Role of Chromium in Human Metabolism, with Special Reference to Type 2 Diabetes

S Chowdhury*, K Pandit**, P Roychowdury***, B Bhattacharya****

INTRODUCTION

Chromium is a naturally occurring lustrous metallic element found in rocks, soil, volcanic dust and gases and also in animals and plants. Metallic chromium is mined for use in steel and other metal products. Many chromium-containing compounds are used for plating, manufacturing paints and dyes, tanning leather and preserving wood. Less toxic forms are used to make flooring materials, video and audio recording tapes and copy machine toner. The most common forms of chromium are the metallic form, chromium (0), trivalent chromium (III), and hexavalent chromium (VI). The hexavalent form is a known toxin, mutagen and carcinogen. Its cell penetration is 1000 times more than the trivalent form; it enters erythrocytes and binds to the globin fraction of hemoglobin where it is reduced to the trivalent form. Conversely, chromium (III) is essential for proper insulin action, is required for normal protein, fat and carbohydrate metabolism and is acknowledged as a dietary supplement. Trivalent chromium is the most stable form and exists as soluble and insoluble salts as well as complexed with organic ligands e.g., glucose tolerance factor (GTF) in yeast and as low molecular weight chromium-binding substance (LMWCr) in animal cells. It is slowly absorbed, binds to DNA and resides in the nucleus in association with chromatin.1

In 1929 Galser et al discovered that brewer’s yeast had a potentiating effect on the hypoglycemic action of insulin.2 This observation was rediscovered by Schwartz and Mertz in 1957 who postulated it to be due to a ‘glucose tolerance factor’ and trivalent chromium was found to be the active component of GTF.3

The mammalian need for dietary chromium for maintenance of normal glucose tolerance was first postulated in 1959.4 This prompted studies in a variety of laboratory animals including rats, mice and squirrel monkey5-7 and by the 60’s, the role of chromium in animals had been established. However, the importance of chromium in glucose metabolism and insulin sensitivity in humans first came to light in 1977,8 when severe diabetic symptoms of a female patient on prolonged total parenteral nutrition (deficient in chromium) were alleviated by supplemental chromium. Two other similar studies on chromium supplementation in malnourished children and elderly people established the role of chromium in carbohydrate metabolism.9-12

It is recognised as a nutritionally essential element with daily adequate intake (AI) of 25 µg for women and 35 µg for men13 and with serum levels in healthy humans from developed countries of 2.3 - 40.3 nmol/l.14 The US Environmental Protection Agency (EPA) has replaced acceptable daily intake with calculated reference dose (RfD). The RfD is calculated from the ‘no observed adverse effect level’ from animal or human experiments and applying a ‘uncertainty and modifying factor’ to it.15 The reflects a staggering 350 times the ‘estimated safe and adequate dietary intake’ of 50-200 µg. The ratio of RfD to estimated safe intake is less than two for zinc, about two for manganese and about six for selenium. The ‘estimated safe and adequate dietary intake’ being 350 times less than the RfD reflects the lack of toxicity or adverse effects of chromium III, and probably dietary supplementation is greatly underdosed.16

MECHANISM OF ACTION OF CHROMIUM

Chromium possibly influences glucose metabolism by enhancing or, potentiating the action of insulin.17 However, no chromium-containing enzyme has been identified. The biologically active form of chromium has been isolated from brewer’s yeast and kidney powder and has been termed “Glucose Tolerance Factor” (GTF). GTF is an organic, low molecular weight complex containing trivalent chromium, nicotinic acid and the amino acids glycine, glutamic acid and cysteine.18 GTF appears to function as a carrier of chromium to the chromium-deficient proteins of the cell.19 However, its exact structure, site and pathway of action are yet unknown. More recently identified low molecular weight chromium-binding substance (LMWCr) has been postulated to be a part of an insulin signal amplification mechanism.20 LMWCr oligopeptide is composed of cysteine, glutamate, aspartate and glycine, and in contrast to GTF does not contain nicotinic acid.21 The binding of chromium to the apo-form of LMWCr results in stabilisation of the active conformation of insulin receptor tyrosine kinase, thereby facilitating the action of insulin.22 And in addition to that LMWCr also causes inhibition of phosphotyrosine phosphatase, an inactivator of enzyme tyrosine kinase.13 Due to its similarity to calmodulin
in structure and function, it has been named chromomodulin. In 1999, a synthetic multinuclear chromic assembly [Cr₃O(C₂H₅COO)(H₂O)₆] or, compound I, was found to mimic the insulin receptor tyrosine kinase stimulating action of LMWCr. This functional biomimetic has striking effect on lipid profile and may affect body weight and fat content. This molecule may be the chemical identity of LMWCr. 

In 1999, a synthetic multinuclear chromic assembly [Cr₃O(C₂H₅COO)(H₂O)₆] or, compound I, was found to mimic the insulin receptor tyrosine kinase stimulating action of LMWCr. This functional biomimetic has striking effect on lipid profile and may affect body weight and fat content. This molecule may be the chemical identity of LMWCr. 

