

Role of Chromium in Human Health and in Diabetes

WILLIAM T. CEFALU, MD¹
FRANK B. HU, MD, PHD²

Despite widespread use by patients with diabetes and anecdotal reports in the past regarding its efficacy, until recently, data in humans concerning chromium's effects on insulin action in vivo or on cellular aspects of insulin action were scarce. Consequently, significant controversy still exists regarding the effect of chromium supplementation on parameters assessing human health. Furthermore, elucidating the cellular and molecular mechanisms by which chromium supplements affect carbohydrate metabolism in vivo is necessary before specific recommendations can be made regarding its routine use in the management of diabetes. This review focuses on providing current information about this trace mineral's specific mechanisms of action and clinical trials in patients with diabetes.

Chromium, one of the most common elements in the earth's crust and seawater, exists in our environment in several oxidation states, principally as metallic (Cr^0), trivalent (+3), and hexavalent (+6) chromium. The latter is largely synthesized by the oxidation of the more common and naturally occurring trivalent chromium and is highly toxic. Trivalent chromium, found in most foods and nutrient supplements, is an essential nutrient with very low toxicity.

The interest in chromium as a nutritional enhancement to glucose metabolism can be traced back to the 1950s, when it was suggested that brewer's yeast

contained a glucose tolerance factor (GTF) that prevented diabetes in experimental animals (1). This factor was eventually suggested to be a biologically active form of trivalent chromium that could substantially lower plasma glucose levels in diabetic mice (2). Interest regarding chromium administration in patients with diabetes was kindled by the observation in the 1970s that it truly was an essential nutrient required for normal carbohydrate metabolism. A patient receiving total parenteral nutrition (TPN) developed severe signs of diabetes, including weight loss and hyperglycemia that was refractory to increasing insulin dosing (3). Based on previous animal studies and preliminary human studies, the patient was given supplemental chromium. In the following 2 weeks, signs and symptoms of diabetes were ameliorated, with markedly improved glycemic status and greatly reduced insulin requirements (exogenous insulin requirements decreased from 45 units/day to none). Other studies (4,5) of the beneficial effects of chromium in patients receiving TPN have also been documented in the scientific literature. Chromium is now routinely added to TPN solutions (5).

The results of these studies strongly implicated chromium as a critical cofactor in the action of insulin (6,7). Whereas chromium replacement in deficiency states is well established, the role of chromium supplementation to enhance glucose metabolism in subjects is

controversial and serves as the basis for this review.

Trivalent chromium is found in a wide range of foods, including egg yolks, whole-grain products, high-bran breakfast cereals, coffee, nuts, green beans, broccoli, meat, brewer's yeast, and some brands of wine and beer (8,9). Chromium is also present in many multivitamin/mineral supplements, and there are also specific chromium picolinate (CrP) supplements that contain 200–600 μg chromium per tablet (10). The U.S. National Academy of Sciences has established the Recommended Daily Allowances for chromium as 50–200 $\mu\text{g}/\text{day}$ for adult men and women (11), which is also the Estimated Safe and Adequate Daily Dietary Intake (ESADDI) for chromium for children aged 7 years to adulthood (7,12). However, it appears that Americans normally ingest ~50–60% of the minimum suggested daily intake of 50 μg (7). Results from one study (10) indicated that daily chromium intakes for men and women in the U.S. were 33 and 25 μg , respectively. Therefore, normal dietary intake of chromium for adults may be suboptimal.

At dietary intakes >50 $\mu\text{g}/\text{day}$, chromium absorption is ~0.4%, but the trivalent formulation also significantly influences bioavailability. At a dose of 1,000 $\mu\text{g}/\text{day}$, absorption of chromium from chromium chloride (CrCl_3) is ~0.4%, whereas that from CrP may be as high as 2.8% (7,13,14). Once absorbed, chromium is distributed widely in the body, with the highest levels being found in the kidney, liver, spleen, and bone (14).

BIOLOGIC ACTIONS OF CHROMIUM

How chromium serves as a cofactor for insulin action is not fully understood. From several in vivo and in vitro studies (15), it was initially thought that chromium potentiated the actions of insulin as part of an organic complex, GTF. More recent studies (15) have suggested that chromium may function as part of the oligopeptide low-molecular weight (MW) chromium (LMWCr)-binding substance (MW

From the ¹Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana; and ²Harvard University School of Public Health, Boston, Massachusetts.

Address correspondence and reprint requests to William T. Cefalu, MD, Division of Nutrition and Chronic Disease, The Pennington Biomedical Research Center, Louisiana State University, 6400 Perkins Rd., Baton Rouge, LA 70808. E-mail: cefaluwt@pbrc.edu.

Received for publication 15 July 2004 and accepted in revised form 21 July 2004.

F.B.H. has received grant support from Nutrition 21.

