Chromium Picolinate and Biotin Combination Reduces Atherogenic Index of Plasma in Patients with Type 2 Diabetes Mellitus: A Placebo-Controlled, Double-Blinded, Randomized Clinical Trial

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ABSTRACT: *Background:* The atherogenic index of plasma (AIP), defined as logarithm [log] of the ratio of plasma concentration of triglycerides to high-density lipoprotein (HDL) cholesterol, has recently been proposed as a predictive marker for plasma atherogenicity and is positively correlated with cardiovascular disease risk. The nutrient combination of chromium picolinate and biotin (CPB) has been previously shown to reduce insulin resistance and hyperglycemia in patients with type 2 diabetes (T2DM). *Methods:* Thirty-six moderately obese subjects with T2DM and with impaired glycemic control were randomized to receive CPB or placebo in addition to their oral hyperglycemic agents for 4 weeks. Measurements of blood lipids (including ratio of triglycerides to HDL cholesterol), fructosamine, glucose, and insulin were taken at baseline and after 4 weeks. *Results:* At the final visit, the active group had a significantly lower AIP compared to the placebo group ($P < 0.05$). A significant difference in triglyceride level ($P < 0.02$) and the ratio of low-density lipoprotein (LDL) to HDL cholesterol ($P < 0.05$) was also observed between the groups at the final visit. In the active group, the changes in urinary chromium levels were inversely correlated with the change in AIP ($P < 0.05$). Urinary chromium levels were significantly increased in the CPB group. In the CPB group, glucose levels decreased at 1 hour and 2 hours and glucose area under the curve and fructosamine level were significantly decreased. Ratios of total to HDL cholesterol, LDL to HDL cholesterol, and non-HDL to HDL cholesterol were significantly decreased between the treatments at final visit. No significant adverse events were observed in the CPB or placebo groups. *Conclusions:* These results suggest that the combination of chromium picolinate and biotin may be a valuable nutritional adjuvant therapy to reduce AIP and correlated CVD risk factors in people with T2DM.
KEY INDEXING TERMS: Chromium; Biotin; Diabetes; Dyslipidemia; Atherogenic index. **[Am J Med Sci 2007; 333(3):145–153.]**

Recent prevalence and epidemiologic data suggest that patients with type 2 diabetes (T2DM) should be treated aggressively to reduce risk of coronary heart disease (CHD). In its third revision, National Cholesterol Education Program guidelines[1–3] acknowledged that diabetes was as important as treating major (CHD) risk factors and CHD risk equivalence. This information provides the rationale for treating cardiovascular risk factors as aggressively in patients with diabetes as in patients with CHD.[3] The incidence of sudden cardiac death after the onset of chest pain is nearly twice as high in diabetic men as in nondiabetic men and 3.5 times higher in diabetic women than in nondiabetic women.[4,5] The higher mortality rate in patients with diabetes persists after hospitalization. In the initial year after a first myocardial infarction, mortality rates are 1.4 times higher in diabetic than in nondiabetic men and 1.8 times higher in diabetic than in nondiabetic women. Patients with CHD and diabe-

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tes are at especially high risk for recurrent events; their incidence of myocardial infarction at 7 years is nearly 50%.[6] These data establish the need for aggressive therapies to reduce initial and recurrent cardiovascular events in patients with diabetes. High plasma cholesterol levels are a strong predictor of cardiovascular events in patients with diabetes.[7,8] The cardiovascular mortality rate is 2.83 to 4.46 times higher in diabetic than in nondiabetic men at various levels of serum cholesterol.[9] In the UK Prospective Diabetes Study,[10] high levels of low-density lipoprotein (LDL) cholesterol were highly correlated with cardiovascular events. However, low levels of high-density lipoprotein (HDL) cholesterol reached nearly equal significance. In addition, the prevalence of hypertriglyceridemia in patient with T2DM is two to three times higher than in nondiabetic patients.[11]

Lipoprotein subclass abnormalities that accompany insulin resistance are characterized by large, triglyceride-enriched very low density lipoprotein particles; small, cholesterol-depleted LDL particles; and small HDL particles.[12] In addition, more severe states of insulin resistance have been associated with progressively higher numbers of very low density lipoprotein particles, intermediate-density lipoprotein particles, and, most importantly, LDL particles.[13]

