Original Article

Lower levels of serum high-density lipoprotein cholesterol are associated with a worse Duke treadmill score in men but not in women

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ABSTRACT

Background: High-density lipoprotein cholesterol (HDL-C) levels are inversely related to the atherosclerotic burden and are higher in women than in men. We aimed to investigate the sex-specific relationship between serum HDL-C levels and the Duke treadmill score (DTS) in this study. **Materials and Methods:** A total of 111 patients (59 men, 42 women) with suspected coronary artery disease (CAD) who underwent exercise treadmill test (EST) were included. Fasting blood samples were obtained for the assessment of serum lipid levels. DTS was calculated for each patient based on EST findings including ST segment deviation and symptoms. **Results:** Patients were categorized into a moderate to high risk group based on the DTS score (group-I: 38 patients) and a low risk group (group-II: 63 patients). There was a significant positive correlation between serum HDL-C levels and DTS ($r = 0.230$; $P = 0.021$). The mean HDL-C level was significantly higher in group-II relative to group-I (49.25 ± 11.21 vs. 44.43 ± 11.18, respectively, $P = 0.04$). An HDL-C level less than the cut-off value of 41.39 mg/dL predicted a moderate to severe risk DTS with 65% sensitivity and 69% specificity in men (area under curve = 0.732, $P = 0.004$), but not in women (area under curve = 0.505, $P = 0.958$). After adjustment for traditional CAD risk factors (age, sex, and smoking status), the relationship of DTS to HDL-C remained significant. ($P = 0.030$; adjusted OR = 0.948 [95% CI, 0.904-0.995]). **Conclusion:** Low HDL-C levels may be associated with a moderate to high risk Duke treadmill score in men, but not in women. Further research is required to clarify the sex-specific relationship between HDL-C and DTS.

KEY WORDS: Duke treadmill score, high-density lipoprotein cholesterol, sex-specific relationship

Introduction

Coronary artery disease (CAD) due to atherosclerosis is the leading cause of morbidity and mortality in the industrialized world. Atherosclerosis is a chronic inflammatory disorder that develops in response to injury to the vessel wall. It is characterized by infiltration of mononuclear lymphocytes into the intima, migration of vascular smooth muscle cells, and accumulation of extracellular matrix.[1] Low serum levels of high-density lipoprotein cholesterol (HDL-C) are known to accelerate the development of atherosclerosis because of impaired reverse cholesterol transport (RCT), and possibly because of the absence of other protective effects of HDL-C, such as decreased oxidation of other lipoproteins.[2]

The exercise treadmill test (EST) is widely utilized in the evaluation of symptomatic patients to predict the presence and extent of CAD and the short- and long-term prognosis. Although a large number of noninvasive stress testing modalities are currently available, the EST is still used as a benchmark for other risk markers. It is also the least costly of all provocative noninvasive tests.[3] The Duke treadmill score (DTS) is a composite index designed to provide survival estimates based on results from an exercise test, including ST-segment depression, chest pain, and exercise duration. This score is derived from a simple formula easy to apply in clinical decision making. The score uses three prognostic variables from the treadmill test: The amount of net exercise-induced ST-segment deviation in any lead except aVR, the presence and severity of exercise-induced angina, and the duration of exercise on the standard Bruce protocol.[3,4] Both HDL-C levels and the prognostic value of EST display prominent sex-related variations: On average, women have higher HDL-C levels than men do.[5] Moreover, both the sensitivity and the specificity of EST are reported to

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be lower in women when compared with men.[6,7] Therefore, we aimed to test the following hypotheses that low HDL-C levels are associated with more profound coronary atherosclerosis and thus lower DTS and that the above-mentioned relationship is sex-dependent, given the differences between women and men in terms of the diagnostic value of EST and HDL-C levels.

Materials and Methods

Ethics

The study protocol was approved by the institutional ethics committee and written informed consent was obtained from all participants.

Inclusions

Age 18 years or above, signs and symptoms suggestive of ischemic heart disease, an EST tracing clear enough to enable thorough evaluation of ST segment deviation.

