

The Effect of Chromium Picolinate and Biotin Supplementation on Glycemic Control in Poorly Controlled Patients with Type 2 Diabetes Mellitus: A Placebo-Controlled, Double-Blinded, Randomized Trial

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ABSTRACT

Background: Preclinical studies have shown that the combination of chromium picolinate and biotin significantly enhances glucose uptake in skeletal muscle cells and enhances glucose disposal. The present pilot study was conducted to determine if supplementation with chromium picolinate and biotin can improve glycemic control in patients with type 2 diabetes mellitus with suboptimal glycemic control despite use of oral antihyperglycemic agents.

Methods: Forty-three subjects with impaired glycemic control (2-h glucose >200 mg/dL; glycosylated hemoglobin $\geq 7\%$), despite treatments with oral antihyperglycemic agents, were randomized to receive 600 μg of chromium as chromium picolinate and biotin (2 mg/day) (Diachrome[®], Nutrition 21, Inc., Purchase, NY) in addition to their prestudy oral antihyperglycemic agent therapy. Measurements of glycemic control and blood lipids were taken at baseline and after 4 weeks.

Results: After 4 weeks, there was a significantly greater reduction in the total area under the curve for glucose during the 2-h oral glucose tolerance test for the treatment group (mean change -9.7%) compared with the placebo group (mean change $+5.1\%$, $P < 0.03$). Significantly greater reductions were also seen in fructosamine ($P < 0.03$), triglycerides ($P < 0.02$), and triglycerides/high-density lipoprotein cholesterol ratio ($P < 0.05$) in the treatment group. No significant adverse events were attributed to chromium picolinate and biotin supplementation.

Conclusions: This pilot study demonstrates that supplementation with a combination of chromium picolinate and biotin in poorly controlled patients with diabetes receiving antidiabetic therapy improved glucose management and several lipid measurements. Chromium picolinate/biotin supplementation may represent an effective adjunctive nutritional therapy to people with poorly controlled diabetes with the potential for improving lipid metabolism.

INTRODUCTION

DESPITE COMPELLING EVIDENCE from outcomes trials that glycemic control reduces cardiovascular morbidity and mortality,^{1,2} re-

cent data from the National Health and Nutrition Examination Survey IV indicate that only a third of adults with diabetes mellitus (DM) achieve currently recommended glycemic targets.³ Several lifestyle and pharmacological

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agents are available for the treatment of diabetes. Treatment, however, is often difficult and may require adjunctive therapy to available medications.

Data on the benefits of chromium supplements in diabetes management are inconclusive.⁴ However, it has been reported that chromium deficiencies contribute to glucose intolerance, hyperglycemia, and hypertriglyceridemia as well as dyslipidemia.⁴ Supplementation with chromium picolinate has shown promise in limited clinical studies.⁴ Biotin is a water-soluble vitamin that is recognized as an integral component in a variety of carboxylation reactions, playing a role in glucose-stimulated insulin secretion, hepatic glucose uptake, and suppression of glucose synthesis in the presence of high plasma glucose.⁵ Although supplementation with dietary biotin has been proposed to improve glycemic control, this has not been widely investigated in humans.

Earlier data from *in vitro*⁶ and *in vivo* studies⁷ using chromium picolinate and biotin have demonstrated greater effects on glucose disposal and lipid metabolism when these nutrients were combined. This pilot study was undertaken to demonstrate the effect of dietary supplementation with the combination of chromium picolinate (600 μg of chromium/day) and biotin (2 mg/day) on glycemic regulation and lipid metabolism in patients with type 2 DM who were receiving antidiabetic and lipid-lowering therapy.

SUBJECTS AND METHODS

Study design

The study was a 30-day, placebo-controlled, double-blinded, randomized, single-center clinical trial. The study protocol was approved by an institutional review board. All study subjects gave written and oral informed consent. Study subjects were assigned to the treatment or placebo group using a 1:1 randomization.

