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# APOLIPOPROTEIN PROFILES IN SUBJECTS WITH AND WITHOUT PERIPHERAL ARTERY DISEASE

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## Abstract

We compared plasma apolipoprotein profiles in subjects with peripheral artery disease (PAD) treated with statin medications (n = 21), subjects with PAD who are untreated with statins (n = 18), and control subjects (n = 70). Subjects were assessed on plasma apolipoproteins, medical history, physical examination, ankle/brachial index, and exercise performance using a treadmill test. The percentage of subjects with an abnormal value of ApoB (≥ 95 mg/dL) was 53% in the PAD group untreated with statins, 29% in the treated PAD group, and 13% in the controls ($p<0.001$). The PAD group untreated with statins had higher values for ApoB ($p<0.001$), triglycerides ($p<0.01$), LDL-cholesterol/HDL-cholesterol ratio ($p<0.05$), and glucose ($p<0.01$) than the control group. In contrast, when the statin treated PAD group was compared with controls, none of the variables were different except that the treated PAD group had lower LDL-cholesterol ($p<0.01$) and higher glucose ($p<0.01$). Furthermore, the PAD group treated with statins had lower ApoB ($p<0.01$), triglycerides ($p<0.001$), LDL-cholesterol ($p<0.05$), LDL-cholesterol/HDL-cholesterol ratio ($p<0.05$), and non-HDL-cholesterol ($p<0.05$) than the untreated PAD group. In conclusion, subjects with PAD who are untreated with statin medications have higher levels of ApoB than controls, whereas subjects treated with statins have a more favorable risk profile, characterized by lower ApoB, LDL-C, LDL-C/HDL-C ratio, and non-HDL-C concentrations. Statin therapy may be efficacious for improving apolipoprotein profiles in subjects with PAD and intermittent claudication.

### Keywords

Apolipoproteins; Intermittent Claudication; Lipids; Peripheral Artery Disease; Statins

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## INTRODUCTION

Peripheral artery disease (PAD) is prevalent in more than 12% of the US population 65 years of age and older,[1] and is associated with elevated rates of mortality[2–5] and morbidity,[6] as over 60% of subjects have concomitant cardiovascular and/or cerebrovascular disease.[7] Additionally, subjects with PAD have numerous cardiovascular risk factors[1] and are physically limited by ambulatory leg pain.[8, 9] We have previously found that cardiovascular risk factors are associated with ambulation and vascular function in subjects with PAD and intermittent claudication.[10] In particular, dyslipidemia is associated with impaired calf muscle hemoglobin oxygen saturation during ambulation,[11] which suggests that dyslipidemia impairs the microcirculation and may be a physiologic mechanism for worse ambulatory function.

Dyslipidemia is typically evident by an elevation in low-density lipoprotein cholesterol (LDL-C), which is a primary risk factor for cardiovascular disease. Recently, the multinational INTERHEART study showed that Apolipoprotein B (ApoB) was a stronger predictor of myocardial infarction than LDL-C,[12] and it is inversely related to physical activity[13] and modifiable with exercise training.[14] Thus, apolipoprotein measures may be of particular relevance for subjects with PAD and intermittent claudication because dyslipidemia is prevalent in 85–90% of subjects,[15] and physical activity levels are low.[16] Women with both localized aortic stenosis and diffuse segmental stenosis have impaired apolipoprotein profiles compared to controls,[17] and men with aneurysmal and stenotic aorto-iliac disease have similar, abnormal profiles.[18] However, these investigations did not focus on patients with PAD who were limited with intermittent claudication. In fact, little is known about apolipoprotein measures in subjects with intermittent claudication, and whether apolipoproteins are associated with claudication pain during ambulation. Improved claudication measures with statin therapy[19] suggests that lowering lipids has a role in improving symptoms, but it is not clear whether apolipoproteins are improved with statin medications in subjects with intermittent claudication.

The purposes of this study are (1) to compare plasma apolipoprotein profiles in subjects with PAD treated with statin medications, subjects with PAD who are untreated with statins, and control subjects, and (2) to determine whether apolipoprotein measures are associated with clinical characteristics of subjects with PAD. We hypothesize that subjects with PAD have impaired apolipoprotein profiles compared to controls, that those treated with statin medications have more favorable apolipoprotein profiles than untreated subjects, and that PAD and previous cardiovascular events are associated with unfavorable apolipoprotein profiles.

