Chromium Picolinate Supplementation Attenuates Body Weight Gain and Increases Insulin Sensitivity in Subjects With Type 2 Diabetes

JULIE MARTIN, MS, RD[1]
ZHONG Q. WANG, MD[2]
XIAN H. ZHANG, BS[2]
DEBORAH WACHTEL, NP, MPH[1]
JULIA VOLAUFOVA, PHD[3]
DWIGHT E. MATTHEWS, PHD[1]
WILLIAM T. CEFALU, MD[2]

OBJECTIVE — Chromium picolinate (CrPic) supplementation has been suggested to improve glycemia, but there are conflicting reports on efficacy. We sought to determine the effect of CrPic on insulin sensitivity, glycemic control, and body composition in subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Thirty-seven subjects with type 2 diabetes were evaluated. After baseline, subjects were placed on a sulfonylurea (glipizide gastrointestinal therapeutic system 5 mg/day) with placebo for 3 months. Subjects were then randomized in a double-blind fashion to receive either the sulfonylurea plus placebo ($n = 12$) or the sulfonylurea plus 1,000 μg Cr as CrPic ($n = 17$) for 6 months. Body composition, insulin sensitivity, and glycemic control were determined at baseline, end of the 3-month single-blind placebo phase, and end of study.

RESULTS — Subjects randomized to sulfonylurea/placebo, as opposed to those randomized to sulfonylurea/CrPic, had a significant increase in body weight (2.2 kg, $P < 0.001$ vs. 0.9 kg, $P = 0.11$), percent body fat (1.17%, $P < 0.001$ vs. 0.12%, $P = 0.7$), and total abdominal fat (32.5 cm^2, $P < 0.05$ vs. 12.2 cm^2, $P < 0.10$) from baseline. Subjects randomized to sulfonylurea/CrPic had significant improvements in insulin sensitivity corrected for fat-free mass (28.8, $P < 0.05$ vs. 15.9, $P = 0.4$), GHb (−1.16%, $P < 0.005$ vs. −0.4%, $P = 0.3$), and free fatty acids (−0.2 mmol/l, $P < 0.001$ vs. −0.12 mmol/l, $P < 0.03$) as opposed to sulfonylurea/placebo.

CONCLUSIONS — This study demonstrates that CrPic supplementation in subjects with type 2 diabetes who are taking sulfonylurea agents significantly improves insulin sensitivity and glucose control. Further, CrPic supplementation significantly attenuated body weight gain and visceral fat accumulation compared with the placebo group.

Diabetes Care 29:1826–1832, 2006

The primary strategy to improve metabolic control in patients with type 2 diabetes consists of lifestyle modification combined with pharmacologic intervention (1). However, alternative strategies, e.g., nutritional supplementation with over-the-counter agents, are extensively practiced by a large number of patients and are frequently undertaken without first informing the medical provider. According to the Food and Drug Administration, there are more than 29,000 different nutritional supplements available to consumers, and Americans spend over 12 billion dollars per year on these supplements (2,3). Unfortunately, considerable controversy exists regarding use of dietary supplements in subjects with diabetes because efficacy data for many of the supplements consist of only uncontrolled studies and anecdotal reports. As such, there is a paucity of data in humans in regard to the effect of most commercially available supplements to improve metabolic abnormalities.

One supplement that has attracted considerable clinical interest is chromium (4). However, routine use of chromium in subjects with diabetes is not currently recommended, and the most recent 2006 Clinical Practice Recommendations from the American Diabetes Association stated that "the existence of a relationship between chromium picolinate and either insulin resistance or type 2 diabetes was highly uncertain" (5). Interestingly, such statements have not deterred its use, and chromium supplementation by the general public and in subjects with diabetes in particular has surpassed our ability as a scientific community to provide evidence regarding its safety and efficacy. In part, the controversy surrounding chromium supplementation stems from the lack of definitive randomized trials, the lack of "gold standard" techniques to assess glucose metabolism in the studies reported, the use of differing doses and formulation, and the study of heterogeneous study populations (4). As such, conflicting data have been reported that have contributed greatly to the confusion among healthcare providers concerning chromium supplementation. To provide a comprehensive clinical evaluation of chromium, we conducted a randomized, double-blind, placebo-controlled trial in subjects with type 2 diabetes and over a 10-month period of observation, used established techniques to assess changes in insulin sensitivity, body composition, and glycemic control.

From the [1]Division of Endocrinology and Metabolism, University of Vermont, Burlington, Vermont; the [2]Division of Nutrition and Chronic Diseases, Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, Louisiana; and the [3]Biostatistics Program, School of Public Health, Louisiana State University Health Sciences Center, New Orleans, Louisiana.

