

CHROMIUM IN THE PREVENTION AND CONTROL OF DIABETES

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SUMMARY - Chromium is an essential nutrient involved in the metabolism of glucose, insulin and blood lipids. Suboptimal dietary intake of chromium is associated with increased risk factors associated with diabetes and cardiovascular diseases. Within the past five years, chromium has been shown to improve glucose and related variables in subjects with glucose intolerance and type 1, type 2, gestational and steroid-induced diabetes. Severe neuropathy and glucose intolerance of a patient on total parenteral nutrition, who was receiving currently recommended levels of chromium, were reversed by additional supplemental chromium. Chromium increases insulin binding to cells, insulin receptor number and activates insulin receptor kinase leading to increased insulin sensitivity. Additional studies are urgently needed to elucidate the mechanism of action of chromium and its role in the prevention and control of diabetes.

Key-words: glucose, insulin, diabetes, trace elements, steroid-induced diabetes, gestational diabetes, chromium.

RÉSUMÉ - **Chrome, prévention et contrôle des diabètes.**

Le chrome est un nutriment impliqué dans le métabolisme du glucose et des lipides. Une carence d'apport modéré s'accompagne d'un risque cardio-vasculaire et de diabète accru. Dans les cinq dernières années, des études ont mis en évidence le rôle du chrome dans l'amélioration du contrôle glycémique et d'autres paramètres biologiques liés, chez des sujets intolérants au glucose, diabétiques de type 1 et de type 2, diabètes gestationnels et diabètes cortico-stéroïdes induits. Une situation exemplaire concernant un patient en nutrition parentérale est analysée. Le chrome améliore la liaison de l'insuline à son récepteur, accroît le nombre de ces récepteurs, active la tyrosine kinase de ce récepteur, le tout conduit à un accroissement de la sensibilité à l'insuline. Des travaux doivent être rapidement entrepris pour approfondir les mécanismes d'action du chrome et son rôle dans la prévention des états diabétiques et leur meilleur contrôle métabolique.

Mots-clés : glucose, insuline, diabète, éléments traces, chrome, diabète gestationnel, diabète corticostéroïde induits.

The worldwide prevalence of diabetes is expected to double between 1994 and 2010 to more than 240 million people [1]. The fundamental question is why is the incidence of diabetes doubling in a 10 to 15-year period? Genetics are often used to rationalize the incidence of diseases and obviously are part of the reason but certainly cannot be used to explain increases occurring in decades. This basically leaves environmental and lifestyle changes including stress, exercise and diet.

It is unlikely that there are any environmental factors including industrial pollutants that would alter the incidence of diabetes in several countries simultaneously. Life style changes including increased stress and decreased exercise certainly may be part of the answer. This may help explain the increase in the incidence of diabetes when people move from an active rural life to the more sedentary urban life style. The incidence of diabetes in some rural areas of mainland China ranges from less than 1% to 6-12% among Chinese living in Hong King, Singapore and Taiwan to 16% in a small group of Chinese living in Mauritius [2]. The dominating factor in the rapid rise in the incidence of diabetes is likely to be dietary factors. Increased intakes of simple sugars and fats, which are known to decrease insulin sensitivity, are likely causes of the increasing incidence of diabetes. Simple sugars and fats are also low in the micronutrients, chromium, copper, manganese, selenium, vanadium, and zinc. Of these micronutrients, the one most limiting in the diet and shown to have the largest effects on the signs of diabetes in humans is chromium [3].

Chromium was first reported to play a role in controlling blood glucose in the late fifties [4, 5] and several recent studies have documented its effects in people with glucose intolerance and diabetes (see review, 3).