Patients

Participants included male and female, overweight or obese, volunteers (body mass index $\geq 25 \text{ kg/m}^2$ and $\leq 35 \text{ kg/m}^2$) between the ages

of 18 and 65 years with persistent impaired glucose control (2-h glucose $>200 \text{ mg/dL}$) and glycated hemoglobin (HbA1c) $\geq 7\%$ with at least a 1-year history of type 2 DM. Patients were on stable oral drug therapy, including sulfonylureas, biguanides, and/or thiazolidinediones. No change in lifestyle modification was suggested during the period of the study. Patients on or requiring insulin were excluded.

Treatment

Patients were randomized to receive a combination of 600 μg of chromium in the form of chromium picolinate plus 2 mg of biotin (Diachrome[®], Nutrition 21, Inc., Purchase, NY) and placebo for 4 weeks (30 days). Patients took one capsule per day in the morning for the duration of the trial. This formulation has proven to be bioavailable. Placebo capsules contained dicalcium phosphate and were identical to the treatment capsules in size, shape, and color. Prior to study approval, samples were tested for purity and were found to contain the stated amounts of chromium picolinate and biotin.

Assessment

Patients fulfilling selection criteria returned for fasting metabolic and lipid assessments [total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and apolipoproteins A (ApoA) and B (ApoB)] including a 2-h oral glucose tolerance test (OGTT) (0, 30, 60, 90, and 120 min) and measurements of fructosamine and insulin concentrations. Baseline and final urine chromium levels were assessed in order to determine compliance. Area under the curve for glucose (AUC_g) was calculated using trapezoidal integration.⁸

Patients completed daily diaries that documented: (1) their compliance with diabetes medications, assigned supplements, and other medications, (2) morning blood sugar levels, (3) exercise activity, and (4) any instances of illness or symptoms of hypoglycemia, as well as (5) any disturbance in their daily routine or any illnesses that occurred during the trial. Diaries were monitored midway through the study. Interview and diary review were evaluated for

adverse reactions; pill counts were completed to determine compliance.

Statistical analysis

Analyses were performed to determine the effects of combination of chromium picolinate and biotin supplementation on postprandial glycemia and fasting lipids in patients with type 2 diabetes. Estimating pooled standard deviations of the means from previous studies,^{9,10} the expected magnitude of the difference between means of 50% for 2-h glucose and 30% for AUCg achieved a power of estimate of 0.73 and 0.82, respectively, for a sample size of 10 and α set to 0.05. The two-group *t* test procedure in SAS (Cary, NC) ASSIST (version 8.2) was used in all analyses. Change scores between groups were computed by comparing AUCg and 2-h glucose levels from baseline and Day 30. Similar analyses for changes in fasting blood glucose levels, fructosamine, insulin, lipids, and lipoproteins, and lipid ratios were calculated; the chronic effects of 4 weeks of supplementation was limited in the current sample size. Only data from patients who had baseline and final data and who were not protocol violators were used in the calculations.

RESULTS

One hundred fourteen patients were screened, 43 patients were randomized to treatment, and 36 patients fulfilled the inclusion/exclusion criteria and provided evaluable data (treatment group, $n = 20$; placebo group, $n = 16$). Seven subjects were not included in the analysis; four subjects were protocol violators (one treatment and three placebo patients), and three subjects did not return for the final study visit (three placebo patients). The active and placebo groups were similar at baseline, without significant differences in age, sex, body mass index, blood pressure, or HbA1c (Table 1). Baseline laboratory assessment of urine chromium levels, fasting glucose, insulin, fructosamine, lipid panel, and initial OGTT were similar between the groups. Despite the use of one or more hypoglycemic medications in addition to recommended lifestyle modifications, HbA1c levels at baseline were 9.2% and 8.8%, respectively, in the treatment and placebo groups. The difference in baseline HbA1c levels was not statistically significant. Both fasting glucose and 2-h postprandial glucoses were similar between groups. Urinary chromium concentrations were significantly elevated in the treatment group ($P < 0.0001$), but not placebo.