The atherogenic index of plasma (AIP) is a logarithmically transformed ratio of molar concentrations of triglycerides to HDL cholesterol. The strong correlation of AIP with lipoprotein particle size may explain its association with cardiovascular disease (CVD) risk. The AIP, defined as log(triglycerides/HDL cholesterol), has recently been proposed as a marker of plasma atherogenicity because it is increased in people at higher risk for CHD and is inversely correlated with LDL particle size.[14,15]

Nutritional intervention is an alternate approach to the management of T2DM and, subsequently, to lowering the risk for diabetes complications. Chromium is a cofactor of insulin that is directly involved as an integral component of glucose homeostasis. Epidemiologic data suggest that low levels of chromium in serum,[16] hair,[17] and toenail tissues[18,19] are significantly correlated with diabetes, and diabetes with cardiovascular disease and CVD.

In addition, strong evidence from human clinical trials suggests that supplemental chromium, in the form of chromium picolinate, improves insulin sensitivity and glycemic control in diabetic patients and improves diabetic symptomatology; significant lowering of HbA1c has also been demonstrated with administration of chromium picolinate in cases of T2DM.[20,21]

Data are also available suggesting that biotin supplementation favorably affects abnormalities in glucose regulation. In vitro and in vivo studies point to biotin's role in enhancing the activity of glucokinase, a pancreatic enzyme involved in glucose uptake in the liver, and subsequently, its ability to lower blood glucose level and increase insulin release from pancreatic beta cells.[22]

Preclinical studies suggest that the combination of chromium picolinate and biotin (CPB) enhances glucose uptake, glycogen synthesis, glucose disposal and HDL cholesterol levels.[23] In a recent open-label program, CPB improved glycemic control.[23] Lipid profiles are affected by metabolic abnormalities, and alterations in lipid metabolism, in addition to changes in glucose metabolism, have been implicated in atherosclerosis and coronary heart disease in patients with T2DM. This study was designed, in part, to estimate the effect of CPB on atherogenic index in plasma and glycemic control in subjects with T2DM.

Subjects and Methods

Subjects

The study was a 30-day, placebo-controlled, double–blinded, randomized, parallel-arm, single-center clinical trial. Participants included male and female subjects who were overweight or obese (body mass index between 25 and 35), between the ages of 18 and 65 years with persistent impaired glucose control (2-hour oral glucose tolerance test result ≥200 mg/dL), HbA1c greater than or equal to 7%, and at least a 1-year history of T2DM. Patients were receiving stable oral antidiabetic medications (OADs) that were stable for at least 60 days prior to entry. Based on poor glycemic control and stable concurrent OADs, this subject population was defined as failing their OAD therapy. No changes in participants' diet or physical activity regimen were allowed during the study period. Patients who were taking or required exogenous insulin were excluded. All study subjects gave written and oral informed consent. Referrals were accepted from local area primary healthcare physicians who agreed to assist the investigative site with recruitment. The patient database was accessible to investigators so that they could obtain the names and addresses of clinic patients who met the initial eligibility criteria for the study. Demographic characteristics, family history, medial history, concurrent medications, and vital signs were recorded for each subject.

Diets

Subjects were asked to record 3-day dietary intakes in which participants were to record the time and quantity or portion of size of each meal (breakfast, lunch, snack, dinner, and bedtime snack). Three-day dietary intakes of the participants were analyzed for nutrient content using Nutritionist V software (NUTRITIONIST PRO, Version 2.1, First Databank, The Hearst Corporation). The diets of subjects with T2DM were assessed using the USDA Healthy Eating Index (HEI) (a measure of dietary quality based on a 100-point scale) as an assessment of dietary status through its correlation with clinical indices of diabetes risk factors. Criteria for minimum and maximum scores for each HEI component were categorized. A score of 10 on these components was attained by the subject's consuming at or below the maximum recommended levels. Care was taken to ensure that there was proportional distribution of week and weekend days for the dietary intakes. All participants received detailed instructions from a trained dietitian at the research center on how to accurately provide the food and beverages consumed and to complete the 3-day dietary intake records.