Address correspondence and reprint requests to William T. Cefalu, MD, Pennington Biomedical Research Center, 6400 Perkins Rd., Baton Rouge, LA 80808. E-mail: cefaluwt@pbrc.edu.

Received for publication 31 January 2006 and accepted in revised form 25 April 2006.

Abbreviations: AUC, area under the curve; AUC-B, glucose AUC from the fasting glucose at time 0; CrPic, chromium picolinate; DEXA, dual-energy X-ray absorptiometry; FFA, free fatty acid; GITS, gastrointestinal therapeutic system; OGTT, oral glucose tolerance test.

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

DOI: 10.2337/dc06-0254. Clinical trial reg. no. NCT00283777, clinicaltrials.gov

© 2006 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Downloaded from http://diabetesjournals.org/care/article-pdf/29/8/1826/593598/zdc00806001826.pdf by guest on 17 May 2022

RESEARCH DESIGN AND METHODS

— Subjects aged 25–75 years with type 2 diabetes diagnosed at least 6 months earlier were evaluated. All subjects had been previously maintained on dietary therapy only or on low dose of oral antidiabetic agents for a minimum of 2 months. They were required to have a fasting plasma glucose ≥125 mg/dl but <170 mg/dl at time of screening. Subjects on medications known to affect glucose metabolism were excluded. All procedures were approved and conducted in strict compliance with institutional human research guidelines.

The study was double blinded, randomized, and placebo controlled. It consisted of a 4-week washout period (baseline) and a 12-week period of treatment with glipizide gastrointestinal therapeutic system (GITS) (Glucotrol XL) only (period 1), followed by a 24-week period of either glipizide GITS with placebo or glipizide GITS with 1,000 μg of chromium as chromium picolinate (CrPic) (Period 2; Fig. 1*A*). A sulfonylurea, i.e., glipizide GITS, was provided to all subjects for several reasons. First, due to the long-term period of observation from screening, e.g., 10 months, it was not desirable to have hyperglycemic subjects remain on placebo only. Thus, an agent from an established antidiabetic drug class, i.e., sulfonylurea, was provided to all subjects as monotherapy. Secondly, as the objective was to evaluate the effect of chromium on insulin sensitivity, use of agents such as thiazolidindiones or biguanides would have provided additional confounders. Therefore, the study design allowed for a stable baseline to be obtained on all subjects while on an accepted therapy before assessing the effect of supplemental chromium (Fig. 1*A*).

