Elevated Intakes of Supplemental Chromium Improve Glucose and Insulin Variables in Individuals With Type 2 Diabetes

Richard A. Anderson, Nanzheng Cheng, Noella A. Bryden, Marilyn M. Polansky, Nanping Cheng, Jiaming Chi, and Jinguang Feng

Chromium is an essential nutrient involved in normal carbohydrate and lipid metabolism. The chromium requirement is postulated to increase with increased glucose intolerance and diabetes. The objective of this study was to test the hypothesis that the elevated intake of supplemental chromium is involved in the control of type 2 diabetes. Individuals being treated for type 2 diabetes (180 men and women) were divided randomly into three groups and supplemented with: *1*) placebo, *2*) 1.92 μmol (100 μg) Cr as chromium picolinate two times per day, or *3*) 9.6 μmol (500 μg) Cr two times per day. Subjects continued to take their normal medications and were instructed not to change their normal eating and living habits. HbA_{1c} values improved significantly after 2 months in the group receiving 19.2 μmol (1,000 μg) Cr per day and was lower in both chromium groups after 4 months (placebo, 8.5 ± 0.2%; 3.85 μmol Cr, 7.5 ± 0.2%; 19.2 μmol Cr, 6.6 ± 0.1%). Fasting glucose was lower in the 19.2-μmol group after 2 and 4 months (4-month values: placebo, 8.8 ± 0.3 mmol/l; 19.2 μmol Cr, 7.1 ± 0.2 mmol/l). Two-hour glucose values were also significantly lower for the subjects consuming 19.2 μmol supplemental Cr after both 2 and 4 months (4-month values: placebo, 12.3 ± 0.4 mmol/l; 19.2 μmol Cr, 10.5 ± 0.2 mmol/l). Fasting and 2-h insulin values decreased significantly in both groups receiving supplemental chromium after 2 and 4 months. Plasma total cholesterol also decreased after 4 months in the subjects receiving 19.2 μmol/day Cr. These data demonstrate that supplemental chromium had significant beneficial effects on HbA_{1c}, glucose, insulin, and cholesterol variables in subjects with type 2 diabetes. The beneficial effects of chromium in individuals with diabetes were observed at levels higher than the upper limit of the Estimated Safe and Adequate Daily Dietary Intake. *Diabetes* 46:1786–1791, 1997

From the Beltsville Human Nutrition Research Center (R.A.A., N.A.B., M.M.P.), U.S. Department of Agriculture, Beltsville, Maryland; Beijing Hospital, Beijing Medical University, and the General Hospital of Armed Police Force (Nanz.C., Nanp.C., J.C., J.F.), Beijing, China.

Address correspondence and reprint requests to Dr. Richard A. Anderson, USDA, ARS, BHNRC, NRFL, Bldg. 307, Rm. 224, BARC-East, Beltsville, MD 20705-2350. E-mail: anderson@307.bhnrc.usda.gov.

Received for publication 3 March 1997 and accepted in revised form 8 July 1997.

Mention of trade name, proprietary product, or vendor does not constitute a warranty of the product by the U.S. Department of Agriculture or imply its approval to the exclusion of other products or vendors that may also be suitable.

Conclusive evidence of the role of trivalent chromium in human nutrition was reported in 1977 (1) when the severe diabetic symptoms of a female patient on total parenteral nutrition were alleviated by supplemental chromium. Diabetic symptoms, in addition to elevated blood glucose, included unexpected weight loss, impaired nerve conduction, and abnormal respiratory quotient that were refractory to exogenous insulin. Upon the daily addition of 4.81 μmol supplemental Cr to her total parenteral nutrition solution for 2 weeks, the diabetic symptoms were alleviated and the exogenous insulin requirement dropped from 45 U/day to zero. This work has been verified on many occasions and documented in the scientific literature on three occasions (2–4). Chromium is now routinely added to total parenteral nutrition solutions (5). However, the chromium concentrations in total parenteral nutrition solutions may not be adequate, since the normalization of nerve conduction occurred in a patient on home parenteral nutrition after the administration of supplemental chromium (6).

Signs of chromium deficiency in humans are not limited to subjects on total parenteral nutrition. Improvements in glucose and/or lipid concentrations have been reported in children with protein calorie malnutrition (7,8); the elderly (9); and individuals with type 1 and type 2 diabetes (10–13), hypoglycemia (14,15), and marginally impaired glucose tolerance (16,17).

Individuals with diabetes have altered chromium metabolism, compared with nondiabetic control subjects, with higher chromium absorption but also greater chromium excretion (18). Hair and tissue chromium levels of individuals with diabetes are lower than those of nondiabetic control subjects. Depending on the stage of diabetes, individuals with diabetes tend to lose the ability to convert chromium to a useable form (18). Diabetic mice also lose the ability to convert inorganic chromium to a useable form that potentiates insulin (19).

