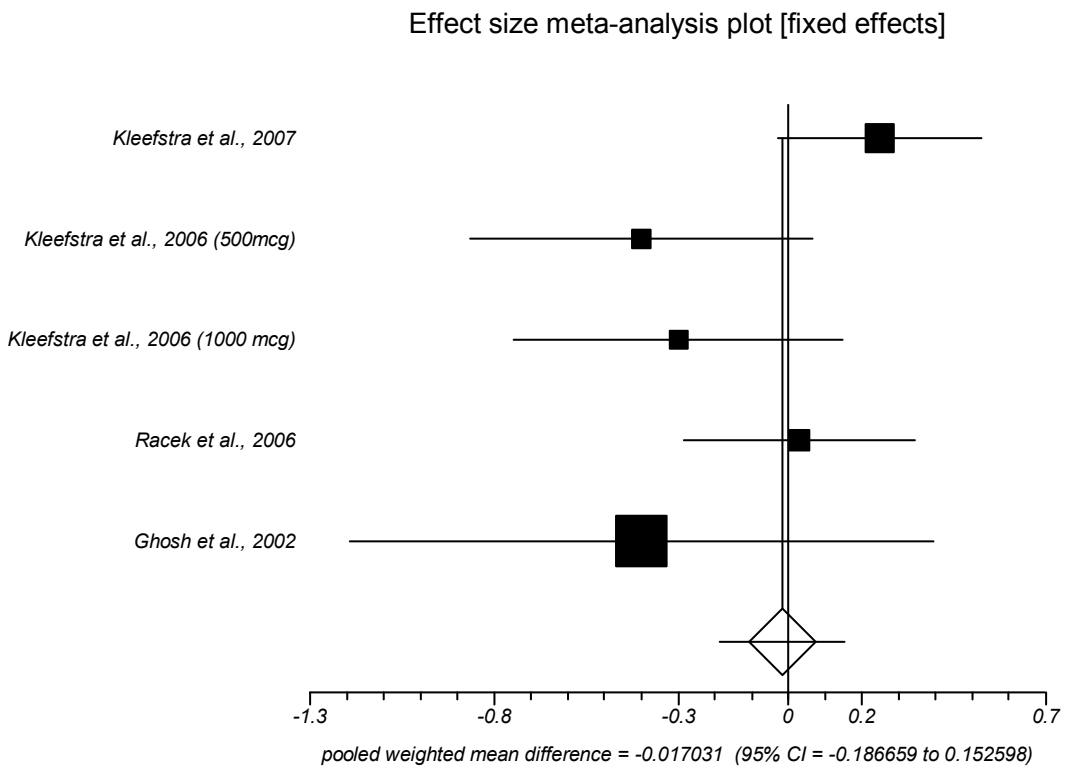

Figure 6-a. Individual and pooled effect size for weighted mean differences for the outcome of "ΔLDL-C" in the studies considering chromium supplement comparing to placebo therapy for diabetic patients

