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No favourable effects of Cr (III) supplementation on lipid metabolism on type 2 Diabetes Mellitus: a meta-analysis of single and double-blind, randomized, placebo controlled trials.

Ningún efecto favorable de la suplementación de cr (III) en el metabolismo de lípidos en Diabetes tipo 2: meta-análisis de ensayos clínicos, simple y doble ciego, controlados con placebo.

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Abstract
Introduction. Type 2 diabetes mellitus is an important global health issue which prevalence has been increasing in the last years. Many studies have linked chromium supplementation with improvement of type 2 diabetes mellitus.
Aim. Perform a meta-analysis of single and double-blind, randomized, placebo controlled trials, where participants diagnosed of type 2 DM or glucose intolerants were supplemented with Cr (III).
Methods. Systematic literature search in electronic databases was conducted, using the following search terms: (diabetes) AND (chromium), until July, 2016. Eligible studies were limited to double or single-blind, parallel group, placebo-controlled, randomized clinical trials, comparing Cr mono or combined supplementation at least for 30 days against placebo, in subjects diagnosed of type 2 DM or with glucose intolerance.
Results. Total doses of Cr supplementation and brewer's yeast ranged from 20 to 1000 µg/day, and duration of supplementation ranged from 30 to 120 days. No statistically significant reduction was found in HDL-C (p=0.63), LDL-C (p=0.53) and TG (p=0.34) compared to placebo; with a weighted average effect size of -0.44 (95% CI: -2.2 to 1.33) mg/dL, -1.43 (95% CI: -5.94 to 3.08) mg/dL and -7.43 (95% CI: -22.67 to 7.82) mg/dL, respectively.
Conclusion. Evidence in our study suggests no favourable effects of chromium supplementation on lipid metabolism control in patients with type 2 diabetes.

KEYWORDS
Type 2 Diabetes mellitus; chromium; supplementation; hyperglycaemia.

Resumen
Introducción. Diabetes mellitus tipo II es un importante problema de salud mundial cuya prevalencia ha aumentado en los últimos años. Muchos estudios han relacionado los suplementos de cromo con la mejora de la diabetes mellitus tipo 2.
Objetivo. Realizar un meta-análisis de ensayos individuales y doble ciego, aleatorizados, controlados con placebo, en los que los participantes diagnosticados de DM tipo 2 o intolerantes a la glucosa fueran suplementados con Cr (III).
Métodos. Se llevó a cabo una búsqueda bibliográfica sistemática en bases de datos electrónicas, utilizando los términos de búsqueda: (diabetes) y (cromo), hasta julio de 2016. Los estudios elegibles se limitan a doble o simple ciego, de grupos paralelos, controlados con placebo, ensayos clínicos aleatorios, comparando la suplementación mono Cr o combinada durante al menos 30 días en comparación con placebo, en sujetos diagnosticados de DM tipo 2 o con intolerancia a la glucosa.
Resultados. La dosis total de la suplementación con Cr y levadura osciló de 20 a 1000 mg / día, y la duración de la administración de suplementos varió de 30 a 120 días. No se encontró reducción estadísticamente significativa en los niveles de HDL-C (p = 0,63), LDL-

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C (p = 0,53) y TG (p = 0,34) en comparación con el placebo; con un efecto medio ponderado de -0.44 (95% CI: -2.2 to 1.33) mg/dL, -1.43 (95% CI: -5.94 to 3.08) mg/dL y -7.43 (95% CI: -22.67 to 7.82) mg/dL, respetivamente.
Conclusión. La evidencia de nuestro estudio no sugiere que existen efectos favorables de los suplementos de cromo sobre el control del metabolismo lipídico en pacientes con diabetes tipo II.

PALABRAS CLAVE
Diabetes mellitus tipo II; cromo; suplementación; hiperglucemia.

INTRODUCTION

Type 2 diabetes mellitus is an important global health issue which prevalence has been increasing in the last years. Estimations indicate that in 2013 382 million people had diabetes, and in 2035 probably this number will rise to 592 million [(1)]. In addition, this disease is associated with numerous comorbidities, which affect seriously patients' quality of life and has a great impact on economy of health systems [(2)].