Treatment

Patients were randomized to receive a bioavailable combination of 600 μg chromium in the form of chromium picolinate plus 2 mg biotin (Diachrome, Nutrition 21, Purchase, New York) or placebo once daily for 4 weeks (30 days). For the duration of the trial, patients took one capsule per day in the morning. Placebo capsules contained dicalcium phosphate and were identical in size, shape, and color to the treatment capsules. Diaries were

monitored midway though the study and again after 30 days. Fasting laboratory studies, comprehensive metabolic and chemistry panels, were collected from all participants at the baseline and final visits to assess the efficacy and safety of the active pills. Patients' adverse experiences were assessed via study visit interviews and patient diary reviews at the final visit. Study dosing compliance was assessed using a standard pill count and exit interviews at the final visit.

Plasma Biomarkers

Subjects returned for fasting metabolic and lipid assessments: total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, apolipoproteins A and B, oral glucose tolerance test (0, 1, 2 hrs), and fructosamine and insulin concentrations. Baseline and final urine chromium levels were assessed to determine compliance. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated from fasting glucose and insulin levels as described by Matthews et al[24] as follows: resistance = [glucose] × [insulin] ÷ 22.5. The value of the beta cell function (%) was given by the following formula: 20 × plasma insulin concentration/(plasma glucose − 3.5). The calculation of the beta-cell function was based on the HOMA, as described initially by Matthews et al.[24] AIP was computed for each patient at baseline and at each subsequent visit according to the following equation:

AIP = log(triglycerides/HDL cholesterol), with units for triglycerides and HDL cholesterol in milligrams per decaliter.

The study protocol was approved and overseen by the New England Institutional Review Board (NEIRB), Wellesley, Massachusetts.

Statistical Analysis

Analyses were performed to determine the effects of CPB supplementation on glycemic control and lipid profile, including atherogenic lipid ratios, in patients with T2DM. The two-group *t*-test procedure in SAS ASSIST (Version 8.2) was used in all analyses. Change scores between groups were computed by comparing biomarkers from baseline and day 30. The study also showed differences between CPB and placebo groups in mean percentage change from baseline. Only data from patients who had baseline and final data, and who did not significantly deviate from the protocol, were used in the calculations.

Results

One hundred fourteen patients were screened for the study, 43 patients were randomized to treatment, and 36 patients fulfilled the inclusion/exclusion criteria and provided evaluable data (active group, n = 20; placebo group, n = 16). Seven subjects were not included in the analysis; 4 subjects deviated from protocol (one active and 3 placebo patients), and 3 subjects did not return for the final study visit (3 placebo patients).

Baseline Characteristics

The active and placebo groups were similar at baseline, without significant differences in age, sex, body mass index, blood pressure or $HbA1_c$, and OADs (Table 1). Baseline laboratory assessments of urine chromium levels, fasting glucose, insulin, fructosamine, and lipid panel yielded results that were similar between the groups. No significant differences were observed between the groups. T1

Diets

The mean total HEI score was 49.8. Forty-seven percent of the subjects scored less than 50 on the

Table 1. Baseline Characteristics of Subjects[a]

