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Apolipoproteins A-I, B and C-III in Young Adult Cherokee with The Metabolic Syndrome; with or without Type 2 Diabetes

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Abstract

BACKGROUND—Since type 2 diabetes (T2D) is a coronary artery disease risk equivalent, it is important to identify difference in risk markers between cases with T2D and the metabolic syndrome (MetS) compared to those with MetS alone. We evaluated apolipoproteins as possible distinguishing markers in the Oklahoma Cherokee.

OBJECTIVE—To assess apolipoproteins A-I, B and C-III in young adult Cherokee who have the metabolic syndrome (MetS), as defined by the National Cholesterol Education Program (NCEP), either with or without T2D.

METHODS—A cross-sectional comparison of young adult Oklahoma Cherokee, aged 18 to 40 years, was conducted to assess differences in the apolipoproteins due to the presence or absence of T2D among those with the MetS, after adjusting for age and gender.

RESULTS—ApoA-I ($p=0.0222$) and HDL-C ($p=0.0364$) were lower, and apoB ($p=0.0106$) and the apoB to A-I ratio ($p<0.0001$) were higher in participants with the MetS and T2D than in those with MetS but without T2D. However, cholesterol, triglyceride, LDL-C, non-HDL-C, total apoC-III, non-HDL apoC-III and the bimodal lipoprotein distribution of apoC-III (apoC-III ratio) were not significantly different between the two groups.

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CONCLUSION—ApoA-I and HDL-C are lower and apoB and the apoB:A-I ratio are higher in those with MetS and T2D than in those who have the MetS but without T2D, suggesting that the presence of diabetes adversely influences plasma apoA-I and apoB levels. However, apoC-III and non-HDL apoC-III are unchanged by the addition of diabetes suggesting that the increased levels associated with the metabolic syndrome may precede T2D.

Keywords

ApoA-I; apoB; apoC-III; diabetes; risk factors

INTRODUCTION

Since apolipoproteins have had increasing potential to predict cardiovascular events [1, 2], we evaluated whether apoA-I, apoB, apoC-III and plasma lipids differed between those with the metabolic syndrome (MetS) and T2D, and those with the MetS but without T2D. Since there is good support for insulin resistance as a central component and driving factor for the MetS [3], it follows that American Indian populations who are more prone to develop diabetes also have a high prevalence of the MetS, as we have previously shown in the Cherokee [4]. Furthermore American Indians are known to lose their innate protection from atherosclerosis following the development of insulin resistance and diabetes [5], making it important to know if risk markers associated with the metabolic syndrome precede diabetes onset and are different when they also have T2D.

We selected apoA-I since it plays a central role in formation of HDL and cellular cholesterol efflux [6], and apoB which represents the total number of atherogenic lipoproteins since there is one apoB molecule per lipoprotein particle [7]. Both apoB and apoA-I have been shown to be significant independent risk factors for cardiovascular events and targets for therapy [8]. ApoC-III, a significant predictor of coronary events, cardiovascular mortality and progression of cardiovascular disease, has been shown to be associated with the MetS [4] and in subjects with T2D, it has been shown to be an independent risk factor for cardiovascular disease [9]. Consequently we assessed total plasma apoC-III and non-HDL apoC-III, using a method which separates apoC-III bound to apoB-containing lipoprotein particles by precipitation of apoB with heparin-manganese [4, 10], the same method as is often used to separate HDL-C from non-HDL-C.

MATERIALS AND METHODS

The Cherokee Diabetes Study is a cross-sectional population-based study designed to evaluate risk factors in the Cherokee residing in a 5-county area in northeastern Oklahoma. With collaboration of the Cherokee Nation of Oklahoma, a subset of 1232 adults aged 18–40 years (females, n=721; males, n=511) was selected from the original cohort of participants aged 5 to 40 years for analysis. 283 had the MetS and 65 had the MetS with T2D. Informed consent was obtained from each subject or his/her legal guardian, following approval of the Institutional Review Boards of the University of Oklahoma Health Sciences Center and the Cherokee Nation.