We conducted a double-blind placebo-controlled study involving 180 people with type 2 diabetes to determine the role of supplemental chromium in the control of diabetes. Our hypothesis was that the elevated intake of supplemental chromium is involved in the control of type 2 diabetes. The study was conducted in China to obtain a relatively homogeneous study group free of nutrient supplementation.

RESEARCH DESIGN AND METHODS

Subjects. A total of 303 individuals being treated for diabetes at two hospitals in Beijing, China, were screened to obtain 180 subjects meeting the selection criteria. To be eligible for the study, subjects had to be free of disease other than type

2 diabetes and 35–65 years of age and have a fasting blood glucose concentration of 7.2–15.5 mmol/l, a 2-h blood glucose concentration of 9.4–16.7 mmol/l, and an HbA_{1c} level of 8.0–12.0%. Subjects were informed of the purpose of the study, that there were no known risks associated with the study other than the minimal risks associated with blood drawing, and that they were free to drop out of the study with no effect on their present health care. Subjects were not reimbursed for their participation. Subjects were motivated to participate because of the possible benefits of the study. Compliance appeared to be very good and was assessed by personal communication and pill count. The study was approved by the Beijing Medical Review Committee with concurrence from the U.S. Department of Agriculture Human Studies Review Board.

A total of 180 individuals with diabetes were randomly divided into three groups. Sixty subjects received placebo, 60 received 1.92 μmol Cr as chromium picolinate (furnished by Nutrition 21, San Diego, CA) 2 times per day, and the remainder received 9.6 μmol Cr as chromium picolinate twice per day. Subjects were instructed to take one tablet in the morning and one in the evening between meals. Subjects were also urged to maintain their normal eating and exercise habits. Subjects continued their normal visits to monitor their diabetes. A fasting blood sample and a blood sample after a 2-h glucose challenge (75 g glucose) were obtained at the beginning of the study and after 2 and 4 months. Subjects were middle-aged healthy subjects of normal height, weight, and BMI with diabetes for <10 years (Table 1). Nineteen subjects did not complete all three testing dates, and six subjects had missing values for at least one variable; their results were not included in the final analyses. Data from these subjects were omitted to maintain a complete homogeneous data set with all subjects represented during each study period. Data for all subjects who completed all phases of the study were included in all of the respective analyses, and there were no samples omitted. Of the 155 subjects who were included in the final analyses, most of the subjects (92) were taking sulfonylurea drugs (i.e., glibenclamide, glinclazid, glipizide). Sixty-nine were on phenformin, 38 were on traditional Chinese medicines, 22 were on no medication, and nine were on insulin. Several subjects were taking more than one medication. Medications were constant during the study.

Study design was double blind and placebo controlled. Placebo tablets were indistinguishable from those containing either level of chromium. Measured chromium content of the placebo capsules was 0.01 ± 0.001 μmol and was 2.04 ± 0.16 and 11.0 ± 1.2 μmol for the 1.92- and 9.6-μmol capsules, respectively. Data are means ± SD for six capsules from each batch. A crossover study design was discarded because of the possible carryover effects of 1,000 μg Cr/day.

Glucose was analyzed by glucose oxidase method (20), and insulin was analyzed by radioimmunoassay (21). HbA_{1c} values were measured using BioRad HbA_{1c} columns (BioRad, Richmond, CA). Total cholesterol was determined by chemical hydrolysis (22), HDL cholesterol by phosphotungstate-Mg precipitation (23), and triglycerides by direct enzymic measurement (24). Blood urea nitrogen was determined by a direct method (25). Analyses presented were completed in China. Several dozen samples were exchanged between the U.S. and China laboratories to ensure accuracy and reproducibility of the data.

The variables HbA_{1c}, total cholesterol, blood urea nitrogen, HDL cholesterol, triglycerides, fasting and 2-h glucose, and insulin were analyzed as three-factor repeated-measures mixed linear models, using PROC MIXED (SAS Institute, Cary, NC). Since the variables were measured at 0, 2, and 4 months for each subject, repeated measures analyses were used. Several covariance structures were modeled, and the unstructured model was found to fit best, except for triglycerides and total cholesterol, where the compound symmetry model was best. For HbA_{1c}, cholesterol, and triglycerides, the $\log_{10}$ transformed values fit the model better and were used in the analyses. Data in the table and figures are means ± SE for the nontransformed data.

RESULTS

Fasting blood glucose concentrations were significantly lower in the group receiving 19.2 μmol Cr daily after both 2 and 4 months (Fig. 1). Similar results were observed for blood glucose concentrations 2 h after the ingestion of 75 g glucose (Fig. 2). Fasting and 2-h glucose concentrations of the subjects in the placebo group also decreased, but the decreases in the subjects receiving 19.2 μmol supplemental Cr were much larger. The chromium × time interaction was significant at $P < 0.0001$.