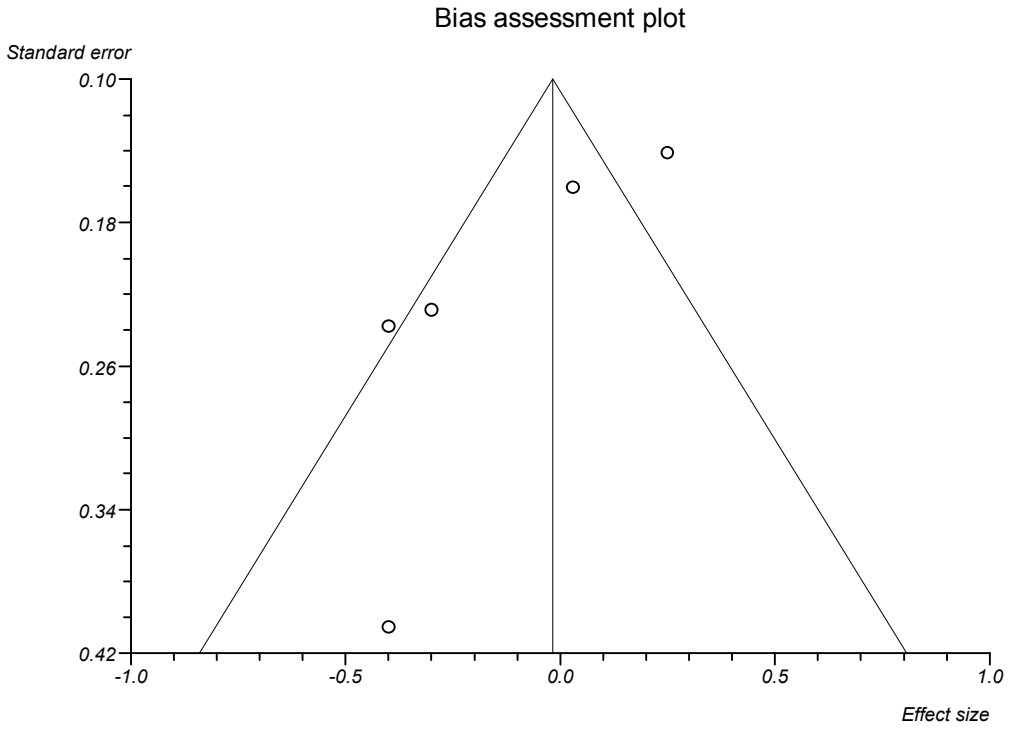

Figure 6-b. Publication bias indicators for the outcome of "ΔLDL-C" in the studies considering chromium supplement comparing to placebo therapy for diabetic patients

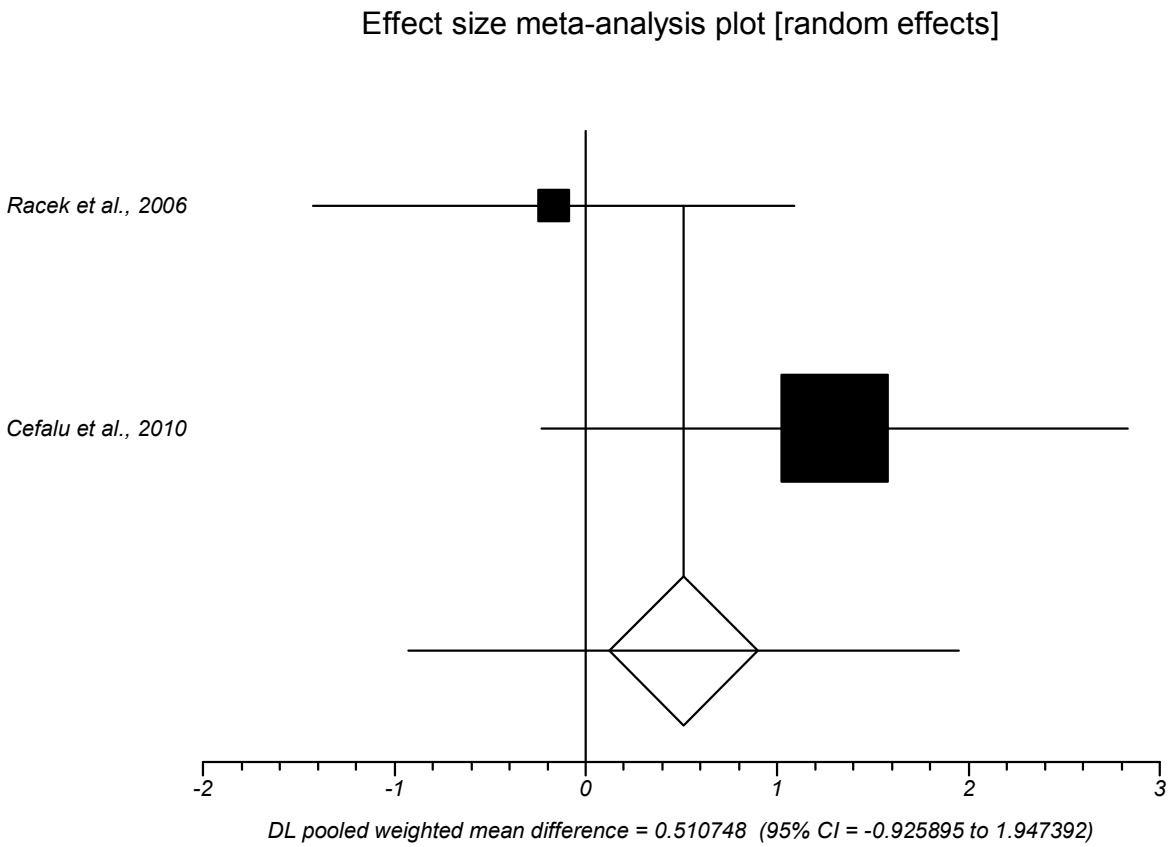

Figure 7. Individual and pooled effect size for weighted mean differences for the outcome of "ΔVLDL-C" in the studies considering chromium supplement comparing to placebo therapy for diabetic patients

