

# Essentiality of Chromium for Human Nutrition and Health

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## Abstract

The aim of this paper is to review current knowledge about the essentiality of trivalent chromium for animal and human nutrition, and its biological function with special reference to its role in carbohydrate and lipid metabolism, dietary intake and recommendations.

**Keywords:** Chromium, glucose tolerance, dietary intake

## Introduction

Chromium occurs in three valence states: Cr (II), Cr (III) and Cr (VI).

Cr (II) is unstable and easily oxidised to Cr (III). Cr (VI) is a strong oxidant - in the form of chromates and dichromates it penetrates biological membranes and reacts with cell contents, proteins or nucleic acids, while being reduced to Cr (III). Chronic poisoning by chromium compounds has been observed at the work place, by direct contact with skin and mucus membrane, or inhalation of dusts or aerosols [1]. The reaction with genetic material is the basis for the carcinogenicity of some Cr (VI) salts. Several studies were carried out on occupational exposure to chromium in relation to its possible carcinogenic effects. Reports from the chromate production industry have identified Cr (VI) as a potential carcinogen [2].

In contrast, Cr (III) is the most stable form in biological systems [3, 4] it does not penetrate biological membranes easily, and it appears that the transport of specific chromium compounds is strictly regulated by the organism. Cr (III) ion has a strong tendency to form co-ordination compounds with a very slow reaction rate [5].

That slow rate suggests that chromium would exert a structural function rather than an active site in an enzyme, which may explain that no chromium-containing enzymes have been identified [5].

## Chromium Absorption, Blood Transport, Excretion and Toxicity

Chromium is present in the diet both as the inorganic form and organic complexes. The rate of absorption of inorganic Cr is low, from 0.4-3%, and is a function of daily dose supplied. According to Anderson et al. [6] ingestion of daily dose of 10 µg, up to 2% is absorbed, while at the dose of 40 µg, absorption decreases to 0.5%, and at the higher doses, it remains constant at 0.4%. The absorption of Cr from CrCl<sub>3</sub> and acetate [7] is approx. 0.5%, and approx. 40% for chromium trisacetylacetonate in rats [6]. Chromium chloride, chromium pinacolate and chromium polynicotinate are the most common supplemental sources available. Although absorption of chromium picolinate is lower than 4%, it is still significantly greater than that of chromium chloride [7]. There is also a report claiming that niacin-bound chromium was 672% better absorbed than chromium chloride and 311% better than chromium picolinate [8]. Chromium is absorbed in the intestinal mucosa. In rats the middle section of the small intestine was the most active segment for Cr absorption, followed by the ileum and duodenum [9]. In humans, the site of absorption also includes the jejunum [10]. The mechanism responsible for the intestinal absorption of Cr is not known.

Absorbed Cr is bound to transferrin that possesses two binding sites: A and B with different affinities for Fe

as a function of pH. It has been shown that Cr binds exclusively to site B. Thus, there is antagonism between Cr and Fe competing for this carrier [11].

Absorbed Cr is excreted principally in the urine, and in small quantities in the hair, sweat and bile. The major route of elimination after absorption is faecal. Urinary excretion is the major route of elimination of Cr from the body, is a good reflection of the ingestion, but not necessarily of body status [12].

It is thought that Cr (VI) is carcinogenic while Cr (III) has such a low toxicity that deleterious effects from excessive intake of this form do not occur readily. It becomes toxic only at extremely high amounts. For example, cats tolerate 1000 µg Cr (III)/day and rats 100 µg Cr (III)/kg b.w. Industrial exposure to high doses of Cr, usually airborne, can cause allergic dermatitis, skin ulcers, and bronchogenic carcinoma. Because Cr is a potent sensitizer, external contacts with chromates and dichromates can induce allergic eczema in some people [13].

### Biological Function of Chromium

The concentration of Cr in the lungs, aorta, heart and spleen decreases during the first months of life, whereas the liver and kidneys maintain their neonatal level up to the age of 10 years. The biological function of chromium is not fully known yet. It is postulated that chromium interacts with the thyroid metabolism in humans. Binding of Cr (III) with nucleic acids has been found to stimulate the DNA-dependant RNA synthesis [5]. The third interaction of Cr (III) is with the hormone insulin and its receptors. This suggests that Cr (III) acts with insulin on the first step in the metabolism of sugar entry into the cell, and facilitates the interaction of insulin with its receptor on the cell surface.

