Considerations about chromium, insulin and physical exercise

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ABSTRACT

Chromium is an essential trace mineral present in trace amounts in some foods such as meat, whole grains, oleaginous plants and legumes. This mineral is currently being used as a food supplement in sports in order to promote a greater muscle mass gain and loss of body fat. However, the participation of chromium in metabolism is limited to an increase on the insulin sensitivity by the binding of four chromium atoms to a specific intracellular protein denoted apochromodulin that, in turn, binds to the insulin receptor of peripheral tissue cells concomitantly with insulin, although at another site located in the intracellular domain. This binding amplifies the cascade of intracellular signals responsible for stimulating the translocation of GLUT4 and increases glucose and amino acid uptake. Chromium may also inhibit the key enzyme in the synthesis of cholesterol, thus improving the lipid profile of individuals with dyslipidemia. The alterations on the body composition occurring in individuals who practice sports are not significant but, on the other hand, chromium supplementation may improve the lipid profile and the symptoms of type II diabetes of individuals affected by these types of metabolic unbalances.

Keywords: Chromium. Insulin. Exercise. Apochromodulin. Diabetes. Cholesterol.

INTRODUCTION

In the beginning of the sportive age, the advantage obtained by high-level athletes was considered as an insurmountable barrier. Currently, the distance between elite athletes in competitions have been so reduced that a small improvement on performance may result in large gains in the general classification. This fact has induced athletes, coaches and scientists to search, besides the training techniques, different methods in order to optimize the performance by means of the use of ergogenic resources. Among the methods aimed at increasing the performance allowed by the International Olympic Committee, the nutritional interventions stand out. However, the use of nutritional supplements by athletes or physically active individuals with the objective of improving the sportive performance, muscular hypertrophy, immunocompetence, among others, awakes the scientific community for the permanent search for biological evidences to support the use and validity of such supplements.

Among the nutritional supplements used in the sportive environment, the mineral chromium is emphasized, which dietary efficiency contributes for the glucose intolerance and to harmful alterations associated to the lipid profile. The prime function of chromium is to improve the insulin effects and thus to change the metabolism of carbohydrates, lipids and amino acids. Moreover, the chromium supplementation has been used with the objective of promoting the increase on the muscular mass and to reduce the body fat. However, scientific evidences corroborating these possible positive effects of the chromium supplementation are scarce. Thus, the objective of this reviewing is to provide up-to-date information on the physiological and especially nutritional functions associated to chromium as well as the relation between this mineral, physical exercise and the insulin action mechanisms.

CHROMIUM METABOLISM

Chromium is an essential trace mineral that participates actively in the carbohydrate metabolism, mainly co-acting with insulin, improving the glucose tolerance[1]. However, due to its action in stimulating the insulin sensitivity, chromium may also influence the protein metabolism, causing higher stimulation in the amino acids uptake and hence increasing the synthesis of proteins[2].

The chromium action does not seem to be limited to the coadjuvant participation with insulin. Although no chromium-dependent enzyme has been identified, this mineral seems to inhibit the hydroxymethyl glutaryl-CoA reductase hepatic enzyme, reducing the cholesterol plasmatic concentration[3]. A lipolytic effect is also attributed to chromium that, in addition to its possible anabolic effects stimulate the sportive population in particular to use chromium as dietary supplement in order to obtain desirable effects on the body composition[4].

Origin and recommendations

Chromium is a mineral that occurs in valences from –2 to +6, and the most common are +2 (Cr^{2+}), +3 (Cr^{3+}) and +6 (Cr^{6+})[5]. Its most common form present in food is the Cr^{3+}. Among the alimentary chromium sources, oleaginous plants, asparagus, beer, mushroom, plum, whole grains, meats, viscera, leguminous plants and vegetables[2]. The daily and safe ingestion of chromium in adults is estimated between 50 and 200 μg/day, and despite being considered as an essential element, there is no recommended dietary ingestion (RDA) specific for chromium[2,6]. However, recent publication of new dietary reference ingestions (DRI) brought an adequate ingestion value (AI) for this mineral of 25 and 35 μg/day for adult women and men, respectively. However, no ingestion tolerable upper limit (UL) for this mineral was yet defined, in other words, the highest continued daily ingestion value of a nutrient that apparently offers no adverse effect to health in almost all individuals of a life stage or gender[7].

