Chromium treatment has no effect in patients with type 2 diabetes in a Western population

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Chromium Treatment Has No Effect in Patients With Type 2 Diabetes in a Western Population

A randomized, double-blind, placebo-controlled trial

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OBJECTIVE — Chromium treatment has been reported to improve glycemic control in patients with type 2 diabetes. However, concern exists about the possible toxic effects of chromium picolinate. The aim of this study was to determine the effect of chromium treatment in the form of chromium yeast on glycemic control in a Western population of patients with type 2 diabetes who were being treated with oral hypoglycemic agents.

RESEARCH DESIGN AND METHODS — In this 6-month, double-blind study, patients with moderate glycemic control, being treated with oral hypoglycemic agents, were randomly assigned to receive either a placebo or treatment with 400 μg of chromium daily in the form of chromium yeast. The primary efficacy parameter was a change in A1C. Secondary end points were changes in lipid profile, BMI, blood pressure, body fat, and insulin resistance.

RESULTS — No differences were found for the change in A1C between the intervention and placebo groups, nor were any differences found between the groups for the secondary end points.

CONCLUSIONS — There is no evidence that chromium in the form of chromium yeast is effective in improving glycemic control in Western patients with type 2 diabetes who are taking oral hypoglycemic agents.

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Type 2 diabetes is a chronic, progressive illness that causes considerable morbidity and premature mortality (1,2). The worldwide prevalence of type 2 diabetes is high and is increasing steadily (3). The majority of patients are insulin resistant (4). Although these patients may be treated with well-established hypoglycemic agents, studying alternative treatment options directed toward improving insulin sensitivity is important.

For many decades, we have known that chromium plays a role in glucose metabolism, and, as early as 1957, it was already being referred to as "a glucose tolerance factor" (5). In vitro and animal studies have shown that chromium improves insulin resistance (6,7). One of the intracellular proteins that influences the insulin receptor is the oligopeptide apolipoprotein low–molecular weight chromium-binding substance (Apochromomodulin) (7). This peptide has the ability to increase tyrosine kinase activity eightfold, depending on the chromium concentration (8), thus strengthening the idea that chromium plays an influential role in glucose metabolism (5).

The largest study (n = 180) to date investigating the effect of chromium in patients with type 2 diabetes was published by Anderson et al. (9). They found that the A1C of Chinese patients treated with 1,000 μg of chromium in the form of chromium picolinate decreased almost 2 percentage points compared with a placebo group after 4 months. However, two systematic reviews that addressed the effects of chromium on glycemic control concluded that, on the basis of the currently available data, the effects of chromium on glycemic control are inconclusive (10,11). Randomized studies with results on glucose, insulin, and/or A1C were collected by Althuis et al. (10) in their review. Reasons for the inconclusive findings are that too few trials in patients with diabetes have been conducted to allow conclusive findings (three trials with a total of 38 subjects).

Furthermore, in recent years, the safety of chromium supplements has been called into question because of mixed results in studies investigating the mutagenicity of chromium picolinate in vitro (12–14). Although toxic effects were reported in neither the systematic reviews (10,11) nor in the study of Anderson et al. (9), chromium picolinate was banned by the Food Standards Agency until December 2004 (15). This meant that investigations into the effects of chromium compounds on type 2 diabetes had to involve compounds other than chromium picolinate. Some studies, in which the effects of chromium-enriched yeast in nondiabetic patients were investigated, showed mixed results (16–19). Bahijri et al. (20) investigated the effects of different forms of chromium with a double-blind cross-over design and concluded that fasting glucose in patients with type 2 diabetes improved after 8 weeks of daily di-

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Abbreviations: ALT, alanine aminotransferase; CONSORT, Consolidated Standards of Reporting Trials; GLM, general linear model; HOMA-IR, homeostasis model assessment of insulin resistance.

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

etary supplementation with brewer's yeast containing 23.2 μg of chromium. We performed a double-blind, randomized, placebo-controlled study to investigate the effects of chromium in the form of chromium yeast (*Saccharomyces cerevisiae*) on glycemic control, insulin resistance, and factors associated with the metabolic syndrome in subjects with type 2 diabetes in a Western population.

