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A STUDY DESIGN OF CLINICAL INTERVENTION OF CHROMIUM IN DIABETICS AND ITS BIOLOGICAL SIGNIFICANCE

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ABSTRACT
Cr (III) is the most stable form in biological systems[3,4] it does not penetrate biological membranes easily and it appears that the transport of specific chromium compounds is strictly regulated by the organism. Cr (III) ion has a strong tendency to form co-ordination compounds with a very slow reaction rate.[5] That slow rate suggests that chromium would exert a structural function rather than an active site in an enzyme, which may explain that no chromium-containing enzymes have been identified.[5] The oligopeptide chromodulin binds chromic ions in response to an insulin-mediated chromic ion flux and the metal-saturated oligopeptide can bind to an insulin-stimulated insulin receptor, activating the receptor's tyrosine kinase activity. Thus, chromodulin appears to play a role in an auto amplification mechanism in insulin signaling. The molecular agent responsible for transporting chromium from mobile pools to insulin-sensitive cells is probably the metal transport protein transferrin. Chromium from the popular dietary supplement chromium picolinate enters cells via a different mechanism. Release of chromium from chromium picolinate for use in cells requires reduction of the chromic center, a process that can lead potentially to the production of harmful hydroxyl radicals. On the other side Chromium is an essential trace element required for normal carbohydrate metabolism. The biological function of chromium is closely associated with that of insulin and most chromium-stimulated reactions are also insulin dependent. Proper chromium nutrition leads to a decreased requirement for insulin and also an improved blood lipid profile. Most fresh foods and minimally processed foods are good sources of dietary chromium. Inorganic chromium does not potentiate insulin action and must be converted to an organic biologically active form. An organic form of chromium capable of potentiating insulin action has been isolated from brewer's yeast and was shown to contain: Cr, nicotinic acid and a combination of amino acids. Synthetic insulin potentiating organic chromium complexes containing chromium, nicotinic acid, glycine, cysteine and glutamic acid or chromium, nicotinic acid and glutathione have been prepared. These complexes have not been purified to homogeneity since they dissociate during purification. Suitable analytical bioassays are available to measure total chromium and the organic biologically-active forms of chromium, respectively. A clinical intervention study was carried out of chromium. Results from the trials noted above support the view that chromium supplementation, especially in the form of CrP, in patients with type 1, type 2, gestational, or steroid-induced diabetes can improve both glucose and insulin metabolism.

KEYWORDS: Chromium, Diabetes mellitus, insulin, Glutamic acid, nicotinic acid.

INTRODUCTION
The interest in chromium as a nutritional enhancement to glucose metabolism can be traced back to the 1950s, when it was suggested that brewer's yeast contained a glucose tolerance factor (GTF) that prevented diabetes in experimental animals.[1] This factor was eventually suggested to be a biologically active form of trivalent chromium that could substantially lower plasma glucose levels in diabetic mice.[2] Interest regarding chromium administration in patients with diabetes was kindled by the observation in the 1970s that it truly was an essential nutrient required for normal carbohydrate metabolism. A patient receiving total parenteral nutrition (TPN) developed severe signs of diabetes, including weight loss and hyperglycemia that was refractory to increasing insulin dosing.[3] Based on previous animal studies and preliminary human studies, the patient was given supplemental chromium. In the following 2 weeks, signs and symptoms of diabetes were ameliorated, with markedly improved glycemic status and greatly reduced insulin requirements (exogenous insulin requirements decreased from 45 units/day to none). Other studies[7] of the beneficial effects of chromium in patients receiving TPN have also been documented in the scientific

literature. Chromium is now routinely added to TPN solutions.[7] The results of these studies strongly implicated chromium as a critical cofactor in the action of insulin.[6,7] Whereas chromium replacement in deficiency states is well established, the role of chromium supplementation to enhance glucose metabolism in subjects is controversial and serves as the basis for this review.

