

A Meta-analysis on the Effect of Chromium Picolinate on Glucose and Lipid Profiles Among Patients with Type 2 Diabetes Mellitus

Perpetua C. Patal, M.D.¹, Marbert T. Cardino, M.D.¹ and Cecilia A. Jimeno, M.D.²

Abstract

Background: The role of chromium in human nutrition was first reported in 1977 on a patient on total parenteral nutrition manifesting with neuropathy and impaired glucose tolerance attributed to chromium deficiency. After correction, nerve conduction and glucose tolerance tests normalized. Chromium is postulated to act as a cofactor for insulin action by enhancing insulin receptor phosphorylation and stimulating insulin receptor tyrosine kinase.

Objective: To compare the effect of chromium picolinate versus placebo on glycated hemoglobin (HbA1c), fasting blood sugar (FBS), 2-hour postprandial blood sugar (2HPPBS), fasting insulin (FI) and lipid profile among T2DM patients.

Methods: Literature search in MedLine, Cochrane and Herdin was made using terms such as chromium, chromium picolinate, T2DM, glycated hemoglobin and RCT. Eligible studies were randomized controlled trials (RCT) of chromium picolinate intake of ≥ 3 months among T2DM patients. Two reviewers independently screened abstracts

and full articles. Results were plotted using Revman 4.2.

Results: Thirty four trials were found and six trials were included in the meta-analysis. The pooled data for 467 patients with T2DM reported lowering of HbA1c -0.34% (CI -0.45, -0.24 p 0.06); FBS -16.6mg/dL (CI -18.9, -14.41 p 0.30); 2HPPBS -17.33mg/dL (CI -20.21, -18.81 p<0.01) and FI -19.51mg/dL (CI -20.21, -18.81 p <0.01). Chromium picolinate has no effect on lipids.

Conclusion: Chromium picolinate lowers HbA1c, FBS, 2HPPBS and FI moderately but it has no effect on lipids. However, the short duration of studies, variable quality and large heterogeneity across these data limits the strength of our conclusion, hence further studies are recommended.

Keywords: chromium picolinate, type 2 diabetes mellitus, glycated hemoglobin

Research Question: Will addition of chromium picolinate to hypoglycemic agents improve glucose and lipid profiles among type 2 diabetes mellitus patients?

Introduction

Chromium is a trace element essential in carbohydrate, lipid and protein metabolism. It is complexed to Glucose Tolerance Factor in yeast and in low molecular weight Chromium-like substance (LMWCr) in animal cells. It is the second largest selling mineral supplement in the United States. Approximately 10 million Americans take chromium supplements, sometimes for prevention or treatment of diabetes.

The role of trivalent chromium in human nutrition was first reported in 1977 when the severe diabetic symptoms of a female patient on total parenteral nutrition were alleviated by supplemental chromium. In another case report of a post surgical repair of a thoracic aortic aneurysm patient requiring 2110 units of insulin over 40 hours while receiving glucocorticoid and vasopressor, blood sugar was normalized after chromium infusion at 3ug/h and insulin therapy was subsequently discontinued. Chromium is also reported to improve glucose and / or lipid profile among children with

protein energy malnutrition, the elderly, impaired glucose tolerance and type 1 and type 2 diabetes mellitus patients.

Chromium is a cofactor for insulin action. It increases insulin binding to cells due to increased number of insulin receptors, enhances insulin receptor phosphorylation and LMWCr-binding substance may function as a part of a novel insulin-signaling autoamplification by stimulating insulin receptor tyrosine kinase several folds.

Chromium is available in four forms namely - chromium yeast, CrCl₃, chromium nicotinate and chromium picolinate. Chromium picolinate is a formulation designed to improve absorption.

To clarify the effect of chromium picolinate on the glucose and lipid profiles among type 2 diabetic patients, we conducted a meta-analysis of randomized controlled trials.

Review of Literature

By 1948, chromium was recognized as a consistent component of plants and animals. In 1954, chromium was found to enhance the synthesis of cholesterol and fatty acids from acetate. In 1959, trivalent chromium was identified as the active component of the "glucose tolerance factor,"

¹ Fellow-in-training, Section of Endocrinology, Diabetes and Metabolism, UIP-PGH

² Consultant, Section of Endocrinology, Diabetes and Metabolism, UIP-PGH

which alleviated the impaired glucose tolerance in rats fed diets inadequate in chromium.