Fasting insulin concentrations were significantly lower in the group receiving 3.85 μmol Cr daily with a mean fasting insulin concentration of 95 ± 2 pmol/l after 4 months, which was identical to that of the group receiving the higher level of chromium, compared with 118 ± 3 pmol/l in the placebo group (Fig. 3). Fasting insulin concentrations were also significantly lower after 2 months in both of the groups receiving supplemental chromium. Similar results were observed for the insulin 2 h after a glucose challenge (Fig. 4). The fasting

TABLE 1
Characteristics of control and chromium-supplemented subjects at the beginning of the study

	Supplemental chromium (μmol/day)		
	0	3.85	19.2
Height (meters)			
All	1.67 ± 0.01 (50)	1.67 ± 0.01 (53)	1.65 ± 0.01 (52)
Women	1.61 ± 0.01 (17)	1.60 ± 0.01 (20)	1.59 ± 0.01 (26)
Men	1.70 ± 0.01 (33)	1.71 ± 0.01 (33)	1.70 ± 0.01 (26)
Weight (kg)			
All	69.1 ± 1.3	69.0 ± 1.5	67.8 ± 1.4
Women	66.4 ± 2.5	63.4 ± 2.5	63.4 ± 1.6
Men	70.5 ± 1.4	72.6 ± 1.5	72.0 ± 1.8
BMI (kg/m^2)			
All	24.8 ± 0.5	25.0 ± 0.5	24.8 ± 0.4
Women	25.8 ± 1.1	25.0 ± 0.9	25.0 ± 0.6
Men	24.3 ± 0.5	25.0 ± 0.5	24.6 ± 0.6
Duration of diabetes (years)			
All	5.4 ± 0.7†	8.0 ± 1.0*	5.3 ± 0.7†
Women	5.6 ± 1.0*	8.4 ± 1.6*	6.8 ± 1.1*
Men	5.2 ± 0.9*†	7.8 ± 1.2*	3.7 ± 0.7†
Age (years)			
All	55.5 ± 1.2	55.7 ± 1.2	54.6 ± 1.4
Women	56.4 ± 1.8	53.8 ± 1.8	54.1 ± 2.3
Men	55.1 ± 1.5	56.8 ± 1.7	55.2 ± 1.8

Number in parentheses denotes number of subjects who completed all phases of the study and had no missing experimental analyses. *†Values in the same row with different superscripts are significantly different at $P < 0.05$.

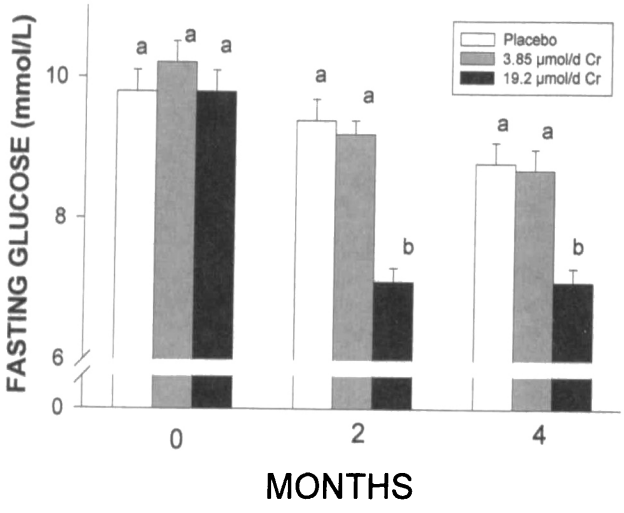

FIG. 1. Supplemental chromium effects on fasting serum glucose. Chromium was taken in two doses between meals. There were 50 subjects in placebo group, 53 in the 3.85-µmol group, and 52 in the 19.6-µmol group. Bars with different letters are significantly different from other groups for the same time period at $P < 0.05$.

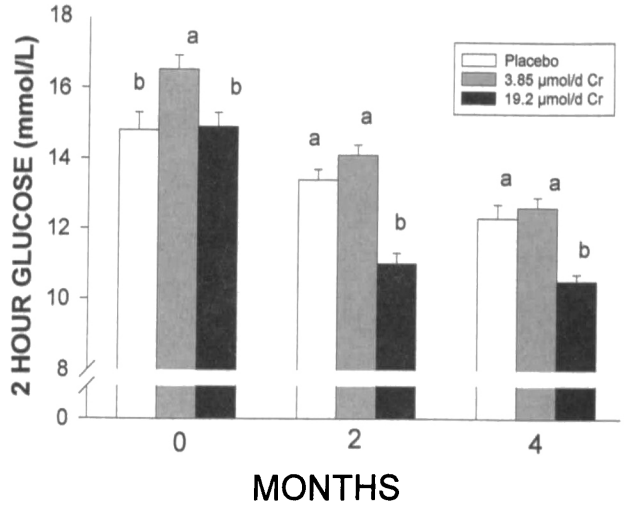

FIG. 2. Supplemental chromium effects on 2-h glucose concentrations. Subjects were given a 75-g glucose challenge at time 0, and blood was drawn 2 h later. Conditions are described in Fig. 1.

and 2-h insulin values of the placebo subjects also decreased over the duration of the study, but the decreases in the chromium groups were much larger. The chromium × time interaction was also significant at $P < 0.0001$.

