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ScienceDirect
Metabolism Clinical and Experimental 55 (2006) 1610–1615
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Relationship of low-density lipoprotein particle size to insulin resistance and intima-media thickness in nondiabetic Koreans

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Received 20 May 2006; accepted 24 July 2006

Abstract

The aim of this study was to investigate whether low-density lipoprotein (LDL) particle size is associated with insulin resistance and to explore the association between LDL particle size and preclinical atherosclerosis in nondiabetic Korean population. We measured the carotid intima-media thickness (IMT), LDL particle size, and insulin resistance in 136 nondiabetic subjects. Low-density lipoprotein particle size was significantly correlated with insulin resistance, but the independent risk factors of LDL particle size determined by the multiple regression analysis were age, triglyceride, and high-density lipoprotein cholesterol (HDL-C). Carotid IMT was associated with traditional risk factors of atherosclerosis, which are age, HDL-C, LDL cholesterol, systolic and diastolic blood pressure, but LDL particle size was not correlated with carotid IMT. We conclude that LDL particle size was associated with insulin resistance, but age, triglyceride, and HDL-C contributed independently to the variability in LDL particle size, and LDL particle size was not a predictor of preclinical atherosclerosis in nondiabetic Koreans.

1. Introduction

Low-density lipoprotein (LDL) particles consist of a number of subspecies that vary in size, density, and composition. The size of the LDL particles and the amount of free cholesterol in LDL decreases as the LDL density and the amount of lipoprotein increases [1]. The determinant factors of LDL particle size have not yet been clarified. However, it is known to be influenced by age, sex [2], genetic factors [3], and lifestyle factors such as diet and exercise [4]. Small dense LDL (sdLDL) particles have been associated with most individual components in insulin resistance syndrome such as hypertriglyceridemia and low concentration of serum high-density lipoprotein cholesterol (HDL-C). Hence, it is generally believed that LDL particle size may be associated with insulin resistance.

Small LDL particle size has been suggested to be associated with the development of atherosclerosis as measured by coronary angiography [5-10]. Patients with sdLDL particles have also been shown to have a 3-fold increased risk of myocardial infarction [5-7]. The Physician's Health Study [8], Stanford Five Cities Project [9], Quebec Cardiovascular Study [10], and other prospective studies were performed to assess the correlation of the LDL particle size and coronary artery disease. The results from these studies suggest that sdLDL particles were associated with increased risk of coronary artery disease. The Quebec Cardiovascular Study have reported the independent relationship between sdLDL particles and coronary artery disease, but the Physician's Health Study and Stanford Five Cities Project found that the correlation of coronary artery disease and the LDL particle size was no longer significant after adjustment for postprandial triglyceride (TG) and the ratio of total cholesterol to HDL-C; the LDL particle size was not an independent predictive factor of coronary artery disease.

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doi:10.1016/j.metabol.2006.07.022

In Korea, with the westernization of the lifestyle, cardiovascular disease is now an increasing problem. However, there have been few studies on the correlation of LDL particle size and atherosclerosis and the determinant factors of LDL particle size in nondiabetic Koreans.

The aim of this study was to investigate whether LDL particle size is associated with insulin resistance as measured with insulin tolerance test and to explore the association between LDL particle size and preclinical atherosclerosis as measured by ultrasound in the carotid artery of nondiabetic Korean population.

2. Methods

2.1. Subjects selection

The study population consisted of 136 individuals (47 males and 89 females) who visited Yongdong Severance Hospital for a health screening program. The age range was 31 to 70 years. Exclusion criteria were cardiovascular disease, clinical diabetes or clinically overt disease, treatment with cardiovascular medications that might disturb the measurements performed in the study, or unwilling to participate. This study was approved by our human research ethics committees. Informed consent was obtained from each participant.

2.2. Clinical characteristics

Height, weight, blood pressure, and waist circumference were measured. Body mass index was calculated as the weight in kilograms divided by the square of height in meters. Established questionnaire was used to evaluate the history of previous and current disease.

