

Chromium and insulin resistance

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Insulin resistance leads to the inability of insulin to control the utilization and storage of glucose. It is associated initially with elevated levels of circulating insulin followed by glucose intolerance which may progress to type 2 diabetes, hyperlipidaemia, hypertension, obesity and cardiovascular diseases. While the causes of these diseases are multifactorial, one nutrient that is associated with all of these abnormalities is Cr. In the presence of Cr, in a biologically active form, much lower levels of insulin are required. Modern diets, which are often high in refined carbohydrates, are not only low in Cr, but lead to enhanced Cr losses. In response to the consumption of refined carbohydrates, there is a rapid rise in blood sugar leading to elevations in insulin that cause a mobilization of Cr. Once mobilized, Cr is not reabsorbed but lost via the urine leading to decreased Cr stores. Several studies involving both human subjects and experimental animals have reported improvements in insulin sensitivity, blood glucose, insulin, lipids, haemoglobin A1c, lean body mass and related variables in response to improved Cr nutrition. However, not all studies have reported beneficial effects associated with improved Cr nutrition. Well-controlled human studies are needed to document an unequivocal effect of Cr on insulin sensitivity in human subjects. Studies need to involve a significant number of subjects with insulin resistance, glucose intolerance or early stages of diabetes, who have not been taking supplements containing Cr for at least 4 months, and involve at least 400 to 600 µg supplemental Cr daily or more. Studies should be at least 4 months to document sustained effects of supplemental Cr on insulin resistance and related variables. Cr is a nutrient and not a therapeutic agent and therefore will only be of benefit to those whose problems are due to suboptimal intake of Cr.

Chromium: Insulin resistance: Type 2 diabetes mellitus: Glucose metabolism: Supplementation

Introduction

The signs and symptoms of insulin resistance including glucose intolerance, hyperinsulinaemia, increased LDL-cholesterol, increased triacylglycerols, elevated total cholesterol and decreased HDL-cholesterol, increased fat mass and decreased lean body mass are also all associated with decreased dietary intakes of the essential nutrient, Cr. All of these variables have been shown to be improved in human volunteers and experimental animals following improved Cr nutrition (Anderson, 1998a). The controlling factor for all of these variables is the activity of insulin. In the presence of Cr, in a biologically active form, much lower amounts of insulin are required; Cr increases insulin sensitivity. However, a number of other factors also alter these variables and Cr will only be of benefit to those individuals whose problems are associated with marginal intakes of Cr. The present review will discuss the role of Cr primarily on

factors related to insulin sensitivity. The reader is urged to consult earlier reviews for the physiology of Cr and how it is handled in the body (Anderson, 1997, 1998a,b, 2002; Vincent, 2000).

Chromium intake and requirements

The estimated safe and adequate daily dietary intake (ESADDI) for Cr for children aged 7 years to adults of 50–200 µg/d was established by committees of the US National Academy of Sciences in 1980 and affirmed in 1989. The ESADDI is similar to a recommended dietary allowance and is usually established before the recommended dietary allowance. The Food and Drug Administration proposed a reference dietary intake for Cr effective in 1997 of 120 µg/d. However, the new committee of the National Academy of Sciences has proposed that the normal intake of Cr should serve as the adequate intake of 20 µg for

Abbreviations: DM, diabetes mellitus; ESADDI, estimated safe and adequate daily dietary intake.

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women and 30 µg for men more than 50 years and 25 µg for women and 35 µg for men aged 19 to 50 years (Institute of Medicine Staff, 2001). It is unclear why the adequate intake for Cr is lower for those older than 50 years when the primary function of Cr is to combat problems associated with insulin and glucose metabolism which increase with age. Indices of Cr status such as the Cr content of hair, sweat and urine were shown to decrease with age in a study involving more than 40 000 participants (Davies *et al.* 1997).

