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The influence of chromium chloride–containing milk to glycemic control of patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled trial

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Abstract

The aim of this study is to evaluate the effect and safety of chromium-containing milk powder in patients with type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial was conducted in Taiwan. A total of 60 patients with type 2 diabetes mellitus, aged 30 to 75 years, and on a dose of gliclazide sulfonylurea agent (≤160 mg/d) for at least 3 months were enrolled. Their glycosylated hemoglobin ranged from 7.5% to 12%, fasting plasma glucose (FPG) from 140 to 250 mg/dL, and body mass index from 20 to 35 kg/m^2. The subjects were divided into 2 groups, one group to receive chromium-containing milk powder (chromium 200 μg/20 g milk powder) and the other to receive placebo twice a day for 16 weeks. Frequently sampled intravenous glucose tolerance test (IVGTT) was performed before and after treatment. The chromium group demonstrated a lower FPG and fasting insulin (-38.1 ± 9.2 vs 63 ± 8.5 mg/dL and -1.7 ± 0.2 vs 1.9 ± 0.3 μU/mL, respectively; $P < .05$), especially in male patients (-41 ± 9.2 vs 85 ± 11.7 mg/dL and -2.7 ± 0.2 vs 3.1 ± 0.3 μU/mL, respectively; $P < .01$), at the end of the study. Lower glycosylated hemoglobin was observed in chromium-treated male patients (-1.1 ± 0.5 vs 0.7 ± 0.2; $P < .05$). However, there were no significant changes in other metabolic parameters (lipid profiles including total cholesterol, triglyceride, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol), except improvement of insulin resistance (homeostasis model assessment for insulin resistance and insulin sensitivity index from frequently sampled intravenous glucose tolerance test) observed in male patients (-2.1 ± 1.1 vs -0.41 ± 1.12 and 0.18 ± 0.11 vs -0.15 ± 0.2, respectively; $P < .05$). There were no adverse events in both groups, except for mild complaints in the chromium group on constipation (5%) and flatulence (5%). Intake of milk powder containing 400 μg/d of chromium for 16 weeks in subjects with type 2 diabetes mellitus resulted in lowering of FPG, fasting insulin, and improvement of metabolic control in male patients.

1. Introduction

Diabetes mellitus (DM) is the fourth leading cause of death in Taiwan, with a 5-fold increase in mortality incidence of complications from DM in the recent 20 years [1]. The existing oral hypoglycemic agents cannot provide long-term blood glucose control; the most convincing is the result of the United Kingdom Prospective Diabetes Study, showing the longer the patient has the disease, the less effective the medication becomes [2]. A recent study in Taiwan also indicated that diabetic patients in Taiwan were not under satisfactory glucose control; the average fasting plasma glucose and glycosylated hemoglobin (HbA_{1c}) were 160 mg/dL and 8.1%, respectively, among 2500 patients from 25 large hospitals island-wide [3].

Trivalent chromium is one of the essential micronutrients; it activates insulin receptors through chromodulin to increase insulin signal transduction and insulin sensitivity [4]. Animal studies have shown that supplementing chromium could improve glucose and lipid metabolism [5,6]. Clinical case reports have shown that chromium deficiency results in hyperglycemia, impaired growth, increased lipid levels, increased atherosclerosis, and reduced fertility [7]. Other studies have also shown that, as diabetic patients age, loss of chromium increases [8,9]. Therefore, it is possible that chromium deficiency is associated with the development of diabetes [10].

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Individuals with diabetes have altered chromium metabolism, whereas nondiabetic subjects have higher chromium absorption but also greater excretion [11]. The hair and tissue chromium levels of diabetic patients are lower than that of nondiabetic subjects [12]. Depending on the stage of diabetes, individuals with diabetes tend to lose the ability to convert chromium to a useable form [13]. A human study conducted by Anderson et al [14] showed that the supplement of a high dose of chromium (200-1000 μg/d) could improve the metabolic control of type 2 DM.

