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

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OBJECTIVE — Chromium treatment has been reported to improve glycemic control and insulin sensitivity in specific populations of patients with type 2 diabetes. The aim of this study was to determine the effect of chromium treatment on glycemic control in a Western population of insulin-dependent patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — In this 6-month double-blind study, patients with an HbA_{1c} (A1C) >8% and insulin requirements of >50 units/day were randomly assigned to receive treatment with placebo or 500 or 1,000 μg chromium daily in the form of chromium picolinate. The primary efficacy parameter was a change in A1C. Secondary end points were changes in lipid profile, BMI, blood pressure, and insulin requirements.

RESULTS — In this per-protocol analysis ($n = 46$), the decrease in A1C was approximately equal across the three groups (0.4%). All patients had a BMI >25 kg/m². No differences were found in the secondary end points. We found a weak relationship between an increasing serum chromium concentration and improvement of the lipid profile.

CONCLUSIONS — There is no evidence that high-dose chromium treatment is effective in obese Western patients with type 2 diabetes.

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W ith the ever-growing epidemic of type 2 diabetes, investigations are directed toward prevention and pharmaceutical and lifestyle interventions to treat type 2 diabetes. Since insulin resistance is seen as a major contributor to the development of overt type 2 diabetes, efforts are being directed toward the improvement of insulin sensitivity. One possible method to improve insulin sensitivity is chromium supplementation.

In vitro and animal studies (1,2) have shown chromium to have a positive effect on insulin sensitivity. One of the intracellular proteins influencing the insulin receptor is the oligopeptide apolipoprotein, low molecular–weight, chromium-binding substance (apo-chromomodulin) (2). In vitro, this peptide has the ability to increase tyrosine kinase activity eightfold, depending on the chromium concentration (3). This in turn promotes insulin receptor activity, thus eliciting improved insulin sensitivity. Therefore, for some time now, chromium has been thought to play a beneficial role in glucose metabolism and, as early as 1957, was referred to as a "glucose tolerance factor" (4). It has been marketed as such by some companies in the U.S.

There are studies that support this proposed effect. Anderson et al. (5) studied the effects of chromium treatment in a group of Chinese patients with type 2 diabetes. They reported an average decrease in HbA_{1c} (A1C) of almost 2 percentage points after only 4 months of treatment with 1,000 μg chromium daily. Since then, the effects of chromium on glycemic control, lipid profile, weight, and muscular strength have been investigated, both in nondiabetic healthy subjects and in patients with type 2 diabetes. Two systematic reviews (6,7) on the effects of chromium on glycemic control have been published. Both reviews concluded that based on the currently available data, the effects of chromium on glycemic control are inconclusive. Too few well-designed studies have been performed, especially in Western populations, to allow any definitive conclusions.

A recent study in subjects with impaired glucose tolerance did not show any effects with chromium supplementation (800 μg daily) on glucose tolerance, insulin sensitivity, or lipid profile (8). We have performed a double-blind randomized placebo-controlled study investigating the effects of chromium on glycemic control and on factors associated with the metabolic syndrome in subjects with type 2 diabetes within a Western population.

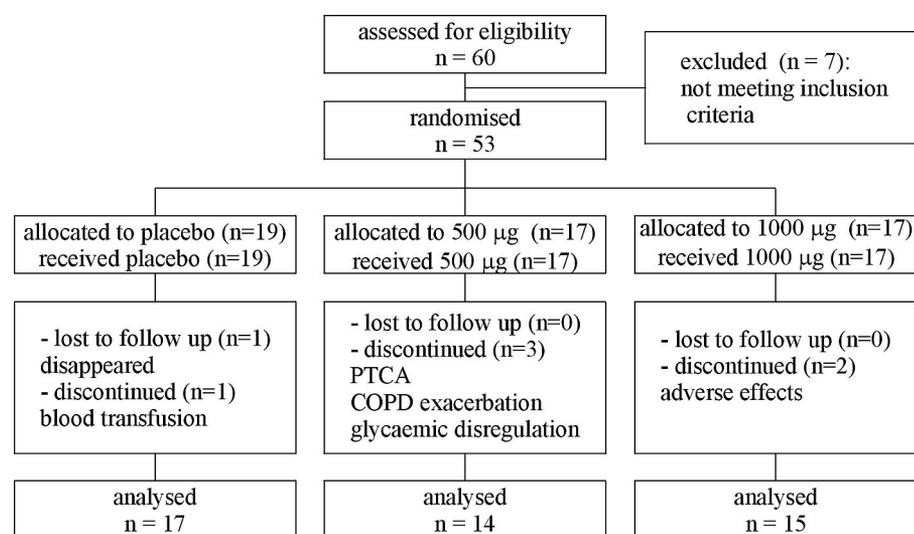## RESEARCH DESIGN AND METHODS — Using our local Diabetes Electronic Management System, we selected patients with type 2 diabetes who

