Chromium does not belong in the diabetes treatment arsenal

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REVIEW

Chromium does not belong in the diabetes treatment arsenal: Current evidence and future perspectives

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Abstract

Chromium is considered to have positive effects on insulin sensitivity and is marketed as an adjunctive therapy for inducing glucose tolerance in cases of insulin resistance ("the glucose tolerance factor"). Case reports on patients who received prolonged parenteral nutrition indeed showed that the absence of trivalent chromium caused insulin resistance and diabetes. However, whether patients with type 2 diabetes can develop a clinically relevant chromium deficiency is unclear. This review summarizes the available evidence regarding the potential effectiveness of chromium supplementation on glycemic control (Hemoglobin A1c levels) in patients with type 2 diabetes. No studies investigating the long-term safety of chromium in humans were found. All clinical trials that have been performed had a relative short follow-up period. None of the trials investigated whether the patients had risk factors for chromium deficiency. The evidence from randomized trials in patients with type 2 diabetes demonstrated that chromium supplementation does not effectively improve glycemic control. The meta-analyses showed that chromium supplementation did not improve fasting plasma glucose levels. Moreover, there were no clinically relevant chromium effects on body weight in individuals with or without diabetes. Future studies should focus on reliable methods to estimate chromium status to identify patients at risk for pathological alterations in their metabolism associated with chromium deficiency. Given the present data, there is no evidence that supports advising patients with type 2 diabetes to take chromium supplements.

Key words: Chromium; Type 2 diabetes mellitus; Insulin resistance; Therapy; Supplements

Core tip: In some patients who received prolonged parenteral nutrition, absence of trivalent chromium caused insulin resistance and diabetes and supplementation with trivalent chromium "cleared" this metabolic disease. The question is, whether chromium deficiency is a relevant factor in the cause of type 2 diabetes in general and whether supplementation with trivalent chromium can have beneficial effects in type 2 diabetes. Unfortunately, no reliable methods to estimate chromium status exists and according to current evidence, chromium does not improve glycemic control in patients with type 2 diabetes and patients should be advised not to take chromium supplements.

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INTRODUCTION

Insulin resistance is an important target for pharmacological and non-pharmacological interventions in patients with type 2 diabetes. In addition to the well-established interventions, a multitude of suggested alternative solutions outside the field of regular conventional medicine is available. One of these suggested beneficial interventions is oral supplementation with chromium. Chromium is marketed as a substance that improves insulin sensitivity (being as part of the "Glucose Tolerance Factor" molecule), weight loss and improving glycemic control in patients with diabetes[1,2]. Chromium has become the second most popular dietary supplement after calcium in the United States, with sales amounting to approximately 100 million dollars annually[1,2].

Some studies have demonstrated that chromium supplementation in chromium deficient states indeed led to beneficial effects[3-6]. There are strong arguments supporting the hypothesis that chromium supplementation improves glycemic control in chromium deficient patients by improving insulin sensitivity[7]. In addition, patients with diabetes are thought to have a chromium deficient status that is induced by an altered chromium metabolism[4,8,9]. However, other studies have suggested that chromium metabolism is not altered in type 2 diabetes[10]. Unfortunately, cut-off points for chromium levels correlating with relevant changes in glucose metabolism and insulin resistance are lacking. There is no clinically defined chromium deficiency state, nor is there a validated method for estimating the total body chromium status[11-13]. A reliable assessment of the chromium status in biological tissues and fluids is difficult due to extremely low chromium levels[12]. Although some studies have demonstrated successful chromium level determination in hair, sweat, and blood, there is still no exact method for defining chromium deficiency[8]. In this theoretical framework the "diabetic state" is linked to chromium deficiency and chromium supplementation would amend glycemic control by improving insulin sensitivity. This review discusses chromium physiology and summarizes the current evidence that chromium supplementation improves glycemic control in patients with type 2 diabetes.