Abbreviations: CrP, chromium picolinate; CVD, cardiovascular disease; FPG, fasting plasma glucose; GTF, glucose tolerance factor; HPFS, Health Professionals' Follow-up Study; LMWCr, low-molecular weight chromium; MI, myocardial infarction; MW, molecular weight; TPN, total parenteral nutrition.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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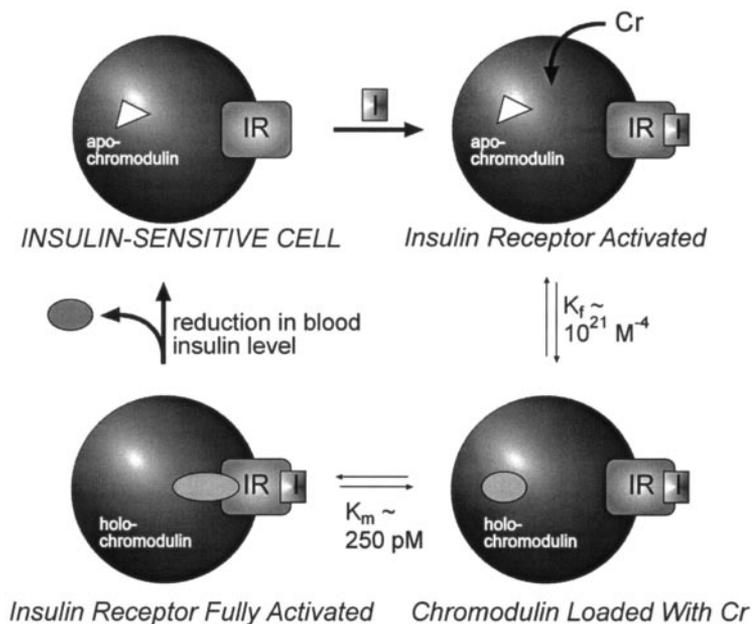


Figure 1—Proposed mechanism of action for chromium and LMWCr potentiating the action of insulin (15).

~1,500 Da), which is composed of glycine, cysteine, glutamic acid, and aspartic acid. The interaction of chromium with LMWCr and the manner in which this complex influences insulin metabolism is considered in greater detail below.

Biochemistry

Very little chromium (<2%) in the form of inorganic compounds is absorbed but may be higher with certain organic formulations (14). Once absorbed, chromium is distributed to various tissues of the body, but appears to be most concentrated in the kidney, muscle, and liver (16). The principal carrier protein for chromium is transferrin, which also plays a critical role in the movement of chromium from blood to LMWCr. It has been suggested that migration of transferrin receptors to the plasma membranes of insulin-insensitive cells after insulin stimulation is the initial step in this process. Transferrin containing the plasma-bound chromium is postulated to bind to the transferrin receptors and is internalized by endocytosis (Figs. 1 and 2). The pH of the internalized vesicle is reduced by ATP-driven proton pumps, chromium is released from transferrin, and the resulting free chromium is postulated to be sequestered by LMWCr (15,17). With this step, chromium is transferred from transferrin to LMWCr, which normally

exists in insulin-dependent cells in the apo, or inactive, form. Binding with chromium ions converts inactive LMWCr to its holo, or active, form. It is proposed that LMWCr then participates as part of an insulin signal amplification system (Fig. 1) as it binds to insulin-activated insulin receptors and results in stimulating its tyrosine kinase activity. The result of this process is the activation of insulin receptor kinase and potentiation of the actions of insulin (15,18,19). Importantly, LMWCr without bound chromium or in the presence of other metal ions is ineffective in activating insulin-dependent kinase activity and thus enhancing the actions of insulin (19).

Chromium has also been demonstrated to inhibit phosphotyrosine phosphatase, the enzyme that cleaves phospho-phosphate from the insulin receptor, leading to decreases in insulin sensitivity. Activation of insulin receptor kinase and inhibition of insulin receptor phosphatase would lead to increased phosphorylation of the insulin receptor and increased insulin sensitivity (20). The balance between kinase and phosphatase activity may facilitate the role of insulin in rapidly moving glucose into cells. In addition, it has been suggested (7) that chromium enhances insulin binding, insulin receptor number, insulin internalization, and β -cell sensitivity.

The controversy surrounding chromium supplementation is due in part to substantial variability in the results of studies that have evaluated the effects of chromium in patients with or without diabetes. Results from some trials (21–26) have indicated that chromium supplementation increases muscle gain and fat loss associated with exercise and improves glucose metabolism and the serum lipid profile in patients with or without diabetes. In contrast, those from other studies (27–32) have indicated little or no benefit of chromium on any of these variables.

Recent meta-analyses (33,34) of results from studies that evaluated the effects of chromium supplementation have suggested limited benefit in individuals with or without diabetes. The major conclusions from these analyses were that chromium has a very small effect versus placebo in reducing body weight and that the clinical relevance of this small decrease is debatable and should be interpreted with caution. It was also concluded that chromium has no effect on glucose metabolism or insulin concentrations in individuals without diabetes and that data for patients with diabetes are currently inconclusive. It is important to note that these conclusions are based largely on data from patients without diabetes and failed to include key positive results for chromium supplementation in diabetic patients and subjects with gestational diabetes or the metabolic syndrome.

There is no clinically defined state of chromium deficiency, but diabetes has been shown (32) to develop because of low chromium levels in experimental animals and in humans sustained by prolonged TPN. These results suggest that there may be a more general relationship between chromium levels and glucose and/or lipid metabolism. It has also been suggested (35–37) that low chromium concentrations and the associated impairments in insulin, glucose, and lipid metabolism may also result in increased cardiovascular risk. In a cross-sectional analysis (38), lower toenail chromium levels have also been associated with increased risk of type 2 diabetes. Adequate dietary chromium intake may be especially problematic in the elderly (39,40). Consumption of refined foods, including simple sugars, exacerbates the problem of insufficient dietary chromium because