The proposed adequate intakes appear to be simply the average intakes as reported in 1985 (Anderson & Kozlovsky, 1985) of 25 (SD 1) µg for women and 33 (SD 3) µg for men. There have been more than thirty studies reporting beneficial effects of supplemental Cr on individuals with blood glucose values ranging from hypoglycaemia to diabetes when consuming diets of similar Cr content. In a controlled diet study, consumption of normal diets in the lowest quartile of normal Cr intakes, but near the new adequate intakes, led to detrimental effects on glucose (Anderson *et al.* 1991) in subjects with marginally impaired glucose tolerance (90 min glucose between 5.5 and 11.1 mmol/l; 1000 to 2000 mg/l) following an oral glucose load of 1 g/kg body weight. The average adult older than 25 years has blood glucose in this range. Consumption of these same diets by individuals with good glucose tolerance (90 min glucose less than 5.5 mmol/l) did not lead to changes in glucose and insulin variables. This is consistent with previous studies demonstrating that the requirement for Cr is related to the degree of glucose intolerance and demonstrates that an intake of 20 µg Cr/d is not adequate for individuals with decreased insulin sensitivity such as those with marginally impaired glucose tolerance and certainly not for those with impaired glucose tolerance or diabetes.

Stress increases chromium losses

Even with the new lower established adequate intakes for Cr, there are still a number of individuals consuming diets at or below the adequate intake since more than 80 % of the individual daily diets contain less than 40 µg (Anderson & Kozlovsky, 1985). In addition, stresses such as increased sugar intake, exercise, infection and physical trauma have all been shown to lead to increased losses of Cr and consequently may lead to a compromised Cr status (Anderson, 1994). Urinary Cr losses can be used as a measure of the response to stress because once Cr is mobilized in response to stress it is not reabsorbed by the kidney but is lost in the urine (Anderson, 1994). Acute exercise was shown to roughly double basal Cr losses on an exercise day *v.* a sedentary day (Anderson *et al.* 1982). However, chronic exercise or physical training leads not only to improved insulin sensitivity but also improved Cr status and increased Cr absorption. This was determined using a stable isotope of Cr that can be used to differentiate between increased losses of endogenous Cr and the increased absorption of the newly administered stable-isotopic form of Cr (Rubin *et al.* 1998). As the degree of stress increases the amount of Cr lost also increases and the stress hormone, cortisol, can be correlated with Cr losses (Anderson *et al.* 1991). Severe stresses such as those associated with physi-

cal trauma of sufficient intensity to require treatment at a shock trauma centre led to a more than 50-fold increase in Cr losses (Borel *et al.* 1984).

Chronic consumption of diets high in simple sugars not only leads to increased levels of glucose and insulin and the associated increased Cr losses, but simple sugars are also low in dietary Cr (Kozlovsky *et al.* 1986). Therefore, this pattern of decreased intake and increased excretion may ultimately lead to compromised Cr status leading to impaired insulin sensitivity and ultimately increased signs and symptoms associated with diabetes and cardiovascular diseases. The increases in chronic diseases such as type 2 diabetes mellitus (DM) and cardiovascular diseases may not be normal consequences of ageing but rather the consequences of suboptimal dietary patterns that manifest with age.

Stress also leads to increased Cr losses in farm animals. Chang & Mowat (1992) demonstrated that average daily gain and feed efficiency increased more than 25 % due to Cr in steer calves following the stress of transporting the animals. Cr was without effect in the non-stressed periods. Humoral immune response in cattle due to the stress of lactation also improves due to supplemental Cr (Chang & Mowat, 1992). Supplemental Cr also counteracts the negative effects of the stress of growth hormone administration to pigs on glucose and insulin levels (Evocek-Clover *et al.* 1993). Uptake and utilization of Cr have also been shown to be impaired during endotoxin-induced stress in pigs (Mandali *et al.* 2002).

Chromium supplementation and insulin sensitivity in human subjects

There have been more than fifteen studies that have reported improved insulin sensitivity in response to improved Cr nutrition (Anderson, 1998a; Vincent, 2000); however, a number of studies has also reported no improvements in circulating insulin in response to supplemental Cr. A meta-analysis of the published studies failed to find a significant effect of Cr on insulin concentration (Althuis *et al.* 2002). However, several positive studies were not included in the analysis due to lack of specific data, inability to have access to the original data or for other reasons. Several studies reporting no effects of supplemental Cr on insulin sensitivity also involved healthy normal college-age students with good glucose tolerance and insulin values who were part of studies designed to detect the effects of Cr on lean body mass. Subjects that are not displaying signs of insulin resistance would probably not improve when given factors to improve insulin resistance.