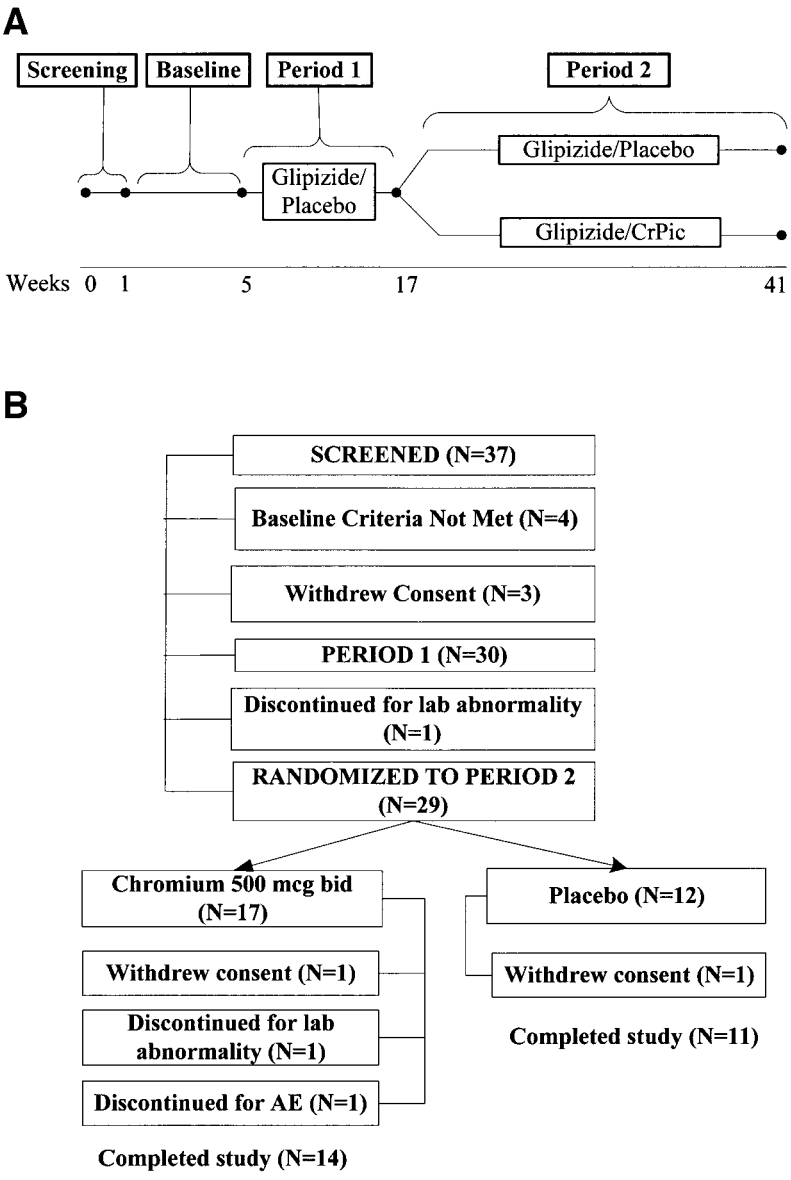

Figure 1—*Study design* (A) *and study flow and numbers* (B) *for each study period.*

Study stages

Baseline (weeks 1–5). After entry criteria had been met, subjects were instructed on a weight maintenance diet and home blood glucose monitoring, and oral agents (if applicable) were discontinued. At the end of the 4-week baseline, GHb, urinary chromium, and oral glucose tolerance tests (OGTTs) were assessed. Body fat distribution was assessed with computed tomography and dual-energy X-ray absorptiometry (DEXA) scans. Insulin sensitivity was assessed with hyperinsulinemic-euglycemic clamps.

Period 1 (sulfonylurea/placebo phase): end of week 5–17. After baseline, the subjects were randomized and had treatment initiated with glipizide GITS at 5 mg/day plus two placebo capsules. Subjects returned to the clinic monthly. At week 16, a repeat inpatient stay was conducted for assessment of body composition, urinary chromium excretion, free fatty acid (FFA) levels, and insulin sensitivity. At week 17, a second OGTT was assessed. After completion of period 1, subjects randomized to receive chromium continued with glipizide GITS once daily but were given two 500-μg CrPic capsules to take daily, one in the morning and the other in the evening. Those randomized to placebo were instructed to continue to take glipizide GITS daily plus the two placebo capsules. The placebo capsule and chromium supplement were identical in physical characteristics.

Period 2 (sulfonylurea/placebo versus sulfonylurea/CrPic): end of week 17 to week 41. Subjects were evaluated monthly. At week 40, a repeat inpatient stay was conducted for assessment of body composition, urinary chromium excretion, FFA levels, and insulin sensitivity. At week 41, OGTT was repeated.

Variables

Insulin sensitivity. Hyperinsulinemic-euglycemic clamps were used to assess insulin sensitivity after a 10-h overnight fast (6). During the morning of the test, volunteers had an antecubital vein catheterized for infusion purposes, and a second

Downloaded from http://diabetesjournals.org/care/article-pdf/29/8/1826/593598/zdc00806001826.pdf by guest on 17 May 2022

catheter was placed in a dorsal vein of the hand of the contralateral arm for blood sampling. The hand was warmed in a heated box (air temperature held at 55°C) to produce arterialized venous blood samples (7). Insulin was administered as a primed-continuous infusion at a rate of 40 mU · m^{-2} · min^{-1} for 120 min. Plasma glucose was measured every 5 min, and dextrose (20%) was infused at variable rates (adjusted every 5 min) to maintain fasting glucose concentrations. The steady-state insulin levels achieved during the three clamps over the study period were not significantly different between control and CrPic randomized groups (means ± SD; 636 ± 126 vs. 612 ± 180 pmol/l, respectively; P = NS). In addition, no differences in the steady-state glucose levels were observed during the clamps over the study period between control and CrPic randomized groups (95.4 ± 4.2 vs. 96.0 ± 4.1 mg/dl, respectively; P = NS). Whole-body insulin-mediated glucose disposal was calculated as described (6,8,9). Before and during the last hour of the clamp, resting energy expenditure and respiratory quotient were assessed for each subject by indirect calorimetry for 45 min using the ventilated hood technique and substrate oxidation calculated as described (10).

Urinary chromium excretion. Urine samples were collected in prescreened urine collection cups and sent to the Centers for Disease Control and Prevention Environmental Health Laboratory frozen on dry ice. The samples were analyzed for chromium in accordance with Centers for Disease Control and Prevention urine chromium method 0485A by means of graphite furnace atomic absorption spectrometry (model 4100-ZL with Zeeman background correction) (11). Matrix-matched calibration method was used, which resulted in an analytical limit of detection of 0.3 μg/l.

Body composition. Total abdominal, intra-abdominal, and subcutaneous fat distribution at the level of the umbilicus was assessed by computed tomography. DEXA was used to measure body fat.