TABLE 1. BASELINE CHARACTERISTICS OF STUDY SUBJECTS

Characteristic	Placebo (n = 16)	Treatment (n = 20)	P
Age (years)	48 ± 9	53 ± 9	0.1430
Male/female ratio	10/6	9/11	
Race			
African American	8	9	
White	5	4	
Hispanic	0	3	
Asian	2	2	
Other	1	2	
Body mass index (kg/m ²)	30 ± 4	30 ± 4	0.9787
Blood pressure (mm Hg)			
Systolic	131 ± 17	132 ± 15	0.8158
Diastolic	78 ± 9	80 ± 10	0.4696
HbA1c (%)	8.8 ± 1.4	9.2 ± 1.3	0.3261
Oral antihyperglycemic medication			
Sulfonylurea	5	3	
Biguanide	1	5	
Sulfonylurea + biguanide	10	5	
Sulfonylurea + thiazolidinedione	1	0	
Biguanide + thiazolidinedione	2	2	
Sulfonylurea + biguanide + thiazolidinedione	1	0	

Data are mean ± SD values.

Glucose effects

Blood glucose levels assessed after 30 days of treatment revealed changes in blood glucose parameters (Table 2). Mean postprandial glucose levels (total AUCg) significantly decreased after a glycemic challenge from $40,349 \pm 7,398$ mg/dL ($2,239$ mmol/L) at baseline to $35,648 \pm 6,872$ mg/dL ($1,978$ mmol/L) after 30 days in the treatment group ($P < 0.05$). The mean total AUCg increased in the placebo group from $38,329 \pm 6,941$ mg/dL ($2,127$ mmol/L) at baseline to $39,978 \pm 9,145$ mg/dL ($2,219$ mmol/L) after 30 days ($P < 0.57$). Glucose levels decreased in the treatment group at different time points compared with placebo (Fig. 1A). Total AUCg reduction compared with baseline was statistically significant in the treatment group compared with placebo ($P < 0.03$) (Fig. 1B). Mean change in fructosamine levels was significantly different between treatment and placebo groups: -23.0 ± 56 mg/dL (-1.3 mmol/L) versus 12.9 ± 33 mg/dL (0.7 mmol/L) ($P < 0.03$), respectively. Fasting plasma glucose decreased, but not significantly, in the treatment group compared with baseline ($P < 0.0525$).

Lipid effects

Effects of chromium picolinate/biotin on lipid metabolism were evaluated by comparison of total cholesterol, TG, HDL-C, LDL-C, TG/HDL-C, and lipid subfractions (ApoA and ApoB) after 30 days of treatment. A nonsignificant decrease in total cholesterol (-6% , $P = 0.29$) was seen in the treatment group compared with baseline. HDL-C and LDL-C levels remained unchanged. Significant between-group changes were seen in TG levels ($P < 0.02$) and TG/HDL-C ($P < 0.05$). Nonsignificant reductions were seen in lipid subfractions ApoA and ApoB.

Tolerability

During the course of the 30-day study, supplementation with the combination of chromium picolinate and biotin was well tolerated. Sixteen subjects experienced a total of 19 adverse events. In the chromium picolinate and biotin group, six subjects experienced eight

adverse events, while 10 subjects assigned to the placebo group experienced 11 adverse events. There was one significant adverse event of "abscess removal, right buttock" recorded in the placebo group, and no significant adverse events were recorded for the chromium picolinate/biotin group. Review of the adverse events revealed that adverse events were mild to moderate and not dissimilar from placebo. There were no reports of hypoglycemia.

DISCUSSION

Prevalence of uncontrolled diabetes continues to be a growing challenge and a major contributor to cardiovascular risk,³ with insulin resistance playing an increasing role in dyslipidemia.¹¹⁻¹³ Despite current pharmacological and lifestyle modifications, many people with diabetes continue to have poorly controlled blood glucose levels. Current dietary consumption patterns of nutrients suggest that Americans may require nutritional supplementation in order to meet the requirement of essential nutrients as they age.¹⁴ Micronutrient supplementation as a modality to improve glycemic control may represent an adjunctive strategy for improving diabetes management.

The current pilot study demonstrated that the combination of chromium picolinate with biotin improved AUCg, fructosamine, TG, and TG/HDL-C ratio in patients with poorly controlled diabetes when faced with a glycemic challenge. Effects on lipid metabolism were encouraging. The sample size and duration of the study preclude conclusions on long-term use, but identify trends for further investigation.