2.3. Low-density lipoprotein subtypes

Electrophoresis was performed using a 3% polyacrylamide gel and a Lipoprint system LDL subfractions kit (Quantimetrix, Redondo Beach, CA). The Liposure system (Quantimetrix) was used to assess the quality. In brief, 25 μL of sample was mixed with 200 μL of Lipoprint loading gel, and then placed upon the upper part of 3% polyacrylamide gel. After 30 minutes of that photopolymerization in room temperature, 60 minutes of electrophoresis with 3 mA for each gel tube was performed. Scanning was done 30 minutes after completion of electrophoresis. To quantitate, a scan was performed at 610 nm using Artixscan 1100 scanner (Microtek, Carson, CA) and an iMac personal computer (Apple Computer, Cupertino, CA). After scanning, electrophoretic mobility (Rf) and the area under the curve (AUC) were obtained qualitatively by using the NIH image program version 1.62 (US National Institutes of Health, Bethesda, MD). Low-density lipoprotein subfractions were calculated between the very low-density lipoprotein (VLDL) fraction with the Rf of 0 and the HDL fraction with the Rf of 1.0. Low-density lipoprotein was distributed from Rf 0.32 to Rf 0.64 as 7 bands, whose Rfs were 0.32, 0.38, 0.45, 0.51, 0.56, 0.60, and 0.64. They were defined as LDL1 to LDL7. Low-density lipoproteins 1 and 2 were defined as the large LDL and LDL3 to LDL7 were defined as small LDL. According to the data provided by the manufacturer, the intra-assay coefficients of variation (%) for LDL subfractions were as follows: LDL1, 1.67 to 3.58; LDL2, 2.19 to 16.8; LDL3, 1.65 to 11.79; LDL4, 2.45 to 4.53; LDL5, 1.72; LDL6, 4.62; and LDL7, 17.89. The corresponding interassay values were as follows: LDL1, 3.67 to 3.92; LDL2, 3.85 to 13.5; LDL3, 5.59 to 19.21; LDL4, 3.45 to 6.05; LDL5, 2.58; LDL6, 12.06; and LDL7, 33.9. The relative area of the lipoprotein fraction equivalent to each band was obtained. The mean LDL particle size (in Å) was provided automatically according to the relative area and the particle size in each LDL fraction by the LDL Lipoprint system. Based on the average size of the LDL particle, type A was classified as more than 268 Å, type I as between 265 Å and 268 Å, and type B, a pattern also known as sdLDL, as less than 265 Å [11].

2.4. Ultrasonographic evaluation of carotid arteries

Carotid intima-media thickness (IMT) was evaluated by a single operator with high-resolution B-mode ultrasonography on a single machine (Toshiba SSA-270A, Tokyo, Japan) with a 7.5-MHz linear array transducer. All recordings were obtained with the patient resting in a supine position, with the head turned slightly to the contralateral side. Intima-media thickness was the distance between the

Table 1
Clinical characteristics of subjects

	Female	Male	P[a]
No. of subjects	89	47	–
Age (y)	52.1 ± 9.0	50.4 ± 7.8	.265
BMI (kg/m^2)	23.1 ± 2.7	24.6 ± 2.62	<.01
WC (cm)	76.7 ± 7.5	86.3 ± 7.3	<.001
Smoking (%)	2 (2.2)	28 (59.6)	<.001
SBP (mm Hg)	121.9 ± 14.1	124.8 ± 12.3	.250
DBP (mm Hg)	78.7 ± 8.0	76.5 ± 9.8	.188
FBG (mmol/L)	5.13 ± 0.62	5.30 ± 0.54	.114
HbA_{1c} (%)	5.8 ± 0.5	5.9 ± 0.6	.212
C-peptide (nmol/L)	0.49 ± 0.18	0.54 ± 0.26	.191
Insulin (pmol/L)	37.6 ± 19.7	49.7 ± 32.1	.087
Total cholesterol (mmol/L)	5.11 ± 0.83	5.00 ± 0.70	.357
TG (mmol/L)	1.16 ± 0.83	1.51 ± 0.73	<.01
HDL-C (mmol/L)	1.47 ± 0.29	1.24 ± 0.22	<.001
LDL-C (mmol/L)	3.11 ± 0.74	3.05 ± 0.62	.624
LDL particle size (Å)	268.5 ± 4.4	265.8 ± 6.1	<.01
Type B (%)	19 (21.3)	18 (38.3)	<.05[b]
Kitt	3.8 ± 1.1	3.3 ± 1.2	<.01
Mean IMT (mm)	0.63 ± 0.12	0.68 ± 0.14	.062

Values are expressed as mean ± SD except for the frequency data. WC indicates waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose.

[a] P values of the χ^2 test between male and female for smoking (%) and type B (%), and P values of the Student t test between male and female for other variables.