## METHODS

### SUBJECTS

**IRB Approval and Informed Consent—**The procedures used in this study were approved by the Institutional Review Board at the University of Oklahoma Health Sciences Center and by the Research and Development committee at the Oklahoma City VA Medical Center. Written informed consent was obtained from each subject prior to investigation.

**Recruitment—**Subjects participated in this study at the General Clinical Research Center, at the University of Oklahoma Health Sciences Center. Subjects with PAD and intermittent claudication were recruited by referrals from vascular and primary care clinics at the University of Oklahoma Health Sciences Center and the Oklahoma City VA Medical Center for possible enrollment into a randomized controlled exercise rehabilitation study for the treatment of leg pain secondary to PAD.[15] Control subjects were recruited by newspaper

advertisements for the assessment of cardiovascular risk factors in individuals without a history of cardiovascular diseases. A consecutive series of 59 subjects with PAD were evaluated for study eligibility, and a consecutive series of 82 control subjects were evaluated.

### Screening of the Intermittent Claudication Group

Subjects with intermittent claudication secondary to vascular insufficiency were included in this study if they met the following criteria: (a) a history of ambulatory leg pain, (b) ambulation during a graded treadmill test limited by leg pain consistent with intermittent claudication,[8] and (c) an ankle-brachial index (ABI) ≤ 0.90 at rest[1] or an ABI ≤ 0.73 after exercise.[20] Subjects were excluded for the following conditions: (a) absence of PAD (ABI > 0.90 at rest and ABI > 0.73 after exercise), (b) inability to obtain an ABI measure due to non-compressible vessels, (c) asymptomatic PAD determined from the medical history and verified during the graded treadmill test, (d) use of cilostazol and pentoxifylline initiated within three months prior to investigation, (e) exercise tolerance limited by factors other than leg pain, (f) active cancer, (g) end stage renal disease defined as stage 5 chronic kidney disease, and (h) abnormal liver function. A total of 39 subjects with intermittent claudication were deemed eligible for this investigation, whereas 20 subjects were ineligible.

### Screening of the Control Group

Control subjects were included in this study if they met the following criteria: (a) negative test on the San Diego claudication questionnaire,[21] (b) no other ambulatory leg pain, and (c) an ABI ≥ 1.00. Controls were excluded from this study for the following conditions: (a) an ABI < 1.00, (b) inability to obtain an ABI measure due to non-compressible vessels, (c) poorly controlled hypertension (resting systolic blood pressure > 200 mm Hg or resting diastolic blood pressure > 120 mm Hg), (d) history of cardiovascular disease, cerebrovascular disease, myocardial infarction, or peripheral revascularization, (f) active cancer, (g) end stage renal disease defined as stage 5 chronic kidney disease, and (h) abnormal liver function. A total of 70 control subjects were deemed eligible for this investigation, whereas 12 subjects were ineligible.

## PRIMARY OUTCOME MEASURES

**Plasma Apolipoproteins, Lipoprotein Lipids, and Glucose—**Subjects arrived at the General Clinical Research Center in the morning fasted, but were permitted to take their usual morning medication regimen. Blood samples were drawn into chilled EDTA (1 mg/dl of blood) containing tubes after an overnight fast. Blood was analyzed for fasting lipids, ApoB, apolipoprotein C-III (ApoC-III), and glucose levels. Total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) were measured by standardized enzymatic procedure.[22, 23] Very low-density lipoprotein cholesterol (VLDL-C) was calculated as one-fifth of the triglycerides, low-density lipoprotein cholesterol (LDL-C) was estimated by the Friedewald formula, and non-HDL-C was calculated as total cholesterol minus HDL-C. The fasting glucose concentrations were measured as part of the automated chemistry battery (complete metabolic panel).

Blood was frozen for subsequent analysis of apolipoprotein levels. ApoB and C-III were measured by immunoturbidimetric procedure of Riepponen et al. [24] using corresponding monospecific polyclonal antisera. Because heparin manganese has a high affinity for ApoB, ApoC-III in the heparin-manganese precipitate (HP) is ApoC-III bound to ApoB-containing lipoproteins, which is the most atherogenic component of the lipoproteins. ApoC-III in the heparin-manganese supernate (HS) is ApoC-III bound to ApoA-containing lipoproteins. ApoC-III is measured in the total plasma sample and in the precipitate following

reconstitution to the original volume to obtain ApoC-III HP. The value for ApoC-III HS was derived by subtracting ApoC-III HP from total plasma ApoC-III.