■ CHROMIUM, INSULIN RESISTANCE AND GLUCOSE INTOLERANCE

Reduced insulin efficiency or insulin resistance may precede the development of diabetes by many years and is the time frame where nutritional intervention to prevent the onset of type 2 DM is likely to have the most significant effects. The first detectable sign of insulin resistance is a rise in circulating insulin concentrations. As insulin resistance increases, the body compensates for this inefficiency of insulin function by progressive increases in insulin production and release by the pancreas. This is followed by rises in blood glucose. It is well established that life style changes including weight loss and increased exercise are effective in increasing insulin sensitivity but long-term success of these are usually poor.

Improved fasting and glucose tolerance with lower or similar levels of circulating insulin have been re-

ported in more than 10 studies involving Cr supplementation of people with varying degrees of glucose intolerance (see review, 3). Cefalu *et al.* [13] presented data showing an effect of Cr (1000 µg per day as Cr picolinate) on insulin sensitivity of obese subjects with a family history of type 2 DM. Twenty-nine subjects were evaluated in a double-blind randomized, placebo-controlled study. Specific fat content in the abdominal area assessed by magnetic resonance imaging tended to be lower but differences were not significant. Improvements in insulin sensitivity without a significant change in body fat implies a direct effect of Cr on the effects on muscle insulin action [13].

These studies in humans are supported by animal studies. In addition to humans, Cr has been shown to have beneficial effects on the glucose tolerance of mice, rats, fish, guinea pigs, turkeys, squirrel monkeys, pigs and cattle [14]. Demonstration of overt signs of Cr deficiency in experimental animals simply by decreasing the Cr content of the diet and raising animals under highly controlled conditions to minimize trace metal contamination have met with limited success. Dietary stresses are usually required to enhance the signs of Cr deficiency. Striffler *et al.* [15] used a high sucrose diet with altered concentrations of minerals to enhance signs of Cr deficiency in rats. Low Cr animals exhibited decreased insulin sensitivity with an approximate doubling of insulin secretory responses and decreases in cyclic adenosine monophosphate-dependent phosphodiesterase activity in spleen and testes. Feeding a high fat diet to rats, which has been shown to decrease insulin sensitivity, also enhances the signs of Cr deficiency [16]. Glucose clearance was lower in the low Cr animals following IV glucose administration and insulin response was greater. These effects on glucose and insulin metabolism were accompanied by effects on triglyceride values which may suggest that Cr may be required for the maintenance of the normal antilipolytic action of insulin [16].

■ CHROMIUM AND TYPE 1 DIABETES MELLITUS

There have been more than 17 studies involving Cr supplementation of subjects with diabetes. The overwhelming majority of these reports involved subjects with type 2 DM but there are several smaller studies involving Cr and type 1 DM (see review, 3). Chromium absorption of people with insulin dependent or type 1 DM is approximately double that of control or subjects with type 2 DM (17). Urinary Cr excretion of subjects with type 1 DM is also more than twice that of control subjects [18]. People with type 1 diabetes also have lower hair and tissue Cr [19]. It appears that the metabolic control mechanisms of people with type 1 DM sense a need for additional Cr, which is re-

flected by increased absorption, but this absorbed Cr does not appear to be utilized and is excreted in the urine.

This is consistent with the observation that genetic diabetic mice are also unable to convert Cr to a useable form [20]. Supplementation of genetic diabetic mice with inorganic Cr is without significant effects on the glucose, insulin and lipid variables while addition of Cr in a biologically active form (form that potentiates insulin activity in vitro in epididymal fat tissue or cells) [21] leads to significant improvements in these variables. There have been several small-scale studies involving Cr supplementation of people with type 1 DM but the one of Ravina *et al.* [22] appears to be the most convincing. Study involved 162 patients with diabetes, 48 with type 1 DM and 114 with type 2 DM. The patients with type 1 DM were able to reduce their insulin dosage by 30% and their blood sugar variations were much smaller following 10 days of supplemental Cr (200 µg per day of Cr as Cr picolinate). Seventy-one percent of the patients with type 1 DM responded positively to Cr supplementation. The positive response to supplemental Cr in the patients with type 2 DM was similar (74%).

