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Reduced High-Density Lipoprotein Level is Linked to Worse Ankle Brachial Index and Peak Oxygen Uptake in Postmenopausal Women with Peripheral Arterial Disease

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Abstract

Background—Lipid abnormalities are associated with lower extremity peripheral arterial disease (PAD), and contribute to vascular damage and functional impairment. Women with PAD have more limited walking and physical function than men, but the mechanisms for their lower exercise performance are not clear. We determined if alterations in individual lipid components, such as decreased high-density lipoprotein cholesterol (HDL-C), are associated with worsening lower extremity claudication in postmenopausal women with PAD.

Methods—This cross-sectional cohort study included 69 postmenopausal women with intermittent claudication (Fontaine stage II PAD). Lower extremity walking performance was assessed using a validated treadmill test to measure initial claudication distance (ICD), absolute claudication distance (ACD), peak oxygen uptake, and ankle systolic blood pressure. The lipid profile was determined from a standard lipid panel drawn in a fasted state to obtain cholesterol, triglyceride, HDL-C, and low-density lipoprotein cholesterol (LDL-C).

Results—HDL-C was positively correlated with ankle brachial index ($r = 0.29$, $p = 0.019$). No other individual components of the lipid profile were associated with exercise performance and hemodynamic measures. Among women with impaired HDL-C (below 50 mg/dL, $n=43$), the median peak oxygen uptake level was significantly lower ($p=0.021$) relative to women with normal HDL-C (above 50 mg/dL, $n=26$).

Conclusion—Lower HDL-C levels are associated with worse ankle brachial index and decreased peak oxygen uptake in post-menopausal women with PAD.

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INTRODUCTION

Subjects with lower extremity peripheral arterial disease (PAD) have impaired blood lipid levels [1,2], lower physical function, and faster functional decline than subjects without PAD [3,4]. The lipid abnormalities associated with lower extremity PAD include elevated total cholesterol and low-density lipoprotein cholesterol (LDL-C), decreased high-density lipoprotein cholesterol (HDL-C), and hypertriglyceridemia [5]. Lipids play a key role in the initiation and progression of atherosclerosis in large vessels [6], which is the major cause of lower extremity PAD [5]. Hypercholesterolemia may also contribute to increased damage at the micro vessel level, as reflected by shorter walking distances and calf muscle hemoglobin oxygen saturation (StO₂) during exercise in patients limited by intermittent claudication [7].

Women with PAD are more likely to present with cardiovascular risk factors, such as hypercholesterolemia [8], and to have greater walking impairment than men with PAD [9,10]. The mechanisms for their lower exercise performance are not clear, but could be linked to an altered lipid profile. In addition, data pertaining to traditional risk factors and their relation to objective measures of exercise performance is limited in patients with PAD, particularly in women. Therefore, we determined if alterations in individual lipid components, such as decreased high-density lipoprotein cholesterol (HDL-C), are associated with worsening lower extremity claudication in postmenopausal women with PAD.

METHODS

Study Population

This cross-sectional cohort study included 69 postmenopausal women with PAD and stable symptoms of intermittent claudication evaluated at the General Clinical Research Center in the University of Oklahoma Health Sciences Center. The subjects were recruited from the vascular laboratory and clinics on campus, as well as from advertisements in local newspapers. All patients were classified as having Fontaine stage II PAD [5] defined by the following inclusion criteria: (a) a history of intermittent claudication, (b) ambulation during a graded treadmill test limited by intermittent claudication [11] and (c) an ankle/brachial index (ABI) at rest <0.90 [12]. Subjects were required to have cholesterol measures available that could be used to classify them according to dyslipidemia status.

Patients were excluded for the following conditions: (a) absence of PAD, (b) inability to obtain an ABI measure due to non-compressible vessels, (c) asymptomatic PAD (Fontaine stage I), (d) rest pain PAD (Fontaine stage III), (e) exercise tolerance limited by factors other than claudication (e.g. severe coronary artery disease, dyspnea, poorly controlled blood pressure), and (f) active cancer, renal disease, or liver disease. All patients lived independently at home. Patients were evaluated for dyslipidemia and were characterized as having dyslipidemia or not according to the published Evidence-Based Guidelines for Cardiovascular Disease Prevention in Women [13] and Consensus Conference Report from the American Diabetes Association and the American College of Cardiology [14]. Dyslipidemia was defined as having one or more of the following criteria: 1) LDL-C level greater than 100 mg/dL or greater than 70 mg/dL if considered very high risk, 2) HDL-C level below 50 mg/dL, 3) non-HDL-C (total cholesterol minus HDL-C) greater than 130 mg/dL or greater than 100 mg/dL if considered very high risk, and/or 4) triglyceride level greater than 150 mg/dL. Criteria for very high cardiovascular risk included established cardiovascular disease plus diabetes mellitus and/or smoking [13].