### SECONDARY OUTCOME MEASURES

**Medical History and Physical Examination—**After the blood samples were drawn, subjects were seen by a study physician. Demographic information, height, weight, cardiovascular risk factors, co-morbid conditions, claudication history, and a list of current medications were obtained from a medical history and physical examination.

**ABI—**After 10 minutes of supine rest, the ankle and brachial systolic blood pressures were obtained as previously described.[25] Briefly, ankle systolic pressure was measured in the posterior tibial and dorsalis pedis arteries of both legs using a bidirectional Doppler and probe (Model MD6, D.E. Hokanson, Inc., Belleview, WA) and standard size ankle blood pressure cuffs (10 cm width). The higher of the two arterial pressures from the more severely diseased leg was recorded as the resting ankle systolic pressure. Similarly, brachial blood pressure was taken from both arms using appropriate sized blood pressure cuffs, and the arm yielding the higher systolic pressure was recorded as the brachial systolic pressure. The ABI was then calculated as ankle systolic pressure/brachial systolic pressure. The test-retest intraclass reliability coefficient for the measurement of ABI in our laboratory is R = 0.96 for ABI.[8]

**Graded Treadmill Test—**Subjects with PAD performed a progressive, graded treadmill protocol (walking speed of 2 mph beginning at 0% grade, which then increased by 2% every 2 minutes) to determine study eligibility, and then repeated the test within one week for the assessment of outcome measures related to exercise performance.[8] The claudication onset time, defined as the walking time at which the subjects first experienced pain, and the peak walking time, defined as the walking time at which ambulation could not continue due to maximal pain, were both recorded to quantify the severity of claudication.

### STATISTICAL ANALYSES

The means of clinical characteristics for measurement variables were compared among the three groups using one way Analysis of Variance (ANOVA). Proportions for dichotomous variables were compared between the groups using Chi Square tests. Apolipoprotein, lipid, and glucose measures were compared among the groups using Analysis of Covariance (ANCOVA) followed by 3 planned comparisons. Covariates were selected from the set of clinical characteristics. As a guard against over parameterized models, covariates were selected in a sequential manner to select a set of covariates all of which were significant in ANCOVA model at $p< 0.10$. Pearson correlation coefficients were computed as the measure of associations of clinical characteristics and apolipoprotein measures in subjects with peripheral artery disease. Two-tailed statistical significance was defined as $p< 0.05$. All summary statistics and test were computed using the NCSS computer package.

## RESULTS

### CLINICAL CHARACTERISTICS

The clinical characteristics of the PAD groups and the control group are shown in Table 1. The PAD groups had lower ankle/brachial index ($p < 0.001$), higher body weight ($p = 0.031$), higher body mass index ($p = 0.003$), more components of metabolic syndrome ($p < 0.001$), and higher prevalence of diabetes ($p < 0.001$), hypertension ($p < 0.001$), dyslipidemia ($p < 0.001$), obesity ($p = 0.035$), and metabolic syndrome ($p < 0.001$) than the control group. Furthermore, the PAD groups had higher prevalence of previous myocardial infarction ($p < 0.001$), cerebrovascular accident ($p = 0.002$), and peripheral revascularization

($p < 0.001$). The groups were not significantly different on age ($p = 0.759$), sex ($p = 0.521$), race ($p = 0.235$), and prevalence of renal disease ($p = 0.056$).

### APOLIPOPROTEIN, LIPID, AND GLUCOSE MEASURES

The apolipoprotein, lipid, and glucose measures of the PAD groups and the control group are displayed in Table 2. After statistical adjustment for group differences on significant clinical characteristics, the groups were different on ApoB ($p < 0.001$), triglycerides ($p < 0.001$), LDL-C ($p = 0.019$), LDL-C/HDL-C ratio ($p = 0.048$), and glucose ($p = 0.007$). The percentage of subjects with an abnormal value of ApoB (≥ 95 mg/dL) was 53% in the PAD group untreated with statins, 29% in the treated PAD group, and 13% in the controls ($p < 0.001$).

For the pair-wise comparison between the PAD group untreated with statins and the controls, the untreated PAD group had higher values for ApoB ($p < 0.001$), triglycerides ($p < 0.01$), LDL-C/HDL-C ratio ($p < 0.05$), and glucose ($p < 0.01$). When the statin treated PAD group was compared with controls, none of the variables were different except that the treated PAD group had lower LDL-C ($p < 0.01$) and higher glucose ($p < 0.01$). Finally, the comparison between the two PAD groups showed that the group treated with statins had lower ApoB ($p < 0.01$), triglycerides ($p < 0.001$), LDL-C ($p < 0.05$), LDL-C/HDL-C ratio ($p < 0.05$), and non-HDL-C ($p < 0.05$).