Chemistries. Glucose was measured using Yellow Springs Instruments model 2300 (Yellow Springs, OH). Glucose tolerance was assessed by performing a standard 75-g challenge with determination of glucose and insulin levels at 0, 0.5, 1, 1.5, 2, and 3 h after challenge. Total GHb was determined by automated affinity high-pressure liquid chromatography (12). C-peptide was analyzed using a kit from Diagnostic Products (San Diego, CA). Insulin and adiponectin were assessed with radioimmunoassay (Linco, St. Charles, MO). FFAs and triglycerides were measured using an enzymatic method on a Beckman Coulter Synchron CX5 and CX7 (Brea, CA), respectively.

Statistical analysis

Baseline was taken as the parameters obtained through end of week 5 and before period 1. Change from baseline was defined as value at time t minus value observed during baseline for all response measures. Insulin was log transformed for analysis of change from baseline; however, untransformed values were used in calculating change in integrated insulin response to oral glucose tolerance. Integrated response for insulin and glucose was calculated based on trapezoid method applied to the data series, corrected for the response value measured 5 min before the glucose tolerance.

To evaluate treatment effect on change in response (plasma glucose, insulin [log transformed]), GHb, and the derived measures of glucose disposal during clamp, relative to baseline levels, repeated-measures models were employed. These models included "week" and "treatment" in a factorial structure as fixed effects and the value of the response variable observed at baseline as a covariate. Week was considered as repeated factor with dependencies modeled by unstructured covariance matrix. In the model, treatment and week were considered main effects with the interaction term included. The approximate F tests and denominator degrees of freedom were based on a Kenward-Roger method. Tests of model means for change in response (from baseline) at given time points are tests of the null hypothesis of no change over time. Tests of differences in estimated treatment group means at a given time point address the hypothesis of no treatment effect at that time (an interaction effect slice). Statistical significance for these tests is reported relative to a two-sided 5% type 1 error rate. All analyses were carried out using the statistical software system SAS, version 9.1.2 (Cary, NC).

RESULTS — Figure 1 demonstrates study design, subject flow, and numbers for each study period. A total of 25 subjects (17 men and 8 women) completed the protocol. Subjects that were randomized had an average age of 59.7 ± 8 years, GHb of 9.7 ± 0.5%, fasting glucose of 170 ± 10 mg/dl, BMI of 30 ± 0.8 kg/m^2, body weight of 86.9 ± 3.1 kg, and whole-body glucose disposal (by clamp) of 214.7 ± 22.5 mg/min.

Chromium status

Mean urinary chromium levels for all subjects were determined to be at the lower limits of detection at study initiation (<0.3 μg/l). At end of period 1, mean chromium excretion in all subjects remained <0.3 μg/l. However, at end of period 2, urinary chromium levels were significantly increased in those subjects randomized to CrPic versus placebo (6.0 ± 4.5 vs. <0.3 μg/l, $P < 0.01$).

Metabolic and physiologic parameters

The initiation of the sulfonylurea in period 1 resulted in a significant change in fasting glucose in all subjects (Table 1). At the end of period 2 and when compared with baseline, subjects randomized to the sulfonylurea/CrPic had significantly lower fasting glucose as opposed to those randomized to sulfonylurea/placebo. There was a mean decrease in GHb in all subjects at end of period 1. At end of period 2 and when compared with baseline, subjects randomized to receive CrPic maintained the significant decrease in GHb as opposed to those randomized to sulfonylurea/placebo (Table 1). Both the total glucose area under the curve (AUC) and the glucose AUC from the fasting glucose at time 0 (AUC-B), derived from the OGTT, were significantly decreased in all subjects at end of period 1. Total glucose AUC remained significantly decreased in both groups at end of study when compared with baseline, but the decrease appeared to be greater in those randomized to CrPic (Table 1). Glucose AUC-B remained significantly decreased only for the CrPic group at end of study. When compared with the baseline, subjects randomized to sulfonylurea/CrPic had significant improvements in insulin sensitivity as opposed to those randomized to sulfonylurea/placebo (Table 1). Insulin AUC and AUC-B, derived from the OGTT, were higher in all subjects at end of period 1 when compared with baseline. There appeared to be no further increase in either treatment group at study end. There was no treatment effect for respiratory quotient, resting energy expenditure, adiponectin, or C-peptide levels. FFA levels decreased significantly in both the placebo and CrPic treatment groups; however, the drop in FFA levels was greater

Downloaded from http://diabetesjournals.org/care/article-pdf/29/8/1826/593598/zdc00806001826.pdf by guest on 17 May 2022