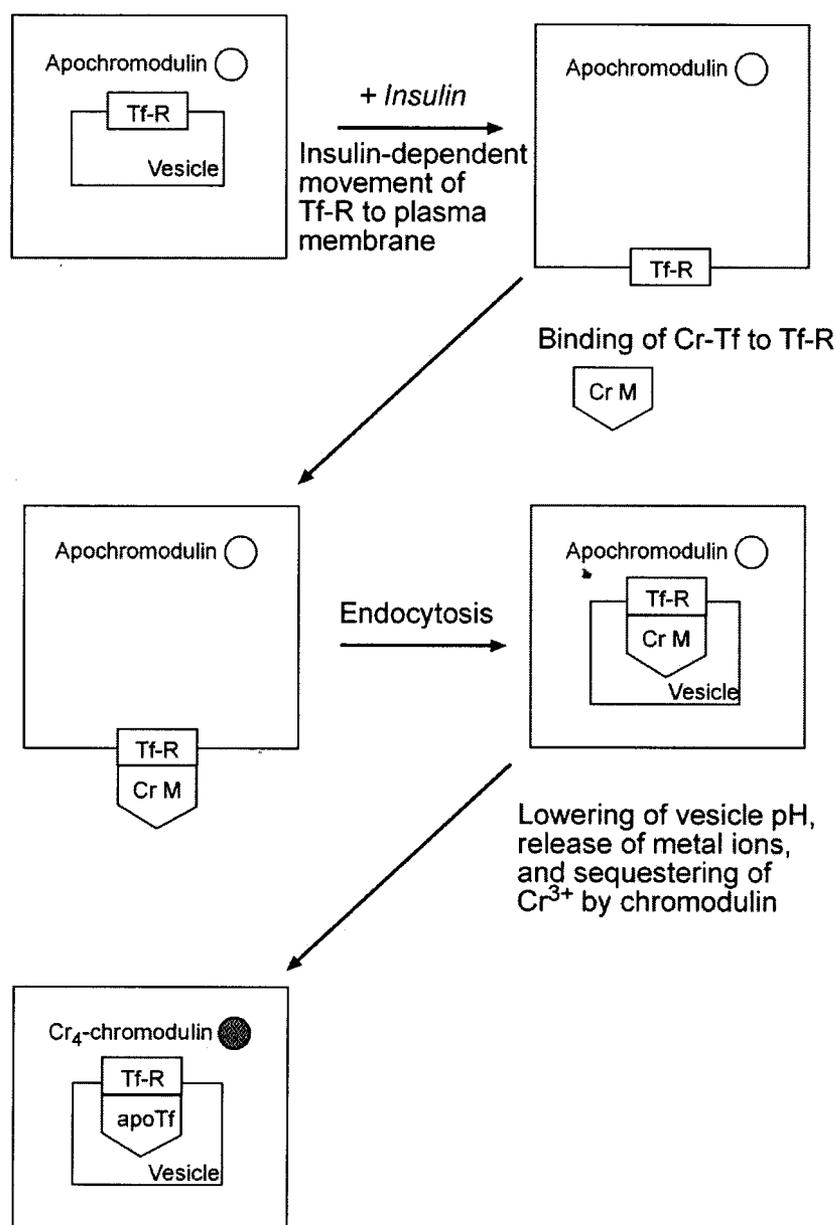


Figure 2—Proposed mechanism for the movement of chromium from the blood to LMWCr (18). Cr, chromic ion; M, metal ion; Tf, transferrin; Tf-R, Tf receptor.

these foods are not only low in dietary chromium but also increase its loss from the body (41). Chromium losses are also increased during pregnancy and as a result of strenuous exercise, infection, physical trauma, and other forms of stress (40). Reduced chromium levels are reported in the elderly and in patients with diabetes (42,43). However, one of the major problems with assessing chromium status in biological tissues and fluids is extremely low levels of chromium in these tissues. Regardless, recent studies have demonstrated the successful determina-

tion of chromium. One study reported that in >40,800 patients from ages 1 to >75 years, chromium levels in hair, sweat, and blood diminished significantly with age, with values decreasing from 25 to 40% depending on the tissue of interest (43). Additionally, it appears that diabetic subjects may have altered chromium metabolism compared with nondiabetic subjects, as both absorption and excretion may be higher (44,45). Hair and blood levels are reported (46) to be lower in diabetic subjects, with mean levels of plasma chromium of ~33% lower in 93

type 2 diabetic subjects compared with control subjects. Another study reported that chromium levels were reduced >50% in both diabetic men and women compared with control subjects (42), which was supported by Elmekcioglu et al. (47), who reported significantly lower chromium levels in the plasma of type 2 diabetic individuals compared with nondiabetic healthy control subjects. Yet, another study (48) suggested no alteration of chromium levels in type 2 diabetes; however, only 11 subjects were reported.

CLINICAL INTERVENTION WITH CHROMIUM

The most recent recommendations of the American Diabetes Association state that “at the present, benefit from chromium supplementation in persons with diabetes has not been conclusively demonstrated” (49).

Review of the literature

A review of the literature has revealed numerous conflicting studies evaluating chromium supplementation and parameters assessing carbohydrate metabolism (21,30–32,50–60) (Table 1). Considerable differences in efficacy were reported that essentially confused health care providers regarding routine use of chromium in diabetic states. These earlier studies (12) are difficult to interpret, as many were open label and therefore generated substantial bias. Additional concerns are the lack of gold standard techniques to assess glucose metabolism, use of differing doses and formulations, and heterogeneous study populations. Specifically, the limitations of the earlier studies can be classified as follows.

Study design. The use of a control group is of paramount importance when evaluating the effect of chromium given the possibility that patients who choose to use chromium may be different from nonusers. Thus, only a randomized intervention can definitely establish the overall effects of chromium on insulin action, as it is this design that controls for biases, whether known or unknown, that may confound the association and assessment of chromium supplementation and carbohydrate metabolism. Unfortunately, many of the reported studies evaluating chromium supplementation were open-label studies (Table 1).