Figure 1—*CONSORT flow diagram.*

met the following eligibility criteria: A1C ≥8%, daily use of insulin ≥50 units, creatinine ≤150 μmol/l for men and ≤120 μmol/l for women, creatinine clearance ≥50 ml/min, alanine aminotransferase ≤ 90 units/l, and age <75 years. Exclusion criteria included pregnancy (including patients who were trying to conceive) and a history of liver or renal disease. To test our hypothesis that chromium reduces A1C (primary outcome measure) (with a power of 80%, α = 0.05, two tailed), a sample size of 14 per group is required to detect a 1% absolute reduction in A1C. To compensate for nonevaluable patients, we planned to enroll 20 patients per group. Secondary outcome measures were changes in lipid profile, body weight, blood pressure, and plasma chromium concentration. After the potential participants had been informed of the study by their attending internist and by information sent by mail, the researchers contacted the patients by telephone at home and asked whether they would be willing to participate. Patients were included after written informed consent was obtained. This study was approved by the medical ethics committee of the Isala Clinics, Zwolle, the Netherlands.

The study was carried out in a diabetes outpatient clinic situated in one of the hospitals in Zwolle. Seven patients were not randomized since they did not meet the eligibility criteria (one patient was excluded because he used <50 units of insulin per day, and six patients had an A1C <8%) (Fig. 1; 9). A total of 53 patients were randomized into the following three groups: one group was given a placebo (n = 19), one group received 250 μg

chromium picolinate twice daily (n = 17), and one group received 500 μg chromium picolinate twice daily (n = 17). In total, 46 patients completed the study period of 6 months. Patients were asked not to change their diet and their insulin dosages. In general, they were asked not to change anything in their lifestyles and to continue their lives as normally as possible. Additionally, no changes were made in cholesterol-reducing, blood pressure–lowering, or oral hypoglycemic agents during the study period. In the case of complaints related to hypoglycemia or symptomatic hyperglycemia, the insulin scheme was adjusted.

All capsules, including placebo, were furnished by our hospital pharmacy and were indistinguishable from each other. Neither the researchers nor the patients knew into which group they had been randomized. Independent pharmacists dispensed either chromium capsules or placebo in numbered containers according to a computer-generated randomization list. No restrictions were used. The code was revealed to the researchers once recruitment, data collection, and laboratory analyses were complete. The chromium capsules were made with chromium picolinate containing 12% chromium (Fagron Pharmaceuticals, Nieuwerkerk aan de IJssel, the Netherlands). Patients were instructed to take one tablet at breakfast time and one during the evening meal. In case of side effects, patients were requested to stop taking the study medication for 1 week and then to resume the twice-daily dosing if the side effects had disappeared.

At baseline, we recorded the duration

of the diabetes, diabetes medication(s), any other medication(s), and insulin requirements. Patients were weighed barefooted and clothed. Height was measured with the patients not wearing shoes, and blood pressure was measured with the patient in a sitting position. The mean of two blood pressure measurements taken with a minimal interval of 15 s from the right arm was calculated. The validated automated blood pressure device Omron HEM-711 was used (10). Serum creatinine, hemoglobin, alanine aminotransferase, A1C, serum total cholesterol, LDL, HDL, triglycerides, and plasma chromium were measured according to standard hospital procedure. We used the Cockcroft and Gault formula to estimate glomerular filtration rate from serum creatinine, age, and body weight (11).