Response to Cr is due not only to the Cr status of the subjects, but also the forms and amount of Cr consumed. Subjects with diabetes or glucose intolerance who consume 250 µg daily of supplemental Cr or less often do not respond to supplemental Cr while these subjects may respond to 400 to 600 µg daily or more (Anderson, 1998a). A dose-related response to Cr for subjects with type 2 DM was reported by Anderson *et al.* (1997b) (Fig. 1). Subjects had been diagnosed with diabetes for approximately 5 years, had taken no Cr supplements and had mean BMI of 24.8 (SD 0.5) kg/m². There was a progressive decline in the

haemoglobin A1c after 2 and 4 months of consuming 200 or 1000 µg daily of Cr as chromium picolinate. There were also dose-dependent improvements in glucose, insulin and cholesterol.

The changes in insulin sensitivity associated with the progression of diabetes are reflected by changes in Cr metabolism. Mean plasma Cr levels were 2.88 (SEM 0.19) nmol/l for patients with diabetes and 3.85 (SEM 0.38) nmol/l for the controls ($P < 0.001$). While control subjects have higher levels of Cr in the blood, the losses of Cr in the urine are lower (0.32 (SEM 0.3) v. 0.62 (SEM 0.02) µmol Cr/mol creatinine for the control subjects and the subjects with diabetes, respectively) (Morris *et al.* 1999).

During a euglycaemic-hyperinsulinaemic clamp, plasma Cr decreased more than 50 % in healthy control subjects but there were no significant drops in the insulin-dependent diabetic subjects, indicating that the subjects with diabetes lose the ability to mobilize Cr in response to an insulin challenge (Morris, 1999). There was also an inverse relationship between plasma Cr and plasma insulin in healthy control subjects but not in subjects with insulin-dependent diabetes. The plasma glucose of the two groups of subjects was similar but subjects with the highest Cr excretion also had the highest levels of circulating insulin (102 (SEM 9) v. 63 (SEM 7) pmol/l) and the highest calculated insulin resistance (2.88 (SEM 0.28) v. 1.75 (SEM 0.2); $P < 0.03$) (Morris *et al.* 2000).

The subjects with diabetes have a need for additional Cr, which is reflected by the increased absorption of these subjects (Doisy *et al.* 1971). However they are unable to utilize the Cr and it is consequently lost in the urine. Diabetic mice also lose the ability to convert Cr to a useable form, do not respond to inorganic Cr and are therefore dependent upon an intake of Cr in a biologically active form (Tuman & Doisy, 1977).

The efficacy of supplemental chromium picolinate on insulin sensitivity, using the modified minimal model, of obese individuals at high risk of developing type 2 DM was assessed in twenty-nine subjects (Cefalu *et al.* 1999). Insulin sensitivity was improved after 4 months and was maintained for an additional 4 months in subjects consuming 1000 µg Cr/d as chromium picolinate (Fig. 2). There were no significant differences in the groups at baseline but significance at the $P < 0.05$ level after 4 months that improved 10-fold in significance after 8 months. There was also a trend in the reduction of insulin throughout the course of the study that did not reach significance. Intra-abdominal fat mass measured by magnetic resonance image scans at the umbilicus changed 6 % in the control group but only 1 % in the Cr group. However, differences were not significant. This study appears to be carefully controlled, used adequate amounts of supplemental Cr (1000 µg) and was of sufficient duration (8 months). Subject selection was also carefully controlled employing only subjects with a family history of diabetes who also had central obesity (increased truncal fat) which is highly related to the insulin-resistance syndrome (Cefalu *et al.* 1999). However, larger numbers of subjects may be needed to demonstrate significant effects on fasting insulin concentration, insulin area under the curve following a glucose challenge and changes in fat mass.

Kaats *et al.* (1996) have demonstrated effects of Cr on percentage fat and fat-free mass but again these effects have not been observed in other studies (Anderson, 1998b). These studies are also plagued by selection of subjects, duration of the study and form and amount of supplemental Cr employed. 'Additional studies involving 200 µg of supplemental Cr or less and/or studies shorter than 24 weeks will be of minimal benefit and will serve mainly to cloud the issue of whether supplemental Cr has an effect on body