Effect of Cr on TG in diabetic patients

The summary for effect size of weighted mean differences of TG change "ΔTG" in diabetic patients in Cr supplement therapy for six included trials comparing to Pl retrieved from five studies (14-16, 18, 19) was -0.15 with 95%CI= -0.36 to 0.07 (P= 0.18, Figure 8-a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (P= 0.85) and could be combined, thus the fixed effects for individual and summary of effect size for weighted mean differences was applied. For evaluation of publication Egger bias regression of normalized effect vs. precision for all included studies for "ΔTG" in diabetic patients among Cr supplement vs. Pl therapy was= -0.92 (95% CI= -1.61 to -0.23, P= 0.02) and Begg-Mazumdar Kendall's test on standardized effect vs. variance indicated tau= -0.6, P= 0.06 (Figure 8-b, unbiased meta-analysis).

Effect of Cr on BMI in diabetic patients

The summary for effect size of weighted mean differences of BMI change "ΔBMI" in diabetic patients in Cr supplement therapy for six included trials comparing to Pl retrieved from five studies (13, 15-17, 19) was -0.07 with 95% CI= -0.37 to 0.23 (P= 0.66, Figure 9-a). The Cochrane Q test for heterogeneity indicated that the studies are not heterogeneous (P= 0.73) and could be combined, thus the fixed effects for individual and summary of effect size for weighted mean differences was applied. For evaluation of publication Egger bias, regression of normalized effect vs. precision for all included studies for "ΔBMI" in diabetic patients among Cr supplement vs. Pl therapy was= -0.05 (95% CI= -1.92 to 1.82, P= 0.95) and Begg-Mazumdar Kendall's test on standardized effect vs. variance indicated tau= -0.2, P= 0.47 (Figure 9-b, unbiased meta-analysis).