Subject selection. The clinical characteristics of the study subjects varied tre-

Table 1—Comparison of chromium studies in humans

| Reference | Study type | Study length | Chromium supplement (dose) | Subjects | n | Technique assessed | Results | | | |
|---|------------|--------------|--|----------------------|--------|--------------------------------------|---------|---------|----------------------|----|
| | | | | | | | Glucose | Insulin | HbA _{1c} IS | |
| Studies using CrCl ₃ , brewer's yeast, and CrN formulation | | | | | | | | | | |
| Trow et al. (50) | OL | 2 months | Brewer's yeast (100 µg/day Cr ³⁺) | Type 2 | 12 | OGTT | — | — | NA | NA |
| Sherman et al. (51) | DB | 4 months | CrCl ₃ (150 µg/day) | Type 1/2/Nondiabetic | 14 | OGTT | — | NA | NA | NA |
| Rabinowitz et al. (32) | DB | 4 months | CrCl ₃ (150 µg/day), brewer's yeast (13 µg/day Cr ³⁺) | Type 2 | 43 | Meal challenge | — | — | NA | NA |
| Uсутupa et al. (30) | DB | 6 months | Brewer's yeast (160 µg/day Cr ³⁺) | IGT, elderly | 26 | OGTT | — | — | — | NA |
| Uсутupa et al. (52) | DB | 6 weeks | CrCl ₃ (200 µg/day) | Type 2 | 10 | OGTT, HbA _{1c} | — | ↓ | — | NA |
| Potter et al. (21) | OL | 3 months | CrCl ₃ (200 µg/day) | IGT | 5 | Hyperglycemic clamp | — | — | — | ↑ |
| Mossop (53) | DB | 3 months | CrCl ₃ (600 µg/day) | Type 1/2 | 26 | FBG | ↓ | NA | NA | NA |
| Nath et al. (54) | OL | 2 months | CrCl ₃ (500 µg/day) | Type 2 | 12 | OGTT | ↓ | ↓ | NA | NA |
| Glinnmann and Mertz (55) | OL | 18–133 days | CrCl ₃ (180–3,000 µg/day) | Type 1/2 | 6 | IVGTT, OGTT | ↓ | NA | NA | NA |
| Wilson and Gandy (31) | DB | 3 months | CrN (220 µg/day) | Nondiabetic, young | 26 | FBG/insulin | — | ↓* | NA | NA |
| Studies using CrP formulation | | | | | | | | | | |
| Anderson et al. (45) | R | 4 months | CrP (200 or 1,000 µg/day) | Type 2 | 180 | OGTT, HbA _{1c} | ↓ | ↓ | ↓ | NA |
| Amato, Morales, and Yes (56) | DB | 2 months | CrP (1,000 µg/day) | Nondiabetic, elderly | 19 | Minimal model | — | — | NA | — |
| Jovanovic, Gutierrez, and Peterson (57) | DB | 2 months | CrP (320 or 640 µg/day)* | Gestational diabetes | 20 | OGTT, HbA _{1c} | ↓ | ↓ | — | NA |
| Ravina et al. (58) | OL | 1–7 days | CrP (600 µg/day) | Diabetes | 3 | FBG | ↓ | NA | NA | NA |
| Morris et al. (59) | OL | 3 months | CrP (400 µg/day) | Type 2 | 5 | Insulin tolerance, HOMA | — | ↓ | NA | ↑ |
| Cheng et al. (60) | OL | 1–10 months | CrP (500 µg/day) | Type 2 | 833 | Fasting, postmeal | ↓ | NA | NA | NA |
| Ghosh et al. (22) | DB | 3 months | Cr ₃ (200 µg/day) | Type 2 | 50 | FBG, HbA _{1c} | ↓ | NA | ↓ | NA |
| Cefalu et al. (64) | R | 8 months | CrP (1,000 µg/day) | Pre-diabetes | 29 | Minimal model | — | ↓ | NA | ↑ |
| Ravina et al. (68) | OL | 10 days | CrP (200 µg/day) | Type 1/2 | 48/114 | Insulin tolerance, HbA _{1c} | NA | NA | ↓ | ↑ |
| Lee and Reasner (70) | DB, | 2 months | CrP (200 µg/day) | Type 2 | 30 | FBG, HbA _{1c} | — | NA | — | NA |
| Evans (78) | DB | 42 days | CrP (200 µg/day) | Type 2 | 11 | FBG, HbA _{1c} | ↓ | NA | ↓ | NA |

↑, increased; ↓, decreased; —, no change; CrCl₃, chromium chloride; CrN, chromium nicotinate; DB, double blind; FBG, fasting blood glucose; IGT, impaired glucose tolerant; IS, insulin sensitivity; IVGTT, intravenous glucose tolerance test; NA, not assessed; OGTT, oral glucose tolerance test; OL, open label; R, randomized. *In hyperinsulinemic patients only; †β-cell sensitivity to glucose.

mendously as several studies grouped type 1 and type 2 diabetic subjects together in the evaluation of chromium's effect (Table 1). Indeed, even in studies in which only subjects with type 2 diabetes were reported, subjects were assessed while on various therapies (e.g., diet, sulfonylureas, metformin, insulin) and at different levels of glycemic control (32,50,55,58,60). It is well established that hyperglycemia secondary to glucose toxicity may contribute to attenuation in insulin action (61), and the effect of medications to alter insulin action is well studied (62,63).

