Role of Chromium in Human Health and in Diabetes

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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 μg/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 μg/day, chromium absorption is ~0.4%, but the trivalent formulation also significantly influences bioavailability. At a dose of 1,000 μg/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

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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.

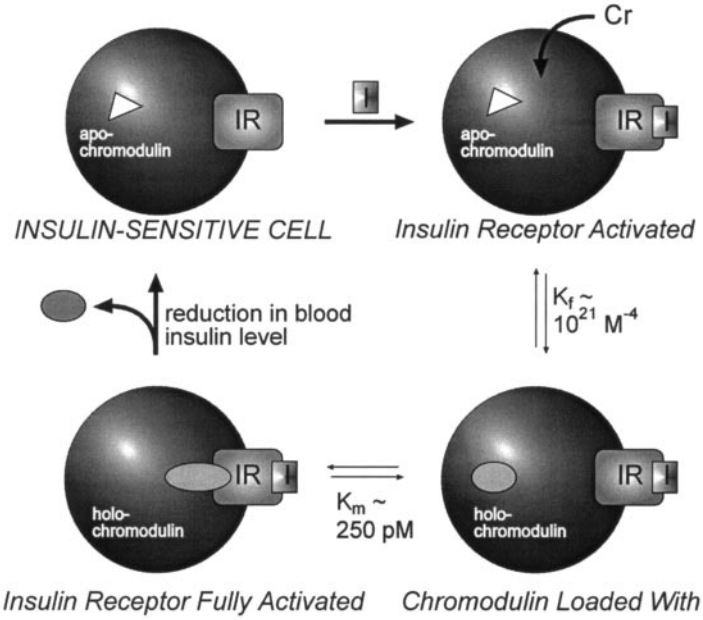

Figure 1—*Proposed mechanism of action for chromium and LMWCr potentiating the action of insulin (15).*

~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 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

