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Phenotype of subjects with type 2 diabetes mellitus may determine clinical response to chromium supplementation

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Abstract

Considerable controversy exists regarding the use of chromium (Cr) supplementation to modulate carbohydrate metabolism in subjects with diabetes. Recently, we reported that Cr supplementation, provided as 1000 μg/d as Cr picolinate, enhanced insulin sensitivity in subjects with type 2 diabetes mellitus. Our data agreed with some, but not all, studies that evaluated a similar dose and formulation in type 2 diabetes mellitus and suggested that subject selection and characteristics may be important considerations when assessing the clinical response. Thus, the goal of this study was to assess which metabolic or clinical characteristics, when obtained at baseline, best determine a clinical response to Cr when assessing changes in insulin sensitivity. Seventy-three subjects with type 2 diabetes mellitus were assessed in a double-blinded, randomized, placebo-controlled study. Subjects were assessed at baseline for glycemic control with glycated hemoglobin measures, oral glucose tolerance tests, and body weight and body fat measures (dual-energy x-ray absorptiometry). After baseline, insulin sensitivity in vivo was assessed with the use of hyperinsulinemic-euglycemic clamps. After the baseline clamp, subjects were randomized to receive Cr supplementation (1000 μg Cr/d provided as Cr picolinate) or placebo daily for 6 months. All study parameters were repeated after 6 months. The relationship of the baseline characteristics of the study subjects to the change in insulin sensitivity was determined. Sixty-three percent of the subjects with type 2 diabetes mellitus responded to the Cr treatment as compared with 30% with placebo. The only subject variable significantly associated with the clinical response to Cr was the baseline insulin sensitivity, as assessed with the hyperinsulinemic-euglycemic clamp (partial R^2 = .4038) (P = .0004). Subject phenotype appears to be very important when assessing the clinical response to Cr because baseline insulin sensitivity was found to account for nearly 40% of the variance in the clinical response to Cr.

1. Introduction

It is well observed in clinical trials that the measured response to an identical pharmacologic or lifestyle intervention will vary greatly among individuals. The reasons that explain a minimal as opposed to a very robust effect for subjects provided the same clinical intervention are not precisely known, but may be secondary to differences in genetic or physiologic makeup, in addition to differences in other subject characteristics. Such an observation may partially explain the considerable controversy that exists regarding the use of chromium (Cr) supplementation to modulate carbohydrate metabolism in subjects with diabetes. In part, the controversy regarding the differences reported for Cr's effect in humans stems from the lack of definitive randomized trials, the lack of "gold standard" techniques to assess glucose metabolism, the use of differing doses and formulations, and the study of heterogeneous study populations [1]. We recently reported that Cr supplementation, provided as 1000 μg/d as Cr picolinate, enhanced insulin sensitivity in subjects with type 2 diabetes mellitus [2]. However, our data agreed with some, but not all, studies that evaluated a similar dose and formulation in subjects with type 2 diabetes mellitus [3,4]. We concluded that patient selection may be an important consideration when assessing the clinical response to this nutritional supplement [2]. If a

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specific patient phenotype is shown to be more responsive to Cr or, alternatively, if a particular characteristic suggests that a patient is not likely to respond, such information would prove clinically invaluable. Therefore, the goal of this study was to assess which metabolic or clinical patient factors, when obtained at baseline, appear to best determine the clinical response to Cr. To accomplish our goal, we assessed insulin sensitivity with the use of hyperinsulinemic-euglycemic clamps before and after a specified period of Cr supplementation in subjects with type 2 diabetes mellitus. We then determined which subject characteristic accounted for the greatest contribution to the change in insulin sensitivity.

2. Research design and methods

Subjects were required to have type 2 diabetes mellitus for more than 6 months, an age range of 25 to 70 years, and a fasting glucose ≥125 mg/dL at the time of screening. All procedures were approved and conducted in strict compliance with institutional human research guidelines.