After 1, 3, and 6 months, the same measures as at baseline were reassessed, except for height. Any reported side effects were also recorded. Plasma chromium was analyzed by the method of additions calibrate, using a Perkin-Elmer AA 800 Zeeman furnace electrothermal atomic absorption spectrophotometer (PerkinElmer Benelux, Hoevestein, Oosterhout, the Netherlands), based on a previously described method (12). Assay performance was monitored with standard reference material (bovine serum; Dutch Foundation for Quality Assessment in Clinical Laboratories, Nijmegen, the Netherlands) with a target value of 20.6 ± 2.1 nmol/l chromium. Three different samples were analyzed per patient with concentration value variations not exceeding 15%. The detection limit was 10 nmol/l.

Statistical analyses
In Fig. 1, the CONSORT diagram of this study is presented (9). Per-protocol analyses were performed. To evaluate differences in target variables over time and between the groups, we used the general linear model (repeated measures with Greenhouse-Geiser test). The assumption of the general linear model that the distribution of the residual scores should be normal was checked by inspecting the distribution of the residuals using normal probability plots. The Spearman's rank correlation was used to investigate associations between continuous variables. SPSS software, Version 11.0, was used for all the analyses.

Table 1—*Baseline characteristics per intervention group*

	Placebo	500 μg	1,000 μg
n	17	14	15
Sex (male)	10 (59)	4 (29)	5 (33)
Age (years)	62 ± 7.5	60 ± 8.8	59 ± 6.4
Diabetes duration (years)	18.4 ± 8.3	12.5 ± 5.0	10.9 ± 6.3
Total dose of insulin (units)	90 ± 26	105 ± 43	78 ± 22
A1C (%)	9.41 ± 1.01	9.43 ± 1.02	9.67 ± 0.91
Systolic blood pressure (mmHg)	159 ± 20	147 ± 24	156 ± 25
Diastolic blood pressure (mmHg)	83 ± 10	85 ± 10	84 ± 14
BMI (kg/m^2)	34 ± 4.3	35 ± 7.2	33 ± 4.2
Total cholesterol (mmol/l)	5.00 ± 0.99	4.85 ± 0.75	4.47 ± 0.85
Total-to-HDL cholesterol ratio	4.50 ± 1.1	3.72 ± 1.40	3.85 ± 1.29
Triglycerides (mmol/l)	2.1 ± 1.2	2.0 ± 1.3	1.9 ± 1.1
HDL (mmol/l)	1.15 ± 0.26	1.47 ± 0.54	1.26 ± 0.40
LDL (mmol/l)	2.90 ± 1.02	2.50 ± 0.48	2.34 ± 0.75
Chromium (nmol/l)*	10	15 (10–37)	14 (10–32)

Data are means ± SD, mean (range), or n (%). *No patient in the placebo group had at baseline a chromium concentration >10 nmol/l.

RESULTS — Eligible participants were recruited from March 2002 to August 2002. Of 53 patients randomized, 1 patient was lost to follow-up (Fig. 1 [ref.9]), and all attempts to locate this subject were in vain (telephone contact, letters, and visits). Six other subjects, one in the placebo group, three in the 500-μg group, and two in the 1,000-μg group, discontinued the study for the following reasons: one patient required a blood transfusion and was hospitalized, and three other patients were hospitalized due to percutaneous transluminal coronary angioplasty, chronic obstructive pulmo-

nary disease, and glycemic disregulation. Two patients discontinued the study due to possible adverse effects. Both patients were randomized in the 1,000-μg group. One patient complained of frequent watery stools, weakness, dizziness, nausea, and headaches. One day after the medication was discontinued, the complaints disappeared and remained absent for 1 week. The symptoms reappeared when the patient restarted the medication. The other patient developed complaints of vertigo with nausea and vomiting. This patient retired from the study and was not prepared to try stopping for 1 week and

then restarting the medication. A total of 46 subjects, 17 in the placebo group, 14 in the 500-μg group, and 15 in the 1,000-μg group were included in the analyses.