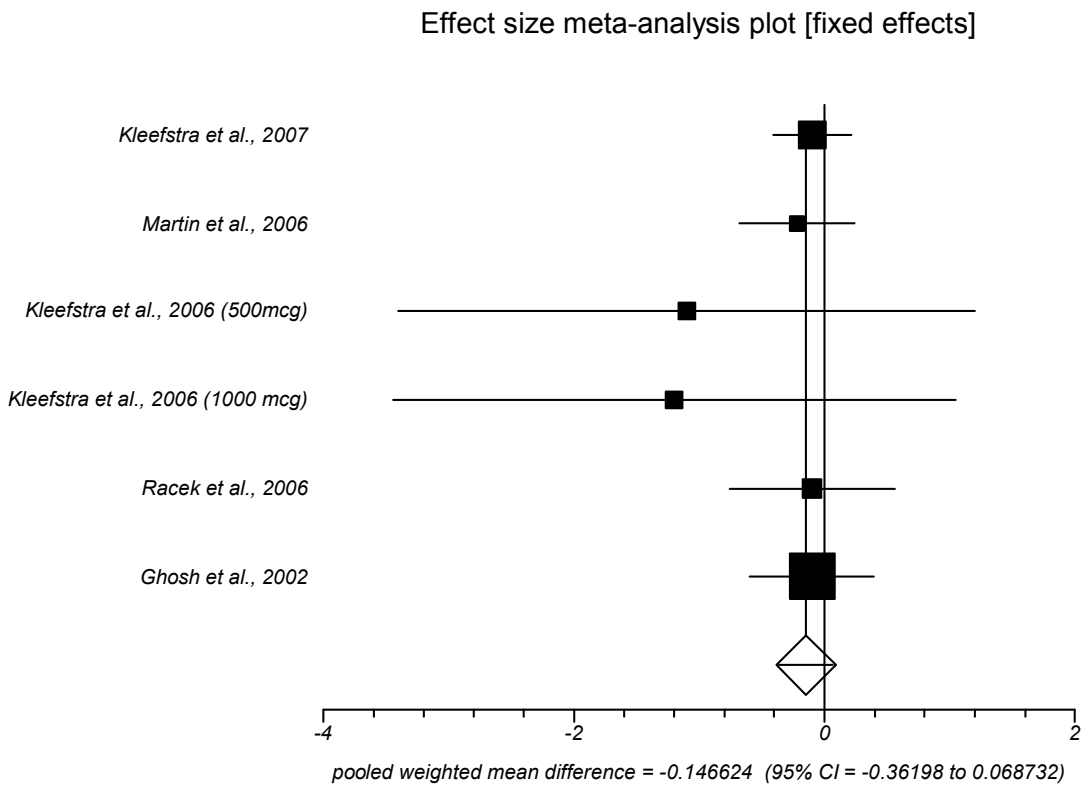

Figure 8-a. Individual and pooled effect size for weighted mean differences for the outcome of "ΔTG" in the studies considering chromium supplement comparing to placebo therapy for diabetic patients

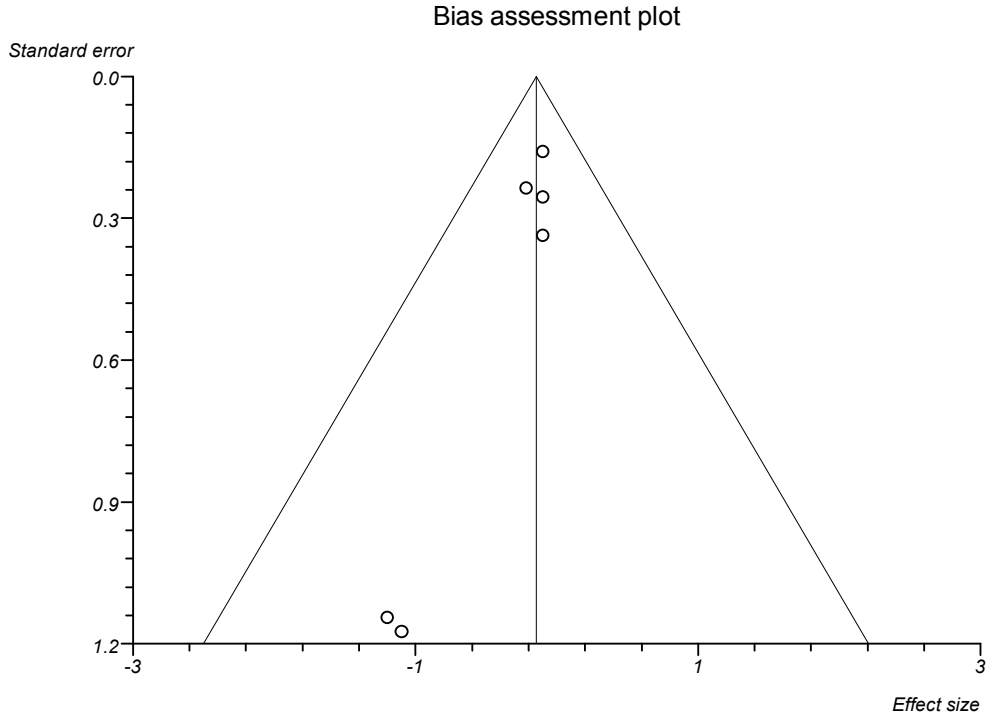

Figure 8-b. Publication bias indicators for the outcome of "ΔTG" in the studies considering chromium supplement comparing to placebo therapy for diabetic patients