Doisy *et al.* [17], Nath *et al.* [23] and Canfield [24] have also reported beneficial effects of supplemental Cr on people with type 1 DM. Chromium (200 µg three times daily as Cr picolinate) was also reported to lead to a decrease in glycosylated hemoglobin from 11.3% to 7.9% following three months of Cr supplementation in a 28-year-old female with an 18 year history of type 1 DM [25]. It is clear that controlled double-blind studies are needed to substantiate a role for Cr in the regulation of type 1 DM.

■ CHROMIUM AND TYPE 2 DIABETES

Chromium supplementation studies employing 400 µg or more of Cr as Cr chloride have usually reported beneficial effects of supplemental Cr on people with type 2 DM [23, 26, 27] and essentially all of the studies employing the more bioavailable Cr picolinate have reported positive effects [22, 28-31] with greater effects at 1000 µg per day compared with 200 µg per day [31].

In a double-blind placebo controlled study involving 180 people with type 2 DM, two-hour blood glucose values were significantly lower after 2 months in the group receiving 1000 µg per day of supplemental Cr and after 4 months were lower in both groups receiving supplemental Cr. Insulin was significantly lower in both Cr groups after two and four months. Hb_{A1c} was 8.5 ± 0.2% in the placebo group, 7.5 ± 0.2% in the 200 µg group and 6.6 ± 0.1% in the group receiving 1000 µg of Cr per day for four months. Plasma total cholesterol also decreased after consuming 1000 µg of Cr per day for 4 months [31]. In a follow-up study involving more than 800 patients with

type 2 DM, blood glucose and symptoms of diabetes including excessive thirst, urination and fatigue improved in over 80% of the patients [32].

Improvements in glucose, insulin and related variables in response to Cr normally occur within a few weeks or less. However, improvements in blood lipids may take longer. In the study of Abraham *et al.* [33] involving supplementation (250 µg per day of Cr as Cr chloride) of 25 patients with diabetes and atherosclerotic diseases, improvements in HDL and triglycerides took more than 6 months.

A limited number of studies [34-36] reported no beneficial effects of supplemental Cr. These all involved 200 µg or less of supplemental Cr which is usually not adequate for people with diabetes, especially if it is in a form with low absorption.

■ CHROMIUM AND GESTATIONAL DIABETES

Pregnancy is a state of insulin-resistance and if a woman's pancreas cannot increase insulin production and/or efficiency to compensate for the increasing needs throughout pregnancy, gestational diabetes occurs [37]. Gestational diabetes increases both maternal and fetal morbidity [37]. The stresses associated with pregnancy not only alter glucose and insulin metabolism but pregnancy has been associated with depletion of Cr stores [38, 39]. Hair Cr concentrations of multiparous women are reported to be significantly lower than those of parous women and repeat pregnancies within a 4-year period lead to reduced hair Cr concentrations [40].

Thirty women with gestational diabetes (20-24 gestational week) were divided into three groups and given 0, 4 or 8 µg of Cr per kg body weight as Cr picolinate for eight weeks [41]. Chromium supplementation of women with gestational diabetes improved glucose intolerance and lowered hyperglycemia. Chromium effects in the group receiving 8 µg of Cr per kg body weight were greater than those receiving 4 µg per kg body weight. The authors concluded that "chromium picolinate supplementation may be an adjunctive therapy when dietary strategies are not sufficient to achieve normoglycemia in women with gestational diabetes" [41].

■ STEROID-INDUCED DIABETES

Glucocorticoid administration leads to insulin resistance in experimental animals [42, 43] and humans [44, 45]. These steroids are often administered as anti-inflammatory agents in the treatment of common chronic diseases such as asthma, allergies, arthritis and are also administered following organ transplan-

tation. Steroid-induced diabetes is reported in 2 to 46% of patients undergoing kidney transplantation [46].