The Institutional Review Board at the University of Oklahoma Health Sciences Center approved the procedures used in this study. Written informed consent was obtained from each subject before investigation.

Medical History

Demographic information, height, weight, cardiovascular risk factors, co-morbid conditions, claudication history, blood samples, and a list of current medications were obtained from a medical history and physical examination at the beginning of the study.

Walking Impairment Questionnaire (WIQ)

Self-reported ambulatory ability was assessed using a validated questionnaire that evaluates the ability to walk at various speeds and distances and to climb stairs in patients with PAD [15].

Ankle-brachial index (ABI) Measurement

Prior to the treadmill test, ABI was determined by obtaining the ankle and brachial systolic blood pressures following 10 min of supine rest as previously described [16]. The test-retest intraclass reliability coefficient is $R = 0.96$ for ABI [11]. Ankle systolic blood pressure was then obtained from the more severely diseased lower extremity by the Doppler ultrasound technique 1, 3, 5, 7, 9, 11, 13, and 15 min after the progressive graded treadmill test [17]. The reduction in ankle systolic blood pressure following the treadmill test from the resting value was quantified by calculating the area under the curve (AUC) referred to as the ischemic window [18].

Treadmill Test

Patients performed a progressive graded treadmill protocol (2 mph, 0% grade with 2% increase every 2 min) until maximal claudication pain occurred [11]. The initial claudication distance (ICD), the distance at which the patient first experienced pain, and the absolute claudication distance (ACD), the distance at which ambulation could not continue due to maximal pain, were both obtained and used to classify the severity of claudication. Exercise capacity was quantified by measuring oxygen uptake at peak exercise with a Medical Graphics VO2000 metabolic system (Medical Graphics Inc, St Paul, Minn). Using these procedures, the test-retest intraclass reliability coefficient is $R = 0.89$ for ICD [11], $R = 0.93$ for ACD [11], and $R = 0.88$ for peak oxygen uptake [19].

Hemoglobin Oxygen Saturation (StO₂) of the Calf Musculature

Muscle oxygen saturation measurement provides clinically objective information regarding the severity of intermittent claudication [20]. Calf muscle StO₂ was measured before and during exercise using a continuous-wave, NIRS spectrometer (InSpectra model 325; Hutchinson Technology Inc, Hutchinson, Minn), as described before [7]. The noninvasive NIRS technique is a measure of the balance between local oxygen delivery and oxygen demand that quantifies the percentage of StO₂ in the microvasculature of the tissue below the NIRS probe, which is useful in assessing patients with PAD [21,22]. In patients limited by intermittent claudication, shorter ICD and ACD values are associated with reaching a minimum value in calf muscle StO₂ sooner during treadmill exercise, and with having a delayed recovery in calf muscle StO₂ after exercise [23]. Calf muscle StO₂ at baseline was recorded after patients stood on the treadmill for two minutes to allow for equilibration. Following initiation of treadmill exercise, the StO₂ measure at the end of each minute was recorded, as well as the StO₂ value at the occurrence of ICD and ACD.

Calf Blood Flow

Calf blood flow was obtained under resting and maximal hyperemic conditions in the more severely diseased leg using venous occlusion mercury strain gauge plethysmography as previously described. Briefly, resting calf blood flow was obtained after 10 min of supine rest, whereas maximal calf blood flow was obtained after patients stood and performed heel

rises for as long as they could tolerate while a blood pressure cuff placed above the knee was inflated to 300 mm Hg. The test-retest intraclass reliability coefficient is $R = 0.86$ for calf blood flow [24].