Table 1—*Changes observed from baseline for metabolic and phenotypic parameters*

	Period 1		Period 2			
	Sulfonylurea + placebo		Sulfonylurea + placebo		Sulfonylurea + CrPic	
Glycemia						
Fasting glucose (mg/dl)	−19.98 ± 5.33	0.0009	−11.33 ± 8.03	NS	−31.00 ± 7.37	0.0002
GHb (%)	−1.07 ± 0.26	0.0006	−0.44 ± 0.43	NS	−1.16 ± 0.38	0.0049
Glucose AUC	−7,794 ± 1238	0.0001	−6,454 ± 2289	0.0092	−11,131 ± 2108	0.0001
Glucose AUC-B	−2,531 ± 873	0.008	−2,501 ± 1412	NS	−3,981 ± 1269	0.0043
Insulin						
Glucose disposal (mg/min per fat-free mass)	21.9 ± 11.8	NS	15.9 ± 18.5	NS	28.9 ± 11.3	0.0209
Insulin AUC	3,460 ± 522	0.0001	2,969 ± 1102	0.013	3,498 ± 985	0.0016
Insulin AUC-B	2,604 ± 518	0.0001	1,618 ± 754	0.042	2,022 ± 657	0.0052
Fasting C-peptide (ng/ml)	−0.007 ± 0.030	NS	0.136 ± 0.111	NS	0.173 ± 0.093	NS
Indirect calorimetry						
Respiratory quotient	0.005 ± 0.006	NS	−0.006 ± 0.010	NS	0.005 ± 0.009	NS
REE	53.74 ± 28.1	NS	59.43 ± 40.3	NS	29.14 ± 36.4	NS
DEXA scans						
% fat	0.22 ± 0.44	NS	1.17 ± 0.31	0.0008	0.12 ± 0.35	NS
Fat-free mass	0.59 ± 0.40	NS	0.68 ± 0.46	NS	1.07 ± 0.44	0.0227
Lipids/adipocytokines						
FFAs (mmol/l)	−0.12 ± 0.05	0.018	−0.12 ± 0.05	0.028	−0.20 ± 0.05	0.0007
Triglycerides (mg/dl)	11.43 ± 13.04	NS	3.68 ± 18.86	NS	30.32 ± 18.19	NS
Log (Triglycerides)	0.09 ± 0.07	NS	0.06 ± 0.090	NS	0.13 ± 0.087	NS
Adiponectin (mg/ml)	2.06 ± 0.60	0.002	0.74 ± 0.75	NS	0.93 ± 0.702	NS

Data are means ± SE or *P* values. REE, resting energy expenditure.

in the subjects randomized to receive CrPic (Table 1).

Body weight and body fat distribution

During period 1, subjects gained an average of 0.9 kg in body weight from baseline (Fig. 2*A*). During period 2, subjects randomized to sulfonylurea/placebo, as opposed to those randomized to sulfonylurea/CrPic, had significant increases in both body weight (Fig. 2*A*) and percent body fat (Table 1) from baseline. In addition, there were significant increases in fat-free mass in subjects randomized to sulfonylurea/CrPic as opposed to sulfonylurea/placebo (Table 1). Subjects randomized to sulfonylurea/placebo, as opposed to those randomized to sulfonylurea/CrPic, had significant increases in total abdominal, visceral, and abdominal subcutaneous fat from baseline (Fig. 2*B*).

CONCLUSIONS — The major findings of this study were that the addition of CrPic to a regimen consisting of a sulfonylurea in subjects with type 2 diabetes improved glycemic control, increased insulin sensitivity, and significantly attenuated body weight gain as opposed to subjects maintained on a sulfonylurea