Dosage, formulation, duration of study. The duration of supplementation evaluated (ranging from 1 day to 8 months) and the dose used (ranging from 100 to 3,000 μg daily) varied tremendously in earlier studies. Studies that specifically evaluated ≤ 200 μg of chromium chloride failed to elicit a clinical response in those with type 2 diabetes (Table 1). Uusitupa et al. (52) demonstrated a positive effect at 200 μg of the CrCl salt; however, the remaining variables in that study did not appear to be altered by supplemental chromium. A more consistent clinical response is observed with daily supplementation of chromium > 200 $\mu\text{g}/\text{day}$ for a duration of ≥ 2 months (Table 1). In addition, other forms of chromium, especially CrP, appear to be more bioavailable and clinically more effective than chromium chloride in both human and animal studies. Evidence for a dose effect of CrP was provided by a study of Chinese type 2 diabetic subjects (45). Short-term (2 months) and long-term (4 months) efficacy were observed, as evidenced by reductions in fasting and 2-h glucose and insulin values and long-term reductions in HbA_{1c} concentrations utilizing varying doses of CrP (200 or 1,000 μg). The effectiveness of the 1,000- μg dose in the Chinese study was reproduced in a study of individuals with the metabolic syndrome (64). In a study (57) of 30 women with gestational diabetes receiving placebo or 4 or 8 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ of CrP, after 8 weeks the two groups taking chromium had significantly lower glucose and insulin levels. Finally, another (58) observed that corticosteroid-treated subjects have accelerated chromium losses and that steroid-induced diabetes was reversed with CrP supplementation at 600 $\mu\text{g}/\text{day}$.

Assessment of chromium status. Many of the earlier reported studies did not address the role of chromium blood levels at baseline or recorded changes, if any, with supplementation. In addition, objective markers to measure compliance with the regimen were not evaluated.

Techniques to assess response. The major limitation of the earlier studies, however, may be the lack of sophisticated metabolic techniques used to assess carbohydrate metabolism. Many of the studies evaluated response by fasting blood levels only or used glucose tolerance or mixed-meal tests (Table 1). Although these tests are frequently used in clinical studies, they do not provide the sensitivity required to precisely assess insulin action. Our literature search did not find any study that evaluated the effect of chromium supplementation on insulin sensitivity by using the gold standard for assessing insulin action, i.e., the hyperinsulinemic-euglycemic clamp. One study (65) used the euglycemic clamp, but only to assess the relationship of blood chromium and insulin and did not supplement the subjects. Another study (21) evaluated subjects with a hyperglycemic clamp and demonstrated that significant increases in glucose utilization were observed and associated with increases in β -cell sensitivity to glucose following chromium supplementation. Of the other three studies that evaluated a more sophisticated technique to assess insulin action, one did not show an improvement in insulin sensitivity (56) using the minimal model technique, in contrast to Cefalu et al. (64). A separate study (59) demonstrated beneficial effects in type 2 diabetics using the insulin tolerance test and homeostasis model assessment method.

Individuals with diabetes

Type 1 and 2 diabetes. Chinese patients with type 2 diabetes receiving CrP experienced significant improvements in HbA_{1c}, fasting plasma glucose (FPG), 2-h glucose (i.e., glucose levels 2 h after challenge), and fasting and 2-h insulin (45). Other investigators studied the effects of brewer's yeast (23.3 μg chromium/day) and chromium chloride (200 μg chromium/day) on glucose tolerance, serum lipids, and antidiabetic drug dosage in a 16-week, randomized, double-blind, crossover trial that included 78 patients with type 2 diabetes (23,66). Both forms of chromium supplementation resulted in

significant decreases in mean FPG, 2-h glucose, and fructosamine. Chromium treatment also slightly reduced required doses of antidiabetic drugs, and this decline achieved statistical significance for glibenclamide. Another group assessed the effects of jiangtang kang (8 g t.i.d.), a chrysanthemum product high in chromium, on glucose and insulin metabolism in 188 patients with type 2 diabetes (67). After 2 months, jiangtang kang treatment reduced fasting and postprandial blood glucose and HbA_{1c} without any corresponding change in plasma insulin. A 16-month, double-blind, randomized, crossover trial (32) of chromium chloride, brewer's yeast that contained chromium as GTF, brewer's yeast extract without GTF, and a placebo in 43 patients with diabetes also demonstrated positive effects of chromium on glucose and insulin metabolism. FPG and the glucose response to either a standard meal or tolbutamide were not significantly altered by any of the treatments, but ketosis-resistant patients experienced a significant increase in postprandial insulin after treatment with the brewer's yeast that contained GTF. Results from an additional study indicated that chromium supplementation has significant positive effects on glucose and insulin metabolism in patients with diabetes. One study (68) reported that 10 days of treatment with CrP (200 $\mu\text{g}/\text{day}$) significantly increased insulin sensitivity in patients with type 1 or 2 diabetes and also permitted reductions in dosages of insulin and/or oral antidiabetic drugs in these patients.

A large long-term study showed that 10 months of treatment with CrP (500 $\mu\text{g}/\text{day}$) in 833 patients with type 2 diabetes significantly improved both FPG and postprandial plasma glucose versus baseline (Fig. 3) and reduced the incidence of diabetes symptoms, including fatigue, thirst, and frequent urination (60).

Not all studies have demonstrated significant positive effects of chromium supplementation in patients with diabetes. One group (69) reported no significant effect of chromium supplementation (7–16 months of 250 $\mu\text{g}/\text{day}$) versus placebo on serum glucose levels in 76 patients aged 42–83 years (25 of whom had type 2 diabetes) with atherosclerotic disease. These results are consistent with those of another small-scale trial (70) that indicated no significant effects of chro-

