Chromium treatment has no effect in Patients with Type 2 Diabetes Mellitus in a Western Population: A Randomized, Double-Blind, Placebo-Controlled Trial

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Chromium and diabetes

Nanne Kleefstra MD\textsuperscript{1,2}, Sebastiaan T. Houweling MD PhD\textsuperscript{2}, Stephan J.L. Bakker MD PhD\textsuperscript{3}, Simon Verhoeven MD PhD\textsuperscript{2}, Rijk O.B. Gans MD PhD\textsuperscript{3}, Betty Meyboom-de Jong MD PhD\textsuperscript{4}, Henk J.G. Bilo MD PhD FRCP\textsuperscript{1,3}

1. Diabetes Centre, Isala Clinics, Zwolle, The Netherlands
2. Langerhans Medical Research Group, The Netherlands
3. Department of Internal Medicine, University Medical Center Groningen, Groningen, The Netherlands
4. Department of General Practice, University of Groningen, Groningen, The Netherlands

Address for correspondence: Nanne Kleefstra*, MD, Diabetes Centre, Isala Clinics, PO Box 10400, 8000 GK Zwolle, The Netherlands,
E-mail: Kleefstra@Langerhans.com
Abstract
Objective:
Chromium treatment has been reported to improve glycemic control in patients with type 2 diabetes. However, concern exists about 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 HbA1c. Secondary endpoints were changes in lipid profile, BMI, blood pressure, body fat, and insulin resistance.

Results:
No differences were found for the change in HbA1c between the intervention and placebo groups. Nor were any differences found between the groups for the secondary endpoints.

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.

Trial Registry: ClinicalTrials.gov; Registration Number: NCT00145093
Type 2 diabetes mellitus 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 towards 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 chromium to improve insulin resistance (6,7). One of the intracellular proteins that influences the insulin receptor is the oligopeptide Apo low-molecular-weight chromium-binding substance (Apo-chromomodulin)(7). This peptide has the ability to increase tyrosine kinase activity 8-fold, depending on the chromium concentration (8). This strengthens the idea that chromium plays an influential role in glucose metabolism (5).

The largest study (n=180) to date that has investigated the effect of chromium in patients with type 2 diabetes was published by Anderson et al.(9). They found that the HbA1c of Chinese patients treated with 1000 µg of chromium in the form of chromium picolinate decreased almost two percentage points as compared to a placebo group after four months. However, two systematic reviews that addressed the effects of chromium on glycemic control concluded that, based on the currently available data, the effects of chromium on glycemic control are inconclusive (10,11). Randomized studies with results on glucose, insulin and/or HbA1c were collected by the review of Althuis et al. (10). Reasons for the inconclusive findings are, that to 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 Anderson et al.’s study(9), chromium picolinate was banned by the Food Standards Agency until December of 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, which investigated the effects of chromium enriched yeast in non-diabetic patients, showed mixed results (16-19). Bahjiri et al. 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 dietary supplementation with brewer’s yeast, containing 23.2 µg of chromium(20).

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 on 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 (DEMS), we selected patients with type 2 diabetes from a village in the Zwolle region in the North of The Netherlands who met the following eligibility criteria: haemoglobin A1c (HbA1c) 7-8.5% as measured during their latest visit, treatment with oral hypoglycemic agents only, no change in treatment during the preceding three months, creatinine ≤ 150 µmol/l for men and ≤ 120
µmol/l for women, creatinine clearance ≥ 50 ml/min, and alanine aminotransferase (ALAT) ≤ 90 U/l. Exclusion criteria included pregnancy (including patients who were trying to conceive), known allergy or intolerance to yeast, and patients currently taking chromium supplements.

In 5 general practices in a village in the region of Zwolle 63 patients had a HbA1c of 7-8.5%, with a mean of 7.7 ± 0.44. To test our hypothesis that chromium causes a 0.5% absolute reduction in HbA1c (primary outcome measure), with a power of 95%, alpha 0.05, 2-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 (GP) 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, The Netherlands.

The study was carried out in a general practice in the Zwolle region. One patient, who initially agreed to participate in the study, later refused to participate. Two patients were not randomized since they did not meet the eligibility criteria (both creatinine clearances < 50 ml/min) (figure 1: CONSORT flow diagram (21)). 57 patients were randomized 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 chromium yeast twice daily (n=29). 56 patients completed the study, which lasted six months.

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 hypoglycaemia or symptomatic hyperglycaemia.

All of the study medications, including the placebo, were supplied by Pharma Nord (Sadelmagervej 30-32, 7100 Vejle, Denmark) and were indistinguishable from each other. Neither the researchers nor the patients knew into which group the patients had been randomized. 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 one 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 clothed without shoes. Height was measured without shoes. Blood pressure was measured after the patient had been sitting for a minimum of 5 minutes. Blood pressure was measured twice on each arm with a minimal interval of 15 seconds between successive measurements. The mean for each arm was calculated. When there was an inter-arm difference of >10 mm Hg 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, Hb, ALAT, HbA1c, 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-hour urine sample was collected, and volume, creatinine, and albumin were measured. We used the homeostasis model assessment to estimate insulin resistance (HOMA-IR)(24).

