Importance of Chromium in the Diet

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Abstract

Chromium is a micronutrient found in several oxidation states, being trivalent chromium and hexavalent chromium the most prevalent. Although it is present in several foods in small quantities, there is still no recommended average requirement. Studies show that during the various life stages, there are

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different needs of ingestion of this mineral. Despite the low molecular weight, there is a small absorption capacity of chromium and its absorption occurs in the intestine by passive transport. Along with other metallic ions, its transport is related to the performance of transferrin, and there may be competition for sites that bind to iron and other minerals. Chromium is related to changes that encompass carbohydrate and lipid metabolism. Therefore, some studies indicate that chromium-deficient diets may favor insulin resistance, with consequent development of type 2 diabetes. This mineral is also present in nutritional supplements featuring various structures such as chromium picolinate, chromium histidinate, chromium chloride, and chromium nicotinate. Trivalent chromium demonstrated an important role in gene expression, mainly in hepatocytes, insulin activity, and adiposity. Studies have investigated the effects of chromium supplementation on diabetes, obesity, and dyslipidemia, but the results are still incipient for the development of guidelines recommending supplementation in risk groups.

Keywords

Chromium · Biological availability · Nutritional requirements · Glucose · Insulin resistance · Insulin · Type 2 diabetes mellitus · Cholesterol · Dyslipidemias · Deficiency · Micronutrients · Toxicity

List of Abbreviations

AI	Adequate intake
CASQ 1	Calsequestin 1
CIDEA	Cell-death-induced DNA fragmentation factor
Cr^{3+}	Trivalent chromium
Cr^{6+}	Hexavalent chromium
CrCl3	Chromium chloride
CrPic	Chromium picolinate
CrSP	Complex of chelated chromium with small peptides
DGAT 2	Decylglycol transferase
EAR	Estimated average requirement
ENO 3	Enolase 3
Glut 4	Glucose transporter in muscle and adipose tissue dependent on insulin
GPI 1	Glucose phosphate isomerase1
IGF-1	Insulin-like growth factor 1
IRS-1	Insulin receptor substrate 1
IRS-2	Insulin receptor substrate 2
Kg	Kilograms
LDL-c	Low-density cholesterol
mRNA	Messenger ribonucleic acid
NBC	Chromium nicotinate
Ph	Hydrogenation potential
PI3k	Phosphatidylinositol-3-kinase
RDA	Recommended dietary allowance

TPM 1	Tropomyosin-1
TTP	Tocopherol transfer protein
UCP 1	Uncoupled protein 1
UL	Tolerable upper intake levels
VLDL	Very low-density lipoproteins
WHO	World Health Organization
μg	micrograms

Introduction

Since its discovery in the eighteenth century, chromium has had several uses as dyes in the textile industry, manufacture of refractories, and metal alloys due to its corrosion capacity (Ensminger et al. 1990; Zelicoff and Thomas 1998). In the twentieth century, the scientific community obtained important findings about the role of chromium in carbohydrate metabolism through the potentiation of insulin signaling (Jeejeebhoy et al. 1977; Vincent 1999). Due to the importance of this micronutrient in the diet, this chapter aims to present the nutritional needs and the main dietary sources of this element, the processes involved in digestion, absorption, transport, and mechanisms of action of chromium in metabolism and its relation with the modulation of gene expression. Because of the increasing use of chromium as a nutritional supplement, this chapter further discusses its effects on type 2 diabetes mellitus and obesity, as well as adverse reactions and toxicity.

Studies indicate a relationship between chromium, health, and disease. But it is still necessary to better understand this micronutrient, such as food, nutritional, biochemical, and public health aspects in order to enable the findings to determine nutritional recommendations for healthy individuals and support guidelines for chromium supplementation in vulnerable groups.

Nutritional Requirements and Food Source

Chromium is a micronutrient present in nature in various valence states, being trivalent (Cr^{3+}) and hexavalent (Cr^{6+}) the most common. Cr^{3+} is the most stable oxidation state and, possibly, the most common form present in the diet, due to the reducing action of food substances (IOM 2001).

In foods, Cr^{3+}can be found, originally identified in brewer's yeast (Schwarz and Mertz 1959). Despite being found in various foods, its amount in most of them does not exceed 2 μg per serving (Roussel et al. 2007) (Table 1).

Cr^{3+} is an important nutrient in the diet, but in the absence of scientific evidence, the Estimated Average Requirement (EAR) of its daily intake has not been established yet. Adequate Intake (AI) (Table 2) is the only establishment to date. The Tolerable Upper Intake Level (UL) has also not been defined, since only a few serious adverse effects were found as a result of its high intake (IOM 2001).