[b] P = .056, after continuity correction.

Table 2
Pearson correlation coefficients between average LDL diameter and other clinical factors

	R	*P*
Age (y)	−0.185	<.05
BMI (kg/m^2)	−0.150	.088
WC (cm)	−0.203	<.05
Sex (male = 0, female = 1)	0.248	<.01
Smoking (nonsmoker = 0, smoker = 1)	−0.212	.232
SBP (mm Hg)	−0.159	.068
DBP (mm Hg)	−0.198	<.05
Total cholesterol (mmol/L)	−0.170	<.05
TG (mmol/L)	−0.635	<.001
HDL-C (mmol/L)	0.534	<.001
LDL-C (mmol/L)	−0.158	.067
HbA_{1c} (%)	−0.240	<.05
C-peptide (nmol/L)	−0.246	<.05
Insulin (pmol/L)	−0.128	.211
Kitt	0.233	<.01
Mean IMT (mm)	−0.172	.075

lumen intima interface and media adventitia interface. Measurements of carotid IMT were conducted at 3 differential plaque free sites: the greatest thickness and 2 other points, 1 cm upstream and 1 cm downstream from the site of the greatest thickness. The mean of the 3 determinations of right and left IMT was defined as mean IMT. Plaques, defined as a local thickness of more than 2 mm, were documented [12].

2.5. Insulin tolerance test

A short insulin tolerance test was performed and assessed by Kitt to evaluate insulin resistance in all individuals. After 12 hours of fasting, an 18G to 22G catheter was inserted into one arm, a 3-way was connected, and blood was obtained. In the other arm, an antecubital vein was secured to inject an insulin and dextrose solution. After the insertion of the catheter, patients were allowed to rest lying down for 20 to 30 minutes. Insulin diluted 100 times, insulin lispro 0.1 U/kg was injected. At 0 (before injection), 3, 6, 9, 12, and 15 minutes after the injection, blood was obtained through the 3-way connector and stored in an EDTA tube. Using the obtained blood, serum glucose was measured and the Kitt value was obtained using the following formula:

$$Kitt\ (\text{rate constant for plasma glucose disappearance}) = 0.693/t_{1/2} \times 100\ (\%/\text{min})$$ [13].

Table 3
Stepwise multiple regression analyses with average LDL particle size as a dependent variable

	Standardized coefficient (β)	*P*
TG (mmol/L)	−0.403	.000
HDL-C (mmol/L)	0.309	.003
Age (y)	−0.219	.016

R^2 = 0.48.

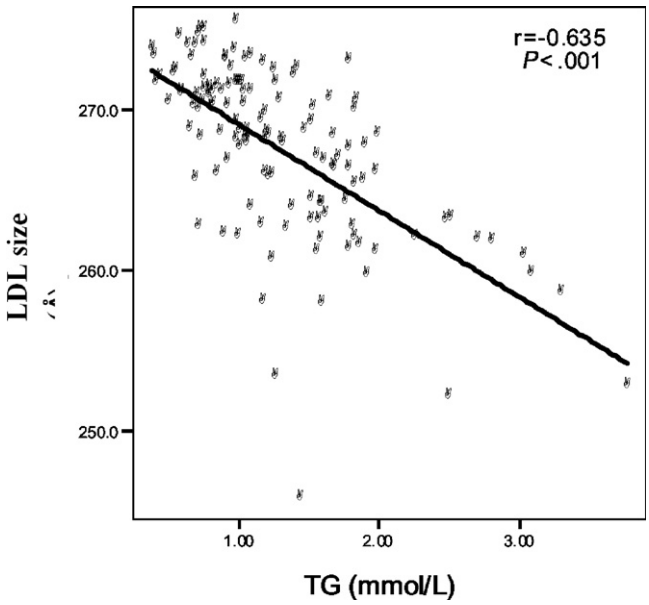

Fig. 1. Triglyceride concentration vs LDL particle size.