Dietary recommendations for chromium, an essential nutrient for glucose metabolism, are poorly understood. Effective assays to determine serum, urine, or tissue concentrations are not standardized. Chromium concentrations among different food types are not easily quantified because of a lack of standardized analytical methods.⁴ Dietary chromium intakes and dietary deficiencies therefore cannot always be accurately determined. Several studies have reported that people in the United States have less than adequate intake of dietary chromium^{4,15} and a significant correlation of

TABLE 2. EFFICACY MEASUREMENTS

End marker	Treatment			Placebo			Change by group		
	Initial	Final	P	Initial	Final	P	Initial	Placebo	P
Urine chromium (ng/mL)	0.166 ± 0.137	5.16 ± 3.4	0.001 ^a	0.074 ± 0.075	0.178 ± 0.275	0.1607	4.73 ± 3.5	0.104 ± 0.25	0.0001 ^b
Fructosamine (mg/dL)	377.1 ± 91.7	353.2 ± 73.9	0.3698	342.4 ± 66.5	355.3 ± 70.7	0.5980	-23.0 ± 56	12.9 ± 33	0.0263 ^a
Insulin (uIU/mL)	6.2 ± 3.2	6.2 ± 2.7	0.9957	6.1 ± 3.6	6.3 ± 3.4	0.8426	0.25 ± 0.64	0.005 ± 0.57	0.7772
Fasting glucose (mg/dL)	211 ± 54	218 ± 52	0.6597	203 ± 53	253 ± 86	0.0580	7.45 ± 65	50.19 ± 62	0.0525
Glucose (mg/dL)									
30 min	308 ± 62	242 ± 79	0.0069 ^a	293 ± 64	267 ± 75	0.3038	-61.895 ± 61	-28.875 ± 52	0.0695
60 min	359 ± 77	333 ± 57	0.2373	342.8 ± 67.9	369 ± 82.3	0.3334	-25.85 ± 90	26.25 ± 87	0.0889
90 min	382 ± 78	357 ± 57	0.2485	368 ± 75.8	389 ± 87	0.4576	-25.35 ± 75	21.75 ± 72	0.0646
120 min	380 ± 77	349 ± 56	0.1575	344 ± 70	360 ± 85	0.5786	-30.9 ± 18	15.5 ± 20	0.0879
AUCg (min · mg/dL)	40,349 ± 7,398	35,648 ± 6,873	0.0441 ^a	383,29 ± 6,941	39,978 ± 9,145	0.5702	-4,701.8 ± 8,959	1,649 ± 7,013	0.0264 ^a
TC (mg/dL)	198 ± 33	187 ± 33	0.2844	206 ± 61	206 ± 41	0.9973	-11.2 ± 21	0.06 ± 41	0.2908
HDL-C (mg/dL)	42 ± 8	42 ± 10	0.9715	38 ± 7	38 ± 9	0.8099	-0.1 ± 4	-0.6875 ± 8	0.7735
LDL-C (mg/dL)	123 ± 33	121 ± 34	0.8408	136 ± 53	134 ± 28	0.9408	-2.15 ± 20	-1.125 ± 49	0.9319
TG (mg/dL)	145 ± 67	135 ± 79	0.6915	147 ± 68	207 ± 139	0.1364	-9.25 ± 41	59.75 ± 113	0.0159 ^a
ApoA (mg/dL)	147 ± 26	130 ± 33	0.0789	140 ± 26	132 ± 33	0.5196	-17.1 ± 25	-6.4 ± 19	0.1737
ApoB (mg/dL)	88 ± 21	89 ± 31	0.8918	96 ± 28	104 ± 28	0.4340	1.15 ± 22	9 ± 15	0.2518
TG/HDL-C	3.8 ± 2.3	3.7 ± 2.7	0.9174	4.2 ± 2.5	5.8 ± 3.9	0.1718	-0.08 ± 1.2	1.6 ± 3.5	0.0453 ^a

Data are mean ± SD values. To convert glucose to mmol/L multiply by 0.0555; total cholesterol (TC), LDL-C, and HDL-C to mmol/L by 0.0259; TG to mmol/L by 0.0113; insulin to pmol/L by 6.945; and ApoA and ApoB to mmol/L by 0.01.

^a*p* < 0.05, ^b*p* < 0.0001.

