Acta clin Croat 2002; 41:5-10 Original Scientific Paper

BLOOD LIPIDS AND CAROTID PLAQUES

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SUMMARY – Increased lipids in the blood could be associated with an increased lipid core of atherosclerotic plaque and plaque echolucency on the B-mode image. The hypothesis that plasma levels of blood lipids predict the echolucency of carotid atherosclerotic plaques on B-mode imaging was tested. A total of 237 outpatients, mean age 62.9±10.2 years, were enrolled in the study. There were 189 symptomatic and 48 asymptomatic patients. All of them underwent duplex sonography of carotid arteries and lipidogram in the last year, and had plaques in common or internal carotid arteries. Other risk factors, i.e. arterial hypertension, diabetes mellitus, aging and gender, were also evaluated. In the model of logistic regression, the type of plaque (hypoechogenic, echogenic) was introduced as a dependent variable, with LDL, HDL and triglycerides as independent variables. The model fitted the data moderately well (r^2=0.19, p<0.001). LDL and HDL appeared to be significant predictors (p<0.01). The association of plaque type with arterial hypertension, diabetes mellitus, aging and gender was tested by logistic regression. The model fitted the data moderately well (r^2=0.24, p<0.001). Arterial hypertension and age were significant (p<0.01) predictors for echogenic plaques, whereas cigarette smoking was indicative of hypoechogenic plaques (p=0.01). In conclusion, LDL and HDL appeared to be associated with hypoechogenic plaques. LDL showed positive, and HDL negative association. Among other risk factors, aging and arterial hypertension showed positive association with echogenic plaques, whereas cigarette smoking showed positive association with hypoechogenic plaques.

Key words: *Arteriosclerosis, physiopathology; Arteriosclerosis, ultrasonography; Lipids, blood; Risk factors*

Introduction

Atherosclerosis is an inflammatory disease[1]. The most common risk factors for carotid atherosclerosis are hypertension, hyperlipidemia, and cigarette smoking[2]. The predominating mechanism is macrophage accumulation in atherosclerotic plaques caused by an accumulation of low-density lipoprotein (LDL). Macrophages at the sites of ongoing inflammation in advanced atherosclerotic plaques may precipitate plaque rupture, leading to acute clinical events such as myocardial infarction[3]. Oxidative modification of LDL is believed to play a major role in atherogenesis because LDL is converted to an atherogenic form that is rapidly taken up by macrophages mediated *via* the scavenger receptor[4]. Since these pathways are not feedback controlled, lipids may be taken up excessively. These lipids are deposited within the macrophages, which thereby develop into lipid-laden foam cells[5]. On the other hand, plasma high density lipoprotein (HDL) levels show an inverse relationship to atherogenesis. HDL removes cholesterol from peripheral cells such as arterial wall macrophages. Particular subfractions of HDL, such as the pre-ß-HDL fraction, may be especially efficient in mediating cholesterol removal from peripheral cells[6]. The disruption of blood flow is thought to be a result of embolization arising from degenerative breakdown or thrombotic occlusion of complex plaques in the extracranial vessel areas that are readily accessible to ultrasound imaging. Recent studies support the notion that not only the degree of stenosis but also the morphology of the carotid artery plaque and surface characteristics such as ulceration may

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Received December 3, 2001, accepted in revised form February 27, 2002

be of pathogenic importance[7]. With the use of high-resolution ultrasound B-mode imaging, carotid plaques evaluated as only weakly reflecting the ultrasound beam (echolucent) have been associated with a higher risk of neurologic events than are plaques strongly reflecting the ultrasound signal (echogenic)[8].

Cholesterol in plasma is distributed among four lipoprotein fractions: HDL, LDL, IDL, and VLDL, in order of increasing particle diameter. In the postprandial state, chylomicrons and chylomicron remnants may also be present in the plasma. Hypercholesterolemia is an important causal risk factor for atherosclerosis[9]. LDL is recognized as the major atherogenic lipoprotein. Accumulation of lipoproteins in the intima is dependent on the balance between the rates at which they enter and leave the arterial wall, and the rate at which they are degraded within it. Studies in humans, rabbits and pigs suggest that the influx of lipoproteins into the intima increases directly with the increasing lipoprotein concentration in the plasma[10]. Hence, the increased concentration of LDL and decreased concentration of HDL lipids in the blood could be associated with an increased volume of lipid core of atherosclerotic plaque and with an increased echolucency of the plaque on B-mode image.

In the present study, we tested the hypothesis that elevated plasma levels of blood lipids in the fasting or postprandial state predict echolucency of the carotid atherosclerotic plaques on ultrasound B-mode imaging.