2.6. Biochemical characteristics

All measurements were obtained in the morning with the patient fasting from midnight on. Hemoglobin A_{1c} (HbA_{1c}) was determined by means of high-performance liquid chromatography (Variant II, Bio-Rad, Hercules, CA). Glucose was measured with a standard glucose oxidase reference method (747 automatic analyzer, Hitachi, Tokyo, Japan). Fasting serum insulin and C-peptide were determined by means chemiluminescence (radioimmunoassay kit, Daiichi, Tokyo, Japan). Total cholesterol, HDL-C, and triglyceride were measured with enzymatic color test

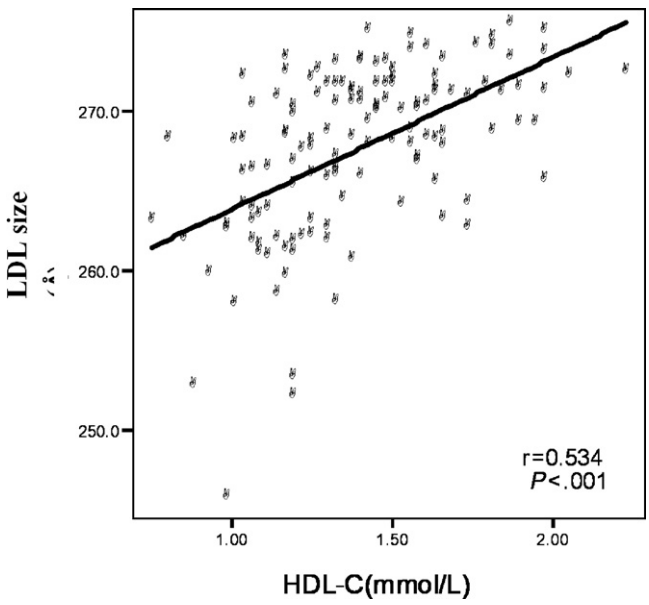

Fig. 2. High-density lipoprotein cholesterol concentration vs LDL particle size.

Table 4
Pearson correlation coefficients between carotid IMT and other clinical factors

	R	P
Age (y)	0.490	<.001
BMI (kg/m^2)	0.101	.307
WC (cm)	0.146	.162
Sex (male = 0, female = 1)	−0.180	.062
Smoking (nonsmoker = 0, smoker = 1)	0.034	.731
SBP (mm Hg)	0.298	<.01
DBP (mm Hg)	0.263	<.01
Total cholesterol (mmol/L)	0.111	.251
TG (mmol/L)	0.046	.635
HDL-C (mmol/L)	−0.251	<.01
LDL-C (mmol/L)	0.211	<.05
HbA_{1c} (%)	0.026	.824
Kitt	0.031	.755
LDL particle size (Å)	−0.172	.075

(Daiichi, Hitachi 747). Low-density lipoprotein cholesterol was calculated according to the Friedewald formula [14].

2.7. Statistics

All data were expressed as mean ± SD. Statistical analysis was performed with Student t test and χ^2 test. Correlation analysis was used to assess the significance of the relationship between LDL particle size and carotid IMT and other variables. To determine the predictable factors of LDL particle size, a multiple stepwise regression analysis was performed. All statistical analysis was performed using the SPSS for Windows 11.0 (SPSS, Chicago, IL), and P values less than .05 were considered to be statistically significant.

3. Results

3.1. Clinical and biochemical characteristics

There were 47 male subjects and 89 female subjects that participated in this study. When compared with the females, body mass index (BMI), waist circumference, and insulin resistance were higher in the males. The males had higher TG concentration and smoking rate, lower HDL-C, and smaller LDL particle size (Table 1).

3.2. Correlation analysis of average LDL particle size

The Pearson correlation analysis on each variable was performed to assess the correlation to the LDL particle size. The variables correlating to the LDL particle size were age, waist circumference, male sex, diastolic blood pressure, total cholesterol, TG, HDL-C, HbA_{1c}, C-peptide, and Kitt (Table 2).

3.3. Multiple stepwise regression analysis on the average LDL particle size

A multiple stepwise regression analysis of the LDL particle size and other risk factors was performed. Triglyceride, HDL-C and age were independent predictive factors of the LDL particle size (Table 3, Figs 1 and 2).

3.4. Analysis of the correlation to the carotid IMT

The variables showing the correlation to IMT in the Pearson correlation analysis were age, systolic and diastolic blood pressure, HDL-C, and LDL cholesterol (LDL-C). However, LDL particle size was not correlated with carotid IMT (Table 4).