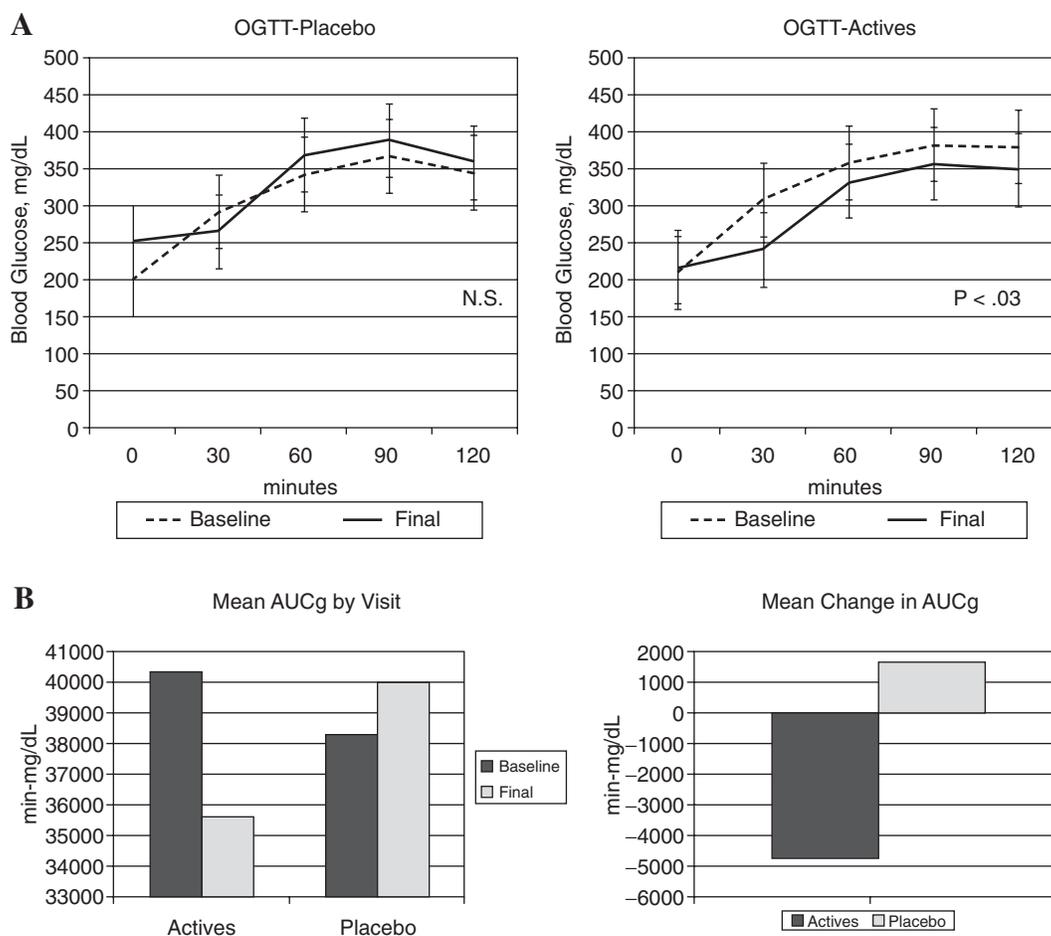


FIG. 1. Effect of chromium picolinate and biotin supplementation on (A) OGTT and (B) AUCg.

low chromium status with the risk of diabetes and cardiovascular disease.¹⁶

In this study, urinary chromium concentrations were significantly elevated in the treatment group, indicating study medication compliance in patients randomized to receive chromium picolinate and biotin supplements.

Both chromium and biotin have been shown to play a role in multiple metabolic pathways, suggesting a possible benefit of supplementation in individuals who are deficient.^{4,5} Previous studies have reported that chromium picolinate supplementation has resulted in significant beneficial effects on HbA1c, glucose, insulin, and cholesterol variables in patients with type 2 DM and dyslipidemia.⁴ Chromium picolinate supplementation has been reported to shortened QTc intervals in people with diabetes; QTc shortening is a surrogate for reduced insulin-induced activation of the

sympathetic nervous system and reduced cardiovascular risk.¹⁷ Direct effects on cardiovascular events, however, have not been carefully evaluated.