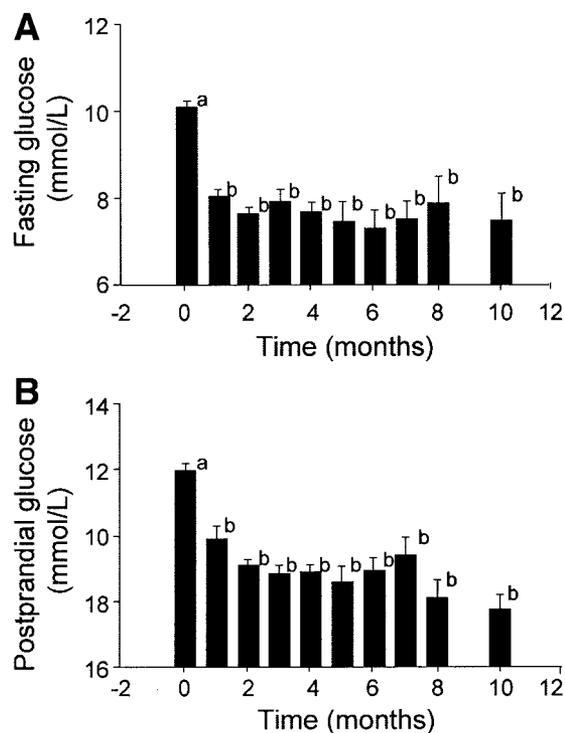


Figure 3—Fasting (A) and postprandial (B) glucose decline over time in patients with type 2 diabetes treated for 10 months with 500 $\mu\text{g/day}$ CrP (60). *b*, significantly different from baseline (*a*).

mium supplementation (200 $\mu\text{g/day}$ for 2 months) versus placebo on either blood glucose or HbA_{1c} in 30 patients with type 2 diabetes. Similarly, another study reported that 6 weeks of supplementation with 200 $\mu\text{g/day}$ chromium in 10 patients with type 2 diabetes was not significantly different from placebo in improving glucose tolerance or fasting or 2-h serum insulin. However, 1-h serum insulin was significantly lower with chromium supplementation than with placebo (52).

The lack of significant effects of chromium supplementation in these three studies may be related to the relatively low chromium doses and specific formulations used for treatment as discussed above. Abraham et al. (69) treated patients with 250 $\mu\text{g/day}$ CrCl₃, Lee and Reasner (70) administered 200 $\mu\text{g/day}$ CrP, and Uusitupa et al. (52) treated patients in their trial with 200 $\mu\text{g/day}$ CrCl₃. Thus, two of the three studies that failed to document significant positive effects of chromium on insulin or glucose metabolism used a poorly absorbed inorganic formulation, and the third administered a very low dose of CrP. These facts underscore the point that chromium formulation and dose must be carefully considered when evaluating results from studies that have assessed its metabolic effects in individuals with or without diabetes.

Gestational diabetes. Chromium supplementation has also shown to be effective in improving glucose and insulin metabolism in women with gestational diabetes. A placebo-controlled study (57) of 30 women with this condition treated with 4 or 8 $\mu\text{g/kg}$ CrP or placebo showed that 8 weeks of chromium supplementation significantly decreased fasting levels of glucose, insulin, and C-peptide versus placebo.

Steroid-induced diabetes. Ravina et al. (58) showed that administration of chromium can also reverse corticosteroid-induced diabetes. They treated three patients with steroid-induced diabetes with 600 $\mu\text{g/day}$ CrP and reported that fasting blood glucose values fell from 250 to 150 mg/dl. The requirement for antidiabetic drugs was also reduced by 50% in these patients.

Summary. Results from the trials noted above support the view that chromium supplementation, especially in the form of CrP, in patients with type 1, type 2, gestational, or steroid-induced diabetes can improve both glucose and insulin metabolism. The reason why chromium supplementation was ineffective in some studies is not clear, but it is worth noting that all of these trials used relatively low chromium doses (≤ 250 $\mu\text{g/day}$), used different forms of chromium, or had

study populations composed of both diabetic and nondiabetic patients.

Individuals with the metabolic syndrome

Many patients with diabetes have additional metabolic abnormalities that, taken together, constitute what has been referred to as the metabolic syndrome. The National Cholesterol Education Program Adult Treatment Panel III has defined the metabolic syndrome as the presence of three or more of the following conditions: waist circumference >102 cm in men and >88 cm in women, serum triglyceride level ≥ 150 mg/dl; HDL cholesterol <40 mg/dl in men and <50 mg/dl in women, blood pressure $\geq 130/85$ mmHg, or serum glucose ≥ 110 mg/dl (71). Insulin resistance is a core feature of the metabolic syndrome and is associated with increased cardiovascular disease (CVD) risk, even in the absence of glucose intolerance (72). Several studies have evaluated the effects of chromium supplementation in patients with components of the metabolic syndrome.

Cefalu et al. (64) assessed the effects of 8 months of treatment with CrP (1,000 $\mu\text{g/day}$) or placebo on glucose tolerance, insulin sensitivity, and body fat in 29 subjects with $>125\%$ of ideal body weight and a family history of diabetes. Study results showed that CrP supplementation significantly improved insulin sensitivity versus placebo (Fig. 4), but had no significant effects on glucose effectiveness, body weight, abdominal fat, or BMI. These investigators suggested that the positive effect of CrP on insulin sensitivity without a corresponding change in body weight or BMI may indicate a direct effect of chromium on muscle insulin action. In contrast, another study (30) reported no significant changes in glucose or insulin metabolism versus placebo after 6 months of treatment with Cr³⁺-rich yeast (160 $\mu\text{g/day}$) in a group of 26 elderly subjects with impaired glucose tolerance and moderate obesity (BMI ~ 30 kg/m² at baseline).