Characteristics	Placebo (n = 16)	CPB (n = 20)	*P*-Value
Age, yrs	48 ± 9	53 ± 9	0.1412
Male/Females	10/6	9/11	0.2960
OADs	12 SU, 3 TZD, 15 BG, 1 NSU, 19 CM	17 SU, 4 TZD, 14 BG, 0 NSU, 17 CM	
Race	8 black, 5 white, 2 Asian, 1 other	9 black, 2 Asian, 3 Hispanic, 4 white, 2 other	
Body mass index, Kg/m^2	30 ± 4	30 ± 4	0.9789
Systolic blood pressure (mm Hg)	131 ± 17	132 ± 15	0.8129
Diastolic blood pressure (mm Hg)	78 ± 9	80 ± 10	0.4768
HbA1c (%)	8.8 ± 1.4	9.2 ± 1.3	0.3254
Fructosamine, mg/dL	342.4 ± 66.5	377.1 ± 91.7	0.2136
Insulin uIU/mL	6.1 ± 3.6	6.2 ± 3.2	0.9324
Urine chromium, μg/L	0.074 ± 0.075	0.166 ± 0.137	0.0215*
Fasting glucose 0 hr, mg/dL	203 ± 53	211 ± 54	0.6646
Glucose 1 hr, mg/dL	342 ± 68	359 ± 77	0.5126
Glucose 2 hr, mg/dL	344 ± 70	379 ± 77	0.1616
AUCgrea under the curve glucose, min · mg/dL	38329 ± 6941	40349 ± 7398	0.8125
Total cholesterol, mg/dL	206 ± 61	198 ± 33	0.6085
HDL cholesterol, mg/dL	38 ± 7	42 ± 8	0.1762
LDL cholesterol, mg/dL	136 ± 53	123 ± 33	0.3803
Triglycerides, mg/dL	147 ± 68	145 ± 67	0.9039
Ratio of total cholesterol to HDL cholesterol	5.52 ± 1.63	4.91 ± 1.2	0.2043
Ratio of LDL to HDL cholesterol	3.62 ± 1.3	3.03 ± 0.98	0.1396
apoA, mg/dL	140 ± 26	147 ± 26	0.3946
apoB, mg/dL	96 ± 28	88 ± 21	0.3418
Log(triglycerides/HDL cholesterol)	1.27 ± 0.58	1.15 ± 0.63	0.5803

[a] *No significant differences were observed between the treatments; values are mean ± SD.*
BG, biguanides; CM, concomitant medications; NSU, nonsulfonylureas; SU, sulfonylureas; TZD, thiazolidinediones.

Table 2. Baseline Nutrient Intake and Food Groups Based on Servings and HEI Score

Food Groups	Mean Servings
Grains	8.2
Vegetables	2.6
Meat	8.4
Fruits	4.9
Milk	0.9
Total HEI score[a]	49.8
Variety of foods	8.9

Nutrients	Nutrient Intake	RDA[a]
Vitamin A (retinol equivalent), μg	987 ± 137	900
Vitamin E, IU	4.56 ± 0.6	20
Folate, μg	243 ± 23	400
Calcium (AI), mg	552 ± 50	1000[b]–1200[c]
Magnesium, mg	190 ± 15	400[c]–420[d]
Zinc, mg	5.2 ± 0.5	15
Iron, mg	12 ± 0.9	18
Chromium, μg	30 ± 0.4	120

AI, adequate intake; HEI score: Healthy Eating Index score; RDA: Recommended Dietary Allowance.
[a] Values are mean ± SD.
[b] 9–50 yrs of age.
[c] 51–70 yrs of age.
[d] 31–70 yrs of age.

T2 HEI (Table 2). Total HEI was significantly correlated with fructosamine ($P < 0.04$), insulin ($P < 0.02$), HOMA-IR ($P < 0.05$), and HOMA-BCF ($P < 0.01$) levels. The subjects' micronutrient intake of minerals and vitamins did not meet the recommended intakes through dietary means compared to an average American diet. Consumption of grains and meat servings were higher and fruits and vegetables servings were less than recommendations. Fifty percent of subjects' diets rated as "Poor and Needs Improvement." It was observed that mean dietary chromium was lower than the minimum suggested recommended daily intakes. These results are an important step in the validation of the HEI, emphasizing its potential as a tool for assessing nutritional status in chronic disease.

Plasma Biomarkers

Plasma biomarkers were assessed at baseline and final visits (Table 3). Mean fructosamine levels, a T3 measure of the average blood glucose level of the past 4 weeks, were significantly reduced ($P < 0.03$) in the active group (−23.0 ± 56 mg/dL [−1.3 mmol/L]) compared to the placebo group (12.9 ± 33 mg/dL [0.7 mmol/L]). Fasting plasma glucose levels were decreased, but not significantly, in the active group compared to baseline ($P < 0.0525$).