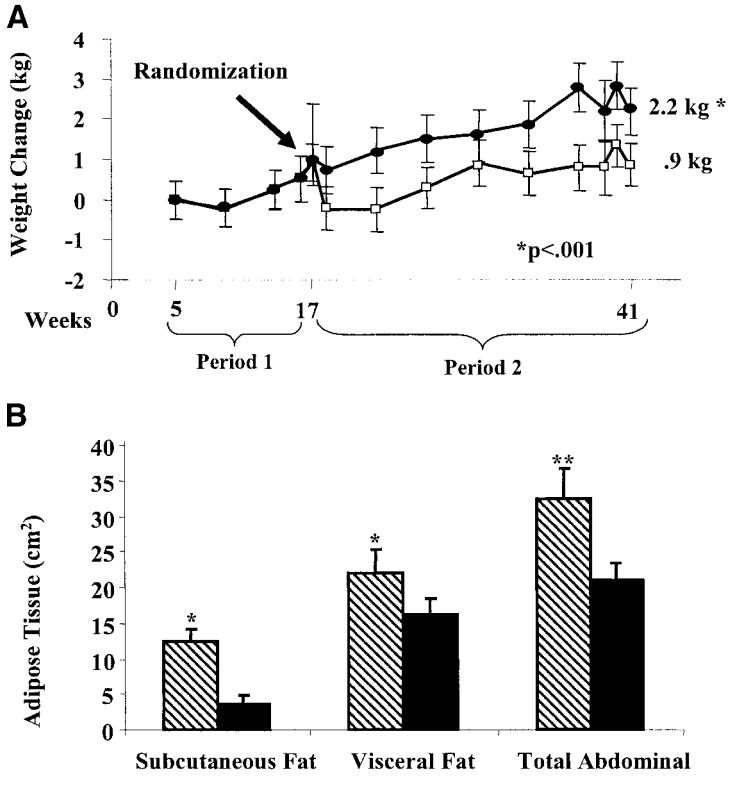

Figure 2—A: *Body weight changes for all subjects over the treatment period.* ●, *placebo;* □, *CrPic.* B: *Abdominal fat distribution for all subjects over the treatment period.* ▨, *control;* ■, *CrPic.* *P < *0.05;* **P < *0.01. Data are means± SE.*

Downloaded from http://diabetesjournals.org/care/article-pdf/29/8/1826/593598/zdc00806001826.pdf by guest on 17 May 2022

only. Specifically, the results from the DEXA and computed tomography scans demonstrated less increase in percent body fat and less accumulation of visceral, subcutaneous, and total abdominal fat in those subjects randomized to CrPic. The data suggests that CrPic supplementation may favorably modulate factors promoting weight gain commonly observed with improvement in glycemic control.

The study design allowed for insulin sensitivity to be first assessed at baseline while subjects were on no pharmacologic therapy and then after 3 months, during which time all subjects were on an accepted form of therapy. As an improvement in insulin action may be seen with sulfonylureas over time, most likely secondary to an improvement in glycemia (13,14), the 3-month time period has been shown by our group to provide a stable baseline for oral sulfonylurea therapy and formed the rationale for the study design (13,15). A third assessment for insulin sensitivity was then obtained after CrPic or placebo was added in a double-blinded fashion while all subjects continued the sulfonylurea. With this design, we observed that subjects randomized to CrPic, as opposed to placebo, had significant improvements in insulin sensitivity from baseline. To the best of our knowledge, this is the first reported study that assessed the effect of chromium on insulin action in subjects with type 2 diabetes with use of techniques as precise as hyperinsulinemic-euglycemic clamps. Previously, we had demonstrated an increase in insulin sensitivity in obese subjects with 1,000 μg of CrPic with use of the modified minimal model (35). The differences in weight gain between treatment groups do provide a confounder in the interpretation of the insulin sensitivity data. However, the glucose disposal was expressed relative to fat-free mass, and despite some weight gain in the sulfonylurea/CrPic group, insulin sensitivity was shown to significantly increase from baseline.

The effects on body weight and fat distribution noted in this study were not expected based on published reports, suggesting that chromium has variable effects on body weight and composition in patients with diabetes (16–26). Of eight double-blind, placebo-controlled trials in individuals without diabetes, chromium supplementation showed decrease in weight and fat in three larger studies (16–19,22,23,25,26). These results generally support the view that chromium supplementation has at best modest effects on body weight or composition in individuals with diabetes.

There are major differences between the reported studies evaluating weight effects with CrPic and the present study. First, prior studies had the primary goal of assessing weight loss, which was markedly different from the goal of the present study to evaluate insulin action. Our expectations did not include observing weight loss. In contrast, we assessed a population for which weight gain would not be unexpected given the improvement in glycemia with use of the specific oral agents (27,28). Thus, we observed an attenuation in weight gain with CrPic supplementation over time, not weight loss. Secondly, most of the prior studies addressing body weight were of relatively short duration and did not use more precise techniques for assessment of body fat. The present study evaluated subjects for 10 months and verified the clinic weight changes with two other independent and objective measures, i.e., DEXA and computed tomography. The mechanism by which CrPic attenuated weight gain is not known. It is well recognized that energy intake needs to match energy output, i.e., energy expenditure, to maintain a stable body weight (29,30). However, neither measures of physical activity nor food intake were assessed in this study. Therefore, it is currently unknown whether the attenuation of weight gain from CrPic supplementation was secondary to modulation of either energy intake or expenditure.