4. Discussion

The results from the present study show that the LDL particle size is associated with insulin resistance as measured by insulin tolerance test, but there is no independent relationship to insulin resistance. In previous studies, Reaven et al [15], Mykkänen et al [16], Ambrosch et al [17], and Fagerberg et al [18] reported that sdLDL particles is associated with insulin resistance and that serum TG concentration modifies this relationship. In other studies, no certain relationship has been found between insulin resistance and LDL particle size; however, the LDL particle size showed a significant correlation to plasma TG concentration [19-22]. Actually, TG concentration was the strongest determinant of LDL size in this study. These results may be because LDL metabolism and its particle size are associated with VLDL metabolism. The precursor of sdLDL, β-pool LDL, is synthesized from VLDL1, and the precursor of large buoyant LDL, α-pool LDL, is synthesized from VLDL2. The synthesis of VLDL1 is increased with higher TG concentrations; thus, when TG concentration is elevated, the synthesis of β-pool LDL is also increased. This β-pool LDL donates cholesterol to VLDL1 by the reaction of cholesteryl ester transfer protein and receives TG from VLDL1. Consequently, β-pool LDL is converted to LDL with high TG concentration and low cholesterol. The TG is hydrolyzed by hepatic lipase and converted to small-diameter sdLDL [23]. Insulin has been known to be an important factor controlling the concentration of VLDL. It controls the influx of the substances required for the synthesis of TG to the liver and the release of free fatty acids degraded from adipose tissues [24]. It is not yet clear, however, whether insulin resistance is a direct cause of hypertriglyceridemia because the impairment of the delivery of plasma free fatty acid, which is another factor involved in hypertriglyceridemia, can increase insulin resistance [25]. Although we could not verify the association between LDL particle size and insulin resistance, it is evident that hypertriglyceridemia is associated with this correlation.

In addition, LDL particle size was positively correlated with serum HDL-C level, and HDL-C concentration was the independent determinant of LDL size as in previous studies [15,16,18,21]. It can be explained by the inverse relationship between HDL-C and VLDL triglyceride concentrations and related at least in part to hepatic lipase activity. Hepatic lipase modulates both LDL particle composition, resulting

in formation of sdLDL species, and remodeling of HDL particles [26].

The carotid IMT has been known to be a predictive marker of atherosclerosis [27,28]. We observed that age, systolic and diastolic blood pressure, plasma LDL-C, and HDL-C were correlated significantly to the average IMT value, like the other studies [12,29,30].

Our results showed that smoking did not correlate to the carotid IMT. This was thought to be due to a small number of subjects with a history of smoking. To better understand the influences of smoking on atherosclerosis, more thorough studies pertaining to the amount of smoking per day and the duration of smoking are needed [31].

In previous research, the correlation of obesity and abdominal obesity to the IMT varied depending on the study [29,30,32,33]. The conclusion of most of these studies was that there was no correlation [29,30,33]; in this study, the correlation of BMI and waist circumference to IMT was not significant.

Regarding the association of TG and atherosclerosis, study results differed from each other [29,30,32,33]. Ryu et al [34] reported that IMT was associated with postprandial TG concentration in patients with hypercholesterolemia.

In addition to traditional risk factors of atherosclerosis, sdLDL has been suggested to be associated with the development atherosclerosis, but again, this is not consistent finding [8-10]. Mechanisms responsible for the atherogenicity of sdLDL particles remain largely unexplained, but it has been suggested that small LDL particles penetrate the vascular intima more readily [35]. The vascular intima is more sensitive to oxidation because the antioxidant content is low and the concentration of polyunsaturated fatty acid is high [36]. The binding affinity to the LDL receptor is low, and the affinity to proteoglycan is high [37]. Hulthe et al [38] have clinically proven that as LDL particles become small, the carotid bulb IMT, the total IMT, and the IMT of the femoral artery become thickened. Nevertheless, such results are not conclusive. Campos et al [39] reported that residents of Costa Rica have been shown to have small LDL size compared with in Americans, and the incidence of coronary artery disease in the residents of Costa Rica was lower. Cho et al [40] also reported that a high-carbohydrate diet may be the one of the possible cause of the high TG concentration in the Korean population, which in turn promoted formation of sdLDL, but such a change in lipid profile may not lead to higher coronary heart disease risk.

In this study with nondiabetic Korean adults, the correlation of the LDL particle size to the carotid IMT was not statistically significant. Regarding these results, the possibility exists that the metabolism and characteristics of the sdLDL fractions in Koreans are different from those in whites.