Steroid-induced diabetes is more prominent in subjects who have impaired glucose tolerance or diabetes prior to the glucocorticoid treatment. However, glucocorticoids have been shown to induce glucose intolerance even in control subjects [47]. Fasting plasma glucose, insulin and C-peptide values of six healthy volunteers were progressively and significantly increased by the glucocorticoids, prednisone and betamethasone. Even inhaled corticosteroids have been shown to lead to steroid-induced diabetes and may explain the progressive decline in glucose tolerance in people with asthma [48].

The mechanisms responsible for steroid-induced diabetes are unknown but decreased insulin sensitivity is an overlying cause. Since the essential nutrient, chromium, improves insulin sensitivity and stresses that alter blood glucose levels often lead to increased Cr losses [14], it was postulated that chromium may be involved in the prevention and regulation of steroid-induced diabetes. Glucocorticoid administration was also shown to increase Cr losses [49].

Supplementation of three patients with steroid-induced diabetes led to a reversal of the signs and symptoms of diabetes. To confirm these results, 50 patients with uncontrolled steroid-induced diabetes were supplemented with Cr. Patients all had fasting blood glucose values greater than 13.9 mmol L^{-1} that did not respond satisfactorily to hypoglycemic drugs and/or insulin therapy. The duration of the corticosteroid treatment varied depending upon the nature of the illness. The steroid-induced diabetes of 47 of the 50 patients was controlled by supplemental Cr, $200 \mu\text{g}$ of Cr as Cr picolinate, 3 times daily. To be considered controlled, fasting blood glucose had to be less than 8.3 mmol L^{-1} (150 mg d L^{-1}) and 2-hour postprandial blood glucose below 10 mmol L^{-1} (180 mg d L^{-1}). Prior to the initiation of supplemental Cr, hypoglycemic agents were also reduced 50%. Following two weeks of $600 \mu\text{g}$ per day of supplemental Cr, daily Cr intake was reduced to $200 \mu\text{g}$. Five patients were able to stop all forms of hypoglycemic medications and blood glucose remained normal simply by taking $200 \mu\text{g}$ of Cr daily. Three patients stopped taking chromium as well as their medications. However, blood glucose started to increase but returned to acceptable levels upon the restoration of supplemental Cr, $200 \mu\text{g}$ per day. Patients continued to receive glucocorticoid treatment [50].

Although glucocorticoid therapy carries a risk of promoting or exacerbating hyperglycemia, there are currently no established medical guidelines for detecting or managing patients initiating glucocorticoid therapy (51). While improved Cr nutrition may be of benefit to a significant portion of the general popula-

tion, it may be of particular importance to those who are treated with corticosteroids.

■ CHROMIUM AND TOTAL PARENTERAL NUTRITION

Conclusive evidence for a role of Cr in human diabetes was reported almost two decades after the initial studies in experimental animals when it was shown that a patient on total parenteral nutrition developed severe signs and symptoms of diabetes that were resistant to the daily administration of 200 units of insulin. Since conventional methods for the treatment of diabetes were failing, the patient was given supplemental Cr based upon the successful effects from the earlier animal studies and the preliminary human studies [6]. Within two weeks of addition of $200 \mu\text{g}$ of supplemental Cr as chromium chloride, unresponsive weight loss, impaired nerve conduction, abnormal respiratory quotient and elevated blood glucose values improved. A maintenance dose of $20 \mu\text{g}$ of Cr per day was adequate to sustain these improvements. Exogenous insulin requirements dropped from 200 units per day to zero following Cr supplementation. Patient has remained relatively free of diabetes in the ensuing two decades. Beneficial effects of supplemental Cr on patients receiving TPN have been reported by others [7, 8]. Anderson [9] reported that blood glucose of a trauma patient receiving approximately $12 \mu\text{g}$ of Cr daily decreased from 25.0 to 8.3 mM when Cr was increased by $12 \mu\text{g}$ daily. Blood glucose returned to more than 20 mM when additional Cr was omitted and returned to approximately 8 mM when the additional $12 \mu\text{g}$ of Cr were added. This study was part of a larger study examining the effects of supplemental Cr on trauma patients [10]. Chromium is now routinely added to TPN solutions and Cr recommendations for TPN patients have been reviewed [11].