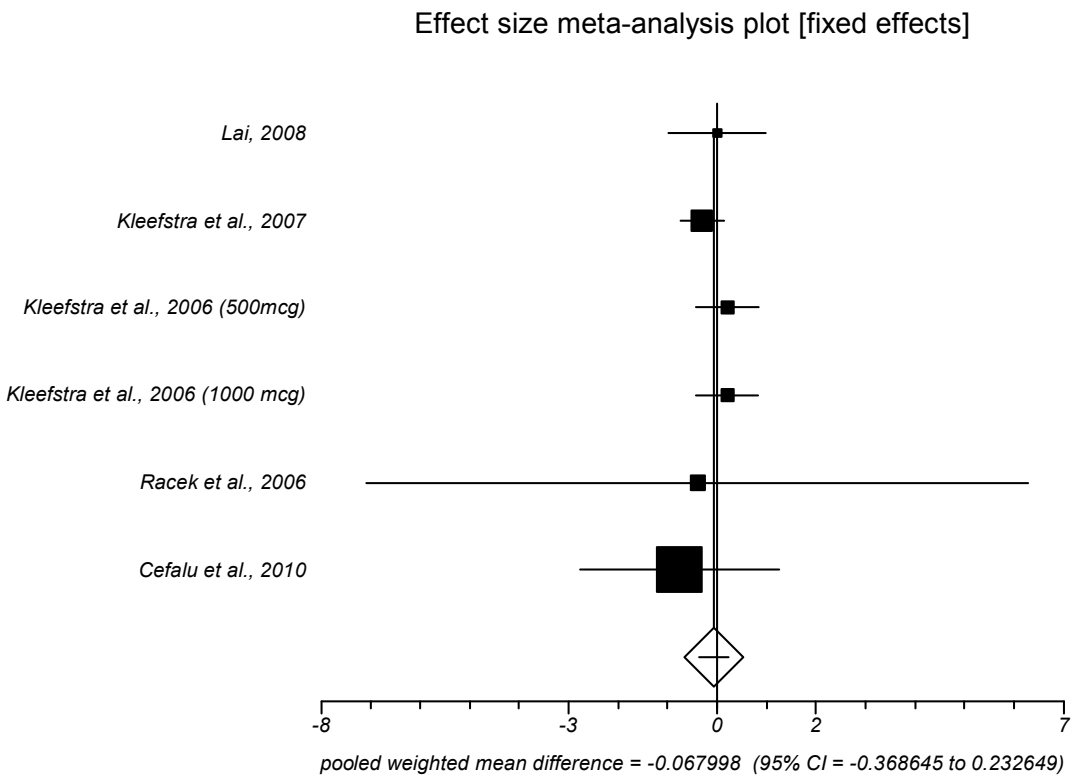

Figure 9-a. Individual and pooled effect size for weighted mean differences for the outcome of "ΔBMI" in the studies considering chromium supplement comparing to placebo therapy for diabetic patients