In one human study on type 2 diabetes patients, chromium supplementation has been found to decrease insulin resistance as was measured by the HOMA technique. And on stopping chromium supplementation the insulin resistance returns to the baseline levels.

Overall, chromium has been postulated to act by one or more of the following ways: A) increase in the number of insulin receptors, B) increased binding of insulin to its receptor and C) increased activation of the receptor in the presence of insulin.

**Chromium and Glycemic Control**

Chromium deficiency is difficult to document because of the very low levels present in blood, while tissue levels are 10 times higher. Moreover, raised plasma levels can coexist with negative balance; hyperglycemia may be associated with raised plasma chromium and increased urinary excretion, without reflecting tissue level. Chromium concentrations in urine, hair and other tissues or, body fluids have also been reported not to reflect chromium status. Many studies have, therefore, tried to examine the effects of chromium supplementation.

Studies by Glinsmann in 1966 and Nath et al in 1979 had reported beneficial effects of supplemental chromium on glycemic control. Better results were seen, by double-blind study design, by Mossop, Kimurak and Thomas.

However, there are other studies that have shown no benefit, or ambiguous results with chromium supplementation. In both the studies the number of participants was small, and not randomized. Moreover, the role of chromium supplementation was investigated in special subgroups of patients with diabetes, in one study the population constituted of patients with established diabetic macrovascular disease (either myocardial infarction or with intermittent claudication) and in another it was only on patients with gestational diabetes.

In a recently published meta-analysis, on the role of chromium in glucose and insulin responses included 14 randomized controlled trials (618 participants, 193 type 2 diabetics and 425 nondiabetics) looked at the issue with critical statistical analysis. The data from this systematic review showed no evidence of a relation between chromium supplementation and concentrations of glucose or insulin in nondiabetic subjects (pooled mean difference for glucose: 0.028 mmol/L; 95% CI: 0.0896-0.14 mmol/L; pooled mean difference for insulin: 0.25 mmol/L; 95% CI: 6.98-7.48 mmol/L). The individual trials of nondiabetic subjects yielded no association regardless of formulation or dose. The lack of significant findings among healthy subjects may, in part, be explained by a floor effect; we would expect that glucose and insulin concentrations in healthy subjects could be lowered at most by a small amount. Too few trials in diabetic subjects have been conducted to allow conclusive findings for subjects with type 2 diabetes. Anderson et al provided the most definitive support for chromium supplementation in type 2 diabetes in a randomised, double-blind, placebo-controlled study in China in 1997. One hundred and eighty subjects with type 2 diabetes were randomised to placebo, 200 µg chromium picolinate/day or, 1000 µg chromium picolinate/day for four months. Anderson et al were the only investigators to report a dose-response relation between chromium and glucose and insulin concentrations in diabetic subjects. As changes in diet, exercise, and use of some medications remain as confounders for the fluctuations in glucose and insulin concentrations, measurement of glycosylated proteins, such as HbA₁c, is a more reliable method of assessing long-term glycemic control. Only three studies assessed the relation between dietary chromium supplementation and reductions in HbA₁c, one each of healthy subjects, subjects with glucose intolerance, and diabetic subjects. The reduction in HbA₁c concentration was larger in randomized clinical trials of subjects with more severe disease. Specifically, among diabetic subjects, Anderson et al reported a dose-response relation between dietary chromium supplementation and a decrease in HbA₁c concentrations in the control group compared with the treatment groups (200 and 1000 µg chromium picolinate/d). HbA₁c levels were significantly lower at both doses of chromium compared to placebo (placebo 8.5%, 200 µg 7.5%, 1000 µg 6.6%; p < 0.05). Reductions in HbA₁c concentrations were evident after two months of chromium supplementation, with more marked reductions after four months. But it should be noted that the study participants were from a particular ethnic group, were lean in constitution and the serum chromium status were not looked into the study. Similarly, Uusitupa et al reported an association of chromium with a reduction in HbA₁c concentrations (0.3%) in subjects with IGT, but the reduction, which was not statistically significant, was smaller than that reported by Anderson et al among diabetic subjects; moreover, this association may be attributable to differential weight loss in the treatment groups. However, the studies included in the meta-analysis contribute only an estimated 220 person-years of data (both treated and control groups) and < 35 person-years in subjects who received high doses of chromium.

Double blind, placebo controlled study on chromium supplementation in Indian subjects with diabetes is sparse. In a recently published study from this country, it was noted that significant improvement occurs in glycemic control after chromium supplementation for 12 weeks. The serum insulin level showed a decline in the chromium treated group, signifying the effect probably was due to increase in insulin action rather than increase in insulin secretion. Despite the general lack of evidence, at least one previous study had shown that serum chromium values reflect body stores and serum chromium level measured in the Indian diabetic
population compared to the healthy control subjects showed a lower level, raising the possibility of existence of chromium deficiency in Indian subjects with type 2 diabetes.40

In general, studies employing organically bound chromium, particularly chromium picolinate, showed greater benefit than those utilising inorganic forms of chromium; the reason is poor intestinal absorption and intracellular uptake of inorganic chromium. In fact picolinic acid may be a naturally produced ligand that facilitates the absorption and transport of chromium in vivo.42

Also, subjects, who were likely to be chromium-deficient, were more likely to show a positive response. This would suggest that the effect of chromium is ‘physiological’ rather than ‘pharmacological’. Chromium deficiency may be caused by deficient dietary intake or by increased excretion following infection, pregnancy, high glucose diet and stress.43,44 The availability of chromium from the diet is also hampered by competing ions such as Cu++, Fe++, Mn++, and Zn++ and increase in absorption rate in presence of amino acids histidine and glutamic acid which readily form complexes with chromium.45 Good sources of chromium in the diet include whole grain, bean, mushroom, nuts/seeds, wheat germ, broccoli, cheese and beef.