Subjects and Methods

Patients

A total of 237 outpatients (171 men and 66 women, mean age 62.9±10.2 years) were enrolled in the study, 189 of them symptomatic and 48 asymptomatic. Of them, 116 (61%) patients had suffered a stroke, while 69 (36%) patients had experienced transient ischemic attack or amaurosis fugax. All of them underwent color-coded duplex sonography and power sonography examination of carotid arteries during the past year. The criteria for entry in the study were the presence of plaques in common or internal carotid arteries and no use of lipid-lowering medications. Age, sex, height, and weight were recorded. Cardiovascular risk factors were noted: hypertension (current and previous use of antihypertensive drugs and/or blood pressure >160/95 mm Hg) and diabetes mellitus (therapy with oral hypoglycemic agents or insulin, with an antidiabetic diet) as well as cigarette smoking. All of the patients had to have four fraction lipidograms including total cholesterol, LDL, HDL and triglycerides.

Ultrasonography

Carotid arteries were scanned with an Aloca 5500 color-coded duplex ultrasound device with a 10-MHz linear array transducer. High-resolution B-mode and color Doppler images of the plaques from the anterior, lateral and cross-sectional scan plane were evaluated on-line by use of the widely accepted criteria. The ultrasound images were subjectively graded according to the relative contribution of echogenic (high-intensity) and echolucent (low-intensity) material, using the classification of European Carotid Plaque Study Group[11]. The plaques were divided as follows: type I, predominantly echolucent plaque with a thin echogenic cap; type II, substantially echolucent lesions with small areas of echogenicity; type III, predominantly echogenic lesions with small areas of echolucency; type IV, uniformly echogenic lesions (equivalent to homogeneous); and type V, unclassified plaques, mainly calcinated.

Statistical analysis

All values of blood lipids were expressed as mean ± SD. Multiple linear regression was used to test the association between cholesterol and LDL, HDL and triglycerides. Logistic regression was used to evaluate the association between the hypoechogenic and echogenic plaques and blood lipids as well as risk factors. The mean difference was considered significant at a level of $p<0.05$.

Results

Initially, carotid plaques were divided into five classes. For the purpose of further analysis, the plaques were reclassified into two groups according to the contribution of echogenicity or echolucency. Type I (Fig. 1) and type II represented hypoechogenic group, while types III, IV and V were pooled in echogenic group. Preliminary analysis included testing of association of blood lipoproteins with cholesterol levels. In the model of linear regression, cholesterol was introduced as an independent variable, while LDL, HDL and triglycerides were used as dependent variables. The model fitted the data very well

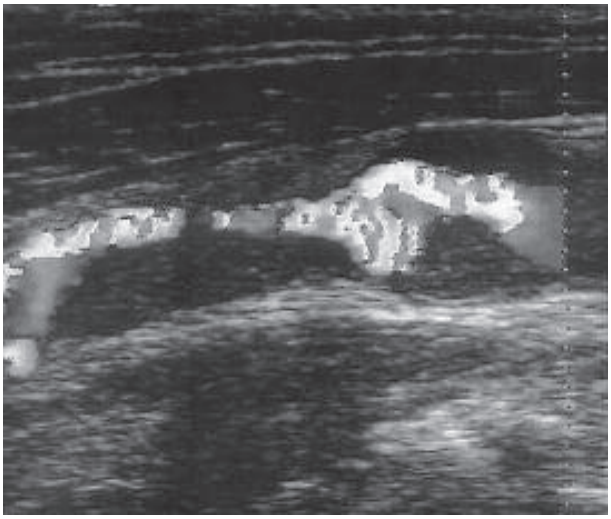

Fig. 1. A hypoechogenic plaque

(r^2=0.73, p<0.001), and it was significant. LDL, HDL and triglycerides appeared to be significant in the model. Thus, we tested the reliability of the data. The results are shown in Table 1.

The association between the type of plaque with HDL, LDL and triglycerides is presented in Table 2. In the model of logistic regression, the type of plaque (0 = hypoechogenic, 1 = echocgenic) was introduced as a dependent variable. HDL, LDL and triglycerides were independent variables. The model fitted the data moderately well (Cox & Snell = 0.19, p<0.001), and it was significant. HDL was positively and significantly (p<0.01) associated with echogenic plaques. It showed the strongest association. In addition, LDL appeared to be significantly (p<0.01) and positively associated with hypoechogenic plaques. Triglycerides did not reach the level of significance.

Logistic regression was used to evaluate the association between the well recognized risk factors and type of plaque (Table 3). The type of plaque was introduced as a dependent variable (0 = hypoechogenic, 1 = echogenic), while diabetes mellitus, arterial hypertension, age, gender and cigarette smoking served as independent variables. The model appeared to be moderately significant (Cox & Snell = 0.24, p<0.001). Arterial hypertension and age (p<0.01) were significantly and positively associated with echogenic plaque, while cigarette smoking was positively associated with hypoechogenic plaques (p=0.01). Diabetes mellitus and gender did not appear to be significant in the model.