Along with usual treatments including changes in lifestyle and drugs, the use of supplements by patients with type 2 diabetes mellitus is increasing [(3)]. Among them, chromium supplements, which in 2014 represented 4,1% of mineral sales ($108 million) in the United States, behind only calcium and magnesium [(4)]. Chromium supplements are made with trivalent chromium (Cr^{3+}). This trace element can be found in small amounts in food [(5)], and although its function in the organism is not well established, it seems to be related with carbohydrate and lipid metabolism [(6)]. Many studies have linked chromium supplementation with improvement of type 2 diabetes mellitus management [(7)-(8)]. It has been related with changes in parameters as fasting plasma glucose (FPG) [(7)-(8)], hemoglobin A1c (HbA1c) [(9)-(8)] and plasmatic lipids.

Nevertheless, there is another studies with controversial results [(10)], therefore there is not enough scientific evidence to support chromium supplementation.

AIM

The aim of the present study is perform a meta-analysis of single and double-blind, randomized, placebo controlled trials, where participants diagnosed of type 2 DM or glucose intolerants were supplemented with Cr (III) in different formulations.

METHODS

Systematic literature search in electronic databases PubMed, Science Direct, Clinicaltrial.gov, Scopus and Web of Science was conducted, using the following search terms and key words: (diabetes) AND (chromium), until July, 2016. Likewise, additional searches for potential trial including review articles were made. All searches were limited to studies in humans and English language publications.

Eligible studies were limited to double or single-blind, parallel group, placebo-controlled, randomized clinical trials, comparing Cr mono or combined supplementation at least for 30 days against placebo, in subjects diagnosed of type 2 DM or with glucose intolerance.

The outcomes of interest were high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG).

Two reviewers independently screened full papers, all duplicated articles, as well as those that did not meet the aforementioned inclusion criteria were excluded, disagreements were resolved by a third author.

Data from individual studies were abstracted: (i) first autor's name; (ii) year of publication; (iii) study location; (iv) study design; (v) number of participants in each group; (vi) type Cr supplementation and dose; (vii) duration of therapy; (viii) subjects characteristics: age, gender, body mass index (BMI); (ix) baseline levels of HDL-C, LDL-C and TG, and (x) data regarding follow-up.

Methodological quality of trials was evaluated independently by two authors using Jadad scale [(11)]. The score range from 0 to 3 points with a low quality report of score 1 or less and a high quality report of score at least 3, the items used for the assessment of each publication was related with adequacy of randomization, appropriate subject or/and investigators blinding, and addressing of dropouts (Table 1).

Statistical analysis was carried out using the SPSS® version 18.0 (SPSS, Chicago, IL, USA). Treatment effect was estimated with mean difference in the final values of outcome measure (HbA1c, FPG, lipid variables) between the treatment group and the placebo group. The pooled mean difference and estimated 95% confidence interval (95% CI) were calculated using the inverse variance-weighted method [(12)]. The Cochran's Q statistic test was used to test heterogeneity and $p < 0.10$ was considered significant [(13)]. In case of heterogeneity, the random effects model was used [(12)]. Funnel plot and Egger's method [(14)] were used as publication bias indicator.

Table 1. Quality score of randomized controlled trial included in the meta-analysis (Jadad scale)

Study	Randomization	Blinding	Dropouts	Total score
Guimarães et al. (18)	Yes	Yes	No	2
Hosseinzadeh et al. (20)	Yes	Yes	Yes	3
Jain et al. (15)	Yes	Yes	Yes	3
Sharma et al. (8)	Yes	Yes	No	2
Albarracin et al. (25)	Yes	Yes	Yes	3
Geohas et al. (17)	Yes	Yes	No	2
Kleefstra et al.,2007 (22)	Yes	Yes	No	2
Singer et al. (16)	Yes	Yes	Yes	3
Martin et al. (21)	Yes	Yes	Yes	3
Pei et al. (23)	Yes	Yes	No	2
Racek et al. (19)	Yes	Yes	No	2
Kleefstra et al.,2006 (26)	Yes	Yes	No	2
Gunton et al. (24)	Yes	Yes	No	2
Liu et al. (7)	Yes	Yes	No	2
Paiva et al. (9)	Yes	Yes	Yes	3

RESULTS

Search results and study characteristics

We initially identified 92 reports of Cr supplementation in type 2 DM or glucose intolerance. After screening, 42 reports were excluded because they did not meet the inclusion criteria, and 35 trials were excluded due to incomplete data. The remaining 15 reports were placebo-controlled randomized, parallel trials. Of these, one trial was rejected because this was a duplicate report. Fifteen trials fulfilled the inclusion criteria and were included in this systematic review (Figure 1).