But the role of chromium in human was discovered in 1977 the severe diabetic symptoms of a female patient on total parenteral nutrition were alleviated by supplemental chromium. This was further emphasized in recent case report of a post surgical repair of a thoracic aorta aneurysm patient who required 2110 units of insulin over 40 hours while receiving glucocorticoid and vasopressor. Blood sugar normalized after chromium infusion at 3ug/h, then insulin therapy was subsequently discontinued.

Reviews on studies on chromium were already available. In 2002, Althuis et. al reviewed glucose and insulin responses to different dietary chromium supplements in healthy subjects and in individuals with impaired glucose tolerance or type 2 diabetes. Only 193 of 618 participants were type 2 diabetes mellitus patients, and of which only 38 were included in the analysis. Data from these RCT show no effect of chromium on glucose or insulin concentrations in nondiabetic individuals and 0.3% decrease in HbA1c.

According to some reports, of available chromium preparations, only chromium polynicotinate and chromium picolinate are readily absorbed by the intestines. To clarify issue whether chromium picolinate studies will support this data, Broadhurst et al, reviewed available studies on chromium picolinate but included all diabetes subgroups. Fifteen studies were included in this review, 11 of which were randomized. A total of 1690 patients were included but more than half of these patients were under an observational study in China which measured FBS and 2HPPBS only. His review showed mean HbA1c reduction of 0.9% in studies spanning 2 weeks to 9 months of supplementation.

The latest review on chromium picolinate came up in 2007 from the group of Balk. Forty one studies were included, 17 of which had type 2 DM population and seven were on chromium picolinate. It showed improvement in the HbA1c by 0.6% and FBS by 14.4 mg/dL. However, the analysis on HbA1c included studies not lasting than 3 months.

The first meta-analysis showed a nonstatistically significant reduction in HbA1c (-0.30%) while the two last reviews agree that chromium picolinate have significant but modest lowering of glucose parameters among type 2 diabetes mellitus (0.6 to 0.9%)

Objectives

To review the effect of chromium picolinate supplementation on glycosylated hemoglobin, fasting blood sugar, 2-hour postprandial blood sugar, fasting insulin and lipid levels.

Rationale

Despite the presence of three reviews on chromium, they have evaluated studies which do not exclusively studied type 2 diabetes mellitus, one study included all study on chromium, though not all chromium has the same absorption

in the gastrointestinal tract and one review included all studies despite some studies were nonrandomized.

Significance

The interest in chromium started for more than a quarter of a century but until the present time the use of chromium as for diabetes prevention or treatment is still not established due to small study population samples and short study periods of published clinical trials. Thus, combining the data gathered from randomized controlled trial is needed to come to a more definitive conclusion.

Research Designs and Methods

Literature search and eligibility criteria

We conducted a literature search in MedLine, Cochrane and Herdin using search terms such as chromium, chromium picolinate, glycosylated hemoglobin, HbA1c, and randomized controlled trials. Eligible studies were randomized controlled trials of chromium picolinate supplement intake of ≥ 3 months among type 2 diabetes mellitus patients. Primary outcome of interest is glycosylated hemoglobin. Secondary outcomes are fasting blood sugar, 2-hour postprandial blood sugar, fasting insulin and lipid levels.

Literature search in PubMed showed the following results:

#27	Search #25 Limits: Publication Date from 1980 to 2008, Humans, Randomized Controlled Trial, English, All Adult: 19+ years	7
#25	Search #21 AND #24	21
#24	Search #22 AND #23	50376
#23	Search "Diabetes Mellitus, Type 2"[Mesh]	50376
#22	Search diabetes mellitus	252206
#21	Search #17 AND #20	157
#20	Search #18 AND #19	329
#19	Search "picolinic acid "[Substance Name]	329
#18	Search chromium picolinate	598
#17	Search chromium	23770

Literature search in Cochrane using search terms chromium picolinate, glycosylated hemoglobin, HbA1c, and randomized controlled trials showed 34 trials. All the seven trials found in Pubmed were mentioned in Cochrane search. No trial was found using Herdin.

We evaluated randomized controlled trials of chromium picolinate supplementation. We excluded studies of less than 3 months duration. Two reviewers independently screened abstracts and articles and subsequently extracted data using Data Extraction Template by the Cochrane Collaboration. Discrepancies were resolved by consensus of the authors. Results were plotted using Revman 4.2. Heterogeneity of samples was resolved using sensitivity

analysis.

