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Nutrición Hospitalaria, vol. 33, núm. 1, enero-febrero, 2016, pp. 156-161
Sociedad Española de Nutrición Parenteral y Enteral
España

Available in: http://www.redalyc.org/articulo.oa?id=309245772026
Chromium supplementation in patients with type 2 diabetes and high risk of type 2 diabetes: a meta-analysis of randomized controlled trials

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Abstract

Introduction: Chromium is an essential trace mineral for carbohydrate and lipid metabolism, which is currently prescribed to control diabetes mellitus. Results of previous systematic reviews and meta-analyses of chromium supplementation and metabolic profiles in diabetes have been inconsistent.

Aim: The objective of this meta-analysis was to assess the effects on metabolic profiles and safety of chromium supplementation in type 2 diabetes mellitus and cholesterol.

Methods: Literature searches in PubMed, Scopus and Web of Science were made by use of related terms-keywords and randomized clinical trials during the period of 2000-2014.

Results: Thirteen trials fulfilled the inclusion criteria and were included in this systematic review. Total doses of Cr supplementation and brewer’s yeast ranged from 42 to 1,000 µg/day, and duration of supplementation ranged from 30 to 120 days. The analysis indicated that there was a significant effect of chromium supplementation in diabetics on fasting plasma glucose with a weighted average effect size of -29.26 mg/dL, p = 0.01, CI 95% = −52.4 to -6.09; and on total cholesterol with a weighted average effect size of -6.7 mg/dL, p = 0.01, CI 95% = −11.88 to -1.53.

Conclusions: The available evidence suggests favourable effects of chromium supplementation on glycaemic control in patients with diabetes. Chromium supplementation may additionally improve total cholesterol levels.

Palabras clave:
- Diabetes tipo 2
- Hiperglucemia
- HbA1c
- Colesterol
- Cromo
- Ensayo clínico controlado aleatorizado

Resumen

Introducción: el cromo es un oligoelemento esencial para el metabolismo de carbohidratos y lípidos, que actualmente está prescrito para controlar la diabetes mellitus. Los resultados de las revisiones sistemáticas anteriores y metaanálisis de los suplementos de cromo y de perfiles metabólicos en diabetes han sido inconsistentes.

Objetivo: el objetivo de este metaanálisis fue evaluar los efectos sobre los perfiles y la seguridad de la suplementación de cromo en la diabetes mellitus tipo 2 y el colesterol.

Métodos: se realizaron búsquedas bibliográficas en PubMed, Scopus y Web of Science mediante el uso de palabras clave relacionadas y ensayos clínicos aleatorizados durante el periodo de 2000-2014.

Resultados: trece ensayos cumplieron los criterios de inclusión y se incluyeron en esta revisión sistemática. Las dosis totales de la suplementación con Cr y levadura de cerveza oscilaron entre 30 a 120 días. El análisis indicó que hubo un efecto significativo de la suplementación de cromo en los diabéticos en la glucemia en ayunas, con un tamaño del efecto promedio ponderado de -29.26 mg/dL, p = 0.01, IC del 95% = -52.4 a -6.09; y sobre el colesterol total, con un efecto promedio ponderado de -6.7 mg/dL, p = 0.01, IC del 95% = -11.88 a -1.53.

Conclusiones: la evidencia disponible sugiere efectos favorables de la administración de suplementos de cromo sobre el control glucémico en pacientes con diabetes. Los complementos de cromo pueden además mejorar los niveles de colesterol total.
INTRODUCTION

Chromium (Cr) is a trace element widely distributed in the earth’s crust, which usually occurs naturally either in a Cr (III) or Cr (VI) oxidation state (1). Foods and supplements mainly contain Cr (III) (2,3). The highest concentrations (> 100 µg/kg) can be found in condiments and spices, cocoa, molasses, pure sugar, walnuts, dry corn, seafood, butter and oil; while the lowest (<100 µg/kg) can be found in meat, grains, cereals, starch, refined rice, vegetables, fruits, milk and dairy products (4). Nevertheless, chromium content can vary considerably depending, for example, on the geographic zone and the soil type (3,4).