Peripheral neuropathy of the axonal type and glucose intolerance of a 40-year-old TPN patient were alleviated by supplemental Cr [12]. Patient was receiving recommended levels of Cr in his TPN solutions (total daily Cr intake of approximately $15 \mu\text{g}$) but still developed Cr deficiency. Despite raised serum Cr levels, the infusion of chromium ($250 \mu\text{g}$ daily as chromium chloride) resulted in the clinical remission of symptoms that was significant four days after initiation of supplemental Cr and normalization of nerve conduction within three weeks. Fractional glucose clearance was also normal three weeks after the initiation of supplemental Cr. Patient was also taking prednisone which has subsequently been shown to increase chromium requirements.

MECHANISMS OF ACTION OF CHROMIUM

The mechanism of action of Cr in the control of blood glucose is due to the potentiation of insulin action. In the presence of Cr in a useable form, much lower levels of insulin are required. In the epididymal fat cell assay, near maximal insulin response can be achieved by adding Cr in a form that potentiates insulin [21]. Inorganic Cr is without effect in the epididymal fat cell assay.

Supplemental Cr leads to increased insulin binding to cells due to increased insulin receptor number [52]. Increased glucose utilization and beta-cell sensitivity have also been demonstrated using the hyperglycemic clamp technique [53]. Chromium also activates insulin receptor kinase [54, 55]. A low molecular weight Cr binding compound stimulates kinase activity 8-fold in the presence of insulin but does not affect the protein kinase activity of rat adipocytes in the absence of insulin. Removal of Cr from this low molecular weight Cr binding compound results in the loss of kinase potentiating activity [54]. Chromium also inhibits phosphotyrosine phosphatase (PTP-1), a rat homolog of a tyrosine phosphatase (PTP-1B) that inactivates the insulin receptor (56, unpublished observation). The specific inhibition of insulin receptor phosphotyrosine phosphatase activity needs to be studied more closely since a low molecular weight Cr binding substance has also been shown to activate a membrane phosphotyrosine phosphatase [57]. The activation by Cr of insulin receptor kinase activity and the inhibition of insulin receptor tyrosine phosphatase leads to increased phosphorylation of the insulin receptor and to increased insulin sensitivity.

SAFETY OF SUPPLEMENTAL CHROMIUM

Trivalent Cr, the form of Cr found in foods and nutrient supplements, is considered one of the least toxic nutrients. The reference dose established by the U.S. Environmental Protection Agency for Cr is 350 times the upper limit of the Estimated Safe and Adequate Daily Dietary Intake (ESADDI) of 3.85 mmol (200 µg per day). The reference dose (RfD) is defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population, including sensitive subgroups, that is likely to be without an appreciable risk of deleterious effects over a lifetime" [58]. This conservative estimate of safe intake has a much larger safety factor for trivalent Cr than almost any other nutrient. The ratio of the RfD to the ESADDI or RDA is 350 for Cr, compared to less than 2 for zinc, roughly 2 for manganese, and 5 to 7 for selenium [59]. Anderson *et al.* [59] demonstrated a lack of toxicity of Cr chloride and Cr picolinate in rats at levels several thousand times

the upper limit of the estimated safe and adequate daily dietary intake for humans (based on body weight). There was no evidence of toxicity in their study and there have not been any reported toxic effects in any of the human studies involving supplemental Cr.

CONCLUSION

In summary, the essential nutrient, chromium, has been shown to have significant beneficial effects on the glucose, insulin and lipid metabolism of humans, experimental and farm animals. Dietary intake for both humans and farm animals is suboptimal. Recent dietary trends including increased intakes of simple sugars and fats exacerbate the signs of marginal Cr deficiency. Supplemental Cr has been shown to lead to significant improvements in people with altered glucose metabolism ranging from mild glucose intolerance to overt diabetes.

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