### Chromium and Diabetes

Diabetes is known to affect over 10 million of Americans and many more may have this disease without knowing it. In the Polish population, like in other European countries the morbidity rate of diabetes ranges between 2% and 6% [14]. In the form of this disease known as maturity-onset diabetes, the pancreas often continues to secrete normal amounts of insulin, but this insulin is ineffective in preventing the symptoms of diabetes which includes heperglycemia, impaired carbohydrate metabolism, glycosuria and decreased insulin sensitivity [15]. In the late 1950s Schwarz and Mertz first demonstrated that the dietary-induced impairment of glucose tolerance in rats could be reversed by the administration of trivalent chromium compounds [16]. Since then, the possible beneficial role of Cr (III) in carbohydrate, protein and fat metabolism has been extensively studied in various experimental systems [17]. Experiments carried out so far in humans can be classified into 3 groups: studies in long-term parenteral nutrition, administration of high glucose doses, supplementation with various compounds of Cr (III) [17].

In 1997 Jeejeebhoy et al. [18] published a case of

a woman who developed severe diabetic symptoms after a log-term intravenous feeding. Also in other parenteral nutritional studies chromium deficiency cases were observed and glucose tolerance was reversed by daily Cr (III) supplementation [19]. Further experiments carried out at constant or elevated glucose concentration in plasma, showed an inverse relationship between plasma insulin and plasma chromium [20].

Anderson et al. [21] studied the effect of Cr (III) supplementation in healthy subjects, in patients with type 2 diabetes and/or lipemia. The results indicated that Cr(III) is in some way required for insulin action improving blood glucose, insulin and lipid indices. Wrobel et al. [17] studied the effect of Cr (III) on glucose, insulin, cholesterol and triglycerides variables in serum in three experimental groups: tannery workers, patients with type 2 diabetes, and control subjects. The results obtained in the tannery workers (with higher serum chromium, lower serum insulin, cholesterol, better glucose tolerance with respect to controls) were similar to those reported in studies on supplementation with different chromium compounds.

Glucose intolerance, related to insufficient dietary chromium is a widespread health problem. On the other hand, improved chromium nutrition leads to improved sugar metabolism in hypoglycemics, hyperglycemics and diabetics [22]. Absorption of chromium from the gut and its urinary excretion are significantly higher in insulin-requiring diabetes than in healthy subjects. Chromium maintains normal glucose tolerance primarily by regulating insulin action. In the presence of chromium, much lower amounts of insulin are required [22]. It is important to keep insulin at low levels to prevent secondary signs of diabetes. There is very strong evidence that insufficient dietary chromium leads to impaired glucose tolerance that can be alleviated by supplemental chromium. Fasting glucose, circulation insulin, insulin binding, circulatory glucagon, and  $\beta$ -cell sensitivity improve with increasing chromium status [18].

Response to chromium is related to degree of glucose intolerance. Subjects with hypoglycemia, hyperglycemia and maturity-onset diabetes have shown to respond to supplemental chromium, while subjects with normal glucose tolerance with no signs of marginal chromium deficiency do not respond to supplementation with chromium.

The role of chromium in glucose homeostasis and diabetes has been conclusively documented in a series of studies conducted over the last years. In a study conducted in China researchers demonstrated that supplemental chromium as Cr (III) picolinate improved the blood glucose, insulin, cholesterol, and hemoglobin A<sub>1c</sub>, in a dose dependent manner, in people with diabetes [23, 24]. To test the hypothesis that chromium supplementation would improve glucose intolerance and hyperinsulinemia in gestational diabetes, thirty women received 4 µg Cr/kg b.w., and 8 µg Cr/kg b.w., while the control group received a placebo. After 8 weeks of treatment, the 4 µg Cr group had a significantly lower glycated Hb compared to their baseline levels, whereas the 8 µg Cr and the placebo showed no change. Both 4 µg Cr and 8 µg Cr groups had markedly lower glucose and insulin levels vs. control [25].

Hypoglycemic symptoms, glucose values, insulin bind-

ing, and insulin receptor number also improve in hypoglycemic patients following chromium supplementation [26]. Stiffer et al. [27] evaluated the hypothesis that insulin-secretory hyper-responsiveness observed in rats with diet-induced insulin resistance may be a characteristic of chromium deficiency. Two groups of weaning rats were fed ad libitum a purified diet containing 64% sucrose, 20% casein, 5% corn oil, and recommended levels of vitamins and minerals with and without added Cr for three months. It was found that insulin responses in Cr-deficient rats were exaggerated, being twofold greater compared to the control group.

