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CHROMIUM AS A SUPPLEMENT[1]

Henry C. Lukaski
US Department of Agriculture, Agricultural Research Service, Grand Forks Human Nutrition Research Center, Grand Forks, North Dakota 58202;
e-mail: hlukaski@gfhnrc.ars.usda.gov

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ABSTRACT

Chromium (Cr) is an essential mineral element that has received considerable public attention. The suggestion that Cr intake is generally low has generated interest regarding the purported beneficial effects of Cr supplementation on biological function and health of animals and humans. This review briefly describes key aspects of Cr nutritional status and evaluates the effects of Cr supplementation on various components of biological function, body composition, and health. A novel biological role of Cr in regulation of insulin function is described. Although promising results of Cr supplementation are presented, the considerable challenge of developing methods for routine assessment of Cr nutriture in humans remains.

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INTRODUCTION

The mineral element chromium (Cr) is viewed with mixed opinions. Although Cr is accepted as nutritionally essential for animals and humans, an understanding of the mechanism of its biological action and the amount of Cr needed for health and optimal function remains elusive. Cr apparently potentiates the action of insulin in glucose utilization and protein anabolism (65, 66). Because there are insufficient appropriate biochemical measures of Cr nutritional status and of the content and the bioavailability of Cr from foods, there is, unfortunately, a paucity of information that describes who would benefit from increased dietary Cr. These factors perpetuate continued interest in Cr and its role(s) in promoting health and biological function, and in the validity of postulated benefits of supplemental Cr.

Some practical issues hinder the advancement of knowledge of Cr in applied nutrition. Analytical determinations of the Cr contents of foods, beverages, body fluids, and tissues are arduous to make because Cr is present in very small concentrations. Also, Cr distribution in nature is so widespread that it contributes to apprehension of Cr contamination. Because the problem of Cr contamination was unrecognized until 1978 (41), spuriously high values of Cr content of foods and biological specimens are cited in the literature. Caution requires that consistent rigorous preparatory and analytical procedures be utilized for accurate determination of Cr in biological and other specimens (100, 101).

Controlled studies to determine Cr bioavailability and the effects of graded intakes of dietary Cr are hampered by the lack of data on the Cr content of feed components and individual foods. Furthermore, sensitive and specific biochemical and functional measures that respond to graded Cr intake are also insufficient. These limitations, as well as differences in experimental designs, contribute to the lack of consensus in reported findings of biochemical, functional, and structural effects of supplemental Cr in animals and humans.

Despite these impediments, evidence is accumulating that Cr is essential to insulin action, particularly glucose homeostasis. Findings that supplemental Cr promotes favorable changes in body composition in livestock and humans are equivocal. This chapter briefly discusses the essentialness of Cr, generalized dietary Cr intake, proposed mechanisms of cellular functions of Cr, the effects of supplemental Cr in animal and human studies, and the potentially adverse effects of Cr supplementation.

CHROMIUM AS A NUTRIENT

Cr Speciation

Although Cr exists in nature in oxidation states from Cr^{-2} to Cr^{+6}, the predominant forms are Cr^{+3} and Cr^{+6}. Bound to oxygen, Cr^{+6} is a strong oxidizing agent that is readily reduced to Cr^{+3} in an acidic environment, such as the stomach. The most stable oxidation state is Cr^{+3}, ostensibly the predominant form in biological systems. Cr^{+3} forms many coordination complexes, among which the principal form is hexadentate. In aqueous solutions, Cr^{+3} complexes are characterized by relative kinetic inertness, which suggests that Cr is unlikely to participate as a metal catalyst at the active site of enzymes in which rapid rates of exchange are required. Such relatively inert Cr complexes, however, may function as structural components that bind ligands in proper spatial orientation to facilitate enzymatic catalysis or maintain tertiary structures of proteins or nucleic acids (63).

Dietary Cr

The estimated safe and adequate daily dietary intake for Cr is 50–200 μg for adults (76). Dietary Cr in the United States and most industrialized countries generally does not achieve the estimated safe and adequate daily dietary intake. Analyses of self-selected diets consumed by US adults indicate a mean daily Cr intake of 25 μg for women and 33 μg for men (8). Intakes of fewer than 50 μg/day have been reported for adults living in the United Kingdom, Finland, Canada, and New Zealand (3). Processed meats, whole-grain products, ready-to-eat bran cereals, green beans, broccoli, and spices have a high concentration of Cr (5). Foods high in simple sugars such as fructose, which is found in soft drinks, and sucrose, or table sugar, are not only low in Cr content, they also promote Cr losses (58). Apparently, Cr intakes of fewer than 50 μg are adequate in diets high in fruits, vegetables, and whole-grains and low in simple sugars (77).

Absorption

Cr speciation affects absorption. Cr^{+6} is absorbed more readily than Cr^{+3}: The ^{51}Cr content in blood is three to five times greater when the isotope is fed as Cr^{+6} rather than as Cr^{+3} (63). Inorganic Cr^{+3} absorption varies inversely

with dietary intake. Humans fed 10 μg of Cr daily absorb about 2% (8). The percentage of Cr absorbed from the diet decreases as the content increases to 40 μg/day, at which point absorption stabilizes at 0.5% (8, 15). With a dietary intake of 40–240 μg/day, Cr absorption is a relatively constant 0.4%. Thus, Cr absorption is generally low, about 0.4–2%.