### CLINICAL CORRELATES OF APOLIPOPROTEIN MEASURES

The associations among clinical characteristics and apolipoprotein measures in subjects with PAD are shown in Table 3. A history of peripheral revascularization was associated with higher ApoC-III ($p < 0.05$) and ApoC-III HP ($p < 0.01$), and a history of myocardial infarction was associated with higher ApoC-III ($p < 0.05$). Caucasian race was associated with higher ApoC-III ($p < 0.05$) and ApoC-III HP ($p < 0.05$), and prevalence of renal disease was associated with lower ApoB ($p < 0.05$).

## DISCUSSION

### SUBJECTS WITH PAD UNTREATED WITH STATINS COMPARED TO CONTROLS

The PAD group untreated with statins had 23% higher ApoB levels than the control group, indicating a greater atherogenic burden in the former group. ApoB directly measures the number of atherogenic particles because there is only one ApoB molecule on the surface of all LDL-C, intermediate-density lipoprotein cholesterol (IDL-C), and very low-density lipoprotein cholesterol (VLDL-C).[26] It is interesting to note that these groups were not different on LDL-C and non-HDL-cholesterol. These data suggest that the PAD group may have had higher levels of IDL-C and VLDL-C, thereby contributing to the greater number of atherogenic particles of the PAD group as reflected by their higher ApoB concentration. Thus, ApoB may be a more sensitive measure of greater atherogenic burden in subjects with PAD than the more traditional cardiovascular risk factors, such as LDL-C and the calculated measure of non-HDL-C.

Another interesting difference between these groups is that subjects with PAD untreated with statins had a 128% higher level of triglycerides, and a 22% higher concentration of glucose. The higher triglyceride level in the PAD group supports a previous observation of a 118% higher triglyceride concentration in subjects with diffuse, stenotic PAD compared to controls.[17] The impairment in triglycerides and glucose are factors that cluster together, and are components of metabolic syndrome.[27] Thus, it is not surprising that metabolic syndrome is highly prevalent in those with PAD in the current study, which is particularly detrimental to their symptomatology. We have previously found that metabolic syndrome is associated

with worse intermittent claudication, physical function, health-related quality of life, and peripheral circulation in subjects with PAD,[28] and that these factors are progressively impaired as the number of metabolic syndrome components increase. We have also found that dyslipidemia is associated with impaired calf muscle hemoglobin oxygen saturation during ambulation,[11] which suggests that dyslipidemia impairs the microcirculation and may be a physiologic mechanism for worse ambulatory function. Thus, higher levels of ApoB in the untreated PAD group in the current study may not only heighten their cardiovascular risk compared to the controls, but it may also increase the risk for worsened microcirculation in the calf muscle during ambulation.

## STATIN THERAPY IN SUBJECTS WITH PAD

Subjects with PAD who were taking statin medications had lower values of ApoB, triglycerides, LDL-C, LDL-C/HDL-C ratio, and non-HDL-C than subjects who were not taking statin medications, and they had lower LDL-C than controls. These findings agree with the observation that subjects with PAD who take statin medications have lower LDL-C,[29] than those not on statins, and that LDL-C is reduced with statin therapy.[30] To our knowledge, this is the first study to examine the relationship between statin therapy and apolipoprotein profiles in subjects with PAD and intermittent claudication. Our findings suggest that statin medications reduce the number of atherogenic particles in subjects with PAD, which may improve survival,[29] event-free survival,[29] and microculation during exercise.[11] Our study also highlights that those with PAD receive suboptimal management for dyslipidemia, as half of the subjects who were not treated with statin medications actually had dyslipidemia and may have benefitted from statin therapy. This agrees with our previous observation of suboptimal control of components of metabolic syndrome in subjects with PAD.[31]

## CLINICAL CORRELATES OF APOLIPOPROTEIN MEASURES

Although ApoC-III and ApoC-III HP were not different between subjects with PAD and controls, these measures were correlated with several characteristics of subjects with PAD. ApoC-III was associated with prior history of peripheral revascularization and myocardial infarction, suggesting that impairments in ApoC-III may not become evident in subjects with PAD until the atherosclerotic burden is severe enough to lead to peripheral and cardiac events. Additionally, caucasians had higher levels of ApoC-III and ApoC-III HP than non-caucasians. Thus, within subjects who have PAD, the most susceptible subgroups for worse apolipoprotein profiles are caucasians, and those with a history of peripheral revascularization and myocardial infarction. As such, they may have the greatest benefit with therapeutic treatment.

