REVIEW ARTICLE

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The role of Chromium III in the organism and its possible use in diabetes and obesity treatment

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Abstract

Introduction. Diabetes and obesity are diseases characterized by their increasing incidence every year. When comparing with healthy subjects, the serum levels of chromium (Cr) are lowered in these two diseases. Several studies conducted in laboratory animals with experimentally- induced diabetes demonstrated that supplementation with chromium ions (III) decreased glucose concentration in the blood, reduced the probability of atherosclerosis and heart attack, lowered the levels of cholesterol and low density lipoprotein (LDL). The Importance of chromium is actually challenged due to lack of clear manifestations of Cr deficiency in humans and animals.

Objective. The *aim* of *this review* was to present current knowledge about Cr its role in the organism and possible mechanisms of its action also in metabolic disorders such as diabetes or obesity.

State of knowledge. In the last decade, Cr was established to be rather a beneficial than essential trace element in mammals, and has gained popularity as a nutritional supplement and a component of many multivitamin/mineral formulations, fortified food and energy drinks. Cr supplements are widespread for diabetes and obesity treatment, despite conflicting reports on its efficacy. It was suggested that Cr shows a beneficial influence upon glucose and lipid disturbances.

Conclusions. The recent clinical trials provided evidence both in favor and against the importance of Cr in healthy and ill organisms. Unfortunately, also the molecular mechanism by which chromium affects glucose and lipid metabolism is still unclear. Beneficial effects of diet supplementation with different sources of Cr^{3+} can be potentially explained by rather pharmacological than nutritional effects.

Key words

chromium, diet, diabetes, obesity, sugar/lipids metabolism

INTRODUCTION

Chromium (Cr) is an ubiquitous metal, occurring in water, soil and biological systems. The three most stable forms of chromium occurring in the environment are: 0, +3, and +6 valence state; metal and alloys, trivalent chromium, and hexavalent chromium, respectively. Trivalent chromium is considered to be an essential element, both in animal feeding and human nutrition. In late 1950s, Schwarz and Mertz reported that feeding rats with a Torula- yeast-based diet resulted in the development of impaired glucose tolerance, and the authors indentified Cr^{3+}as an integral part of the protein recognized as glucose tolerance factor (GTF) [1]. The evidence on the essential Cr role in total parenteral nutrition (TPN) of patients has been presented [2,3]. However, a limited number of patients demonstrating a variety of symptoms and their different health status make these observations questionable. In animals, no symptoms of adverse effects of low levels of Cr in feeds have been observed. Furthermore, reproduction of experiments in rats fed with Torula yeast did not provide evidence that chromium is an essential element [4]. However, other authors regard chromium (III) as an essential trace element and/or showing beneficial effects in humans [5].

This trace element is involved in the metabolism of carbohydrates, lipids, and proteins mainly by increasing the efficiency of insulin. Chromium deficiency affects the maintenance of normal glucose tolerance and healthy lipid profiles. The suggestion that Cr intake is generally low has generated interest regarding the supposed beneficial effects of Cr supplementation on biological function and health of animals and humans. In the USA in 2001, the dietary guidelines for daily chromium uptake was lowered from 50–200 for adults to 35 and 25 μg for men and women, respectively (Food and Nutrition Board at the Institute of Medicine).

This review presents current knowledge about chromium, its role in the organism and possible mechanisms of action. The role of Cr supplementation in metabolic disorders such as diabetes and obesity, as well as in healthy organisms, is discussed.

Absorption, bio-distribution and excretion. Chromium is absorbed together with other metal ions in the gut through the unsaturated passive transport [6]. The efficiency of this process is very low with the average absorption ranging from

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0.4 – 2.5% [7]. The absorption process depends on the Cr content in the diet and on the chemical form of this element and other food components. Studies conducted in rats showed increased absorption of Cr used in the form of nicotinate (1.3%) and picolinate (1.1%) in comparison to chromium chloride (0.9%) [8]. It was shown that absorption of Cr in humans in the form of chromium chloride is much lower (0.1–0.4%) than of chromium picolinate (2.8%) or chromium given as the yeast chromium (5–10%) [7,9]. Organic sources of Cr (i.e. picolinate, or propionate-methionine salt) are much better absorbed than inorganic forms (e.g. oxides), and lead to the increase of these compounds concentration in tissues [10]. The highest dose-accumulation correlation of Cr in the tissues is observed after administration of Cr nanoparticles [11,12]. However, other factors present in the diet show a significant impact on the amounts of Cr absorbed from the gastrointestinal tract. Starch, simple sugars, ascorbic acid, oxalic acid, nicotinic acid, some amino acids, aspirin increase absorption of this element [13–16], while high concentrations of phosphate, calcium, magnesium, titanium, zinc, vanadium and iron reduce the rate of this process [13,17].