Individuals without diabetes

Available data suggest the chromium supplementation has at best limited effects on glucose and insulin metabolism in individuals without diabetes. A small-scale study (56) that included 19 nonobese elderly subjects treated with 1,000 $\mu\text{g/day}$ CrP or placebo for 8 weeks indicated no

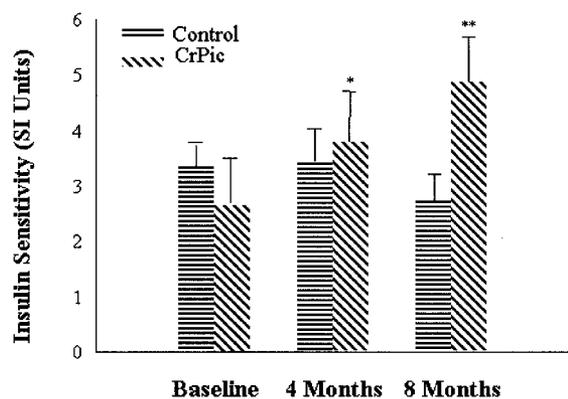


Figure 4—Effects of chromium supplementation on insulin sensitivity in overweight subjects with a family history of diabetes treated for 8 months with 1,000 $\mu\text{g}/\text{day}$ CrP (64). Data are means \pm SD. * $P < 0.05$, ** $P < 0.005$ versus baseline.

significant effect of active treatment on insulin sensitivity. Another team (73) reported that administration of 400 $\mu\text{g}/\text{day}$ chromium for 12 weeks in 44 moderately obese middle-aged women who were also participating in a weight-training and walking program had no significant effects versus placebo on FPG, serum insulin, plasma glucagon, or serum C-peptide. Chromium supplementation (220 $\mu\text{g}/\text{day}$ chromium delivered as chromium nicotinate) also had no significant effect versus placebo on fasting glucose or immunoreactive insulin in 26 young volunteers. However, chromium administration did significantly reduce immunoreactive insulin levels in subjects with baseline concentrations >35 pmol/l (31). In contrast, results from another trial (74) in which 24 elderly subjects (8 with diabetes) were treated for 8 weeks with either 9 g/day Cr^{3+} -rich brewer's yeast or Cr^{3+} -poor torula yeast indicated that the Cr^{3+} -rich supplement significantly improved glucose tolerance and decreased insulin output.

Chromium effects on body weight and composition

The prevalence of obesity in the U.S. is high, and more than one-half of all adults are currently overweight or obese. Obesity significantly increases the risk for development of type 2 diabetes, hypertension, and CVD (75). Several studies have evaluated the effects of chromium supplementation on body weight and composition in individuals with and without diabetes.

Chromium supplementation has variable effects on body weight and composition in patients with diabetes (26–30,45,56,73,76,77). One study of patients with diabetes indicated no significant effects on either body weight or BMI

(45), while another in elderly subjects with impaired glucose tolerance demonstrated significant reductions in BMI (30). Of the eight double-blind, placebo-controlled trials in individuals without diabetes, chromium supplementation showed decreases in weight and fat in three larger studies (26–29,56,73,76,77).

These results generally support the view that chromium supplementation has at best modest effects on body weight or composition in individuals with diabetes and perhaps more consistent positive effects in healthy volunteers. However, it must be noted that most of the studies addressing this question included only small numbers of subjects and were of relatively short duration.

Effects of chromium supplementation on the serum lipid profile

Many of the studies that evaluated the effects of chromium supplementation on glucose and insulin metabolism also assessed the effects of such treatment on serum lipids. Results obtained in studies of patients with diabetes or glucose intolerance as well as those from normal subjects have indicated variable effects of chromium supplementation on one or more components of the serum lipid profile (22, 25,30–32,45,52,56,64,66–70,73,74,78–81) (Table 2).

Relationship between tissue chromium levels and disease state

Risk for coronary heart disease. Two epidemiologic studies have evaluated the relationship between Cr^3 levels in toenails (a measure that can best reflect long-term intake of trace elements) and risk of coronary heart disease in men. The Health Professionals' Follow-up Study (HPFS) is

a prospective study including 33,737 male health care professionals in the U.S. who were free of chronic disease and provided toenail samples in 1987. During 7 years of follow-up, there were 367 confirmed myocardial infarctions (MIs). Two control subjects were matched to each case subject. Study results showed that the risk for MI was significantly reduced in men in the highest quintile for toenail Cr^{3+} . However, this relationship was only significant for subjects with BMI ≥ 25 kg/m^2 (37).

In a second study conducted in the HPFS (38), mean toenail chromium (microgram per gram) was 0.71 in healthy control subjects ($n = 361$), 0.61 in diabetic subjects ($n = 688$), and 0.52 in diabetic men with prevalent CVD ($n = 198$, $P = 0.003$ for trend). In the cross-sectional analysis, after adjustment of potential confounders, the odds ratio (OR) between extreme quartiles was 0.74 (95% CI 0.49–1.11; $P = 0.18$ for trend) comparing diabetic with healthy control subjects. A similar comparison between diabetic men with prevalent CVD and healthy control subjects yielded an OR of 0.45 (95% CI 0.24–0.84; $P = 0.003$ for trend). A nested case-control analysis comparing diabetic men with incident CVD with healthy individuals yielded similar results. These findings suggest that adequate chromium may be important for both diabetes and CVD prevention.

The results of the HPFS are consistent with those from the European Community Multicenter Study on Antioxidants, Myocardial Infarction, and Breast Cancer (EURAMIC), an incident, population-based, case-control study conducted in eight European countries and Israel to determine whether low toenail chromium concentrations are significantly associated with increased risk for MI. The study included 684 case subjects (men with a first diagnosis of MI within 24 h of admission to the hospital) and 724 control subjects (men with similar demographic characteristics, but without MI). Average toenail chromium was 1.10 mg/kg in the case subjects vs. 1.30 mg/kg in the control subjects. Additional analysis indicated that the adjusted ORs for MI for chromium quintiles 1–5 were 1.00, 0.82, 0.68, 0.60, and 0.59, respectively (82). The results of EURAMIC thus indicate that toenail chromium concentration has a clearly inverse relationship with MI risk