The difficulty in establishing a RDA for chromium is especially due to the limitations on the ingestion estimative of this mineral. These limitations include since the absence of data relative to the amount of chromium present in foods to the analysis difficulties of this mineral in most foods due to the trace concentrations and to environmental contamination problems[6].

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Chromium bioavailability

The chromium bioavailability is generally low, presenting values never above 3%, and this absorption percentage seems to be inversely proportional to the amount of chromium in diet. Several factors influence the chromium absorption, among them, phytate and the higher amounts of minerals such as zinc, iron and vanadium in the intestines as inhibitors, and amino acids, oxalate, vitamin C and starch as stimulators[8].

After absorption, chromium may be stored in many tissues of the organism at no specific site necessarily, but summing up a pool of 4 to 6 mg, on average[9]. The largest amount of chromium seems to be distributed in liver, kidney, spleen and epididymis[10], however, high concentrations of chromium were already observed in the heart and kidney of rats[11]. In rats, in which marked chromium was injected, a high retention of this mineral was verified in the liver as well as the highest proportion of the intracellular chromium was present in the cytosol in relation to the other organelles[12].

Biological function

Functions including the carbohydrate metabolism are also attributed to chromium, but in lower degree, the protein and lipid metabolism are also attributed to chromium[2,13].

Its participation on the carbohydrate metabolism is more specifically related to the stimulation of the glucose uptake by target-tissue cells. This effect, originally, is not caused by chromium alone, or even as an enzymatic co-factor as most minerals[1]. This metal, therefore, acts under the form of a low molecular weight organic complex called as "glucose tolerance factor" (GTF) formed by Cr^{3+}, nicotinic acid, glycine, cysteine and glutamic acid. The study of this complex began in 1929, when researches achieved isolating the GTF in yeasts[14]. In 1957, the existence of this complex was verified in human beings and the Cr^{3+} was defined as the active component of this complex[15]. Later, in 1959, one postulated on the necessity of ingesting chromium for the maintenance of the normal glucose tolerance in mammals, fact that unchained the beginning of researches on the relation between chromium and glucose metabolism[16].

In the decade of 1960, the role of chromium in animals was well established based on studies with rats, mice and monkeys. The importance of chromium in the insulin sensitivity in humans was emphasized from 1977 on by means of observations in diabetic patients submitted to long periods of parenteral nutrition (free of chromium) in which a worsening of the metabolic state was verified[17,18].

In relation to the description of the mechanisms through which chromium acts, one proposed that this mineral increases membrane fluidity in order to facilitate the binding of insulin with its receptor[19] and that the GTF acts as a chromium-binding substance to low-chromium content cellular proteins[20]. More recently, chromium was characterized as component of the insulin cellular signalization amplification mechanism, in other words, a collaborating factor of the increase on insulin receptors sensitivity in the plasmatic membrane[21].

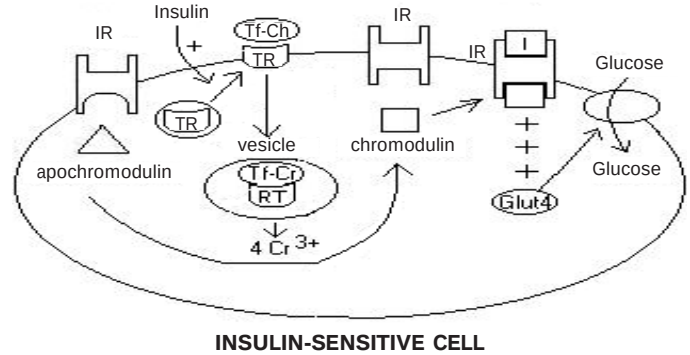
The chromium participation mechanisms in the insulin action started being cleared in the middle of the decade of 1980 by means of a chromium binding oligopeptide that was initially called as low-molecular weight chromium-binding substance – LMWCr[22-24]. This 1.5 kDa oligopeptide with only four types of amino acid residues (glycine, cysteine, glutamate and aspartate) presents tetranuclear aspect and binds four Cr^{3+} atoms, being isolated in the tissue of several species of mammals, including in the liver of rats. The difference between GFT isolated from yeasts and LMWCr from tissue of mammals are basically the presence of nicotinic acid, only present in the GTF from yeasts[23] and the absence of effects of this GFT on the insulin action and the chromium in an isolated way[3].

The LMWCr, due to its similarity with calmodulin in relation to structure and function, receives the name of chromodulin when bound to four chromium atoms, while in the free of minerals form is denoted as apochromodulin, predominantly found in the intracellular environment, more specifically in cytosol and nucleus[22].