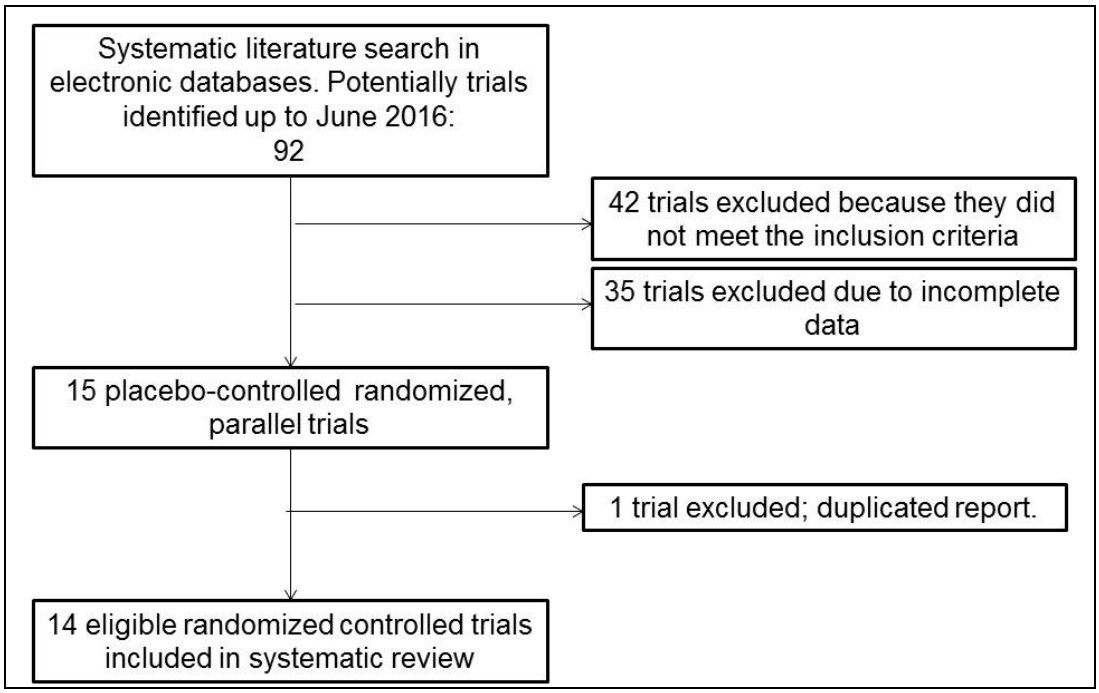
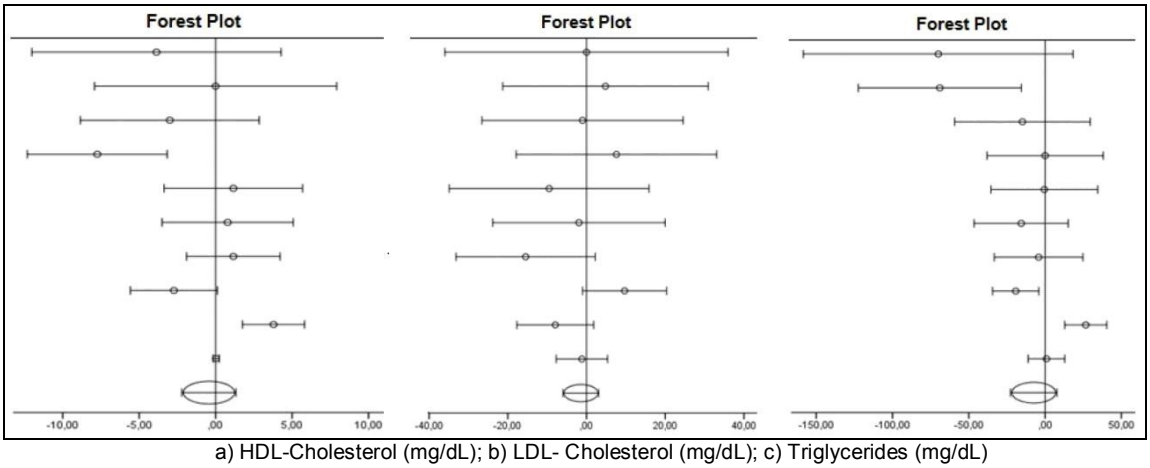