Decreases in blood glucose and insulin concentrations due to supplemental chromium (Figs. 1–4) were reflected by decreases in HbA_{1c} values, with significant effects of chromium in both chromium groups after 4 months and in the 19.2-µmol group after 2 months (Fig. 5).

Supplemental chromium at 19.2 µmol/day also led to decreased total cholesterol (Fig. 6). The total cholesterol of the men was higher than that of the women, and both sexes responded to supplemental chromium similarly. There were no chromium × sex or time × sex interactions. The chromium × time interaction was significant at $P < 0.02$. There were no significant effects of supplemental chromium on HDL cholesterol, triglycerides, blood urea nitrogen, weight, or BMI (data not shown).

DISCUSSION

These data demonstrate significant effects both statistically and clinically of supplemental chromium at 3.85 and 19.2 µmol/day on glucose and insulin variables in individuals with type 2 diabetes. Improvements in fasting glucose and insulin concentrations as well as those after a glucose challenge document the role of elevated intakes of supplemental chromium in the control of type 2 diabetes. The improvements due to chromium are not due to changes in body weight, since weight did not change significantly over the duration of the study.

The chromium intake of these subjects is not known, but total dietary chromium intake does not accurately reflect chromium status since other factors affect chromium requirements. For example, different forms of stress including diet, exercise, and diabetes all increase chromium requirements (26). Increased intake of simple sugars also increases chromium losses (27). Urinary chromium losses are correlated with the stress hormone cortisol (28), and chromium's effects on morbidity and immune function are only observed in stressed animals (29).

There are no methods to predict chromium status. The only method is to measure glucose, insulin, and lipid variables before and after chromium supplementation. Chromium concentrations in blood, hair, urine, and other tissues or body fluids have not been shown to reflect chromium status.

There have been several studies involving chromium supplementation of people with diabetes. The results of these studies are varied, but in retrospect may be consistent (10–13,30–35). The majority of the studies involving daily chromium supplementation with 4.81 µmol Cr as chromium chloride or less to individuals with diabetes reported no significant consistent improvements (31–33). Improved glucose tolerance and blood cholesterol were reported in roughly half the subjects supplemented daily with 2.89–4.81 µmol Cr as chromium chloride (9–10). Mossop (12) reported significant improvements in fasting blood glucose in 13 people being treated for diabetes. Fasting blood glucose concentrations decreased from 14.4 to 6.6 mmol/l after 2 to 4 months of 11.5 µmol supplemental Cr as chromium chloride daily. Fasting blood glucose, glycosylated hemoglobin, total cholesterol, and LDL cholesterol all improved significantly in 11 individuals with type 2 diabetes who consumed 3.85 µmol/day Cr as chromium picolinate for 6 weeks (35). Ravina et al. (13) also reported improved glucose control in 162 individuals with diabetes after daily chromium supplementation with 200 µg Cr as chromium picolinate.

The reasons for the discrepancy in the response to supplemental chromium appear to be due to the amount and form of chromium consumed. In this study, we used chromium as chromium picolinate, which is utilized more efficiently than chromium chloride (36), used chromium twice per day, and used higher levels than most previous studies. The beneficial effects of 19.2 µmol/day Cr, compared with 3.85 µmol, demonstrate that 3.85 µmol Cr is not sufficient to elicit maximal significant improvements in diabetic subjects.

Chromium picolinate is a convenient form of chromium that is used more efficiently than some other forms of chromium. The active compound is chromium, not picolinate,

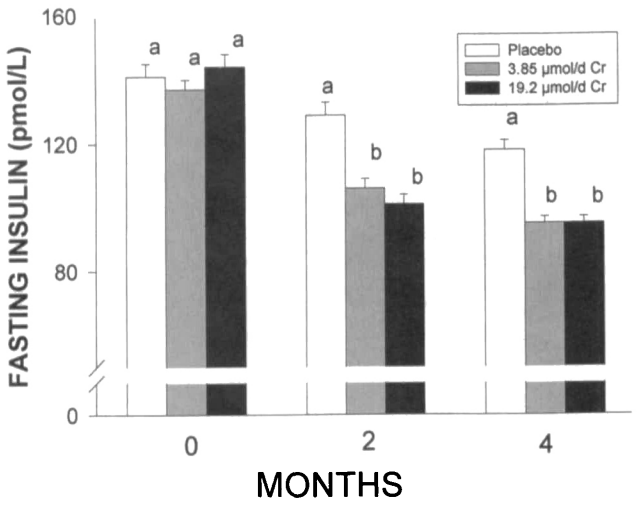

FIG. 3. Supplemental chromium effects on fasting insulin concentrations. Conditions are described in Fig. 1.