Cr absorption and utilization are impacted by other dietary factors. Amino acids chelate with dietary Cr, prevent precipitation in the alkaline milieu of the small intestine, and thus enhance Cr absorption (44). Phytate also forms chelates with Cr, and these complexes inhibit in vivo and in vitro transport of Cr across the intestine of the rat (24). Absorption of ^{51}Cr is increased in zinc-deficient rats and reduced by zinc administration (42). Oxalate, which is found in vegetables and grains, significantly increases Cr uptake (24). In humans, ascorbic acid promotes Cr absorption (76), as does nicotinic acid. When either Cr or nicotinic acid is given separately, there is no response in glucose tolerance among glucose-intolerant men who respond favorably when both substances are given together (97). Some dietary components have been used to induce Cr deficiency in rodents. Specifically, low dietary protein (68) and high dietary fat (94) in conjunction with restricted Cr have been used to induce Cr deficiency.

Organic complexes that contain Cr may enhance its absorption and distribution. Preliminary findings suggest that Cr in the glucose tolerance factor (GTF) is better absorbed than Cr^{+3} (25), but subsequent findings have not confirmed this hypothesis (65). GTF, which was proposed to include Cr, nicotinic acid, and possibly the amino acids glycine, cysteine, and glutamic acid (63), has neither been isolated nor synthesized. Thus, the defined structure of GTF and whether it is the most biologically active form of Cr remain controversial.

Recent studies have shown that the chemical form of the Cr compound influences Cr absorption and tissue distribution in rodents. Olin et al (82) found that short-term (1–12 h postgavage) retention of ^{51}Cr in tissues (muscle, liver, kidney, blood) and urine was significantly greater when the Cr was administered as Cr nicotinate (CrNic) rather than as $CrCl_3$ or as Cr picolinate (CrPic). Anderson et al (6) evaluated the bioavailability of a wide variety of inorganic and organic Cr compounds fed at 5 μg of Cr per g of diet in weanling male rats. Cr absorption at 4 h and retention after 24 h were not affected by the chemical form of the Cr. However, CrNic promoted Cr accumulation in the kidney; Cr incorporation into the liver was increased with CrPic, CrNic, and Cr acetate. Thus, Cr complexed with some organic ligands apparently enhances absorption and tissue accumulation.

The mechanism of Cr absorption by the intestinal mucosal cell has not been clearly described (65). Because of evidence that certain chemical forms of Cr are preferentially absorbed, more complex processes than simple diffusion probably are involved.

Excretion

Absorbed Cr^{+3} is excreted primarily through the kidney, with small amounts lost in hair, sweat, and bile. In humans, renal tubular resorption of filtered Cr is efficient at 80–95% (32). Organic Cr is excreted in bile (65). In one study, approximately 40% of a dose of ^{51}Cr–tris-acetylacetonate was absorbed from the gastrointestinal tract of rats (2). As much as 45% of the ^{51}Cr was found in the bile; this finding suggests a rapid absorption and resecretion of Cr.

Stressors

Cr deficiency may be promoted by increasing Cr losses in response to physiologic stressors. Some notable stressors include physical trauma, acute but not chronic exercise (62), lactation, and consumption of a diet high in simple sugars (4). These factors, when combined with a marginal Cr intake, may promote Cr depletion in humans.

Assessment of Cr Nutriture

Evaluation of Cr nutritional status in humans is severely hampered by the lack of accurate and sensitive biochemical markers that reflect tissue Cr or alterations in metabolic function. The use of plasma or serum Cr concentration has been dismissed because intravenous (i.v.) ^{51}Cr disappears rapidly, rather than equilibrating with tissue pools (65); and circulating Cr does not reflect tissue Cr concentrations (6, 82). Serum Cr, although it responds to Cr supplementation (62), does not correlate with serum glucose or insulin in the fasting state or after a glucose load (79). Similarly, urinary Cr concentration and output are responsive to Cr supplementation but are inadequate indicators of Cr status because they fail to correlate with glucose, insulin, or lipid concentrations (79). Thus, assessment of Cr nutriture remains elusive.

Biological Functions

Signs of Cr deficiency have been reported in mammals and center on disturbances involving insulin insensitivity (27). The signs and symptoms of chromium deficiency in mammals are as follows: impaired glucose tolerance, elevated circulating insulin concentration, glycosuria, fasting hyperglycemia, impaired growth, hypoglycemia, elevated circulating cholesterol and triglyceride concentrations, neuropathy, encephalopathy, increased intraocular pressure, decreased insulin binding, decreased insulin receptor number, and impaired humoral immune response. Evidence suggesting that Cr is essential came from Schwarz & Mertz (90) who showed that glucose intolerance in rats is ameliorated with supplemental Cr from yeast. The active ingredient of the yeast was identified as Cr^{+3} that was complexed in an organic molecule, subsequently termed GTF (91). Other studies have confirmed marked improvement

in glucose tolerance with Cr supplements, primarily with brewer's yeast, given to rodents (70, 89, 105) in different stages of Cr deprivation with varying degrees of glucose intolerance.

Emphasis was placed on the importance of Cr in glucose metabolism after the discovery that Cr supplementation was beneficial to patients receiving long-term total parenteral nutrition (TPN). Jeejeehboy et al (51) described hyperglycemia, weight loss, ataxia, and peripheral neuropathy in a patient who received TPN without Cr for more than 3 years. Glucose tolerance and neurological function returned to normal and lost body weight was regained after addition of 250 μg of Cr as $CrCl_3$, without insulin, to the TPN solution for 2 weeks. Normal glucose tolerance was maintained with a daily i.v. dose of 20 μg. Freund et al (37) reported that a daily i.v. dose of 150 μg of Cr administered for 3 days improved glucose homeostasis in a patient receiving TPN for 5 months. A maintenance dose of 20 μg of Cr added to the daily TPN solution maintained normal carbohydrate metabolism. It was also found that 200 μg of Cr^{+3} added to the daily infusate reversed hyperglycemia, glycosuria, and weight loss in a patient receiving a daily dose of TPN containing 6 μg of Cr for 7 months (14). These findings reveal that Cr deficiency can be detected retrospectively in patients whose unexplained hyperglycemia is successfully treated with Cr supplements, but they do not confer any insight into practical diagnostic indicators of Cr deficiency.

