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Erectile Dysfunction in Type 2 Diabetic Men: Relationship to Exercise Fitness and Cardiovascular Risk Factors in the Look AHEAD Trial

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Abstract

Introduction—Determinants of erectile dysfunction in diabetic men have not been adequately investigated as potential mediators of change.

Aim—To determine the prevalence and correlates of erectile dysfunction (ED) in overweight men with type 2 diabetes in the multicenter, Look AHEAD trial (Action for Health in Diabetes).

Main Outcome Measures—International Index of Erectile Function (IIEF), self-reported use of phosphodiesterase type 5 inhibitors, laboratory measures of adiposity, cardiometabolic parameters, and exercise fitness.

Methods—Male participants aged 45–75 in the Look AHEAD trial in a committed relationship were recruited for an ongoing study of sexual function and diabetes. Eligible participants completed the IIEF questionnaire and provided updated information on use of medical treatments for sexual dysfunction. Baseline sexual function results for participants in the male ancillary study are reported here; intervention data and results for female participants are presented elsewhere.

Results—A total of 373 eligible male participants completed all sexual function questionnaires, of whom 263 (68.7%) were sexually active at the time of the study. Almost half (49.8%) of the men reported mild or moderate degrees of ED, and 24.8% had complete ED. Among sexually active participants, 42.6% had sought medical help for their problem, and 39.7% reported use of ED medications. ED was significantly associated with age (odds ratio [OR] = 1.05; confidence interval [CI]: 1.01–1.10) baseline HbA_{1c} (OR = 1.31; CI: 1.05–1.63), hypertension history (OR = 2.41; CI: 1.34–4.36), and metabolic syndrome (OR = 3.05, CI: 1.31–7.11). Of note, cardiorespiratory fitness was found to be protective of ED in a multivariable analysis (OR = 0.61; $P < 0.001$).

Conclusions—ED is prevalent in this sample of obese, type 2 diabetic men in the Look AHEAD study. Cardiovascular risk factors were highly associated with ED in this population, and cardiorespiratory fitness was protective in this analysis.

Keywords

Type 2 Diabetes; Erectile Dysfunction; Phosphodiesterase Type 5 Inhibitors; Physical Activity

Erectile dysfunction (ED) is a highly prevalent and bothersome complication of diabetes mellitus [1–3]. Diabetic men have increased prevalence, severity, and rate of progression of ED relative to nondiabetic men [2,4,5]. Based on results from the National Health and Nutrition Examination Survey (NHANES III), 51.3% of diabetic men have self-reported symptoms of ED [6]. Diabetic men are three times as likely to develop ED as nondiabetic men of similar age [3,4], and experience ED onset about 10–15 years earlier than men with erection difficulties due to other causes [2,5].

In the recent multinational survey study Men's Attitudes to Life Events and Sexuality (MALES), diabetic men rated their ED as more severe and debilitating than nondiabetic men and were more likely to seek professional help for their disorder [7,8]. Other studies have shown a strong link between ED in men with diabetes and a range of adverse psychosocial outcomes, including reduced quality of life and increased depression, compared with similarly aged men with normal sexual function [2,9]. However, none of these studies has evaluated the impact of lifestyle change in men with type 2 diabetes and obesity, as is our goal in the current Look AHEAD trial [10,11].

The present ancillary study was designed to evaluate the prevalence and correlates of ED at baseline in a subgroup of men participating in Look AHEAD, a large, multicenter clinical trial examining the long-term effects of lifestyle intervention on cardiovascular morbidity and mortality in 5,145 overweight individuals with type 2 diabetes [10,11]. Look AHEAD is the largest randomized trial to evaluate prospectively the effects of lifestyle change on cardiovascular and other outcomes in a large, representative cohort of men and women with obesity and type 2 diabetes. This article reports baseline prevalence of ED and other male sexual dysfunctions, and examines help seeking, comorbidities, and sociodemographic correlates associated with ED. In addition to cardiovascular and metabolic risk factors, we examined the role of cardiorespiratory fitness and body adiposity as potentially modifiable determinants of ED in our type 2 diabetic population.

