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Metabolism Clinical and Experimental 54 (2005) 227–234

Metabolism
Clinical and Experimental

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Low-density lipoprotein size and subclasses are markers of clinically apparent and non-apparent atherosclerosis in type 2 diabetes

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Received 20 May 2004; accepted 17 August 2004

Abstract

The atherogenic lipoprotein phenotype is characterized by an increase in plasma triglycerides, a decrease in high-density lipoprotein (HDL), and the prevalence of small, dense low-density lipoprotein (LDL) particles. The present study investigated the clinical significance of LDL size and subclasses as markers of atherosclerosis in diabetes type 2. Thirty-eight patients with type 2 diabetes, total cholesterol of less than 6.5 mmol/L, and hemoglobin A_{1c} (HbA1c) of less than 9% were studied. Median age was 61 years, mean (± SD) body mass index 29 ± 4.3 kg/m^2, and mean HbA1c 7.1 ± 0.9 %. Laboratory parameters included plasma lipids and lipoproteins, lipoprotein (a), apolipoprotein (apo) A-I, apo B-100, apo C-III, and high-sensitivity C-reactive protein. Low-density lipoprotein size and subclasses were measured by gradient gel electrophoresis and carotideal intima media thickness (IMT) by duplex ultrasound. By factor analysis, 10 out of 21 risk parameters were selected: age, body mass index, systolic blood pressure, smoking (in pack-years), HbA1c, high-sensitivity C-reactive protein, lipoprotein (a), LDL cholesterol, HDL cholesterol, and LDL particle size. Multivariate analysis of variance of these 10 risk parameters identified LDL particle size as the best risk predictor for the presence of coronary heart disease ($P = .002$). Smaller LDL particle size was associated with an increase in IMT ($P = .03$; cut-off > 1 mm). Within the different lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, apo B, apo A-I, apo C-III, LDL particle size), LDL particle size was most strongly associated with the presence of coronary heart disease ($P = .002$) and IMT ($P = .03$). It is concluded that LDL size is the strongest marker for clinically apparent as well as non-apparent atherosclerosis in diabetes type 2.

1. Introduction

A distinct low-density lipoprotein (LDL) subclass pattern characterized by a predominance of small, dense LDL particles has been identified as being associated with a higher risk of coronary heart disease (CHD). Low-density lipoprotein particle subclasses can be determined by denaturing gradient gel analysis [1] or ultracentrifugation [2,3] and nuclear magnetic resonance [4]. The prevalence of the small, dense LDL particle phenotype, also called pattern B phenotype, is estimated to account for approximately 5% to 10% in men younger than 20 years, 30% to 35% in adults older than 20 years, and 5% to 10% in premenopausal women (reviewed in Ref. [5]). A significantly higher prevalence (up to 50%) was discovered in patients with type 2 diabetes [6]. Prospective results investigating the correlation of the LDL particle size with the development of CHD have been derived from in the Physician's Health Study [7], the population-based Stanford Five Cities Project [8], and the Quebec Cardiovascular Study [9-11]. In these studies, a reduced LDL particle diameter was a significant univariate predictor of CHD.

The worldwide incidence of type 2 diabetes mellitus is increasing and accounting for 6% to 12% of total health care expenditure in industrialized countries [12]. An association of LDL particle size with the cluster of risk factors that characterize the insulin resistance syndrome has also been demonstrated [13], and there is strong evidence that the small, dense LDL particles can be added to the group of changes described as the metabolic syndrome [14]. Hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), and an increased fraction of small, dense LDL particles are frequent lipoprotein

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doi:10.1016/j.metabol.2004.08.017

abnormalities in insulin resistance and type 2 diabetes mellitus [14-16] and are associated with increased cardiovascular mortality [17,18].

This is the first study to investigate the relationship of LDL size and LDL subclass distribution in patients having type 2 diabetes with clinically apparent atherosclerosis (CHD) and non-apparent atherosclerosis by determination of intima media thickness (IMT) of the arteria carotis in direct comparison with other risk factors.