Three consecutive blood pressure measurements were performed on the right arm according to a standard protocol using a Baum mercury sphygmomanometer (W.A. Baum Co., Copiague, NY), and the average of the second and third measurements was recorded. Diabetes was defined as having a fasting glucose greater than 126 mg/dl or evidence for being on treatment for T2D as defined by the American Diabetes Association criteria [11]. Fasting blood specimens were collected for determining fasting plasma glucose, insulin and lipids. Occurrence of the MetS was defined as presence of any three of the following

components: increased waist circumference (>102 cm in men and >88 cm in women), elevated triglyceride (≥ 1.69 mmol/L or 150 mg/dl), low HDL-C (< 1.03 mmol/L or 40 mg/dl in men and < 1.29 mmol/L or 50 mg/dl in women), elevated blood pressure (≥ 130/85 mmHg) or treated hypertension and high fasting glucose (≥ 6.25 mmol/L or 100 mg/dl) or treated T2D, based on The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults [12].

Lipids and apolipoproteins

Lipid assays included triglycerides, cholesterol, and HDL-cholesterol. An Abbott VP-Super System automatic analyzer and commercial reagents were used to determine levels of glucose, cholesterol (Boehringer, Mannheim, Federal German Republic) and triglyceride (Miles Inc., Tarrytown, NJ) by enzymatic methodology. HDL-C was measured following the heparin-manganese precipitation procedure of the Lipid Research Clinics program and LDL-C was calculated by the Friedewald formula. ApoA-I, apoB and apoC-III were determined by validated electroimmunoassays [13–15]. ApoC-III was assayed in the heparin-manganese supernate and designated HDL apoC-III. This value was subtracted from the total plasma apoC-III to derive non-HDL apoC-III [10]. The apoC-III ratio, the HDL apoC-III divided by the non-HDL apoC-III, used as an index of apoC-III transfer during lipolysis and bimodal apoC-III lipoprotein distribution, was computed [16].

Statistical Analysis

The mean values for each apolipoprotein in the two groups, those with the metabolic syndrome and T2D (MetS+T2D+) and those with the metabolic syndrome but without T2D (MetS+T2D–), were estimated. Generalized linear modeling was used to test the means difference after adjusting for age and gender. The continuous variables, triglyceride and apoC-III were log transformed for analysis since they had skewed distribution.

RESULTS

There were no significant differences in age, gender, waist, weight, BMI and blood pressure between those in the MetS+T2D+ group and MetS+T2D– group, but fasting glucose was significantly higher in the MetS+T2D+ group (Table 1). ApoA-I and HDL-C were lower and apoB, the apoB:A-I ratio, cholesterol:HDL-C ratio were higher in the MetS+T2D+ group than in the MetS+T2D– group, but apoC-III, its separated fractions and its bimodal distribution (apoC-III ratio) were not different (Table 2).

DISCUSSION

The finding that apoA-I, apoB and the apoB:apoA-I ratio distinguish the addition of diabetes to the MetS suggests that they contribute to increased cardiovascular risk in T2D and may have wider application for risk evaluation and treatment decisions than is currently practiced. However, total apoC-III, non-HDL apoC-III, and the apoC-III ratio, an index of the bimodal lipoprotein distribution and transfer to HDL during lipolysis [16], did not distinguish the two groups. Although we have shown previously that increases in non-HDL apoC-III occur in the metabolic syndrome and are proportionate to the number of MetS criteria [4], our data indicate that the presence of T2D does not result in a further increase. Since apoC-III has been shown to have an increasingly important role in atherosclerosis prediction and negatively predicts reversal during treatment [10], the finding that there was no change in apoC-III with the addition of diabetes appears contradictory. However, individuals with and without diabetes have insulin resistance which increases hepatic apoC-III transcription [17] and has been associated with increases in apoC-III in insulin-resistant