Cr has been implicated in two additional physiological functions. Preliminary evidence suggests that an interaction between Cr and thyroid function occurs in animals and humans (59). However, the physiological significance and mechanism of this interaction have not been studied. Cr also has been involved in protein metabolism. Early findings suggest that Cr may have a role in nucleic acid metabolism because of a significant increase in stimulation of amino acid incorporation into liver protein in vitro (104). Okada et al (80) provided evidence of a direct interaction of Cr with DNA templates that resulted in a significant stimulation of RNA synthesis in vitro and subsequently identified a unique protein containing 5–6 atoms of Cr to which the anabolic function was ascribed (81). These reports suggest that Cr acts to facilitate insulin action.

Proposed Mechanism of Action

The insight that Cr enhances insulin function came from in vitro studies with epididymal adipose tissue from Cr-deficient rats and revealed a mild but significant potentiation of insulin on glucose oxidation by inorganic Cr complexes (70). Other studies that measured the transport of D-galactose, a nonutilizable sugar, showed a greater response to insulin with added Cr, and this finding led to the conclusion that Cr influenced cellular action of insulin (67).

Subsequent studies have confirmed this initial conclusion. Addition of Cr to in vitro liver preparations stimulated the rate of insulin-induced swelling of isolated mitochondria (17). The in vitro addition of Cr significantly enhanced the respiratory quotient of epididymal adipose not only by the increased slope of the dose-response, but also by the pronounced shortening of the lag phase of the response (69).

Among the mechanisms speculated for this Cr-insulin interaction was an early theory that Cr joined with insulin and membrane sulfhydryl groups to form a ternary complex (25). This speculation was discarded because the tendency of Cr to coordinate with sulfur is weak. Recent experimental data suggest a novel Cr-binding substance that may explain the mechanism of Cr in potentiating insulin action.

A low-molecular-weight Cr-binding substance (LMWCr) that activates a phosphotyrosine phosphatase in isolated adipocyte membranes provides evidence of a functional link between Cr and insulin action (30). It was shown that the LMWCr, isolated from bovine liver, potentiated the effect of insulin on the conversion of glucose into lipid and carbon dioxide in isolated adipocytes (29). Kinetic studies indicated that the LMWCr activates the phosphotyrosine phosphatase activity in adipocyte membranes while having no intrinsic phosphatase activity. The activation was directly proportional to the amount of added LMWCr. Additional kinetic studies found that LMWCr has an intrinsic role in these insulin-dependent cells; it functions after insulin binds to the active site of the β subunit of the insulin receptor (28). It has been proposed that the biological function of the LMWCr is stimulation of insulin receptor protein tyrosine kinase activity after the receptor is activated by insulin binding (29). The LMWCr increased the kinase activity of isolated rat insulin receptor by eightfold in the presence of 100 μM insulin; LMWCr activation of the insulin receptor required insulin. It is important to note that apoLMWCr was inactive in stimulating receptor kinase activity; and titration of LMWCr with Cr^{+3} ions resulted in complete restoration of activity. Other metallic ions, however, did not restore receptor kinase activity. Four Cr^{+3} ions per oligopeptide were required for maximal activity. Thus, these findings provide key evidence of a biological function for Cr and indicate that the LMWCr may act as a constituent of a novel insulin-signaling amplification mechanism.

CHROMIUM SUPPLEMENTATION OF ANIMAL DIETS

Animal scientists have examined the effect of Cr supplements on some aspects of livestock production. Overall, the results have been ambiguous, probably

because the Cr contents of the diets have been adequate to meet the physiologic needs of the animals.

Cr Supplements

Two general forms of Cr have been used in supplementation trials. Chromic chloride, $CrCl_3 \cdot 6H_2O$, is the inorganic form of Cr that has been used in many studies. Organic forms that seem to have greater biological availability include high-Cr yeast, CrNic, Cr-AA-nicotinate complex, and CrPic. Cr doses are expressed as micrograms of Cr per kilogram of diet, or parts per billion.

Growth Performance

Cr supplementation studies with ruminants have yielded inconsistent results. Chang & Mowat (22) examined whether an interaction between supplemental Cr (high-Cr yeast, 400 ppb) and antibiotic treatment affected growth performance in calves. During the initial 28-day feeding period, Cr supplementation significantly increased the average daily weight gain of feeder calves by 30% and feed efficiency by 27%. Cr did not affect morbidity. During the subsequent 70-day growing period, Cr supplementation (200 ppb) did not affect weight gain or feed efficiency. Steer calves supplemented with graded Cr intakes (0, 200, 500, and 1000 ppb as high-Cr yeast) for 28 days also had significant increases in weight gain and in dry matter intake when Cr was added at 200 and 1000 ppb, but not at 500 ppb (73). No improvement in performance, however, was found in bull calves fed either 0 or 400 ppb Cr as $CrCl_3$ or CrNic for 63 days (55), or in lambs with a supplement of either 0 or 250 ppb Cr as CrPic for 85 days (56). Similarly, Cr supplements (370 ppb) added to basal diets containing approximately 530 and 340 ppb Cr for 87 days did not benefit weight gain or feed efficiency of steer and heifer calves (16).