Exclusions

Familial hyperlipidemias, being on any lipid-lowering therapy,current pregnancy, cardiomyopathy, severe valvular heart disease, previous myocardial infarction (history of myocardial infarction or had pathological Q waves on their ECGs) or any previous revascularization procedure (whether percutaneous transluminal coronary angioplasty or coronary artery bypass grafting), unstable angina pectoris, history of congenital heart disease, any condition that would interfere with the interpretation of EST tracing (permanent pacemaker, digoxin use, Wolff-Parkinson-White syndrome, left bundle branch block), and any orthopedic disorder that would render EST impossible.

Patients

The sample was derived from a population of 189 consecutive patients who underwent EST due to chest discomfort (including typical and atypical angina, atypical chest pain, exertional dyspnea) on exertion attributable to myocardial ischemia in the outpatient clinic. In total, 88 of them were excluded for the above listed reasons. Finally, 101 patients formed the study sample.

Study procedure
Exercise stress testing
EST involved maximal treadmill protocols selected according to the age and functional status of the patient. EST, following the standard Bruce protocol, was performed by specialized EST laboratory personnel. The patients underwent clinical and ECG monitoring throughout the test. Standard end points were used, and the test was terminated if any of the following conditions occurred: Profound fatigue, severe ischemia (severe angina, >2 mm ST segment depression, or ST segment elevation), profound hypertension (systolic blood pressure >220 mmHg), hypotension (decrease in systolic blood pressure by more than 20 mmHg), achieving 100% of the age-predicted maximum heart rate (220-age for male subjects and 200-age for female subjects), or serious arrhythmias. Data derived from the test were used to calculate the DTS.

Calculation of the Duke treadmill score
The equation used for obtaining the DTS was; DTS = exercise time−(5 × ST deviation)−(4 × exercise angina), in which severity of angina is scored as: 0 = none, 1 = nonlimiting, and 2 = exercise-limiting. The score typically ranges from−25 to +15. These values correspond to low-risk (with a score of ≥+5), moderate-risk (with scores ranging from −10 to +4), and high-risk (with a score of ≤−11) categories.[3,4]

Coronary angiography
Coronary angiography was offered to patients with moderate to high risk DTS. Selective coronary angiography was performed by the femoral approach using the Judkins technique and the General Electric angiographic system. Multiple views were obtained, with visualization of the left anterior descending (LAD) and left circumflex coronary artery in at least four projections and of the right coronary artery in at least two projections. Coronary angiograms were recorded on compact discs in DICOM format. All angiograms were analyzed by two cardiologists blinded to the clinical data. The extent and severity of the CAD were evaluated by the Gensini score. In this scoring system, a severity score is derived for each coronary stenosis based on the degree of luminal narrowing and its topographic importance. Reduction in the lumen diameter and the roentgenographic appearance of concentric lesions and eccentric plaques are evaluated. A Gensini score between 1 and 19 denotes mild CAD and a score equal to or greater than 20 denotes significant CAD.[8]

Biochemical analysis
Venous blood samples were obtained after 8 h of fasting. The biochemical examination of blood including the lipid panel was performed in all patients using an automated system and commercially available kits before the EST.

Statistical analysis
The data were analyzed utilizing the software package PASW Statistics version 18. The normal distribution of variables was verified with the Kolmogorov — Smirnov test. Data are shown as mean ± SD for continuous variables and as absolute numbers and percentages for dichotomous variables. A Spearman's rho correlation was employed when one or both of the variables were not normally distributed. Comparisons between the groups were made either with independent samples *t*-test when the distribution was normal, or with the Mann — Whitney U test when the distribution was not normal. A chi-square (X^2) test was used to investigate whether distributions of categorical variables differed within groups. Adjustment was made according to age, sex, and smoking status. A *P* value less than 0.05 denoted statistical significance.

Results

Demographic data
The age of the 101 patients was 47.71 ± 11.71 years (mean ± SD), comprising 59 men (58.4%, mean age 48.1 ± 12.5) and 42 women (41.6%, mean age 47.3 ± 10.7).Mean HDL-C and DTSs of the study population were 47.5 ± 11.4 mg/dL and 5.8 ± 4.9, respectively. Baseline characteristics and biochemical

examinations according to DTS are shown in Table 1. There was no significant difference between men and women in relation to age, body mass index (BMI), history of hypertension(HT), and diabetes mellitus (DM) (*P* = 0.743, *P* = 0.146, 0.214, and 0.529, respectively) but the ratio of smokers was higher in men than in women (*P* = 0.015).