Statistical Analyses

Between-group comparisons were made using a Wilcoxon rank sum test when comparing median values and a Chi-square or Fisher's exact test, in the presence of low expected cell counts, when comparing proportions. The association between 2 continuous measures was quantified using a partial Spearman's rank correlation coefficient with adjustment for age and body mass index. Linear regression modeling was used to adjust between-group comparisons for the potential confounding effects of age and BMI. Linear regression modeling assumptions were assessed using plots of residual values. A two-sided alpha level of 0.05 was used to define statistical significance. Analyses were performed using SAS version 9.1.3 Service Pack 4 for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

Among the 69 women included in this analysis, 15 (22%) were classified as very high cardiovascular risk, and 45 (67%) were receiving lipid-lowering treatment. Dyslipidemia was highly prevalent (88%) in the total cohort, regardless of whether the women were on lipid-lowering therapy (87%) or not (91%). Twenty-one out of 61 women with dyslipidemia (34%) were not on lipid lowering treatment. Table 1 summarizes the distribution of lipid profile values among the subjects.

Table 2 summarizes the association between individual components of the lipid profile and exercise performance and peripheral hemodynamic measures after adjustment for age and BMI. HDL-C is positively correlated with ABI ($p=0.019$), and there is a trend for a positive correlation with ACD and ICD ($p=0.11$ for each), although not statistically significant. None of the other lipid measures were significantly associated with exercise performance and peripheral hemodynamic measures.

To further explore the association between HDL-C and exercise performance, the subjects were divided according to HDL-C status ($\text{HDL-C} < 50 \text{ mg/dL}$ versus $\text{HDL-C} \geq 50 \text{ mg/dL}$). All subjects with $\text{HDL-C} < 50 \text{ mg/dL}$ ($n=43$) were classified as having dyslipidemia compared to 18 (69%) of the 26 subjects with $\text{HDL-C} \geq 50 \text{ mg/dL}$ (Table 3). Women with $\text{HDL-C} < 50 \text{ mg/dL}$ had a higher prevalence of coronary artery disease compared to women with $\text{HDL-C} \geq 50 \text{ mg/dL}$ (42% versus 15%, $p=0.022$), and had a trend for a higher prevalence of diabetes ($p=0.11$), although not statistically significant. The median peak oxygen uptake level was significantly lower among women with $\text{HDL-C} < 50 \text{ mg/dL}$ ($p=0.021$) and there was a trend for the median ACD to be lower as well ($p=0.11$), although not statistically significant (Table 4). Based on regression modeling, the difference in peak oxygen uptake levels between women with $\text{HDL-C} < 50 \text{ mg/dL}$ and women with $\text{HDL-C} \geq 50 \text{ mg/dL}$ remained significant after adjusting for age and BMI (mean peak oxygen uptake levels $2.03 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ lower for women with $\text{HDL-C} < 50 \text{ mg/dL}$, 95% CI: 0.14 to $3.92 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ lower, $p=0.036$).

DISCUSSION

The major findings of this investigation were that higher HDL-C levels were positively associated with ABI and, conversely, women with PAD and low HDL-C had poorer exercise capacity as reflected by lower peak oxygen uptake and a trend towards shorter ACD than women with normal HDL-C.

Our findings are supported by previous studies which found that HDL-C has been significantly associated with incident symptomatic PAD in women followed for over 12 years [1], and HDL-C levels have been correlated with lower extremity function measured by knee extension torque and walking speed [25]. Higher HDL-C has been associated with better functional performance among elderly subjects [26] and low HDL-C has been linked with disease severity in early-onset PAD in young subjects [27]. Collectively, these data suggest that there may be a direct relation between an altered lipid profile and walking capacity.

Physiologic mechanisms for the association between unfavorable HDL-C and impaired exercise performance include a potentially greater atherosclerotic compromise in the micro vasculature. HDL-C exerts its atheroprotective function by favoring the reverse cholesterol transport, a process by which cholesterol is extracted from the vessel wall and delivered back to the liver for elimination [28]. In addition, HDL-C appears to reduce acute vascular inflammation, exert direct nitric oxide-mediated vasodilatory effects, and improve endothelial function [29]. Low HDL-C has been associated with higher blood viscosity [30], which may be linked to significant deterioration of blood flow properties and higher HDL levels may ameliorate impaired micro vascular blood flow. Another possibility is that HDL-C has also been shown to favor angiogenesis in human cell models [31] and murine ischemic hind limb models [32]. In speculation, higher HDL levels may be linked to collateral vessel formation that favors blood flow to the affected limb. All of these possible physiologic mechanisms may explain the better exercise performance, as measured by peak oxygen uptake, in patients with higher levels of HDL-C. However, further studies are required to evaluate these possibilities.