2. Research design and methods

2.1. Subjects

Patients were recruited from the diabetes outpatient clinic of the Basel University Hospital Bruderholz, Switzerland. Written informed consent was obtained. A total of 38 patients fulfilled the inclusion criteria, that is, World Health Organization criteria for type 2 diabetes, hemoglobin A_{1c} (HbA1c) of less than 9%, total cholesterol of less than 6.5 mmol/L with or without hypolipidemic treatment, and no medical history for other systemic diseases. All patients were asked using a standardized questionnaire regarding history of diabetes, medication, complications due to diabetes, smoking, alcohol drinking, and cardiovascular events. Patients were classified as having CHD (CHD^+, n = 9) or not having CHD (CHD^-, n = 29). The diagnosis of CHD in 9 patients was based on documented myocardial infarction (hospital files) in 8 patients and documented coronary artery bypass graft surgery in 1 patient. The other 29 diabetic patients had no history of myocardial infarction and no history of angina pectoris in the past.

The study protocol was reviewed and approved by the Ethics Committee of Basel and Baselland, Switzerland.

2.2. Sample preparation

Overnight fasting blood samples were drawn while the subjects remained in a sitting position. Plasma was prepared from blood within 30 minutes and kept at 4°C. Plasma for analysis for LDL particle size was frozen at −80°C until further analysis (within 1-4 weeks).

2.3. Determination of lipids

Triglycerides and total cholesterol were measured enzymatically on the Beckman Coulter Synchron LX-20 analyzer. The direct HDL-C determination is a homogeneous assay using a polyanionic detergent to eliminate (by complex formation) interfering lipoproteins and at the same time to solubilize the HDL particles. Cholesterol derived from HDL particles was measured enzymatically. Low-density lipoprotein cholesterol was calculated using the Friedewald formula. Apolipoprotein (apo) C-III was analyzed turbidimetrically with polyclonal antibodies (WAKO Chemicals, Japan) adapted on the Synchron LX-20 chemistry analyzer.

2.4. Determination of apo B-100, A-I, lipoprotein (a), and high-sensitivity c-reactive protein

Determination of apo B-100, A-I, lipoprotein (a), and high-sensitivity c-reactive protein (hs-CRP) were performed on the Image immunonephelometer using mono- and polycloncal antibodies (system and methods handbook of Image Beckman Coulter Inc, Fullerton, Calif).

2.5. Nondenaturing polyacrylamide gradient gel electrophoresis

Nondenaturing polyacrylamide gradient gel electrophoresis of plasma was performed at 10°C to 14°C in 2% to 16% polyacrylamide gradient gels. Gels were subjected to electrophoresis for 24 hours at 125 V in Tris-borate buffer (pH 8.3) as described elsewhere [19,20]. Gels were fixed and stained for lipids in a solution containing oil red O in 60% ethanol at 55°C. Gels were placed on a light source and photographed with a Canon G3 digital camera. Migration distance for each absorbance peak was determined and the molecular diameter corresponding to each peak was calculated from a calibration curve generated from the migration distance of size standards of known diameter, which includes carboxylated latex beads (Duke Scientific, Palo Alto, Calif), thyroglobulin, and apoferritin (HMW Std, Pharmacia, Piscataway, NJ) having a molecular diameter of 380, 170, and 122 Å, respectively, and lipoprotein calibrators

Table 1
Subjects characteristics

	All (n = 38)	CHD^- (n = 29)	CHD^+ (n = 9)	*P*
Age (y)	61.1 ± 10.1	61.4 ± 11	60.2 ± 7	.9
Gender (F/M)	13/25	12/17	1/8	.1*
Systolic BP (mm Hg)	136 ± 16	134 ± 15	141 ± 19	.2
Diastolic BP (mm Hg)	86 ± 9	86 ± 10	86 ± 7	.7
BMI (kg/m^2)	29.0 ± 4	28.5 ± 4	31 ± 5	.2
HbA1c (%)	7.1 ± 0.9	7.1 ± 1	7.3 ± 0.9	.5
Hypolipidemic treatment %	47	31	100	.1*
Duration of diabetes (y)	8.3 ± 8	9.1 ± 8.8	5.8 ± 4.1	.4
Smoking (pack-years)	13.1 ± 17	9 ± 17	26.5 ± 15	.003
Alcohol (drinks per week)	3.1 ± 4.2	2.2 ± 3	5.9 ± 6	.02

P values of 19 parameters in Tables 1 and 2 were calculated by MANOVA for CHD^+ vs CHD^-.
Results are means ± SD.
* *P* values by χ^2 test.