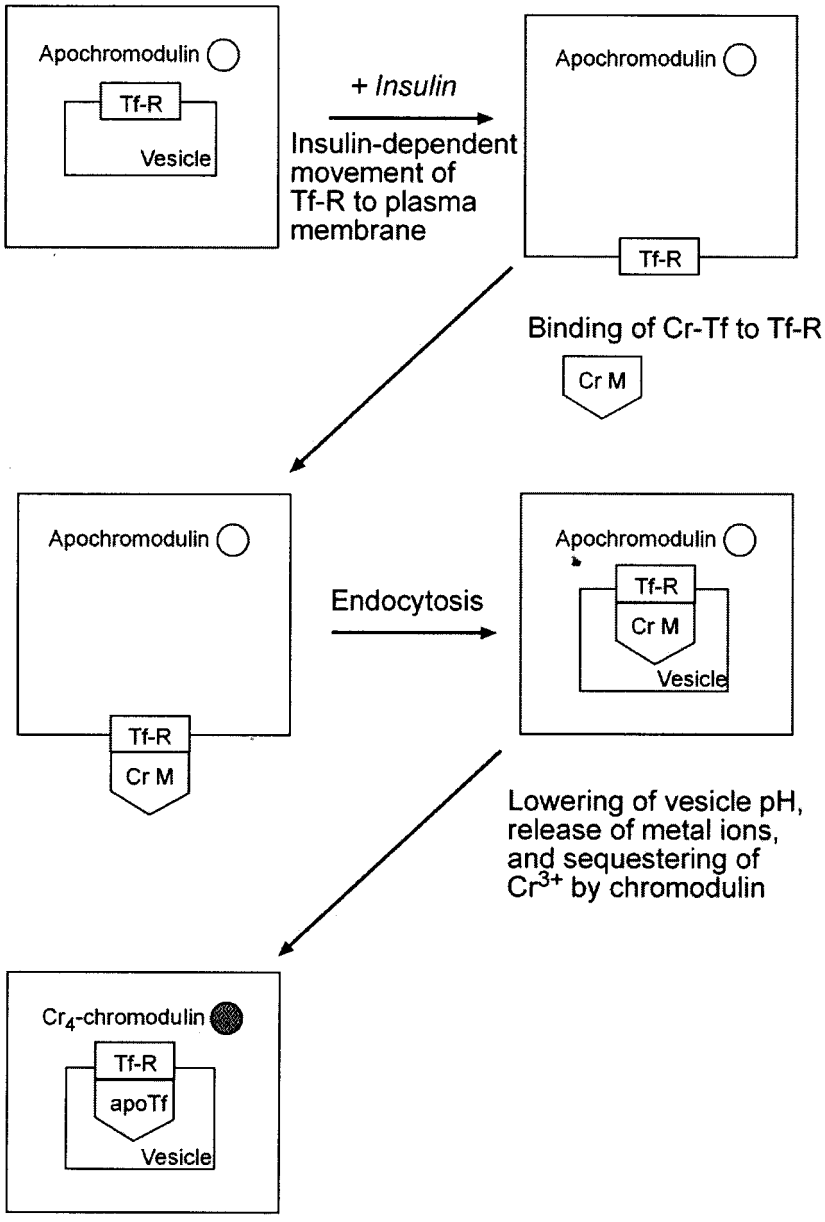

Figure 2—*Proposed mechanism for the movement of chromium from the blood to LMWCr (18). Cr, chromic ion; M, metal ion; Tf, transferrin; Tf-R, Tf receptor.*

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 determination 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, 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
Uusitupa et al. (30)	DB	6 months	Brewer's yeast (160 μg/day Cr^{3+})	IGT, elderly	26	OGTT	—	—	—	NA
Uusitupa 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
Glinsmann 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 Gondy (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 1000 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; CrCl, 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 μg/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 $\mu g \cdot kg^{-1} \cdot day^{-1}$ 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 μg/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 jiangtangkang (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, jiangtangkang 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 μg/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 μg/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 μg/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-

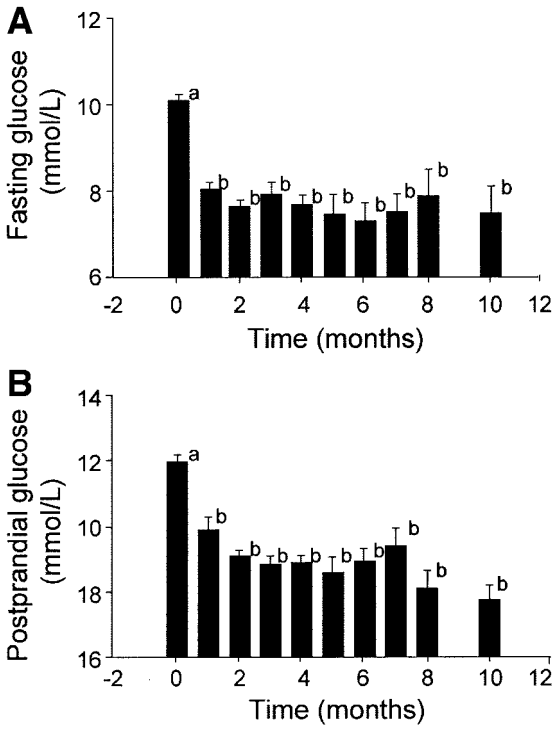

Figure 3—*Fasting* (A) *and postprandial* (B) *glucose decline over time in patients with type 2 diabetes treated for 10 months with 500 μg/day CrP (60). b, significantly different from baseline (a).*

mium supplementation (200 μg/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 μg/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 μg/day $CrCl_3$, Lee and Reasner (70) administered 200 μg/day CrP, and Uusitupa et al. (52) treated patients in their trial with 200 μg/day $CrCl_3$. 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 μg/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 μg/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 μg/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 ≥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 μg/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 Cr^{3+}-rich yeast (160 μg/day) in a group of 26 elderly subjects with impaired glucose tolerance and moderate obesity (BMI ~30 kg/m^2 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 μg/day CrP or placebo for 8 weeks indicated no