RESEARCH DESIGN AND METHODS

— Using our local Diabetes Electronic Management System, we selected patients with type 2 diabetes from a village in the Zwolle region in the northern Netherlands who met the following eligibility criteria: A1C 7–8.5% as measured during their latest visit, treatment with oral hypoglycemic agents only, no change in treatment during the preceding 3 months, creatinine ≤150 μmol/l for men and ≤120 μmol/l for women, creatinine clearance ≥50 ml/min, and alanine aminotransferase (ALT) ≤90 units/l. Exclusion criteria included pregnancy (including patients who were trying to conceive), known allergy or intolerance to yeast, and current use of chromium supplements.

In five general practices in a village in the region of Zwolle, 63 patients had a A1C of 7–8.5%, with a mean ± SD of 7.7 ± 0.44%. To test our hypothesis that chromium causes a 0.5% absolute reduction in A1C (primary outcome measure), with a power of 95% and α of 0.05, two-tailed; a sample size of 22 per group would be required (assuming a correlation of 0.5 between pretest and posttest). To compensate for nonevaluable patients, we planned to enroll 30 patients per group. The secondary outcome measures were changes in lipid profile, body weight, blood pressure, body fat, and insulin resistance. After the potential participants had been informed about the study by their attending general practitioner and by mail, the researchers contacted each candidate patient 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, Netherlands.

The study was carried out in a general practice in the Zwolle region. One patient, who initially had agreed to participate in the study, later refused to participate. Two patients were not randomly assigned because they did not meet the eligibility criteria (both creatinine clearances <50 ml/min). Figure 1 shows the Consolidated Standards of Reporting Trials (CONSORT) flow diagram (21). A total of 57 patients were randomly assigned into the following two groups: one group was given two placebo tablets twice daily (n = 28) and one group received two tablets of 100 μg of chromium yeast twice daily (n = 29); 56 patients completed the study, which lasted 6 months.

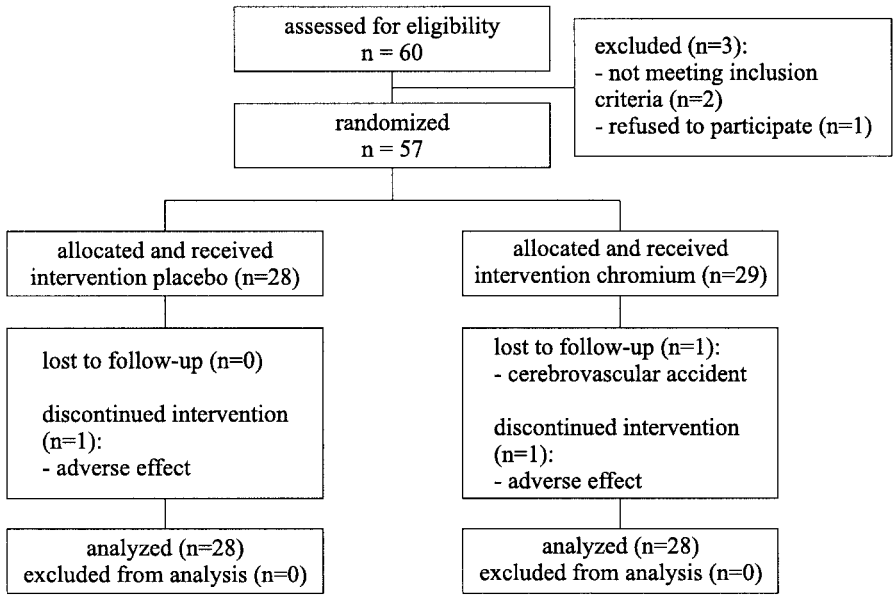

Figure 1—*CONSORT flow diagram.*

The study participants were asked not to make any lifestyle changes. No changes were made in cholesterol-reducing and blood pressure–lowering agents during the study. Adjustments were made to the oral hypoglycemic agents only when patients developed complaints relating to hypoglycemia or symptomatic hyperglycemia.