Research Design and Methods

Participants

The design and methods for the Look AHEAD trial and baseline characteristics of the sample are described in detail elsewhere [10,11]. Eligibility included men and women with type 2 diabetes, aged 45–74 years, and a body mass index (BMI) ≥ 25 kg/m² (≥ 27 kg/m² for individuals taking insulin). Subjects were excluded due to uncontrolled hyperglycemia (HbA1c $> 11\%$), hypertension (BP $> 160/100$ mm Hg), or hyperlipidemia (fasting triglycerides ≥ 600 mg/dL). Participants for the sexual dysfunction ancillary study were recruited from five Look AHEAD sites (University of Pennsylvania, The Miriam Hospital/Brown Medical School, Johns Hopkins University, University of Alabama at Birmingham,

University of Tennessee at Memphis). These sites were selected on the basis of geographic and ethnic diversity of the study participants.

Men at these sites were invited to participate in the sexual dysfunction ancillary study. To be eligible, participants were required to sign a separate informed consent and to have been sexually active in the past 6 months or in a committed relationship. They were provided a modest incentive (\$25 gift certificate) for participation. More than 90% of men approached agreed to participate in the study. Both male and female participants at Look AHEAD ancillary study sites were approached to participate; results for the male participants are reported in this article.

Measurements

All measures were completed at baseline prior to randomization by study staff who were provided standardized training and certification in the study procedures.

Sexual Function

Sexual function was evaluated by means of the International Index of Erectile Function (IIEF), a widely-used, validated measure of male sexual function [12]. The IIEF questionnaire assesses sexual functioning across five domains, including erectile function (EF), orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction, with higher scores indicating more normal sexual function and greater satisfaction [12,13]. ED is defined specifically as “inability to achieve or maintain erection sufficient for sexual performance.” The IIEF is currently the most widely used questionnaire for assessment of EF and other domains of male sexual function [13]. Since validation studies of the IIEF were conducted in sexually active men only [12,13], we examined our results first for the full ancillary study sample, and for sexually active men separately.

Previously established norms on the EF domain from similarly aged men were used to define mild, moderate, and severe ED [12]. These were respectively scores of 26–30 (no ED), 22–25 (mild ED), 11–21 (moderate ED), and 6–10 (severe ED). Additionally, participants were asked whether or not they had sought medical help for their ED problem and about prior use of medical treatments for ED.

Physical Measures

Waist circumference was measured at the level of the iliac crest to the nearest 0.1 cm. Height was recorded to the nearest 0.5 cm. Body weight was recorded to the nearest 0.1 kg. BMI was calculated as weight (kg) divided by height (m)². Systolic and diastolic blood pressure readings were obtained 1 minute apart (after the subject had been seated for 5 minutes) using a Dinamap Monitor Pro 100 automated blood pressure device (GE Medical Systems, Tampa, FL, USA).

Metabolic syndrome was defined according to the Adult Treatment Panel (ATP III) guidelines as consisting of three or more of the five criteria described by Grundy et al. [14].

Cardiorespiratory fitness was measured by a symptom-limited graded exercise treadmill test to voluntary exhaustion. Peak exercise capacity expressed as metabolic equivalents (METS)

[15] was estimated from treadmill speed and elevation using standardized equations. Age-adjusted (z-transformed) fitness was calculated as each individual's peak METS score minus the sample mean and corrected for the standard deviation (SD) by age and gender.

Medication use, including use of phosphodiesterase type 5 (PDE-5) inhibitors, was obtained from interviewer-administered questionnaires. We included use of other medications (e.g., antihypertensives) in a multiple regression analysis (see below).

Mood and Quality of Life Variables

Depressive symptoms were assessed using the Beck Depression Inventory [16]. Higher scores on this scale indicate more frequent depressive symptoms.

Health-related quality of life was measured using the Social Functioning Health Index (SF-36) measure [17], including composite measures of mental health (Mental Component Score [MCS] scale) and physical health (Physical Component Score [PCS] scale).

Demographic Variables

Standardized interviewer-administered questionnaires were used to obtain self-reported data on medical history, employment, education, family income, smoking, prescription medications, alcohol use, and family medical history [10]. Race/ethnicity was self-reported using questions from the 2000 U.S. Census questionnaire.