Some studies have observed that Cr (III) could improve insulin action (5-7), but the relation between Cr and insulin is not well known. This element also could participate in lipid metabolism and could have some effect on body composition (7). However, these effects are controversial, and scientific evidence seems to be stronger towards glycaemia. For this reason Cr (III) supplements, which are considered safe, are often recommended to type 2 diabetes mellitus (DM) diagnosed patients. For instance, recently the European Food Safety Agency (EFSA) established the Daily Tolerable Intake of Cr in 300 µg/kg of body weight (4), a much larger amount than the daily chromium intake of European people that was estimated around 0.6-5.9 µg/kg of body weight (4).

However, some randomized controlled trials (RCTs) had demonstrated that Cr (III) supplementation lead a significant improvement in some alterations associated with type 2 DM. By contrast, some RCTs reported no additional protection provided by Cr (III).

Given the controversies of impact of Cr (III) on alterations associated with type 2 DM, in the present study, we performed 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


Eligible studies were only double or single-blind, parallel group, placebo-controlled, randomized trials comparing Cr mono or combined supplementation at least for 30 days against placebo in type 2 DM patients. Two reviewers independently screened full papers, and disagreements were resolved by a third author. The outcomes of interest were fasting plasma glucose (FPG), glycosilated hemoglobin (HbA1c), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG). All duplicated articles, as well as those that did not meet the aforementioned inclusion criteria were excluded.

Data from individual studies were abstracted and methodologic quality of trials was evaluated independently by two authors using Jadad scale (8). 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 (Table I).

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 (9). The Cochrane Q test was used to test heterogeneity and p < 0.10 was considered significant (10). In case of heterogeneity, the random effects model was used (9). Funnel plot and Egger’s method (11) were used as publication bias indicator.

RESULTS

SEARCH RESULTS AND STUDY CHARACTERISTICS

We initially identified 88 reports of Cr supplementation in type 2 DM. After screening, 40 reports were excluded because they did not meet the inclusion criteria, and 34 trials were excluded due to incomplete data. The remaining 14 reports were placebo-controlled randomized, parallel trials. Of these, one trial was rejected because this was a duplicate report.

Thirteen trials fulfilled the inclusion criteria and were included in this systematic review (Fig. 1). 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), and chromium milk powder (CMP). Total doses of Cr supplementation and brewer’s yeast ranged from 42 µg/day to 1.000 µg/day, and duration of supplementation ranged from 30 to 120 days (Table I).

META-ANALYSIS OF EFFECT OF Cr ON FPG 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 12 studies (12-23) (843 participants) of the effect of Cr on FPG showed an effect size of weighted mean differences of FPG change in type 2 DM patients in Cr supplementation therapy equal to -29.26 (95% CI = -52.44 to -6.09) mg/dL, p = 0.01 (Fig. 2). No publication bias was detected.

META-ANALYSIS OF EFFECT OF Cr ON HbA1c 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 9 studies (12,13,17,18,20,21,23) (734 participants), and results obtained showed that effect size of weighted mean differences of HbA1c change in type 2 DM patients in Cr supplement therapy was not significant: mean difference -0.41 (95% CI = -0.98 to 0.16)%., \( p = 0.16 \). No publication bias was detected.

### META-ANALYSIS OF EFFECT OF Cr ON TC IN TYPE 2 DM

The Cochrane Q test showed homogeneity \( (p = 0.96) \), so the fixed effects model was used. This meta-analysis, which incorporated data from a total of 9 studies (13-17,22-24) (652 par-
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Figure 1.
Flow diagram of the trial selection process.

Participants) of effect of Cr on TC showed an effect size of weighted mean differences of TC change in type 2 DM patients in Cr supplement therapy equal to -6.70 (95% CI = -11.88 to -1.53) mg/dL, p = 0.01. No publication bias was detected.

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 8 studies and 612 participants (13-17,20,23,24) and results obtained showed that effect size of weighted mean differences of HDL-C change in type 2 DM patients in Cr supplement therapy was not significant: mean difference -0.13 (95% CI = -2.04 to 1.77) mg/dL, p = 0.90. 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 8 studies and 621 participants (13-15,17,19,22-24) 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 -9.78 (95% CI = -27.82 to 8.27) mg/dL, p = 0.29 (Fig. 3). No publication bias was detected.