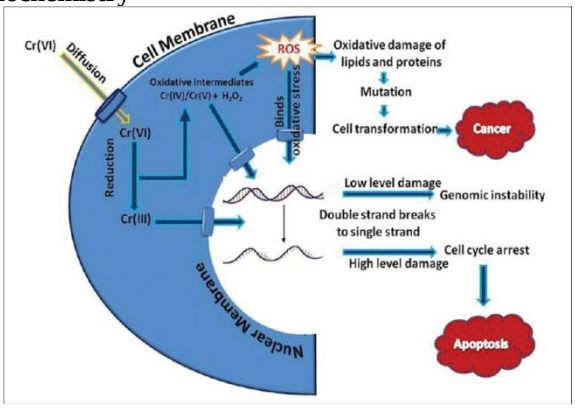
Trivalent chromium is found in a wide range of foods, including egg yolks, whole-grain products, high-bran breakfast cereals, coffee, nuts, green beans, broccoli, meat, brewer's yeast and some brands of wine and beer.[8,9] Chromium is also present in many multivitamin/mineral supplements and there are also specific chromium picolinate (CrP) supplements that contain 200–600 µg chromium per tablet.[10] The U.S. National Academy of Sciences has established the Recommended Daily Allowances for chromium as 50–200 µg/day for adult men and women.[11] which is also the Estimated Safe and Adequate Daily Dietary Intake (ESADDI) for chromium for children aged 7 years to adulthood.[7,12] However, it appears that Americans normally ingest ~50–60% of the minimum suggested daily intake of 50 µg.[7] Results from one study[10] indicated that daily chromium intakes for men and women in the U.S. were 33 and 25 µg, respectively. Therefore, normal dietary intake of chromium for adults may be suboptimal. At dietary intakes >50 µg/day, chromium absorption is ~0.4%, but the trivalent formulation also significantly influences bioavailability. At a dose of 1,000 µg/day, absorption of chromium from chromium chloride ($CrCl_3$) is ~0.4%, whereas that from CrP may be as high as 2.8%. Once absorbed, chromium is distributed widely in the body, with the highest levels being found in the kidney, liver, spleen and bone.[14]

REVIEW

BIOLOGIC ACTIONS OF CHROMIUM

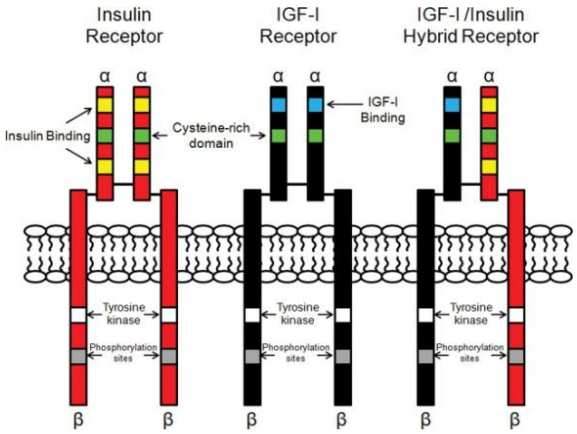
How chromium serves as a cofactor for insulin action is not fully understood. From several in vivo and in vitro studies[15] it was initially thought that chromium potentiated the actions of insulin as part of an organic complex, GTF. More recent studies[15] have suggested that chromium may function as part of the oligopeptide low–molecular weight (MW) chromium (LMWCr)-binding substance (MW ~1,500 Da), which is composed of glycine, cysteine, glutamic acid and aspartic acid. The interaction of chromium with LMWCr and the manner in which this complex influences insulin metabolism is considered in greater detail below.

