Role of chromium compounds in diabetes

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Abstract

Diabetes Mellitus is a complex disease where the carbohydrate, protein and fat metabolism is deranged and co-exists with insulin resistance. The defect is either in the secretion of insulin, in the insulin receptors or post receptor events[1]. It manifests as hyperglycemic state with dyslipidemia and other metabolic defects. Insulin promotes glucose uptake through its receptor located in the cell surface by generating signal that results in the translocation of glucose transporter (GLUT) to cell surface. Thereafter, glucose is transported to the cytoplasm through these receptors by facilitated diffusion in the muscle cell and the adipose tissues. In type 2 DM, the muscle cells and adipose tissues are resistant to this signaling pathway[2-7]. Trivalent chromium (Cr) vital micronutrient obtained from diet which serves to potentiate insulin action and maintenance of normal glucose tolerance. Studies suggest, chromium is an essential cofactor that is required for optimum insulin activity[9-11]. Cr increases insulin receptor numbers[8] on cell surface of the target cells hence facilitates more insulin-receptor binding. Trivalent Cr, especially Cr tri-picolinate and chromium histidinate are effective in insulin resistance. Chromium replacement is essential in deficient conditions and this fact has been well established, the aim of this review is to assess the role of chromium in the pathology of diabetes.

Keywords: Chromium, Diabetes mellitus, Insulin, Glucose

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Introduction

Diabetes mellitus is a common metabolic disorder that is prevalent in developing countries like ours. The factors that may lead to hyperglycemia are a decreased insulin secretion, fall in glucose utilization, and an increased production of glucose. Type 2 Diabetes (T2DM) is a disease characterized by a triad of insulin resistance, disturbances in insulin secretion, and increased production of glucose. Glucose homeostasis is impaired before the onset on diabetes, followed by insulin resistance and an abnormal secretion of insulin. Studies indicate that a period of insulin resistance generally preceeds a defect in the insulin secretion and eventually diabetes develops when the insulin secretion becomes inadequate[12]. Therefore T2DM is a triad consisting of impaired insulin secretion, insulin resistance and excessive hepatic glucose production that coexists with an abnormal fat metabolism. When the disease has just started, the glucose tolerance is near normal inspite of the presence of insulin resistance because the pancreatic beta cells are still able to compensate by increasing the production of insulin. With progression of disease insulin resistance develops due to a compensatory rise in insulin levels. Further, the cells of the pancreas are unable to cope up with this hyperinsulinaemic state leading to an impaired glucose tolerance, which manifests as raised post prandial glucose levels. Subsequent decline in the secretion of insulin along with excessive hepatic production of glucose, leads to a full blown diabetic state with fasting hyperglycaemia[13].

In insulin resistance, the efficiency of insulin on target tissues declines. This is the characteristic feature of T2DM and develops due to presence of genetic predisposition and obesity together. Insulin resistance reduces glucose utilization and causes an increase in the hepatic glucose output, both contributing to hyperglycemia[14].

Chromium as the essential nutrient

Chromium is an essential micronutrient with valency between -2 to +6[5]. Biological activity of chromium depends on valency. Inert chromium, hexavalent chromium and trivalent chromium Cr, are the stable forms available[16,17]. Cr(VI) has been documented to show carcinogenic properties and is also a respiratory irritant that causes lipid peroxidation, damage to DNA, eventually leading to cell death.[18,19] Cr(III) i.e. trivalent chromium is an essential micronutrient and is needed for optimum carbohydrate, protein and fat metabolism along with glucose-insulin sensitivity[20]. The exact mechanism by which trivalent chromium plays a role is not clear but multiple in vitro and in vivo studies indicate that Cr(III) has a crucial role in normal glucose and lipid homeostasis and also helps in reduction of plasma triglycerides and cholesterol. Trivalent chromium has been seen to inhibit cytokine release and reduce oxidative stress[21]. Various sources from which chromium can be obtained are fruits, green beans, cheese, seafood, whole grains and broccoli. Brewer’s yeast is another important source of trivalent chromium and is rich in organic Cr[22]. Naturally obtained glucose tolerance factor as it is found in the brewer's yeast comprises of Cr (III), glutathione and nicotinate and has essentially glucose lowering properties[23]. Thus trivalent chromium has been complexed with nicotinate and other chromium complexes and being widely used as dietary supplements[24]. The daily dietary requirement for Cr(III) so far is 50–200 µg/day, which amounts to about 0.71–2.9 µg/kg/day for a 70 kg adult[25,26]. The Food and Drug Administration (FDA) estimated a comparable value of 120 µg /day [27].