Effects of CPB on lipid metabolism were evaluated by comparison of total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, log triglycerides/HDL cholesterol, and lipid subfractions (apoA and apoB) after 30 days of treatment. At the baseline visit (initial visit), no significant differences in lipid profiles were observed between the treatment groups. In the placebo group, a significant increase in levels of fasting glucose, triglycerides, apoB, and AIP and a trend of significance in fructosamine levels were observed after 30 days treatment (Table 3). In the active group a significant decrease in area under the curve of glucose (AUCg), fructosamine, total cholesterol, ratio of total to HDL cholesterol, and an increase in

Table 3. Change in Plasma Biomarkers in Subjects with Type 2 DM

	Placebo Group (*P*-Value)[a]	CPB Group (*P*-Value)[a]	Change by Treatment *P*-Value
Fructosamine, mg/dL	12.9 ± 33 (0.06)	−23.0 ± 56 (0.04[b])	0.0263[b]
Fasting insulin, uIU/mL	0.005 ± 0.57 (0.18)	0.25 ± 0.64 (0.49)	0.7772
Fasting glucose, mg/dL	50.19 ± 62 (0.03[b])	7.45 ± 65 (0.31)	0.0525
Glucose 1 hr, mg/dL	26.25 ± 87 (0.12)	−25.85 ± 90 (0.1)	0.0889
Glucose 2 hr, mg/dL	15.5 ± 20 (0.24)	−30.9 ± 18 (0.05[b])	0.0879
AUCg, min/mg/dL	1649 ± 7013 (0.18)	−4701.8 ± 8959 (0.014[b])	0.0264[b]
Total cholesterol, mg/dL	0.06 ± 41 (0.49)	−11.2 ± 21 (0.01[c])	0.2908
HDL cholesterol, mg/dL	−0.6875 ± 8 (0.36)	−0.1 ± 4 (0.46)	0.7735
LDL cholesterol, mg/dL	−1.125 ± 49 (0.46)	−2.15 ± 20 (0.31)	0.9319
Triglycerides, mg/dL	59.75 ± 113 (0.02[b])	−9.25 ± 41 (0.1)	0.0159[b]
Ratio of total cholesterol to HDL cholesterol	0.18 ± 0.9 (0.23)	−0.21 ± 0.51 (0.04[b])	0.0730
Ratio of LDL to HDL cholesterol	0.12 ± 1.1 (0.34)	−0.01 ± 0.5 (0.45)	0.3311
apoA, mg/dL	−6.4 ± 19 (0.1)	−17.1 ± 25 (0.003[c])	0.1737
apoB, mg/dL	9 ± 15 (0.02[b])	1.15 ± 22 (0.41)	0.2518
Log(triglycerides/HDL cholesterol)	0.28 ± 3.5 (0.03[b])	−0.09 ± 1.2 (0.1)	0.05[b]
Urine chromium, μg/L	0.104 ± 0.25 (0.06)	4.73 ± 3.5 (0.0004[e])	<0.0001[d]

Values are mean ± SD.
[a] The P-values in parenthesis are for the paired Student t-test within the groups.
[b] $P < 0.05$.
[c] $P < 0.01$.
[d] $P < 0.0001$.
[e] $P < 0.0005$.