In this study, we aimed to evaluate the effect and safety of chromium-containing milk powder in patients with type 2 DM.

2. Materials and methods

2.1. Patients

This is a randomized, double-blind, placebo-controlled prospective study conducted at the Buddhist Tzu Chi General Hospital. A total of 60 patients with type 2 DM from outpatient clinics who met the following criteria were recruited: male or female, aged 30 to 75 years, diagnosed as having type 2 DM at least 4 months before study entry; on a stable dose of gliclazide less than 160 mg/d alone for 3 months before screening; fasting plasma glucose (FPG) of 140 to 250 mg/dL at screening (visit 0); HbA_{1c} of 7.5% to 12% within 3 months before screening; and body mass index (BMI) of 20 to 35 kg/m^2. The study received the approval of the Human Studies Review Board in Taiwan. Patients were informed of the purpose of the study, were free to ask questions throughout the study, and signed an informed consent form witnessed by one of the investigators.

Patients were excluded from the study if they met any of the following criteria: lactose intolerance; pregnant and lactating women; recently underwent surgery or had an acute infection; renal dysfunction with serum creatinine of 1.5 mg/dL or higher; elevated hepatic enzymes aspartate aminontransferase (AST) and alanine aminontransferase (ALT) above 2.5 times the upper normal limit; significant gastrointestinal disorder, peptic ulcer, severe constipation, or diarrhea requiring long-term medication; received insulin injection during the past 3 months; alcoholism; or drug abuse.

2.2. Study population

After 4 weeks of run-in period, eligible subjects were randomized into 1 of the 2 treatment groups, one group to receive 20 g of chromium milk powder (each sachet contained chromium 200 μg) and the other group to receive 20 g of placebo milk powder (both were provided by Maxluck Biotechnology, Taipei, Taiwan) for 16 weeks. Patients were instructed to take gliclazide with a glass of water and 1 sachet of study product stirred into a glass of water (about 150 mL, 60°C-70°C) before breakfast and dinner everyday. Subjects were instructed to store the study products in a dry, cool, and dark place. The quantity of chromium was verified by chemical analysis. The patients received a regular dietary education at each visit by a dietitian and were asked to return the nonused sample for auditing of their compliance. Subjects were also interviewed regarding any possible side effects and their degrees of compliance.

2.3. Biochemical analysis

Blood samples were drawn after an overnight fast at the beginning and at the end of the study for the analysis of FPG, fasting insulin (FPI), HbA_{1c}, blood urea nitrogen, creatinine, AST, ALT, uric acid, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and electrolytes (Na, K, Cl). Serum concentrations of blood urea nitrogen, creatinine, AST, ALT, uric acid, TC, TG, and electrolytes were measured with a dry multiplayer analytic slide method in the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Minato-Ku, Tokyo, Japan). Serum HDL-C levels were determined with an enzymatic cholesterol assay method after dextran sulfate precipitation. The plasma glucose concentration was determined with the glucose oxidase method in the Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Plasma insulin was measured with a commercial radioimmunoassay kit (Coat-A-Count Insulin Kit, Diagnostic Products, Los Angeles, CA). The intra- and interassay coefficients of variance for insulin were 3.3% and 2.5%, respectively. The HbA_{1c} was measured by the Bio-Rad Variant II automatic analyzer (Bio-Rad Diagnostic Group, Los Angeles, CA). Efficacy end points included the changes from baseline in FPG, HbA_{1c}, insulin resistance (homeostasis model assessment for insulin resistance [HOMA-IR]) [15], and lipid profiles before and after treatment.

2.4. Experimental design

An insulin-modified frequently sampled intravenous glucose tolerance test (FSIGT) with 21 blood samples was performed to evaluate insulin sensitivity before and after the study. After a 12-hour fast, an indwelling cannula was inserted into an antecubital vein for injection of glucose and insulin. Another cannula for blood sampling was inserted into the antecubital vein of the opposite arm. Fasting blood samples for the measurement of plasma-specific insulin and 2 successive blood samples (5 minutes apart) for the measurement of fasting blood glucose and plasma immunoreactive insulin (IRI) levels were taken. An intravenous glucose bolus (0.3 g glucose/kg body weight as 50% solution administered for 90 seconds) was then injected through the cannula in the arm opposite to the sampling arm.

