Author reply: Characterization of the metabolic and physiologic response to chromium supplementation in subjects with type 2 diabetes mellitus

Reply

We are responding to the specific comments from Dr Nanne Kleefstra as outlined in the Letter to the Editor in response to our recent article in your journal [1]. First and foremost, Dr Kleefstra stated concerns with the methodology and interpretation of our results in which we suggested that chromium supplements might be beneficial in a selected population of insulin-resistant patients with poor glycemic control. Dr Kleefstra stated that they performed a trial in such a patient group, which showed that chromium supplementation did not result in any significant effect compared with placebo [2]. With all due respect, we have carefully evaluated Dr Kleefstra's study in comparison to our study to evaluate the reasons for the different outcomes and actually have reported the findings [3]. In this regard, patient selection may be playing a major role. In the studies reported by Kleefstra et al [2], subjects were also from a Western population and were considered obese (body mass index range, 33-35). However, the subjects evaluated by Kleefstra et al [2] were more advanced in their disease process; for example, diabetes duration ranged from 10.9 to 18.4 years as compared with our recently reported study in subjects who were much earlier in their disease process, generally less than 5 years [1]. In addition, by design, the cohort evaluated by Kleefstra et al [2] were taking high-dose insulin (dose, 78-105 U/d), in addition to many subjects already taking metformin [2,3]. Subjects from our recent study evaluating individuals with type 2 diabetes mellitus (DM) were excluded if they were on medications known to affect carbohydrate metabolism, including antidiabetic medication. With these data, it remains unclear as to what are the specific differences that account for the conflicting results among carefully controlled trials. One consideration that appears very likely is that differences in subject characteristics may be one of the reasons that may explain the differences noted in efficacy as reported for various studies.

Our data suggesting that phenotype may be important when evaluating chromium response are supported by preclinical data [4,5]. For example, we evaluated the response to chromium in both lean and obese JCR rats, a model of obesity and insulin resistance, and reported that response to Cr was dependent on baseline phenotype. In a pilot human study, we reported that baseline patient characteristics can influence the response to Cr, as the baseline insulin sensitivity was significantly associated with the clinical response to Cr (P = .0004) and accounted for 40% (partial R^2 = 0.4038) of the variance in the clinical response [6]. Finally, our conclusion that a clinical response to chromium is more likely in insulin-resistant individuals with type 2 DM who have more elevated fasting glucose and A_{1c} levels appears to agree with other prior reports [7].

Dr Kleefstra commented that reporting the overall results and then dividing the intervention group in 2 separate cohorts of responders and nonresponders seem to be stretching statistical possibilities. However, as pointed out in his letter, data management was indeed designed not only to look at the effect in the total cohort, but to specifically evaluate what characteristics define a response.

The final point made by Dr Kleefstra was our definition of chromium status.

However, we would like to point out that our study is the most comprehensive study to date for which an overall assessment of chromium status was defined as multiple plasma samplings over time combined with urinary excretion. With this design, we demonstrated that chromium "status" in plasma and urine did not predict response. The point to be made is that we do not feel that a clinical response to chromium is dictated by serum levels or urinary excretion. Clearly, other factors are involved that predict or are responsible for the effect. This information alone is novel and clarifies a major controversy in human chromium research.

The last point we would like to make is that our study represents the largest cohort to date that has been evaluated for chromium supplementation with the use of "state of the art" metabolic techniques including use of euglycemic-hyperinsulinemic clamps for measuring insulin sensitivity, metabolic chambers for measuring energy expenditure, ingestive behavior laboratories for assessing dietary intake, and magnetic resonance spectroscopy for assessing myocellular and hepatic fat. Thus, our completed study reported in the recent volume of *Metabolism* represents the most comprehensive, double-blinded, placebo-controlled trial to date on chromium supplementation in subjects with type 2 DM.

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