Figure 1. Flow diagram of the trial selection process

Formulations of Cr included chromium picolinate (CP), chromium picolinate and biotin combination (CPB); chromium nicotinate (NC), chromium dinicocysteinate (CDNC); chromium yeast (CY), brewer's yeast (BY), chromium chloride (CC), and chromium milk powder (CMP). Total doses of Cr supplementation and brewer's yeast ranged from 20 µg/day to 1000 µg/day, and duration of supplementation ranged from 30 to 120 days.

Meta-analysis of effect of Cr on HDL-C in type 2 DM

The Cochrane Q test indicated that studies were heterogeneous ($p < 0.0001$), so the random effects model was used. This meta-analysis incorporated data from a total of 10 studies [7–9,16,18,22,25,26] (735 participants), and results obtained showed that effect size of weighted mean differences of HDL-Col change in type 2 DM patients in Cr supplement therapy was not significant: mean difference - 0.44 (95% CI: -2.20 to 1.33) mg/dL; $p = 0.63$ (Figure 2). No publication bias was detected.



a) HDL-Cholesterol (mg/dL); b) LDL- Cholesterol (mg/dL); c) Triglycerides (mg/dL)

Figure 2. Overall effect expressed as mean difference (95% CI), mg/dL

Meta-analysis of effect of Cr on LDL-C in type 2 DM

The Cochrane Q test showed heterogeneity ($p < 0.0001$), so the random effects model was used. This meta-analysis, which incorporated data from a total of 10 studies [7–9,16–19,22,25,26] (735 participants) of effect of Cr on LDL-Col showed a non significant effect size of weighted mean differences of LDL-Col change in type 2 DM patients in Cr supplement therapy: -1.43 (95% CI: -5.94 to 3.08) mg/dL; $p = 0.53$ (Figure 2). No publication bias was detected.

Meta-analysis of effect of Cr on TG in type 2 DM

The Cochrane Q test indicated that studies were heterogeneous ($p < 0.0001$), so the random effects model was used. This meta-analysis incorporated data from a total of 10 studies [7–9,16,17,21,22,24,25] (744 participants), and results obtained showed that effect size of weighted mean differences of TG change in type 2 DM patients in Cr supplement therapy was not significant: mean difference -7.43 (95% CI: -22.67 to 7.82) mg/dL; $p = 0.34$ (Figure 2). No publication bias was detected.

DISCUSION

Results from this meta-analysis suggest that Cr supplement therapy to type 2 diabetes patients has no statistically significant reduction in HDL-C ($p=0.63$), LDL-C ($p=0.53$) and TG ($p=0.34$) compared to placebo. These results agreed with those of our previous meta-analysis [27].

However, some limitations of this meta-analysis should be noted. First the high level of heterogeneity with regard to results of the studies included, these could be due to differences in the extent of glycaemic control at baseline, duration of diabetes, dose and form of Cr and duration of supplementation. Another factor could be changes over the time in the standard of care for type 2 diabetes mellitus patients or the ethnic background of participants in each study and life style differences.

CONCLUSION

Results did not suggest that Cr supplement therapy to type 2 diabetes patients improve HDL-c, LDL-c and TG levels. The short duration of studies, variable quality of data and large heterogeneity across these studies limit the strength of conclusions. Further studies are recommended. Our meta-analysis highlights the questions that remain unanswered and the issues that need to be addressed in future randomized clinical trials of Cr on lipid metabolism.

AUTHORSHIP

All authors have contributed to the conception and design of the work, data collection, data analysis and interpretation, article writing and critical review. All authors have approved the final version for publication.

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CONFLICT OF INTERESTS

No conflict of interests.

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