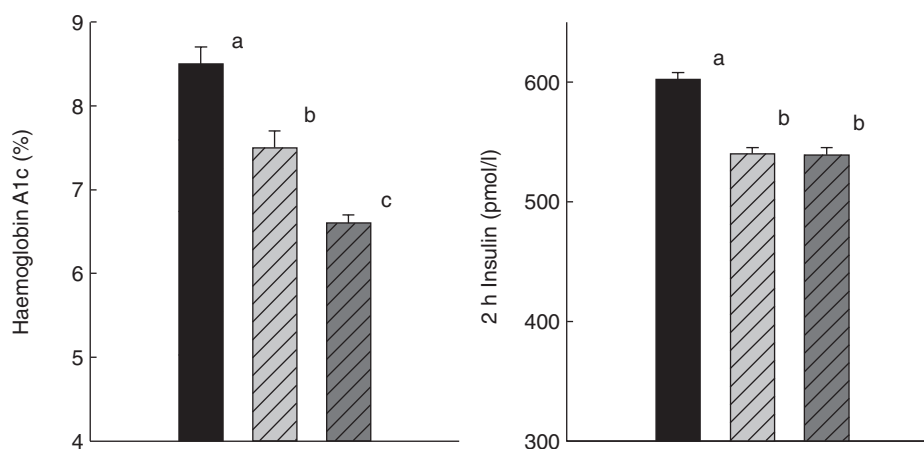


Fig. 1. Supplemental Cr effects on haemoglobin A1c and 2 h insulin. Subjects ($n = 180$) with type 2 diabetes were divided randomly into three groups and given capsules containing placebo (■), 200 µg Cr/d as chromium picolinate (▨) or 1000 µg daily (▩). Insulin values are 2 h after a 75 g glucose challenge. Values are means and standard deviations. ^{a,b,c} Mean values with unlike superscript letters were significantly different ($P < 0.05$). (From Anderson *et al.* 1997b.)

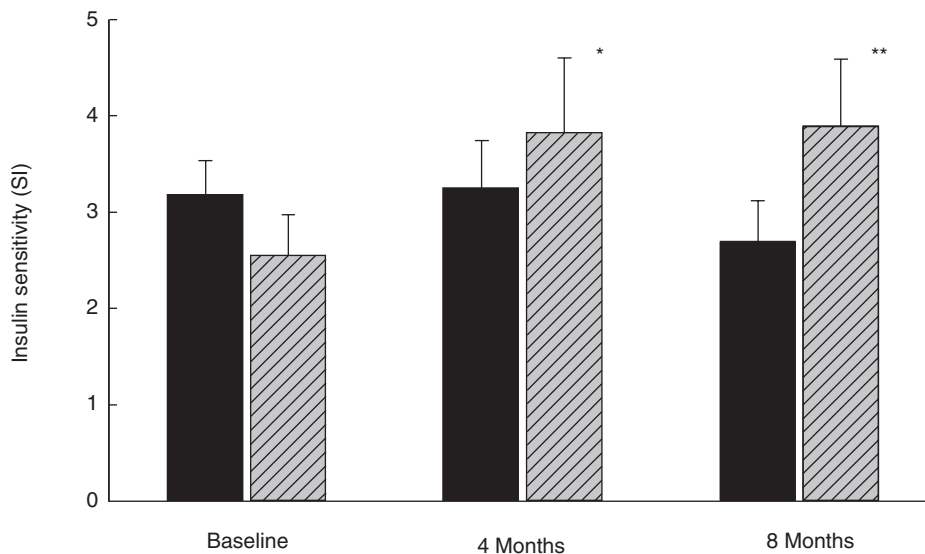


Fig. 2. Cr effects on insulin sensitivity. Obese subjects, fourteen men and fifteen women, with first-degree relatives with type 2 diabetes mellitus were assigned randomly into two groups and supplemented daily with 1000 μg Cr as chromium picolinate (▨) or placebo (■). Insulin sensitivity was determined using the modified minimal model. SI, sensitivity index. Values are means and standard deviations. Mean values were significantly different: * $P < 0.05$; ** $P < 0.005$. (From Cefalu *et al.* 2002.)

composition and weight loss in humans' (Anderson, 1998b). Studies involving changes in lean body mass and body fat are obviously of importance to insulin sensitivity since increased fat-free mass and decreased percentage body fat would also lead to increased insulin sensitivity.

Gestational diabetes

Pregnancy leads to insulin resistance and if the insulin system is unable to respond to the increased stresses associated with pregnancy, gestational diabetes may result (Jovanovic *et al.* 1999). The stresses associated with pregnancy on the glucose–insulin system also lead to a depletion of Cr stores based upon hair Cr analyses and response to supplemental Cr. Thirty women with gestational diabetes were divided into three groups and given daily either placebo, 4 or 8 μg Cr as chromium picolinate/kg body weight (Jovanovic *et al.* 1999). After 8 weeks of treatment, the two Cr-supplemented groups had significantly lower glucose and insulin levels compared with the baseline values and when compared with those of the placebo group. The group receiving 8 μg Cr/kg body weight had significantly lower postprandial glucose levels than the 4 $\mu\text{g}/\text{kg}$ group. These data demonstrate that supplemental Cr aids in combating the insulin resistance associated with pregnancy.