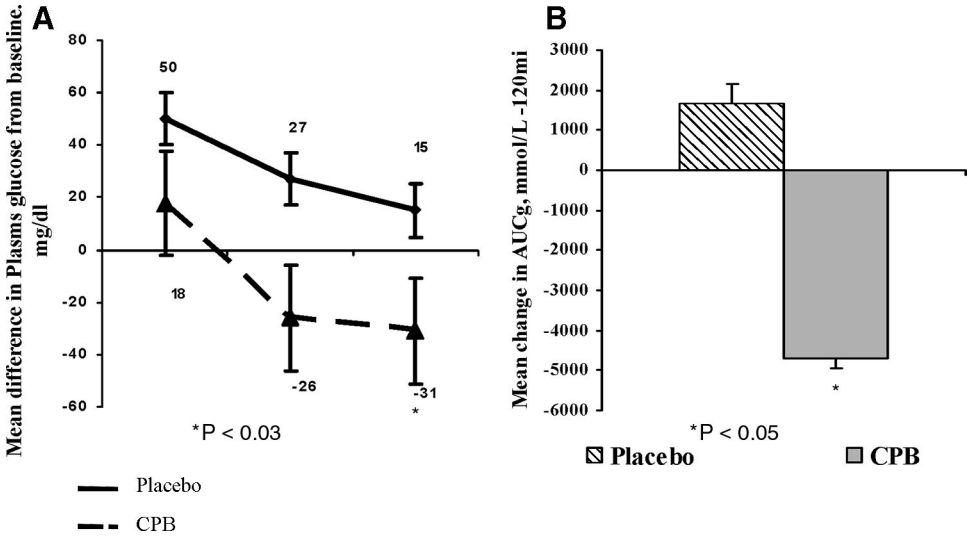

Figure 1. (A) Change in glucose level in the treatment groups (placebo and CPB) at different time points (0, 1, 2 hrs). (B) Mean change in area under curve of glucose (AUCg) in the CPB and placebo groups.

urinary chromium levels were observed. The active group had a significantly lower AIP compared to the placebo group ($P < 0.05$). The AIP in the active group dropped from 1.15 to 1.06, whereas the AIP increased ($P < 0.1$) from 1.27 to 1.55 in the placebo group. A significant difference in triglycerides ($P < 0.02$) and ratio of LDL to HDL cholesterol ($P < 0.05$) was also observed between the groups. Nonsignificant reductions were seen in lipid subfractions apolipoproteins A and B. Urinary chromium concentrations were significantly elevated in the active group ($P < 0.0001$), but not in the placebo group.

During the course of the 30-day study, CPB supplementation was well tolerated. A comprehensive review of the adverse events revealed that they were mild to moderate and not dissimilar from those associated with placebo. There were no reports of hypoglycemia or weight gain commonly associated with OADs.

Discussion

Atherogenic dyslipidemia results in increased atherosclerotic plaque formation because of an imbalance between an increased number of small, dense LDL particles (which carry cholesterol to the vascular endothelium) and a decreased number of HDL particles (which remove cholesterol from atherosclerotic vessels). Insulin resistance is the initial physiologic defect in the pathogenesis of diabetes (T2DM); the associated atherogenic lipoprotein phenotype considerably enhances the risk of CVD. Hence there is ongoing interest in a treatment that is capable of lowering the glucose and atherogenic lipid profile in patients with T2DM. Chromium picolinate supplementation used for glycemic control in patients with T2DM seems to hold promise in this respect. In the present study, we observed significant decreases in blood sugar levels at 1 hour and 2 hours in the CPB group (Figure 1A; $P < 0.03$) and a significant change in fructosamine (Table 3) and AUCg (Figure 1B; $P < 0.05$). A significant increase in glucose, AIP, triglyceride level, and apoB level and a nonsignificant increase in fructosamine ($P < 0.06$) was observed after 30-day placebo treatment. In the active group, a significant decrease in fructosamine, AUCg, and total cholesterol was observed.

McGarry[25] explained that primary defects in triglyceride and fatty acid metabolism may lead insulin resistance, and the lipotoxic effects of free fatty acids may be responsible for beta cell destruction. Dobiasova and Frohlich[26] studied 1433 subjects from 35 cohorts with various risk of atherosclerosis (cord plasma, children, healthy men and women, pre- and postmenopausal women, patients with hypertension, T2DM, and dyslipidemia, and patients with positive or negative angiography findings). Dobiasova and Frohlich[26] observed a strong positive correlation between HDL and log (triglyceride/HDL cholesterol) and AIP directly related to the risk of atherosclerosis in these cohorts. They also confirmed a significant inverse correlation of LDL size with fractional esterification rate (FER_{HDL}) and AIP in normal subjects. Hu et al[27] previously reported the relationship of AIP, an indirect indicator of LDL particle size, positively related to carotid intima-media thickness in patients with T2DM among Han Chinese. Several lipoprotein-related indices—plasma concentrations of lipids (LDL cholesterol, HDL cholesterol, and triglycerides), molar ratios (triglyceride to HDL cholesterol and LDL to HDL cholesterol), and particle size (LDL and HDL)—have been used to predict CHD risk. In the current study, at the final visit, the active group had a significantly lower AIP compared to the placebo group (Figure 2; $P < 0.05$). The AIP in the active group dropped from 1.15 to 1.06, whereas the AIP increased from 1.27 to 1.55 in the placebo group.