Statistical Analysis

Descriptive statistics were used to characterize the ancillary study sample and to compare our sample to the main Look AHEAD trial with respect to relevant demographic and medical history variables. Group differences for continuous variables were examined using Student's unpaired *t*-tests and ANOVA models, and sexual function data in the ancillary study was compared with historical norms from similarly aged, nondysfunctional men. Bivariate and multivariate analyses were used to characterize the association between the usual risk factors for ED and PDE-5 use while adjusting for known risk factors, such as age, duration of diabetes, and HbA1c levels. Forward logistic regression models were tested, including ED status and ED medication as dependent variables in the model. Correlational analyses (both parametric and non-parametric) were used to assess and control for the effects of collinearity. The final model was tested by means of the Hosmer and Lemeshow goodness-of-fit test. Analyses were performed using SAS (version 8.2) software (SAS Institute, Inc., Cary NC USA).

Results

Characteristics of the Sample

Three hundred ninety men, aged 45–75, with type 2 diabetes and a committed, partner relationship, signed a consent form and were enrolled in the sexual dysfunction ancillary study. Of these, 373 men provided complete data on the sexual function and help-seeking questionnaire and were included in the analyses. The majority (68.7%) reported that they were sexually active and in a long-term partner relationship. As shown in Table 1, ancillary

study subjects were found to be representative of the main trial participants in respect to age, duration of diabetes, race, HbA_{1c}, BMI, and waist circumference. In both the main trial and ancillary study samples, approximately 25% of the men were African American or from another minority group, and more than 80% of participants reported being currently married or in a stable partner relationship.

Sexual Function Characteristics

Sexual function characteristics of the sample are shown in Figure 1, which presents composite scores for each of the sexual function domains. Look AHEAD ancillary study participants had reduced sexual function scores across all five domains of sexual function compared with similarly aged, normal controls in an earlier validation study [12]. Of note, sexual function domain scores were approximately 20–30% below normal in each of the sexual function domains.

Approximately three in four men in our sample of diabetic men had varying degrees of erectile dysfunction (See Table 2). Specifically, 49.8% had mild or moderate ED, and 24.8% had severe ED. In addition, 42.5% of sexually active participants had consulted with a physician about their sexual problems, and 39.7% had used erection medication (PDE-5 inhibitors) in the recent past. Similarly, more than half of the sexually active participants had varying degrees of ED, although less than 10% had severe or complete ED (Table 2). No differences were observed in the rates of ED or PDE-5 inhibitor use among minority and nonminority participants in the study.

Risk Factors and Comorbidities

The association between baseline demographic, psychosocial, and cardiometabolic risk factors and correlates of ED were examined. After controlling for age, the presence of metabolic syndrome was found to be highly associated with ED (odds ratio [OR] = 3.05; confidence interval (CI): 1.31–7.12), along with hypertension history (OR = 2.41; CI: 1.34–4.36) and other cardiovascular risk factors. Age, duration of diabetes, and higher hemoglobin A1C levels, measured by standard assay methods, were similarly associated with ED in our age-adjusted analyses. Conversely, exercise fitness levels at baseline, including both unadjusted and age-adjusted fitness levels (maximum METS; age-adjusted *z*-scores), were protective of ED in these analyses (Max METS OR = 0.76; CI: 0.65–0.85; *z*-adjusted fitness OR = 0.61; CI: 0.47–0.78). Men with improved levels of fitness were about 40% less likely to have ED compared with those in the lowest group (see Table 3). Additionally, self-reported ED was associated significantly with lower physical health ratings on the SF-36 scale (OR = 0.94; CI: 0.90–0.98) and age-adjusted depression scores, as measured by the BDI (OR = 1.07; CI = 1.01–1.14).

The independent protective effect of cardiorespiratory fitness on ED was shown in a stepwise, forward logistic regression model. After adjusting for age and other covariates, cardiopulmonary fitness (age-adjusted fitness score) was highly protective of EF (OR = 0.61; 0.47–0.78). Concomitant medications previously associated with ED (e.g., ACE inhibitors, beta-blockers, and calcium channel blockers) were also entered into the regression model, but were not significant predictors in the final model.