Table 1 Chromium content of foods

Foods	Cr content (μg/serving)
Radish	2.61
Beef steak	2.88
Grapefruit juice	2.94
Grilled chicken	3.83
Pork rib	4.20
Broccoli gratin	4.40
Leek	5.18
Kiwi	5.09
Orange	6.22
Apple	6.80
Boiled potatoes	10.20
Dark chocolate	14.28

Roussel et al. (2007)

Table 2 Daily adequate intake (AI) of chromium (μg)

		Female		
Age	Male		Pregnancy	Lactation
0–6 months	0.2	0.2		
7–12 months	5.5	5.5		
1–3 years	11	11		
4–8 years	15	15		
9–13 years	25	21		
14–18 years	35	24	29	44
19–30 years	35	25	30	45
31–50 years	35	25	30	45
51–70 years	30	20		
>70 years	30	20		

IOM (2001)

Considering life stages, healthy individuals do not represent risk groups for chromium deficiency. Thus, the AI of chromium was based on the average of food consumption. In this case, for children from 0 to 6 months of exclusive breastfeeding, the nutritional recommendation was based on the content of chromium in breast milk, and for children from 7 to 12 months, the quantity of this mineral present in breast milk and in healthy complementary foods was considered (IOM 2001).

For people from 1 to 50 years, there appears to be no increased nutritional requirements of chromium; therefore, the AI of this mineral was based on the average of chromium present in an adequate diet (IOM 2001). For individuals above 51 years, the AI of chromium was also determined from the average amount of this nutrient found in a balanced diet, within the energy requirement for this age group (IOM 2001). There is not sufficient scientific evidence to prove a greater

requirement for chromium in this age group for the prevention of diseases, such as diabetes mellitus type 2 (Mccormick 2012).

In the case of pregnant women, there are no studies that confirm the requirement for chromium supplementation during pregnancy (IOM 1990). Therefore, to obtain the AI of chromium, the recommendation for a nonpregnant woman, of the same age group, added to the requirement for this mineral to fetal supply was considered (IOM 2001). For lactation, the AI of chromium was based on the AI for women of the same age group added to the amount of chromium required for replacement of chromium found in breast milk (IOM 2001).

For individuals with chronic diseases such as diabetes, several studies used additional doses in order to verify the effects of chromium in humans and generate evidence for supplementation recommendations. However, the current evidence does not support a positive effect to the supplementation with chromium in the treatment of diabetes (Abdollahi et al. 2013).

Digestion, Absorption, and Transportation

Although Cr^{3+} is the most stable oxidation state, its absorption is low because it presents difficulty in crossing the plasma membrane (Mertz 1992). As for Cr^{6+}, it has strong oxidative capacity, mainly in acid media, and is linked to oxygen in the form of chromate (CrO_4^{2-}) or dichromate ($Cr_2O_7^{2-}$), which are the easiest compounds to absorb by the plasma membrane. During transport through the membrane, Cr^{+6} is detoxified to Cr^{+3} and reacts with protein components and nucleic acids inside the cell (Pechova and Pavlata 2007).

Specifically during ingestion, the Cr^{+6} dichromate is mixed with saliva and in the stomach it is reduced in Cr^{+3} by hydrochloric acid and thermosensitive-reducing agents present in the gastric juice (Kirman et al. 2013). An enzyme of great importance in the process of chromium reduction is pent gastrin, which stimulates gastric secretion, and Cr^{6+} is reduced into Cr^{3+} by hydrochloric acid, especially in individuals who remain in prolonged fasting (Stollenwerk and Grove 1985).

An in vitro study also demonstrated the conversion of Cr^{6+} to Cr^{+3} by the enzyme glutathione (GSH). By means of the spectrophotometric analysis, it was observed that the excess of the GSH enzyme accelerated the conversion reaction of Cr^{6+} to Cr^{+3}. It has also been shown that this reaction is strongly pH-dependent, being slower in pH 7.4 solutions than at pH values below 5.0 (Wiegand et al. 1984).

The absorption of chromium occurs in the intestine by passive transport, along with other metal ions, mainly in the portion of the jejunum and, to a lesser extent, in the ileum and duodenum, as demonstrated in an experiment with rats (Chen et al. 1973). In humans, there is also evidence that the absorption of chromium begins in the jejunum (Ducros 1992). Chromium in foods has increased absorption by the presence of amino acids, ascorbic acid, high levels of carbohydrates, oxalate, and aspirin in the diet, while phytates and antacids (sodium hydrogen carbonate, magnesium hydroxide) reduce Cr concentrations in the blood and in others tissues (Stoecker 1999).