To determine whether or not chromium is effective in humans, Press and Geller [15] studied 28 volunteer subjects who were given chromium picolinate (200 µg) or placebo daily for 42 days. It was found that levels of total cholesterol, LDL and apolipoprotein B decreased markedly in the subjects ingesting supplemental chromium. These observations show that chromium picolinate is effective in lowering blood lipids in humans.

Glucose tolerance and chromium status decline with age. Recent, well-controlled, double-blind studies reported that the glucose tolerance of the elderly subjects given supplemental chromium improved. However, if subjects were eating well-balanced diets with a mean Cr intake more than 37 µg Cr/d, glucose tolerance was unchanged. Urberg and Zempel [28] showed that fasting glucose and glucose tolerance of elders also improved following daily supplementation with 200 µg Cr as CrCl<sub>3</sub> together with 100 µg of nicotinic acid, but not with Cr alone [22]. Cefalu [29] demonstrated that chromium picolinate appears to increase insulin sensitivity in moderately obese, nondiabetic subjects.

### Chromium and Body Composition and Lipid Peroxidation

Another effect of chromium supplementation that could be a result of its potentiation of insulin sensitivity is the redistribution of body fat, protein and water. The mechanism of this regulatory action of Cr is not known. It has been proposed that the positive effect of chromium picolinate on body composition is through its ability to improve insulin use, thereby reducing fat deposition and improving entry of glucose and amino acids into muscle cells.

Chromium has been reported to increase lean body mass in people who exercise, such as football players, however, some follow-up studies have not supported these observations [30]. However, the role of chromium in the regulation of lean body mass, percentage body fat, and weight reduction is still controversial because a significant number of studies do not support the effect of chromium on body composition. A randomized, double-masked, placebo-controlled study carried out by Kaats et al. [31] showed that supplementation with a minimum of 200 µg Cr in the form of chromium picolinate per day can lead to significant reduction in body composition. Further studies [32] performed on 130 subjects receiving 400 µg Cr as chromium picolinate and placebo revealed significant reduction in percent body fat and fat mass without any loss in fat-free mass. Similar

results are reported by Evans [33] and Bulbalian et al. [34]. On the other hand, studies carried out by Lukaski et al. [35], Hallmark et al. [36] and Passman et al. [37] did not confirm the effect of chromium supplementation on lean body mass in male and female subjects.

In addition to its role in glucose and lipid metabolism, chromium also functions as an antioxidant. Recent studies have shown that chromium protects rats from oxidative stress associated with exposure to CCl<sub>4</sub>. Also chromium protects against lipid peroxidation in isolated rat hepatocytes [30], and decreases the effects of free radicals in people with type 2 diabetes [38].

### Interactions of Chromium with Other Nutrients

The absorption of Cr is facilitated by certain amino acids, such as histidine, which chelates Cr and prevents the precipitation of Cr at the basic pH in the small intestine [39]. Nicotinic acid and ascorbic acid are required for Cr absorption and act in synergy with this element. Ascorbic acid has been reported to enhance chromium transport or absorption in animals [40] and humans [39]. Compared with simple sugars such as glucose, fructose and sucrose, starch increased tissue chromium in mice [40]. Metals can form complexes or compete with Cr and modify its absorption. For example: Zn, V and Fe supplementation decreased the absorption of Cr [9]. On the other hand, absorption of <sup>51</sup>Cr was elevated in Zn-deficient rats and was reduced by zinc supplementation [41]. Phytates significantly decrease the absorption of Cr in the intestines of rats, whereas oxalate act inversely [9].

### Dietary Chromium Intake and Recommendations

Trivalent chromium, the form found in foods and nutrient supplements, is considered one of the safest nutrients [42]. The Environmental Protection Agency has established a reference dose, defined as "an estimate of a daily exposure to humans, including sensitive subgroups, that is likely to be without an appreciable risk of deleterious side effects over a lifetime, that is 350 times the National Research Council's upper limit of the "safe and adequate range".

The Estimated Safe and Adequate Daily Dietary Intake (ESADDI) of Cr as proved by the Food and Nutrition Board of the US National Academy of Science in 1989 is presented in Table 1 [42]. Similar values were proposed in 1980 [43].