Multiple studies have examined the cardiovascular effects of elevated plasma glucose in the setting of OGTT.¹⁸ Adverse effects of postprandial hyperglycemia have been demonstrated. Postprandial hyperglycemia has been implicated as having independent direct toxic effects on vascular epithelium.¹⁹ The Framingham Offspring Study,²⁰ the Helsinki Policemen Study,²¹ and the Islington Diabetes Survey²² have all demonstrated that elevated 2-h postglycemic challenge glucose correlated with increased cardiovascular events better than HbA1c without a significant impact from fasting glucose levels. Further, the DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) Study evaluated

more than 22,000 patients without diabetes using a glucose challenge and found that 2-h post-challenge hyperglycemia was a better predictor of mortality than fasting glucose.²³

This study targeted the effects of glycemic management during a glucose challenge. Data from OGTTs demonstrated that patients who were supplemented with chromium and biotin adapted better to a glycemic challenge than patients on placebo. Treatment subjects achieved reduced glucose levels after 2 h compared with placebo subjects. Overall, the AUC_g was significantly reduced in treatment group patients receiving the chromium picolinate and biotin supplement.

Fructosamine levels, a measurement of blood glucose levels over the 3 weeks prior to testing, significantly decreased in the treatment group compared with placebo, demonstrating improved glycemic control. Other studies have suggested positive benefits on HbA_{1c}.⁴ The duration of this study did not permit for meaningful evaluations of this measurement.

Mean fasting blood glucose and TG levels were elevated in the placebo group at the final visit. Data indicated that 12 of 16 subjects on placebo had higher fasting blood glucose levels after 30 days. Four subjects (two placebo and two treatment) had TG levels more than 2 SD above the mean. When these subjects were removed from the analysis, a significant difference in mean change in TG between treatment and placebo groups (-8.8 vs. 21.5 , $P < 0.03$) was still noted.

Effects on lipid metabolism in the active chromium/biotin group trended favorably. This has been noted in other studies.^{4,5} Downward trends of TG, total cholesterol, and coronary risk lipid ratios in the active group may reflect increased efficiency in glycemic control; lipid subfractions were not, however, affected. Chromium picolinate/biotin supplementation effects on lipid metabolism remain uncertain, and further studies in a larger group and over a longer time period are indicated. A larger 400-patient, 3-month randomized placebo controlled study is ongoing to determine the effects of chromium picolinate/biotin on HbA_{1c} and other risk factors in type 2 DM.

Supplementation with chromium picolinate and biotin was well tolerated in this study. Ad-

verse events were limited and similar between groups. The safety of both chromium picolinate and biotin is well established; both are generally recognized as safe.

CONCLUSIONS

This pilot study demonstrated that the combination of chromium picolinate and biotin supplements in patients with poorly controlled diabetes receiving antidiabetic therapy positively affected glucose management as measured by the response to a glucose challenge and fructosamine levels. Chromium picolinate/biotin supplementation may represent an effective adjunctive therapy for patients with poorly controlled diabetes with dyslipidemia. Results of this study warrant further evaluation of the effects of this supplement on metabolic risk factors.

REFERENCES

1. Song SH, Brown PM: Coronary heart disease risk assessment in diabetes mellitus: comparison of UKPDS risk engine with Framingham risk assessment function and its clinical implications. *Diabet Med* 2004;21:238–245.
2. Colagiuri S, Cull CA, Holman RR: Are lower fasting plasma glucose levels at diagnosis of type 2 diabetes associated with improved outcomes?: UK Prospective Diabetes Study 61. *Diabetes Care* 2002;25:1410–1417.
3. Saydah SH, Fradkin J, Cowie CC: Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA* 2004;291:335–342.
4. Cefalu WT, Hu FB: Role of chromium in human health and in diabetes. *Diabetes Care* 2004;27:2741–2751.
5. Fernandez-Mejia C: Pharmacological effects of biotin. *J Nutr Biochem* 2005;16:424–427.
6. Wang ZQ, Zhang XH, Cefalu WT: Chromium picolinate and biotin enhance glycogen synthesis and glycogen synthase gene expression in human skeletal muscle culture [abstract]. *Diabetes Res Clin Pract* 2000;50(Suppl 1):395.
7. Komorowski JR, de la Harpe J, Cefalu WT, Zhang XH, Wang ZQ, Greenberg D: JCR:LA-cp rats show improved lipid profiles in response to diets containing chromium picolinate and biotin [abstract-80]. In: SSIB Program. San Antonio, TX: Society for the Study of Ingestive Behavior, 2001:41.
8. Matthews JNS, Altman DG, Campbell MJ, Royston P: Analysis of serial measurements in medical research. *BMJ* 1990;300:230–235.