obesity [18, 19] and in the metabolic syndrome with the number of MetS criteria [4]. This supports the view that apoC-III is an important marker of atherosclerosis preceding diabetes and persisting after onset. Furthermore, multivariate analysis of the Cholesterol and Recurrent Events (CARE) trial data showed that the presence of diabetes did not account for the predictive association of non-HDL apoC-III (determined by the same methodology) with coronary events [2]. Also there is evidence that apoC-III gene transcription is responsive to glucose mediated by carbohydrate response element-binding protein (ChREBP) and hepatic nuclear factor-4 α (HNF-4 α) in human hepatocytes and apoC-III appears to be regulated by glucose in overweight subjects [20] suggesting that higher glucose in the T2D subjects might increase apoC-III and override the effect of insulin resistance common to both groups, but this appeared not to be the case. It is also possible that ingestion of fructose in the form of high-fructose corn syrup could have raised apoB in both groups [21].

Consistent with previous findings that Pima Indians appear to have a particularly low HDL-C [22], we find that the low HDL-C and apoA-I observed in those with the MetS are even lower when they have acquired diabetes. This finding is consistent with the observation that hyperglycemia is associated with increased catabolism of apoA-I [23], and with HDL triglyceride-enrichment resulting in enhanced clearance by hepatic triglyceride and lipoprotein lipase, and apoA-I dissociation, degradation and renal clearance [24]. In a multivariate analysis improvement in diabetes control predicted increases in HDL-C, apoA-I and the apoA-I:apoB ratio but not changes in apoB, cholesterol and triglyceride [25], supporting a relationship of low apoA-I and HDL-C to diabetes onset and degree of glycemic control.

The increase in apoB in association with MetS can be accounted for by increased fatty acid flux to the liver associated with insulin resistance [26]. Furthermore accentuated flux with changes in glycemic control account for even higher apoB levels in the subjects with T2D. There is also evidence that increased apoB glycation occurs in individuals with diabetes [27] but the functional significance has been questioned [28]. Diabetes-associated structural and compositional modifications of LDL may reduce receptor-mediated uptake by hepatocytes [29] resulting in increased plasma retention and elevation in apoB levels. The increased apoB has added significance since it represents the total number of atherogenic lipoproteins; one apoB molecule being present on each lipoprotein particle [7] and since 90–95% of apoB-containing particles are LDL, the LDL particle concentration would be a good alternative measure [30, 31] but was not available to us for this study. However, in a nested case control study derived from the Nurses Health Study (NHS) and Health Professionals Follow-up Study (HPFS), LDL particles containing apoB and apoC-III predicted coronary events whereas LDL with apoB without apoC-III had no effect [32]. However, the LDL particles are susceptible to glycation and oxidation in diabetes [33] rendering them harmful to the arterial wall. Although non-HDL-C is considered a measure of cholesterol in apoB-containing particles, since apoB is often precipitated by heparin-manganese to separate it from HDL, differences in non-HDL-C between in the diabetic and non-diabetic groups did not attain significance.

Recent studies have indicated that the apoB:apoA-I ratio, representing the compounding influence of two major lipoproteins, is a predictor of both non-fatal and fatal myocardial infarction [1, 34, 35]. It has been shown to be significantly associated with insulin resistance in non-diabetic subjects, and the association is independent of traditional risk factors including MetS components [36], suggesting that the ratio is clinically valuable as a predictor of risk in insulin resistant individuals. The difference in the ratio in those with the MetS and the addition of TD2, has not to our knowledge been reported.

There was no participant in the MetS+T2D– and only one participant in MetS+T2D+ group who took lipid-lowering a medication based on records of all medications that the participants brought with them at the baseline evaluation. Therefore, the results in Table 1 and 2 are unlikely to be affected by lipid-lowering medications. Furthermore, it was reported that lipid lowering treatments may not change their predictive effects (8).