Hb and HbA1c were measured at three months. At six months, all of the assessments done at baseline were repeated with the exception of height. Any reported side effects were recorded at three months and at six months.

At 1 month (telephone contact), three months, and six months, we asked patients how they were faring with the study medication in order to check and stimulate compliance. At three and six months, all remaining tablets were collected and counted. At six months, we asked the patients to guess into which group they had been randomized. 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 less than 90%. Furthermore, patients were excluded for 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
The CONSORT diagram for this study is presented in figure 1(21). The Mann-Whitney-U test was used for non-normal variables, and the Chi-square 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). In case of variables measured at baseline, after 3 and after 6 months the GLM repeated measures with the Greenhouse-Geiser test were used and the three variables were used as within-subject variables and randomization to chromium or placebo as between-subject factor. In case of variables measured at baseline and after 6 months we used the GLM univariate with change in variable over 6 months as dependent variable and randomization to chromium or placebo as Fixed factor. In both the repeated measures and the univariate GLM, the baseline value was set as covariate. SPSS software, version 11.0, was used for all the analyses.

Results
Eligible participants were recruited in August 2004. Of the 57 patients who were randomized, one patient did not complete the study (figure 1: CONSORT flow diagram (21)), 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 non-specific stomach problems, which disappeared during cessation and reappeared after restart.

Table 1 shows the baseline characteristics of the patients. Randomization 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 case of 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 (median (25%-75%) = 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 of this was found for two patients (one in each group). For the other patients, the reasons were: stopped during a hospital stay (n=2), stopped during a flu period (n=2), and one patient took one tablet twice daily for a brief time by mistake. 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, HbA1c, blood pressure, body fat percentage, weight, lipid profile, and insulin resistance. Also after three months, there were no significant difference in HbA1c between the chromium and placebo group (0.03% (-0.19 to 0.25)). After three and six months Hb remained the same in both groups.

25 of the 56 patients (45%) had no idea into which group they were randomized. 17 patients, 8 of whom were correct, thought that they had been randomized into the chromium treatment group. 8 of 14 patients correctly guessed that they had been randomized 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 HbA1c, weight, blood pressure, insulin resistance, body fat, and lipid profile compared with placebo 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 due to 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 this review conducted by Althuis et al. (10), five randomized controlled trials (RCT) 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 glycemic control worsened in the placebo group compared to the group treated with 400 µg chromium picolinate. HbA1c remained stable (+0.7%) in the treatment group (27). In the second study, in patients with an impaired glucose tolerance, treatment with 800 µg of chromium picolinate was not found to have any beneficial effect on glycemic control (28). We previously conducted an RCT examining the effects of treatment with 500 and 1000 µg of chromium picolinate in patients with poorly controlled insulin-treated type 2 diabetes. No improvement in glycemic control was seen after six 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 1000 µg of chromium picolinate compared with placebo after 24 weeks of therapy (30). In the fifth study, with Czech patients with type 2 diabetes, a lower fasting glucose level in the group treated with 400 µg of chromium in the form of chromium yeast after 12 weeks, however no change in HbA1c was found(19).

A limitation of our study is that we selected patients based on a HbA1c measurement during a previous visit to the local GP or practice nurse. Although no hypoglycemic medication was changed in the 3 months preceding this study, it is notable that the
baseline HbA1c’s in both groups are relatively low. Also the standard deviation of HbA1c was larger than in our power calculation. However with a standard deviation of 0.59 (standard deviation for change in HbA1c was 0.57) in our study it would still leave a high power of 93% to detect a 0.5 difference in HbA1c in 28 subjects per group. Another limitation was the inability to select patients based on chromium deficiency, as there is still no real standard for this (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 six months.

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

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References


29. Kleefstra N, Houweling ST, Jansman FG, Groenier KH, Gans RO, Meyboom-de Jong B, Bakker SJ, Bilo HJ. Chromium treatment has no effect in Patients with Poorly Controlled, Insulin-Treated Type 2 Diabetes Mellitus in a Western population: A Randomized, Double Blind, Placebo-Controlled Trial. *Diabetes Care* 29:521-5, 2006