Risk stratification based on DTS score

According to DTS, 38 of the patients (37.6%) had moderate to high risk (with a score of ≤4) (group-I), and 63 of the patients (62.4%) had low risk (with a score of ≥+5) (group-II). Mean DTS was 0.89 ± 3.74 in group-I and 8.80 ± 2.63 in group-II (*P* < 0.001).When the patients were sub classified according to sex and DTS, it was seen that 39 men and 24 women were in group-II, and 20 men and 18 women were in group-I.HDL-C levels were lower in group-I than in group-II (44.43 ± 11.18 vs. 49.25 ± 11.21, respectively, *P* = 0.04)

Corelation analysis

There was a significant positive association between DTS and HDL-C (*P* = 0.021, r = 0.230). The association between HDL-C and DTS is demonstrated by the scatter plot graphic in Figure 1. As expected, mean HDL-C level was higher in women than it was in men (51.38 ± 12.47 vs. 44.75 ± 9.78, respectively, *P* = 0.004). There was a positive association between DTS and HDL-C in men but not in women (*P* = 0.046, r = 0.260; *P* = 0.336, r = 0.154, respectively).A HDL-C level less than the cut-off value of 41.39 mg/dL predicted the probability of having a moderate to severe risk DTS with 65% sensitivity and 69% specificity in men (area under curve = 0.732, *P* = 0.004) [Figure 2]. However, in women, no such relationship was observed (area under curve = 0.505, *P* = 0.958). After adjustment for covariates (age, sex, and smoking status), the relationship of DTS to HDL-C maintained its significance (*P* = 0.030; adjusted OR = 0.948 [95% CI, 0.904-0.995] [Table 2].

Coronary angiography

This was offered to patients with moderate to high risk DTS, and 28 of them agreed to undergo this procedure. Of these, 14 had

### Table 1: Baseline characteristics and biochemical examinations

Baseline characteristics	Group-I (*n* = 38) (%)	Group-II (*n* = 63) (%)	*P* value
Sex (men/women)	20/18	39/24	0.408
Diabetes mellitus	4 (10.5)	12 (19)	0.399
Hypertension	16 (42.1)	22 (34.9)	0.528
Hyperlipidemia	21 (55.3)	34 (54)	0.532
Current smoker	20 (52.6)	21 (33.3)	0.063
BMI (kg/m^2)	29.5±2.8	28.9±3.5	0.776
Age (years)	48.73±10.72	47.09±12.32	0.391
LDL-C (mg/dL)	139.36±26.35	141.95±33.26	0.234
HDL-C (mg/dL)	44.43±11.18	49.25±11.21	0.040
Tot-C (mg/dL)	216.93±34.37	221.84±42.22	0.070
Tg (mg/dL)	178.49±90.45	185.93±98.40	0.376
TC/HDL-C ratio	4.88±1.16	4.75±1.45	0.654
FBG (mg/dL)	102.45±14.25	107.88±31.43	0.721
PBG (mg/dL)	138.29±36.08	145.61±33.04	0.490
CRP (mg/L)	4.80±3.33	3.31±4.30	0.320
MDRD Cr Cl	107.94±21.12	112.84±32.34	0.736

Group-I defined as moderate to high risk DTS (≤4), and group-II defined as low risk DTS (≥+5); FBG = Fasting blood glucose; HDL-C = High-density lipoprotein cholesterol; LDL-C = Low-density lipoprotein cholesterol; MDRD Cr Cl = Modification of diet in renal disease creatinine clearance (mL/min/1.73 m^2); PBG = Postprandial blood glucose; Tot-C = Total cholesterol; CRP = C-reactive protein; Tg = Triglyceride

Table 2: Multivariate analysis of Duke treadmill test DTS (logistic regression model without interaction)

Covariates	*P*	OR (crude or adjusted)	95% CI
Age	0.311	1.020	0.981-1.060
Sex	0.058	0.389	0.147-1.034
Smoking	0.062	0.416	0.165-1.046
HDL-C	0.030	0.948	0.904-0.995