Cr supplementation trials using growing pigs also produced contradictory results. In cross-bred, growing-finishing pigs supplemented with graded Cr as CrPic, weight gain significantly increased with Cr at 50 and 200 ppb, but it decreased with Cr at 100 ppb; feed efficiency was not influenced by Cr supplementation (83). Other studies (71, 72) confirmed that supplemental Cr (200 ppb) increased daily weight gain without improving feed efficiency. In contrast, Cr supplemented at 0–800 ppb significantly reduced feed intake and weight gain when the Cr dose was increased, but it had no effect on feed efficiency (83). Other studies (1, 13, 35, 60) also found that Cr, as CrPic, supplemented at less than 250 ppb has no effect on weight gain of pigs during the growing phase. Cr supplementation per se, therefore, does not enhance weight gain and performance.

Carcass Traits and Composition

The inconsistent effects of Cr supplementation on growth performance apparently reflects the lack of specificity in performance measures. Changes in body

weight do not reveal alterations in body components that are sensitive to dietary Cr. Thus, attention has turned toward evaluation of changes in the lean and fat contents of the carcass in response to Cr supplementation. Changes in regional body composition after Cr supplementation have also been inconsistent. Longissimus muscle area and percentage of muscling increased significantly, and tenth rib fat decreased significantly with Cr supplementation (100 or 200 ppb) as CrPic (13, 60, 83, 102). However, Cr supplementation (300 ppb Cr as CrPic) did not affect backfat and loin eye area in growing pigs, whereas administration of porcine somatotropin significantly decreased backfat and increased loin eye area (35).

Other studies showed changes in the chemical composition of swine carcasses after Cr supplementation. As compared with control subjects, supplementation with CrPic (200 ppb Cr) significantly increased the total gain of dissected muscle and decreased the total gain of dissected fat; it also significantly increased the daily accretion of muscle and bone and decreased the accretion of fat (71). Pigs fed the Cr supplement had a significantly increased rate of protein accretion with a decreased percentage of fat accumulation (71). Compared with the effects of the chemical form of Cr supplements, CrPic and $CrCl_3$, both supplements significantly increased the percentages and accretion rates of carcass protein and muscle tissue and significantly decreased the percentages of fat (72). However, CrPic had a significantly greater impact on protein accretion than did $CrCl_3$.

Recent studies with rats indicate no benefit of supplemental Cr to growth and body composition. Weanling male rats fed a basal diet containing Cr (180 ppb) with added Cr supplements as CrPic, CrNic, and $CrCl_3$ of 300 ppb for 12 weeks did not improve in weight gain or body composition (45). Similarly, CrPic supplements in amounts ranging from 75 to 1500 ppb Cr failed to improve growth rate and lean mass accretion when compared with those of rats fed a basal diet containing 180 ppb Cr per kg of diet (46). These findings demonstrate that supplemental Cr has no beneficial effect on growth performance or body composition when dietary Cr is adequate.

Metabolic Responses

Cr supplementation apparently affects glucose metabolism in animals. Pigs supplemented with 200, as compared with 0, ppb Cr as CrPic responded to both i.v. glucose tolerance (IVGTT) and insulin challenge (IVICT) tests with increased rates of glucose disappearance and a decreased glucose half-life, respectively (1). Compared with control animals, calves supplemented with 400 μg of Cr, either as CrNic or $CrCl_3$ per kilogram of diet, had significantly decreased plasma glucose concentrations during an IVICT; the effect was greatest among the calves fed Cr-Nic (56). Calves whose diets were supplemented with $CrCl_3$ had lower serum insulin concentrations at 10–25 min during the

IVGTT than the calves fed the Cr-AA-nicotinate complex or control diets. Similarly, steer and heifer calves whose diets were supplemented with 370, as compared with 0, ppb Cr as CrPic had significantly higher glucose clearance rates during both IVGTT and IVICT tests (16). The chemical form of Cr in the supplement had no effect on the insulin responses during either of these tests. In contrast, the glucose clearance rate and half-life during an IVGTT and an IVICT test did not differ between groups of lambs supplemented with either 0 or 250 ppb Cr as CrPic for 10 weeks (56). However, after 2 weeks of Cr supplementation, plasma insulin increased and glucose decreased during the IVGTT test.

Supplemental Cr apparently does not influence nitrogen metabolism of animals. CrPic supplementation with 250 ppb Cr in the diets of growing lambs (56) or with 200 ppb Cr in the diets of growing-finishing pigs (57) did not significantly affect nitrogen balance, although nitrogen absorption and dry matter digestibility increased, as compared with animals whose diets were not supplemented with Cr.

Immune Function

Immune function may benefit from Cr supplementation. Total immunoglobulins and immunoglobulin M increased, and serum cortisol decreased, during high-Cr yeast supplementation (200 vs 0 ppb) in growing feeder calves fed either urea-corn or soybean meal diets that contained 160 ppb Cr (23). Similarly, supplemental Cr also improved humoral immune function with no effect on expression of contact sensitivity in feeder calves fed 160 ppb Cr (73). Low-level supplementation with amino acid—chelated Cr (140 ppb Cr) reduced morbidity of feeder calves to a level comparable to that sustained with commercially available vaccines for bovine respiratory disease in calves fed a high-quality diet (107).

Cr may enhance some aspects of cell-mediated immunity. Feeder calves fed a high-quality corn diet supplemented with 140, as compared with 0, ppb Cr had increased proliferation of peripheral blood lymphocytes (21). Blastogenic activity of peripheral blood lymphocytes incubated with a mitogen increased in the calves whose diets were supplemented with Cr. A comparison of the efficacy of the chemical form of Cr (chelated vs $CrCl_3$) showed that the chelated Cr was more effective in promoting peripheral blood lymphocyte activity than was the inorganic form of Cr. In contrast, there was no positive effect of Cr supplementation (3 mg/day) on immune function in bull calves inoculated with bovine herpes virus-1 (12). No differences were detected in lymphocyte proliferative responses to mitogen stimulation and neutrophil bactericidal function or serum cortisol levels. Cr concentrations of the basal and supplemented diets were 6 and 32 ppb, respectively. Thus, beneficial effects of Cr supplementation

on immune function, particularly on cell-mediated immunity, apparently occur when an organic, rather than an elemental, Cr compound containing at least 140 ppb is used.