Inorganic chromium compounds exhibit low absorption, less than 3%, regardless of the dose or chromium status. On the other hand, chromium complexes in the diet are more available than simple chromium salts (Fairweather-tait 1992), that is, the organic sources of Cr^{+3} are better absorbed (Ohh and Lee 2005).

In nutritional supplements, studies on the bioavailability of chromium are controversial; some show that chromium chloride has less bioavailability (0.1–0.4%) than chromium picolinate (2.8%) (Commission 2002). However, due to the toxic effect of picolinate in inducing renal insufficiency, anemia, and hemolysis, the nicotinate compound of chromium has shown greater bioavailability and lower toxicity (Bagchi et al. 2002). More recently, the soluble and ionic forms of chromium phenylalaninate [Cr (D-Phen3), Cr (L-Phen3)] and chromium hydrochloride (CrCl3) have been found to be better absorbed than the organic chromium trispicolinate (CrPic3), chromium nicotinate (CrNic2), and chromium propionate (CrProp) compounds (Laschinsky et al. 2012).

After absorption, chromium is transported in the blood by transferrin and can compete with binding to iron and other minerals (Quarles et al. 2011). The transferrins are proteins (molar mass ~ 80 kDa) that bind reversibly to metal ions, exhibiting greater selectivity for Fe^{+3}. However, the binding of Cr^{+3} to the Fe^{+3} sites of the carrier protein may be related to the detoxification process, more than the transport of an essential trace element (Levina et al. 2016).

The affinity of transferrin to metal ions varies according to environmental conditions, especially pH (Brock 1985). The binding of transferrin to chromium occurs similarly to its attachment to iron. The chromium binds to transferrin's two sites. When each chromic ion binds to the tyrosine residues of transferrin, changes occur in the ultraviolet spectrum of the protein, which was detected by means of Raman resonance (Aisen et al. 1969; Ainscough et al. 1980).

Chromium in Glucose and Lipid Metabolism

Chromium is postulated with functions that mainly cover carbohydrate metabolism. Increased plasma glucose levels stimulate insulin secretion, which binds to the α subunit of its trans membrane receptor and favors the transport of Cr^{+3} through the chromo-transferrin (Cr-Tf) complex. In the intracellular medium, four chromium atoms bind to a protein called apo-chromodulin which becomes active in the form of holo-chromodulin (Fig. 1). Holochromodulin binds to the β subunit of the insulin receptor, amplifies the signal, and activates the kinase activity of the receptor (Vincent 2000). However, the European Food Safety Authority (EFSA) by the Scientific Opinion on Dietary Reference Values for Chromium suggests there is insufficient evidence on chromium's action mechanism that supports its essentiality on glucose metabolism (EFSA 2014).

Intracellular signaling of insulin begins with its binding to the α subunit, which promotes conformational change and β subunit auto-phosphorylation, with a consequent increase in receptor kinase activity. Activation of the insulin

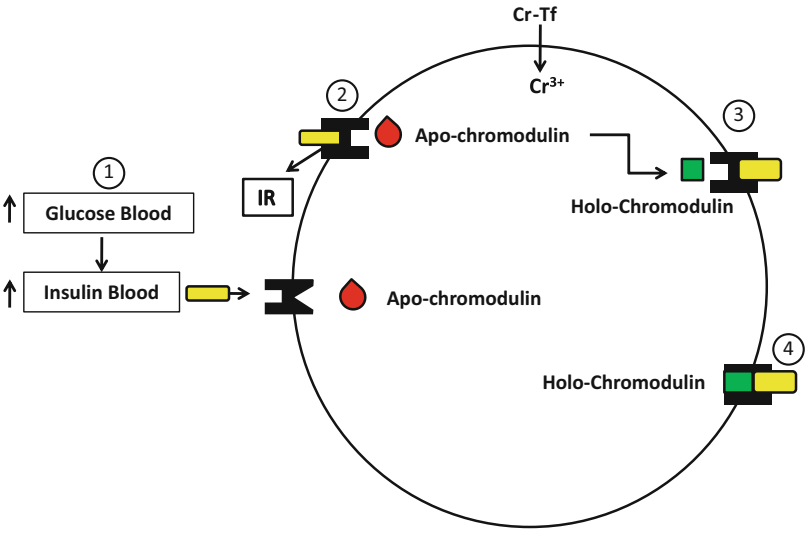

Fig. 1 Action of chromium in glucose metabolism. ◯: Increased glucose and insulin secretion that bind to the α subunit of its receptor, ➡ ▬, ◯: The insulin receptor (*IR*) becomes active through insulin binding and promotes conformational change in the β subunit (▬) and favors the entry of Cr^{+3} into the cell through the chromo transferrin complex (*Cr-Tf*), ◯ to ◯: conversion of the inactive form apo-chromodulin (●) to the active form holochromodulin (■), ◯: Final active form holo-chromodulin attaches to the site at the insulin receptor (▬) (Adapted from Vincent 2000)