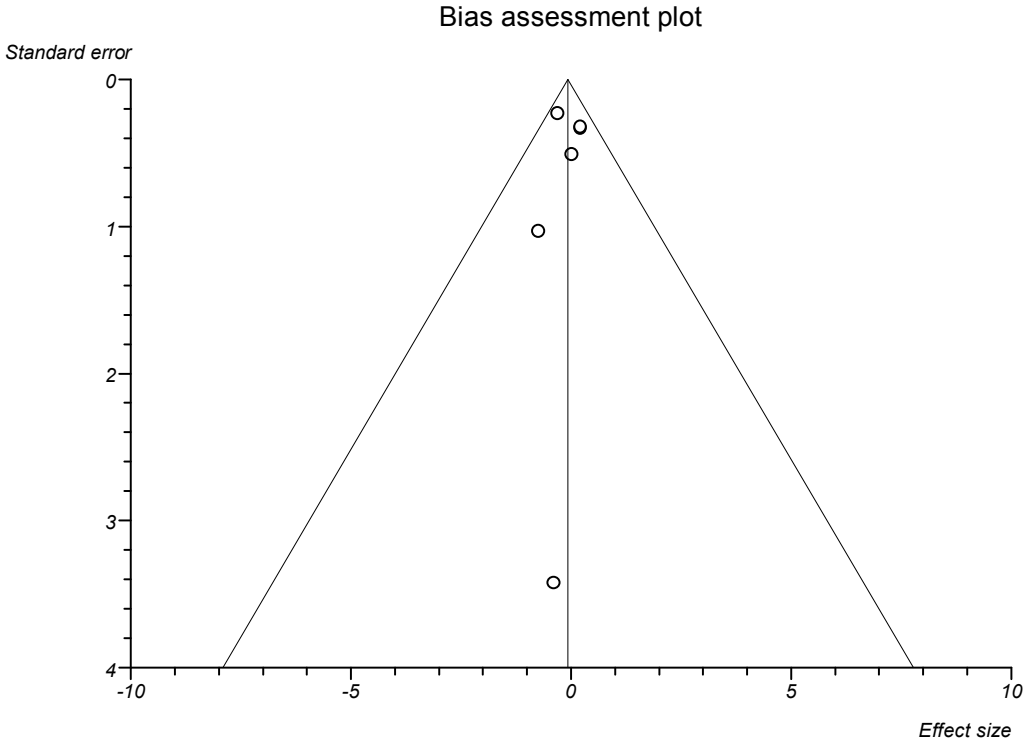

Figure 9-b. Publication bias indicators for the outcome of "ΔBMI" in the studies considering chromium supplement comparing to placebo therapy for diabetic patients

DISCUSSION

The present meta-analysis indicates that in patients with type 2 DM, Cr supplementation does not change HbA1c. To reach a better analysis, we eliminated the studies with duration of lesser than three months where changes in HbA1c is not properly observed. The present result on HbA1c is contrary to a recent review which reported the positive effect of Cr in HbA1c reduction by 0.34% through including 6 RCTs in patients with type 2 DM who had HbA1c higher than 7% (10). However, the present meta-analysis is specific for type 2 DM patients and includes Cr with biotin formulations. In the other hand, reviews by two other groups showed 0.6% and 0.9% reduction in HbA1c, respectively (20, 21). The meta-analysis of Balk et al. included type 2 DM patients and all forms of Cr formulations. The most controversial issue in that meta-analysis is the inclusion of trials that measured HbA1c in a period of less than 3 months which seems a major bias but they reported that all included papers showed a significant reduction in HbA1c. In the second review (21), fifteen papers were included while three of them were not RCT. They included both type 1 and type 2 DM, gestational DM, and even steroid-induced diabetes. In the present meta-analysis, four studies showed that Cr has no significant effect on HbA1c (13, 15, 16, 19). In two other studies (17, 18), a 0.7% and 1.16% reductions in HbA1c was reported for Cr, respectively. In another study (14), Cr could prevent increase of HbA1c in comparison to Pl. In other studies (16, 17, 19), Cr in the form of Cr-enriched yeast was used and only one of them (17) reported significant reduction in HbA1c.

We found that Cr supplementation significantly reduces FBS up to 7 mmol/L ($P< 0.0001$) as reported in three RCTs (14, 17, 18) with a level of 1.4, 1.72, and 0.5 mmol/L, respectively. Ghosh et al. (2002) explained that because of an increase in insulin action, Cr could control hyperglycemia in type 2 DM. Among these reports, only Lai et al. (2008) evaluated the Cr-enriched yeast. Also, Patal et al. (2010) reported that FBS decreases post Cr treatment to 0.67 mmol/L. However, Broadhurst and Domenico (2006) showed a mean FBS of 1.5 mmol/L.

The present meta-analysis indicates that Cr has no benefit on lowering TC, HDL-C, LDL-C, VLDL-C, and TG that is consistent with previous reviews (10, 20). Furthermore, our meta-analysis indicates that Cr had no significant effect on BMI. Taking collectively, we can conclude that current evidences do not support positive effects for Cr in the management of DM as it only reduces FBG that is not sufficient in long-term therapy of DM patients.

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Table 2. Characteristics of studies included in the meta-analysis