Stressors

The majority of the reports indicating positive effects of Cr supplementation involve the use of young animals that were recently transported after weaning. The transport and exposure to pathogens contribute to stress that may increase the Cr requirement. Other stressors have been found to increase the apparent need for Cr in growing livestock. Pigs fed a diet with 80% of the lysine requirement and supplemented with Cr (400 vs 0 ppb) had increased weight gain and increased feed efficiency (107). There was a significant interaction between dietary lysine and Cr supplementation that indicated a benefit from Cr only when lysine intake was less than optimal. However, Cr supplementation did not benefit performance when restricted pen space was a stress factor (107). Thus, supplemental Cr apparently is beneficial to performance when nutritional status is compromised.

Reproduction

Because Cr may potentiate insulin action in tissues, there has been an interest in the use of Cr supplementation to increase litter size. Sows fed supplemental Cr, 200 versus 0 ppb as CrPic, had larger litters, notably with repeated pregnancies, and maintained body weight despite increased demand for lactation (60). Although no mechanism was determined, the authors speculated that the effects may be attributed to an increased action of insulin.

CHROMIUM SUPPLEMENTATION OF HUMAN DIETS

Awareness of the findings from animal studies of the potentially beneficial effects of Cr on glucose, lipid, and protein metabolism prompted investigations into the effects of supplemental Cr in human diets. Many, although not all, studies found that there were salutary effects of Cr supplementation on glucose disposal and lipid profiles in adults and children.

Glucose Intolerance

Cr supplementation apparently improves glucose utilization and decreases exogenous insulin requirements in patients with glucose intolerance and insulin resistance. The effects depend on the degree of glucose intolerance and the form, amount, and duration of the Cr supplementation. Glinsmann & Mertz (38) found that three out of six diabetics showed improved glucose tolerance after long-term (weeks) but not after short-term (1–7 days) supplementation

with $CrCl_3$. Sixty days of supplementation with 500 μg of Cr/day as $CrCl_3$ resulted in significantly lowered glucose and insulin after a glucose challenge in 12 maturity-onset diabetics (75). Doisy et al (31) found that supplemental brewer's yeast decreased the need for exogenous insulin by insulin-dependent diabetics. Ravina et al (86) also found that 200 μg of Cr as CrPic improved glucose control in diabetic patients. Other studies, however, found no significant and consistent improvements in glucose tolerance with $CrCl_3$ supplementation (85, 92, 98).

Cr supplementation may also normalize blood glucose in adults who have a tendency toward impaired glucose utilization. Seventy-six normal, free-living adults received either 200 μg of Cr as $CrCl_3$ or placebo in a double-blind crossover study for 3 months (10). Twenty of the subjects had serum glucose concentration at or exceeding 100 mg/dl 90 min after a glucose load (1 g of glucose/kg of body weight). Cr supplementation significantly decreased the 90-min mean glucose concentration from 135 to 116 mg/dl, as well as the fasting glucose after 2 and 3 months of Cr supplementation. Participants whose 90-min serum glucose was less than at fasting concentrations responded to Cr supplementation with an increase in mean serum glucose from 71 to 81 mg/dl. Cr supplementation had no effect on the subjects whose 90-min glucose was greater than at fasting but less than 100 mg/dl. These data suggest that Cr may normalize blood glucose concentrations in adults with tendencies toward moderate hyperglycemia and hypoglycemia but has no effect on individuals with normal blood glucose concentrations.

Other studies have provided support for these initial findings. Glucose-intolerant elderly patients who were supplemented daily with 200 μg of Cr as $CrCl_3$ for 12 weeks showed small, but significant, improvements in glucose utilization during hyperglycemic clamp studies (84). Women with reactive hypoglycemia supplemented with 200 μg of Cr as $CrCl_3$ for 3 months in a double-blind crossover study experienced an alleviation of the hypoglycemic symptoms and had normalized blood glucose concentrations after an orally administered glucose load (9). Glucose tolerance improved in older adults characterized as at-risk for hyperglycemia after diet supplementation with Cr, as brewer's yeast or $CrCl_3$, for periods ranging from several weeks to a few months (64, 78). In contrast, elderly people not at risk who received either 5 g of brewer's yeast (equivalent to 200 μg of Cr) or 200 μg of Cr as $CrCl_3$, experienced no changes in glucose or insulin (79). Based on self-reported records, these elderly peoples' diets apparently met the recommended intakes for all nutrients except calcium. Offenbacher et al (79) concluded that such a diet probably contained adequate amounts of Cr to meet the needs of the subjects. Similarly, elderly patients with glucose intolerance showed no improvement in hyperglycemia with 160 μg of Cr as Cr-rich yeast (99). In contrast, Cr

supplementation marginally improved glucose tolerance and insulin response in other groups of middle-aged and older adults (61, 87). These findings indicate that supplemental Cr can improve glucose utilization in some adults. Perhaps this improvement in glucose homeostasis occurs in individuals with low Cr nutritional status.

The effect of Cr supplementation on the glucose tolerance of children with protein-calorie malnutrition is paradoxical. A single dose of 250 μg of Cr as $CrCl_3$ improved glucose disappearance in 19 malnourished infants (48). Similar studies undertaken in groups of children with kwashiorkor showed $CrCl_3$ supplementation did not change glucose tolerance (19) but did improve glucose clearance rates in marasmic Turkish children (40). Interpretation of these findings was confounded by the use of concurrent restorative interventions, independent of supplemental Cr, that may have affected carbohydrate metabolism.