receptor kinase triggers a cascade of intracellular phosphorylation. Initially, phosphorylation of its intracellular protein substrates (IRS-1 and IRS-2, respectively) phosphorylates the p85 regulatory subunit and activates the p110 subunit of phosphatidylinositol-3-kinase (PI3k), favoring the conversion of phosphatidylinositol-4,5 -phosphate (PI3k -inactive) in phosphatidylinositol-3,4,5-triphosphate (PI3k-active) (White and Kahn 1994).

Active PI 3-kinase is important in regulating mitogenesis, cell differentiation, and insulin-stimulated glucose transport. It promotes phosphorylation of protein kinase B (AKT) and other phosphoinositois kinase-dependent (PDKs) (White and Kahn 1994; Myers and White 1993).

The phosphorylation mechanism of the p110 subunit of PI3K is stimulated by the chromium present in the cytosol of the cell. Chromium also activates AKT, which stimulates the translocation of the glucose transporter (GLUT4) to the membrane, which is important for the glucose uptake process (Whiteman et al. 2002). The activated AKT phosphorylates other pathways assisting in the conduction of glucose transport (Wang et al. 2006; Dong et al. 2008). Chromium still inactivates PTP-1B which is a protein phosphatase considered to be a negative regulator of insulin signaling (path not shown in the figure) (Goldstein 2002; Sreejayan et al. 2002).

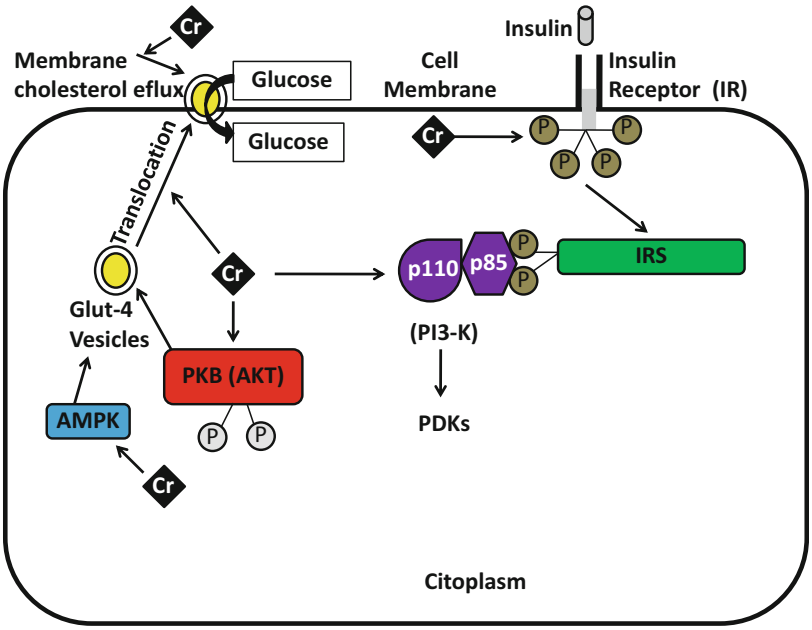

Fig. 2 Putative mechanisms by which chromium augments cellular glucose uptake. Chromium (*Cr*) showed increased kinase activity via phosphorylation of the insulin receptor β (*IR-β*), which was associated with the downstream insulin receptor (*IRS-1, IRS-2* respectively), which was phosphorylated thereby the p85 regulatory subunit and p110 subunit of the phosphatidylinositol 3-kinase (*PI3K*) protein and phosphoinositde-dependent kinases (*PDKs*). Chromium also assists in the signaling and phosphorylation of protein kinase B (*AKT*) leading to translocation of vesicles of glucose 4 (*Glut4*). The transient upregulation of cyclic adenosine monophosphate-activated protein kinase (*AMPK*) leads to increased uptake of glucose. Chromium mediates cholesterol efflux from membranes causing Glut4 translocation and glucose uptake (Adapted from Hua et al. 2012)

The transient positive regulation of AMPK by chromium leads to a higher uptake of glucose, that is, chromium favors the cholesterol efflux of membranes, which causes GLUT4 translocation and consequently glucose uptake (Fig. 2) (Chen et al. 2006).

Although chromium is involved in various mechanisms of glucose metabolism, it was found that chromium nicotinate supplementation did not promote increased insulin sensitivity and reduce blood glucose in diabetic subjects (Guimarães et al. 2013; Abdollahi et al. 2013).