Additional samples for blood glucose and plasma IRI levels were taken at 1, 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 25, 30, 40, 50, 70, 100, 140, and 180 minutes. At 20 minutes, an intravenous injection of regular insulin (0.05 U/kg body weight) was administered to increase the accuracy of the modeling analysis. Glucose utilization was analyzed with

Table 1
Clinical characteristics and biochemical values of the study subjects

	Chromium group (n = 30)	Placebo group (n = 30)
Age (y)	54.2 ± 7.1	55.6 ± 8.2
Sex (male/female)	16/14	17/13
BMI (kg/m^2)	25.2 ± 4.1	26.2 ± 3.2
Duration of diabetes (mo)	58.1 ± 16.1	60.1 ± 15.2
FPG (mg/dL)	197 ± 22.3	185 ± 23.1
Fasting plasma insulin (μU/mL)	12.5 ± 2.2	11.7 ± 8.5
HbA_{1c} (%)	9.3 ± 0.9	9.1 ± 1.1
HOMA-IR	4.42 ± 1.82	4.17 ± 2.01
S_I (10^{-5} min^{-1}/pM)	0.21 ± 0.67	0.25 ± 0.52
E_G (min^{-1})	0.138 ± 0.49	0.126 ± 0.32
Acute insulin response (pmol/L)	222 ± 146.2	246 ± 126.8

Values are expressed as mean ± SD.

the minimal model of glucose disappearance of Bergman et al [16] and Welch et al [17]. The minimal model provides a measure of the sensitivity of glucose elimination to insulin (S_I; inversely proportional to insulin resistance). Estimates of S_I from this model have been validated against the glucose clamp technique. Acute insulin response is the increment in the plasma IRI concentration above baseline in the first 10 minutes (measured at 4, 6, 8, and 10 minutes) after glucose administration. E_G is the effect of glucose, independent of insulin, on the glucose utilization rate, which is also obtained by using a minimal model algorithm.

2.5. Adverse events

Patients were interviewed at each visit to elicit any spontaneously reported adverse events. The details of the events included date of onset, description of symptoms, duration, severity, and outcome. In addition, the investigator indicated whether the adverse event was therapy-related. If adverse drug reactions occurred, then chromium milk powder was immediately discontinued, and patient was withdrawn from the study.

2.6. Statistical analysis

All of the data were expressed as mean ± SD. Statistical significance between before and after treatment groups was compared using the paired t tests where the data were normally distributed. A P value of less than .05 was considered significant.

3. Results

The baseline clinical characteristics and biochemical values of study subjects are shown in Table 1. These 2 groups (chromium-treated [n = 30] and placebo-treated [n = 30]) were similar in age, sex, BMI, duration of diabetes, HOMA-IR, S_I from FSIGT, and biochemical data including FPG, FPI, HbA_{1c}, lipid profiles (TC, low-density lipoprotein cholesterol, HDL-C, and TG).

Table 2 shows that the chromium group demonstrated a lower FPG and FPI (−38.1 ± 9.2 vs 63 ± 8. 5 mg/dL and −1.7 ± 0.2 vs 1.9 ± 0.3 μU/mL, respectively; $P < .05$), especially in male patients (−41 ± 9.2 vs 85 ± 11.7 mg/dL and −2.7 ± 0.2 vs 3.1 ± 0.3 μU/mL, respectively; $P < .01$), at the end of the study. Lower HbA_{1c} was observed in chromium-treated male patients (−1.1 ± 0. 5 vs 0.7 ± 0. 2; $P < .05$). However, there were no significant changes in other metabolic parameters (lipid profiles including TC, TG, low-density lipoprotein cholesterol, HDL-C), except improvement of insulin resistance (HOMA-IR and S_I from FSIGT), observed in male patients (−2.1 ± 1.1 vs −0.41 ± 1.12 and 0.18 ± 0.11 vs −0.15 ± 0. 2, respectively; $P < .05$).