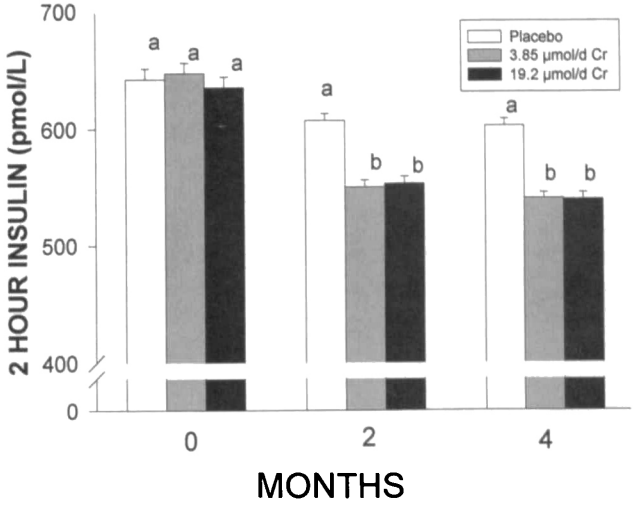

FIG. 4. Supplemental chromium effects on 2-h insulin concentrations. Conditions are described in Fig. 2.

since other studies have shown beneficial effects of chromium as chromium chloride. Chromium chloride is usually the least available of the chromium compounds tested (36). Patients on total parenteral nutrition and individuals with glucose intolerance, hypoglycemia, and diabetes have all been shown to respond to chromium as $CrCl_3$. Several different forms of chromium are likely to elicit similar effects but at different intakes due to the varying absorption, transport, and utilization of the different chromium compounds.

The measurement of glycated proteins, such as HbA_{1c}, is the most reliable method of assessing long-term glycemic control in individuals with diabetes (37–42). HbA_{1c} values were originally postulated to reflect the simple mean plasma glucose level over a certain period, and considering the erythrocyte life span, glycated hemoglobin was thought to be uniformly accumulated in erythrocytes over 120 days. However, theoretical and experimental evidence demonstrates that following a consistent drop in blood glucose, HbA_{1c} values change rapidly in the first 1 to 2 months, followed by a steady-state level after 4 months (41,42). Half of the HbA_{1c} level is determined by the plasma glucose values during the preceding 1-month period and an additional 25% of the HbA_{1c} level in the preceding month (42). Therefore, 75% of the HbA_{1c} level is proportional to the changes in blood glucose over the preceding 2 months. In our study, we saw a rapid drop in HbA_{1c} values in the first 2 months with HbA_{1c} values of 7.4 ± 0.2% for individuals receiving 19.2 µmol Cr daily, compared with 8.6 ± 0.2% for those receiving placebo. The drop in HbA_{1c} value in the group receiving 3.85 µmol Cr daily after 4 months was accompanied by a decrease in both fasting and postprandial insulin, but differences in blood glucose for the corresponding subjects were not significant. However, there were significant drops from the glucose concentrations determined at the onset of the study. Similar results were observed in both male and female subjects.

Changes in serum lipids in this study are consistent with those observed in our previous studies (14,16,17), namely that the effects of supplemental chromium are greater for glucose and insulin than for lipid concentrations. The delayed response of supplemental chromium on blood lipids is con-

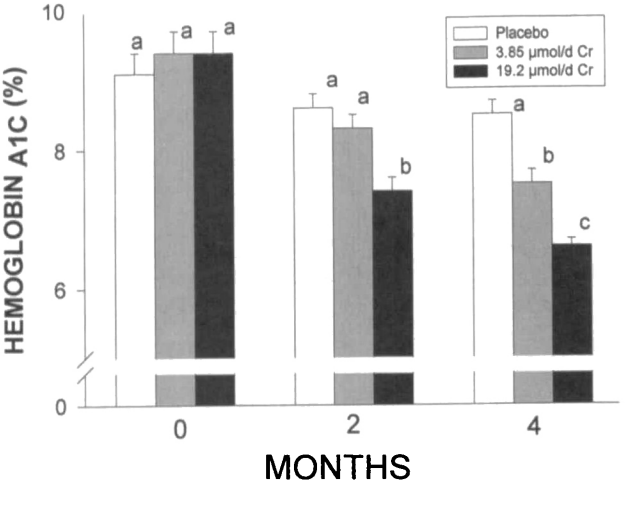

FIG. 5. Supplemental chromium effects on HbA_{1c} values. Conditions are described in Fig. 1.