DISCUSSION

The results of the meta-analysis show an effect size of weighted mean differences of FPG (p = 0.01) and TC (p = 0.01) change in type 2 DM patients in Cr supplement therapy was not significant: mean difference -0.13 (95% CI = -2.04 to 1.77) mg/dL, p = 0.90. No publication bias was detected.
HDL-C (p = 0.90), LDL-C (p = 0.51) and TG (p = 0.29) change in type 2 DM patients in Cr supplement therapy was not significant.

In relation to the effects on lipid profiles, some results of this meta-analysis are in line with that observed in Suksomboon et al. 2014 (25) review, in which no significant difference in LDL-C was observed between chromium monotherapy and placebo. Similarly, LDL-C level did not change with Cr plus biotin.

However, fifteen studies with 974 patients examined by them concluded that Cr single supplement (in the forms of CP, Cr chloride, C, BY or Cr complexed with nicotinic acid) had no effect on TC level, while ours did. Likewise, TC did not improve with Cr combined with biotin.

By the same token, Cr monosupplementation significantly lowered TG level by 0.30 mM, particularly by treatment with CP and Cr combined with biotin, and increased HDL-C significantly but not by Cr combined with biotin; while we did not find any significant changes in any case.

Other sources of information (Abdollahi et al. [26]) claim that Cr does not affect HbA1c (p = 0.1) and lipids (p = 0.54 for TC, p = 0.18 for TG). They indicate that Cr has no benefit on lowering TC, HDL-C, LDL-C, VLDL-C, and TG that is consistent with previous reviews (27,28) and our meta-analyses, except for TC.

Previous meta-analyses and systematic reviews have indicated that Cr supplementation results in a significant lowering of FPG in diabetics but not in nondiabetics. However, sixteen studies with 809 participants (440 diabetics and 369 nondiabetics) were included in the analysis of Bailey 2014 (29), which indicated that there was no significant effect of Cr supplementation in diabetics or nondiabetics, with a weighted average effect size of 0.02 (SE = 0.07), p = 0.787, CI 95% = −0.12 to 0.16. Cr supplementation appears to provide no benefits to populations where Cr deficiency is unlikely.

Two of the most recent meta-analyses of diabetic subjects reported a significant lowering of FPG in type 2 DM (26,27). Patal et al. 2010 (27) analyzed two studies and reported a 0.92 mmol/L decrease in FPG of type 2 DM, while Abdollahi et al. 2013 (26) analyzed six studies and found a significant decrease in FPG of type 2 DM, which supplemented with Cr reduces FPG up to 7 mmol/L, p = < 0.0001, as we observed. Suksomboon et al. 2014 (25) also affirmed that Cr daily monosupplementation of 200 mg and up to 1,000 mg improved HbA1c and slightly decreased in effect on FPG.

These meta-analyses provide some evidence for effects of Cr supplementation on FPG in diabetic subjects but all have methodological limitations. These previous meta-analyses made no checks for publication bias except in the most recent analysis by Abdollahi et al. (26), and they used various methodologies to reach their conclusions.

Going into detail, 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 placebo was -0.33 with 95% CI = -0.72 to 0.06 (p = 0.1), while our result was -0.41 (95% CI = -0.98 to 0.16%), p = 0.16. 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 placebo was -0.95 with 95% CI = -1.42 to -0.49 (p < 0.0001), a great difference compared to our result: -29.26 (95% CI = -52.44 to -6.09) mg/dL, p = 0.01 (26).

Abdollahi et al. (26) meta-analysis indicates that in patients with type 2 DM, Cr supplementation does not change HbA1c. This 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% (27). On the other hand, reviews by two other groups showed 0.6% and 0.9% reduction in HbA1c, respectively (28,30).

Therefore, we can state that, depending on the examined clinical trials, current evidences support positive effects for Cr supplementation in the management of type 2 DM as it reduces FPG and TC in long-term therapy of DM patients.

Some limitations of this meta-analysis should be noted. First, there was a significant 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.
CONCLUSION

As a consequence, the short duration of studies, variable quality of data and large heterogeneity across these studies limit the strength of our conclusion. Further studies are recommended.

By elucidating the body of evidence on Cr supplementation, our meta-analysis highlights the questions that remain unanswered and the issues that need to be addressed in future RCT of Cr on glucose and lipid metabolism.

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