Effect of Chromium on Glucose Profile in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

BACKGROUND: Chromium plays an essential role in normal carbohydrate, protein and lipid metabolism, and its deficiency is implicated in diabetes mellitus. This randomized, double-blinded, placebo-controlled study evaluated the efficacy of chromium picolinate on glycemic control.

METHODS: Sixty subjects who were referred to Loghman Hakim Hospital with poorly controlled type 2 diabetes and mean BMI 28.5kg/m² were randomized into the picolinate group (received 200µg chromium picolinate/day) and the placebo group (received placebo). All patients used stable oral anti-diabetic agents (OADs). The serum level of fasting plasma glucose (FPG), glycated hemoglobin A1C (HbA1c), and blood glucose 2 hours postprandial (BS2hpp) was measured before and after the 90 days of the treatment.

RESULTS: In the chromium picolinate group the level of HbA1c, BS2hpp and FPG significantly decreased after 90 days of treatment (P<0.001). In the placebo group, although the level of HbA1c and BS2hpp did decrease after 90 days of treatment, the difference in values between baseline and 90 days after treatment was not significant. However, the level of FPG significantly decreased after 90 days. The difference between chromium and control group regarding HbA1c, BS2hpp and FPG level after 90 days treatment was not significant(P>0.05).

CONCLUSION: Although administration of chromium picolinate as an adjunct to a stable regimen of OADs decreased BS2hpp, FPG and HbA1c levels in patients with poorly controlled type 2 diabetes mellitus, it is not more effective than placebo.

Keywords: Type 2 Diabetes; Chromium; HbA1c; FPG; BS2hpp; Poor Control

INTRODUCTION

Diabetes mellitus (DM) is one of the most important risk factors for morbidity and mortality in the developed world [1-3]. The pathophysiology of type 2 DM is characterized by peripheral insulin resistance, impaired regulation of hepatic glucose production and declining β-cell function, eventually leading to β-cell failure [4]. Type 2 DM is expected to affect 439 million adults worldwide by 2030 [5,6]. Undiagnosed, untreated, or poorly controlled DM may lead to serious complications such as nephropathy, retinopathy, neuropathy, atherosclerosis and delayed healing of wounds [7,8]. Glycated hemoglobin A1C (HbA1c) and fasting plasma glucose (FPG) are equally effective screening tools for the detection of type 2 DM. Moreover, HbA1c and FPG are predictors of development of retinopathy and nephropathy [9-11]. Although most of the diabetic patients are being treated, many of them are unable to achieve a goal of HbA1c <7%. Therefore, there is a need to find some new adjunctive supplements that are safe, efficient and cost-effective[12]. More than 29000 nutritional supplements are available and patients spend more than 12 billion dollars every year on these supplements [13,14]. One of these supplements is chromium that is
required for normal carbohydrate, protein and lipid metabolism, and its deficiency is implicated in DM [15,16]. A requirement for chromium in regulating blood sugar was first described in the late 1950s by Mertz and Schwarz [17]. The necessity of chromium in human nutrition became obvious when it was found that chromium supplementation reversed glucose intolerance in hospitalized patients receiving long-term total parenteral nutrition [18,19]. There are several controversies about its relevance to improving glycemic control in DM [20,21], however, some studies reported that chromium has a consistent effect on glycemia, attenuates body weight gain, and enhances insulin sensitivity in patients with type 2 DM [22,23]. Because of conflicting data on the effects of chromium in patients with type 2 DM, this randomized, double-blind, placebo-controlled trial was conducted to assess the effect of chromium picolinate as a supplementary substance on FPG, HbA1c and blood glucose 2 hours postprandial (BS 2hpp) level over three months of use.

METHODS

This randomized, double-blinded, placebo-controlled study was carried out in the diabetes clinic of Loghman Hakim Hospital in collaboration with Taban diabetes clinic in Tehran. Patients were selected by screening volunteers with uncontrolled type 2 DM aged 30-65 years with stable levels of HbA1c (7%≤HbA1c≤10%) and body mass index (BMI) (25≤BMI≤35 kg/m²). The exclusion criteria were as follow: serum creatinine >1.5 mg/dL for males and >1.4 mg/dL for females, liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) more than two times the upper limit of normal, pregnancy, heart failure, chronic liver disease, uncontrolled hypertension, immunosuppressive disease or immunosuppressive drug consumption, alcohol consumption, psychiatric illness, and confined to bed during last one year. Duration of DM in all subjects was at least 2 years and they were treated using anti-diabetic drugs (OADs) such as metformin, glyburide, gliclazide, repaglinide, or acarbose. They were required not to change their diet, levels of physical activity, or anti-diabetic drugs for 3 months before and during enrollment in the study. Subjects with changes in their diet or anti-diabetic drugs were excluded from the study.