Studies with a larger number of subjects would be essential to answer the question whether sdLDL play a crucial role in the development and progression of atherosclerosis in Koreans. The comparison and analysis of patients with symptomatic atherosclerosis to healthy individuals are also necessary. A study assessing if there is the difference between Koreans and whites regarding the permeability of vascular endothelium with high sdLDL, the sensitivity to oxidation, the reduced affinity to LDL receptors, and a strong affinity to proteoglycan needs to be performed.

In conclusion, LDL particle size was associated with insulin resistance, but age, TG, and HDL-C contributed independently to the variability in LDL particle size, and LDL particle size was not associated with preclinical atherosclerosis in nondiabetic Koreans.

Acknowledgement

This study was supported by a grant from the Seoul R&BD Program, Republic of Korea (10526), and the Korea Health 21 R&D Project, Ministry of Health &Welfare, Republic of Korea (03-PJ1-PG1-CH05-0005).

References

[1] Chapman MJ, Laplaud PM, Luc G, et al. Further resolution of the low-density lipoprotein spectrum in normal human plasma: physicochemical characteristics of discrete subspecies separated by density gradient ultracentrifugation. J Lipid Res 1988;29:442-58.

[2] McNamara JR, Campos H, Ordovas JM, et al. Effect of gender, age, and lipid status on low density lipoprotein subfraction distribution. Arterioscler Thromb 1987;17:483-90.

[3] Edwards KL, Mahaney MC, Motulsky AG, et al. Pleiotropic genetic effects on LDL size, plasma triglyceride, and HDL cholesterol in families. Arterioscler Thromb 1999;19:2456-64.

[4] Lamarche B, Lemieuz I, Despres JP. The small, dense LDL phenotype and the risk of coronary heart disease: epidemiology, pathophysiology and therapeutic aspects. Diabetes Metab 1999;25:199-211.

[5] Campos H, Genest JJ, Blijlevens E, et al. Low density lipoprotein particle size and coronary artery disease. Arterioscler Thromb 1992; 12:187-95.

[6] Austin MA, Breslow JL, Hennekens CH, et al. Low-density lipoprotein subclass patterns and risk of myocardial infarction. J Am Med Assoc 1988;260:1917-21.

[7] Griffin BA, Freeman DJ, Tait GW, et al. Role of plasma triglyceride in the regulation of plasma low density lipoprotein subfractions: relative contribution of small dense LDL to coronary heart disease. Atherosclerosis 1994;106:241-53.

[8] Stampfer MJ, Krauss RM, Ma J, et al. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. J Am Med Assoc 1996;276:882-8.

[9] Gardener CD, Fortmann SP, Krauss RM. Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. J Am Med Assoc 1996;276:875-81.

[10] St-Pierre AC, Ruel IL, Cantin B, et al. Comparison of various electrophoretic characteristics of LDL particles and their relationship to the risk of ischemic heart disease. Circulation 2001;104:2295-9.

[11] Hoefner DM, Hodel SD, O'Brien JF, et al. Development of a rapid, quantitative method for LDL subfraction with use of the Quantrimetrix Lipoprint LDL System. Clin Chem 2001;47:266-74.

[12] Kang ES, Kim HJ, Ahn CW, et al. Relationship of serum high sensitivity C-reactive protein to metabolic syndrome and microvascular complications in type 2 diabetes. Diabetes Res Clin Pract 2005;69:151-9.