Recent evidence, however, suggests a beneficial effect of supplemental Cr in the form of CrPic on glucose metabolism in some conditions of glucose intolerance. Women with gestational diabetes whose diets were supplemented with Cr [4 μg/(kg $\cdot$ day) as CrPic] responded with decreased fasting plasma glucose and insulin concentrations after 8 weeks, as compared with placebo-treated volunteers (52). Peak plasma glucose and insulin responses after a 100-g glucose load were also significantly lower than the responses measured in the women whose diets were not supplemented with Cr. The CrPic supplement did not improve the severe hyperglycemia in pregnant women with severe glucose intolerance; thus, insulin therapy was still required to normalize the glycemia.

A preliminary report implies that CrPic improves insulin utilization in non–insulin-dependent diabetic patients (20). Twenty-six moderately obese non–insulin-dependent diabetic patients participated in a double blind, placebo-controlled trial in which 1000 μg of Cr as CrPic was administered daily for 8 months. The Cr-supplemented patients had a significant increase in insulin sensitivity.

CrPic supplementation was shown recently to improve glucose homeostasis in type 2 diabetic patients (7). Free-living male and female non–insulin-dependent diabetic adults in China received either Cr (100 μg or 500 μg) or a placebo twice daily for 4 months. Hemoglobin A_{1C} and fasting glucose and insulin concentrations decreased significantly after 2 months in the 1000-μg group and after 4 months in the 200-μg group. The placebo-treated individuals also experienced changes in fasting and 2-h glucose concentrations. However, the magnitude of the changes was greater in the adults with Cr-supplemented diets. Supplemental Cr was associated with significant decreases in serum total cholesterol, but there were no changes in triglyceride or high-density lipoprotein cholesterol. Because dietary intake was not assessed, it is unclear whether the beneficial effects were only the result of Cr supplementation. The beneficial

effects of supplemental Cr were manifested at Cr intakes exceeding recommendations for the general population.

Hyperlipidemia

Cr supplementation results in equivocal responses in circulating lipid and lipoprotein concentrations. Supplemental Cr causes significant decreases in serum total cholesterol concentration with larger decreases observed in subjects with the highest concentration prior to supplementation (31). Riales & Albrink (87) found no change in serum total cholesterol but did find a significant increase in high-density lipoprotein cholesterol and a decrease in tryglyceride concentrations after 12 weeks of supplementation with 200 μg of Cr as $CrCl_3$. This finding is consistent with other reports (59, 74). However, no effect of Cr supplementation was found in other studies of adults (10, 79, 84, 85, 98, 99). These inconsistent responses of lipid and lipoprotein concentrations to Cr supplementation may reflect differences in the Cr status of the subjects and in a failure to control the dietary factors that influence circulating lipid levels.

Body Composition and Exercise

Cr supplementation in the diets of humans participating in physical activity have produced confounding responses (Table 1). The vast majority of these studies have examined the effect of Cr supplementation, in the form of CrPic, with concurrent resistive exercise. The first study involved 10 male college students who were randomly assigned to receive either 200 μg of Cr as CrPic or a placebo daily for 40 days while participating in weight training (34). Anthropometry (skinfold thicknesses and limb circumferences) was used to estimate body composition before and after the training period. The fat-free mass (FFM) of the men whose diets were supplemented with Cr increased significantly by 1.6 kg with a slight increase (0.8%) in body fatness. The placebo-treated men also had a significant increase in FFM (1.25 kg) and a significant increase in body fatness (1.1%). A second study was initiated (34) as a double-blind placebo trial in which 42 collegiate football players, of which only 31 completed the study, received either Cr, 200 μg as CrPic, or a placebo for 6 weeks while participating in a supervised weight-training program. After 14 days of training and supplementation, the men supplemented with Cr had a significant gain of 1.8 kg in FFM and a loss of body fatness, as assessed with anthropometry. At the end of 6 weeks of Cr supplementation and exercise training, body weight decreased 1.2 kg, FFM increased 2.6 kg, and fat mass (FM) decreased 3.4 kg. In contrast, the men who received the placebo showed no significant changes until after 6 weeks, when they gained 1.8 kg in FFM and lost 1.0 kg of FM. These optimistic findings triggered other investigations to confirm the potential ergogenic effects of Cr supplements.

Table 1 Summary of effects of supplemental chromium (Cr) on body composition of humans[a]

Source (Ref.)	Subjects	Cr supplement (μg/day)	Exercise	Duration (week)	Method	Outcome
Evans (34)	10 M students	CrPic (200)	Resistive	5–6	Anthropometry	↑FFM
Evans (34)	31 football players	CrPic (200)	Resistive	6	Anthropometry	↑FFM, ↓% fat
Hasten (47)	37 M, 27 F students	CrPic (200)	Resistive	12	Anthropometry	↑Circumferences
Clancy (26)	36 football players	CrPic (200)	Resistive	9	Densitometry	No effects
Trent (95)	95 M & F	CrPic (200)	Aerobic	16	Anthropometry	No effects
Lukaski (62)	36 M students	CrPic, $CrCl_3$ (170–180)	Resistive	8	DXA	No effects
Hallmark (43)	16 M students	CrPic (200)	Resistive	12	Densitometry	No significant Δ
Grant (39)	43 obese F	CrPic, CrNic (200)	Aerobic	9	Densitometry	↑Weight (CrPic, no exercise)
Kaats (53)	154 adults	CrPic (200, 400)	Sedentary	10–11	Densitometry	Improved BCI
Kaats (54)	122 adults	CrPic (400)	Variable	9	DXA	↓Weight, ↓fat
Campbell (18)	18 elderly M	CrPic (1000)	Resistive	12	Densitometry	No significant Δ

[a]Abbreviations: M, male; F, female; FFM, fat-free mass; % fat, percent body fat; DXA, dual X-ray absorptiometry; BCI, body composition index (see text for details); CrNic, chromium nic.