There are also studies that report the relationship of chromium with lipid metabolism. Elevated blood cholesterol levels and aortic plaque formation were observed in rats fed a chromium-deficient diet, but not in animals supplemented with chromium chloride (Schroeder 1969). Later, a reduction in atherosclerotic plaque was observed in rabbits when they received potassium chromate injection (Abraham et al. 1980).

In humans, evidence on the importance of chromium in lipid metabolism has occurred from analyses of aortas of people who died of cardiovascular disease. They had less chromium than aorta from healthy people who were victims of an accident (Schroeder et al. 1970). Later, it was found that people with cardiovascular disease

had lower serum chromium concentrations when compared with healthy people (Newman et al. 1978; Simonoff et al. 1984).

Studies on the effect of chromium supplementation on improving lipid disorders are controversial. Press et al. (1990) have shown the potential of chromium picolinate in improving the lipid profile of people aged 25–80 years; however, Amato et al. (2000) found no promising effect of chromium picolinate on dyslipidemia in the elderly. In a study performed with diabetic subjects who received chromium supplementation by means of brewer's consumption, it showed a decrease in the levels of triglycerides and low-density lipoprotein (LDL-c) (Sharma et al. 2011). However, another study with diabetic subjects showed no change in total cholesterol, LDL-c, high-density lipoprotein (HDL-c), and triglycerides after 90 days of supplementation with chromium nicotinate (Guimarães et al. 2013).

Status, Toxicity and Adverse Chromium Effects

As previously discussed, chromium is a potentiating agent for insulin signaling (Vincent 1999; Chen et al. 2011). Thus, it is assumed that their dietary deficiency may contribute to the development of type 2 diabetes mellitus (IOM 2001). Most of the patients with diabetes mellitus have low concentrations of serum chromium (Guimarães et al. 2013), which makes clear the inverse relationship between HbA1c and serum levels of chromium (Rajendran et al. 2015). Thus, hyperglycemia may lead to a decrease in serum chromium concentrations and increase its urinary excretion, worsening diabetes (Gaméz et al. 2002). In healthy subjects, urinary excretion of chromium did not differ after high glycemic index diets compared to low glycemic index diets (Hajifaraji and Leeds 2008). Regarding age, there is a decrease in serum chromium levels in healthy individuals (Rocha et al. 2016). Table 3 shows studies on chromium status in health and disease.

Regarding obesity, serum chromium levels among obese and eutrophic children did not differ (Azab et al. 2014). The relationship between serum chromium and obesity was also not observed in obese women (Yerlikaya et al. 2013). Despite this, the relationship between obesity and insulin resistance is well established (Zhang et al. 2015). In this sense, chromium status in adults with visceral obesity plays an important role in insulin resistance, due to the inverse relationship between capillary chromium level and HOMA-IR (Kim and Song 2014). The chromium status of the toenails was also inversely associated with the incidence of metabolic syndrome, as a function of its relationship with blood lipids (Bai et al. 2015).

Regarding the deficiency diseases, the majority of anemic children due to iron deficiency presented chromium deficiency (Angelova et al. 2014). Despite the antagonistic effect of chromium on iron, by competing for the binding to apotransferrin (Quarles et al. 2011), insufficient intake of iron from the diet can be accompanied in many cases by borderline or insufficient intake of other micronutrients. On the other hand, in vitamin A deficiency, children with nocturnal blindness presented high levels of chromium in biological samples (blood, scalp, and urine (Afridi et al. 2011).

Table 3 Chromium status in health and disease

Reference	Study design	Sample characteristics	Sample size	Results
Healthy individuals				
Rocha et al. 2016	Cross-sectional study	Healthy individuals 18 to 74 years old	240	There was no difference in serum and urinary levels of chromium between the sexes. Serum chromium levels decreased with age.
Metabolic syndrome				
Bai et al. 2015	Cohort	American adults, aged 20–32 years	3648	Higher toenail chromium levels in young adulthood were associated with lower incidence of metabolic syndrome.
Prediabetic individuals				
Rafiei et al. 2014	Cross-sectional study	Prediabetic patients	132	In the group with a normal level of Cr, serum chromium levels decreased with age.
Type 2 diabetes				
Rajendran et al. 2015	Cross-sectional comparative study	Newly diagnosed type 2 diabetes mellitus patients without any pre-existing complications	42	Mean serum chromium concentration was significantly lower in uncontrolled type 2 diabetic patients. There is a decrease in serum chromium levels with age. The decrease in serum levels of chromium is greater after 40 years old.
Harani et al. 2012	Cohort	Adults aged 40 to 60 years	278	Serum chromium levels vary according to glycemic control in subjects with type 2 diabetes. Individuals with poor glycemic control had chromium levels 33% lower than healthy individuals. Serum chromium levels correlated strongly with insulinemia and HOMA-IR.
Guimarães et al. 2013	Randomized double-blind clinical trial	Adults with type 2 diabetes	42	Serum chromium deficiency was observed in 72% of individuals with type 2 diabetes.