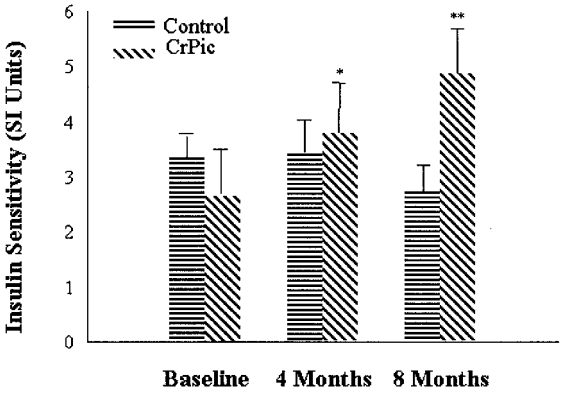

Figure 4—*Effects of chromium supplementation on insulin sensitivity in overweight subjects with a family history of diabetes treated for 8 months with 1,000 μg/day CrP (64). Data are means ± SD.* *P < *0.05,* **P < *0.005 versus baseline.*

significant effect of active treatment on insulin sensitivity. Another team (73) reported that administration of 400 μg/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 μg/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 ↑
Bahijri 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)	JKT	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				
Roeback 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 Gondy (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, Cr_3, trivalent chromium, CrN, chromium nicotinate, DB, double blind; JKT, jiangtangkang; 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.