Table 1. Baseline characteristics per intervention group

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=28)</th>
<th>Chromium (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>17 (49%)</td>
<td>18 (51%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66 ± 8.6</td>
<td>68 ± 8.2</td>
</tr>
<tr>
<td>Diabetes duration (year) †</td>
<td>4.5 (2.0,9.5)</td>
<td>6.0 (4.0,10.0)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>87 ± 17</td>
<td>88 ± 20</td>
</tr>
<tr>
<td>Body Mass Index (kg/m$^2$)</td>
<td>30 ± 5.6</td>
<td>30 ± 5.9</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>34 ± 7.7</td>
<td>34 ± 7.8</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>153 ± 19</td>
<td>151 ± 20</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>88 ± 10</td>
<td>88 ± 13</td>
</tr>
<tr>
<td>Hb (mmol/L)</td>
<td>8.8 ± 0.7</td>
<td>8.7 ± 0.8</td>
</tr>
<tr>
<td>ALAT (U/L)</td>
<td>30 ± 16</td>
<td>34 ± 18</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>97 ± 16</td>
<td>95 ± 18</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>88 ± 24</td>
<td>97 ± 36</td>
</tr>
<tr>
<td>Albuminuria (mg/24 hour) †</td>
<td>4.44 (3.00,29.13)</td>
<td>4.9 (3.00,17.00)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>8.0 ± 1.8</td>
<td>8.7 ± 2.3</td>
</tr>
<tr>
<td>HbA$_{1c}$ (%)</td>
<td>7.01 ± 0.50</td>
<td>6.92 ± 0.67</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.60 ± 1.34</td>
<td>4.46 ± 1.15</td>
</tr>
<tr>
<td>Cholesterol/HDL ratio</td>
<td>3.70 ± 1.25</td>
<td>3.68 ± 1.14</td>
</tr>
<tr>
<td>Triglycerides (mmol/L) †</td>
<td>1.46 (0.91,2.34)</td>
<td>1.70 (1.11,2.10)</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.31 ± 0.38</td>
<td>1.28 ± 0.36</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>2.50 ± 0.95</td>
<td>2.42 ± 1.01</td>
</tr>
<tr>
<td>HOMA-IR (Units) †</td>
<td>3.8 (2.7,5.5)</td>
<td>5.8 (2.7,8.9)</td>
</tr>
</tbody>
</table>

Data are means ± SD or n (% of known data).
† Data are median (P$_{25}$,P$_{75}$)
Table 2. Changes per intervention group after 6 months (Mean values ± SD within the group and mean differences between groups with 95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=28)</th>
<th>400 µg (n=28)</th>
<th>Change (corrected for baseline) 400 µg vs. Placebo (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>0.7 ± 1.7</td>
<td>0.9 ± 2.3</td>
<td>0.5 (-0.5 to 1.5)</td>
<td>0.311</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>0.26 ± 0.47</td>
<td>0.51 ± 0.64</td>
<td>0.24 (-0.06 to 0.54)</td>
<td>0.161</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>9 ± 15</td>
<td>6 ± 17</td>
<td>-3 (-12 to 6)</td>
<td>0.490</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>3 ± 8</td>
<td>0 ± 9</td>
<td>-3 (-7 to 2)</td>
<td>0.195</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>0.2 ± 2.6</td>
<td>-0.1 ± 1.4</td>
<td>-0.3 (-1.5 to 0.8)</td>
<td>0.569</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>0.4 ± 0.9</td>
<td>0.1 ± 0.8</td>
<td>-0.3 (-0.8 to 0.2)</td>
<td>0.226</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>0.23 ± 0.64</td>
<td>0.46 ± 0.42</td>
<td>0.23 (-0.07 to 0.52)</td>
<td>0.128</td>
</tr>
<tr>
<td>Cholesterol/HDL ratio</td>
<td>-0.11 ± 0.52</td>
<td>-0.11 ± 0.64</td>
<td>-0.01 (-0.29 to 0.28)</td>
<td>0.964</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.13 ± 0.68</td>
<td>0.03 ± 0.49</td>
<td>-0.10 (-0.42 to 0.22)</td>
<td>0.526</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>0.11 ± 0.15</td>
<td>0.14 ± 0.18</td>
<td>0.03 (-0.06 to 0.12)</td>
<td>0.536</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>0.06 ± 0.63</td>
<td>0.31 ± 0.4</td>
<td>0.25 (-0.04 to 0.52)</td>
<td>0.087</td>
</tr>
<tr>
<td>HOMA-IR (Units)</td>
<td>1.9 ± 4.7</td>
<td>-0.4 ± 4.7</td>
<td>-1.3 (-3.7 to 1.1)</td>
<td>0.293</td>
</tr>
</tbody>
</table>
Figure 1. CONSORT flow diagram

- assessed for eligibility: n = 60
  - excluded (n=3): not meeting inclusion criteria (n=2), refused to participate (n=1)
- randomized: n = 57
- allocated and received intervention placebo (n=28)
  - lost to follow-up (n=0)
  - discontinued intervention (n=1): adverse effect
  - analyzed (n=28), excluded from analysis (n=0)
- allocated and received intervention chromium (n=29)
  - lost to follow-up (n=1): cerebrovascular accident
  - discontinued intervention (n=1): adverse effect
  - analyzed (n=28), excluded from analysis (n=0)