Steroid-induced diabetes

Glucocorticoid administration leads to insulin resistance in experimental animals and human subjects (Stojanovska *et al.* 1990). 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 transplantation (Ekstrand *et al.* 1992). Steroid-induced diabetes is more prominent in

subjects who have impaired glucose tolerance or diabetes before the glucocorticoid treatment. However, glucocorticoids have been shown to induce glucose intolerance even in control subjects (Pagano *et al.* 1989). 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 individuals with asthma (Faul *et al.* 1998).

The mechanisms responsible for steroid-induced diabetes are unknown but decreased insulin sensitivity is an overlying cause. Since the essential nutrient, Cr, improves insulin sensitivity, and stresses that alter blood glucose levels often lead to increased Cr losses (Anderson, 1994), it was postulated that Cr may be involved in the prevention and regulation of steroid-induced diabetes. Glucocorticoid administration was shown to increase Cr losses (Ravina *et al.* 1999a). Supplementation of three patients with steroid-induced diabetes was shown to lead to a reversal of the signs and symptoms of steroid-induced diabetes. To confirm these results, fifty patients with uncontrolled steroid-induced diabetes were supplemented with Cr. Patients all had fasting blood glucose values greater than 13.9 mmol/l that did not respond to hypoglycaemic drugs or insulin therapy. The duration of the corticosteroid treatment varied depending upon the nature of the illness. The steroid-induced diabetes of forty-seven of fifty patients was controlled by supplemental Cr, 200 μg Cr as chromium picolinate, three times daily (Ravina *et al.* 1999b). To be considered controlled, fasting blood glucose had to be less than 8.3 mmol/l (1500 mg/l) and 2 h postprandial blood glucose below 10 mmol/l (1800 mg/l). Before the initiation of supplemental Cr, hypoglycaemic agents were also

reduced 50 %. Following 2 weeks of 600 µg/d of supplemental Cr, Cr intake was reduced to 200 µg/d. Three patients stopped taking Cr as well as their medications. However, blood glucose started to increase but returned to acceptable levels upon the restoration of supplemental Cr, 200 µg/d. Five patients were able to stop all forms of hypoglycaemic medications and blood glucose remained normal simply by taking 200 µg Cr daily. Patients continued to receive glucocorticoid treatment (Ravina *et al.* 1999b).

Cr was also shown to block the negative effects on glucose and insulin in dexamethasone-treated rats (Kim *et al.* 2002). There were no effects on the fasting levels of cholesterol and triacylglycerols but the 1 h and 2 h plasma triacylglycerols and area under the curve were significantly lower in the animals receiving the supplemental Cr. However, there was no evidence that dexamethasone treatment led to Cr deficiency since adult rats were used and the duration of the study was only 21 d. Since Cr deficiency is difficult to produce in rats, it is probable that the Cr blocked the effects of the dexamethasone. Further studies are needed.

Although glucocorticoid therapy carries a risk of promoting or exacerbating insulin resistance, there are currently no established medical guidelines for detecting or managing patients initiating glucocorticoid therapy. While improved Cr nutrition may be of benefit to a significant proportion of the general population, it may be of particular importance to those who are treated with corticosteroids.

Recommendations from studies with human subjects

Well-controlled human studies are needed to document an unequivocal effect of Cr on insulin sensitivity in human subjects. Studies need to involve a significant number of subjects with insulin resistance, glucose intolerance or early stages of diabetes, who have not been taking supplements containing Cr for at least 4 months, and involve at least 400 to 600 µg supplemental Cr daily or more. Studies should be of at least 4 months to document sustained effects of supplemental Cr but also responses in blood lipids and lean body mass may take more than 3 months to reach significance.

Experimental animal studies

Human studies documenting effects of Cr on insulin sensitivity are also supported by studies involving experimental animals. Striffler *et al.* (1999) reported that while there were no significant differences due to Cr in glucose clearance and fasting glucose and insulin concentrations, there were significant differences in insulin response during an intravenous glucose tolerance test (Fig. 3). Insulin values for the chow-fed and Cr-supplemented animals were comparable and those for the animals consuming the low-Cr diet were significantly higher ($P < 0.05$). The presence of hyperinsulinaemia with elevated or even normal blood glucose indicates the presence of decreased peripheral tissue sensitivity in the animals not consuming adequate amounts of dietary Cr. Extra insulin secretion, to compensate for the decreased sensitivity to insulin, documents decreased insulin sensitivity, which is an early stage of diabetes.