References

1. Schwarz K, Mertz W: Chromium (III) and the glucose tolerance factor. *Arch Biochem Biophys* 85:292–295, 1959
2. Tuman RW, Doisy RJ: Metabolic effects of the glucose tolerance factor (GTF) in normal and genetically diabetic mice. *Diabetes* 26:820–826, 1977
3. Jeejeebhoy KN, Chu RC, Marliss EB, Greenberg GR, Bruce-Robertson A: Chromium deficiency, glucose intolerance, and neuropathy reversed by chromium supplementation, in a patient receiving long-term total parental nutrition. *Am J Clin Nutr* 30:531–538, 1977
4. Freund H, Atamian S, Fischer JE: Chromium deficiency during total parenteral nutrition. *JAMA* 241:496–498, 1979
5. Anderson RA: Chromium and parenteral nutrition. *Nutrition* 11:83–86, 1995
6. Kimura K: Role of essential trace elements in the disturbance of carbohydrate metabolism. *Nippon Rinsho* 54:79–84, 1996
7. Anderson RA: Nutritional factors influencing the glucose/insulin system: chromium. *J Am Coll Nutr* 16:404–410, 1997
8. Chromium [Internet]. Available from http://www.nums.nwu.edu/nutrition/factsheets/chromium.pdf. Accessed 17 September 2004
9. Chromium [Internet]. Available from http://www.nlm.nih.gov/medlineplus/ency/article/002418.htm. Accessed 17 September 2004
10. Expert Group on Vitamins and Minerals: Review of chromium [Internet], 2002. Available from www.foodstandards.gov.uk/multimedia/pdfs/reviewofchrome.pdf. Accessed 3 February 2004
11. RDA recommendations [Internet]. Available from http://lifestyler.com/lifestyler/rdachart.htm. Accessed 29 January 2004
12. Anderson RA: Chromium, glucose intolerance and diabetes. *J Am Coll Nutr* 17: 548–555, 1998
13. Anderson RA: Chromium as an essential nutrient: the chromium file [Internet]. Available from http://www.chromium-asoc.com/publications/crfile6sep99.htm. Accessed 30 January 2004
14. PDRhealth: Chromium [Internet]. Available from http://www.pdrhealth.com/drug_info/nmdrugprofiles/nutsupdrugs/chr_0073.shtml. Accessed 3 February 2004
15. Vincent JB: Elucidating a biological role for chromium at a molecular level. *Acc Chem Res* 33:503–510, 2000
16. Hepburn DD, Vincent JB: Tissue and subcellular distribution of chromium picolinate with time after entering the bloodstream. *J Inorg Biochem* 94:86–93, 2003
17. Clodfelder BJ, Emamaullee J, Hepburn DD, Chakov NE, Nettles HS, Vincent JB: The trail of chromium (III) in vivo from the blood to the urine: the roles of transferrin and chromodulin. *J Biol Inorg Chem* 6:608–617, 2001
18. Vincent JB: The biochemistry of chromium. *J Nutr* 130:715–718, 2000
19. Vincent JB: Mechanisms of chromium action: low-molecular-weight chromium-binding substance. *J Am Coll Nutr* 18:6–12, 1999
20. Davis CM, Sumrall KH, Vincent JB: A biologically active form of chromium may activate a membrane phosphotyrosine phosphatase (PTP). *Biochemistry* 35: 12963–12969, 1996
21. Potter JF, Levin P, Anderson RA, Freiberg JM, Andres R, Elahi D: Glucose metabolism in glucose-intolerant older people during chromium supplementation. *Metabolism* 34:199–204, 1985
22. Ghosh D, Bhattacharya B, Mukherjee B, Manna B, Sinha M, Chowdhury J, Showdhury S: Role of chromium supplementation in Indians with type 2 diabetes mellitus. *J Nutr Biochem* 13:690–697, 2002
23. Bahijri SM, Mufti AM: Beneficial effects of chromium in people with type 2 diabetes, and urinary chromium response to glucose load as a possible indicator of status. *Biol Trace Elem Res* 85:97–109, 2002
24. Anderson RA: Chromium as an essential nutrient for humans. *Reg Toxicol Pharmacol* 26:S35–S41,1997
25. Roeback JR Jr, Hla KM, Chambless LE, Fletcher RH: Effects of chromium supplementation on serum high-density lipoprotein cholesterol levels in men taking beta-blockers: a randomized, controlled trial. *Ann Intern Med* 115:917–924, 1991
26. Crawford V, Scheckenbach R, Preuss HG: Effects of niacin-bound chromium supplementation on body composition in overweight African-American women. *Diabetes Obes Metab* 1:331–337,1999
27. Campbell WW, Joseph LJ, Anderson RA, Davey SL, Hinton J, Evans WJ: Effects of resistive training and chromium picolinate on body composition and skeletal muscle size in older women. *Int J Sport Nutr Exerc Metab* 12:125–135, 2002
28. Lukaski HC, Bolonchuk WW, Siders WA, Milne DB: Chromium supplementation and resistance training: effects on body composition, strength, and trace element status of men. *Am J Clin Nutr* 63:954–965, 1996
29. Hallmark MA, Reynolds TH, DeSouza CA, Dotson CO, Anderson RA, Rogers MA: Effects of chromium and resistive training on muscle strength and body composition. *Med Sci Sports Exerc* 28:139–144, 1996
30. Uusitupa MI, Mykkanen L, Siitonen O, Laakso M, Sarlund H, Kolehmainen P, Rassanen T, Kumpulainen J, Pyorälä K: Chromium supplementation in impaired glucose tolerance of elderly: effects on blood glucose, plasma insulin, C-peptide and lipid levels. *Br J Nutr* 68:209–216, 1992
31. Wilson BE, Gondy A: Effects of chromium supplementation on fasting insulin levels and lipid parameters in healthy, non-obese young subjects. *Diabetes Res Clin Prac* 28:179–184, 1995
32. Rabinowitz MB, Gonick HC, Levin SR, Davidson MB: Effects of chromium and yeast supplements on carbohydrate and lipid metabolism in diabetic men. *Diabetes Care* 6:319–327, 1983
33. Althuis MD, Jordan NE, Ludington EA, Wittes JT: Glucose and insulin responses to dietary chromium supplements: a meta-analysis. *Am J Clin Nutr* 76:148–155, 2002
34. Pittler MH, Stevinson C, Ernst E: Chromium picolinate for reducing body weight: meta-analysis of randomized trials. *Int J Obes Relat Metab Disord* 27:522–529, 2003
35. Horlick L: Dyslipidemia and metabolic factors in the genesis of heart attack and stroke. *Health Rep* 6:94–99, 1994
36. Khamaisi M, Wexler ID, Skrha J, Strojek K, Raz I, Milicevic Z: Cardiovascular disease in type 2 diabetics: epidemiology, risk factors and therapeutic modalities. *Isr Med Assoc J* 5:801–806, 2003
37. Rimm EB, Guallar E, Giovannucci E, Ascherio A, Stampfer MJ, Willet WC, Hu F: Toenail chromium levels and risk of coronary heart disease among normal and overweight men. Presented at the *American Heart Association 42nd Annual*