## LIMITATIONS

There are limitations to this study. Subjects with PAD and controls who participated in this trial were volunteers and therefore may represent those who were more interested in their health, who had better access to transportation to our research center, and who had relatively better health than subjects with PAD and controls who did not volunteer. The cross-sectional design comparing those with and without PAD does not allow causality be established, as it is possible that unfavorable apolipoprotein and lipid profiles may either precede or be a consequence of the development of PAD and intermittent claudication. The present findings are also limited to PAD subjects with a history of intermittent claudication. Thus, the current findings cannot be generalized to subjects with less severe PAD (i.e., asymptomatic PAD), or more severe symptoms (i.e., critical leg ischemia), or to those who are limited in their exercise performance by other significant co-morbid conditions.

### CONCLUSIONS

Subjects with PAD and intermittent claudication who are untreated with statin medications have higher levels of ApoB than controls, and they have higher concentrations of plasma triglyerides and glucose, both of which are components of metabolic syndrome. Furthermore, subjects who were on statin medications had a more favorable risk profile, characterized by lower ApoB, LDL-C, LDL-C/HDL-C ratio, and non-HDL-C concentrations. Finally, history of peripheral revascularization, history of myocardial infarction, and caucasian race were associated with higher levels of ApoC-III, and a history of peripheral revascularization and Caucasian race were associated with elevated ApoC-III HP. The clinical significance is that statin therapy may be efficacious for improving apolipoprotein profiles in subjects with PAD and intermittent claudication, particularly in Caucasians and in those with a history of additional cardiovascular events such as peripheral revascularization and myocardial infarction.

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## Table 1

Clinical characteristics of subjects with peripheral artery disease and controls. Values are means (standard deviation) or percentage of subjects in each category.

| Variables | Control Group (n = 70) | PAD Group Not Taking Statins (n = 18) | PAD Group Taking Statins (n = 21) | P Value |
|---|---|---|---|---|
| Age (years) | 69 (12) | 67 (13) | 69 (8) | 0.759 |
| Weight (kg) | 73.3 (13.6) | 83.0 (19.4) | 76.9 (8.2) | 0.031 |
| Body Mass Index (kg/m$^2$) | 24.5 (3.5) | 27.4 (5.6) | 27.5 (4.8) | 0.003 |
| Ankle/Brachial Index | 1.15 (0.07) | 0.72 (0.19) | 0.70 (0.25) | < 0.001 |
| Claudication Onset Time (sec) | ----- | 231 (161) | 230 (187) | 0.995 |
| Peak Walking Time (sec) | ----- | 382 (207) | 499 (277) | 0.148 |
| Sex (% Men) | 50 | 33 | 52 | 0.521 |
| Race (% Caucasian) | 77 | 56 | 76 | 0.235 |
| Diabetes (% yes) | 0 | 22 | 24 | < 0.001 |
| Hypertension (% yes) | 19 | 83 | 81 | < 0.001 |
| Dyslipidemia (% yes) | 30 | 50 | 100 | < 0.001 |
| Obesity (% yes) | 9 | 28 | 19 | 0.035 |
| Metabolic Syndrome (% yes) | 4 | 56 | 81 | < 0.001 |
| Metabolic Syndrome Components (n) | 0.6 (0.9) | 2.7 (1.3) | 3.3 (1.1) | < 0.001 |
| Peripheral Revascularization (% yes) | 0 | 22 | 14 | < 0.001 |
| Myocardial Infarction (% yes) | 0 | 17 | 19 | < 0.001 |
| Cerebrovascular Disease (% yes) | 0 | 17 | 10 | 0.002 |
| Renal Disease (% yes) | 0 | 0 | 10 | 0.056 |

**Table 2**

Apolipoprotein, lipid, and glucose measures of subjects with peripheral artery disease and controls. Values are means (standard deviation). Group comparisons were statistically adjusted for significant clinical characteristics using analysis of covariance (ANCOVA).