Elevated triacylglycerols are also associated with insulin resistance and risk factors associated with cardiovascular

diseases are increased in response to factors that cause elevated triacylglycerols (Kraegen *et al.* 2001; Lopez-Candales, 2001). Increased triacylglycerols lead to decreased insulin resistance and decreased triacylglycerols lead to improvements in insulin sensitivity (Kraegen *et al.* 2001). Improved Cr nutrition has been reported to lead to improved levels of triacylglycerols in human subjects (Abraham *et al.* 1992) and circulating triacylglycerols in response to a glucose load are significantly lower in animals consuming adequate Cr (Striffler *et al.* 1998).

Using a rat model of insulin resistance, JCR-LA corpulent rats, Cefalu *et al.* (2002) reported improvements in the clinical sequelae of the insulin-resistance syndrome including hyperinsulinaemia, glucose intolerance and dyslipidaemia. Obese rats given Cr had significantly lower fasting insulin levels, significantly improved glucose disappearance, decreased total cholesterol, increased HDL-cholesterol and enhanced membrane-associated glucose transporter-4 after insulin stimulation compared with obese control rats not given supplemental Cr (Cefalu *et al.* 2002). Thus this study confirmed previous reports in human subjects and suggested that Cr supplementation in an insulin-resistant animal model improves insulin sensitivity and ameliorates dyslipidaemia.

Mode of action

The mode of action of Cr is being elucidated and a mechanism has been proposed (Fig. 4; Vincent, 2000). The mode of action of Cr involves several changes leading to increased insulin sensitivity. Cr increases insulin binding to cells due to increased insulin receptor number (Anderson *et al.* 1987). Once insulin binds to the α subunit of the insulin receptor this leads to a specific phosphorylation of the β subunit through a cascade of intermolecular phosphorylation reactions. The enzyme partly responsible for the

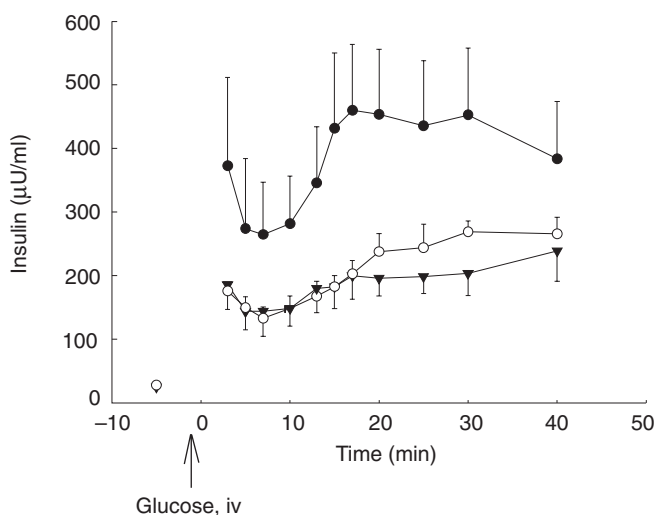


Fig. 3. Cr effects on plasma insulin response during an intravenous (iv) glucose tolerance test. Weanling male Wistar rats were fed a high-sugar low-Cr diet (●), the same diet supplemented with 5 parts per million Cr as chromium chloride in the drinking water (▼) or a commercial chow diet (○) for 12 weeks. Values are means and standard deviations. (From Striffler *et al.* 1999.)

phosphorylation leading to increased insulin sensitivity is insulin receptor tyrosine kinase which is activated by a low-molecular-weight Cr-binding oligopeptide coined chromodulin (Davis & Vincent, 1997). Chromodulin has a molecular weight of approximately 1500 Da and is comprised of only four types of amino acid residues, namely glycine, cysteine, glutamate and aspartate (Yamamoto *et al.* 1988). This low-molecular-weight Cr-binding oligopeptide appears to be widely distributed in mammals and has been isolated from livers of rabbits, pigs, cattle, dogs, rats and mice as well as pork kidney and bovine colostrum but not from human subjects (Vincent, 2000). This low-molecular-weight Cr-binding compound does not affect the protein kinase activity of rat adipocytes in the absence of insulin but stimulates kinase activity 8-fold in the presence of insulin. Removal of Cr from the low-molecular-weight Cr-binding compound results in the loss of kinase-potentiating activity (Davis & Vincent, 1997). The site of activation appears to be located at or near the kinase activation site since addition of chromodulin to a fragment of the β subunit that contains the active site, but does not require insulin for activation, resulted in a similar stimulation of kinase activity. Activation of insulin receptor kinase by the low-molecular-weight Cr-binding substance requires 4 mol Cr/mol oligopeptide and is specific for Cr.