Finally, we examined the association between risk factors for ED and current use of PDE-5 inhibitors (e.g., sildenafil, tadalafil, vardenafil). Only hypertension status was a significant predictor of current PDE-5 use (OR = 2.18; CI: 1.04–4.55). Specifically, participants with a history of high blood pressure were more than twice as likely to have used PDE-5 inhibitors in the past year, or to have sought medical help for their condition.

Discussion

ED is a prevalent complication of diabetes, which has been linked to neuropathic and vascular complications of the disease [2,3,6]. In the present study, about half of our racially diverse sample of more than 300 men with obesity and type 2 diabetes had mild or moderate ED, and a further 25% had severe or complete ED. In addition to common problems with achieving or maintaining erection, Look AHEAD participants had impaired orgasmic function, sexual desire, intercourse satisfaction, and lower overall sexual satisfaction relative to similarly aged controls [12]. Of note, nearly half of the sexually active men in our sample had sought medical help or advice for their sexual difficulties, and 40% had used PDE-5 inhibitors in the recent past. Similarly high rates of sexual dysfunction were observed in minority and non-minority men, as well as among sexually active and inactive participants in our sample.

Several risk factors for ED were determined to be important in our study, both in bivariate and multivariate analyses. Age, hypertension history, and duration of diabetes were significantly associated with the presence and severity of ED in our sample, as shown in other recent studies [2,7,18]. Hemoglobin A1c levels and waist circumference were additional predictors of ED in our sample. Moreover, cardiorespiratory fitness was found to be protective of ED. Previous studies have shown that physical activity is beneficial in reducing rates of ED in nondiabetic men [2,19]. This is the first study, however, to demonstrate a positive effect of cardiorespiratory fitness, measured by means of standard exercise testing.

The mechanisms of diabetic ED have been described previously [20,21]. In particular, increased insulin resistance has been associated with endothelial dysfunction and impaired nitric oxide (NO) signaling in corporal smooth muscle in several studies [20,21–23]. Recent studies have also shown that men with characteristics of metabolic syndrome, including obesity and physical inactivity, are at markedly increased risk for ED [24,25]. In accounting for the protective effects of cardiorespiratory fitness observed in our sample, it is possible that increased physical activity was associated with improved insulin sensitivity and NO regulation in these men. This hypothesis will be evaluated further in the longitudinal phase of the study. As in other recent studies [26–28], our results confirm the strong association between ED and other markers of cardiovascular disease, supporting the need for comprehensive cardiovascular assessment in all diabetic men with ED [29].

Major strengths of the current study include the use of validated measures of sexual function and a wide array of biomedical and psychosocial outcomes in a well-characterized sample of obese men with type 2 diabetes [10,11]. Our study sample was closely matched in age and race/ethnicity to the main Look AHEAD trial, which has been shown to be representative of

type 2 diabetic men and women in the overall U.S. population [11]. Our study findings support those of other recent studies of ED in diabetic men [4,6,18]; however, our study includes other aspects of sexual function in diabetic men in addition to a more in-depth assessment of the role of cardiovascular, metabolic, and psychosocial determinants.

Some limitations of the current study should be noted. First, we report here findings from the baseline observation period in male patients only prior to randomization. Future reports will address the effects of intervention (lifestyle change vs. usual care) on sexual function in our sample of obese men and women with type 2 diabetes. Second, we report results on a subset of men within the larger Look AHEAD trial. Despite the potential risk of selection bias, we have shown that our sample are highly representative of the overall Look AHEAD male population on all the major demographic and background health characteristics (See Table 1). Finally, due to the limitations of the overall Look AHEAD study design, we were not able to evaluate partner sexual function or effects on the couple's relationship in this study.

ED is often viewed as an early-warning sentinel for coronary artery disease, just as endothelial dysfunction is seen as a major risk factor for ED. This study confirms the strong association of cardiovascular risk factors with erectile function. Changes in erectile and sexual function will be reevaluated in these men following randomization to intensive lifestyle change or usual care.

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Figure 1. Sexual function domain scores (percent maximum response) for Look AHEAD study participants compared to nondiabetic controls. Diagonal hash bar column = Look AHEAD participants (N = 373); White column = normal controls (N = 109).