The baseline characteristics of the three groups are shown in Table 1. All patients had a BMI >25 kg/m^2 (means ± SD, 34 ± 5.2). Table 2 shows the changes in the variables per intervention after 6 months. No significant differences were found over time for the three groups. There was a significant difference in HDL levels between the groups. However, after correcting for baseline differences, this was lost. Also, when controlling for weight change and insulin dose adjustments, no significant differences were found for all variables.

Table 3 shows a subgroup analysis of all the patients who showed an increase in their serum chromium concentration. This subgroup analysis was a post hoc analysis, being performed because of notably different serum chromium concentrations after 6 months. The correlation coefficients are shown for the difference in chromium concentration and the differences in the other parameters after 6 months. An increase in chromium concentration yields a trend toward improvement in lipid profile. This is significant after 6 months for LDL, total cholesterol, and the total-to-HDL cholesterol ratio.

CONCLUSIONS — Chromium picolinate treatment had no effect on weight,

Table 2—*Changes per intervention group after 6 months*

	Placebo	500 μg*	1,000 μg*	Change 500 μg vs. placebo	Change 1,000 μg vs. placebo	Change 1,000 μg vs. 500 μg
n	17	14	15			
Total dose of insulin (units)	−1.2 ± 7.3	1.8 ± 5.2	0.0 ± 3.1	3.0 (−2.1 to 8.1)	1.2 (−3.7 to 6.2)	−1.8 (−7.1 to 3.5)
A1C (%)	−0.3 ± 0.8	−0.5 ± 0.8	−0.3 ± 0.8	−0.2 (−1.0 to 0.6)	0.0 (−0.8 to 0.8)	0.2 (−0.6 to 1.0)
Systolic blood pressure (mmHg)	−7 ± 19	−7 ± 15	−1 ± 21	0 (−17 to 17)	6 (−10 to 22)	6 (−11 to 23)
Diastolic blood pressure (mmHg)	−6 ± 7	−4 ± 11	0 ± 11	2 (−6 to 11)	7 (−2 to 15)	4 (−5 to 13)
BMI (kg/m^2)	0.0 ± 0.7	0.2 ± 1.1	0.2 ± 1.0	0.2 (−0.7 to 1.0)	0.3 (−0.5 to 1.1)	0.1 (−0.8 to 1.0)
Total cholesterol (mmol/l)	0.2 ± 1.2	−0.2 ± 0.8	0.1 ± 0.4	−0.4 (−1.2 to 0.4)	−0.2 (−0.9 to 0.6)	0.2 (−0.6 to 1.0)
Total-to-HDL cholesterol ratio	−0.3 ± 0.4	−0.2 ± 0.7	−0.3 ± 0.5	0.2 (−0.3 to 0.7)	0.0 (−0.5 to 0.5)	−0.2 (−0.7 to 0.3)
Triglycerides (mmol/l)	1.0 ± 4.3	−0.1 ± 0.9	−0.2 ± 0.5	−1,1 (−3.5 to 1.3)	−1,2 (−3.5 to 1.2)	0.0 (−2.5 to 2.4)
HDL (mmol/l)†	0.1 ± 0.1	−0.1 ± 0.3	0.1 ± 0.1	−0.2 (−0.3 to 0.0)	0.0 (−0.1 to 0.2)	0.2 (0.0–0.3)
LDL (mmol/l)	0.3 ± 0.7	−0.1 ± 0.6	0.0 ± 0.4	−0.3 (−1.4 to 0.7)	−0.3 (−1.3 to 0.7)	0.1 (−1.0 to 1.1)
Chromium (nmol/l)‡	0	16 ± 16	50 ± 28	16 (−4 to 36)	49 (30–69)	33 (14–52)

Data are means ± SD within the group and mean differences between groups (95% CI) (Bonferroni corrected). *Five hundred μg chromium and 1,000 μg chromium as chromiumpicolinate. †$P = 0.041$. ‡The chromium concentration increased above the detection limit in no patients in the placebo group. The chromium concentration increased above this limit in all patients in both intervention groups.