Yamamoto *et al.*[24] proposed that the insulin action stimulation depends on the chromium content in the intracellular chromodulin. The chromodulin furthers the insulin sensitivity by stimulating the tyrosine kinase activity of the insulin receptor in the plasmatic membrane. The activation site seems to be located close to or at the active site of the tyrosine kinase enzyme, which causes the inhibition of the phosphotyrosine phosphatase enzyme, which inactivates the tyrosine kinase[25].

It is well established that in response to the increase on the blood glucose, the insulin is quickly secreted into circulation and binds itself to the subunit a of its receptor, located at the outer side of the plasmatic membrane, what causes a conformational alteration that results in the self-phosphorylation of the tyrosine residues in the subunit α, located in the inner side of the membrane. This alteration unchains a series of cascade phosphorylation reactions with the objective of stimulating the translocation of glucose transporters (GLUTs) into the plasmatic membrane[26].

The model proposed to explain the chromodulin action as part of the insulin signalization self-amplification system suggests that the chromodulin is stored in the form of *apo* in the cytosol and nucleus of insulin sensitive cells. The increase on the circulating insulin causes two concomitant situations: (i) higher chromium mobilization into the target-cells, mainly mediated by the transferrin and (ii) mobilization of the transferrin receptors from intracellular vesicles in order to bind to the membrane. Thus, the chromium saturated transferrin binds to its respective receptors and the complex formed is internalized through endocytosis. In the intravesicular space, the acid pH promotes the digestion of this complex and releases chromium to the cytosol. Four Cr^{3+} atoms bind to the apochromodulin making it active under the form of chromodulin that, in turn, binds to the active site in the insulin receptor, fulfilling its activation and amplifying the insulin signal (figure 1)[22,27].



INSULIN-SENSITIVE CELL

IR = Insulin receptor;
TR = Tranferrin receptor;
Tf-Ch = Transferrin bound to chromium;
I = Insulin

***Fig. 1** – Mechanism proposed for the chromium participation in the insulin action*

Besides its main actuation on the carbohydrate metabolism, chromium also participates in the protein metabolism by stimulating the amino acids uptake by cells, once it is directly associated with the insulin activity[4]. There are, also, some evidences about the chromium function on the lipid metabolism, which seem to be related with the increase on the high-density lipoproteins concentration (HDL) and with the reduction on the total cholesterol and the low-density lipoproteins (LDL, VLDL) by means of the increase

on the lipase enzyme activity of lipoproteins in individuals with dyslipidemia[28]. The decrease on the chromium-induced cholesterol plasmatic concentration is related to the fact that this mineral promotes the inhibition of the hydroxymethyl glutaryl-CoA reductase hepatic enzyme, thus causing hypolipemiant effect[3].

Although the chromium action mechanisms have not been yet biochemically demonstrated, signs of marginal chromium deficiency in rodents include decrease on the glucose tolerance and increase on the insulin, cholesterol and triacylglycerol plasmatic concentrations[6]. Moreover, patients with glucose intolerance, diabetes mellitus, hypercholesterolemia and elderly people use to present low chromium serum concentrations[3]. This demonstrates that chromium, besides being associated to the carbohydrate metabolism, also influences the protein and lipid metabolism simultaneously, being more and more an important nutrient for the control of disease in the population.

Role of chromium in physical exercise

During exercise, chromium is mobilized from its organic supplies in order to increase the glucose uptake by the muscular cell, but its secretion is largely increased in the presence of insulin. The increase on the diet-induced blood glucose concentration stimulates the secretion of insulin that, in turn, causes higher release of chromium. The excessive concentration of chromium in blood may not be reabsorbed by the liver, being consequently excreted by the urine. It is frequent observing increased chromium concentration in urine after large ingestion of carbohydrates, especially under the form of sugars[2].

The chromium plasmatic concentration increases during prolonged aerobic exercises and keeps high up to 2 hours after the end of the activity[2]. Both the acute and chronic effects of physical exercise cause higher urinary chromium excretion in days when physical activities are performed[29].

The urinary chromium losses generally are not quickly reestablished in function of the intestinal absorption of this mineral is not sufficient to supply the amount lost. Both aerobic exercises and strength training increase the intestinal chromium absorption, but the urinary loss is still relevant, resulting in negative chromium balance, depletion and redistribution of the body supplies during the post-exercise period. In this context, one postulates that athletes may present chromium deficiency more easily than sedentary or moderately active individuals[29].

