Chromium supplements, glucose, and insulin responses

Dear Sir:

The article by Althuis et al (1) in a recent issue of the Journal raises some interesting questions about the importance of chromium supplementation in persons with and without diabetes. The authors summarized data from 14 selected clinical trials evaluating different forms of chromium in healthy adults (13 studies), subjects with impaired glucose tolerance (2 studies), and subjects with type 2 diabetes (3 studies). No studies evaluating the benefits of chromium picolinate in persons with diabetes were included in the analysis. The omission of these clinical trials (2–10), involving 1349 subjects, precludes any conclusions about the benefits of chromium picolinate in persons with type 2 diabetes. In addition, the studies that were included in the analysis used poorly absorbed forms of chromium (chromium chloride, chromium yeast) or niacin-bound chromium (niacin is known to cause insulin resistance).

The authors omitted data from a study by Anderson et al (9) (n = 155) that showed significant reductions in glycated hemoglobin after chromium picolinate administration, because the study might represent a chromium-deficient population in China. However, there are no supporting data showing that this population is more chromium deficient than are the subjects included in the analysis. Data showing glucose and insulin concentrations significantly lower than those in the study by Jovanovic et al (6) (n = 20) were also mentioned but not included in the analysis. The published data from 6 other well-controlled trials using chromium picolinate in populations with type 2 diabetes (3, 5, 6, 9–11) were not included in the analysis. The authors summarized data from 14 selected clinical trials evaluating different forms of chromium in healthy adults (13 studies), subjects with impaired glucose tolerance (2 studies), and subjects with type 2 diabetes (3 studies). No studies evaluating the benefits of chromium picolinate in persons with diabetes were included in the analysis. The omission of these clinical trials (2–10), involving 1349 subjects, precludes any conclusions about the benefits of chromium picolinate in persons with type 2 diabetes. In addition, the studies that were included in the analysis used poorly absorbed forms of chromium (chromium chloride, chromium yeast) or niacin-bound chromium (niacin is known to cause insulin resistance).

The authors reported no findings of safety issues (daily doses of 10.8–1000 µg Cr) in populations with or without diabetes. These findings are consistent with the lack of adverse effects, including hypoglycemia, found by other researchers and with the fact that no upper limit has been established for chromium.

We strongly agree that additional US studies would be beneficial, especially among African Americans, because the prevalence of diabetes in that population is increasing at an alarming rate. We strongly agree with the conclusions of the authors that if dietary chromium supplementation is efficacious, it will be a great option for the treatment of persons at high risk of insulin resistance or diabetes.

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Dear Sir:

The meta-analysis of Althuis et al (1) examining the effect of supplemental chromium on insulin, glucose, and glycated hemoglobin in controlled studies may be viewed as cogent evidence that functionally significant dietary chromium deficiency is uncommon in the United States. Most of the cited studies used doses of ≥200 μg Cr/d, which is roughly 7 times the average chromium intake of healthy Americans; one would certainly think that such a dose, consumed over several months, would be sufficient to correct a baseline dietary deficiency, and yet the results of most chromium supplementation studies have been paltry, at best.

However, an overview of the data is quite consistent with the possibility that high doses of well-assimilated organic forms of chromium may indeed have clinical utility in selected populations. In a study by Anderson et al (2) in which Chinese subjects with diabetes were supplemented with ≤1000 μg Cr (as chromium picolinate)/d—the largest controlled study yet done with supplemental chromium, but omitted from the meta-analysis because it introduced heterogeneity into the data—glycated hemoglobin fell significantly, by an average of 30%, in those receiving the 1000-μg dose, and the reductions in fasting and postprandial glucose in that group were nearly as large. The fact that the response in the group receiving the 200-μg dose for 4 mo was equivocal, with no significant improvement in either fasting or postprandial glucose relative to the control subjects, strongly suggests that correction of a baseline dietary chromium deficiency was not responsible for the marked improvement in the 1000-μg dose group, and indeed there is no evidence that chromium nutrition is poorer in China than in the United States. (Whether some other reason—eg, genetics, body size, or diet macronutrient profile—might predispose Chinese diabetics to be more responsive to chromium than are their American counterparts remains to be seen.)

Using the same dose and form of chromium in middle-aged overweight US subjects who had first-degree relatives with diabetes, Cefalu et al (3) reported a significant increase of nearly 50% in insulin sensitivity, quantified by the minimal model method, during 4–8 mo of supplementation. Concurrent reductions of 20–25% in fasting and postprandial insulin were not statistically significant, possibly because of the small number of subjects (n = 15). Two other, somewhat shorter, controlled studies of older American subjects failed to observe an effect on insulin metabolism of 1000 μg Cr as chromium picolinate (4, 5).

The available data are thus consistent with the possibility that supranutritional doses of well-assimilated forms of chromium may indeed have useful efficacy in at least some target populations. This view is buttressed by several recent rat studies in which chromium picolinate had substantial metabolic effects (6–8); the control rats in these studies were fed normal (not chromium-depleted) diets, so it cannot be maintained that the observed responses reflected correction of dietary deficiency. It might be added that the chromium doses used in these studies, if corrected for relative body surface area, would be larger than the largest dose used in the Chinese clinical study. A supraphysiologic concentration of chromium picolinate (1 μmol/L) likewise can influence cellular function in vitro (9, 10).