9. Vuksan V, Stavro M, Sievenpiper J, Beljan-Zdravkovic U, Leiter L, Josse R, Xu Z: Similar postprandial glycemic reductions with escalation of dose and administration time of American ginseng in type 2 diabetes. *Diabetes Care* 2000;23:1221–1226.
10. Vuksan V, Sievenpiper J, Koo V, Francis T, Beljan-Zdravkovic U, Xu Z, Vidgen E: American ginseng (*Panax quinquefolius* L) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus. *Arch Intern Med* 2000;160:1009–1013.
11. Reaven GM: Insulin resistance and compensatory hyperinsulinemia: role in hypertension, dyslipidemia and coronary heart disease. *Am Heart J* 1991;121:1283–1288.
12. Grundy SM: Hypertriglyceridemia, insulin resistance, and the metabolic syndrome. *Am J Cardiol* 1999;83:25F–29F.
13. Ford ES, Giles WH, Dietz WH: Prevalence of the metabolic syndrome among US adults—findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002;287:356–359.
14. Cotton PA, Subar AF, Friday JE, Cook A: Dietary sources of nutrients among US adults, 1994 to 1996. *J Am Diet Assoc* 2004;104:921–930.
15. Anderson RA, Bryden NA, Polansky MM: Dietary chromium intake. Freely chosen diets, institutional diet, and individual foods. *Biol Trace Elem Res* 1992;32:117–121.
16. Rajpathak S, Rimm EB, Li T, Morris JS, Stampfer M J, Willett WC, Hu FB: Lower toenail chromium in men with diabetes and cardiovascular disease compared with healthy men. *Diabetes Care* 2004;27:2211–2216.
17. Vrtovec M, Vrtovec B, Briski A, Kocijancic A, Anderson RA, Randovancevic B: Chromium supplementation shortens QTc interval duration in patients with type 2 diabetes mellitus. *Am Heart J* 2005;149:632–636.
18. Ceriello A, Hanefeld M, Leiter L, Monnier L, Moses A, Owens D, Tajima N, Tuomilehto J: Postprandial glucose regulation and diabetic complications. *Arch Intern Med* 2004;164:2090–2095.
19. Brownlee M: Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001;414:813–820.
20. Meigs J, Nathan D, D'Agostino R, Wilson P: Fasting and post-challenge glycemia and cardiovascular disease risk: the Framingham Offspring Study. *Diabetes Care* 2002;25:1845–1850.
21. Pyorala K, Savolainen E, Lehtovirta E, Punsar S, Siltanen P: Glucose tolerance and coronary heart disease: Helsinki Policemen Study. *J Chronic Dis* 1979;32:729–745.
22. Jackson CA, Yudkin JS, Forrest RD: A comparison of the relationships of the glucose tolerance test and the glycated hemoglobin assay with diabetic vascular disease in the community: the Islington Diabetes Survey. *Diabetes Res Clin Pract* 1992;17:111–123.
23. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE Study Group. European Diabetes Epidemiology Group. *Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. Lancet* 1999;354:617–621.

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2. 2007. Current literature in diabetes. *Diabetes/Metabolism Research and Reviews* **23**:5, i-ix. [[CrossRef](#)]
3. Cesar Albarracin, Burcham Fuqua, Jeff Geohas, Vijaya Juturu, Manley R. Finch, James R. Komorowski. 2007. Combination of Chromium and Biotin Improves Coronary Risk Factors in Hypercholesterolemic Type 2 Diabetes Mellitus: A Placebo-Controlled, Double-Blind Randomized Clinical Trial. *Journal of the CardioMetabolic Syndrome* **2**:2, 91-97. [[CrossRef](#)]