Table 3 shows there were no adverse events in both groups, except for mild complaints in the chromium group on constipation (1 case, 5%) and flatulence (1 case, 5%).

4. Discussion

Trivalent chromium is an essential nutrient required for normal glucose and lipid metabolism, and insufficient dietary chromium is associated with maturity-onset diabetes and/or cardiovascular disease, which can be improved by supplementation [18,19]. There is evidence that human tissue chromium levels decline with advancing age [20]. Despite increased absorption of chromium from the gut, the 3-fold increase in urinary chromium excretion in diabetic patients might contribute to negative chromium

Table 2
Mean changes in plasma glucose and insulin levels and results before and after 16 weeks of treatment with chromium or placebo milk power

	Chromium group (n = 30)			Placebo group (n = 30)		
	All	Male	Female	All	Male	Female
FPG (mg/dL)	−38.1 ± 9.2*	−41 ± 9.2**	−22.2 ± 9.3	63 ± 8.5	85 ± 11.7	23.1 ± 9.6
Fasting plasma insulin (μU/mL)	−1.7 ± 0.2*	−2.7 ± 0.2**	0.9 ± 0.5	1.9 ± 0.3	3.1 ± 0.3	1.2 ± 0.7
HbA_{1c} (%)	−0.21 ± 0.2	−1.1 ± 0.5*	−0.1 ± 0.3	0.1 ± 0.2	0.7 ± 01.12	0.5 ± 0.2
HOMA-IR	−1.31 ± 0.45	−2.1 ± 1.1*	−1.01 ± 1.2	0.72 ± 1.32	0.41 ± 1.12	0.83 ± 0.46
S_I (10^{-5} min^{-1}/pM)	0.06 ± 0.11	0.18 ± 0.11*	−0.18 ± 0.21	−0.08 ± 0.15	−0.15 ± 0.20	−0.11 ± 0.12
E_G (min^{-1})	0.12 ± 0.25	−0.15 ± 0.26	−0.11 ± 0.09	−0.11 ± 0.31	−0.11 ± 0.31	−0.08 ± 0.2
Acute insulin response (pmol/L)	−30.1 ± 28.2	−40.6 ± 32.6	−20.2 ± 16.7	−21.1 ± 16.8	−32.1 ± 20.2	−16.5 ± 11

Values are expressed as mean ± SD.

* $P < .05$ compared with the corresponding placebo group by paired t test.

** $P < .01$ compared with the corresponding placebo group by paired t test.

Table 3
Incidence of common adverse events during 16 weeks of treatment with chromium or placebo milk power

	Chromium group (n = 30)	Placebo group (n = 30)
Constipation	1 (5%)	0
Diarrhea	0	0
Flatulence	1 (5%)	0
Dizziness	0	0
Dry mouth	0	1 (5%)

balance, indicating that plasma chromium concentration is significantly (60%) lower in diabetic patients [20]. Thus, chromium deficiency could be another factor predisposing to insulin resistance, type 2 DM, dyslipidemia, and atherosclerosis [18,21].

The previous study revealed that chromium may increase the number of insulin receptors, enhance receptor binding, potentiate insulin action, and improve insulin resistance [22]. The overall effect of chromium is to improve insulin resistance, which is associated with glucose intolerance [23], decreased risk factors associated with cardiovascular diseases, improved immunity, and increased life span [24], but the mechanism of chromium enhancement of insulin sensitivity remains to be determined [25-27]. Chromium, like insulin, affects protein phosphorylation-dephosphorylation reactions. The activation by chromium of insulin receptor kinase activity and the inhibition of insulin receptor tyrosine phosphatase would lead to increased phosphorylation of the insulin receptor, which is associated with increased insulin sensitivity, increased glucose utilization, and beta-cell sensitivity [13]. In our study, the improvement of insulin resistance (HOMA-IR and insulin sensitivity from FSIGT) in the chromium group is obvious, especially in the male sex.