The efficacy of supplemental chromium may prove to be analogous to that of vitamin E. In subjects who are not overtly vitamin E deficient, a nutritional dose of this vitamin will have no discernible effect on the oxidizability of LDL, whereas a megadose (eg, 800 IU) may have a substantial effect. The all-too-common presumption that nutrients can do nothing more than correct deficiency states is clearly wrong. The rodent and tissue culture studies cited above suggest that the physiologic effect of chromium is not always maximized at ordinary tissue concentrations; because we still do not know how chromium functions at the level of molecular biology, there are no firm grounds for assuming otherwise. In light of the fact that oral trivalent chromium has been proven to be safe in animals at any dose tested, future clinical studies with chromium should evaluate a range of daily doses of ≥1 mg, while attempting to identify those groups most apt to respond to high-dose chromium.

Note that my remarks pertain to dietary chromium deficiency. It is an open possibility that tissue deficiencies of chromium, attributable to metabolic perturbations that disrupt chromium transport, may be a contributory factor in various disorders. However, there is no reason to assume that ordinary dietary intakes of chromium could correct such tissue deficiencies.

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LETTERS TO THE EDITOR

Chromium picolinate and type 2 diabetes

Dear Sir:

The article by Althuis et al (1) in a recent issue of the Journal appears to be an imbalanced review of the publications to date regarding the potential benefit of chromium picolinate in persons with type 2 diabetes. Among the current published works, there are at least 9 noteworthy reports of clinical trials that show the relative efficacy of chromium picolinate (2–10). These studies concentrated on the effects of chromium picolinate on markers of blood glucose or on insulin regulation in subjects with type 2 diabetes or in persons with induced diabetes. The major fault in the conclusions of Althuis et al is that no studies of persons with diabetes were included in their final analysis.

In reading the 9 reports, it is easy to see that 1349 total subjects were studied over the past 10 y. With such a large number of subjects having participated in single- and double-blind trials, the findings are consistent: chromium picolinate has a positive effect on fasting insulin values and on hemoglobin A1C. The data also indicate that, when used with standard treatments, chromium picolinate improves clinical results (eg, those for biguanides, sulfonylureas, or metformin alone) (10). Additional benefits have been found with chromium picolinate supplementation for coronary disease risk profiles [ie, lipids and lipoprotein(a)] that are important in the diabetic and nondiabetic communities. It is agreed that the dose for clinical benefit has not been universal, ranging from 200 to 1000 μg, but this only shows that “one size does not fit all,” and thus a dose that is dependent on body surface area is indicated.

In any event, with the relative safety and inexpensiveness of chromium picolinate, there seems to be no reason for it not to be used in people who have poor blood sugar control or insulin resistance syndrome (11, 12). The benefit-to-risk ratio favors benefit. Continued research on the positive effects of chromium picolinate on biomarkers of blood sugar regulation is needed to expand the body of evidence for its utility as an adjunctive treatment of conditions that affect blood glucose. In addition, because the current data imply that some people respond better to chromium picolinate than do others (nonresponders), it may be that a test to identify the best candidates for treatment with chromium picolinate is indicated. However, we as scientists and clinicians cannot dismiss the current body of work that indicates the efficacy of this mineral, nor should we dismiss consumer sup-

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Reply to DS Kalman, MF McCarty, and V Juturu and JR Komorowski

Dear Sir:

We thank the authors of the letters for their comments on our article. Our review and meta-analysis summarized randomized clinical trials (RCTs) designed to assess glucose and insulin responses to dietary chromium supplements (1). We limited our review to RCTs to avoid the potential for bias inherent in nonrandomized studies. We attempted to include every RCT in the literature.

The letters by Kalman and by Juturu and Komorowski cite several studies they say our review omitted (2–11). Our review in fact included 4 of these studies (2–5); the other 6 studies they mentioned (6–11) were not RCTs and therefore were not eligible for inclusion. Specifically, 1 of the 4 RCTs cited as being omitted was both discussed in the review and combined analytically in the meta-analysis (3). In addition, we discussed in detail the findings from the other 3 RCTs although they were not included in the meta-analysis (2, 4, 5, 10). One of these RCTs (4) was excluded from the meta-analysis because the study population—women with gestational diabetes—was not a focus of our review; one of the others was excluded simply because data presented in the original report were insufficient for abstraction, and updated data were not available from the investigators (5).
The authors of all 3 letters express concern that we did not analytically combine the study by Anderson et al (2) in the meta-analysis. First, the Chinese population described by Anderson et al was very different from the populations of the other trials, such that its inclusion would lead to violation of the statistical assumption of heterogeneity in models pooling all 4 studies. Second, because the odds ratio estimated by meta-analytic techniques is weighted more heavily for large studies, pooling the data from Anderson et al (n = 155) with the data for the 38 subjects from the other 3 studies would overwhelm the results, making the effects of the smaller studies—ie, studies from populations more similar to that of the United States—difficult if not impossible to assess. Thus, we believe that separating the presentation of the results of the Western studies from that of the results of the one non-Western study better facilitates critical review.