Table 2
Lipids, apolipoproteins, hs-CRP, LDL size, and IMT in diabetic patients with and without CHD

	All (n = 38)	CHD^- (n = 29)	CHD^+ (n = 9)	*P*
Total cholesterol (mmol/L)	4.74 ± 0.9	4.93 ± 0.9	4.14 ± 0.6	.02
LDL-cholesterol (mmol/L)	2.84 ± 0.9	2.99 ± 0.9	2.17 ± 0.5	.02
HDL-cholesterol (mmol/L)	1.05 ± 0.27	1.1 ± 0.3	0.86 ± 0.1	.02
Triglycerides (mmol/L)	1.88 ± 1	1.72 ± 0.9	2.37 ± 1.28	.1
Apo B-100 (g/L)	1.07 ± 0.3	1.09 ± 0.3	1.0 ± 0.24	.4
Apo A-I (g/L)	1.46 ± 0.3	1.51 ± 0.4	1.31 ± 0.21	.2
Apo C-III (mg/L)	116 ± 47	109 ± 46	134.6 ± 48	.2
hs-CRP (mg/L)	3.19 ± 2	3.2 ± 2.2	3.15 ± 1.71	.9
Lipoprotein (a) (g/L)	0.25 ± 0.32	0.2 ± 0.3	0.32 ± 0.28	.3
LDL particle size (Å)	260.7 ± 7.2	262.7 ± 6	254.2 ± 6.9	.002
Intima media (mm)[a]	0.92 ± 0.2	0.88 ± 0.2	1.05 ± 0.2	.01/0.03[b]

P values of 19 parameters in Tables 1 and 2 were calculated by MANOVA for CHD^+ vs CHD^-.
Results are means ± SD.
[a] n = 36, CHD^- n = 27, CHD^+ n = 9.
[b] After adjustment for gender.

of previously determined particle size. Low-density lipoprotein subclass distribution (LDL I, IIA, IIB, IIIA, IIIB, IVA, and IVB) as percentage of total LDL was calculated as described previously [19].

2.6. Common carotid artery ultrasound

Common carotid ultrasound was performed using a Philips ATL 3500 device. The far walls of the right and left common carotid artery were scanned in 36 patients (not performed in 2 patients from the CHD^- group). Intima media thickness was evaluated by measuring the linear distance, perpendicular to the luminal axis, between 2 points defined by the ultrasonic interfaces, 1 cm distal to the carotid bifurcation. Mean IMTs were calculated in each patient from the measurements from both sides and which consisted of 3 independent far wall measurements.

2.7. Statistical analysis

Two dichotomous (gender, hypolipidemic treatment) and 19 continuous parameters (as listed in Tables 1 and 2) were analyzed. χ^2 tests for dichotomous (frequencies) and multivariate analysis of variance (MANOVA) for continuous parameters were computed. Factor analysis (orthotran/varimax transformation method) was used to identify the main factors, that is, the factors contributing the most information to the statistical model. By factor analysis, a reduction from 21 to 10 factors (age, body mass index [BMI], systolic blood pressure, smoking, HbA1c, hs-CRP, lipoprotein (a), LDL cholesterol [LDL-C], HDL-C, and LDL particle size) was possible without considerable loss of information. Multivariate analysis of variance was used for direct comparison of the discrimination of these 10 main factors regarding the presence/absence of CHD and IMT (cut-off >1 mm). In addition, MANOVA was used for the lipid factors only (total cholesterol, LDL-C, HDL-C, triglycerides, apo B, apo A-I, apo C-III, LDL particle size) regarding the presence/absence of CHD and IMT (cut-off > 1 mm). Multivariate analysis of variance statistics was also used for direct comparison of differences between males and females. Linear regression analysis was performed to calculate correlations of LDL particle size with the traditional lipid parameters and apolipoproteins. Calculations

Table 3
Lipids, apolipoproteins, hs-CRP, LDL size, and IMT in female and male diabetic patients