Moderate to high risk Duke treadmill test was defined as the score <5; OR is statistically significant (CI does not include 1); OR = Odds ratio; CI = Confidence interval; HDL-C = High-density lipoprotein cholesterol
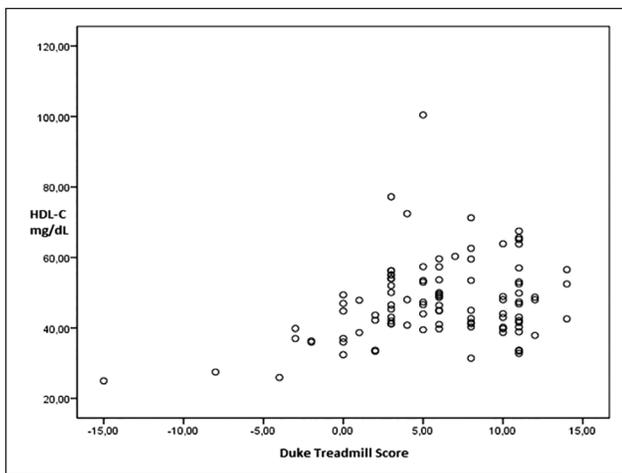
Figure 1: Thescatter plot graphicdepicting the relationship between Duke treadmill score and HDL-C. HDL-C = High-density lipoprotein cholesterol
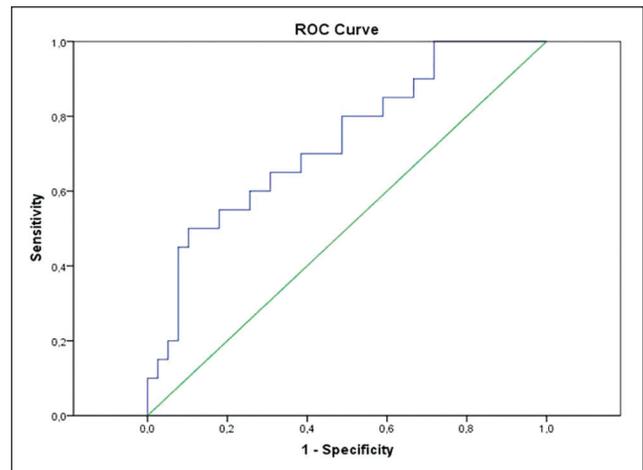
Figure 2: ROC curve for DTS and HDL-C levels in men. An HDL-C level less than the cut-off value of 41.39 mg/dL predicted the probability of having a moderate to severe risk DTS with 65% sensitivity and 69% specificity (area under curve = 0.732, *P* = 0.004)

normal coronary arteries (NCA) (6 men and 8 women), 8 had minimal CAD (5 men and 3 women), and 6 had significant CAD (3 men and 3 women). No correlation was found between the Gensini and Duke scores ($P = 0.863$, r $= -0.034$).Moreover, a significant inverse correlation between DTS and CRP levels was determined ($P = 0.035$, r $= -0.264$).

Discussion

CAD is the leading cause of mortality in the industrialized world. Many parameters and tests are used to determine the risk of CAD. The EST is used in the evaluation of symptomatic patients to predict the presence and extent of CAD and the prognosis.[3] The DTS is a useful and well-established method that can help clinicians determine the prognosis and decide whether to refer outpatients with suspected CAD for cardiac catheterization. The DTS is the currently accepted standard for risk stratification on treadmill testing. The DTS provides accurate diagnostic and prognostic information for the evaluation of symptomatic patients with clinically suspected CAD. It provides critical decision-making information in patients identified as having low or high risk.[4] Patients with moderate risk, however, may be considered for further testing, such as myocardial perfusion imaging.[9]

