



# Association of LDL cholesterol with carotid atherosclerosis in menopausal women affected by the metabolic syndrome

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## KEYWORDS

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**Summary** *Background and aim:* The metabolic syndrome is a highly prevalent condition associated with cardiovascular disease. However, the contribution of LDL to cardiovascular risk is not estimated since it is not part of ATP III criteria.

*Methods and results:* This is an observational study evaluating the association between metabolic syndrome and carotid atherosclerosis, according to LDL cholesterol levels. Two hundred and sixty-five menopausal women were consecutively enrolled, they all underwent clinical examination, biochemical characterization and ultrasound evaluation. In particular, carotid atherosclerosis, a well known marker of cardiovascular disease, was evaluated. Women affected by cardiovascular disease were excluded from the study.

The metabolic syndrome was found strongly associated with carotid atherosclerosis in our study population. In individuals with normal or near normal LDL, the incidence of carotid atherosclerosis was significantly lower than in subject with high LDL. A high plasma LDL concentration was independently associated with carotid atherosclerosis ( $p = 0.026$ ) among women with the metabolic syndrome.

*Conclusions:* High LDL cholesterol levels are associated with carotid atherosclerosis in menopausal women with the metabolic syndrome.

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Although it remains prudent to recommend an integrated control of all modifiable risk factors to prevent cardiovascular disease, decreasing LDL levels should be considered a high priority.

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The metabolic syndrome is a cluster of lipid and non-lipid risk factors related to insulin resistance as recently defined by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) [1]. It is highly prevalent among adults [2]. Several studies have shown an association between the metabolic syndrome and cardiovascular events [3–6]. Most experts agree that the increased cardiovascular risk seen in these subjects is probably due to the clustering of known cardiovascular risk factors. However, even though there have been reports of an increased prevalence of coronary heart disease in these individuals, the impact of LDL cholesterol was not studied in detail. Accordingly, we evaluated the association between metabolic syndrome and the prevalence of asymptomatic carotid atherosclerosis, a marker correlated to increased cardiovascular mortality [7,8], according to LDL cholesterol level, in a cohort of menopausal women with and without the metabolic syndrome.

## Methods

The study population consisted of 265 menopausal women who were undergoing health-screening tests for menopause in our University hospital. All the participants, consecutively enrolled, were Caucasian and aged 45–75 years; they were in menopausal status, defined as no natural menses for at least one year and serum FSH levels above 40 IU/L. Women with a history of cardiovascular disease were excluded from the study. All subjects gave their informed consent and filled a research questionnaire approved by the local ethics committee. The clinical evaluation of the population sample included collection of information on demographics, risk factors for cardiovascular disease, medical history, medication use, as well as a physical examination to assess blood pressure and anthropometric measurements, and blood sampling in the fasting state for lipid and glucose evaluations. LDL cholesterol was calculated by the Friedewald formula, since no women had triglycerides levels above 400 mg/dL.

The ATP III criteria [1] were used to classify study participants as being with or without the metabolic syndrome based on the presence or absence of  $\geq 3$  of the following factors: (1) waist circumference  $> 88$  cm, (2) fasting triglycerides  $> 150$  mg/dL, (3) HDL cholesterol (HDL-C)  $< 50$  mg/dL, (4) hypertension (systolic blood pressure  $\geq 130$  mmHg, diastolic blood pressure  $\geq 85$  mmHg), and (5) fasting glucose  $\geq 110$  mg/dL. According to the LDL cholesterol level, calculated by the Friedewald formula, women were also classified with normal LDL (LDL  $\leq 130$  mg/dl) or high LDL (LDL  $> 130$  mg/dL).

## Assessment of carotid atherosclerosis

The subjects underwent B-mode ultrasonography of the extracranial carotid arteries by use of a duplex system (a high resolution ultrasound instrument ATL, HDI 5000 with a 5- to 12-MHz linear array multifrequency transducer). All the examinations were performed by the same ultrasonographer blinded to the patient's clinical information. The right and left common, internal and external carotid arteries (including bifurcations) were evaluated with the subjects in the supine position, with the head turned away from the sonographer and the neck extended with mild rotation. Intima–media thickness, defined as the distance between the intimal–luminal interface and the medial–adventitial interface, was measured as previously described.[9] Briefly, in posterior approach and with the sound beam set perpendicular to the arterial surface, 1 cm from the bifurcation, three longitudinal measurements of intimal–medial thickness were completed on the far wall of the right and left common carotid arteries, at sites free of any discrete plaques. The mean of the three right and left longitudinal measurements was then calculated. Plaque, detected in longitudinal and transverse planes with anterior, lateral and posterior approaches, was defined as an echogenic focal structure encroaching the vessel lumen with a distinct area 50% greater than the intimal–medial thickness of neighboring sites. Stenosis was defined as a peak systolic velocity  $> 120$  cm/s, and occlusion was

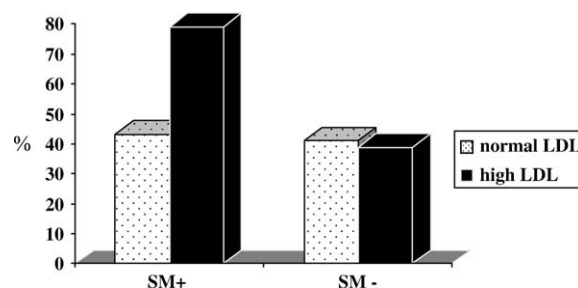
defined as absence of Doppler signal. According to these criteria, subjects were considered as normal if no lesion was detected, or as having carotid atherosclerosis when a plaque, stenosis or occlusion was detected in at least one segment of the carotid tree. The coefficient variation of the method for intima–media thickness was 3.3%.