Other important findings of our study included the high prevalence of untreated dyslipidemia in our cohort of women with PAD. Although nearly 90% of the women in this investigation were dyslipidemic, only 67% were medically managed for this condition and 34% were not receiving any treatment at all. Furthermore, of the patients on lipid lowering treatment, many may have been receiving suboptimal management. These findings compare favorably with previous reports that show diagnosis and treatment of dyslipidemia is often suboptimal in patients with PAD [33,34]. Dyslipidemia is often treated with lipid lowering agents, such as statins and in patients with intermittent claudication its use has been associated with superior leg functioning [35] and improved pain-free walking distance and activity [36]. The clinical significance is that reduced HDL-C has been associated with poor cardiovascular outcomes and effective treatment of dyslipidemia should be offered to all PAD patients to decrease subsequent risk of myocardial infarction, stroke and vascular death [37,38]. Early recognition, risk factor modification and lipid-modifying therapy could substantially reduce morbidity and mortality in this patient population, but the relative benefit remains unclear and further studies are needed.

Limitations of this study include small sample sizes and therefore, statistical power is limited. The cross-sectional design of the study does not allow us to clarify any cause-effect mechanism. Further studies are required to confirm the association of HDL-C levels and objective markers of walking performance, and to evaluate if management of the dyslipidemic profile improves walking ability and therefore clinical cardiovascular endpoints.

CONCLUSION

Lower HDL-C levels are associated with lower ABI and decreased peak oxygen uptake in post-menopausal women with PAD. The clinical implication is that women with intermittent claudication and low HDL-C levels represent a subgroup of PAD patients whose

dyslipidemia should be managed aggressively and who should receive high priority for exercise rehabilitation to improve physical function.

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Table 1

Prevalence of favorable and altered lipid profile in our cohort.

	Total group (n=69)	Without lipid lowering treatment (n=23)	With lipid lowering treatment (n=46)
Favorable lipid profile	8 (12%)	2 (9%)	6 (13%)
Dyslipidemia	61 (88%)	21 (91%)	40 (87%)
LDL-C greater than 100 mg/dL or greater than 70 mg/dL (in very high risk women ^{**})	39 (58%)	16 (73%)	23 (51%)
HDL-C below 50 mg/dL	43 (62%)	14 (61%)	29 (63%)
Non-HDL-C greater than 130 mg/dL or greater than 100 mg/dL (in very high risk women ^{**})	39 (57%)	17 (74%)	22 (48%)
Triglycerides greater than 150 mg/dL	21 (30%)	4 (17%)	17 (37%)

* A favorable lipid profile is defined as having: 1) LDL-C below 100 mg/dL or 70 mg/dL if very high risk, 2) HDL-C greater than 50 mg/dL, 3) non-HDL-C below 130 mg/dL or 100 mg/dL if very high risk, and 4) triglyceride level below 150 mg/dL [13,14].

** Criteria for very high risk include established cardiovascular disease (any indication of CAD, MI, Angina, PTCA, Coronary stent, CABG, CBVD, Stroke, TIA, Carotid stent, CEA, or Carotid surgery) plus diabetes and/or current smoking

Table 2

Association between individual components of the lipid profile and their associations with exercise performance and peripheral hemodynamic measures in female patients with PAD and intermittent claudication. Data are summarized using a partial Spearman's rank correlation coefficient with adjustment for age and body mass index (p-value).

	ABI	ICD	ACD	Ischemic window	StO2 at 1 min of exercise	Peak oxygen uptake
LDL-C	-0.14 (0.26)	0.12 (0.33)	0.10 (0.45)	-0.18 (0.14)	-0.003 (0.98)	0.008 (0.95)
HDL-C	0.29 (0.019)	0.20 (0.11)	0.20 (0.11)	-0.06 (0.62)	0.01 (0.93)	0.17 (0.18)
Non-HDL-C	-0.19 (0.12)	0.13 (0.31)	0.07 (0.57)	-0.12 (0.33)	-0.11 (0.48)	0.09 (0.46)
Triglycerides	-0.03 (0.83)	-0.04 (0.75)	-0.06 (0.64)	0.10 (0.42)	-0.20 (0.16)	0.19 (0.14)

ABI, ankle-brachial index; ICD, initial claudication distance; ACD, absolute claudication distance; StO2, hemoglobin oxygen saturation of the calf musculature

Table 3

Clinical characteristics of female PAD patients according to HDL-C status (HDL-C < 50 mg/dL versus HDL-C ≥ 50 mg/dL). Data are summarized as the median (25th–75th percentile) or count (%).