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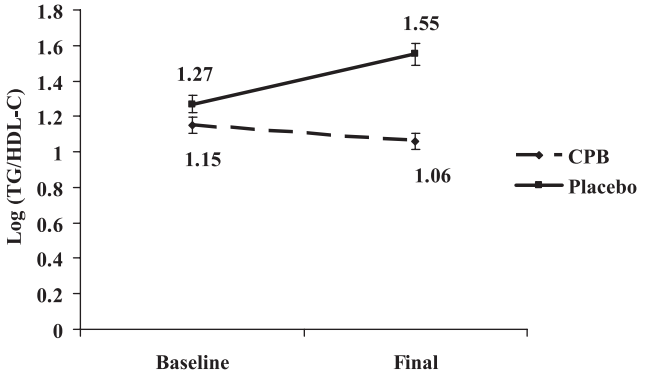

Figure 2. Mean atherogenic index in plasma at baseline and final visits by treatments (placebo and CPB groups).

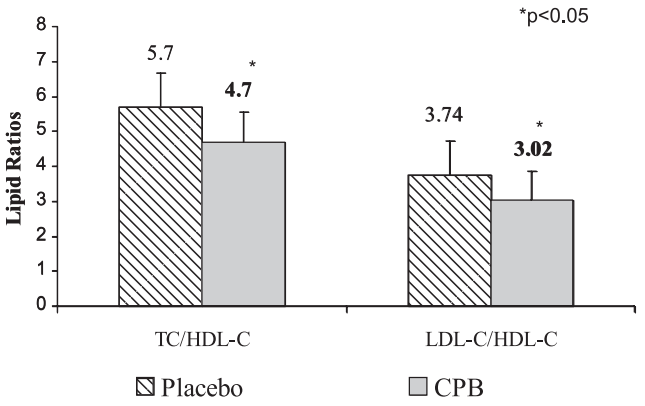

Figure 3. Mean lipid ratios of total cholesterol to HDL cholesterol and LDL cholesterol to HDL cholesterol at final visit by treatments (placebo and CPB groups).

As noted, the total to HDL cholesterol and LDL to HDL cholesterol molar ratios have good predictive value for future cardiovascular events.[28] Log(triglyceride/HDL cholesterol) is also a significant independent predictor of CHD.[29] In a recent study, patients with T2DM have the highest AIP; they also have a higher FER_{HDL} compared with nondiabetic individuals, and there is a direct correlation between FER_{HDL} and waist-to-hip ratio in these patients.[30] In addition, they are more likely to have a predominance of small, dense LDL particles compared with nondiabetic controls.[31]

All of these factors suggest that AIP is a suitable marker for plasma atherogenicity in patients with T2DM. Cross-sectional studies have reported that patients with T2DM and CVD have fasting hyperinsulinemia compared to those without cardiovascular disease.[32] Because hyperinsulinemia is often clustered with other cardiovascular risk factors, the presence of endogenous hyperinsulinemia combined with hypertriglyceridemia, increased body mass index, and a decreased HDL cholesterol increases the risk of CHD death in patients with T2DM.[33] Despres et al[34] also reported that people with hyperinsulinemia and high triglyceride levels have an increased risk for CHD. AIP, therefore, may be an important tool for analyzing the results of clinical trials in which atherogenicity is assessed.