The evaluations were double blinded, randomized, and placebo controlled. After entry criteria had been met, each subject met with the study nutritionist, who provided instructions for a weight maintenance diet. During the baseline period of 4 weeks, measures consisting of glycated hemoglobin (GHb), oral glucose tolerance testing (OGTT), body weight, and percentage of body fat were obtained. Forty-eight subjects had baseline measures assessed while on dietary therapy only. An additional 25 subjects had baseline measures assessed while on maintenance sulfonylurea therapy. Specifically, these subjects were evaluated only after a 3-month period during which all subjects received stable doses of glipizide gastrointestinal therapeutic system (GITS) at 5 mg/d. Subjects are part of an ongoing double-blinded, randomized clinical trial supported by the National Institutes of Health that is evaluating the effect of Cr on insulin sensitivity and assessing the specific cellular mechanism of action. No subject was studied while maintained on agents known to affect insulin sensitivity, that is, metformin or thiazolidinediones. After completing all baseline measures, subjects were then admitted to the inpatient unit for assessment of insulin sensitivity with the use of hyperinsulinemic-euglycemic clamps. After completion of the clamp procedure and assessment of baseline insulin sensitivity, subjects were randomized to receive either two 500-μg capsules of Cr provided as Cr picolinate or 2 placebo capsules that were identical in physical characteristics. Subjects took assigned study capsules daily for 6 months. The Cr picolinate formulation was selected for these studies based on reports that it has a higher bioavailability compared with other formulations [1]. Subjects returned to the clinic monthly for assessment of compliance of study medication, to receive new monthly allotment of study capsules, for vital sign recording and adverse event monitoring, and to ensure that no change was occurring in dietary intake or lifestyle. All parameters, including assessment of insulin sensitivity with hyperinsulinemic-euglycemic clamps, were repeated at the end of study, that is, 6 months after randomization. The specific methodology for the hyperinsulinemic-euglycemic clamp, dual-energy x-ray absorptiometry scan, OGTT, and GHb has been described [2].

Multiple linear regression was used to analyze the data on SAS (SAS Institute, Cary, NC). All the investigated variables were involved in the model as independent variables. Dependent variable was the *response to Cr*, defined as the change in insulin sensitivity (assessed with clamp studies) at the end of study as compared with the baseline value. Model selection was based on the F test.

3. Results

A total of 73 subjects (38 male, 35 female) completed the protocol, in which 38 were randomized to Cr. The subjects had an average (±SD) age of 57.8 ± 8.7 years, GHb of 7.4% ± 2.4%, fasting glucose of 145.7 + 46.5 mg/dL, body mass index (BMI) of 30.4 ± 4.2, body weight of 87.4 + 12.7 kg, and whole-body glucose disposal (by clamp) of 287 ± 144 mg/min.

The response rate (defined by an increase in insulin sensitivity from baseline clamp to the end of study clamp) was 63% for the subjects randomized to Cr as opposed to 30% for those assigned to placebo. Table 1 summarizes the contribution of the study variables to the prediction model for change in insulin sensitivity. The only subject variable significantly associated with the clinical response to Cr was

Table 1
Summary of the contribution of the study variables to the prediction of clinical response for insulin sensitivity[a] from Cr supplementation

Predictor	Partial R^2	Model R^2	F	P	Parameter
Intercept					−130.1956
Glucose disposal[b]	0.4038	0.4038	17.88	.0004	−0.3632
Age	0.0000	0.4038	0.00	.9646	−0.7147
Weight	0.0003	0.4041	0.01	.9094	−1.9348
Insulin (fasting)	0.0033	0.4074	0.15	.7070	−0.5779
Glucose (fasting)	0.0050	0.4124	0.22	.6431	0.5107
% Body fat	0.0080	0.4204	0.35	.5583	3.3720
GHb	0.0017	0.4221	0.08	.7870	5.4212
BMI	0.0052	0.4273	0.23	.6367	7.5196
Glucose AUC	0.0368	0.4641	1.63	.2165	0.2674
Glucose (2 h)[c]	0.0463	0.5104	2.05	.1676	−1.4854
Insulin AUC	0.0017	0.5120	0.07	.7894	−0.0753
Insulin (2 h)[c]	0.0024	0.5144	0.11	.7475	0.1160
Sex	0.0105	0.5249	0.46	.5035	34.0174
Race	0.0235	0.5484	1.04	.3196	64.1322

AUC indicates the area under the curve obtained from 3-hour OGTT.