Table 1. Cholesterol association with LDL, HDL and triglycerides

	Nonstandardized coefficients		Standardized coefficient	t	Significance
	B	SE	Beta		
LDL	0.949	0.037	0.886	25.736	0.000
HDL	0.254	0.119	0.071	2.140	0.033
TG	0.241	0.038	0.217	6.315	0.000

SE=standard error; HDL=high-density lipoprotein; LDL=low-density lipoprotein; TG=triglycerides

Table 2. Association between plaque type and blood lipids

	B	SE	Wald	df	Significance	Exp (B)
HDL	1.482	0.496	8.917	1	0.003	4.404
LDL	-0.818	0.169	23.531	1	0.000	0.441
TG	-0.185	0.157	1.384	1	0.239	0.831

SE=standard error; HDL=high-density lipoprotein; LDL=low-density lipoprotein; TG=triglycerides

Table 3. Type of plaque association with risk factors

Risk factor	B	SE	Wald	df	Significance	Exp (B)
Diabetes mellitus	0.328	0.296	1.222	1	0.269	1.388
Arterial hypertension	0.918	0.286	10.295	1	0.001	2.504
Age	0.108	0.023	21.646	1	0.000	1.114
Smoking	-0.749	0.292	6.568	1	0.01	0.473
Gender	0.036	0.287	0.016	1	0.901	1.036

Discussion

Echolucency on the subjective evaluation of carotid atherosclerotic plaques has previously been associated with an increased incidence of neurologic symptoms[12], and an increased incidence of asymptomatic brain infarction on CT scans[13]. One important new observation in the present study was that elevated plasma levels of LDL in the fasting or postprandial state predicted the appearance of hypoechogenic carotid atherosclerotic plaques. Studies have shown that LDL is the best lipid predictor for the extent of atherosclerosis[14]. Particularly elevated rates of the occurrence of arterial hypertension and hyperlipidemia were detected in younger individuals exposed to chronic stress[15].

A number of studies used ultrasound B-mode to measure wall thickness of the extracranial part of carotid arteries (intima-media thickness, or IMT) as an indicator of atherosclerotic diseases. There is evidence that an increase in IMT is linked with different risk factors for atherosclerosis, such as age, systolic blood pressure, a history of coronary heart disease, diabetes mellitus, levels of LDL, and smoking habits[16]. However, none of the previous studies evaluated LDL as a risk factor for hypoechogenic plaques. Furthermore, it has been suggested that plasma LDL reduction causes reduction in the lipid content of plaques with a lipid-rich core and thin fibrous cap, thereby reducing the likelihood that these otherwise vulnerable plaques will rupture, causing either an embolism or thrombosis leading to infarction. Double-blind intervention trials have demonstrated that reduction in plasma LDL levels leads to reduced progression or even regression of atherosclerotic plaques in coronary arteries[17]. The biologically important modification of LDL is oxidation leading to the formation of oxidized LDL (OX-LDL). Recently, there has been increasing evidence that OX-LDL may play a fundamental role in atherosclerosis[18]. Increased levels of OX-LDL are found in atherosclerotic plaques[19].

A search for determinants in the blood for hypoechogenic plaques suggests that triglyceride-rich lipoproteins in particular seem to predict for echolucent plaques[20]. In our study, we did not succeed in confirming this finding. Like LDL, triglyceride-rich lipoproteins can transfer from plasma into the arterial intima where such particles appear to be retained selectively[21]. It is important to note that triglyceride-rich lipoproteins of the size of chylomicrons (>75 nm) do not seem to enter the intima, whereas smaller triglyceride-rich lipoproteins are able to enter it[22]. In contrast to LDL, triglyceride-rich lipoproteins can without prior modification be taken up directly by macrophages to produce foam cells[23].

Other studies have shown that low levels of HDL cholesterol are associated with an increased risk of having echolucent, rupture-prone atherosclerotic plaques[24]. Our study also showed strong association of HDL with the type of plaque. Lower levels appeared to be associated with hypoechogenic plaques, and higher levels of HDL with echogenic plaques. Multiple regression analysis showed age to be directly and HDL cholesterol indirectly related to IMT ($p<0.05$)[25]. An underlying component of the inverse relationship between the plasma HDL levels and risk of cardiovascular disease is the ability of HDL to protect against or even to reverse LDL oxidation. Also, HDL protects against the development of atherosclerosis through its role in reverse cholesterol transport[24], thus increasing the level of HDL, decreasing the plaque lipid content, and promoting plaque organization.