Study Quality Assessment

Methodological quality refers to the design and reporting of the clinical studies. The quality of each study was assessed by two authors using Quality Scale for Meta-analytic Reviews. Studies were reviewed for selection, performance, exclusion and detection biases. They were subsequently graded A, B, or C depending on the lowest score on each parameter. Grade A studies had the least bias; they provided clear description of the populations, settings, interventions and comparison groups, reported blinding and allocation concealment, had < 20% dropout rate and clear reporting of dropouts. Grade B studies included those with unclear blinding and allocation concealment, intention-to-treat analysis. Grade C studies were those who had serious errors in design, had missing information and poorly reported estimates that could not be assessed by the reader.

Results

There were 34 studies cited in Cochrane, 7 of which were also cited in Pubmed and none was seen from Herdin. One study was indexed from a review on clinical studies on chromium picolinate supplementation in diabetes mellitus by Broadhurst. Of the 34 studies, 22 were rejected because of the following reasons; 1. different chromium preparation used – 5 studies used CrCl3, 5 studies used chromium yeast complex, 1 study used chromium nicotinate, 1 study used bean bud chromium and 1 study used organic bound chromium; 2. measured different outcomes – 2 studies on

atherogenic index, 2 studies on antioxidant effect and 1 hair chromium concentration, 1 measured urinary chromium response to glucose load, 1 measured insulin sensitivity in vivo and one on the effect of chromium on erythrocyte insulin receptors.; 3. study population – 1 on gestational diabetes mellitus, 1 on obese women, 1 non-diabetic patients and 1 study used same study population; 4. duration of treatment – 2 studies with duration of treatment less than 3 months, one article was not retrieved and one study was open-labeled.

Six studies were included in the metaanalysis. Of the said studies, one was graded A, four were graded B and one was graded C.

Effect of chromium picolinate supplementation on HbA1c

All six trials reported data on glycosylated hemoglobin. Combining the six trials showed lowering of glycosylated hemoglobin level by 0.7 % (95% CI 0.73 to 0.68). However, data were heterogeneous (p <0.01, I² 99.8%). Sensitivity analysis was done. Three studies – those by Anderson, Martin and Albarracin accounted for the heterogeneity of data. Removing the said studies showed lowering of glycosylated hemoglobin by 0.34% (95% CI 0.45 to 0.24, p>0.06).

Effect of chromium picolinate supplementation on fasting blood sugar

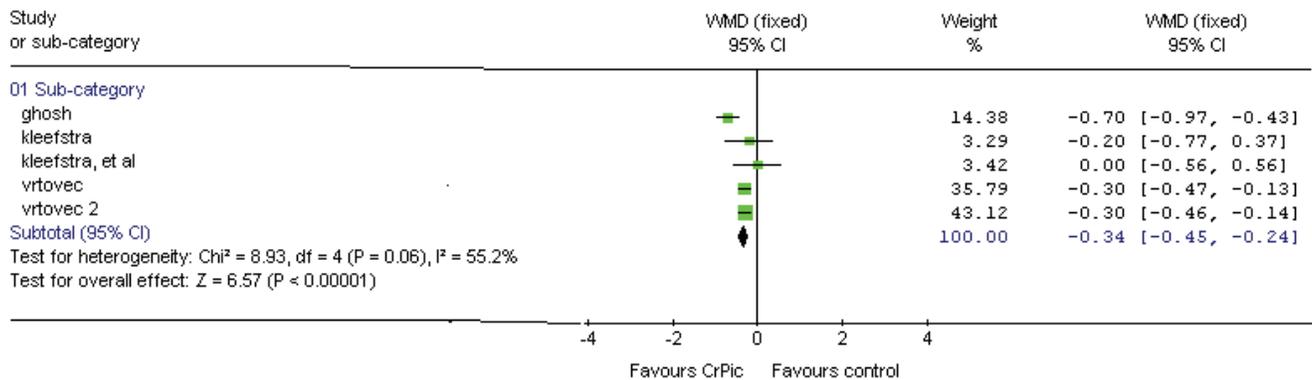
Five trials reported data on fasting blood sugar. Combining the five trials showed lowering of fasting blood sugar by 12.6 mg/dL (95% CI 13.41 to 11.79). However, data were heterogenous (p <0.01, I² 99.2%). Sensitivity analysis was done. Three studies – those by Anderson,