Hasten et al (47) supplemented the diets of novice, collegiate weight-training students, 35 men and 22 women, with either 200 μg of Cr as CrPic or with a placebo for 12 weeks. The sum of three circumferences (chest, upper arm, and thigh) increased and the sum of skinfold thicknesses decreased significantly in all participants, with no significant effect of Cr supplementation on these measurements, on body composition, or on strength gain. The only significant effect was a larger gain in body weight among the women whose diets were supplemented with CrPic. This study, therefore, did not corroborate the previous finding (34) that Cr-enhanced resistance training induces increases in FFM.

More recent studies also have failed to confirm that CrPic supplementation promotes alluring changes in body composition during resistance training. Thirty-six male collegiate football players completed a double-blind study involving diet supplementation with Cr (200 μg/day), a placebo, and supervised weight training for 9 weeks (26). Body composition changes, assessed with hydrodensitometry, were independent of Cr supplementation. Strength, however, did not increase after training in either group. This unexpected finding indicates that the technique used to measure strength, a dynamometer, was different than the method used for strength training, weight-lifting.

Underwater weighing was used in another study of 16 young men who were randomly assigned in a double-blind study to receive either 200 μg of Cr as CrPic daily or placebo for 12 weeks and participate in strength training (43). Both groups gained similar amounts of strength, and body composition did not change in response to the physical training.

The chemical form of the Cr supplement does not influence body composition changes associated with resistance training (62). Men participating in an 8-week weight-training program were matched by initial body composition and strength into groups that received Cr supplements, 200 μg/day either as CrPic or $CrCl_3$, or a placebo. It was estimated that dietary Cr was 50–60 μg/day. Strength, mesomorphy, FFM, and muscle mass, determined by dual X-ray absorptiometry, increased significantly with resistance training and independently of either Cr supplement.

A lack of enhanced performance and body composition also was reported in older men who were administered diets supplemented with 924 μg of Cr daily as CrPic, as compared with a group of men whose diets were not supplemented but who consumed whole-food diets containing 60 to 100 μg of Cr/day (18). Consistent with the previous study (62) in which nonsupplemented dietary Cr intake was estimated to be adequate, these data indicate that when dietary Cr meets population standards for adequate intake, supplemental Cr has no independent effect on performance and body composition in weight-stable adults.

Body Composition, Exercise, and Weight Loss

The use of Cr supplements in conjunction with exercise did not promote favorable changes in body composition in overweight adults. Ninety-five active-duty Navy personnel whose body fat exceeded the Navy's body fat standard completed a 16-week, supervised exercise program designed to optimize fat loss (95). The participants consumed either 400 μg of Cr as CrPic daily or a placebo. CrPic was ineffective in enhancing body fat reduction and was not recommended as an adjunct to military weight loss programs.

The effects of Cr supplementation (400 μg of Cr per day either as CrPic or CrNic) on body composition and glucose tolerance of mildly obese women during a 9-week weight loss program provided contradictory results (39). Obese women consuming the CrPic supplement and not participating in the exercise program had a significant gain in body weight (2 kg), and FFM and FM increased 1 kg each. No women remained sedentary and consumed CrNic. The exercising women given CrNic had a significant body weight loss (1.1 kg) with a concurrent, nonsignificant loss of FM (1.2 kg) and no change in FFM. Although no changes were observed in hemoglobin A_{1C} in any treatment group, the women supplemented with CrNic who participated in the aerobic exercise program had a lowered insulin response to a standard glucose load. Thus, CrNic supplementation combined with an aerobic exercise program may be more beneficial than exercise training alone in ameliorating mild glucose intolerance, but not in improving body composition, in women.

Weight Loss

The effects of CrPic supplementation on weight loss and body composition are conjectural. CrPic supplementation apparently improved body composition in a randomized, double-blind, placebo-controlled study (53). One hundred fifty-four free-living adults received either a Cr supplement (200 or 400 μg/day) or a placebo for 72 days. Body composition was measured by hydrodensitometry before and after supplementation. No instruction was provided to the participants regarding dietary intake or exercise. Subjects consumed at least two servings of a protein/carbohydrate drink that contained the different amounts of Cr. There was no control of the total amount of servings ingested by a subject. Physical activity and food intake also were not controlled. Body composition improvement, an index that accounts for fat loss and maintenance of FFM, was calculated to emphasize changes in body composition that occurred during the study. CrPic supplementation resulted in significantly higher positive (i.e. beneficial) changes in body composition improvement compared with results from the placebo. The interpretation of this finding was that CrPic enhanced both FFM retention and loss of FM. No significant differences were found in the body composition improvement of the groups supplemented with 200 or 400 μg of Cr/day.

In a second study, 122 free-living adults consumed a capsule containing either 400 μg of Cr daily as CrPic or a placebo for 90 days (54). Participants monitored themselves and reported daily caloric intake and energy expenditure. Comparisons of change in body composition variables, determined by using dual X-ray absorptiometry, from baseline to after supplementation were made by using covariance analysis to control for individual differences in estimated energy intake and output. Change in body fat was predicted on the basis that 3500 kcal energy output reflected a 1-lb pound loss of body fat. After controlling for presumable differences in caloric intake and output, as compared with the placebo group, the subjects with Cr-supplemented diets lost significantly more weight (7.8 vs 1.8 kg) and FM (7.7 vs 1.5 kg) without loss of FFM.