Conference on Cardiovascular Disease, Epidemiology and Prevention, 23–26 April 2002, Honolulu, Hawaii
38. Rajpathak S, Rimm EB, Li T, Morris JS, Stampfer MJ, Willett WC, Hu FB: Lower toenail chromium in men with diabetes and cardiovascular disease compared with healthy men. *Diabetes Care* 27:2211–2216, 2004
39. Vaquero MP: Magnesium and trace elements in the elderly: intake, status and recommendations. *J Nutr Health Aging* 6:147–153, 2002
40. Anderson RA: Chromium metabolism and its role in disease processes in man. *Clin Physiol Biochem* 4:31–41, 1986
41. Leeds AR: Glycemic index and heart disease. *Am J Clin Nutr* 76:286S–289S, 2002
42. Ding W, Chai Z, Duan P, Feng W, Qian Q: Serum and urine chromium concentrations in elderly diabetics. *Biol Trace Elem Res* 63:231–237, 1998
43. Davies S, McLaren Howard J, Hunnisett A, Howard M: Age-related decreases in chromium levels in 51,665 hair, sweat, and serum samples from 40,872 patients: implications for the prevention of cardiovascular disease and type II diabetes mellitus. *Metabolism* 46:469–473, 1997
44. Anderson RA, Kozlovsky AS: Chromium intake, absorption and excretion of subjects consuming self-selected diets. *Am J Clin Nutr* 41:1177–1183, 1985
45. Anderson RA, Cheng N, Bryden NA, Polansky MM, Cheng N, Chi J, Feng J: Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes. *Diabetes* 46:1786–1791, 1997
46. Morris BW, MacNeil S, Hardisty CA, Heller S, Burgin C, Gray TA: Chromium homeostasis in patients with type II (NIDDM) diabetes. *J Trace Elem Med Biol* 13:57–61, 1999
47. Ekmekcioglu C, Prohaska C, Pomazal K, Steffan I, Schernthaner G, Marktl W: Concentrations of seven trace elements in different hematological matrices in patients with type 2 diabetes as compared to healthy controls. *Biol Trace Elem Res* 79: 205–219, 2001
48. Zima T, Mestek O, Tesar V, Tesarova P, Nemecek K, Zak A, Zeman M: Chromium levels in patients with internal diseases. *Biochem Mol Biol Int* 46:365–374, 1998
49. American Diabetes Association: Nutrition principles and recommendations in diabetes (Position Statement). *Diabetes* Care 27 (Suppl. 1):S36–S46, 2004
50. Trow LG, Lewis J, Greenwood RH, Sampson MJ, Self KA, Crews HM, Fairweather-Tait SJ: Lack of effect of dietary chromium supplementation on glucose tolerance, plasma insulin and lipoprotein levels in patients with type 2 diabetes. *Int J Vitam Nutr Res* 70:14–18, 2000
51. Sherman L, Glennon JA, Brech WJ, Klomberg GH, Gordon ES: Failure of trivalent chromium to improve hyperglycemia in diabetes mellitus. *Metabolism* 17: 439–442, 1968
52. Uusitupa MI, Kumpulainen JT, Voutilainen E, Hersio K, Sarlund H, Pyorala KP, Koivistoinen PE, Lehto JT: Effect of inorganic chromium supplementation on glucose tolerance, insulin response, and serum lipids in noninsulin-dependent diabetics. *Am J Clin Nutr* 38:404–410, 1983
53. Mossop RT: Effects of chromium (III) on fasting glucose, cholesterol and cholesterol HDL levels in diabetics. *Cent Afr J Med* 29:80–82, 1983
54. Nath R, Minocha J, Lyall V, Sunder S, Kumar V, Kapoor S, Dhar KL: Assessment of chromium metabolism in maturity onset and juvenile diabetes using chromium 51 and therapeutic response of chromium administration on plasma lipids, glucose tolerance and insulin levels. In *Chromium in Nutrition and Metabolism*. Shapcott D, Hubert J, Eds. Amsterdam, Elsevier/ North Holland, 1979, p 213–222
55. Glinsman WH, Mertz W: Effect of trivalent chromium on glucose tolerance. *Metabolism* 15:510–520, 1966