## Statistical analysis

Differences in baseline demographic and clinical characteristics between the groups were assessed by  $\chi^2$  tests for categorical variables and unpaired Student's *t* test for continuous variables. Logistic regression analysis was used to obtain adjusted estimates of the odds of having carotid atherosclerosis in relation to LDL cholesterol and metabolic status. Covariates in adjusted models included age and those with a probability value of  $<0.10$ , as determined by forward stepwise regression. Ninety-five percent confidence intervals are reported. All the *p* values reported are two-sided. Significant differences were assumed to be present at  $p < 0.05$ . All comparisons were performed using the statistical package SPSS 11.0 for Windows.

## Results

Compared with normal women, individuals with metabolic syndrome had higher levels of glucose, triglycerides, systolic and diastolic blood pressure and lower level of HDL cholesterol (Table 1). They were less likely to smoke cigarettes (10% vs 24%,  $p = 0.03$ ). Women with high LDL levels were 65% and 73% among the group with and without metabolic syndrome, respectively, ( $p = \text{NS}$ ). The common carotid intima–media thickness adjusted



**Figure 1** Prevalence of carotid atherosclerosis according to the metabolic syndrome and LDL levels.

for age was similar in the two groups. In women with normal metabolic status, the prevalence of carotid atherosclerosis was similar as in those with normal and high LDL cholesterol levels (Fig. 1), whereas in women with the metabolic syndrome the prevalence was significantly higher with elevated LDL cholesterol (Fig. 1) ( $p < 0.001$ ). No carotid stenosis or occlusion was found. The relation between high LDL levels and prevalence of carotid atherosclerosis in the metabolic syndrome persisted and remained statistically significant in a multivariate analysis that included age and other confounding variables (Table 2). Specifically, compared with normal LDL levels, women with metabolic syndrome and high LDL levels had approximately six times greater likelihood of having carotid atherosclerosis.

## Discussion

In the present study which examined individuals free of cardiovascular disease we observed a significant relationship between increased LDL levels and carotid atherosclerosis in the metabolic syndrome. This despite high LDL does not represent a criterion for the diagnosis of the metabolic

**Table 1** Population characteristics according to metabolic syndrome

	Without metabolic syndrome (n = 210) Mean $\pm$ SD	With metabolic syndrome (n = 55) Mean $\pm$ SD	<i>p</i>
Age (years)	56.39 $\pm$ 7.62	58.64 $\pm$ 7.45	NS
Glucose (mg/dL)	92.84 $\pm$ 11.39	124.86 $\pm$ 37.60	$<0.0001$
TC (mg/dL)	230.66 $\pm$ 42.47	231.24 $\pm$ 38.17	NS
LDL-C (mg/dL)	144.73 $\pm$ 36.01	147.35 $\pm$ 31.89	NS
HDL-C (mg/dL)	63.09 $\pm$ 13.95	50.12 $\pm$ 11.13	$<0.0001$
Triglycerides (mg/dL)	119.34 $\pm$ 95.40	197.12 $\pm$ 180.28	$<0.0001$
BMI (kg/m <sup>2</sup> )	27.55 $\pm$ 4.53	32.78 $\pm$ 5.99	$<0.0001$
SBP (mmHg)	125.98 $\pm$ 16.28	142.40 $\pm$ 18.61	$<0.0001$
DBP (mmHg)	77.08 $\pm$ 8.67	81.86 $\pm$ 8.46	$<0.001$

Abbreviations: TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

**Table 2** Logistic regression analysis – traditional cardiovascular risk factors in women with the metabolic syndrome ( $n = 55$ )

	Odds ratio (CI 95%)	<i>p</i>
Age	1.10 (0.95–1.26)	0.191
Glucose	1.032 (0.99–1.08)	0.143
Triglycerides	0.996 (0.98–1.01)	0.598
Systolic blood pressure	1.024 (0.97–1.082)	0.415
Diastolic blood pressure	0.959 (0.85–1.08)	0.495
LDL (> 130 mg/dL)	6.913 (1.26–37.83)	0.026

Dependent variable: carotid atherosclerosis.

syndrome. Previous epidemiological studies have reported that the metabolic syndrome is independently associated with cardiovascular disease [3–6], due to the cluster of risk factor present in the former condition. Therefore, almost all the studies analyzed which factor was correlated to cardiovascular disease, without including LDL cholesterol in the evaluation of risk factors.

Our results are biologically plausible and consistent with the finding that LDL cholesterol is a strong predictor of coronary heart disease in diabetic individuals with insulin resistance [10–15]. And this is further confirmed by the fact that when LDL are not small and dense there is no difference in carotid plaque prevalence (Fig. 1).

Moreover, Golden et al. found that in individuals with risk factors related to insulin resistance a high LDL cholesterol was associated with an excess of carotid atherosclerosis [16].

The present data suggest an important role for LDL. This lipoprotein is well known to be the strongest predictors of circulating oxLDL levels; oxLDL is a key mediator in atherogenesis and a marker of coronary artery disease [17,18]. The metabolic syndrome is associated with increased LDL oxidation [19]; indeed low HDL levels might affect the HDL-associated antioxidant defense and these mechanisms may in part explain our observation.

These results suggest that the evaluation of LDL cholesterol should play a more important role in cardiovascular risk stratification in women with the metabolic syndrome and, since the presence of high LDL cholesterol levels was significantly associated with early carotid atherosclerosis, it is justified to indicate LDL cholesterol lowering as a priority. Controlled clinical trials evaluating the impact of LDL cholesterol reduction in individuals with the metabolic syndrome will help to definitively state which is the best lipid lowering treatment in the metabolic syndrome.

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