All of the study medications, including the placebo, were supplied by Pharma Nord (Sadelmagervej, Vejle, Denmark) and were indistinguishable from each other. The researchers did not know into which group the patients had been randomly assigned nor did the patients. The drug packages were labeled with a randomization code by the pharmacy. No restrictions were used. The code was only revealed to the researchers once recruitment, data collection, and laboratory analyses were complete. The patients were instructed to take two tablets with breakfast and two with the evening meal. If the patients developed any side effects, they were requested to stop taking the study medication for 1 week and then to resume.

At baseline, we recorded the duration of the type 2 diabetes and any medication(s) the patients were taking. The patients were weighed with clothing on but without shoes. Height was measured without shoes. Blood pressure was measured after the patient had been sitting for a minimum of 5 min. Blood pressure was measured twice on each arm with a minimal interval of 15 s between successive measurements. The mean for each arm was calculated. When there was an interarm difference of >10 mmHg between the systolic and/or diastolic blood pressures, the follow-up measurements were continued on the arm with the higher blood pressure. When the difference was less, an arbitrary arm was taken for the next measurements. The validated automated blood pressure device Omron HEM-711 was used (22). We used the validated Omron HBF-306-E to estimate the patients' body fat percentages and used the mean of two consecutive measurements (23).

Serum creatinine, hemoglobin, ALT, A1C, fasting plasma glucose, serum total cholesterol, LDL, HDL, triglycerides, and fasting insulin were measured according to the standard hospital procedures of the Isala clinics. A 24-h urine sample was collected, and volume, creatinine, and albumin were measured. We used the homeostasis model assessment to estimate insulin resistance (HOMA-IR) (24).

Hemoglobin and A1C were measured at 3 months. At 6 months, all of the as-

Table 1—*Baseline characteristics per intervention group*

	Placebo	Chromium
n	28	29
Sex (male)	17 (49)	18 (51)
Age (years)	66 ± 8.6	68 ± 8.2
Diabetes duration (years)	4.5 (2.0,9.5)	6.0 (4.0,10.0)
Body weight (kg)	87 ± 17	88 ± 20
BMI (kg/m^2)	30 ± 5.6	30 ± 5.9
Body fat (%)	34 ± 7.7	34 ± 7.8
Systolic blood pressure (mmHg)	153 ± 19	151 ± 20
Diastolic blood pressure (mmHg)	88 ± 10	88 ± 13
Hemoglobin (mmol/l)	8.8 ± 0.7	8.7 ± 0.8
ALT (units/l)	30 ± 16	34 ± 18
Creatinine (μmol/l)	97 ± 16	95 ± 18
Creatinine clearance (ml/min)	88 ± 24	97 ± 36
Albuminuria (mg/24 h)	4.44 (3.00,29.13)	4.9 (3.00,17.00)
Fasting plasma glucose (mmol/l)	8.0 ± 1.8	8.7 ± 2.3
A1C (%)	7.01 ± 0.50	6.92 ± 0.67
Total cholesterol (mmol/l)	4.60 ± 1.34	4.46 ± 1.15
Cholesterol-to-HDL ratio	3.70 ± 1.25	3.68 ± 1.14
Triglycerides (mmol/l)	1.46 (0.91,2.34)	1.70 (1.11,2.10)
HDL (mmol/l)	1.31 ± 0.38	1.28 ± 0.36
LDL (mmol/l)	2.50 ± 0.95	2.42 ± 1.01
HOMA-IR (units)	3.8 (2.7,5.5)	5.8 (2.7,8.9)

Data are means ± SD, *n* (% of known data), or median (P_{25},P_{75}).

sessments done at baseline were repeated with the exception of height. Any reported side effects were recorded at 3 and at 6 months.

At 1 month (telephone contact), 3 months, and 6 months, we asked patients how they were faring with the study medication to check and stimulate compliance. At 3 and 6 months, all remaining tablets were collected and counted. At 6 months, we asked the patients to guess into which group they had been assigned. If the study was successfully blinded, the ability of participants to accurately guess their group assignment should not be better than chance.