56. Amato P, Morales AJ , Yen SS: Effects of chromium picolinate supplementation on insulin sensitivity, serum lipids, and body composition in healthy, nonobese, older men and women. *J Gerontol A Biol Sci Med Sci* 55:M260–M263, 2000
57. Jovanovic L, Gutierrez M, Peterson CM: Chromium supplementation for women with gestational diabetes mellitus. *J Trace Elem Exp Med* 12:91–97, 1999
58. Ravina A, Slezak L, Mirsky N, Bryden NA, Anderson RA: Reversal of corticosteroid-induced diabetes mellitus with supplemental chromium. *Diabet Med* 16:164–167, 1999
59. Morris BW, Kouta S, Robinson R, MacNeil S, Heller S: Chromium supplementation improves insulin resistance in patients with type 2 diabetes mellitus. *Diabet Med* 17:684–685, 2000
60. Cheng N, Zhu X, Shi H, Wu W, Chi J, Cheng J, Anderson R: Follow-up survey of people in China with type 2 diabetes mellitus consuming supplemental chromium. *J Trace Elem Exp Med* 12:55–60, 1999
61. Rossetti L, Giaccari A, DeFronzo RA: Glucose toxicity. *Diabetes Care* 13:610–630, 1990
62. Inzucchi SE, Maggs DG, Spollett GR, Page SL, Rife FS, Walton V, Shulman GI: Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. *N Engl J Med* 338:867–872, 1998
63. Cefalu WT, Bell-Farrow AD, Wang ZQ, McBride D, Dalgleish D, Terry JG: Effect of glipizide GITS on insulin sensitivity, glycemic indices, and abdominal fat composition in NIDDM. *Drug Dev Res* 44:1–7, 1998
64. Cefalu WT, Bell-Farrow AD, Stegner J, Wang ZQ, King T, Morgan T, Terry JG: Effect of chromium picolinate on insulin sensitivity in vivo. *J Trace Elem Exp Med* 12:71–83, 1999
65. Morris BW, MacNeil S, Stanley K, Gray TA, Fraser R: The inter-relationship between insulin and chromium in hyperinsulinaemic euglycaemic clamps in healthy volunteers. *J Endocrinol* 139:339–345, 1993
66. Bahijri SM, Mira SA, Mufti AM, Ajabnoor MA: The effects of inorganic chromium and brewer's yeast supplementation on glucose tolerance, serum lipids and drug dosage in individuals with type 2 diabetes. *Saudi Med J* 21:831–837, 2000
67. Chen SH, Sun YP, Chen XS: Effect of jiangtangkang on blood glucose, sensitivity of insulin and blood viscosity in non-insulin dependent diabetes mellitus [in Chinese]. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 17:666–668, 1997
68. Ravina A, Slezak L, Rubal A, Mirsky N: Clinical use of the trace element chromium (III) in the treatment of diabetes mellitus. *J Trace Elem Exp Med* 8: 183–190, 1995
69. Abraham AS, Brooks BA, Eylath U: The effects of chromium supplementation on serum glucose and lipids in patients with and without non-insulin-dependent diabetes. *Metabolism* 41:768–771, 1992
70. Lee NA, Reasner CA: Beneficial effect of chromium supplementation on serum triglyceride levels in NIDDM. *Diabetes Care* 17:1449–1452, 1994
71. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285: 2486–2497, 2001
72. Kendall DM, Harmel AP: The metabolic syndrome, type 2 diabetes, and cardiovascular disease: understanding the role of insulin resistance. *Am J Manag Care* 8:S635–S653, 2002
73. Volpe SL, Huang HW, Larpadisorn K, Lesser II: Effect of chromium supplementation and exercise on body composition, resting metabolic rate and selected biochemical parameters in moderately obese women following an exercise program. *J Am Coll Nutr* 20:293–306, 2001
74. Offenbacher EG, Pi-Sunyer FX: Beneficial effect of chromium-rich yeast on glucose tolerance and blood lipids in elderly subjects. *Diabetes* 29:919–925, 1980
75. Sowers JR: Obesity as a cardiovascular