The objective of suggesting chromium as dietary supplement aimed at those who practice sports is not a result only of the concern with the organic deficiency occurrence, but mainly because chromium may further the anabolic via by means of the increase on insulin sensitivity that, in turn, stimulates the amino acids uptake and hence the synthesis of protein, increasing the adaptive metabolic response as result of training. This fact may lead to an increase on the lean body component due to the muscular mass gain. Some authors still speculate on a possible lipolytic effect caused by chromium, however, results of studies involving human beings are still controversial. On the other hand, chromium supplementation may aid on the blood glucose control of diabetic individuals engaged in physical activity programs[2,4,8,18,20,25,28].

The World Health Organization (WHO) does not establish an exact safe value for chromium ingestion, but reports that doses from 125 to 200 μg/day beyond regular diet may further the blood glucose control and improve the lipid profile[30]. Thus, the maximum dose within safe limits is of up to 250 μg/day, what represents, for example, about ten times the AI recommended for women.

Possible side effects from the high ingestion of chromium are unknown – reaching up to 800 μg/day – as well as its toxicity[30]. However, it seems that doses between 200 μg/day and 800 μg/day within a short period of time produce no positive effects with regard to the loss of fat mass and gain of lean mass[31]. However, one postulates that the effects associated to the insulin sensitivity are unchained with chromium doses equivalent to 1000 μg/day, what represents 13 μg/kg of body mass (body mass estimated in 75 kg on average)[32]. However, it is worth emphasizing that physical exercises associated with chromium supplementation with the objective of enhancing the blood glucose control may decrease the necessity of ingesting this mineral.

It is well known that the practice of physical exercises decreases the blood glucose and insulinemia levels in individuals with peripheral insulin resistance. These effects may be observed even in only one exercise session and may last for several hours after the end of the physical activity, being chronically incorporated with the regular practice of physical exercises[33]. The chromium concentration also remains increased after exercise, once again demonstrating its association with the insulin function.

During physical exercise, the muscular contraction increases the translocation of GLUT4 regardless the presence of insulin. The most accepted suggestion in order to explain this fact is that of the calcium intracellular increase. The release of calcium from the cisterns of the smooth endoplasmatic reticulum at the depolarization moment required for the interaction of the myosin and actin myofilaments also acts as mediator of the glucose transport. This hypothesis is based on the observation of the increase on the glucose transport, which is correlated with contraction frequency rather than with the movement tension or duration[34]. The increase on the content of calcium in the cytoplasm may start or facilitate the activation of molecules or proteins involved in cascade of intracellular signals, which promote the immediate and prolonged effects of exercise on the glucose transport. A good example is the protein kinase C (calcium-dependent and intermediate signaling agent), which is activated through the muscular contraction and seems to be involved in the regulation of the glucose transport stimulated through the muscular contraction[33].

The combination of insulin and physical exercise results in additive effects in relation to the glucose transport associated to the recruitment of the GLUT4 transporter into the plasmatic membrane, what corroborates the hypotheses suggested on the stimulation of two different mechanisms in which two different glucose transporter intracellular pools were observed, in other words, one of them responds to exercise and the other responds to insulin[33]. A reasonable justification for this hypothesis regards the insulin capacity – and not the exercise capacity – in promoting a redistribution of Rab4, a GTP transporting protein (GTP-binding protein), which is involved in the regulation of the translocation of GLUT4 in adipose cells[35].

With insulin and exercise acting in different pools, the result would be the same – the translocation of GLUT4 – and this effect may be improved or not in the concomitant presence of both. Not much is known about the effects of chromium and physical exercise when related to the insulin sensitivity. The target population of studies on chromium and body composition is generally composed of athletes or those who practice strength activities with the objective of improving the muscular mass gain and reducing the body fat content. Body composition analyses with more precise methods such as DEXA and hydrostatic weighing in individuals who practice strength activities have demonstrated that the supplementation with 200 μg/day of chromium does not promote significant increase on the muscular mass in 8-12 weeks of resistive training. However, in studies involving longer periods of time (12-24 weeks) associated to higher doses of chromium (400 μg/day), the athletes presented significant body composition alterations with reduction on the fat mass of 5%[4,31,36-38]. This fact indicates that the effects of chromium on body composition may occur; however, these effects require long periods and higher doses when compared to those described, also associated to a higher training volume.