The remaining 6 studies cited as being omitted were not RCTs, but rather uncontrolled investigations (6–11). In addition to an uncontrolled study, one report described a small controlled clinical trial that assessed 10 subjects who were not randomly assigned to receive treatment or placebo (11). Although the data were not presented in the report, those authors reported no difference between the placebo and chromium groups (11).

McCarty is correct that the studies we reviewed did not address the use of high doses of chromium. He points out that data from uncontrolled and animal studies suggest that chromium may be valuable as a dietary supplement or in pharmaceutical doses. Nonetheless, before making recommendations for use by the general public, we urge that investigators test dietary chromium supplements, particularly those with high doses, in a well-designed RCT. The limited data from RCTs on dietary chromium supplementation have yet to prove that it is either efficacious or safe for healthy persons or for those with type 2 diabetes.

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Relation between physical activity and obesity
Dear Sir:

It was with great interest that we read the recent publication by Ekelund et al (1) on reduced physical activity in obese 18-y-old adolescents. In this carefully designed study, the authors measured physical activity by using the doubly labeled water method in conjunction with accelerometry. They discerned that obese adolescents are less physically active than are matched control subjects, despite no significant differences in the energy cost of physical activity between the groups. In addition, the physical activity level (PAL) was lower in the obese group than in the control group, and there was a negative relation between PAL and percentage body fat in the cohort. As the authors point out, many contradictory results in the literature show positive, negative, or no relations between physical activity and adiposity, including our own results, which showed no relation between activity and adiposity in 5-y-old Pima Indians (2). Ekelund et al also note that in cross-sectional studies such as their own, it is not possible to discern whether an inactive lifestyle causes obesity or whether obesity causes an inactive lifestyle.

We recently published a follow-up study of the same Pima Indian cohort, in whom metabolic measurements were made at 5 and 10 y of age, which may cast some light on this relation (3). At 5 y of age, there was little relation between PAL and adiposity (percentage body fat by dual-energy X-ray absorptiometry: \( r = -0.05, P = 0.55 \)); however, at 10 y of age this relation was significant and negative (\( r = -0.28, P = 0.05 \)). In keeping with this, 5-y-old children who were “overweight” [by National Center for Health Statistics criteria: body mass index (BMI) \( \geq 95 \)th percentile] or “at risk of overweight” (95th > BMI \( \geq 85 \)th percentile) showed a very modest rise in PAL over time, whereas in children at low risk (BMI < 85th percentile), PAL increased by 70% over baseline by age 10 y. PAL at age 5 y, which tracked only modestly to age 10 \( y (r = 0.34, P = 0.008) \), was not an independent predictor of weight gain by 10 y of age.

Our study illustrates many points. First, our results show that PAL, at least at age 5 y, is not an important correlate of adiposity.
or a predictor of future weight gain. This suggests that food intake may be the critical determinant of excess weight gain at these early ages. Second, our data show that even in the same cohort, the relation of adiposity with PAL varies with age. This may help to explain some of the discrepancies in the literature, eg, that PAL is generally negatively related to adiposity in older children and adults and positively related to adiposity in younger children.

Hypothetically, this may in turn reflect an increased role of physical activity in the etiology of obesity in older children. Although the negative relation between PAL and adiposity at 10 y of age in our study and in adolescents (r = −0.53, P = 0.0001) in the study by Ekelund et al may in part reflect developing social consequences of overweight at older ages (obesity causing lifestyle change), it is hard to escape the conclusion that the lack of increase in PAL in heavier children by age 10 y compared with their leaner peers is at least exacerbating their weight gain (lifestyle causing obesity). Further prospective assessment of these cohorts should help to determine whether PAL predicts weight gain in early adolescence and adult life, as suggested by Ekelund et al.

We appreciate the comments of Salbe et al on our recently published paper (1). We agree with Salbe et al that further assessments of their and our own cohorts and other well-designed longitudinal studies are needed to shed light on the issue of whether physical activity is a predictor of weight gain or whether obesity causes a sedentary lifestyle in children, adolescents, and young adults. In fact, it was recently suggested that physical inactivity did not predict later obesity, whereas, on the other hand, the degree of obesity predicted later inactivity in adults (7). However, to determine the effect of various aspects of physical activity, including sedentary behavior, on future weight gain, sophisticated energy expenditure and body-movement assessment methods are needed, especially when examining this relation in young people.

From a public health perspective, more research is required to better understand the minimal amount of physical activity needed to prevent weight gain as well as the complex interaction between genetic and environmental factors in the development of obesity during various stages of life. An enhanced understanding of these issues can only be achieved by combining accurate methods for assessing physical activity and energy expenditure. We therefore suggest that future research combines measures of energy expenditure and objective body-movement assessment techniques to unravel which dimensions of physical activity may predict obesity and its related disorders.

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