risk factor. *Am J Med* 115:37S–41S, 2003
76. Kaats GR, Blum K, Fisher JA, Adelman JA: Effects of chromium picolinate supplementation on body composition: a randomized, double-masked placebo-controlled study. *Cur Ther Res* 57:747–756, 1996
77. Kaats GR, Blum K, Pullin D, Keith SC, Woods R: A randomized, double-masked, placebo-controlled study of the effects of chromium picolinate supplementation on body composition: a replication and extension of a previous study. *Curr Ther Res* 59:379–388, 1998
78. Evans GW: The effect of chromium picolinate on insulin controlled parameters in humans. *Int J Biosoc Med Res* 11:163–180, 1989
79. Riales R, Albrink MJ: Effect of chromium chloride supplementation on glucose tolerance and serum lipids including high-density lipoprotein of adult men. *Am J Clin Nutr* 34:2670–2678, 1981
80. Press RI, Geller J, Evans GW: The effect of chromium picolinate on serum cholesterol and apolipoprotein fractions in human subjects. *West J Med* 152:41–45, 1990
81. Preuss HG, Wallerstedt D, Talpur N: Effects of niacin-bound chromium and grape seed proanthocyanidin extract on the lipid profile of hypercholesterolemic subjects: a pilot study. *J Med* 31:227–246, 2000
82. Guallar E: Toenail chromium status and cardiovascular disease risk in Europe. Presented at *Chromium in Health and Disease, a CADRE Research Summit, 1–2 April 2003, Boston, Massachusetts*
83. Wasser WG, Feldman NS, D'Agati VD: Chronic renal failure after ingestion of over-the-counter chromium picolinate (Letter). *Ann Intern Med* 126:410, 1997
84. Institute of Medicine (IOM): Chromium picolinate: prototype monograph. In *Dietary Supplements: A Framework for Evaluating Safety*. Washington, DC, Institute of Medicine, 2004, p. B1–B80
85. Berner TO, Murphy MM, Slesinski R: Determining the safety of chromium tripicolinate for addition to foods as a nutrient supplement. *Food Chem Toxicol* 42:1029–1042, 2004
86. Jeejeebhoy KN: The role of chromium in nutrition and therapeutics and as a potential toxin. *Nutr Rev* 57:329–335, 1999