Table 3—*Correlations between differences in chromium concentrations and differences in parameters after 6 months in chromium-treated patients* (n = 29)

Parameters	0–6 months	
	r	P
ΔA1C	−0.020	0.920
ΔSystolic blood pressure	−0.003	0.989
ΔDiastolic blood pressure	−0.194	0.331
ΔBMI	−0.108	0.598
ΔTotal cholesterol	−0.456	0.017
ΔTotal-to-HDL cholesterol ratio	−0.437	0.023
ΔTriglyceride	−0.353	0.071
ΔHDL	0.105	0.603
ΔLDL	−0.397	0.040

blood pressure, A1C, or lipid profile compared with placebo in this double-blind randomized, controlled trial of 6 months in obese patients with poorly controlled type 2 diabetes in a Western society. Two patients stopped the study medication of 1,000 μg chromium picolinate per day due to adverse effects. In a post hoc analysis, we did find a relationship between increase in chromium concentration in blood and improvements in lipid profile. After 6 months, LDL, total-to-HDL cholesterol ratio, and total cholesterol showed significant improvement.

We were not able to reproduce the results of Anderson et al. (5). Their study was not included in the systematic reviews described earlier (6,7), in which no effects of chromium on glycemic control was found. Anderson's study was performed in a large cohort (*n* = 180) of Chinese patients with type 2 diabetes and showed a decrease of almost 2% in A1C levels after a period of 4 months. After the systematic reviews, a randomized controlled trial (13) with chromium was published that reported significant results. This study population consisted of Indian patients with type 2 diabetes. A1C increased from 7.2 to 7.9% in the placebo group, whereas in the group treated with 400 μg chromium picolinate it remained 7.2%. Anderson et al. did not report any side effects for 1,000 μg chromium picolinate per day and neither did other randomized controlled trials.

A possible explanation for the absence of a significant difference between the treatment group and the placebo group may be that the 1% decrease in A1C in our power calculation was an overestimate (despite the fact that it is half the decrease in A1C found by Anderson et al.). Another reason may be that our population was less chromium deficient compared with the Chinese population of Anderson et al. and that our population was far more obese (BMI 34 vs. 25 kg/m^2) (5). Unfortunately, there is still no real standard for chromium deficiency, and as such it is not possible to select patients on this basis (14). Western diabetic patients may require higher quantities of chromium, or may need it for a longer period of time, compared with Chinese diabetic patients. Unfortunately, intention-to-treat analyses were not possible because for five of six excluded patients follow-up data were lacking. However, the main conclusions of the per-protocol analyses would likely not have been different in an intention-to-treat analyses. We have to point out however, that our results may not be applicable to every Western patient with type 2 diabetes, since we only included poorly controlled patients who needed large quantities of insulin. Another limitation of our study is the lack of a pill count. However, the chromium concentration of every patient treated with 500 and 1,000 μg chromium increased, which was not the case in any of the patients in the placebo group. Furthermore, we did not investigate the patients' usual dietary intake of chromium. We were therefore not able to investigate possible different effects between patients with poor or an adequate intake of chromium.

Based on our results, there is no convincing evidence that chromium therapy in an obese Western diabetic population will improve glycemic regulation or the parameters of the insulin resistance syndrome (6). Treatment with chromium had no effect on these parameters in patients with poorly controlled type 2 diabetes. Therefore, it would be premature to recommend using chromium as a part of standard diabetes therapy (15). Although found in a post hoc analysis, it is of interest that an increasing chromium concentration was related to an improvement in the lipid profile. Further independent (larger-designed) studies may be necessary to further investigate the possible effects of chromium supplementation on glycemic control or lipid profile in Western populations. Whether it is possible to select subgroups of patients with suitable certain phenotypes that may or may not benefit from chromium therapy also needs further attention (16).

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