| Variables | Group 1: Control Group (n = 70) | Group 2: PAD Group Not Taking Statins (n = 18) | Group 3: PAD Group Taking Statins (n = 21) | ANCOVA P Value | Groups 1 vs. 2 Adjusted Mean Difference | Groups 1 vs. 3 Adjusted Mean Difference | Groups 2 vs. 3 Adjusted Mean Difference |
|---|---|---|---|---|---|---|---|
| ApoB (mg/dL) | 80.6 (12.7) | 99.2 (16.1) | 83.0 (21.6) | <0.001 *2,7,8,9* | −15.4 *** | 0.3 | 15.7 ** |
| ApoC-III (mg/dL) | 9.7 (2.3) | 10.4 (2.6) | 10.1 (2.5) | 0.823 *1,7* | −0.3 | 0.1 | 0.4 |
| ApoC-III HP (mg/dL) | 2.4 (0.5) | 2.7 (0.9) | 2.5 (0.9) | 0.116 *4,6,7,8* | −0.1 | 0.4 | 0.4 |
| ApoC-III HS (mg/dL) | 7.3 (2.0) | 7.6 (1.8) | 7.6 (2.0) | 0.970 *1,7* | −0.1 | 0.1 | 0.1 |
| ApoC-III Ratio | 3.1 (0.8) | 2.9 (0.5) | 3.3 (1.1) | 0.443 | 0.2 | −0.2 | −0.4 |
| Triglycerides (mg/dL) | 79.4 (39.6) | 180.9 (138.3) | 130.7 (64.0) | 0.003 *6,7,8,10* | −47.4 ** | 18.2 | 65.6 *** |
| Total Cholesterol (mg/dL) | 186.5 (36.7) | 191.3 (28.7) | 170.1 (31.0) | 0.115 | −4.8 | 16.4 | 21.2 |
| HDL-C (mg/dL) | 54.7 (16.0) | 43.6 (15.2) | 49.2 (13.3) | 0.451 *1,2,5,7* | 5.0 | 0.9 | −4.1 |
| LDL-C (mg/dL) | 116.0 (31.1) | 119.2 (34.1) | 94.7 (27.3) | 0.019 | −3.2 | 21.3 ** | 24.5 * |
| LDL-C/HDL-C | 2.27 (0.95) | 2.90 (1.25) | 2.11 (1.08) | 0.048 *2,3,5* | −0.61 * | 0.17 | 0.78 * |
| Non-HDL-C (mg/dL) | 131.8 (33.2) | 147.7 (30.0) | 120.9 (33.1) | 0.067 *2,8,9* | −14.7 | 10.4 | 25.2 * |
| Glucose (mg/dL) | 80.2 (10.0) | 98.2 (23.0) | 96.8 (24.3) | 0.007 *4,10* | −10.3 ** | −10.7 ** | −0.4 |

Significant covariates used in ANCOVA model:

*1* Age,

*2* BMI,

*3* CVA,

*4* Diabetes,

*5* Gender,

*6* Metabolic Syndrome,

*7* Myocardial Infarction,

*8* Obesity,

*9* Renal Disease,

$^{10}$Weight.

## Table 3

Associations among clinical characteristics and apolipoprotein measures in patients with peripheral artery disease (n = 39). Values are Pearson correlation coefficients.

| Variables | ApoB | ApoC-III | ApoC-III HP |
|---|---|---|---|
| Age | −0.11 | 0.24 | 0.11 |
| Weight | 0.16 | 0.30 | 0.15 |
| Body Mass Index | −0.02 | 0.20 | −0.02 |
| Ankle/Brachial Index | 0.17 | −0.02 | −0.10 |
| Claudication Onset Time | −0.21 | −0.20 | −0.27 |
| Peak Walking Time | −0.25 | −0.18 | −0.27 |
| Sex (reference = men) | −0.13 | −0.19 | −0.27 |
| Race (reference = non-Caucasian) | 0.12 | 0.35 * | 0.34 * |
| Diabetes † | −0.10 | −0.05 | −0.18 |
| Hypertension † | −0.00 | 0.07 | −0.05 |
| Dyslipidemia † | −0.01 | 0.16 | 0.05 |
| Obesity † | −0.04 | −0.00 | −0.19 |
| Metabolic Syndrome † | 0.10 | 0.24 | 0.24 |
| Metabolic Syndrome Components | 0.08 | 0.31 | 0.11 |
| Peripheral Revascularization † | 0.28 | 0.36 * | 0.44 ** |
| Myocarial Infarction † | 0.20 | 0.37 * | 0.24 |
| Cerebrovascular Disease † | 0.00 | 0.19 | 0.06 |
| Renal Disease † | −0.33 * | −0.07 | −0.18 |

* $p < 0.05$,

** $p < 0.01$.

† reference is absence of condition.