The sample size was calculated based on similar studies conducted by Albarracin et al [26]. 0.05 was considered for type I error with power of 80%, standard deviation (SD) 0.15 for HbA1c in both groups and the effect size of 0.15. Sixty subjects were randomly assigned to the two treatment groups, with 30 patients in each group. Sequential numbers were used for randomization, the first number was given to the first patient and received 200 µg chromium picolinate/day (century 21) for 90 days (chromium group n=30) and sequentially the next number was given to next patient who received placebo (which resembled chromium picolinate in shape and color, produced in Faculty of Pharmacy at Azad University, Tehran, Iran) for 90 days (placebo group=30). FPG, HbA1c and BS 2hpp levels were measured both before and after the 90 days of treatment. Both participants and study staff (site investigators and trial coordinating center staff) were masked to treatment allocation.

All patients were informed of the purpose and risks of this study and they gave voluntary written informed consent to participate in the study. All the procedures were conducted in compliance with institutional human research guidelines; the study was approved by ethical committee of Loghman Hakim Hospital and registered in Iranian randomized controlled trials database (www.irct.ir) with code of IRCT2013012812311N1.

Data was analyzed using SPSS version 20. Categorical data is presented as numbers (%), and continuous data as mean ± SD. We used the Chi-square or Fisher’s exact test to compare categorical variables and Student’s t-test, paired t-test, or the Mann-Whitney’s U test for comparing continuous variables. A P <0.05 was considered as significant.

RESULTS

Of the 60 patients, there were 11 males and 19 females in the chromium-treated group and 10 males and 20 females in the placebo group. The mean age was 54.8±1.1 years in chromium group and 55.8±1.7 in the placebo group (Table 1). At baseline, the mean of age, FPG, HbA1c and BS 2hpp did not show any significant difference between the two groups (Table 1). In addition, there was no difference between the groups in terms of OADs use.

At baseline, HbA1c in the chromium group was 8.2±0.13%, and significantly decreased to 7.6±0.13% (0.64% decrease) after 90 days of treatment (P=0.001). In the control group, the difference between HbA1c at baseline and after
Table 1: Demographic data and FPG, HbA1c and BS 2hpp level in two groups at baseline

<table>
<thead>
<tr>
<th></th>
<th>Chromium group (N=30)</th>
<th>Placebo group (N=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11(33%)</td>
<td>10(33%)</td>
<td>0.85*</td>
</tr>
<tr>
<td>Female</td>
<td>19(67%)</td>
<td>20(67%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age, yr</strong></td>
<td>54.8±1.1</td>
<td>55.8±1.7</td>
<td>0.64**</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>28.00±2.55</td>
<td>28.66±3.02</td>
<td>0.37**</td>
</tr>
<tr>
<td><strong>FPG, mg/dl</strong></td>
<td>144±4.34</td>
<td>142±4.81</td>
<td>0.39**</td>
</tr>
<tr>
<td><strong>HbA1c, %</strong></td>
<td>8.23±0.13</td>
<td>7.95±0.11</td>
<td>0.38**</td>
</tr>
<tr>
<td><strong>BS 2hpp, mg/dl</strong></td>
<td>223±0.27</td>
<td>220.03±57.70</td>
<td>0.36**</td>
</tr>
</tbody>
</table>

* Chi square test. ** Student t test

BMI: body mass index, FPG: fasting plasma glucose, HbA1c: glycated hemoglobin A1C, BS 2hpp: blood glucose 2 hours postprandial

Table 2: Comparison of FPG, HbA1c and BS 2hpp at baseline and after 90 days of treatment in two groups

<table>
<thead>
<tr>
<th></th>
<th>Chromium group (N=30)</th>
<th>Placebo group (N=30)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>28.21±2.51</td>
<td>28.13±2.57</td>
<td>0.28</td>
</tr>
<tr>
<td>After 90 days</td>
<td>28.11±2.57</td>
<td>28.02±2.35</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>FPG, mg/dl</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>144±4.34</td>
<td>142±4.81</td>
<td>0.001</td>
</tr>
<tr>
<td>After 90 days</td>
<td>128±5.61</td>
<td>135±4.04</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>HbA1c, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.23±0.13</td>
<td>7.95±0.11</td>
<td>0.001</td>
</tr>
<tr>
<td>After 90 days</td>
<td>7.64±0.13</td>
<td>7.88±0.62</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>BS 2hpp, mg/dl</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>223±54.27</td>
<td>220.03±55.03</td>
<td>0.001</td>
</tr>
<tr>
<td>After 90 days</td>
<td>192.39±48.99</td>
<td>219.22±55.16</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Data presented as mean ± standard deviation (SD).
* Paired t test

BMI: body mass index, FPG: fasting plasma glucose, HbA1c: glycated hemoglobin A1C, BS 2hpp: blood glucose 2 hours postprandial

90 days of treatment was not significant (p=0.06) (Table 2). Moreover, BS 2hpp level in the chromium group significantly decreased after 90 days of treatment (P=0.001), while there was no significant decrease in the placebo group (P=0.8). FPG levels significantly decreased by 16 mg/dL (11%) in the chromium group (P=0.001), and in the placebo group, the reduction was about 7mg/dl (5%) (P=0.03) (Table2). After 90 days of treatment, the mean change in FPG, HbA1c and BS 2hpp did not show a significant difference between the two groups (P>0.05) (Table 2).