The result of chromium supplementation in patients with type 2 DM varies [28]. The possible reasons for the discrepancy in response appear to be because of the dose and form of the chromium consumed. Chromium picolinate is a convenient form of chromium that is used more efficiently than some other forms of chromium. Chromium picolinate (400-600 μg/d) showed beneficial effects in reducing blood glucose and HbA_{1c} levels and in improving insulin sensitivity in patients with type 2 DM [15]. However, recent in vivo study in fruit flies reveals that chromium picolinate greatly enhances the rate of appearance of lethal mutations and dominant female sterility [29]. Chromium chloride, which was used in our study, is less efficiently used, but less toxic compared with chromium picolinate [30].

In general, chromium has no effect on blood glucose in nondiabetic subjects. Low doses of chromium chloride (50-200 μg/d) do not significantly affect blood glucose in diabetic subjects either [31]. Anderson et al [14] were the only investigators to report a dose-response effect of chromium (200-1000 μg/d) on glucose and insulin concentrations in diabetic subjects. This study was conducted in China, and subjects enrolled had low BMI (22-23 kg/m^2), which may indicate poor nutritional status of the population at baseline. The applicability of the results worldwide remains to be clarified. The reports of the positive effects of supplemental chromium on people with diabetes usually involve 400 μg or more of chromium. In our study, we used 400 μg/d of chromium for 16 weeks in patients with type 2 DM. For the chromium group, blood glucose–lowering effect is substantiated.

If chromium has an effect on those with impaired glucose tolerance and type 2 DM, then why do not all the studies show a constant favorable result? There are a number of reasons. First, human studies include subjects of diverse genetic and nutritional backgrounds living in environments of varying degrees of stress, all of which may affect chromium metabolism [31]. Varying results of supplemental chromium may also be because of the diet, the selection of subjects, the duration of the study, and the amount and type of supplemental chromium. In addition, response to chromium is related to the degree of glucose intolerance. Subjects with good glucose tolerance having no need of additional chromium do not respond to supplemental chromium. Subjects consuming adequate chromium and well-balanced diets also do not respond to additional chromium [32]. Chromium is a nutrient and not a drug, and it will therefore benefit only those who are deficient or marginally deficient in chromium. In addition, glucose intolerance and type 2 DM are due to a number of causes, only one of which is chromium deficiency.

In addition to improvement of blood glucose and insulin sensitivity to supplemental chromium, we did not see any beneficial effect on lipid profiles. Unlike the results seen with glucose, chromium does not appear to be more efficacious at reducing higher levels of cholesterol and TG [33]. The explanation of the variable response to chromium in blood lipids is likely similar to the above-mentioned response of blood glucose to chromium supplementation.

Recent studies disclosed that chromium could improve the cellular antioxidant capacity and, thus, its supplementation is an effective treatment strategy to minimize increased oxidative stress in type 2 diabetic patients with an HbA_{1c} level of more than 8.5%. Restoration of chromium deficiency in people with type 2 DM may counteract the deleterious effects of oxidative stress and may help prevent complications associated with diabetes [1]. There was no evidence of toxicity in our study, nor are there any reported toxic effect in any of the human studies involving supplemental chromium, even in subjects receiving 1000 μg of chromium daily [15].

In conclusion, the current study suggests that 400 μg/d of chromium supplementation in Chinese patients with type 2 diabetes mellitus appears to be safe, effective, and well tolerated. Chromium could be used as adjunctive therapy, along with diet, exercise, and traditional pharmacotherapy for the management of type 2 DM. More comprehensive studies in human and at molecular levels are needed to

verify the role of chromium in the correction of hyperglycemia and insulin resistance.

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