[13] Akinmokun A, Selby PL, Ramaiya K, et al. The short insulin tolerance test for determination of insulin sensitivity: a comparison with the euglycaemic clamp. Diabet Med 1992;9:432-7.
[14] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
[15] Reaven GM, Chen YD, Jeppensen J, et al. Insulin resistance and hyperinsulinemia in individuals with small, dense low density lipoprotein particles. J Clin Invest 1993;92:141-6.
[16] Mykkänen L, Haffner SM, Rainwater DL, et al. Relationship of LDL size to insulin sensitivity in normoglycemic men. Arterioscler Thromb Vasc Biol 1997;17:1447-53.
[17] Ambrosch A, Mühlen I, Kopf D, et al. LDL size distribution in relation to insulin sensitivity and lipoprotein pattern in young and healthy subjects. Diabetes Care 1998;21:2077-84.
[18] Fagerberg B, Hulthe J, Bokemark L, et al. Low-density lipoprotein particle size, insulin resistance, and proinsulin in a population sample of 58-year-old men. Metabolism 2001;50:120-4.
[19] Lahdenperä S, Sane T, Vuorinen-Markkaola H, et al. LDL particle size in mildly hypertriglyderidemic subjects: no relation to insulin resistance or diabetes. Atherosclerosis 1995;113:227-36.
[20] Stewart MW, Laker MF, Dyer RG, et al. Lipoprotein compositional abnormalities and insulin resistance in type II diabetic patients with mild hyperlipidemia. Arterioscler Thromb 1993;13:1046-52.
[21] Suehiro T, Ohguro T, Sumiyoshi R, et al. Relationship of low-density lipoprotein particle size to plasma lipoproteins, obesity, and insulin resistance in Japanese men. Diabetes Care 1995;19:333-8.
[22] Slyper AH, Zvereva S, Schectman G, et al. Insulin resistance in not a major determinant of low density lipoprotein particle size. Metabolism 1997;46:1275-80.
[23] Packard CJ, Demant T, Stewart JP, et al. Apolipoprotein B metabolism and the distribution of VLDL and LDL subfractions. J Lipid Res 2000;41:305-18.
[24] Lewis GF, Steiner G. Acute effects of insulin in the control of VLDL production in humans. Implications for the insulin-resistant state. Diabetes Care 1996;19:390-3.
[25] Steiner G. Altering triglyceride concentrations changes insulin-glucose relationships in hypertriglyceridemic patients. Double blind study with gemfibrozil with implications for atherosclerosis. Diabetes Care 1991;14:1077-81.
[26] Kuusi T, Saarinen P, Nikkila EA. Evidence for the role of hepatic endothelial lipase in the metabolism of plasma high density lipoprotein in man. Atherosclerosis 1980;36:589-93.
[27] Pignoli P, Tremoli E, Poli A, et al. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation 1986;74:1399-406.
[28] Wong M, Edelstein J, Wollman J, et al. Ultrasonic-pathological comparison of the human arterial wall: verification of intima-media thickness. Arterioscler Thromb 1993;13:482-6.
[29] Bonithon-Kopp C, Scarabin PY, Taquet A, et al. Risk factors for early carotid atherosclerosis in middle-aged French women. Arterioscler Thromb 1991;11:966-72.
[30] O'Leary DH, Polak JF, Kronmal RA, et al. Distribution and correlates of sonographically detected carotid artery disease in the cardiovascular health study. Stroke 1992;23:1752-60.
[31] Weber F. Risk factors for subclinical carotid atherosclerosis in healthy men. Neurology 2002;59:524-8.
[32] Heiss G, Sharrett R, Barnes R, et al. Carotid atherosclerosis measured by B-mode ultrasound in populations: associations with cardiovascular risk factors in the ARIC study. Am J Epidemiol 1991; 134:250-6.
[33] Rubens J, Espeland MA, Ryu J, et al. Individual variation in susceptibility to extra cranial carotid atherosclerosis. Arterioscler Thromb 1988;8:389-97.
[34] Ryu JE, Howard G, Craven TE, et al. Postprandial triglyceridemia and carotid atherosclerosis in middle-aged subjects. Stroke 1992; 23:823-8.
[35] Nordestgaard BG, Nielson LB. Atherosclerosis and arterial influx of lipoproteins. Curr Opin Lipidol 1994;4:252-7.
[36] Dejager S, Bruckert E, Champman MJ. Dense LDL subspecies with diminished oxidative resistance predominate in combined hyperlipidaemia. J Lipid Res 1993;34:295-308.
[37] Hurt-Camejo E, Camejo G, Rosengreen B, et al. Differential uptake of proteoglycan selected subfractions of LDL by human macrophages. J Lipid Res 1990;31:1387-98.
[38] Hulthe J, Bokemark L, Wikstrand J, et al. The metabolic syndrome, LDL particle size, and atherosclerosis: the atherosclerosis and insulin resistance (AIR) study. Arterioscler Thromb 2000;20:2140-7.
[39] Campos H, Willett WC, Peterson RM, et al. Nutrient intake comparisons between Framingham and rural and urban Puriscal, Costa Rica. Associations with lipoproteins, apolipoproteins, and low density lipoprotein particle size. Arterioscler Thromb 1991;11: 1089-99.
[40] Cho HK, Shin G, Ryu SK, et al. Regulation of small dense LDL concentration in Korean and Scottish men and women. Atherosclerosis 2002;164:187-93.