After absorption from the intestine, chromium (III) is released into the bloodstream where it is bound by proteins involved in iron metabolism. *In vitro* and *in vivo* studies in rats have shown that about 80% Cr in the blood is associated with transferrin [18]. In this complex, Cr is transported to the cells, and the efficiency of Cr transfer through the cell membrane depends on insulin concentration [19].

Chromium is found in all animal tissues and is present at the concentrations of several to tens of μg/kg, rarely exceeding 100 μg/kg [20]. The highest concentrations are found in the liver, kidneys and spleen, while slightly lower levels are observed in heart, muscle, pancreas, lungs, bones and brain [21, 22]. It has been shown that certain tissues, such as bones, testis and epididymis, are capable of storing CR in a long-term manner, in comparison to heart, pancreas or brain, where the turnover of chromium ions is relatively short [23].

Supplementation with chromium ions in livestock reveals differences in the accumulation of this element in the tissues. In pigs, feed enrichment with 0.2 mg of Cr/kg caused its accumulation in the liver and kidneys, with no clear impact on the concentration in the muscle, while in cattle, no significant changes of Cr levels in the tissues and major organs were observed [24]. Studies in poultry revealed that Cr administration in various forms (yeast, chromium, picolinate, chromium chloride) cause accumulation of this element in the liver, kidneys and muscles, without significant differences found for the eggs of hens [25, 26].

More than 80% of Cr is removed from the body in the form of urine, while the remaining part of this element is excreted via faeces and sweat [27]. In humans, consumption of large amounts of sugar, exhaustive physical exercise, pregnancy and lactation leads to increased Cr excretion in the urine [28]. Negative Cr balance was observed in patients suffering from diabetes type 1 [29]; enhanced secretion of this element in the urine was also found in rats after intramuscular injection of insulin [30].

The role of chromium in the body. The first information in the literature suggesting a biological role for chromium appeared in the late 1950s [1], while in 1996, Cr was considered as a trace element necessary for proper functioning of living organisms [31]. Currently, the essential role of Cr is questioned, mainly due to the lack of clear manifestations of Cr deficiency in mammals [4, 32]. It has been suggested that Cr should be classified as a factor nutritionally or pharmacologically beneficial [33, 34].

Chromium III is involved in many different processes including sugar and lipids metabolism. In the studies conducted in cattle and rats, diet supplementation with high amounts of Cr decreased the levels of total cholesterol, LDL-cholesterol, triglycerides and non-esterified fatty acids; the increased levels of HDL-cholesterol and the beta-oxidation process were also observed [35–38]. Similar properties of Cr were noticed in experiments with murine myogenic C2C12 cell lines [39]. Supplementation with chromium ions (III) (above 1 mg/kg body weight) also caused a dose-dependent reduction in serum leptin concentrations in rats. A similar trend was observed in human studies [35, 40]. It was shown that Cr supplementation increased the rate of amino acids transport into the cells. In the study by Lindeman et al. in 2007, a trend to decrease serum level of a stress hormone – cortisol, was noticed, however, without a clear correlation between these two factors [41]. Chromium can affect biological effects induced also by other trace elements. The common transport mechanism for chromium and iron makes these metals compete for the binding site of transferrin. In rats treated intraperitoneally with chromium ions, reduction in the bioavailability of iron in the body, with the onset of symptoms characteristic of anaemia, was observed [42]. It was shown that oral administration of Cr (as chromium nitrate) counteracts the effects of the selenium anti-carcinogenic mechanisms in the growth and latency of murine mammary tumour induced by the MMTV virus [43]. Chromium is engaged in the proper functioning of the immune system [44]. The use of Cr to both *in vivo* and *in vitro* studies modified the levels of several cytokines: IL-1, IL-2, IL-6, IFN and TNF-α [45, 46]. It was suggested that a nutrigenomic study may shed more light on the mechanisms of Cr-gene interaction, and provide a better understanding of the chromium mode of action [47].