Recent studies obtained as part of the Trace Elements in Food Research Programme of the FAO European Research Network on Trace Elements [44] demonstrated that the Cr content in animal foodstuffs such as meat, poultry and fish is low providing 2 µg Cr [45]. Most dairy products are also low in Cr and provide < 0.6 µg/serving. Whole wheat and wheat flour contain 5-10 µg of Cr/kg [45]. Pulses, seeds and dark chocolate may contain more chromium than most other foods [46]. Certain species such as black pepper contain high concentrations of Cr [45]. Some brands of beer contain significant amounts of

Table 1. The Estimated Safe and Adequate Daily Dietary Intake (ESADDI) of Cr as proved by the Food and Nutrition Board of the US National Academy of Science in 1989 [42].

| Category                 | Age, year | ESADDI, $\mu\text{g Cr/d}$ |
|--------------------------|-----------|----------------------------|
| Infants                  | 0–0.5     | 10–40                      |
| Infants                  | 0.5–1     | 20–60                      |
| Children                 | 1–3       | 20–80                      |
| Children                 | 4–6       | 30–120                     |
| Children                 | 7–10      | 50–200                     |
| Children and adolescents | > 11      | 50–200                     |
| Adults                   |           | 50–200                     |

Cr, some of which presumably comes from the brewing containers [47]. According to Mertz et al. [48] the best known chromium complex is the glucose tolerance factor, found in brewer's yeast.

Most of the average daily dietary Cr intake estimates representing various populations living in 14 different countries ranges between 30–60  $\mu\text{g}$ .

Kumpulainen [49] compared the average dietary Cr in various countries (Table 2). It is thought that dietary chromium intake in the USA and other developed countries is sub-optimal and is 50–60% of the minimum US suggested safe and adequate daily intake of 50  $\mu\text{g}$  [30]. Anderson et al. [45] analysed the chromium content of 22 daily diets in the USA, designed by nutritionists to be well-balanced, ranged from 8.4 to 23.7  $\mu\text{g}/1000\text{kcal}$ , with a mean  $\pm$  SEM Cr content of  $13.4 \pm 1.1 \mu\text{g}/1000\text{kcal}$ . In another study Anderson and Kozlovsky [50] measured

Table 2. Dietary Cr intakes in various countries [after 49].

| Mean Cr intake $\mu\text{g/d}$ | Country     | Type of diet                               |
|--------------------------------|-------------|--|
| 62                             | Germany     | Self-selected                              |
| 62–89                          | USA         | Formulated to meet US dietary requirements |
| 31                             | Finland     | Self-selected                              |
| 56                             | Canada      | Self-selected                              |
| 24.5                           | UK          | Self-selected                              |
| 28                             | USA         | Self-selected                              |
| 49                             | Turkey      | Self-selected                              |
| 50                             | Switzerland | Mixed institutional                        |
| 50                             | Sweden      | Average market basket                      |
| 85                             | Brazil      | Average market basket                      |
| 75                             | Iran        | Self-selected                              |
| 60                             | Italy       | Self-selected                              |
| 60                             | Spain       | Self-selected                              |
| 105                            | Sudan       | Self-selected                              |

the daily intake of Cr for seven consecutive days of 22 adult female and 10 male subjects. Mean intake of females was 25  $\mu\text{g}$ , and males was 33  $\mu\text{g}$ . Not one subject had a mean 7-day intake of 50  $\mu\text{g}$ . Similar results were reported by Bunker et al. [51] in England with slightly higher values for Canadian subjects [52]. Bertrandt et al. [53] calculated the daily Cr intake with food rations planned for consumption in the pensioners house in Poland, and found 118.5  $\mu\text{g Cr}$ , which was higher than the amount recommended by WHO (60  $\mu\text{g/d}$ ). The same authors analysed the 30 daily menus planned in two kindergartens [54]. The content of Cr in food rations ranged between 51.1–55.6  $\mu\text{g}$ . In another study carried out in Poland by Marzec [55], the average daily Cr intake in the canteen food rations ranged from 91 to 164  $\mu\text{g}$ , and in family rations between 77–228  $\mu\text{g}$ , which is higher than that reported in the USA and other countries. Also recent studies carried out in Germany by Anke et al. [56] revealed that the dietary chromium intake ranged from 61 to 84  $\mu\text{g/d}$  on the average for women and men, respectively, thus the individual chromium requirement was met by all test persons.

Although some American experts in chromium nutrition recommend supplementation with small amounts of this element on a daily basis to prevent possible inadequate chromium intake, increased chromium losses, decreasing tissue levels with age, and widespread insulin resistance. However, due to insufficient data concerning the content of Cr in food products and its dietary intake in various sub-populations, it is impossible to draw definite recommendations for Cr supplementation for the general Polish population.

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