	All (n = 38)	Male (n = 25)	Female (n = 13)	*P*
Total cholesterol (mmol/L)	4.74 ± 0.9	4.65 ± 0.8	4.92 ± 1	.8
LDL-cholesterol (mmol/L)	2.84 ± 0.9	2.71 ± 0.8	2.96 ± 1.2	1
HDL-cholesterol (mmol/L)	1.05 ± 0.27	0.98 ± 0.21	1.18 ± 0.32	.04
Triglycerides (mmol/L)	1.88 ± 1	2.09 ± 1.1	1.47 ± 0.75	.1
apo B-100 (g/L)	1.07 ± 0.3	1.04 ± 0.3	1.1 ± 0.3	.7
apo A-I (g/L)	1.46 ± 0.3	1.39 ± 0.4	1.6 ± 0.53	.2
apo C-III (mg/L)	116 ± 47	119 ± 51	108 ± 38	.3
hs-CRP (mg/L)	3.19 ± 2	3.32 ± 1.9	2.93 ± 2.3	.5
Lipoprotein (a) (g/L)	0.25 ± 0.32	0.27 ± 0.3	0.22 ± 0.3	.1
LDL particle size (Å)	260.7 ± 7.2	259.8 ± 6	262.3 ± 8.7	.4
Intima media (mm)[a]	0.92 ± 0.2	0.97 ± 0.2	0.82 ± 0.2	.009

P values were calculated by MANOVA for female vs male.
Results are means ± SD.
[a] n = 36, male n = 25, female n = 11.

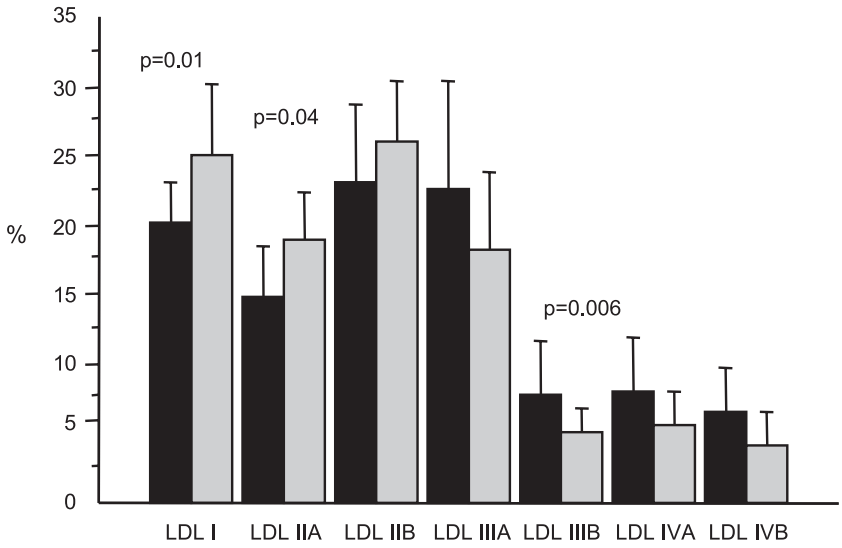

Fig. 1. Distribution of LDL subclasses (percentage) in diabetic patient with (n = 9) ■ and without CHD (n = 29) ■ . Results are means ± SD.

were performed using StatView 4.5 (Abacus Concepts Inc, Berkeley, Calif) and SPSS 9.0 for PC (SPSS Inc, Chicago, Ill). Results are presented as means (± SD).

3. Results

3.1. Subjects characteristics

Diabetic patients having and not having CHD were not different regarding age, systolic blood pressure, BMI, HbA1c, and duration of disease (Table 1). Smoking in pack-years and alcohol consumption in drinks per week were higher in CHD^+ compared with CHD^- patients (P = .003 and P = .02, respectively). All CHD^+ patients and 31% of CHD^- patients were on a hypolipidemic treatment. Hypolipidemic treatment consisted of statins (pravastatin [n = 10], simvastatin [n = 4], and atorvastatin [n = 3]). All of the CHD^+ patients and 72% of CHD^- patients were on antihypertensive treatment. Hypoglycemic treatment consisted of insulin in 6 patients, insulin and oral hypoglycemic drugs in 10 patients, oral hypoglycemic drugs alone in 17 patients, and dietary therapy alone in 5 patients. One out of thirteen women was on hormone replacement therapy and 3 women were younger than 55 years.