Biochemistry



Very little chromium (<2%) in the form of inorganic compounds is absorbed but may be higher with certain organic formulations.[14] Once absorbed, chromium is distributed to various tissues of the body, but appears to be most concentrated in the kidney, muscle and liver[12] The principal carrier protein for chromium is transferrin, which also plays a critical role in the movement of chromium from blood to LMWCr. It has been suggested that migration of transferrin receptors to the plasma membranes of insulin-insensitive cells after insulin stimulation is the initial step in this process. Transferrin containing the plasma-bound chromium is postulated to bind to the transferrin receptors and is internalized by endocytosis (Figs. 1 and 2). The pH of the internalized vesicle is reduced by ATP-driven proton pumps, chromium is released from transferrin and the resulting free chromium is postulated to be sequestered by LMWCr 5, 7. With this step, chromium is transferred from transferrin to LMWCr, which normally exists in insulin-dependent cells in the apo, or inactive, form. Binding with chromium ions converts inactive LMWCr to its holo, or active, form. It is proposed that LMWCr then participates as part of an insulin signal amplification system (Fig.1) as it binds to insulin-activated insulin receptors and results in stimulating its tyrosine kinase activity. The result of this process is the activation of insulin receptor kinase and potentiation of the actions of insulin.[5,8,9] Importantly, LMWCr without bound chromium or in the presence of other metal ions is ineffective in activating insulin-dependent kinase activity and thus enhancing the actions of insulin. Chromium has also been demonstrated to inhibit phosphotyrosine phosphatase, the enzyme that cleaves phosphate from the insulin receptor, leading to decreases in insulin sensitivity. Activation of insulin receptor kinase and inhibition of insulin receptor phosphatase would lead to increased phosphorylation of the insulin receptor and increased insulin sensitivity. The balance between kinase and phosphatase activity may facilitate the role of insulin in rapidly moving glucose into cells. In addition, it has been suggested[7] that chromium enhances insulin binding, insulin receptor number, insulin internalization and β-cell sensitivity. The controversy surrounding chromium supplementation is due in part to substantial variability in the results of studies that have evaluated the

effects of chromium in patients with or without diabetes. Results from some trials have indicated that chromium supplementation increases muscle gain and fat loss associated with exercise and improves glucose metabolism and the serum lipid profile in patients with or without diabetes. In contrast, those from other studies have indicated little or no benefit of chromium on any of these variables. Recent meta-analyses of results from studies that evaluated the effects of chromium supplementation have suggested limited benefit in individuals with or without diabetes. The major conclusions from these analyses were that chromium has a very small effect versus placebo in reducing body weight and that the clinical relevance of this small decrease is debatable and should be interpreted with caution. It was also concluded that chromium has no effect on glucose metabolism or insulin concentrations in individuals without diabetes and that data for patients with diabetes are currently inconclusive. It is important to note that these conclusions are based largely on data from patients without diabetes and failed to include key positive results for chromium supplementation in diabetic patients and subjects with gestational diabetes or the metabolic syndrome. There is no clinically defined state of chromium deficiency, but diabetes has been shown[3,2] to develop because of low chromium levels in experimental animals and in humans sustained by prolonged TPN. These results suggest that there may be a more general relationship between chromium levels and glucose and/or lipid metabolism. It has also been suggested that low chromium concentrations and the associated impairments in insulin, glucose, and lipid metabolism may also result in increased cardiovascular risk. In a cross-sectional analysis[3], lower toenail chromium levels have also been associated with increased risk of type 2 diabetes. Adequate dietary chromium intake may be especially problematic in the elderly. Consumption of refined foods, including simple sugars, exacerbates the problem of insufficient dietary chromium because these foods are not only low in dietary chromium but also increase its loss from the body. Chromium losses are also increased during pregnancy and as a result of strenuous exercise, infection, physical trauma, and other forms of stress. Reduced chromium levels are reported in the elderly and in patients with diabetes. However, one of the major problems with assessing chromium status in biological tissues and fluids is extremely low levels of chromium in these tissues. Regardless, recent studies have demonstrated the successful determination of chromium. One study reported that in >40,800 patients from ages 1 to >75 years, chromium levels in hair, sweat and blood diminished significantly with age, with values decreasing from 25 to 40% depending on the tissue of interest . Additionally, it appears that diabetic subjects may have altered chromium metabolism compared with nondiabetic subjects, as both absorption and excretion may be higher. Hair and blood levels are reported to be lower in diabetic subjects, with mean levels of plasma chromium of ~33% lower in 93 type 2 diabetic subjects compared with control subjects. Another study reported that chromium levels were reduced >50% in both diabetic men and women compared with control subjects, which was supported by Elmekcioglu et al., who reported significantly lower chromium levels in the plasma of type 2 diabetic individuals compared with nondiabetic healthy control subjects. Yet, another study suggested no alteration of chromium levels in type 2 diabetes; however, only 11 subjects were reported.



CLINICAL INTERVENTION WITH CHROMIUM

The most recent recommendations state that "at the present, benefit from chromium supplementation in persons with diabetes has not been conclusively demonstrated".