	HDL-C < 50 mg/dL (n=43)				HDL-C ≥ 50 mg/dL (n=26)				p-value
	n	Median	P25	P75	n	Median	P25	P75	
Age, years	43	63.0	58.0	71.0	26	67.5	58.0	73.0	0.25
Weight, kg	43	82.1	66.3	89.2	26	75.3	61.1	92.7	0.45
BMI, kg/m ²	43	31.0	26.5	34.7	26	27.3	23.2	34.3	0.19
ABI at rest	43	0.7	0.5	0.9	26	0.8	0.6	0.9	0.19
Duration of IC, years	40	3.5	1.0	7.5	24	5.0	3.5	10.0	0.081
WtQ distance score, %	42	13.7	3.1	38.1	25	25.1	3.6	39.6	0.58
WtQ speed score, %	42	15.2	7.6	35.8	25	25.0	10.9	39.1	0.36
WtQ stair climbing score, %	42	12.5	4.1	33.0	25	12.5	0.0	50.0	0.65
WtQ total score	42	50.0	25.0	75.0	26	37.5	25.0	75.0	0.89
	n	Count (%)			n	Count (%)			p-value
Race, % Caucasian	43	19 (44%)			26	13 (50%)			0.64
Coronary Artery Disease, %	43	18 (42%)			26	4 (15%)			0.022
Diabetes, %	43	18 (42%)			26	6 (23%)			0.11
Hypertension, %	42	31 (74%)			26	20 (77%)			0.77
Current Smoking, %	43	18 (42%)			25	9 (36%)			0.63
Obesity, %	43	23 (53%)			26	10 (38%)			0.23
Dyslipidemia, %	43	43 (100%)			26	18 (69%)			-----
On hormone replacement therapy, %	43	6 (14%)			26	6 (23%)			0.35

BMI, body mass index; ABI, ankle-brachial index; IC, intermittent claudication; WtQ, walking impairment questionnaire. Obesity was defined as having a BMI greater than 30 kg/m²

Treadmill and peripheral hemodynamic measurements of female PAD patients according to HDL-C status. Data are summarized as the median (25th–75th percentile) or count (%).

Table 4

	HDL-C < 50 mg/dL (n=43)				HDL-C ≥ 50 mg/dL (n=26)				p- value
	n	Median	P25	P75	n	Median	P25	P75	
ICD, m	43	108.4	61.8	177.4	25	125.4	71.7	250.9	0.23
ACD, m	43	229.4	109.8	330.6	26	318.5	125.4	688.1	0.11
Peak oxygen uptake, mL · kg ⁻¹ ·min ⁻¹	43	10.3	7.2	12.7	26	11.7	10.0	13.7	0.021
StO2 while standing, %	34	47.5	34.0	66.0	18	49.0	34.0	56.0	0.69
StO2 at 1 min of exercise, %	34	18.0	1.0	41.0	17	19.0	2.0	30.0	0.66
StO2 at 2 minutes of exercise, %	31	23.0	2.0	39.0	17	17.0	1.0	31.0	0.37
StO2 at ICD, %	34	22.5	1.0	41.0	17	18.0	1.0	34.0	0.59
StO2 at ACD, %	34	19.5	1.0	41.0	17	20.0	4.0	31.0	0.73
Ischemic window, mmHg x min	43	120.8	59.5	194.3	26	110.7	45.5	210.0	0.61
Calf blood flow: rest, %/min	41	2.6	2.0	3.3	23	3.1	2.4	3.9	0.27
Calf blood flow: maximal, %/min	41	8.8	6.5	11.8	22	9.5	8.2	13.1	0.21

ICD, initial claudication distance; ACD, absolute claudication distance; StO2, hemoglobin oxygen saturation of the calf musculature