Interpretation of the data from these studies is complicated by some important factors. To rely on the calculation of an index of body composition change rather than on actual determinations of body composition is problematic. Similarly, lack of control of the actual Cr intake and failure to maintain constant energy intake and expenditure limit the interpretation of the findings. Furthermore, the calculation of fat loss based on a 3500-kcal energy expenditure resulting from physical activity produces dubious results. Therefore, the suggestion from these findings (53, 54) that CrPic supplementation promotes fat loss with a preservation of FFM conflicts with reports of no changes in body composition in adults given CrPic-supplemented diets and not provided a supplemental exercise program. CrPic supplementation in conjunction with an exercise training program also does not facilitate a preferential loss of FM (18, 39, 43, 47, 62, 95). Thus, CrPic per se does not promote beneficial changes in body composition in humans. The US Federal Trade Commission emphasized this conclusion by ruling in July 1997 (96) that there is no basis for claims that CrPic promotes weight loss and fat loss in humans.

ADVERSE EFFECTS OF CHROMIUM SUPPLEMENTATION

Toxicity

Hexavalent Cr is much more toxic than the trivalent form. Trivalent Cr has a low order of toxicity, and a wide margin of safety exists between the amounts usually ingested. Thus, it is unlikely to induce deleterious effects. For example, cats tolerate 1000 mg of Cr^{+3} daily and rodents have no adverse effects with 100 mg of Cr per kg of diet (106). The Cr^{+3} ion becomes toxic only at extremely high doses; Cr acts as a gastric irritant rather than as a toxic element that adversely affects physiology and metabolism.

Adverse effects of CrPic on cells in culture have been reported. Stearns et al (93) found that CrPic, and picolinic acid per se, promoted mutagenicity in

Chinese hamster ovary cells. The adverse changes were principally attributed to the picolinic acid but also were seen with CrPic use. The concentration of CrPic added to the cell culture system exceeded by more than 1000 times the concentration of Cr reported in human circulation. Consequently, these results should be viewed with caution.

There have been, however, several case reports of toxicity in humans from ingestion of CrPic. One individual developed chronic renal failure after daily ingestion of 600 μg of Cr as CrPic for 6 weeks (103). Another individual had episodes of cognitive, perceptual, and motor changes after ingestion of single doses of 200 and 400 μg of Cr as CrPic (50). A third individual developed hemolysis, thrombocytopenia, hepatic dysfunction, and acute renal failure after daily consumption of 1200–2400 μg of Cr as CrPic for 4–5 months (21).

The reference dose for Cr^{+3} is 1000 μg/(kg · d) (33), and the upper limit of the estimated safe and adequate daily dietary intake is only 3 μg/(kg · d) (76). Therefore, toxic effects of supplemental Cr are highly unlikely.

Interactions with Iron

The Cr^{+3} ion is transported on transferrin for tissue distribution (49). At low levels of iron saturation, Cr and iron preferentially occupy different binding sites. At higher iron concentrations, however, Cr and iron compete for the same binding site. Thus, patients with hemochromatosis retain less Cr than iron-depleted patients or healthy subjects (88).

Cr may adversely impact iron metabolism. Rats injected intraperitoneally with 1 mg of Cr/kg of body weight daily for 45 days developed iron deficiency and anemia (11). Men participating in resistance training and supplemented with 180 μg of Cr as CrPic had a 30% decrease in transferrin saturation, as opposed to other men, also in weight training but who were supplemented with a similar amount of Cr as $CrCl_3$ or a placebo, whose decrease in transferrin saturation was 10–15% (62).

Other data suggest an adverse effect of Cr generally, and CrPic specifically, in altered iron homeostasis. Rats supplemented with 5000 ppb Cr as $CrCl_3$, CrPic, CrNic, and other organic complexes of Cr had excessive accumulation of iron in the liver and spleen as compared with other rats fed 30 ppb Cr (6). Picolinic acid per se has been reported to disrupt iron metabolism and arrest growth in normal rat kidney cells in culture (36). Thus, the interaction among Cr, picolinic acid, and iron status is a topic that requires additional research.

SUMMARY

Although the mineral element Cr is apparently needed for health and function, limitations exist in assessment of the Cr nutritional status of an individual and in availability of guidelines that recommend daily intakes. Generalized

supplementation with Cr has no beneficial effect on body composition or glucose homeostasis. Promising information that describes a biological function of Cr as part of the low-molecular-weight substance that facilitates the action of insulin at the insulin receptor, and the recent finding that Cr ameliorates glycation and impaired glucose homeostasis in type 2 diabetic patients, should stimulate future research on Cr. However, women with gestational diabetes whose diets are supplemented with Cr do not consistently respond with improved glucose and insulin homeostasis. Emphasis should be placed on the development of accurate and sensitive measures for assessment of human Cr nutriture and for expanding nutrient databases for the evaluation of dietary Cr intakes of individuals. A key concern is to confirm the promising findings of a salutary effect of Cr supplementation on improvement of glucose homeostasis in insulin-insensitive individuals. If research efforts yield sensitive and specific measures of Cr nutriture and confirm beneficial effects of Cr supplementation on normalization of glucose homeostasis among glucose-intolerant individuals, then evidence will be available for the establishment of health-promoting dietary guidelines for Cr. It is important to acknowledge that propitious effects of Cr on health and biological function must be related to the role of Cr as a nutrient and not as a therapeutic agent. Therefore, beneficial effects of Cr supplementation must be related to measurements of Cr nutriture and functional measures of metabolism.

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