The literature attests to the role of HDL-C as a marker inversely and independently associated with the risk of developing CAD.[5,10] Low HDL-C is an independent risk factor for CAD.[11] The Framingham study revealed that HDL-C was the principal factor accounting for CAD risk and was significantly associated with CAD ($P < 0.001$), coronary attacks ($P < 0.01$), and angina pectoris ($P < 0.01$-0.001) in all men and women, and this association persisted after adjustment for other lipid parameters.[12] A pooled analysis of data from four major prospective trials indicates that each decrease in HDL-C of 1mg/dL (0.03mmol/L) was associated with an increase in the risk of CAD by 2% in men and by 3% in women.[13] Recently, the pleiotropic cardioprotective actions of HDL-C and the multiple pathogenetic links between low HDL-C and atherosclerotic disease have been defined.[14,15] The most likely mechanistic explanation is that HDL-C enhances uptake of peripheral cholesterol and its return to the liver for excretion in the bile and feces, a concept first introduced by Glomset in 1968[16] and subsequently termed RCT. Later Ross and Glomset speculated that RCT could be a protective mechanism against atherosclerosis;[17] moreover, Miller and Miller suggested that HDL-C might protect against atherosclerosis by promoting RCT.[5] More recently, a variety of other functions of HDL-C have been described, primarily based on *in vitro* assays, including antiinflammatory, antioxidant, antithrombotic, and nitric oxide-inducing mechanisms.[15,18] While their relevance to human physiology is not fully understood, these mechanisms are likely to contribute to the antiatherosclerotic effects.

High-risk DTS has been previously reported to be associated with significant CAD.[3,19] Contrary to the literature, no correlation was found between the DTS and the Gensini score in our study. The lack of association between DTS and Gensini score can be attributed to the small sample size.

An EST has a sensitivity of 67% (false negative rate of 33%) and a specificity of 72% (false positive rate of 28%) of significant narrowing of a coronary artery.[20] Unlike to this, 50% of the individuals was associated with NCA in our study. The relatively high ratio of individuals with NCA can be explained by the small sample size and this may probably be due to play of chance.

The assessment of CAD is more challenging in women than it is in men for several reasons. The clinical presentation is often with atypical symptoms and the female sex is associated with a propensity to experience mental stress-evoked angina and rest angina more frequently when compared to the male sex.[21] EST appears to be less accurate in women for the diagnosis of CAD, and both sensitivity and specificity have been reported to be lower compared with those in men.[6,7] This sex difference persists even after incorporating ST-segment deviation with exercise time and exercise-induced symptoms into the DTS.[20,22] Likewise, in our study, there was a positive correlation between DTS and HDL-C levels in men, but not in women. This may be explained by the lower sensitivity and specificity of EST in women. Contrary to our findings, some other studies reported the DTS to have diagnostic value in both sexes.[3,4] In a study, which evaluated 2758 symptomatic patients (30% women) who underwent EST with subsequent coronary angiography, a high-risk DTS predicted 376-fold more likelihood of having significant CAD when compared with those with a low-risk DTS.[23] Comparable findings for the diagnostic value of DTS have been found in a series of 976 symptomatic women referred for EST and coronary angiography. CAD presence correlated with category of DTS risk. While women had less CAD when compared with men at each level of DTS, the correlation of DTS and CAD was similar.[24] Thus, the reports on the predictive value and accuracy of EST and DTS in particular are somewhat controversial, and these issues warrant further research.

The positive correlation between HDL-C and DTS may be explained by the antiatherogenic properties of HDL-C. It can be speculated that higher HDL-C levels alleviate ischemia by decreasing the extent and severity of CAD and/or improving endothelial function. Therefore, we speculate that HDL-C is positively associated with DTS, probably owing to its antiatherosclerotic effects. Nevertheless, this correlation is only significant in men, and this may be explained by the lower sensitivity and specificity of EST in women.[6,7]

The main limitation of our study was the relatively small sample size. A study with a larger number of cases could have not only corroborated our findings more efficiently, but also allowed analysis of data obtained from several subgroups of patients. Due to the small sample size, we could not come up with a combined HDL-C level and DTS score and then tested its sensitivity and specificity in predicting CAD by comparing it with gold standard angiography. Another limitation of this study was the subjective analysis of the ST-segment deviation during the EST which we think was minimized by two blinded examiners.

Our findings suggest that DTS, a simple prognostic score based on data derived from the standard treadmill exercise test, is

positively associated with serum HDL-C levels in men, but not in women and may prove to be a useful tool in future. This sex-related difference may be attributed to the lower sensitivity and specificity of EST in women. This issue needs to be verified and clarified with further studies with larger numbers of patients.

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