	Anderson, 1997 (China)	Ghosh, 2002 (India)	Vrtovec, 2005 (Slovenia)
Inclusion Criteria	DM patients with no comorbids DM duration of <10years Normal BMI FBS 7.2-15.5mmol/L 2HPPBS 9.4-16.7mmol/L HbA1c 8-12%	DM patients on diet or OAD	Diet-treated patients *QTc shortening in treatment group
Exclusion Criteria		Chronic diabetic complication Pregnant Patients on multi mineral supplementation Allergy to CrPic	Hepatic or renal dysfunction Heart failure, CAD, CVD Meds-thiazides, corticosteroids, phenothiazines, sympathomimetics, antiarrhythmics
Study Design	Double blind, placebo controlled trial	Double blind, placebo controlled cross-over	Double blind, randomized, placebo-controlled cross-over
# of subjects	155 (53, 52)	43(43)	50 (27)
CrPic (ug)	200, 1000	400	1000ug
Duration	4 months	7 months	3
Baseline HbA1c	9.4%	7.2%	7%
Result	HbA1c Placebo 0.6±0.2 200ug 1.9± 0.2 1000ug 2.8 ±0.1 p 0.01	HbA1c Cr (nmol/L) Placebo 0.7±0.1 0±0.2 Treatment 0±0.9 3.4±0.4 p 0.04 0.0001	HbA1c HbA1c Placebo 0.4±0.2 0.1±0.4 Treatment 0.1±0.4 -0.2±0.1 p NS NS

	Kleefstra, 2006 (Netherlands)	Martin, 2006 (USA)	Albarracin, 2008 (USA)
Inclusion Criteria	HbA1c ≥ 8 BMI >25 Insulin requirement ≥ 50u/d < 75 years old Crea < 150 ♂; < 120 ♀	Newly diagnosed DM Age 25-75 year old (59.7±8) FBS 125-170mg/dL *glipizide given in the first 3 months *randomized to receive placebo or Cr in the next 6 months	T2DM ≥12 months OAD ≥ 60 days HbA1c ≥ 7% BMI 25-35kg/m2 TG <400mg/dL
Exclusion Criteria	Pregnancy Liver and renal disease		T1DM Hypoglycemic event or DKA ≤12 months Crea >2x normal Use of chromium supplement
Study Design	Randomized Control Trial	Randomized Control Trial	Randomized Control Trial
# of subjects	46(14, 15)	29(17)	348 (226)
CrPic (ug)	500, 1000	1000	600 + biotin 2mg
Duration	6	6	3
Baseline HbA1c	9.4% 9.7%	9.7%	8.5%
Result	HbA1c Cr (nmol/L) Placebo -0.3±0.8 0 500ug -0.5±0.8 16±16 1000ug -0.3±0.8 50±28	HbA1C Cr(ug/L) Placebo -0.44±0.43 <0.3 Treatment -1.16±0.38 6±4.5 p 0.0049 <0.01	HbA1c Placebo 0.34±0.15 Treatment 0.54±0.15 p 0.03

Figure 1. The effect of chromium picolinate on HbA1c after sensitivity analysis

Review: Chromium and T2DM
Comparison: 01 chromium picolinate vs placebo
Outcome: 01 change in HbA1c



Vrtovec and Albarracin accounted for the heterogeneity of data. Removing the said studies showed lowering of fasting blood sugar by 16.66 mg/dL (95% CI 18.9 to 14.43, p>0.30, I² 6.6%).

Effect of chromium picolinate on 2 hour postprandial blood sugar, fasting insulin and lipid profile

Two trials reported data on 2 hour postprandial blood sugar. Combining the trials showed lowering of 2 hour postprandial blood sugar by 17.33mg/dL (95% CI 18.06 to 15.01 p<0.01, I²=99.7). Fasting insulin was lowered by 19.51mg/dL (95% CI 20.21 to 18.81, p<0.01, I² 99.4)