Table 4
Multivariate analysis of variance of 10 cardiovascular risk factors for CHD and IMT

	CHD (+/−) (MANOVA P)	IMT (>1 mm) (MANOVA P)
LDL-particle size (Å)	0.002	0.03
Smoking (pack-years)	0.005	0.003
LDL-cholesterol (mmol/L)	0.01	0.06
HDL-cholesterol (mmol/L)	0.01	0.06
BMI (kg/m^2)	0.2	0.8
Systolic BP (mm Hg)	0.2	0.6
Lipoprotein (a) (g/L)	0.5	0.06
HbA1c (%)	0.5	0.3
hs-CRP (mg/dL)	0.9	0.3
Age (y)	0.9	0.2

3.2. Lipids, apolipoproteins, and hs-CRP

In MANOVA, there were significant differences in total cholesterol (P = .02), LDL-C (P = .02), and HDL-C (P = .02) concentrations between diabetic CHD^+ vs CHD^- patients (Table 2). Diabetic patients having CHD had a nonsignificant tendency to higher triglycerides compared with CHD^- diabetic patients (P = .1). Women had significantly higher HDL-C (P = .04) and a nonsignificant trend toward lower triglyceride levels compared to men (P = .1; Table 3).

3.3. Diabetic patients having CHD have smaller, denser LDL particles

Low-density lipoprotein particle size in CHD^+ diabetic patients was smaller compared with CHD^- diabetic patients (P = .002; Table 2). There were no differences in LDL particle size between male and female diabetic patients (P = .4; Table 3). Diabetic patients having CHD had less LDL I (P = .01) and LDL IIA (P = .04) and more LDL IIIB (P = .006) compared with CHD^- patients (Fig. 1). In 2 different MANOVA models, first of a total of 10 risk parameters (age, BMI, systolic blood pressure, smoking, HbA1c, hs-CRP, lipoprotein (a), LDL-C, HDL-C, and LDL particle size) and second of 8 lipid parameters (total cholesterol, LDL-C, HDL-C, triglycerides, apo B, apo A-I, apo C-III, LDL particle size), LDL particle size showed the strongest association with the presence/absence of CHD (P = .002, P = .002, respectively; Tables 2 and 4).

3.4. Low-density lipoprotein size correlates with HDL-C, apo AI, triglycerides, and apo C-III

Low-density lipoprotein particle size in patients with type 2 diabetes correlated positively with other lipid parameters such as the ratio of LDL-C/apo B-100 ($R^2 = 0.24$, $P = .002$), HDL-C ($R^2 = 0.49$, $P < 0.0001$), and the major structural protein of HDL, apo A-I ($R^2 = 0.271$, $P = .0008$), and correlated negatively with plasma triglycerides ($R^2 = 0.49$, $P < 0.0001$) and apo C-III ($R^2 = 0.31$, $P = .0003$).

3.5. Carotideal IMT is associated with small, dense LDL

Far wall measurements of IMT were regarded as positive when exceeding 1 mm (ie, as a measure of the presence of apparent or clinically inapparent atherosclerosis). To determine the cut-off, a receiver operating characteristics analysis was performed (Fig. 2). Multivariate analysis of variance revealed that of 10 parameters (age, BMI, systolic blood pressure, smoking, HbA1c, hs-CRP, lipoprotein (a), LDL-C, HDL-C, and LDL particle size), LDL particle size was the second strongest associated with IMT ($P = .03$; Fig. 3) after smoking ($P = .003$; Table 4). Of the 8 lipid parameters (total cholesterol, LDL-C, HDL-C, triglycerides, apo B, apo A-I, apo C-III, LDL particle size), LDL particle size was the most strongly associated with IMT ($P = .03$). Patients having CHD had increased IMT compared with CHD^- patients ($P = .01$/$P = .03$ after correction for gender; Table 2). Men had increased IMT compared to women ($P = .009$; Table 3).