For humans, the National Academy of Sciences has proposed that the normal intake of chromium should serve as the adequate intake of 20 μg for women and 30 μg for men over 50 years of age and 25 μg for women and 35 μg for men 19–50 years (31). Assuming an average 75-kg body mass, this would relate to an intake of elemental chromium ranging from 0.27 to 0.47 μg/kg. At daily dietary intakes of 10 μg, chromium absorption is ~2%, and at intakes of 40 μg, it is 0.5% (32). This leads to absorption of ~0.2 μg per day, which appears to be a minimal basal level. The form of chromium also influences the absorption. Absorption of chromium from chromium chloride is usually in the region of 0.4%, and chromium from CrPic has been reported to range from 0.7 to 5.2% (33,34). Given the range of body weights of subjects in the present study, intake of chromium ranged from 10 to 13 μg/kg.

Another major difference in the present study compared with prior studies is the dose of CrPic. We demonstrated improved insulin sensitivity with 1,000 μg/day of chromium as CrPic. This dose was selected based on prior experience and from previously reported studies (21,35). In addition, this dose, in controlled clinical trials, has not been observed to result in any adverse effects (21,35,36). A recent study that evaluated much lower daily doses (~100 μg/day of elemental chromium as CrPic) reported negative results in individuals with impaired glucose tolerance (37,38). In addition, Kleefstra et al. (39) evaluated 1,000 μg/day of chromium as CrPic and reported no significant benefit in obese patients with type 2 diabetes. However, in that study, patient selection differed greatly from the present study. *1*) Subjects were more obese (BMI means ranging from 33 to 35 kg/m^2) and were on high-dose insulin therapy (mean daily dose ranged from 78 to 105 units/day). *2*) Subjects were more advanced in their disease process (mean diabetes duration range 10.9–18.4 years). *3*) Subjects were taking other medications in addition to insulin, as it was stated that "no changes were made in cholesterol-reducing, blood pressure–lowering, or oral hypoglycemic agents during the study period" (39). As we had excluded subjects on medications known to affect carbohydrate metabolism, ~30% of the subjects as reported by Kleefstra et al. (39) were on metformin in addition to insulin (N. Kleefstra, personal communication). Therefore, based on the above factors including duration of observation, higher dose of elemental chromium, subject selection, and techniques assessed, this study differed greatly from prior studies.

In summary, our study demonstrated that subjects with type 2 diabetes randomized to CrPic as opposed to placebo had significant attenuation in body weight gain, body fat distribution changes, improved glycemic control, and enhanced insulin sensitivity. The mechanisms for these findings are not precisely known, but clinical research studies addressing dietary intake, skeletal muscle fat oxidation, and insulin signaling are ongoing.

Acknowledgments— This study was supported in part by grants R55 DK060126 and R01 DK060126 awarded to W.T.C. and M01RR00109.

Technical assistance for chromium analysis provided by the Inorganic Toxicology and Radionuclide Laboratories, National Center for

Downloaded from http://diabetesjournals.org/care/article-pdf/29/8/1826/593598/zdc00806001826.pdf by guest on 17 May 2022

Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia.