Safety of chromium compounds

Trivalent chromium is the safest form of chromium that is available from diet and also in form of dietary supplementation. The estimated daily exposure value for chromium that would not cause a harmful effect is estimated to be 350 times more of estimated daily dietary intake. More studies are needed to confirm the safety of chromium in high dose. A review of 19 RCTs where subjects were administered 175-1000µg/day of chromium for 6-64 weeks did not reveal any toxic effects[28]. It is suggested that people who have preexisting kidney or liver diseases may be prone to adverse effects related to high dose chromium. Few confirmed cases of toxicity due to chromium chloride and chromium picolinate have been reported. Cases of acute renal failure, interstitial nephritis and rhabdomyolysis have been reported[29]. Studies for genotoxicity related to cells have been found to be negative. Chromium picolinate is known to be stable, but if reduction of this compound occurs within cells, it can lead to hydroxyl radical generation & DNA lipid damage. Few studies are suggestive of DNA damage due to chromium picolinate and tri-picolinate. It is therefore essential to evaluate the genetic toxicities associated with a variety of chromium complexes when given in high doses[30]. We do not have data that report teratogenicity in humans, but animal studies have reported reduction in fertility, reduced implantation and decrease in the number of viable fetuses in mice due to chromium supplementation[31].

Mechanism

A proposed mechanism of action of Chromium in increasing insulin sensitivity is as follows. Chromium is seen to increase the number of insulin receptors and also the binding of insulin to cells[32]. Chromium activity as a glucose tolerance factor and also as an insulin sensitizer has been suggested to be the possible mechanism of its role in type 1 and type 2 diabetes. The fact that chromium plays a role in normal insulin function and activity and also fat and carbohydrate metabolism, has been well established by various animal and human studies. Chromium also reduces insulin levels and leads to better glycemic control in the obese populations with type 2 diabetes. CrPic is a commonly used as a dietary supplement in the United States. A few studies show that CrPic decreases the blood glucose levels without increasing insulin secretion, and CrPic has been considered as an insulin sensitizer. CrPic has showed multiple beneficial effects in T2DM patients including attenuation of body weight gain, improvement in lipid profiles, and enhancement of endothelial function. The exact mechanism responsible for the action of CrPic is still obscure. Multiple pathways of action have been proposed, including a decreased hepatic glucose production, an increased peripheral glucose disposal, and a reduced intestinal glucose absorption[33]. Chromium Histidinate, another chromium compound, has been seen to have the highest degree of absorption due to the addition of amino acid histidine[34].

Chromium, affects protein phosphorylation - dephosphorylation reactions and is therefore similar in action to insulin. Insulin binds to the alpha subunit of the insulin receptor, followed by specific phosphorylation of the beta subunit through a cascade of phosphorylation reactions[35,36,37]. Insulin tyrosine kinase, which is activated by Cr is the enzyme partly responsible for the phosphorylation, leading to increased insulin sensitivity[38].

Cr has been seen to inhibit phosphotyrosine phosphatase (PTP-1), a type of tyrosine phosphatase present in rats, which causes inactivation of insulin receptor[39]. This specific activity of insulin receptor phosphotyrosine phosphatase needs further research and monitoring[40]. Cr is seem to activate insulin receptor kinase and also inhibit insulin receptor tyrosine phosphatase resulting in increased phosphorylation of the insulin receptor, and increased insulin sensitivity[35,36,41].

CrPic has been seen to activate 5′-adenosine monophosphate (AMP) – activated protein kinase (AMPK). Thus, AMPK is a most important signal of Chromium picolinate in causing a decreased lipogenesis and fatty acid oxidation. CrPic administration also increases glucose uptake in the skeletal muscle. Increase in intracellular signaling may also improve the action of insulin in obese rats that are insulin resistant.[55,56] A study revealed the activity of sterol regulatory element binding protein, in controlling the cholesterol balance at cellular level and was found to be upregulated in presence of chromium picolinate. This protein is a membrane bound regulatory factor. It is therefore assumed that chromium supplementation decreases plasma membrane cholesterol. All these responses indicate a significant effect of chromium on cholesterol homeostasis[57].