Several case reports demonstrated beneficial effects of chromium supplementation in patients requiring total parenteral nutrition for prolonged periods[3,5-7,14,15]. One case report, published in 1977, discussed a 40-year-old woman who had undergone a total enterectomy after mesenterial thrombosis and became dependent on total parenteral nutrition[14]. After three years, she started losing weight and developed diabetes mellitus. She was young, had a low body weight, and required 50 IE of insulin daily to reach a near-normoglycemic state. Chromium deficiency was considered as a possible cause. The chromium concentration in her serum and hair was measured and found to be low [154 ng/g (N > 500 ng/g) and 0.55 ng/g (N = 4.9-9.5 ng/g), respectively]. She was treated intravenously with 250 micrograms of chromium chloride daily for two weeks. This treatment decreased the amount of insulin needed, and after four months of chromium supplementation, she remained normoglycemic without insulin. After this and several other case reports[3,9,14], chromium was added to parenteral nutrition as a standard ingredient[6]. Nevertheless, the extent of chromium supplementation necessary during total parenteral nutrition is still debated[16,17].

CHROMIUM PHYSIOLOGY

The two most common forms of chromium are the trivalent (3+) and the hexavalent (6+) forms. Chromium 6+ is not present in nature and is toxic. The chromium found in food and in dietary supplements is the trivalent form. Whole grain products, such as whole grain bread, vegetables, nuts, and some spices contain low concentrations of trivalent chromium. Chromium supplements are available as chromium chloride, chromium nicotinate, chromium picolinate, high-chromium yeast, and chromium citrate. Chromium chloride appears to have a poor bioavailability, although there is limited data on chromium absorption in humans[12,15,18].

The role of trivalent chromium in glucose metabolism has been known since the 1950s[15]. Chromium can alter insulin sensitivity at the cellular level. The oligopeptide Apo-Low-Molecular-Weight-Chromium binding peptide (also known as Apo-chromodulin) plays an important role in potentiating the insulin response in insulin sensitive cells[18,19]. The Apo-chromodulin is loaded intracellularly with a maximum of four chromium ions. Chromium-loaded Apo-chromodulin is called Holo-chromodulin. The Holo-chromodulin molecule binds to the insulin receptor and potentiates the insulin response by activating the receptor. The degree of insulin receptor activation depends on the number of chromium ions bound to this peptide, with a minimum of 0 and a maximum of 4 ions. This chromium binding may lead to an 8-fold difference in insulin receptor activation (when 4 ions are bound compared to 0). Experiments using rat adipocyte cells with equal serum insulin concentrations confirmed that insulin receptor activation is eight times stronger in the presence of chromium than in the absence of chromium[18].

ADVERSE EFFECTS OF CHROMIUM

Several cell culture and animal studies using supraphysiological chromium doses yielded results suggesting that chromium may increase DNA damage[20-23]. Chromium is not unique in this respect; a number of other nutrients such as vitamins A and D, nicotinic acid, and selenium have also been implicated in causing toxicity when taken in excess[24]. Clinical trials of oral chromium supplementation did not demonstrate toxicity in patients on parenteral nutrition[24,25]. We could not find long-term chromium safety studies. The DNA damage identified in cases of supraphysiological trivalent chromium concentrations did not translate into potentially carcinogenic effects when a more physiological dose of oral trivalent chromium was

used in humans[24,26].

CLINICAL EVIDENCE FOR CHROMIUM USE

In 1997, the intervention trial by Anderson *et al*[27] was one of the first chromium-intervention studies in patients with type 2 diabetes. In this randomized controlled trial, chromium picolinate supplements or placebo were administered to 180 Chinese patients with type 2 diabetes. The patients were randomized into three groups: placebo, 200 mg chromium, and 1000 mg of chromium daily. After four months, the hemoglobin A1c (HbA1c) levels in the placebo group were unchanged (8.5%), while they decreased significantly in the 200 mg group, from 8.5% to 7.5%, and decreased in the 1000 mg group, from 8.5% to 6.6%.