The association of triglycerides and HDL cholesterol in this simple ratio theoretically reflects the balance between risk and protective lipoprotein forces, and both triglycerides and HDL cholesterol are widely measured and available.[35] In this study, significant differences in triglycerides ($P < 0.02$) and ratio of LDL to HDL cholesterol (Figure 3; $P < 0.05$) were also observed between the groups at the final visit. The Copenhagen Male study,[36] the AMORIS study,[37] and several other trials have shown hypertriglyceridemia to be an independent predictor of CHD.[38–40] Hypertriglyceridemia may promote risk both directly and indirectly through association with alterations of lipoprotein size and composition. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) demonstrated that raising the HDL cholesterol level in patients with low HDL cholesterol and LDL cholesterol is associated with a significant reduction in CHD risk.[41] It was shown in the Diabetes Intervention Study,[42] the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),[43] the Münster Heart Study (PROCAM),[44] and the Helsinki Heart Study[45] that decreased HDL cholesterol level and elevated triglyceride level are independent risk factors for atherosclerosis, particularly in patients with T2DM. Several epidemiologic studies demonstrated that total to HDL cholesterol ratios or LDL to HDL cholesterol ratios could be better predictors of atherosclerosis than any single lipid parameter.[46] The decrease in AIP (Figure 2) and decrease in total to HDL cholesterol ratio and LDL to HDL cholesterol ratio in the CPB group in Figure 3 suggest that CPB may be helpful in reducing coronary risk factors in patients with T2DM.

Renal dysfunction is a major complication of T2DM, the potential impact of chromium picolinate on kidney function requires due consideration in T2DM.[47] The body's chromium content may be reduced under several conditions. Diets high in simple sugars (comprising more than 35% of calories) can increase chromium excretion in the urine and can lead to deficiency, especially if chromium intakes are already low.[48] Chromium supplementation in type 2 diabetic mice reduces the symptoms of hyperglycemia and improves renal function by recovering renal chromium concentrations.[49] Since it is known that urinary chromium is one of the measures to observe the bioavailability of chromium compounds, it is worth noting that chromium levels are decreased in patients with T2DM.[50,51] In the current study, urinary chromium levels increased after supplementation in the CPB group (0.166 ± 0.137 vs 5.16 ± 3.4; $P < 0.001$). In the CPB group, the change in the urinary chromium level was inversely correlated with the change in AIP ($P < 0.05$).

The AIP is inversely and significantly correlated with measures of insulin sensitivity. Previously, AIP has been reported to correlate with HOMA-IR in Bermudians.[52] Data from Wu et al[53] suggest that diabetic patients and their normoglycemic first-degree relatives of T2DM genetic ancestry had significantly higher AIP than did control subjects.

There is evidence that an increased plasma concentration of triglycerides is associated with an elevated incidence of coronary artery disease[54]; heightened levels of small, dense LDLs; and enhanced cholesteryl ester mass transfer from HDL to apoB-containing lipoproteins.[55] Triglycerides have also been proposed to be a major determinant of cholesterol esterification/transfer and HDL remodeling in human plasma.[56] Therapeutic hypolipidemic intervention leads to improvements in the spectrum of plasma lipids and apoproteins, including changes in lipoprotein particle sizes and changes in cholesterol esterification and lipolytic rates. Low HDL cholesterol and high triglyceride concentrations induce both an increase in the proportion of small HDL particles and an increase in small, dense LDL particles; FER_{HDL} is also increased. AIP provides information about the atherogenicity of plasma and quantifies the hypolipidemic response to CPB intervention in cases of T2DM. Application of AIP for CPB trials may offer new insights in clinical practice.[57]

A few limitations should be noted for this study. The study duration is for 30 days based on previous reports that chromium supplementation will improve insulin sensitivity in 10 days.[58] This is an attempt to determine the effect of the combination of CPB on atherogenic lipid profile and glycemic control in T2DM.

Conclusion

There are two strategies for treating dyslipoproteinemia in cases of insulin resistance: aggressive lowering of LDL cholesterol and triglyceride levels, and increasing HDL cholesterol levels. Until the optimal approach has been established in a clinical trial, the primary emphasis of lipid-lowering therapy is reduction in triglycerides and more specifically and accurately controlling blood sugar levels in patients with diabetes. AIP can be easily calculated from standard lipid profile. As a marker of atherogenicity, it adds predictive value beyond that of the individual lipids or the total to HDL cholesterol ratio. The combination of chromium picolinate and biotin may be a valuable nutritional adjuvant therapy to reduce AIP and blood glucose levels in people with T2DM.

It must be emphasized that a majority of patients with diabetes remain at high risk despite target lipid profiles and normal control of other major risk factors. Nevertheless, results of randomized clinical trials have firmly established that management of dyslipidemia affords cardioprotection in diabetes patients.

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