[a] Dependent variable is glucose disposal obtained from the end of study clamp − glucose disposal from baseline clamp.

[b] Whole-body insulin-mediated glucose disposal obtained at baseline as assessed with hyperinsulinemic-euglycemic clamp.

[c] Two-hour value from OGTT.

the baseline whole-body insulin-mediated glucose disposal, that is, insulin sensitivity, as assessed with the hyperinsulinemic clamp (P = .0004). This parameter accounted for nearly 40% (partial R^2 = .4038) of the variance in the clinical response to Cr (Table 1).

4. Conclusions

This preliminary report suggests that a major determinant for assessing clinical response to Cr in subjects with type 2 diabetes mellitus is the presence of insulin resistance before intervention. As described, variables assessed in this report included demographic parameters such as age, race, and sex; metabolic parameters that included assessment of GHb, glucose disposal obtained during clamp, insulin, and glucose response to OGTT; and phenotype parameters, as assessed by BMI, percentage of body fat, and body weight. With a statistical model that included all the other parameters, no other demographic or biochemical parameter other than the baseline insulin sensitivity was determined to be significant in the modeling used.

It has been well documented that concerns with past studies evaluating Cr have been the lack of definitive randomized trials and the lack of gold standard techniques to assess glucose metabolism [1]. For this study, we used the most precise measure of assessing insulin action, that is, hyperinsulinemic-euglycemic clamps. An additional strength of the study was the fact that we evaluated response in a randomized, double-blinded fashion. As described, all subjects received the same lifestyle instructions; and the groups consisted of being randomized to daily Cr or placebo. As observed at the end of study, the Cr group had a response rate of 63%, whereas the response rate observed for the placebo group, that is, 30%, would not be unexpected given the study design. Due in large measure to the labor intensity of the clamp technique, the cohort of subjects reported represents the largest database of individuals with type 2 diabetes mellitus evaluated to date with the use of hyperinsulinemic clamps after a specific period of Cr supplementation.

The observation that baseline insulin resistance is important in predicting clinical response was also suggested in animal studies [5,6]. Specifically, Cr supplementation did not increase insulin sensitivity in lean, insulin-sensitive animals, whereas improved insulin action and enhanced cellular signaling were observed in obese, insulin-resistant rats [5,6]. Other studies that evaluated different formulations of Cr have also suggested improved insulin sensitivity in different animal models [7,8]. Thus, it would appear that in clinical states such as obesity and insulin resistance, alterations in Cr metabolism may contribute to the attenuation in insulin action that may be improved with high-dose Cr supplementation. Such an observation, if validated, may partially explain the reported discrepancies in response to Cr in the human population and why Cr supplementation appears to have a more predictable response in hyperinsulinemic or obese states [1,9,10]. The precise molecular mechanism by which Cr improves insulin action in these states is the focus of the ongoing National Institutes of Health–supported clinical trial. However, it is noteworthy that the supplement had its major effect in individuals who were observed to be insulin resistant before the intervention. This observation, if confirmed once the study is completed, is an important public health finding given that insulin resistance was chosen as a primary end point because it is a key pathophysiologic feature of type 2 diabetes mellitus, obesity, and the "metabolic syndrome" and is strongly associated with coexisting cardiovascular risk factors and accelerated atherosclerosis [11].

In conclusion, this study is the first to report that baseline insulin resistance is a major factor in determining whether a patient may respond on a clinical level to supplemental Cr. Insulin resistance was shown to account for approximately 40% of the variance in the insulin sensitivity response to Cr after the treatment period. Although the presence of insulin resistance appears to be the largest contributor to clinical response, it is important to note that more than 60% of the response was not explained, which suggests that other factors, including genetic factors, may also play a major role.

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Authors and contribution to the study:

Zhong Q Wang: study design, manuscript preparation

Jianhua Qin: data analysis, manuscript review

Julie Martin: study coordination, subject recruitment, manuscript review

Xian H Zhang: study conduct, manuscript review

Olga Sereda: study conduct, performance of clamp procedures, manuscript review

Richard Anderson: study design, data review and analysis, manuscript review

Patricia Pinsonat: study coordination, subject recruitment, manuscript review

William T Cefalu: study design, data review and analysis, manuscript preparation

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