We conclude that apoA-I and HDL-C are lower, and apoB and the apoB:A-I ratio are higher in those with the metabolic syndrome and diabetes than in those with the metabolic syndrome alone. ApoB is significantly associated with the addition of diabetes to the metabolic syndrome while LDL-C is not. The reciprocal changes in apoB and apoA-I, as reflected by the apoB:A-I ratio may partly account for increased cardiovascular risk associated with T2D and loss of innate protection from cardiovascular disease in American Indians such as the Cherokee. Total plasma and non-HDL apoC-III are not influenced by the additional presence of diabetes. The study provides data to explain how changes in apolipoproteins associated with T2D may contribute to exacerbating cardiovascular risk in cases with the metabolic syndrome.

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Abbreviations

apo	apolipoprotein
MetS	metabolic syndrome
T2D	type 2 diabetes

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Characteristics of subjects who have the metabolic syndrome and type 2 diabetes (MetS+T2D+) and those who have the metabolic syndrome without diabetes (MetS+T2D-).

Table 1

Variable	MetS+T2D-		MetS+T2D+		P*
	Mean	SD	Mean	SD	
Age, year	30.68	6.14	31.80	6.63	0.1941
Male	49.80%		40.00%		0.1537
Waist, cm	110.44	14.56	113.68	15.21	0.1097
Weight	101.84	19.54	102.19	23.64	0.9014
BMI	36.07	6.50	37.26	7.33	0.1935
SBP, mmHg	127.40	13.04	126.32	15.06	0.5628
DBP, mmHg	82.83	10.04	81.74	9.25	0.4276
FPG, mg/dl	89.57	12.49	178.72	65.27	<.0001

BMI, Body mass index; DBP, diastolic blood pressure; FPG, Fasting plasma glucose; SBP, systolic blood pressure;

* P-value from testing means difference between MetS+T2D- and MetS+T2D+ groups.

Table 2

Apolipoprotein and lipoprotein levels between subjects who have the metabolic syndrome and type 2 diabetes (MetS+T2D+) and those who have the metabolic syndrome without diabetes (MetS+T2D-).

Variable	MetS+T2D−		MetS+T2D+		P*
	Mean	SD	Mean	SD	
Apolipoproteins:					
Non-HDL apoC-III, mg/dl	4.83	2.58	5.04	2.98	0.5554**
Total apoC-III, mg/dl	9.76	3.47	9.69	4.11	0.7973**
C-III ratio	1.10	0.65	0.99	0.51	0.1180
Non-HDL ApoC-III:ApoB	0.06	0.03	0.06	0.03	0.7724
ApoB, mg/dl	95.74	20.18	103.64	25.38	0.0106
ApoA-I, mg/dl	109.89	17.07	105.46	15.71	0.0222
ApoB:ApoA-I	0.89	0.21	1.00	0.31	<0001
Lipids and lipoprotein cholesterol:					
Cholesterol, mmol/L	4.57	0.89	4.77	1.14	0.153
mg/dl	176.68	34.41	184.48	43.89	
Triglyceride, mmol/L	1.61	0.83	1.64	0.94	0.7931**
mg/dl	143.02	73.80	145.18	82.90	
LDL-C, mmol/L	2.84	0.80	3.03	0.83	0.1364
mg/dl	109.93	30.89	117.27	32.29	
non-HDL-C, mmol/L	3.67	0.89	3.92	1.14	0.0620
mg/dl	142.03	34.55	151.57	44.22	
Triglyceride:HDL-C, mmol/L	2.21	1.48	2.53	2.22	0.1097
(mg/dl)	5.06	3.39	5.80	5.09	
HDL-C, mmol/L	0.90	0.20	0.85	0.18	0.0364
mg/dl	34.65	7.72	32.91	6.88	
Cholesterol:HDL-C	5.33	0.89	5.86	2.13	0.0117

* P-value from testing means difference between MetS+DM2- and MetS+DM2+ groups after adjusting for age and gender.

** P-value from testing means difference of log transformed values.