In the intention-to-protocol analyses, patients were excluded when the pill count was <90%. Furthermore, patients were excluded from intention-to-protocol analyses for glycemic, blood pressure, and/or lipid parameters if any change had been made in hypoglycemic, antihypertensive, and/or lipid-lowering drugs, respectively.

Statistical analyses

A CONSORT diagram was used for this study as presented in Fig. 1 (21). The Mann-Whitney *U* test was used for nonnormal variables, and the χ^2 test was applied to categorical variables. To evaluate differences in target variables over time and between the groups, we used the general linear model (GLM). For variables measured at baseline, after 3 and after 6 months the GLM repeated measures with the Greenhouse-Geiser test was used; the three variables were used as within-subject variables and randomization to chromium or placebo was used as a between-subjects factor. For variables measured at baseline and after 6 months, we used the GLM univariate with change in variable over 6 months as the dependent variable and randomization to chromium or placebo as the fixed factor. In both the GLM repeated measures and the univariate, the baseline value was set as the covariate. SPSS software (version 11.0; SPSS, Chicago, IL) was used for all the analyses.

RESULTS — Eligible participants were recruited in August 2004. Of the 57 patients who were randomly assigned, 1 patient did not complete the study (Fig. 1) because of a cerebrovascular accident (intervention group).

Two patients experienced adverse effects. One patient in the intervention group complained of nausea, which disappeared when the medication was stopped and reappeared after restart. One patient in the control group complained of nonspecific stomach problems, which disappeared during cessation of medication and reappeared after restart.

Table 1 shows the baseline characteristics of the patients. Random assignment was successful, as two comparable groups resulted for most variables. Diabetes duration, fasting plasma glucose, and HOMA-IR appear to be longer or higher, respectively, in the chromium group.

The percentage of medication used was calculated and compared with the expected percentage in subjects with 100% compliance (25,26). The mean percentage in the chromium group was 93.1 (median [25–75%] 95.5 [91.1–98.2]), and the mean percentage in the placebo group was 94.4 (97.3 [92.3–98.1]). This difference was not significant ($P = 0.606$). Three patients in the placebo group and four in the chromium group did not reach a minimum pill count of 90%. No explanation for this stoppage was found for two patients (one in each group). For the other patients, the reasons were stopping during a hospital stay ($n = 2$), stopping during a flu period ($n = 2$), and taking one tablet twice daily for a brief time by mistake ($n = 1$). Two patients (one in each group) started insulin therapy during the study. The different intention-to-protocol analyses did not result in any significant difference between the placebo and chromium-treated groups (data not shown).

Table 2 shows the changes in the variables per intervention after 6 months. No significant differences were found over time between the two groups for fasting plasma glucose levels, A1C, blood pressure, body fat percentage, weight, lipid profile, and insulin resistance. Also after 3 months, there were no significant difference in A1C between the chromium and placebo groups (0.03% [95% CI −0.19 to 0.25]). After 3 and 6 months, hemoglobin remained the same in both groups.

Twenty-five of the 56 patients (45%) had no idea into which group they had been randomly assigned; 17 patients, 8 of whom were correct, thought that they had been randomly assigned into the chromium treatment group; and 8 of 14 patients correctly guessed that they had been randomly assigned into the placebo group. These results are not higher than would be obtained by chance ($P = 0.591$).