Among risk factors we found a significant positive association of arterial hypertension and age with echogenic plaque, and negative association with hypoechogenic plaque. Hypertension is a risk factor for the development of atherosclerosis, although the mechanisms have not been well elucidated. The cardinal pathologic features of atherosclerotic lesion development include the presence of monocytes/macrophages and T cells, their localization in the large conduit or elastic arteries in the areas of low

shear stress, proliferation and migration to the intima of medial smooth muscle cells, deposition of increased amounts of connective tissue, and neovascularization[26]. Hypertensive arteries are thickened, and there may be an increased smooth muscle cell mass and/or cell number and increased deposition of connective tissue[27]. Noninvasively, it has been shown that carotid intima-media thickness correlates with blood pressure and is predictive of future cardiovascular events, and can be used as an endpoint in intervention trials. Placebo-controlled studies have shown the beneficial effects of calcium antagonists and beta-blockers, and contradictory responses with angiotensin converting enzyme inhibitors[28]. The mechanistic data showing that monocyte recruitment mechanisms involve redox-sensitive steps have been previously summarized and would lead one to predict that hypertension *per se*, even in the absence of the metabolic stress of hyperlipidemia, might be associated with increased recruitment of mononuclear cells into the arterial wall. In animal models, hypertension is associated with leukocyte adhesion, macrophage accumulation, smooth muscle cell migration and proliferation, and intimal thickening[28]. Lipid accumulation in foam cells and the formation of atherosclerotic plaque are generally not observed if plasma lipoproteins are low[29]. This could explain our association of arterial hypertension with more dense-echogenic plaques.

By analogy with previous reports, age turned out to be the strongest risk predictor of atherosclerosis. This may well be the expression of the intrinsic effects of aging but more likely reflects the cumulative component in the exposure to various risk factors. This indicates that the association of aging with echogenic plaques primarily reflects an advance of the atherosclerotic process[30].

Smoking doubles the risk of myocardial infarction and ischemic stroke[31]. It is known that cigarette smoking is associated with increased lipid peroxidation and therefore increased OX-LDL, which can lead to increased plaque lipid content and to the formation of hypoechogenic plaques[32]. Thus, cigarette smoking promotes the atherosclerotic process. However, it also affects other elements involved in the atherosclerotic process such as endothelium, increases vascular tone and platelet activation, and decreases the levels of free protein S[33].

Our study showed the association of LDL and HDL with hypoechogenic plaques. LDL showed positive, and HDL negative association. We did not establish an association between triglycerides and hypoechogenic plaques. Among other risk factors, aging and arterial hypertension showed positive association with echogenic plaques. Cigarette smoking showed positive association with hypoechogenic plaques. Diabetes mellitus and gender did not correlate with any type of plaques.

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Sažetak

LIPIDI U KRVI I KAROTIDNI PLAK

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Povišeni lipidi u krvi mogli bi biti udruženi s povećanom lipidnom jezgrom aterosklerotskog plaka i eholucencijom plaka na prikazu u B-modu. Ispitana je pretpostavka da plazmatske razine lipida u krvi predskazuju eholucenciju karotidnih aterosklerotskih plakova na prikazu u B-modu. U studiju je bilo uključeno ukupno 237 ambulantnih bolesnika srednje dobi od 62,9±10,2 godina, 189 od njih simptomatskih i 48 asimptomatskih. Svi su bolesnici u protekloj godini podvrgnuti pretrazi karotidnih arterija pomoću dupleks sonografije. Svi su bolesnici imali plakove u skupnoj ili unutarnjoj karotidnoj arteriji i u svih je učinjen lipidogram. Procjenjivani su i drugi rizični čimbenici kao što su arterijska hipertenzija, šećerna bolest, starenje i spol. U model logistične regresije uvedena je vrst plaka (hipoehogeni ili ehogeni) kao zavisna varijabla, uz LDL, HDL i trigliceride kao nezavisne varijable. Model je umjereno dobro odgovarao podacima (r^2=0,19; p<0,001). LDL i HDL pokazali su se značajnim predskazateljima (p<0,01). Udruženost vrste plaka s arterijskom hipertenzijom, šećernom bolešću, starenjem i spolom ispitana je logističnom regresijom. Model je umjereno odgovarao podacima (r^2=0,24; p<0,001). Arterijska hipertenzija i starosna dob bile su značajni (p<0,01) predskazatelji ehogenih plakova, dok je pušenje ukazivalo na hipoehogene plakove (p=0,01). Zaključeno je kako su LDL and HDL udruženi s hipoehogenim plakovima. LDL je pokazao pozitivnu, a HDL negativnu udruženost. Među ostalim čimbenicima rizika starenje i arterijska hipertenzija pokazali su pozitivnu udruženost s ehogenim plakovima, a pušenje pozitivnu udruženost s hipoehogenim plakovima.

Ključne riječi: *Arterioskleroza, fiziopatologija; Arterioskleroza, ultrasonografija; Lipidi, krv; Rizični čimbenici*