DISCUSSION

We evaluated the chromium picolinate effect as an adjunct to a stable regimen of oral anti-diabetic medications (OADs) on HbA1c, FPG and BS 2hpp levels in patients with poorly controlled type 2 DM and showed that chromium picolinate significantly reduced HbA1c, FPG and BS 2hpp levels when compared to baseline. However, when compared to the placebo arm, the decrease in these parameters was not significant. Reduction in HbA1c, especially in patients with poorly controlled DM, is associated with a decrease in diabetes-related deaths, myocardial infarctions, and other micro and macrovascular complications [24,25]. Epidemiological evidence implies that the risk of cardiovascular disease begins well below the current HbA1c target goal of 7.0% [26]. Therefore, additional reductions in HbA1c may be an appropriate target. However, such reductions seem to be difficult to obtain, often require multiple oral drugs with the addition of insulin, and are associated with risk of hypoglycemic events. Reduction of HbA1c by adjunct agents can be a good therapeutic strategy to achieve lower HbA1c levels. Bloomgarden et al. reported that for patients whose HbA1c was ≤8.0%, a modest reduction of HbA1c was difficult to achieve in controlled trials using OADs [26, 27]. For those subjects whose HbA1c was <8.0%, the reduction was minimal, only 0.1 to 0.2% with OADs therapy [27]. Several studies have shown that chromium has no benefit in subjects with type 2 DM [21]. In line with these findings and in comparison with the studies that have shown beneficial effects of chromium, Martin et al. [23] and Wang et al [28]...
indicated that the patients who did not respond to chromium were more obese and more advanced in their disease. Kleefstra et al. reported that chromium picolinate (500 and 1000 µg daily for 6 months) was ineffective in reducing HbA1c in obese, poorly controlled, and insulin-dependent patients with type 2 DM [21]. There are several possible explanations for these contrasting results, such as small sample size, limited statistical power in the latter study to detect a significant change (n=17 for placebo group, n=14 for 500 µg chromium group, n=15 for 1000 µg chromium group, or the greater degree of obesity and insulin resistance at baseline with BMI ranging between 33 and 35kg/m²). Furthermore, these subjects were unable to achieve adequate glycemic control, even with OADs therapy and concomitant high doses of insulin [21]. Some studies have shown that chromium is a required factor for normal carbohydrate, protein and lipid metabolism, and its deficiency is known as one of the causes of DM [15,16,29]. Many studies reported that chromium may enhance insulin receptor binding [30], increase the number of insulin receptors [20], or enable phosphorylation of insulin receptors [31]. These effects cause a reduction in insulin resistance in peripheral tissues [32]. Oligopeptide low molecular weight chromium-binding substance (LMWCr) is one of the intracellular proteins influencing the insulin receptors which is widely distributed in liver, kidneys, spleen, intestine, testicles and brain [33,34]. Activation of this peptide depends on chromium concentration, and upon activation, it in turn activates tyrosine kinase and promotes insulin receptor activity [31].

Another possible mechanism for these effects of chromium is the reduction of content and activity of tyrosine phosphatase PTP-1B [35]. PTP-1B has long been implicated in the regulation of insulin receptor tyrosine phosphorylation and tyrosine kinase activity [36]. Some studies demonstrated that inhibition of PTP-1B increases insulin sensitivity and lowers plasma glucose levels [37,38]. Moreover, Chen et al. reported that chromium picolinate mobilizes glucose transporter, GLUT4, to the plasma membrane in cultured 3T3-L1 adiposities, and at the same time, insulin-stimulated glucose transport was enhanced by chromium treatment [39].

The main limitations of our study are the relatively small sample size and short duration of follow-up (three months). Further investigations are recommended with longer follow-up and larger series to validate the findings reported here, and to confirm the effectiveness of the supplement in patients with other forms of metabolic dysfunction and the exact mechanism of it, too.

CONCLUSION

During this study we found out that although administration of chromium picolinate, as an adjunct to a stable regimen of OADs, decreases BS 2hpp, FPG and HbA1c levels in patients with poorly controlled type 2 diabetes mellitus, it was not more effective than placebo. This effect may be more effective in patients with lower levels of chromium, therefore, it is necessary to measure serum chromium levels before and after supplementation of chromium picolinate to demonstrate response to treatment.

ACKNOWLEDGEMENTS

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REFERENCES

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