(*continued*)

Table 3 (continued)

Reference	Study design	Sample characteristics	Sample size	Results
Enteral nutrition				
Santos et al. 2017	Prospective observational study	Patients aged 26–95 years that underwent percutaneous endoscopic gastrostomy	129	The majority (94%) of individuals with long-term dysphagia due to head and neck cancer or neurological dysphagia had normal serum levels of chromium. None of the patients who had low levels of serum chromium had diabetes or glucose intolerance. Low levels of serum chromium were not related to gender, glycemia, body mass index, serum albumin or transferrin.
Parenteral nutrition				
Capone et al. 2017	Cross-sectional comparative study	Preterm infants receiving parenteral nutrition therapy	706	Chromium supplementation via parenteral nutrition promoted better glucose tolerance and calorie delivery during the first week of life, especially in very low birth weight infants.
Anemia				
Angelova et al. 2014	Cross-sectional study	Children younger than 3 years with iron deficiency anemia	30	Low serum chromium in 73% of children.

High levels of chromium are generally observed in individuals who are submitted to occupational exposure (Scheepers et al. 2008). Inhalation of dust, mist, or vapor and dermal contact of products containing Cr^{+6} are the major routes of occupational exposure to chromium. In humans, there is sufficient evidence for the carcinogenicity of chromium VI compounds. Cr^{+3} compounds, found in foods, were not classifiable as to their carcinogenicity (IARC 2012).

Chromium is also present in nutritional supplements such as chromium picolinate, chromium histidinate, chromium chloride, and chromium nicotinate. The toxicity of supplements containing Cr^{+3} compounds depends on the binder. Study showed chromium picolinate as a mutagenic (Stearns et al. 2002), but the National Toxicology Program's technical report found no evidence of carcinogenic activity of chromium picolinate monohydrate (NTP 2010). Chromium picolinate,

chromium histidinate, and chromium chloride in high concentrations did not result in oxidative damage to DNA, in situations of oxidative stress induced by hydrogen peroxide (Hininger et al. 2007). However, when compared to chromium bound to niacin, chromium picolinate showed higher production of harmful superoxide anion and increased DNA fragmentation. Despite this, Cr^{+3} compounds are relatively nontoxic and exhibit less oxidative stress and DNA damage when compared to Cr^{+6} (Bagchi et al. 2002). The genotoxic effects of Cr^{+3} are unlikely to occur in humans or animals when exposed to the physiological or moderately elevated level of ingestion (Eastmond et al. 2008).

In addition to genotoxicity, adverse effects were reported during studies with chromium supplementation, such as dizziness, headache, nausea, constipation, flatulence, watery stools (Suksomboon et al. 2014), and itching in the palm of the hands (Guimarães et al. 2013). However, short-term chromium supplementation at usual doses of 150–1000 mcg does not increase the risk of adverse effects when compared with placebo. Even so, the safety of long-term supplementation is not established (Suksomboon et al. 2014).

The Role of Chromium in Modulating Gene Expression

Cr^{+3} has been presenting important effects on gene expression. Changes in hepatic cells, insulin activity, and obesity have already been observed (Peng et al. 2010; Rink et al. 2006; Wang et al. 2016).

Regarding hepatic cells, an in vitro study with Cr^{+3} noted improvement in oleic acid-induced steatosis, as it led to a reduction in the accumulation of lipids, fatty acid content, and the amount of triglycerides. This occurred because chromium blocked the transport of oleic acid excess inside the cells to suppress the mRNA and proteins expressed by the gene cluster of differentiation 36 (CD36); and also to downregulate the expression of diacylglycerol acyltransferase 2 (DGAT2) (Wang et al. 2016). CD36 genes express membrane glycoproteins that help in the capture of chylomicrons, VLDL, and long chain free fatty acids by cells (Iqbal and Hussain 2009) as well as stock and secretion of triglycerides in the liver (Kennedy et al. 2011). In turn, the DGAT2 genes express proteins that help to modulate the synthesis of triglycerides, and their excess can lead to the accumulation of this substance in the liver, and, consequently, liver steatosis (Yen et al. 2008).