In 2007, Balk *et al*[28] performed a systematic review of randomized controlled trials investigating chromium supplementation in patients with type 2 diabetes. At that time, 14 studies with 18 different chromium-based interventions had been performed using HbA1c levels as an endpoint. In 11 out of these 14 trials, there was no significant effect of chromium supplementation. The review by Balk *et al*[28] concluded that, due to the poor quality and heterogeneity of the data, additional studies addressing these limitations were needed before definitive claims could be made about the effect of chromium supplementation[28]. Nevertheless, the meta-analysis by Balk *et al*[28] reported an overall significant effect of chromium supplementation on HbA1c levels (-0.6%; 95%CI: -0.9% to -0.2%). This -0.6% mean benefit was largely due to the inclusion of the data reported by Anderson *et al*[27]. When the Anderson study was excluded, the effect of chromium on HbA1c levels was -0.3% (95%CI: -0.5% to -0.1%; NS)[28]. It should be noted however, that the Anderson study was inadequately blinded with concerns for detection bias and selection bias, and should be considered to be of poor-methodological quality[27,28].

Significant effects in the meta-analysis were only found in studies with poor methodological quality or in studies sponsored by chromium supplement producing companies. In addition, the effects of chromium supplementation were shown to be absent or non-relevant after stratifying the studies according to methodological quality, sponsor involvement, and a western *vs* non-western study location[6,29].

After the review written by Balk *et al*[28], a second Dutch double blind trial was performed in 2008 that studied the effects of chromium on HbA1c levels in patients with type 2 diabetes[29]. After 6 mo, the effect of chromium supplementation compared to placebo on HbA1c levels was 0.24% (95%CI: -0.06% to 0.54%). HbA1c levels were lower in the placebo group compared with the chromium group. All of the trials that have been performed had a relatively short follow-up period. No studies have been performed with sufficient follow-up and the ability to reliably investigate cardiovascular and/or microvascular end-points. All studies used surrogate end-points. None of the trials investigated whether patients had risk factors for chromium deficiency.

Although this review focuses on the most relevant method of estimating glycemic control (HbA1c levels)[30-32], several studies investigated the effect of chromium on other markers of glycemic control[11,13,33-35]. Meta-analyses showed that chromium supplementation did not improve fasting plasma glucose levels[33,36] and had no clinically relevant effect on body weight in individuals with or without diabetes[37-39].

DISCUSSION

Chromium plays a role in insulin physiology, and severe chromium deficiency can lead to insulin resistance. Chromium supplementation may be beneficial in rare cases of prolonged total parental nutrition when standard chromium supplementation is lacking[6]. Despite the lack of sufficient evidence that chromium supplementation improves glycemic control[28,29], chromium is still widely marketed as an effective supplement for improving glycemic control in patients with type 2 diabetes.

Do we need to worry that a low chromium status contributes to hyperglycemia in our patients?

For the average patient with type 2 diabetes, the answer is no. Trivalent chromium is sufficiently available in food, and the occurrence of severe chromium deficiency is highly unlikely. The sparse evidence that chromium supplementation might have effects on glycemic control in a broader population is derived from studies with important methodological flaws[27,28]. Well-performed trials and meta-analyses consistently show that there is no evidence for consistent beneficial effects on glycemic control (as assessed by HbA1c levels) that support prescribing chromium supplements to patients with type 2 diabetes[6,40]. Furthermore, the long-term safety of chromium supplementation has not been established.

Is all hope lost for chromium supplementation in patients with type 2 diabetes?

An important concern when interpreting the data from studies investigating chromium effects is the lack of a validated and precise estimate of chromium status. There is no reliable method for assessing the body's chromium status, and there is no information on the bioavailability of the different forms of chromium[41]. Performing randomized trials in patients with type 2 diabetes will become interesting only when we can properly assess the chromium status in patients at risk for chromium deficiency and when clinically relevant end points are defined.

Recommendations

Future research on chromium should focus on establishing a reliable method for assessing the body's chromium status. The bioavailability of different forms of chromium in Western and non-Western patients should be investigated in order to define a potential effective dose

and to identify patients at risk for chromium deficiency. New randomized trials should only be considered in type 2 diabetes patients with an established chromium deficiency. The long-term safety of chromium supplementation should be investigated in large population studies. Currently, chromium supplementation in patients with type 2 diabetes should not be recommended.

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