Possible mechanism of action. Despite numerous studies, there is no clear explanation how chromium ions influence carbohydrate and lipid metabolism. There are several theories which explain chromium impact on the glucose metabolism. Among these, the most widely accepted hypothesis is the involvement of an oligopeptide, named chromodulin (LMWCr, a low-molecular weight chromium-binding substance) [48, 49]. LMWCr is a small peptide with a mass of about 1,500 kDa, built only of amino acids: 2 glycine, 2 cysteine, 4 glutamic acid and 2 molecules of aspartic acid [50]. It has an ability to bind four chromium atoms, and only in this form it shows its full biological activity [51]. Vincent et al. (1999) explained the mechanisms of chromium ions uptake and insulin receptor kinase activation by chromodulin [52]. According to the proposed mechanism, LMWCr is present in the cytoplasm and nucleus of the cells sensitive to insulin in an inactive form called 'apochromodulin'. Upon insulin binding, the transferrin receptor is activated, which further leads to internalization of transferrin-chromium complex into the cell. Internalization of this complex causes activation of the ATP-dependent proton pump, decrease of pH, release of Cr from transferrin and its binding by chromodulin. After binding of four chromium atoms, a chromodulin molecule is converted into a biologically-active 'holochromodulin' which

binds to the insulin receptor beta subunit, previously activated by the hormone, resulting in activation of receptor tyrosine kinase and insulin signal amplification. As a result, activation of the intracellular insulin signal transduction system leads to the co-localization of GLUT4 protein (glucose transporter protein 4) to the cell membrane. GLUT4 is the principal glucose transporter mediating glucose transport through the cell membrane [53]. However, the exact structure of LMWCr remains unknown. New information concerning the sequence of this oligopeptide and Cr binding properties has been recently provided by Chen et al, 2011 [54]. However, the experiments with Cr supplementation can be also interpreted as a result of non-specific binding of Cr to the amino acid sequences. These types of proteins were found in rat liver (9 proteins with a molecular weight from 4 – 97 kDa) and bovine liver (15.6 kDa) [18,55]. Furthermore, chromodulin activity stimulating the insulin receptor tyrosine kinase is unspecific. It was observed that activation of tyrosine kinase by insulin may be also caused by other metal ions, such as zinc, manganese, cadmium and certain xenobiotics, e.g. metformin and pioglitazone [56].

Another theory about the role of Cr in glucose metabolism indicates for a direct insulin receptor activation by chromium ions. Balamurugan et al. [57] showed that high levels of chromium caused induction of ROS synthesis in lymphocytes. A similar effect for the myogenic C2C12 cell line was observed. Chromium increased ROS synthesis (about 400% of initial ROS concentration) after 1 min. of administration, then cyclic decreases and increases were observed with a similar effect to insulin administration. This effect was due to the changes in the membrane phosphatases activity. The authors suggest that ROS are essential and necessary for the optimal metabolic effect of chromium ions.

One of the new concepts of Cr action was proposed by Pattar, et al [58] who formulated a hypothesis that chromium ions affect the membrane fluidity and thereby regulate the uptake of glucose by the cells. This effect was associated with the reduced cholesterol content in the cell membrane, which is considered a factor lowering glucose transport controlled by the insulin receptor. In addition, these authors showed no effect of chromium ions on the phosphorylation of the insulin signal transduction proteins: IR-beta, IRS, PI 3-K and Akt-1. Results a study Raja et al. showed the ability of Cr to interact and modify the structure of lipid bilayers [59].