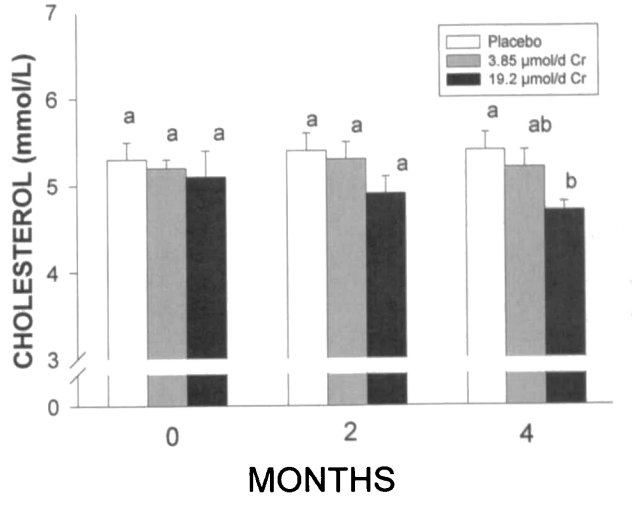

FIG. 6. Supplemental chromium effects on fasting serum cholesterol concentrations. Conditions are described in Fig. 1.

sistent with the study of Abraham et al. (30) that reported no significant effects of supplemental chromium on blood lipids after 3 months but significant decreases in triglycerides and increases in HDL cholesterol after 7–16 months. Similar chromium effects were observed in nondiabetic control subjects and individuals with diabetes.

We did not detect an effect of drug therapy for the control of diabetes and response to supplemental chromium. Diabetic therapy included, in addition to hypoglycemic drugs, traditional Chinese medicines, insulin, and diet alone. Ravina et al. (13) also did not observe an effect of insulin, sulfonylurea, or metformin on improvements in glucose control in diabetic patients receiving 3.85 μmol Cr as chromium picolinate. Supplemental chromium (600 μg/day) was also shown to increase the HDL cholesterol of men taking β-blockers (43). In a separate study, there was a larger effect of chromium on blood lipids of subjects not taking thiazides (44). Martinez et al. (45) also reported no clear effects of 200 μg Cr as chromium chloride daily in women taking medications that affect glucose tolerance but significant effects in 2-h blood glucose concentrations in nonmedicated subjects.

The mechanism of action of chromium on the control of blood glucose concentrations is the potentiation of insulin action. In the presence of chromium in a useable form, much lower levels of insulin are required. In the epididymal fat cell assay, near maximal insulin response can be achieved by adding chromium in a form that potentiates insulin (46). Inorganic chromium is without effect in the epididymal fat cell assay. Supplemental chromium leads to increased insulin binding to cells due to increased insulin receptor number (14). A direct binding of chromium to insulin is postulated (47), and a direct binding of an insulin potentiating form of chromium to insulin has been observed (48). Chromium was also shown to affect β-cell sensitivity measured in euglycemic clamp studies (49). The overall effect of chromium is to increase insulin sensitivity, which is associated with decreased glucose intolerance, decreased risk factors associated with cardiovascular diseases, improved immunity, and increased life span (50).

Trivalent chromium, the form of chromium found in foods and nutrient supplements, is considered one of the least toxic nutrients. The reference dose established by the U.S. Environmental Protection Agency for chromium is 350 times the upper limit of the Estimated Safe and Adequate Daily Dietary Intake of 3.85 μmol (200 μg/day). The reference dose is defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population, including sensitive subgroups, that is likely to be without an appreciable risk of deleterious effects over a lifetime" (51). This conservative estimate of safe intake has a much larger safety factor for trivalent chromium than almost any other nutrient. The ratio of the reference dose to the Estimated Safe and Adequate Daily Dietary Intake or the Recommended Daily Allowance is 350 for chromium, compared to <2 for zinc, roughly 2 for manganese, and 5–7 for selenium (51). Anderson et al. (52) demonstrated a lack of toxicity of chromium chloride and chromium picolinate in rats at levels several thousand times the upper limit of the estimated safe and adequate daily dietary intake for humans (based on body weight). There was no evidence of toxicity in this study, and there have not been any reported toxic effects in any of the human studies involving supplemental chromium.

In summary, supplemental chromium was shown to have pronounced effects on glucose and insulin variables in individuals with type 2 diabetes. A total of 200 μg Cr daily (3.85 μmol) did not appear to be sufficient for the reversal of diabetic symptoms over the 4-month duration of the study, since larger consistent effects were observed in subjects receiving 1,000 μg (19.2 μmol) supplemental Cr daily. Additional studies are needed to establish the form and amount of supplemental chromium required to elicit maximal responses in individuals with diabetes and in the prevention of diabetes.

ACKNOWLEDGMENTS

This work was funded in part by grants from the Diabetes Action Foundation. The authors would also like to acknowledge the support of Nutrition 21, San Diego, California, for support for the analyses that were completed in China.