Cr also inhibits phosphotyrosine phosphatase (PTP-1), a rat homologue of a tyrosine phosphatase (PTP-1B) that inactivates the insulin receptor phosphatase (Davis *et al.* 1996; Anderson, 1998a). The activation by Cr of insulin receptor kinase activity and the inhibition of insulin receptor tyrosine phosphatase would lead to increased phospho-

rylation of the insulin receptor which is associated with increased insulin sensitivity. Insulin binds to the α subunit in the insulin receptor bringing about conformational changes leading to auto-phosphorylation of the β subunit of the insulin receptor. In response to increases in blood sugar, insulin levels increase and there is a movement of Cr from the blood to the insulin-dependent cells (Morris *et al.* 1992; Vincent, 2000) which is facilitated by transferrin. There is a transfer of Cr bound to transferrin to apochromodulin, the low-molecular-weight Cr-binding substance (Sun *et al.* 2000). Apochromodulin has a high binding constant, approximately 10^{21} , and once apochromodulin binds 4 mol Cr, it is fully activated and able to increase the activity of insulin receptor kinase and inhibit that of the insulin receptor phosphatase (Fig. 4).

Transferrin is also the main transport protein for Fe. There are two metal binding sites on transferrin, the α and β sites. The α site has a higher affinity for Fe than the β site which may transport other metals including Cr (Brock, 1985). Under conditions of high Fe or in disease states such as haemochromatosis, both sites are occupied by Fe which may lead to a deficiency of Cr and may explain, in part, the high incidence of type 2 DM in those with haemochromatosis and other diseases characterized by elevated levels of Fe. Plasma membrane transferrin receptors are also sensitive to insulin and when insulin increases there is a movement of transferrin receptors from the vesicles to the plasma membrane (Kandror, 1999). Therefore, controlling insulin sensitivity would also control the function of the transferrin receptors.

When circulating concentrations of insulin decrease, insulin signalling is decreased through loss of the activator,

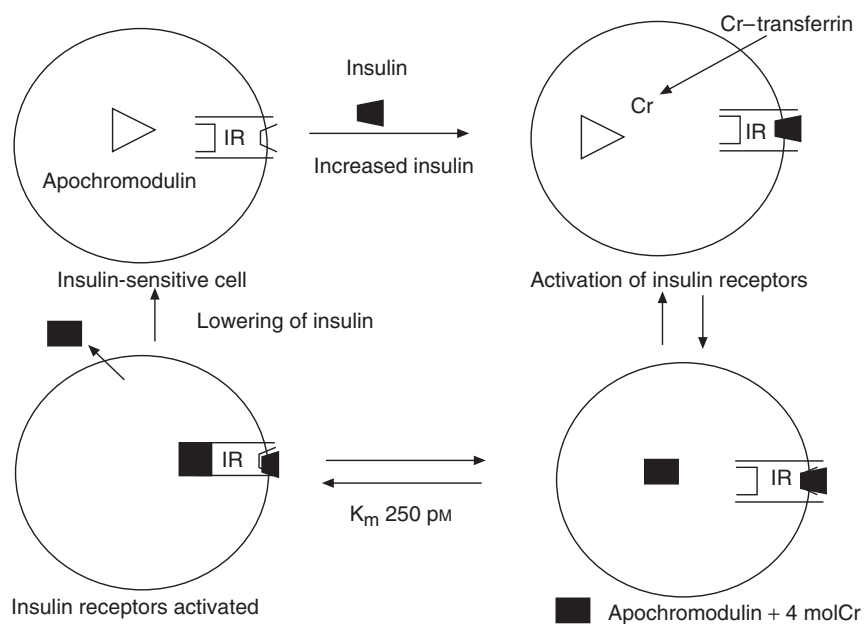


Fig. 4. A proposed mechanism for the activation of insulin receptor (IR) kinase activity by chromodulin in response to insulin. The inactive form of the IR is converted to the active form by binding insulin. This triggers the movement of Cr from transferrin into the insulin-dependent cells and the binding of Cr to apochromodulin. The holochromodulin containing 4 mol Cr/mol chromodulin then binds to the IR further activating IR kinase activity. Apochromodulin is unable to bind to the IR. When the concentration of insulin drops, holochromodulin is released from the cells leading to a return to the insulin-sensitive state of the cell. (From Vincent, 2000.)