CHROMIUM AND LIPID PROFILE

Hypercholesterolemia (an important link in the genesis of coronary artery disease) and aortic plaques occurred in animal studies with diets deficient in chromium and showed regression on introduction of chromium in the diet.46 Also, supplementation of chromium picolinate in rat model of the insulin resistance syndrome results in lowering of plasma total cholesterol and elevation of HDL cholesterol. There is also clinical evidence that chromium supplementation in type 2 diabetes may decrease serum total cholesterol, LDL cholesterol and triglyceride levels and increase HDL cholesterol levels from findings based on several less controlled trials46,47 and some controlled trials.38,49 However, no significant change in lipid profile was seen in some other studies.50,51 Possibility of a positive effect at higher doses of chromium remains.37,52

CHROMIUM AND OSTEOPOROSIS

A placebo controlled trial on postmenopausal women had shown that supplementation with chromium leads to decrease in urinary calcium and urinary hydroxyproline/creatinine ratio, suggesting thereby that chromium supplementation may have an additional benefit, of prevention of osteoporosis.53 In another study on postmenopausal women receiving hormone replacement therapy (HRT) chromium status was measured, and it was concluded that chromium status based on blood and urinary analyses improves in postmenopausal women receiving HRT, and the authors suggested that chromium status may be a contributing factor in the beneficial effects of HRT.54

SAFETY ISSUES

Hexavalent chromium is a known industrial toxin. Acute exposure to high concentrations can cause irritation of mouth, nose, throat and lungs leading to nasal ulcer, asthma and bronchitis; it also causes skin irritation and allergy; it may also lead to kidney and liver damage.55 Hexavalent chromium is also recognised by WHO as a human carcinogen on prolonged exposure, affecting particularly skin and respiratory tract.56 The mechanism of carcinogenesis is, however, not clearly known. Reactive oxygen species (ROS) mediated reactions may play a role. There is also some evidence that intracellular reduction of chromium (VI) to chromium (V) plays a fundamental role in DNA damage leading to carcinogenesis. Fortunately, hexavalent chromium is not present in significant quantities in the food chain. Trivalent chromium, as in chromium picolinate, is, however, relatively safe. No significant hepatic, renal or hematological changes were noted in the Indian study. Even higher doses up to 1000 µg daily have been found safe.37 Safety has been demonstrated even at doses equal to 5000 times the prescribed safe dose.57

Nonetheless, in vitro studies have linked high doses of chromium picolinate to higher rates of chromosomal damage; however, the offending component appears to be the picolinic acid moiety rather than chromium.58 However, such changes have not yet been observed in vivo studies. There are isolated case reports of liver, kidney59,60 or muscle damage and also of hypoglycemia, the majority of the cases appear explainable by other factors, especially when compared to the clinical trials that have monitored patients for adverse side effects for long periods.16 It appears that compared to chromium picolinate, niacin-bound chromium (III) is not only more bioavailable and efficacious, but also causes less oxidative damage and hence less toxicity. Thus, the safety of chromium (III) may be largely dependent on the ligand.

CONCLUSIONS

Reliable direct assessment of the chromium status in human beings is still not feasible, though some studies have shown blood chromium value to reflect body stores.41 The best indirect assessment is by a trial of supplementation. Type 2 diabetes is not generally known to be associated with chromium deficiency, despite some previous studies, as well as the Indian study, suggesting so. Serum chromium levels are generally lower in developed than in developing countries, probably due to refinement and preservation of food61 with little possibility of contamination during preparation and also due to increased stress.62 However, this does not explain the higher prevalence of type 2 diabetes in developing nations like India. Chromium deficiency, important as it may be, probably is not the major factor behind type 2 diabetes.

Benefits of chromium supplementation in type 2 diabetes generally become apparent within 6-12 weeks and hence supplementation should not be continued indefinitely in the
absence of clear benefits. Because the prevalence of chromium deficiency in type 2 diabetes is not generally known and because of potential and as-yet-unidentified hazards, there is no recommendation of routine chromium supplementation in diabetes. However, in selected cases with gross hyperglycemia and glycosuria, heavily restricted diet and increased age (all increasing the risks for micronutrient deficiency), a cautious 8-12 weeks trial of chromium is warranted. This is best in the form of chromium picolinate, and probably also nicrotinate, at a dose of 200-400 µg/day. In case of a beneficial response, it may be continued, at least, with renal and, probably also, hepatic monitoring.

REFERENCES