Parts of this study were presented in abstract form at the 56th annual meeting of the American Diabetes Association, San Francisco, California, 8–11 June 1996.

REFERENCES

1. Jeejeebhoy KN, Chu RC, Marliss EB, Greenberg GR: Chromium deficiency, glucose intolerance, and neuropathy reversed by chromium supplementation in a patient receiving long-term total parenteral nutrition. *Am J Clin Nutr* 30:531–538, 1977
2. Freund H, Atamian S, Fischer JE: Chromium deficiency during total parenteral nutrition. *JAMA* 241:496–498, 1979
3. Brown RO, Forloines-Lynn S, Cross RE, Heizer WD: Chromium deficiency after long-term parenteral nutrition. *Dig Dis Sci* 31:661–664, 1986
4. Anderson RA: Essentiality of chromium in humans. *Sci Total Environ* 86:75–81, 1989
5. Anderson RA: Chromium and parenteral nutrition. *Nutrition* 11:83–86, 1995
6. Verhage AH, Cheong WK, Jeejeebhoy KN: Neurologic symptoms due to possible chromium deficiency in long-term parenteral nutrition that closely mimic metronidazole-induced syndromes. *J Parenteral Enteral Nutr* 20:123–127, 1996
7. Hopkins LL Jr., Ransome-Kuti O, Majaj AS: Improvements of impaired carbohydrate metabolism by chromium (III) in malnourished infants. *Am J Clin Nutr* 21:203–211, 1968
8. Gurson CT, Saner G: Effect of chromium on glucose utilization in marasmic protein-calorie malnutrition. *Am J Clin Nutr* 24:1313–1319, 1971
9. Levine RA, Streeten DHP, Doisy RJ: Effects of oral chromium supplementation on the glucose tolerance of elderly subjects. *Metabolism* 17:114–125, 1968
10. Glinsmann WH, Mertz W: Effect of trivalent chromium on glucose tolerance. *Metabolism* 15:510–520, 1966
11. 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, 1979
12. Mossop RT: Effects of chromium (III) on fasting glucose, cholesterol and cholesterol HDL levels in diabetics. *Cent Afr J Med* 29:80–82, 1983
13. Ravina A, Siezak L, Rubal A, Mirsky N: Clinical use of the trace element chromium (III) in the treatment of diabetes mellitus. *J Trace Elem Exptl Med* 8:183–190, 1995
14. Anderson RA, Polansky MM, Bryden NA, Bhathena SJ, Canary J: Effects of supplemental chromium on patients with symptoms of reactive hypoglycemia. *Metabolism* 36:351–355, 1987
15. Clausen J: Chromium induced clinical improvement in symptomatic hypoglycemia. *J Clin Invest* 17:229–236, 1988
16. Anderson RA, Polansky MM, Bryden NA, Canary JJ: Supplemental chromium effects on glucose, insulin, glucagon, and urinary chromium losses in subjects consuming controlled low-chromium diets. *Am J Clin Nutr* 54:909–916, 1991
17. Anderson RA, Polansky MM, Bryden NA, Roginski EE, Mertz W, Glinsmann WH: Chromium supplementation of human subjects: effects on glucose, insulin and lipid parameters. *Metabolism* 32:894–899, 1983
18. Doisy RJ, Streeten DHP, Freiberg JM, Schneider AJ: Chromium metabolism in man and biochemical effects. In *Trace Elements in Human Health and Disease: Essential and Toxic Elements.* Vol. 2. Prasad AS, Oberleas D, Eds. New York, Marcel Dekker, 1976