As for the effect of chromium on the activity of insulin, an in vitro study demonstrated that the use of chromium picolinate (CrPic), complex of chromium chelated with small peptides (CrSP) and chromic chloride (CrCl3), potentiates the insulin action. In the presence of chromium, insulin increased the expression of insulin-like growth factor 1 (IGF-1) gene, responsible for protein synthesis, and reduced levels of ubiquitin mRNA, responsible for protein degradation (Peng et al. 2010).

Finally, the effect of chromium on obesity was observed with supplementation of niacin-bound chromium (NBC), which acted on adipose tissue by *upregulating* the expression of calsequestrin 1 (CASQ1), tropomyosin-1 (TPM1), enolase 3 (ENO3),

and glucose phosphate isomerase1 (GPI1) genes and downregulating the expression of Cell-death-induced DNA fragmentation factor (CIDEA), thermogenic uncoupled protein 1 (UCP1), and tocopherol transfer protein (TPP) genes (Rink et al. 2006). CASQ1 expressed proteins related to stocks of calcium in the sarcoplasmic reticulum of cells, which may reduce the levels of free calcium inside the cells, thus promoting better insulin signaling in fat cells (Beard et al. 2004; Lau et al. 2008). As for the protein tropomyosin, expressed by TPM1 gene, when their levels are reduced, there is an increasing differentiation of preadipocytes into adipocytes; therefore, the presence of this protein reduces the amount of fat in adipocytes (Lau et al. 2008). ENO3 and GPI 1 genes express key enzymes for glycolysis (Lau et al. 2008; Rink et al. 2006). However, CIDEA and UPC1 genes act on the increase in brown adipose tissue; in addition, a study reported that mice deficient in CIDEA are slim and have better resistance to the development of obesity and diet-induced diabetes, because it presented a higher metabolic rate and lipolysis (Lau et al. 2008; Zhou et al. 2003). TPP gene is involved in the transport of α-tocopherol that will be incorporated into LDL-c; therefore, the reduction in the expression of this gene can reduce levels of this lipoprotein. The increased expression of TPP can also increase the antioxidant defense of adipocytes, making breakage of adipose tissue (Lau et al. 2008; Rink et al. 2006).

Thus, chromium supplementation appears to have beneficial effects regarding the modulation of gene expression and liver health, obesity, and diabetes. Despite these results, further studies are needed to generate scientific evidence, since the studies already carried out were in vitro and in animals.

Policies and Protocol

According to the World Health Organization (WHO), the formulation of a guideline follows the steps to identify the issues and priority outcomes for public health, to observe and evaluate the evidence, so that recommendations and implementation for the prioritized issue solution can be formulated (WHO 2010). The WHO considers some micronutrients deficiency in specific population groups to the proposition of guidelines such as the fortification of multiple micronutrients (sachet containing iron, vitamin A, and zinc and other vitamins and minerals that the country regards necessary) to children aged between 6 and 23 months (WHO 2011) and the daily supplementation of iron and folic acid for pregnant women (WHO 2012). Thus, it appears that the health authorities recommend micronutrient supplementation, whose deficiency in risk groups is well consolidated by the scientific literature.

In the case of chromium, so far, no policies, programs, and guidelines recommend this mineral supplementation for risk groups. The evidence is insufficient to support the use of chromium to improve glycemic control in diabetic subjects. The results of the studies with chromium supplementation are conflicting and confused, due to differences in dosage, micronutrient levels achieved with the initial status of chromium supplementation, and methodologies used (Evert et al. 2013). Thus, although clinical trials are already suggesting that chromium supplementation helps in