Studies indicate the presence of oxidative stress in diabetes due to presence of markers of oxidative stress like plasma and urinary F2-isoprostane along with plasma and tissue levels of nitrotyrosine and •O2–[58-62]. The various pathways of oxidative stress in diabetes are non-enzymatic, enzymatic and mitochondrial. Non-enzymatic sources of oxidative stress arise from the oxidation of glucose. Hyperglycemia can directly cause increased ROS generation and glucose can undergo auto-oxidation and generate •OH radicals[63]. In addition, glucose may also react with proteins in a non-enzymatic manner leading to the development of Amadori products. ROS is produced at various steps during this procedure. Hyperglycemia, involves an enhanced metabolism of glucose through the polyol (sorbitol) pathway, which may also cause enhanced production of •O2-.

In a study, the effect of chromium and zinc supplementation on oxidative stress, using malondialdehyde (MDA) as an indicator of lipid peroxidation and serum status of some antioxidant vitamins and minerals of laying hens reared at low temperatures were evaluated[64]. Low ambient temperature lead to damaging effects on the digestion of nutrients and antioxidants (6.8°C) which was further seen to be decreased by administration of chromium and zinc, simultaneously, in the diet.

Some studies show the protective effects of Chromium picolinate and chromium histidinate against renal impairment by the modulation of NF-κB pathway in high-fat diet fed and Streptozotocin-induced diabetic rats[65]. A study conducted on 60 male wistar rats induced with diabetes, revealed that chromium histidinate supplementation lowers renal MDA, 8-isoprostane, serum urea-N, and creatinine levels, along with reduction in the severity of kidney damage in the STZ-treated group. Chromium histidinate was seen to reduce lipid peroxidation and HSP expression in the kidneys of experimentally induced diabetic rats. This study supported the efficacy of CrHis in reducing renal risk factors and impairment because of diabetes.

Evidence of role of chromium in diabetes

The importance of Cr in human nutrition was documented in 1977[66] when a female patient on total parenteral nutrition (TPN) developed severe diabetic-like symptoms that were refractory to insulin. Without the supplementation of Cr, the patient demonstrated loss of weight, accompanied by glucose intolerance and neuropathy, even on 50 units of insulin per day. After 200 mg of Cr in the form of Cr chloride was added to her TPN for a duration of 3 weeks, her diabetic-like symptoms were improved and insulin administration from outside was no longer required[67,68].

Studies show that suboptimal intake of chromium (III) can be a major contributing factor in Type 2 Diabetes and associated cardiovascular diseases (CVD)[20]. A diet deficient in Cr can lead to increased risk factors such as high levels of blood glucose, circulating insulin, cholesterol and triglycerides, and decreased lean body mass[18]. All these factors are reversed to normal by adequate chromium supplementation[20,69]. Chromium, discovered approximately 5 decades back is therefore an essential factor for maintaining a normal glucose tolerance and thus termed ‘‘glucose tolerance factor’’ (GTF) based on its biological function[70,71]. Supplementation of chromium may therefore play a key role in prevention of Metabolic Syndrome - related diseases.

In another study, twenty-six subclinical chromium deficient, healthy young adults were randomly selected as a placebo group (n = 11) or the Cr-supplemented group (n = 15) receiving 220 µg/day elemental Cr (III) in the form of NBC(niacin bound chromium). No significant difference in the percent change of fasting immunoreactive insulin (IRI) level between the placebo group and the Cr-supplemented group was observed at the end of the trial, but the subjects within the Cr supplemented group (n = 6) with high initial fasting IRI levels (56 pmol/l) exhibited a statistically significant decrease in IRI level (38 pmol/l) after 90 days of supplementation. The results were suggestive of the fact that NBC supplementation may improve insulin sensitivity over time[72]. In a double-blind clinical trial, carried out to evaluate the efficacy of NBC on blood glucose and triglyceride levels, twenty volunteers received a daily dose of 300 µg elemental Cr(III) in the form of NBC or a placebo for a duration of 3 months. The NBC-supplemented group showed significantly lowered mean fasting blood glucose levels, while the levels remained unchanged in the placebo group. NBC also decreased the mean blood triglycerides and glycosylated hemoglobin (Hb1Ac), a biomarker for long-term glucose control[73].