Study design

The use of a control group is of paramount importance when evaluating the effect of chromium given the possibility that patients who choose to use chromium may be different from nonusers. Thus, only a randomized intervention can definitely establish the overall effects of chromium on insulin action, as it is this design that controls for biases, whether known or unknown, that may confound the association and assessment of chromium supplementation and carbohydrate metabolism. Unfortunately, many of the reported studies evaluating chromium supplementation were open-label studies.

Subject selection

The clinical characteristics of the study subjects varied tremendously as several studies grouped type 1 and type 2 diabetic subjects together in the evaluation of chromium's effect Indeed, even in studies in which only subjects with type 2 diabetes were reported, subjects were assessed while on various therapies (e.g., diet, sulfonylureas, metformin, insulin) and at different levels of glycemic control. It is well established that hyperglycemia secondary to glucose toxicity may contribute to attenuation in insulin action and the effect of medications to alter insulin action is well studied.

Dosage, formulation, duration of study

The duration of supplementation evaluated (ranging from 1 day to 8 months) and the dose used (ranging from 100 to 3,000 μg daily) varied tremendously in earlier studies. Studies that specifically evaluated ≤200 μg of chromium chloride failed to elicit a clinical response in those with type 2 diabetes. Uusitupa et al. demonstrated a positive effect at 200 μg of the CrCl salt; however, the remaining variables in that study did not appear to be altered by supplemental chromium. A more consistent clinical response is observed with daily supplementation of chromium >200 μg/day for a duration of ≥2 months. In addition, other forms of chromium, especially CrP, appear to be more bioavailable and clinically more effective than chromium chloride in both human and animal studies. Evidence for a dose effect of CrP was provided by a study of Chinese type 2 diabetic subjects. Short-term (2 months) and long-term (4 months) efficacy were observed, as evidenced by reductions in fasting and 2-h glucose and insulin values and long-term reductions in HbA_{1c} concentrations utilizing varying doses of CrP (200 or 1,000 μg). The effectiveness of the 1,000-μg dose in the Chinese study was reproduced in a study of individuals with the metabolic syndrome. In a study. of 30 women with gestational diabetes receiving placebo or 4 or 8 $\mu g \cdot kg^{-1} \cdot day^{-1}$ of CrP, after 8 weeks the two groups taking chromium had significantly lower glucose and insulin levels. Finally, another observed that corticosteroid-treated subjects have accelerated chromium losses and that steroid-induced diabetes was reversed with CrP supplementation at 600 μg/day.

Assessment of chromium status

Many of the earlier reported studies did not address the role of chromium blood levels at baseline or recorded changes, if any, with supplementation. In addition, objective markers to measure compliance with the regimen were not evaluated.

Summary

Results from the trials noted above support the view that chromium supplementation, especially in the form of CrP, in patients with type 1, type 2, gestational, or steroid-induced diabetes can improve both glucose and insulin metabolism. The reason why chromium supplementation was ineffective in some studies is not clear, but it is worth noting that all of these trials used relatively low chromium doses (≤250 μg/day), used different forms of chromium, or had study populations composed of both diabetic and nondiabetic patients.

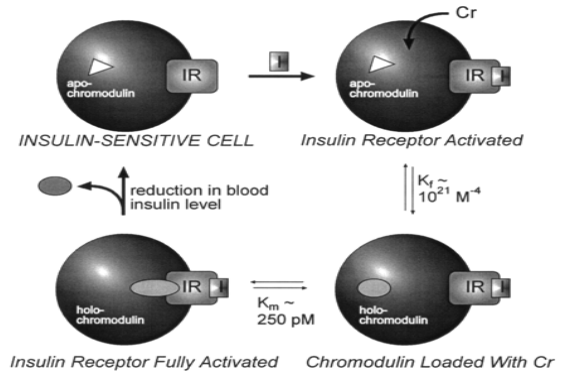


Fig 1- Proposed mechanism of action for chromium and LMWCr potentiating the action of insulin