19. Tuman RW, Bilbo JT, Doisy RJ: Comparison and effects of natural and synthetic glucose tolerance factor in normal and genetically diabetic mice. *Diabetes* 27:49–56, 1978
20. Loft JA, Turner K: Evaluation of Trinder's glucose oxidase method for measuring glucose in serum and urine. *Clin Chem* 21:1754–1760, 1975
21. Albano JDM, Ekins RP, Maritz G: A sensitive, precise radioimmunoassay of serum insulin relying on charcoal separation of bound and free hormone moieties. *Acta Endocrinol* 70:487–509, 1972
22. Deacon AC, Dawson PJG: Enzymic assay of total cholesterol involving chemical or enzymic hydrolysis: a comparison of methods. *Clin Chem* 25:976–984, 1979
23. Warnick GR, Mayfield C, Benderson J: Cholesterol quantitation by phosphotungstate-Mg^{2+} and by dextran sulfate-Mn^{2+}: polypropylene glycol precipitation both with enzymic cholesterol assay compared with the lipid research method. *Am J Clin Nutr* 78:718–723, 1982
24. Kohimeier M: Direct enzymic measurement of glycerides in serum and in lipoprotein fractions. *Clin Chem* 32:63–66, 1986
25. Foster LB, Hockholzer JM: A single-reagent manual method for directly determining urea nitrogen in serum. *Clin Chem* 17:921–925, 1971
26. Anderson RA: Stress effects on chromium nutrition of humans and farm animals. In: *Proceedings of Alltech's Tenth Symposium Biotechnology in the Feed Industry*. Nottingham, England, Univ. Press, 1994, p. 267–274
27. Kozlovsky AS, Moser PB, Reiser S, Anderson RA: Effects of diets high in simple sugars on urinary chromium losses. *Metabolism* 35:515–518, 1986
28. Anderson RA, Bryden NA, Polansky MM, Thorp JW: Effect of carbohydrate loading and underwater exercise on circulating cortisol, insulin and urinary losses of chromium and zinc. *Eur J Appl Physiol* 63:146–150, 1991
29. Mowat DN, Chang X, Yang WZ: Chelated chromium for stressed feeder calves. *Can J Anim Sci* 73:49–53, 1993
30. 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
31. 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
32. Rabinowitz MB, Gonick HC, Levine SR, Davidson MB: Clinical trial of chromium and yeast supplements on carbohydrate and lipid metabolism in diabetic men. *Biol Trace Elem Res* 5:449–466, 1983
33. Uusitupa MIJ, Kumpulainen JT, Voutilainen E, Hersio K, Sarlund H, Pyorala KP, Koivistoinen PE, Lehton 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
34. Uusitupa MIJ, Mykkanen L, Sittonen O, Laakso M, Sarlund H, Kolehmainen P, Rasanen T, Kumpulainen J, Pyorala K: Chromium supplementation in impaired glucose tolerance of elderly: effects on blood glucose, plasma insulin, C-peptide and lipid levels. *Brit J Nutr* 68:209–216, 1992
35. Evans GW: The effect of chromium picolinate on insulin controlled parameters in humans. *Int J Biosoc Med Res* 11:163–180, 1989
36. Anderson RA, Bryden NA, Polansky MM, Gautschi K: Dietary chromium effects on tissue chromium concentrations and chromium absorption in rats. *J Trace Elem Exptl Med* 9:11–25, 1996
37. Bunn HF: Evaluation of glycosylated hemoglobin in diabetic patients. *Diabetes* 30:613–617, 1981
38. MacDonald JM, Davis JE: Glycosylated hemoglobins and diabetes mellitus. *Hum Pathol* 10:279–291, 1979
39. Mayer TK, Freedman ZR: Protein glycosylation in diabetes mellitus: a review of laboratory measurements and their clinical utility. *Clin Chim Acta* 127:147–184, 1983
40. Schleicher E, Weitland OH: Protein glycation: measurement and clinical relevance. *J Clin Chem Clin Biochem* 27:577–587, 1989
41. Takara Y, Shima K: The response of Ghb to stepwise plasma glucose change over time in diabetic patients. *Diabetes Care* 16:1313–1314, 1993
42. Takara Y, Shima K: Kinetics of HbA_{1c}, glycated albumin, and fructosamine and analysis of their weight functions against preceding plasma glucose level. *Diabetes Care* 18:440–447, 1995
43. Roeback JR Jr., Mae K, Chambless LE, Fletcher RH: Effects of chromium supplementation on serum high-density lipoprotein cholesterol levels in men taking beta-blockers. *Ann Inter Med* 115:917–924, 1991
44. Mossop RT: Diabetogenic effect of thiazides and the relation to chromium: a preliminary report. *Cent Afr J Med* 7:129–131, 1985
45. Martinez OB, MacDonald AC, Gibson RS, Bourn O: Dietary chromium and effect of chromium supplementation on glucose tolerance of elderly Canadian women. *Nutr Res* 5:609–620, 1985
46. Anderson RA, Brantner JH, Polansky MM: An improved assay for biologically active chromium. *J Agric Food Chem* 26:1219–1221, 1978
47. Mertz W, Toepfer EW, Roginski EE, Polansky MM: Present knowledge of the role of chromium. *Fed Proc* 33:2275–2280, 1974
48. Anderson RA, Polansky MM, Brantner JH, Roginski EE: Chemical and biological properties of biologically active chromium. In *Trace Element Metabolism in Man and Animals*. Vol. 3. Kirchgessner M, Ed. Freising-Weihenstephan, Germany, Institut für Ernährungsphysiologie, 1978
49. 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
50. Reaven GM: Role of insulin resistance in human diseases. *Diabetes* 37:1595–1606, 1988
51. Mertz W, Abernathy CO, Olin SS: *Risk Assessment of Essential Elements*. Washington, DC, ILSI Press, 1994, p. xix–xxviii
52. Anderson RA, Bryden NA, Polansky MM: Lack of toxicity of chromium chloride and chromium picolinate. *J Am Coll Nutr* 16:273–279, 1997