CONCLUSIONS — Chromium yeast treatment had no effect on A1C, weight, blood pressure, insulin resistance, body fat, and lipid profile compared with pla-

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

	Placebo	400 μg	Change (corrected for baseline) 400 μg vs. placebo	*P* value
n	28	28		
Fasting plasma glucose (mmol/l)	0.7 ± 1.7	0.9 ± 2.3	0.5 (−0.5 to 1.5)	0.311
A1C (%)	0.26 ± 0.47	0.51 ± 0.64	0.24 (−0.06 to 0.54)	0.161
Systolic blood pressure (mmHg)	9 ± 15	6 ± 17	−3 (−12 to 6)	0.490
Diastolic blood pressure (mmHg)	3 ± 8	0 ± 9	−3 (−7 to 2)	0.195
Body fat (%)	0.2 ± 2.6	−0.1 ± 1.4	−0.3 (−1.5 to 0.8)	0.569
BMI (kg/m^2)	0.4 ± 0.9	0.1 ± 0.8	−0.3 (−0.8 to 0.2)	0.226
Total cholesterol (mmol/l)	0.23 ± 0.64	0.46 ± 0.42	0.23 (−0.07 to 0.52)	0.128
Cholesterol-to-HDL ratio	−0.11 ± 0.52	−0.11 ± 0.64	−0.01 (−0.29 to 0.28)	0.964
Triglycerides (mmol/l)	0.13 ± 0.68	0.03 ± 0.49	−0.10 (−0.42 to 0.22)	0.526
HDL (mmol/l)	0.11 ± 0.15	0.14 ± 0.18	0.03 (−0.06 to 0.12)	0.536
LDL (mmol/l)	0.06 ± 0.63	0.31 ± 0.4	0.25 (−0.04 to 0.52)	0.087
HOMA-IR (units)	1.9 ± 4.7	−0.4 ± 4.7	−1.3 (−3.7 to 1.1)	0.293

Data are means ± SD within the group and mean differences between groups (95% CI).

cebo in this 6-month, double-blinded, randomized, controlled trial, in patients with moderately controlled type 2 diabetes in a Western society. Two patients stopped the study medication because of adverse effects, one in the placebo group because of stomach problems and one in the chromium yeast group because of nausea.

The results of this study agree with the results of two systematic reviews that examined the effects of chromium on glycemic control (10,11). After the publication of the review conducted by Althuis et al. (10), results of five randomized controlled trials examining the effects of chromium on glycemic control were published. The first study was conducted in Indian patients with type 2 diabetes (27). It reported that A1C worsened in the placebo group compared with the group treated with 400 μg of chromium picolinate (+0.7%). A1C remained stable in the treatment group (27). In the second study, in patients with impaired glucose tolerance, treatment with 800 μg of chromium picolinate was not found to have any beneficial effect on glycemic control (28). The third study was our previous randomized controlled trial examining the effects of treatment with 500 and 1,000 μg of chromium picolinate in patients with poorly controlled insulin-treated type 2 diabetes. No improvement in glycemic control was seen after 6 months of therapy (29). In the fourth study, in patients with poorly controlled diabetes treated with sulfonylureas, a decrease of 0.7 percentage point was found in the group treated with 1,000 μg of chromium picolinate compared with placebo after 24 weeks of therapy (30). In the fifth study, in Czech patients with type 2 diabetes, a lower fasting glucose level was seen in the group treated with 400 μg of chromium in the form of chromium yeast after 12 weeks; however, no change in A1C was found (19).

A limitation of our study is that we selected patients on the basis of an A1C measurement during a previous visit to the local general practitioner or practice nurse. Although no hypoglycemic medication was changed in the 3 months preceding this study, it is notable that the baseline A1C values in both groups are relatively low. Also, the SD for A1C was larger than that in our power calculation. However, with a SD of 0.59 (the SD for change in A1C was 0.57) in our study, it would still leave a high power of 93% to detect a 0.5 difference in A1C in 28 subjects per group. Another limitation was the inability to select patients on the basis of chromium deficiency, as there is still no real standard for chromium status (20). As a result, it is possible that we gave chromium to subjects with a (relatively) normal chromium status. Furthermore, the duration of this study was only 6 months.

There is no evidence that chromium therapy in a Western population with diabetes who are being treated with oral hypoglycemic agents will improve glycemic regulation or parameters associated with the insulin resistance syndrome, apart from one small study in patients with poorly controlled type 2 diabetes, who were taking sulfonylureas (30). Therefore, there seems to be no reason for recommend the use of chromium as a standard part of diabetes therapy (31).

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