It is also possible that the mode of action of Cr depends on activation of the estrogen receptor. It is assumed that estrogen may act through two signaling pathways: insulin receptor-dependent (IR) and the receptor for insulin-like growth factor (IGF-1) -dependent [60]. It has been shown that Cr is a metal possessing estrogenic properties and it can stimulate transcription of genes in cells containing estrogen receptor [61, 62]. Molecular mechanism of estrogen influence on insulin-stimulated processes is not fully recognized. It can be divided into two parts: a fast signal (related with membrane estrogen receptors activation) and a slow signal (related with nucleus estrogen receptors activation). Some new evidence on the chromium estrogenic properties is provide in the doctoral dissertation by Lewicki [63]. The microarray profiles of Cr and estrogen treated C2C12 cells (mouse myocytes) were almost similar. It was observed that out of 24 genes, the expression of which was altered by supplementation with chromium ions Cr^{3+} 10 ug/L, 19 genes were common with those that were estradiol-induced (10 nM).

Chromium in diabetes and obesity. Diabetes and obesity are diseases of the most serious public health concern. It is estimated that each year the number of new patients with diabetes increases by millions of people (700,000 in the USA, 110,000,000 in Asia), while obesity is a problem for more than 15% of Europeans and 20% of North Americans [64–66]. Treatment of the symptoms and complications of diabetes worldwide consume huge funds; only in USA, billions of dollars are allocated yearly for this purpose [67]. In both cases, serum levels of Cr are lower, compared with healthy individuals [68, 69]. Since chromium (III) modulates insulin action and glucose homeostasis, diabetes and obesity are logical candidates for Cr replacement therapy. Positive outcomes of Cr supplementation included reduction in the used hypoglycaemic medication and decrease in glucose concentration, cholesterol and triglyceride in the blood. However, the results of different studies are often contradictory.

Several studies conducted in laboratory animals with experimentally-induced diabetes, demonstrated that supplementation with chromium ions (III) decreased glucose concentration in the blood, reduced the probability of atherosclerosis and heart attack, as well as lowered cholesterol and low density lipoprotein – LDL [70, 71, 72]. It has been suggested [73, 74, 75] that Cr concentration increases phosphorylation of enzymes associated with the post-receptor insulin signaling: IR, IRS1, GDP and PKCζ (p-IRTyr, p-IRS1Tyr, p-PKBSer, p-PKCζThr). Animals consuming a chromium-enriched diet were tested for tolerance to oral administration of glucose (OGT), and showed a faster metabolism of glucose, compared to those which were treated with a low Cr diet. In human with diabetes 2, Cr supplementation can improve glucose metabolism and insulin action [76, 77, 78]. A similar effect was shown in patients with severe insulin resistance, who were given i.v. infusion of chromium (III) [79, 80]. Based on the own study results, Jain et al. (2012) [81] concluded that Cr supplementation has a potential as an adjunct therapy for patients suffering from type 2 diabetes. Interestingly, Cefalu et al. [82] observed that a consistent effect of Cr action in subjects with type 2 diabetes may be related with their genetic phenotype.

There are also several publications describing a positive role of Cr in the reduction of lipids content and body mass in obese humans and animals [70, 83, 84]. However, other studies showed lack of Cr protective function in metabolic syndrome observed for obese but non-diabetic adults [85].

Unfortunately, there are only a few studies concerning the effect of Cr supplementation on the metabolism of carbohydrates and lipids levels in healthy individuals. These studies are mostly a guesswork. A systematic review of randomized controlled trials evaluating Cr supplementation showed lack of beneficial effects in healthy individuals [86,87]. In studies with a controlled energy intake, no decrease in body weight in Cr supplemented (200 μg Cr/d) subjects was observed [88, 89]. Despite the high popularity of Cr supplementation, it seems that it is not effective in producing a sustained weight loss. However, it was shown for overweight or obese patients that a long-term use of vitamins B6 and B12 and Cr were significantly associated with a lower weight gain [90].

In non-obese, non-diabetic subjects, Cr therapy was shown not only to have no effect on the insulin sensitivity improvement, but it paradoxically declined its sensitivity [91].

CONCLUSIONS

Many report have shown that chromium III ions have beneficial properties for the organism with disturbances of glucose or lipids metabolism. However, data from the experiments conducted in healthy individuals quite often explicitly show lack of any favourable impact of chromium on sugar/lipids metabolism. This in turn leads to the hypothesis that chromium ions supplementations have been beneficial only in 'disordered organisms'. For the other roles of chromium in the body, we should use this supplement in a reasonable manner, being aware of its possible side-effects.

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