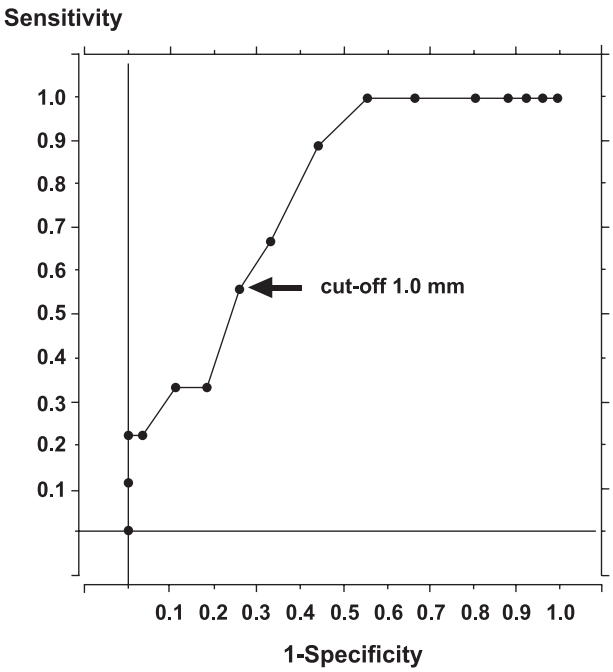

Fig. 2. Receiver operating characteristics curve for IMT. Sensitivity and 1-specificity dependent on the respective cut-off value. Based on the receiver operating characteristics curve, an arbitrary cut-off value of 1 mm was selected for further analyses.

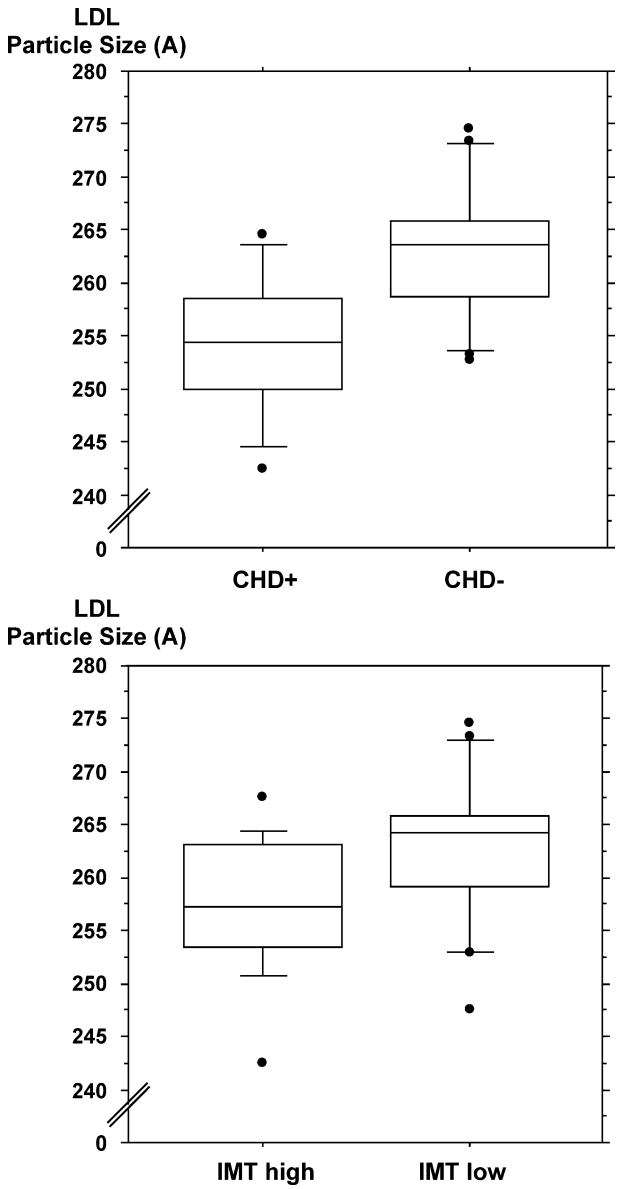

Fig. 3. Upper panel box plots (median, 10%, 25%, 75%, 90%, single values) of mean LDL particle sizes in diabetic patients with (CHD^+; n = 9) and without CHD (CHD^-; n = 29). Lower panel box plots (median, 10%, 25%, 75%, 90%, single values) of mean LDL particle sizes in diabetic patients with IMT above a cut-off of 1 mm (IMT high; n = 15) and with IMT below 1 mm (IMT low; n = 21).

3.6. Effects of hypolipidemic treatment

Lipid-lowering therapy did not result in a significant difference of mean LDL particle size (258.2 Å (±6.65) vs 262.7 Å (±7.3); $P = .06$).