Table 1

Patient characteristics at baseline: main look ahead trial vs. sexual function ancillary study

	Main trial	Sexual function ancillary study	
	Male	Overall ancillary study	Sexually active men
Number (N)	2081	373	268
Age (years) %			
45–55	527 (25.3%)	86 (22.1%)	65 (24.3%)
56–65	1116 (53.5%)	213 (54.6%)	149 (55.6%)
66–76	444 (21.3%)	91 (23.3%)	54 (20.2%)
Race			
White	1581 (76.0%)	303 (77.7%)	199 (74.3%)
African American/black (non-Hispanic)	190 (9.1%)	68 (17.4%)	52 (19.4%)
Other mixed	308 (14.8%)	19 (4.9%)	17 (6.3%)
BMI (mean), kg/m ²	35.9 (35.7–36.2)	35.6 (35.1–36.2)	35.3 (34.7–35.9)
Waist circumference (mean), cm	113.9 (113.4–114.6)	120.1 (118.8–121.4)	118.8 (117.3–120.3)
HbA1c (mean) %	7.28 (7.2–7.3)	7.33 (7.2–7.5)	7.28 (7.1–7.4)
Fasting glucose (mean), mg/dL	153.12 (151.2–155.1)	152.82 (148.4–157.3)	148.90 (143.9–153.9)
Duration of diabetes in years (mean)	6.80 (6.5–7.1)	7.75 (7.1–8.4)	7.15 (6.3–8.0)
Hypertension (%)	1671 (80.3%)	328 (84.1%)	217 (81.0%)
Fitness (maximum METS) (mean)	7.19 (7.1–7.3)	7.66 (7.5–7.9)	7.94 (7.7–9.2)
Metabolic syndrome (%)	1941 (93.3%)	366 (93.9%)	248 (92.5%)
Systolic blood pressure, mm Hg	128.82 (128.1–129.6)	128.76 (127.1–130.4)	128.65 (126.7–130.7)
Diastolic blood pressure, mm Hg	70.17 (69.8–70.6)	72.84 (72.0–73.7)	73.26 (72.2–74.3)
Marital status, n (%)			
Never married	118 (5.7%)	13 (3.3%)	5 (1.9%)
Married/marriage-like relationship	1731 (83.1%)	341 (87.4%)	244 (91.1%)
Widowed	36 (1.7%)	5 (1.3%)	3 (1.1%)
Divorced/separated	199 (9.5%)	31 (8.0%)	16 (6.0%)
Employment status, n (%)			
Full or part time	1395 (80.7%)	251 (64.4%)	176 (65.7%)
Full or part-time student	4 (0.2%)	2 (0.5%)	1 (0.4%)
Not employed	196 (11.3%)	45 (11.5%)	29 (10.8%)
Smoking status, n (%)			
Never	781 (37.6%)	144 (36.9%)	97 (36.2%)
Past	1201 (57.8%)	225 (57.7%)	154 (57.5%)
Present	96 (4.6%)	19 (4.9%)	16 (6.0%)
Any alcohol in past year, n (%)	1470 (70.4%)	260 (66.7%)	185 (69.0%)

BMI = body mass index; METS = metabolic equivalents.

Table 2

Erectile Dysfunction (ED) severity and treatment-seeking

	<u>Overall ancillary study</u>		<u>Sexually active ancillary study participants</u>	
	N [†]	%	N	%
ED severity [*]				
No ED	373	25.4	263	35.6
Mild ED	373	29.1	263	38.2
Moderate ED	373	20.7	263	18.8
Severe ED	373	24.8	263	7.3
Treatment seeking [‡]				
Consulted doctor	373	39.9	263	42.5
Used ED medication	373	32.3	263	39.7

^{*} Based on diagnostic criteria in: Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Urology 1999;54:346–51.

[†] A total of 390 subjects were recruited for the ancillary study. Of these, 373 provided complete data on all sexual function items of the IIEF questionnaire.

[‡] “Have you seen a doctor or other health professional for treatment of erectile dysfunction (impotence)?”

IIEF = International Index of Erectile Function.