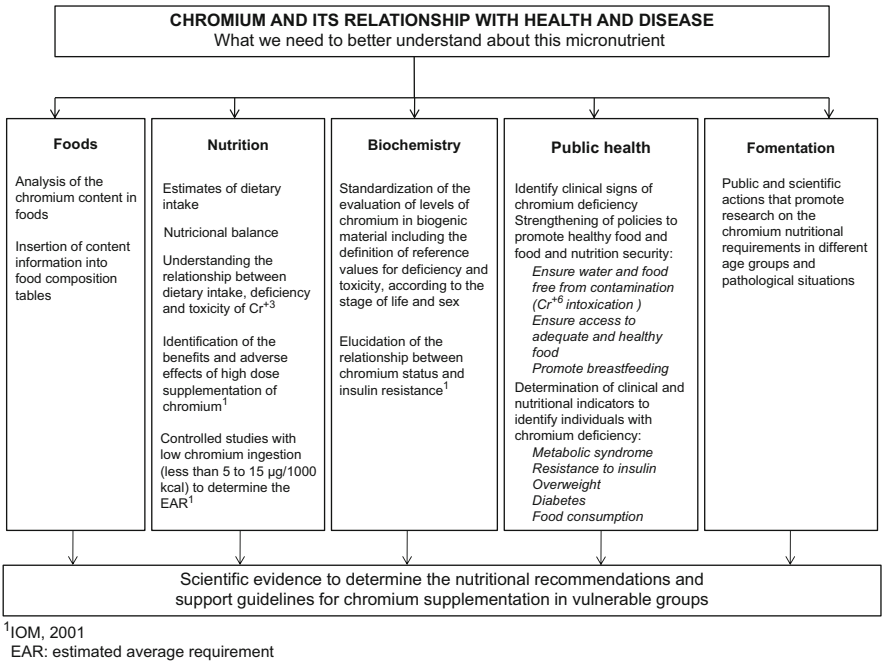

Fig. 3 Research protocol on chromium, health, and disease

controlling diabetes, obesity, and dyslipidemia, the results are still incipient (Onakpoya et al. 2013).

Therefore, chromium still does not meet the requirement of consolidated scientific evidence to develop a guideline recommending supplementation in high-risk groups. More studies are needed on the use of this mineral (Fig. 3), which evaluate the benefits and safety of use in the short, medium, and long term and showing more consistent results, so that it forms part of a policy or program of supplementation for the prevention and/or treatment of both deficiency diseases as chronic. The policies for the promotion of healthy eating and food and nutritional security can be effective initiatives for the prevention of micronutrient deficiencies, including chromium, and for coping with chronic diseases.

Dictionary of Terms

- **Nutritional requirements** – sufficient intake levels to get nutrient requirements in healthy individuals.
- **Adequate intake (AI)** – reference value used when there is insufficient information to determine Recommended Dietary Allowance (RDA).
- **Upper intake levels (UL)** – daily intake limit of the nutrient with no adverse health effects for the majority of the population.

- **Estimated Average Requirements (EAR)** – estimate of daily intake to get needs, indicator, or criteria in half of healthy individuals of a given sex or stage of the life cycle.
- **Recommended Dietary Allowance (RDA)** – daily consumption level that gets the nutrient requirement for almost all healthy individuals at a given stage of life and gender.
- **Bioavailability** – ratio of drug or nutrient concentration to concentration of drug or nutrient at the locus of action.
- **Chromodulin** – low-molecular-weight chromium-binding substance. A 1,5 kDa peptide, composed of four glycine, cysteine, glutamate, and aspartate residues, presenting a tetranuclear characteristic linked to four trivalent chromium ions, being important for insulin signaling.
- **Insulin resistance** – condition where the physiological response induced by insulin is lower than expected considering insulin concentration.
- **Modulation of gene expression** – mechanisms that regulate the synthesis of proteins or other biomolecules by controlling the transcription of genes responsible for the production of these substances.

Summary Points

- Chromium is an important nutrient in food but, because of the lack of scientific evidence, the estimated average requirement (EAR) of its daily intake and the tolerable upper intake levels (UL) have not yet been established.
- Chromium in foods has increased absorption by the presence of amino acids, ascorbic acid, high levels of carbohydrates, oxalate, and aspirin in the diet, while phytates and antacids (sodium hydrogen carbonate, magnesium hydroxide) reduce the absorption of chromium.
- Chromodulin, a low-molecular-weight chromium-binding substance, participates in the mechanism of amplification of insulin-cell signaling.
- Chromium is present in nature in different states of oxidation, with trivalent chromium and hexavalent chromium being the most common forms.
- Chromium is absorbed in the small intestine by passive transport. Due to difficulties in traversing the plasma membrane, the absorption of trivalent chromium is low.
- Hexavalent chromium has strong oxidative capacity and its absorption occurs more easily through the plasma membrane.
- Chromium is transported by ferritin and there may be competition with other metals, such as iron.
- Chromium is present in nutritional supplements in various forms such as chromium picolinate, chromium histidinate, chromium chloride, chromium nicotinate.
- Serum chromium levels vary according to glycemic control in subjects with type 2 diabetes. Serum chromium deficiency appears to be greater in uncontrolled diabetic subjects.

- Serum chromium levels decreased with age in healthy subjects.
- Although chromium is involved in several mechanisms of glucose metabolism, the evidence is not sufficient for long-term therapy in diabetic subjects.
- High levels of chromium are generally observed in individuals who are submitted to occupational exposure.
- In humans, there is sufficient evidence for the carcinogenicity of Cr^{6+} compounds. Cr^{3+} compounds, as found in foods, were not classifiable as to their carcinogenicity.
- Policies to promote healthy eating and food security and nutrition initiatives can be effective for the prevention of micronutrient deficiencies, including chromium, and for coping with chronic diseases.

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