Table 2—Effects of chromium supplementation on serum lipids

| Study | Design | No. of subjects | Chromium supplement (dose) | Key results |
|--------------------------------------|---------------|-----------------------------|--|--|
| Patients with diabetes or IGT | | | | |
| Abraham, Brooks, and Eylath (69) | R, PC | 76 (25 with diabetes) | CrCl ₃ (250 µg/day) | TG ↓, HDL cholesterol ↑ |
| Bahjiri et al. (66) | R, DB, PC, CO | 78 (type 2 diabetes) | CrCl ₃ (250 µg/day), brewer's yeast (23.3 µg/day Cr ³⁺) | TG ↓, HDL cholesterol ↑ |
| Lee and Reasner (70) | DB, PC, CO | 30 (type 2 diabetes) | CrP (200 µg/day) | TG ↓ |
| Anderson et al. (45) | R, PC | 180 (type 2 diabetes) | CrP (200 or 1,000 µg/day) | Total cholesterol ↓ |
| Ghosh et al. (22) | DB, PC, CO | 50 (type 2 diabetes) | Cr ₃ (200 µg/day) | No change |
| Chen S, Sun, and Chen X (67) | R | 188 (type 2 diabetes) | JKI | TG ↓ |
| Uusitupa et al. (52) | DB, PC, CO | 10 (type 2 diabetes) | Cr ₃ (200 µg/day) | No change |
| Rabinowitz et al. (32) | R, DB, PC, CO | 43 | Brewer's yeast | No change |
| Uusitupa et al. (30) | R, PC | 26 (all with IGT) | Brewer's yeast (160 µg/day Cr ³⁺) | No change |
| Offenbacher and Pi-Sunyer (74) | R | 24 (8 with type 2 diabetes) | Brewer's yeast | Total cholesterol ↓ |
| Evans (78) | DB | 11 (type 2 diabetes) | CrP (200 µg/day) | LDL cholesterol ↓, apoB ↓, HDL cholesterol ↑, apoA-I ↑ |
| Individuals without diabetes | | | | |
| Roebuck et al. (25) | R, DB, PC | 72 | GTF-Cr (600 µg/day) | HDL cholesterol ↑ |
| Riales and Albrink (79) | R, DB, PC | 23 | CrCl ₃ (200 µg/day) | HDL cholesterol ↑ |
| Press, Geller, and Evans (80) | DB, PC, CO | 28 | CrP (200 µg/day) | Total cholesterol ↓, LDL cholesterol ↓, apoB ↓, apoA-I ↑ |
| Preuss, Wallerstedt, and Talpur (81) | R, DB, PC | 40 | CrP (400 µg/day) | LDL cholesterol ↓ |
| Volpe et al. (73) | R, PC | 44 | CrP (400 µg/day) | No change |
| Wilson and Gandy (31) | R, DB, PC | 26 | CrN (220 µg/day) | No change |
| Amato, Morales, and Yen (56) | R, DB, PC | 19 | CrP (1,000 µg/day) | No change |
| Cefalu et al. (64) | R, DB, PC | 29 | CrP (1,000 µg/day) | Total cholesterol ↓ |

↑, increased; ↓, decreased; apo, apolipoprotein; CO, crossover; Cr₃, trivalent chromium; CrN, chromium nicotinate; DB, double blind; JKI, jianggangkang; PC, placebo controlled; R, randomized; TG, triglyceride.

in men. This relationship remained significant after adjusting for age, BMI, HDL cholesterol, diabetes, history of hypertension, and smoking.

SAFETY OF CHROMIUM — Most of the concerns regarding the long-term safety of chromium supplementation arise from results of several cell culture studies using supraphysiological doses that suggested that chromium, particularly in the form of CrP, may increase DNA damage. However, there is currently no evidence that chromium increases DNA damage in vivo. There have also been isolated reports (83) of serious adverse events, including kidney failure, associated with CrP treatment, but the relationship of chromium to these events is not clear. Recent reviews of the safety of CrP by the Institute of Medicine (84) and by Berner et al. (85) have concluded that CrP is safe. Results from controlled clinical trials (86) have shown that treatment with chromium at doses up to 1,000 µg/day and for periods as long as 64 months does not result in any toxic effects.

CONCLUSIONS — A large body of literature in both experimental animals and humans indicates that chromium is an essential element involved in the action of insulin as demonstrated in the studies of chromium deficiency. Although chromium deficiency has not been defined beyond that in patients receiving TPN, epidemiologic studies suggest that tissue levels of chromium are reduced among diabetic individuals, especially in those with existing CVD, compared with healthy control subjects. Two case-control studies have also found that lower toenail chromium levels predict risk of MI in apparently healthy subjects. However, further epidemiologic studies are needed to confirm these associations in different populations, and clinical trials are needed to prove the causal relationship.

A more important question, however, is the role of chromium supplementation outside of the rare deficiency states. It is still controversial whether chromium supplements should be recommended for glycemic control among diabetic patients. Growing evidence suggests that chromium supplementation, particularly at higher doses and in the form of CrP, may improve insulin sensitivity and glucose metabolism in patients with glucose intol-

erance and type 1, type 2, gestational, and steroid-induced diabetes and in some individuals without diabetes. However, it must be recognized that most clinical studies have major limitations including small size, short term, nonrandomized design, and different doses of chromium supplementation, which may explain the high variability of the findings across studies. Therefore, more clinical trials are needed in the U.S. population to examine the robustness of the results observed in other populations and appropriate doses. Ideally, these trials should assess effects of treatment on hard end points (e.g., type 2 diabetes and CVD) as well as metabolic parameters, although such trials would be costly and time consuming because they involve a large number of subjects and at least several years of follow-up. Results from such long-term trials would also assess the safety of long-term chromium supplementation.

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