Another population studied is that composed of overweighed and obese individuals in which the chromium supplementation does

not seem to cause significant alterations on body composition alone but associated to the regular practice of physical exercises, demonstrates weight reduction, what may indicate the efficiency of the physical activity only[28].

However, the most beneficial effect of the chromium supplementation is related to the risk factors of developing cardiovascular diseases and diabetes, which are associated with obesity. Once chromium increases the sensitivity of the insulin cellular receptors, this mineral may promote the homeostasis of insulin-dependent diabetic individuals. Moreover, chromium – through mechanisms not yet fully described in literature – seems to improve the lipid profile of these individuals, decreasing the risk of coronary pathologies.

However, these effects attributed to chromium are already observed and corroborated when the individual is engaged in some regular practice of physical exercise, once some of the physiological benefits of the *per se* exercise is to increase the insulin sensitivity, to decrease the plasmatic concentrations of cholesterol, triacylglycerol and low-density circulating lipoproteins, to increase the high-density lipoprotein plasmatic concentration, to decrease body mass and the fat content and to increase the muscular mass. The literature does not explain if chromium aids on the promotion of these effects or even if chromium makes these effects more powerful.

Cautions in relation to the chromium supplementation

Cr^{3+} is not the most toxic form found, however, this form is toxic to the organism when ingested in extremely high dosages. However, the serious problems related to chromium intoxication are associated to Cr^{6+} that is usually inhaled in industrial environments and cause ulceration of the nasal septum, inflammation of the nasal mucosa, chronic bronchitis and emphysema[39].

A possible contraindication in relation to the ingestion of high doses of Cr^{3+} for the organism regards the damage on the iron nutritional status due to the fact that chromium competes with iron in relation to the transferrin, protein responsible for the transport of newly absorbed iron[7,40]. It is worth emphasizing that only 30% on average of transferrin is found loaded with iron, suggesting that this protein also transports other metallic atoms[41]. However, only a few works were conducted with the objective of verifying this condition and there are no significant scientific evidences that this fact actually occurs. On the other hand, once chromium competes with iron in relation to the transferrin enzyme, one verifies that the excess of iron saturation in this protein – as occurs in the hemochromatosis – impairs the chromium transport and concomitantly decreases the Cr^{3+} retention in patients with hemochromatosis[42]. Furthermore, chromium is transported through albumin, globulin and possibly through lipoproteins[2], making the transferrin biding sites available when the demand for this latter is higher.

Based on 21 random clinical studies – described in recent meta-analysis[43] – in which healthy individuals and patients with type-2 diabetes mellitus received daily doses between 10.8 and 1,000 μg of chromium during 28 days to 16 months, no evidences of toxic effect as result of the chromium supplementation were observed. However, other studies have reported harmful effects of the chromium supplementation such as sleep disturbances, mood alterations, headaches, increase on the trace-mineral excretion and alterations on the iron metabolism[44,45]. In another study[46], it was observed that the chromium supplementation (3.3-3.5 μmol as chromium chloride or chromium picolinate) during 8 weeks resulted in non-significant decrease on the transferrin saturation, which was higher for group supplemented with chromium picolinate in relation to the group supplemented with chromium chloride. This fact may have occurred because chromium competes with iron in relation to the transferrin enzyme, what may predispose the individual to the lack of iron.

CONCLUSIONS

The use of chromium in patients with type-2 diabetes associated or not to physical training programs

Studies performed with non-diabetic patients have demonstrated no association between chromium ingestion and the insulin and glucose concentrations. Moreover, most studies involving patients with type-2 diabetes and chromium supplementation are not conclusive in relation to the reduction on the blood glucose and insulinemia levels. The chromium deficiency seems to cause glucose intolerance conditions, and its highest availability increases the insulin sensitivity and decreases the circulating low-density lipoproteins concentration, favoring the control of the type-2 diabetes mellitus.

The use of chromium by athletes

Both the practice of physical exercises and the ingestion of sugars may increase the urinary chromium excretion; however, if these facts induce to a chromium deficiency or if the athletes are capable to increase the chromium efficiency or retention in the organism is still unknown. It is worth emphasizing that there are no scientific evidences to conclude that the chromium supplementation changes body composition significantly. The chromium supplementation possibly acts as an additional factor to the physical exercise in the improvement of the insulin resistance conditions, but still, not many specific works that evaluate the conjoint effect of physical exercise and chromium supplementation on the insulin sensitivity are found in literature. Further studies involving these three factors for the actual comprehension of this alteration on the organism are required.

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