A 6-month randomized, double-blind, placebo-controlled clinical trial, in which Chromium Picolinate was given to overweight, Type 2 Diabetes patients who were receiving more than 50\ units of insulin daily was found to be ineffective in improving lipid profile, BMI, blood pressure, and insulin requirements[138]. The same research group conducted another study using Cr (III) in the form of chromium yeast which also showed no evidence of improved glycemic control in Type 2 Diabetic patients[75]. Thus eventually effect of high dose CrPic administration on middleaged healthy subjects of normal body weight and BMI with T2D was evaluated and the results showed improved glucose and insulin metabolism[76].

Evidence of role of chromium picolinate as a glucose tolerance factor has been demonstrated in various animal studies. In a study, metabolic effects of CrPic in a rat model of T2DM were evaluated. Male Sprague - dawley rats aged 8 weeks, 45 in number were taken into 3 groups. The controls (group I) received a standard diet (12% of calories as fat); group II was given a high-fat diet (HFD; 40% of calories as fat) for 2 weeks and then the animals were given an intraperitoneal injection of streptozotocin (STZ, 40 mg/kg; HFD/STZ) on day 14; group III rats were given group II diets with the addition of 80 µg CrPic per kilogram body weight per day. CrPic in group III rats, reduced serum blood sugar by 63%, total cholesterol by

9.7%, and triglycerides by 6.6% compared to group II rats. CrPic treatment also decreased blood urea by 33%, creatinine level by 25% and free fatty acid by 24%. In comparison with group II rats, glomerular sclerosis decreased. CrPic-group had a normal renal tubular histopathological appearance as compared with the HFD/STZ-treated group. Hepatocytes appeared to be normal in the CrPic treated group. Thus CrPic has a preventive role against microvascular complications. To conclude, HFD/STZ rats are good animal models for T2DM.Treatment with CrPic for a period of 10 weeks decreased risk factors for diabetes and introduced favorable changes in histopathology pancreas liver and kidney, indicating the essentiality of Chromium in the management diabetes[33]. Studies have shown that Chromium histidinate, another compound containing chromium, is stable and has better absorption than any of the other compounds tested in humans and appears to be a suitable nutrient supplement. Further studies are essential to demonstrate that Chromium from Chromium histidinate complex is utilized.[57]

In another animal study, 60 male wistar rats aged 8 weeks(n=60) were taken in four groups. Group 1 was given a diet consisting of 12% of calories in form of fat. Group 2 was put on a standard diet, along with CrHis. Group 3 was given a high-fat diet (40% of calories as fat) for a period of 2 weeks, followed by intraperitoneal injection of STZ on day 14 (STZ, 40mg/kg). Group 4 and group 3 were put on the same treatment (HFD/STZ), along with a supplementation of 110 µg CrHis/kg/bodywt/day. Renal oxidative stress was measured by elevated levels of MDA and 8 - isoprostane. Further, it was noted that Chromium histidinate decreases lipid peroxidation levels. Thus, Chromium histidinate is efficacious in reducing renal risk factors and impairment because of diabetes[65].

Obesity and chromium supplementation

Clinically obesity is a body mass index (BMI) of more than 30 kg/m2. An overweight individual has a BMI greater than 25 kg/m^2 [78]. Obese individuals have a greater propensity to develop Type 2Diabetes[79,80]. Diabetes affects approximately 170 million people in the world and the number is rising alarmingly[59]. T2D is the commonest form of diabetes and almost 90% of the patients who have diabetes are type2 Diabetics[59]. Management of Type 2 Diabetes includes pharmacotherapy, dietary interventions, and lifestyle modifications[83,84]. Trivalent chromium compounds have been widely instituted as supplements to improve insulin resistance and control weight gain[85]. Studies indicate that trivalent chromium compounds not only help in maintaining a normal carbohydrate, fat and lipid metabolism but also help in appetite regulation and reducing sugar cravings. Further, they also have a role in fat reduction and increasing lean mass[96].

In a study, 43 young, obese, sedentary yet healthy adults were selected to show the effects of Chromium supplementation along with exercise for weight reduction over a span of 9 weeks[97]. Chromium supplementation was given two times daily in a dose of 200µg, also, another group received placebo (inert substance). The result showed a significant weight loss only in the group which was on Chromium supplementation and exercise[86]. Also a decreased insulin response to oral glucose supplementation was demonstrated in this group. The body weight of patients showed no change in the group where patients only exercised but no chromium supplementation was given, and also in the group who received the supplements but did not exercise[86].