Four trials reported data on total cholesterol. Combining

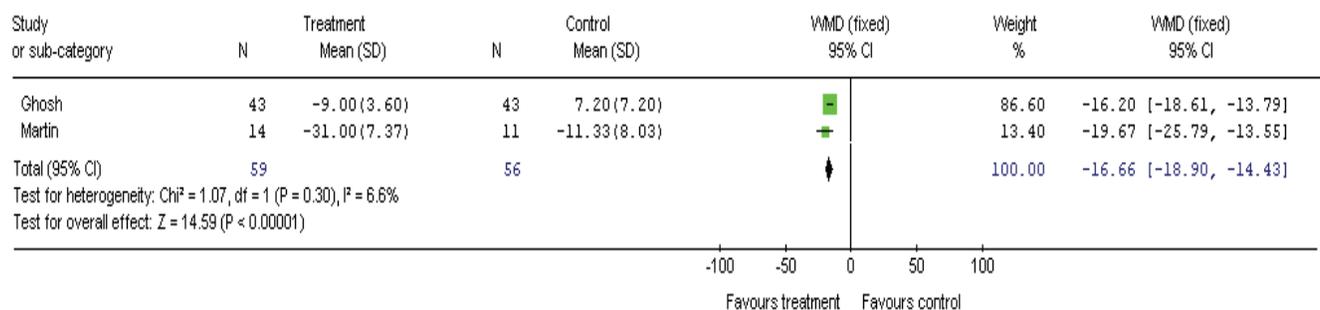
the trials showed minimal lowering of total cholesterol by 0.17mmol/L (95% CI 0.18 to 0.15), HDL cholesterol by 0 (p 0.13, I² 47.4%), LDL cholesterol by 0.03mmol/L (95% CI 0.04 to 0.01) and triglycerides by 0.17mmol/L (95% CI 0.19 to 0.14).

Discussion

In people with type 2 diabetes, our results showed that on the average, chromium picolinate supplementation lowered glycosylated hemoglobin by 0.34%. This result is lower to earlier systematic reviews by Broadhurst and Balk at 0.9 and 0.6% respectively. The review of Broadhurst included

Figure II. The effect of chromium picolinate on fasting blood sugar after sensitivity analysis

Review: Chromium picolinate and T2DM
 Comparison: 01 Chromium picolinate vs placebo
 Outcome: 02 change in FBS



15 studies, of which only 12 were randomized controlled trials. Study population included patients with type 1, type 2, gestational diabetes mellitus and steroid induced diabetes. The metaanalysis by Balk is specific for type 2 diabetes mellitus patients but he included all four chromium formulations. He also included some trials measuring HbA1c despite study duration of < 3 months where we don't expect change in the glycosylated hemoglobin. All three papers agree to a moderate but statistically significant lowering of glycosylated hemoglobin.

Our metaanalysis specifically included randomized controlled trials lasting for at least 3 months of chromium picolinate supplementation among type 2 diabetes mellitus patients. Glycated hemoglobin decreased by 0.7%. However, on sensitivity analysis, its weighted mean difference went down to 0.34%. Studies by Ghosh, Kleefstra and Vrtovec were homogenous. Study by Anderson in China showed the most lowering of glycosylated hemoglobin, 1.9 % and 2.8 % with 200ug and 1000ug chromium picolinate respectively. This effect was never duplicated in the five other trials with lowering of HbA1c in the range of 0 to 1.16%. There was no measurement of chromium levels among subjects. The very large treatment effect may be presumed to be secondary to chromium deficiency. Studies by Albarracin and Martin in USA showed lowering of HbA1c by 0.54% and 1.16% respectively. However, their study population included newly diagnosed diabetes mellitus patients. This may explain the large treatment effect. The study by Albarracin's study design was modified intention-to-treat analysis and 21 patients were removed during analysis due to entrance violations giving rise a 22% drop out rate. Dose effect was not measured.

Fasting blood sugar was significantly decreased with chromium supplementation. Patients were maintained on their previous antidiabetic regimen – diet, oral hypoglycemic agents or insulin. The study by Ghosh and Martin showed homogenous data. Again, the study by Anderson showed the most lowering of fasting blood sugar, not duplicated in

other studies. Vrtovec included patients whose blood sugars were controlled by diet alone, hence we expect minimal treatment effect.

Two hour postprandial blood sugar and fasting insulin were measured in two studies. They showed trend towards lowering of both parameters. However, data were heterogenous.

Chromium picolinate showed no treatment benefit on lipid lowering. This is consistent with the review by Balk.

Conclusion

Chromium picolinate supplementation decreases glycosylated hemoglobin, fasting blood sugar, 2-hour postprandial sugar and fasting insulin moderately among type 2 diabetes mellitus patients. It does not affect the lipid profile in this patients. The short duration of studies, variable quality of data and large heterogeneity across these studies limits the strength of our conclusion, hence further studies are recommended.

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