Table 3

Baseline correlates of ED and PDE-5i Use

Sample characteristics	Bivariate predictors of ED (EF domain 25)						Predictors of PDE-5i Use		
	Unadjusted (N = 373)			Age adjusted (N = 373)			Unadjusted (N = 331)		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Age (in years)	1.05	1.01–1.10	0.01	1.05	1.01–1.10	0.01	1.00	0.97–1.04	0.92
Duration of diabetes (in years)	1.05	1.01–1.09	0.03	1.04	1.00–1.08	0.07	1.01	0.98–1.04	0.57
Hemoglobin a1c (per 1%)	1.27	1.01–1.58	0.04	1.31	1.05–1.63	0.02	1.14	0.94–1.38	0.18
Metabolic syndrome (present vs, absent)	3.26	1.41–7.52	0.01	3.05	1.31–7.11	0.01	0.83	0.31–2.20	0.70
Body mass index (per kg/m ²)	1.02	0.98–1.07	0.29	1.04	1.00–1.09	0.08	0.97	0.93–1.02	0.21
Waist circumference (per cm)	1.02	1.00–1.04	0.04	1.02	1.00–1.04	0.02	0.99	0.97–1.01	0.21
Smoking history									
Past smoker vs. never smoked	0.96	0.59–1.58	0.89	1.15	0.69–1.89	0.60	0.87	0.53–1.42	0.58
Present smoker vs. never smoked	1.25	0.39–4.02	0.71	0.80	0.24–2.62	0.71	0.96	0.34–2.76	0.94
Cardiovascular risk factors									
History of hypertension (yes vs. no)	2.61	1.46–4.69	0.001	2.41	1.34–4.36	0.001	2.17	1.04–4.53	0.04
History of cardiovascular disease (yes vs. no)	1.70	0.70–3.02	0.07	1.48	0.82–2.68	0.19	1.11	0.66–1.88	0.70
Baseline systolic blood pressure (per mm Hg)	1.03	1.01–1.04	0.001	1.03	1.01–1.04	0.001	1.00	0.99–1.02	0.64
Baseline diastolic blood pressure (per mm Hg)	1.01	0.99–1.04	0.34	1.02	0.99–1.05	0.16	1.00	0.98–1.03	0.96
Fitness									
Maximum exercise capacity (per MET)	0.76	0.65–0.85	<0.001	0.76	0.69–0.87	<0.001	1.06	0.95–1.19	0.28
Fitness z-score (per unit)	0.62	0.49–0.80	0.001	0.61	0.47–0.78	<0.001	1.07	0.84–1.36	0.58
Lipids									
Cholesterol in mg/dL	1.00	0.99–1.01	0.98	1.00	0.99–1.01	0.82	1.00	0.99–1.01	0.94
Triglycerides	1.00	1.00–1.01	0.09	1.00	1.00–1.01	0.07	1.00	1.00–1.00	0.27
HDL cholesterol in mg/dL	0.98	0.96–1.01	0.13	0.98	0.95–1.00	0.06	1.01	0.98–1.03	0.70
LDL cholesterol in mg/dL	1.00	0.99–1.01	0.45	1.00	0.99–1.01	0.63	1.00	0.99–1.01	0.46
Mood									
Beck Depression Score (per point)	1.06	1.00–1.13	0.05	1.07	1.01–1.14	0.03	1.01	0.96–1.06	0.76
SF-36 Quality of Life									
Physical Health Score (per point)	0.95	0.92–0.99	0.01	0.94	0.90–0.98	0.001	1.01	0.98–1.04	0.61

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Sample characteristics	Bivariate predictors of ED (EF domain 25)				Predictors of PDE-5i Use			
	Unadjusted (N = 373)		Age adjusted (N = 373)		Unadjusted (N = 331)		Age adjusted (N = 331)	
	OR	95% CI	P		OR	95% CI	P	
Mental Health Score (per point)	0.99	0.96–1.02	0.53		0.98	0.95–1.02	0.34	
					1.01	0.97–1.04	0.69	

Note: In the stepwise, multivariate of analysis of risk of ED, the final, age adjusted model included the age-adjusted fitness score, duration of diabetes, and systolic blood pressure.
ED = erectile dysfunction; PDE-5i = phosphodiesterase type 5 inhibitors; EF = erectile function; OR = odds ratio; CI = confidence interval; METS = metabolic equivalents; HDL = high-density lipoprotein; LDL = low-density lipoprotein.