chromodulin, from the cells. The high affinity of the Cr for the apochromodulin makes it improbable that there is simple dissociation of the chromodulin but rather a loss of the chromodulin complex. Chromodulin is probably then lost in the urine which is consistent with the increased losses of Cr in response to increased intakes of simple sugars (Kozlovsky *et al.* 1986) and the loss of the chromodulin intact in the urine (Vincent, 2000).

To explore the molecular mechanism of how Cr increases insulin sensitivity, Jain & Kannan (2001) cultured U937 cells with high levels of glucose to mimic diabetes. Cr was shown to inhibit the secretion of tumour-necrosis factor- α , a cytokine known to inhibit the sensitivity and action of insulin. Increased tumour-necrosis factor- α production and decreased insulin sensitivity are causally linked in diabetes (Jain & Kannan, 2001; Kern *et al.* 2001). Cr also prevented the secretion of tumour-necrosis factor- α and lipid peroxidation in H₂O₂-treated cells which appeared to be mediated by its antioxidative effects (Jain & Kannan, 2001) similar to that reported for individuals with type 2 DM (Anderson *et al.* 2001). This provides evidence of a novel molecular mechanism by which Cr supplementation may increase insulin sensitivity and decrease oxidation leading to improved glycaemic control.

Safety of 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 US Environmental Protection Agency for Cr is 350 times the upper limit of the ESADDI of 200 $\mu\text{g}/\text{d}$ and more than 2000 times the new adequate intakes. The reference dose 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' (Mertz *et al.* 1994). This conservative estimate of a safe intake has a much larger safety factor for trivalent Cr than almost any other nutrient. The ratio of the reference dose to the ESADDI, adequate intake or recommended dietary allowance is 350–2000 or more for Cr, compared with less than 2 for other trace elements such as Zn, roughly 2 for Mn, and 5 to 7 for Se (Anderson *et al.* 1997a). Anderson *et al.* (1997a) demonstrated a lack of toxicity of chromium chloride and chromium picolinate in rats at levels more than 2000 times the upper limit of the estimated safe and adequate daily dietary intake for human consumers (based on body weight). There have been no documented toxic effects at oral intakes of Cr at 10 to 50 times the normal intakes and most of the studies report beneficial effects. There are several studies reporting toxic effects of injected Cr in animals or in cell-culture systems where there are minimal normal protective measures. The largest protective mechanism for Cr is the gastrointestinal tract which allows usually less than 2 % of the Cr to be absorbed. Once Cr is absorbed, it is converted to a useable form which leads to increased insulin action and sensitivity. Essentially all nutrients can be toxic at doses far out of the nutritional ranges or for compounds that are poorly absorbed, such as Cr, when they are injected. Not even

studies with oral Cr intakes far out of the normal supplemental intake ranges show signs of toxicity for trivalent Cr and the Committee of the Food and Nutrition Board involved with setting recommended intakes as well as upper limits of intake was not able to set an upper limit for Cr since there were no adequate studies reporting signs of Cr toxicity when Cr was consumed by the normal means (Institute of Medicine Staff, 2001). Toxicity studies done with injected Cr should not be confused with those for oral intakes since not only is the absorption of Cr low (usually less than 2 %) but toxic forms of Cr may be changed in the absorption process. For example, low levels of hexavalent Cr can be converted to the relatively non-toxic trivalent form in the normal processes associated with absorption.

Summary

In summary, dietary intakes of Cr are often suboptimal and there are numerous studies documenting beneficial effects of Cr on insulin sensitivity. At suboptimal levels of Cr, higher levels of insulin are required. Response to Cr is dependent upon Cr intake and status, degree of glucose intolerance and stage and duration of diabetes. Obviously there are many factors that alter insulin sensitivity and Cr is only one of these factors and therefore will only be of benefit to those whose insulin resistance is due to suboptimal dietary Cr. Cr is safe at essentially all of the levels tested for oral intakes and therefore may be a safe and inexpensive aid to improved glucose and insulin metabolism.

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