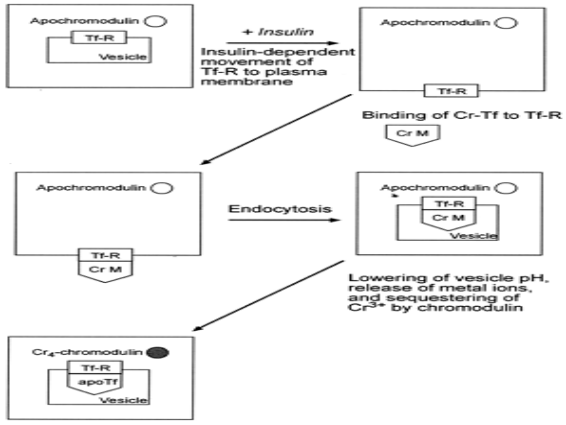


Figure 2: Proposed mechanism for the movement of chromium from the blood to LMWCr

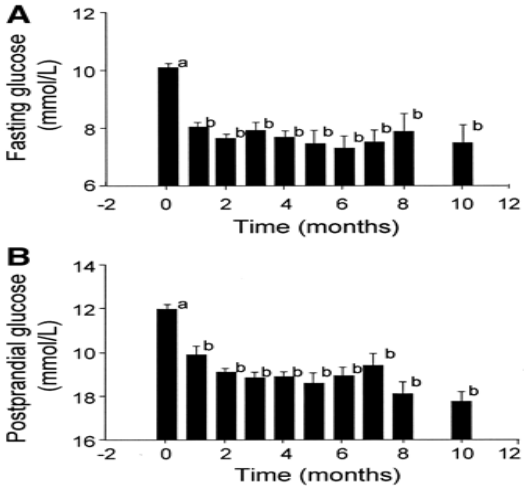


Figure 3: Fasting (A) and postprandial (B) glucose decline over time in patients with type 2 diabetes treated for 10 months

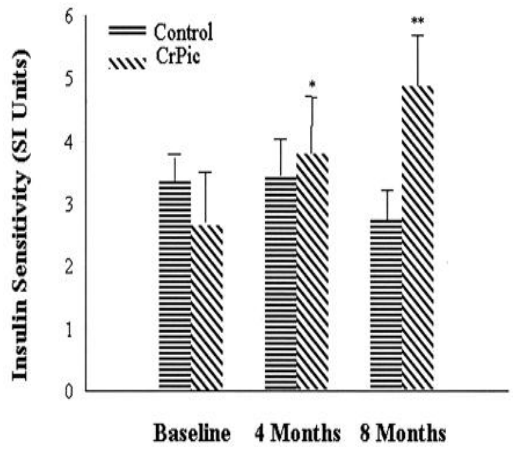


Figure 4: Effects of chromium supplementation on insulin sensitivity in overweight subjects with a family history of diabetes treated for 8 months

CONCLUSIONS

A large body of literature in both experimental animals and humans indicates that chromium is an essential element involved in the action of insulin as demonstrated in the studies of chromium deficiency. Although chromium deficiency has not been defined beyond that in patients receiving TPN. Epidemiologic studies suggest that tissue levels of chromium are reduced among diabetic individuals, especially in those with existing CVD, compared with healthy control subjects. Two case-control studies have also found that lower toenail chromium levels predict risk of MI in apparently healthy subjects. However, further epidemiologic studies are needed to confirm these associations in different populations and clinical trials are needed to prove the causal relationship. A more important question, however, is the role of chromium supplementation outside of the rare deficiency states. It is still controversial whether chromium supplements should be recommended for glycemic control among diabetic patients. Growing evidence suggests that chromium supplementation, particularly at higher doses and in the form of CrP, may improve insulin sensitivity and glucose metabolism in patients with glucose intolerance and type 1, type 2, gestational, and steroid-induced diabetes and in some individuals without diabetes. However, it must be recognized that most clinical studies have major limitations including small size, short term, nonrandomized design and different doses of chromium supplementation, which may explain the high variability of the findings across studies. Therefore, more clinical trials are needed in the U.S. population to examine the robustness of the results observed in other populations and appropriate doses. Ideally, these trials should assess effects of treatment on hard end points (e.g., type 2 diabetes and CVD) as well as metabolic parameters, although such trials would be costly and time consuming because they involve a large number of subjects and at least several years of follow-up. Results from such long-term trials would also assess the safety of long-term chromium supplementation.

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