A study conducted on African- American , given 600µg/day NBC for two months and who were also on diet and exercise routine showed no adverse effects on the muscle mass and visible fat loss[87]. Studies indicate that Chromium has an essential role in CVD by reduction of plaque, triglycerides, low-density lipoprotein, and total cholesterol[88-92]. Studies suggest a role of chromium in the patients of gestational diabetes also.[76,93-95] Various studies suggest the role of NBC supplementation in glucose and insulin regulation[69,96].

Discussion

Chromium is a trace metal, and is an essential micronutrient, used as a supplement to treat insulin resistance. When used in appropriate amount, it enhances the glucose tolerance in human beings and is known as glucose tolerance factor for that reason[70,71]. Chromium appears in various valance states in the earth crust, among them Trivalent Chromium (Cr III) is biologically active[15,16,17]. Among many trivalent chromium studied, Chromium Picolinate, Chromium Chloride and Niacin Bound Chromium (NBC) present in baker's yeast are among the few which have been studied elaborately and the advantages and disadvantages of the micronutrients mentioned above have been documented[72]. A chromium compound, Chromium Picolinate has been known to decrease hyperinsulinemia and in experiments conducted on rodents[33,57] .

Chromium Histidinate, a trivalent compound, is the newest in this series, seemingly for the first time being used as a glucose tolerance factor in streptozotocin induced rats in similar experiments[65].

Chromium Histidinate has a glucose lowering effect on glucose homeostasis on streptozotocin induced type 2 Diabetes model in rats. Though study of this compound is in infancy, it is the right time to document the efficacy and suitability to handle large mass of population, who are predicted to be diabetic in near future. Type 2 diabetes mellitus is sufficiently produced by the intraperitonial use of streptozotocin in rats. Serum blood sugar values in high fat diet with streptozotocin rats is higher than control and high fat diet rats. The insulin level is also higher in high fat diet group than the control group. This is because high fat diet induces insulin resistance in rodents[33,57-62,98].

Trivalent chromium can facilitate insulin binding to it's receptors in the target tissues and modulate post translational activities, a process known as signal transduction and enhances uptake of glucose. In fact, many of the glucose regulatory biological activities of Chromium Picolinate can be achieved by chromium histidinate also, for example enhancing the insulin binding to it's receptors enhances tyrosine kinase activity and increases GLUT-4 translocation to the cell surface. Thus glucose is taken up to the cell in concerted manner.

Insulin resistance has been shown as major contributory factor in the development of type 2 Diabetes Mellitus. Existing literature authenticates the fact that Cr histidinate activates 5' Adenosine Monophosphate (AMP) activated protein kinase (AMPK) a major signal that suppresses lipogenesis and diverts the lipid molecules for oxidation. This indicates the fact that trivalent chromium compounds have a role in cholesterol homeostasis [55-57].

Chromium supplementation may have a role in weight loss in the obese individuals with diabetes mellitus as evidenced in some studies conducted on patients with type 2 diabetes[88-92]. Chromium compounds decrease oxidative stress in experimental rats and other species and human beings. Among many, few important parameters studied were Vit E, an lipid soluble antioxidant vitamin and MDA, a product of lipid peroxidation, and an indicator of oxidative stress. Chromium when supplemented with zinc was seen to reduce MDA levels and caused an increase in levels of vitamin E and C. The supplementation of chromium and zinc together caused increase in the levels of serum Fe, Cr, Mn and Zn in hens. Hence chromium compounds may be useful in decreasing oxidative stress as evident from studies[58-62].

Further, Chromium histidinate decreases lipid peroxidation and HSP expression in the kidneys of diabetic rats. Thus CrHis is efficacious in reducing renal risk factors and impairment because of diabetes[65].

Conclusion

Chromium supplementation, specifically trivalent chromium compounds are beneficial in increasing glucose tolerance as it has been documented to decrease blood glucose levels in human and animal studies. Cr also has an important role in cholesterol homeostasis. Chromium inhibits oxidative stress and also compounds like chromium histidinate decrease renal impairment due to diabetes. Chromium compounds may play a relevant role in prevention of diabetes, metabolic syndrome and related diseases.

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