Authors	Year of publication	Type of study	Sample Size	N	Type of Diabetes	Age	Gender	Dose and type of Chromium/day	Duration of Cr. therapy
Cefalu et al., (13)	2010	RCT	Cr: 70 Pl: 67	137	2	Cr: 58.7±1.0 Pl: 56.1±1.1	Cr:37 M Pl:39 M	1000 µg CrP	6 months
Lai, (17)	2008	RCT	Cr: 10 Pl: 10	20	2	<56	M:9	1000 µg Cr-enriched yeast	6 months
Kleefstra et al., (15)	2007	RCT	Cr: 28 Pl: 28	56	2	Cr: 68±8.2 Pl: 66±8.6	Cr:18 M Pl:17 M	400 µg Cr-enriched yeast	6 months
Martin et al., (18)	2006	RCT	Cr: 14 Pl: 11	25	2	59.7±8	M:17	1000 µg CrP	6 months
Kleefstra et al., (16)	2006	RCT	Cr: 14 Pl: 17	31	2	Cr: 60±8.8 Pl: 62±7.5	Cr: 4 M Pl: 10 M	500 µg CrP	6 months
			Cr: 15 Pl: 17	32	2	Cr: 59±6.4 Pl: 62±7.5	Cr: 5 M Pl: 10 M	1000 µg CrP	6 months
Racek et al., (19)	2006	RCT	Cr: 19 Pl: 17	36	2	-	Cr: 7 M Pl: 2 M	400 µg Cr-enriched yeast	3 months
Ghosh et al., (14)	2002	RCT	Cr: 50 Pl: 50	50	2	53.5±10.9	M:33	400 µg CrP	3 months

Chromium (Cr); Placebo (Pl)

Table 3. Outcomes differences of studies included in the meta-analysis

Study	HbA1c, %		Fasting glucose		Total-C		HDL-C		LDL-C		TG		VLDL-C		BMI	
	Cr	Pl	Cr	Pl	Cr	Pl	Cr	Pl	Cr	Pl	Cr	Pl	Cr	Pl	Cr	Pl
Cefalu et al., (13)	-0.72 ± 4.16	0.13 ± 2.67	-1.10 ± 4.87	0.10 ± 2.95	-	-	-	-	-	-	-	-	1.19 ± 5.58	-0.11 ± 3.18	-0.05 ± 5.55	0.71 ± 6.45
Lai, (17)	-0.70 ± 0.53	0.10 ± 0.56	-1.40 ± 0.66	-0.02 ± 1.02	-	-	-	-	-	-	-	-	-	-	-0.10 ± 1.20	-0.10 ± 1.06
Kleefstra et al., (15)	0.51 ± 0.64	0.26 ± 0.47	0.90 ± 2.30	0.70 ± 1.70	0.46 ± 0.42	0.23 ± 0.64	0.14 ± 0.18	0.11 ± 0.15	0.31 ± 0.40	0.06 ± 0.63	0.03 ± 0.49	0.13 ± 0.68	-	-	0.10 ± 0.80	0.40 ± 0.90
Martin et al., (18)	-1.16 ± 1.42	-0.44 ± 1.43	-1.72 ± 1.50	-0.62 ± 1.46	-	-	-	-	-	-	0.12± 0.52	0.34 ± 0.66	-	-	-	-
Kleefstra et al., 500 µg (16)	-0.50 ± 0.80	-0.30 ± 0.80	-	-	-0.20 ± 0.80	0.20 ± 1.20	-0.10 ± 0.30	0.10 ± 0.10	-0.10 ± 0.60	0.30 ± 0.70	-0.10 ± 0.90	1.01 ± 4.30	-	-	0.20 ± 1.10	0.00 ± 0.70
Kleefstra et al., 1000 µg (16)	-0.30 ± 0.90	-0.30 ± 0.90	-	-	0.10 ± 0.40	0.20 ± 1.30	0.10 ± 0.10	0.10 ± 0.20	0.00 ± 0.40	0.30 ± 0.80	-0.20 ± 0.50	1.00 ± 4.40	-	-	0.20± 1.00	0.00 ± 0.80
Racek et al., (19)	-0.30 ± 2.25	0.17 ± 2.32	-0.43± 2.89	0.80 ± 3.74	-	-	-0.12 ± 1.23	0.03 ± 1.37	-0.01 ± 0.43	-0.04 ± 0.53	-0.14 ± 0.98	-0.04 ± 1.04	0.07 ± 1.38	0.24 ± 2.39	-0.45 ± 8.57	-0.05 ± 11.83
Ghosh et al., (14)	0.01 ± 2.96	0.7 ± 2.75	-0.5 ± 3.67	0.4 ± 4.11	-0.7 ± 2.36	-0.3 ± 2.26	-0.2 ± 0.42	-0.2 ± 0.5	-0.5 ± 2.14	-0.1 ± 1.9	0.2 ± 1.27	0.3 ± 1.27	-	-	-	-

Chromium (Cr); Placebo (Pl)