References

1. Riddle MC: Glycemic management of type 2 diabetes: an emerging strategy with oral agents, insulins and combinations. *Endocrinol Metab Clin North Am* 34:77–98, 2005
2. Gibson JE, Taylor DA: Can claims, misleading information and manufacturing issues regulating dietary supplements be improved in the United States of America? *J Pharmacol Exp Ther* 314:939–944, 2005
3. Neuhouser ML: Dietary supplement use by American women: challenges in assessing patterns of use, motives and costs (Review). *J Nutr* 133: 1992S–1996S, 2003
4. Cefalu WT, Hu FB: Role of chromium in human health and in diabetes. *Diabetes Care* 27:2742–2751, 2004
5. American Diabetes Association: Standards of medical care in diabetes 2006. *Diabetes Care* 29 (Suppl. 1):S4–S42, 2006
6. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 237:E214–E223, 1979
7. Abumrad NN, Rabin D, Diamond MP, Lacy WW: Use of a heated superficial hand vein as an alternative site for the measurement of amino acid concentrations and for the study of glucose and alanine kinetics in man. *Metabolism* 30:936–940, 1981
8. García-Rubi E, Starling RD, Tchernof A, Matthews DE, Walston JD, Shuldiner AR, Silver K, Poehlman ET, Calles-Escandón J: $Trp^{64}Arg$ variant of the β_3-adrenoceptor and insulin resistance in obese postmenopausal women. *J Clin Endocrinol Metab* 83:4002–4005, 1998
9. Toth MJ, Sites CK, Cefalu WT, Matthews DE, Poehlman ET: Determinants of insulin-stimulated glucose disposal in middle-aged, premenopausal women. *Am J Physiol Endocrinol Metab* 281:E113–E121, 2001
10. Ballor DL, Harvey-Berino JR, Ades PA, Cryan J, Calles-Escandon J: Decrease in fat oxidation following a meal in weight-reduced individuals: a possible mechanism for weight recidivism. *Metabolism* 45:174–178, 1996
11. Paschal DC, Bailey GC: Determination of chromium in urine with graphite furnace atomic absorption spectrometry using Zeeman correction. *Atomic Spectroscopy* 12:151–154, 1991
12. Cefalu WT, Wang ZQ, Bell-Farrow A, Kiger FD, Izlar C: Glycohemoglobin measured by automated affinity HPLC correlates with both short-term and long-term antecedent glycemia. *Clin Chem* 40:1317–1321, 1994
13. 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, l998
14. Rossetti L: Glucose toxicity: the implications of hyperglycemia in the pathophysiology of diabetes mellitus. *Clin Invest Med* 18:255–256, 1995
15. Cefalu WT, Schneider DJ, Carlson HE, Migdal P, Gan Lim L, Izon MP, Kapoor A, Bell-Farrow A, Terry JG, Sobel BE: Effect of combination glipizide GITS/ metformin on fibrinolytic and metabolic parameters in poorly controlled type 2 diabetic subjects. *Diabetes Care* 25:2123–2128, 2002
16. 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
17. 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
18. 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
19. 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
20. Uusitupa MI, Mykkanen L, Siitonen O, Laakso M, Sarlund H, Kolehmainen P, Rassanen T, Kumpulainen J, Pyorala 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
21. 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
22. Amato P, Morales AJ, Yen SS: Effects of chromium picolinate supplementation on insulin sensitivity, serum lipids, and body composition in healthy, non-obese, older men and women. *J Gerontol A Biol Sci Med Sci* 55:M260–M263, 2000
23. 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
24. 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
25. 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
26. Evans GW: The effect of chromium picolinate on insulin controlled parameters in humans. *Int J Biosoc Med Res* 11:163–180, 1989
27. Purnell JQ, Weyer C: Weight effect of current and experimental drugs for diabetes mellitus: from promotion to alleviation of obesity. *Treat Endocrinol* 2:33–47, 2003
28. UKPDS Group: UK Prospective Diabetes Study 13: relative efficacy of randomly allocated diet, sulfonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *BMJ* 310:83–88 1995
29. Rampone AJ, Reynolds PJ: Obesity: thermodynamic principles in perspective. *Life Sci* 43:93–110, 1988
30. Webber J: Energy balance in obesity. *Proc Nutr Soc* 62:539–543, 2003
31. Institute of Medicine (IOM) Final Report: Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium and zinc. Washington, DC, National Academy Press, 2001, p. 197–223
32. Anderson RA, Kozlovsky AS: Chromium intake, absorption and excretion of subjects consuming self-selected diets. *Am J Clin Nutr* 41:1177–1183, 1985
33. Gargas ML, Norton RL, Paustenback DJ, Finley BL: Urinary excretion of chromium by humans following ingestion of chromium picolinate: implications for biomonitoring. *Drug Metab Dispos* 23:607–609, 1995
34. Clancy SP, Clarkson PM, DeCheke ME, Nosaka K, Freedson PS: Effect of chromium picolinate supplementation on body composition, strength, and urinary chromium loss in football players. *Int J Sport Nut* 4:142–153, 1994
35. 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
36. Jeejeebhoy KN: The role of chromium in nutrition and therapeutics and as a potential toxin. *Nutr Rev* 57:329–335, 1999
37. Gunton JE, Cheung NW, Hitchman R, Hams G, O'Sullivan C, Foster-PowellK, McElduff A: Chromium supplementation does not improve glucose tolerance, insulin sensitivity, or lipid profile: a randomized, placebo-controlled, double-blind trial of supplementation in subjects with impaired glucose tolerance. *Diabetes Care* 28:1841–1842, 2005
38. Komorowski J, Juturu V: Chromium supplementation does not improve glucose

Downloaded from http://diabetesjournals.org/care/article-pdf/29/8/1826/593598/zdc00806001826.pdf by guest on 17 May 2022

tolerance, insulin sensitivity, or lipid profile: a randomized, placebo-controlled, double-blind trial of supplementation in subjects with impaired glucose tolerance: response to Gunton et al (Letter). *Diabetes Care* 28:712–713, 2005

39. Kleefstra N, Houweling ST, Jansman FGA, Groenier KH, Gans ROB, Meyboom-de Jong B, Bakker SJL, Bilo HJG: Chromium treatment has no effect in patients with poorly controlled, insulin-treated type 2 diabetes in an obese Western population: a randomized, double-blind, placebo-controlled trial. *Diabetes Care* 29:521–525, 2006

Downloaded from http://diabetesjournals.org/care/article-pdf/29/8/1826/593598/zdc00806001826.pdf by guest on 17 May 2022