4. Discussion

The present study is the first report in a western population demonstrating that diabetic patients with manifest CHD have decreased LDL particle sizes and altered LDL subclass distributions, that is, specifically more LDL

III-B and less LDL I and LDL II as compared with diabetic patients without established CHD. Multivariate analysis revealed that LDL size was the strongest marker of CHD as compared with 9 other established cardiovascular risk factors, including plasma lipids and lipoproteins. Our findings of a smaller average LDL particle size are in accordance with recently published findings of Koba et al [21] demonstrating decreased LDL size in Japanese men with CHD irrespective of the presence of diabetes. However, our results are not in line with a Finnish study that found no difference of LDL size in elderly hypercholesterolemic diabetic subjects with and without coronary artery disease. In this latter study the authors had concluded that LDL size was not a predictor of coronary events in these subjects [22]. The main reason for these discrepancies might be a survival bias because of the investigation of elderly people in the Finnish study. Furthermore, the Finnish subjects had much higher LDL-C concentrations as compared with the subjects in the present study. This is, however, not a typical feature of diabetic dyslipidemia. Therefore, the possibility to detect associations between the LDL particle size and CHD events might have been much lower in the Finish study. In the present study, 47% of the diabetic patients and all of the CHD^+ patients were currently under hypolipidemic statin treatment. We cannot exclude that baseline lipid values in CHD^+ subjects could have been different before initiation of hypolipidemic treatment. However, hypolipidemic treatment with statins may result in a shift to larger LDL particle size [23,24]. Thus, our finding of a nonsignificant tendency to smaller, dense LDL particles in diabetic patients under hypolipidemic treatment suggests that these patients had even a smaller LDL particle size before initiation of hypolipidemic treatment. These results underline the value of a decreased LDL size as a marker of cardiovascular risk. Other possible interactions that may affect our conclusions of altered LDL particle size are a nonsignificant tendency to higher systolic blood pressure, a nonsignificant increase in BMI, and more smoking in CHD^+ subjects. However, these cardiovascular risk factors were also included in multivariate testing, therefore, ruling out such limitations with a very high probability. We also demonstrated that LDL size is significantly associated with carotis IMT in patients with type 2 diabetes and MANOVA revealed that LDL size was the second strongest predictor of IMT, after smoking, when compared with 9 other cardiovascular risk factors and the strongest of all lipid parameters. An increased IMT is considered a reliable surrogate marker of early atherosclerosis and it has been demonstrated that small, dense LDL is independently related to common carotid artery IMT in 50-year-old men [25]. Intima media thickness has been shown to correlate significantly with the presence of CHD and to predict coronary events [26-29]. The finding of increased IMT in CHD^+ subjects is in accordance with the literature [30], but is limited due to a gender effect on IMT in the present study. Interestingly, significant relationships of IMT with other lipid parameters such as LDL-C [31] and apo B [30] have been demonstrated in other studies using larger sample sizes as compared with our study.

Diabetic dyslipidemia consists of hypertriglyceridemia, low HDL-C, and an increased fraction of small, dense LDL particles [14-16], whereas LDL or total cholesterol are generally not increased in diabetic patients except for a slight increase of LDL-C in women (UKPDS) [32]. This, however, does not explain increased cardiovascular mortality [17]. Using nuclear magnetic resonance it has been shown that lipoprotein changes in diabetes type 2, including increased large very-low-density lipoprotein (VLDL) particle concentrations and small, dense LDL, can be attributed primarily to the underlying insulin resistance and that these changes are not fully apparent in the conventional lipid panel [4]. In patients with type 1 diabetes mellitus, male gender and poor glycemic control were associated with a more atherogenic nuclear magnetic resonance lipoprotein profile [33]. The features of diabetic dyslipidemia were confirmed in the present study showing positive correlations of LDL size with HDL-C and apo A-I and negative correlations of LDL size with plasma triglycerides and apo C-III. The association of the LDL particle size with apo C-III is most likely explained by a concomitant increase of triglyceride-rich lipoproteins, namely, large VLDL 1 in type 2 diabetes [34]. The strong relationship of LDL size and triglycerides is based on their importance as substrates for the size reduction of LDL particles: By exchange of cholesteryl esters with triglycerides, LDL and HDL can become triglyceride-enriched and can be further processed by lipases. Deckelbaum et al [35] described profound changes in the physicochemical composition of both LDL and HDL particles with increasing triglyceridemia, whereas core cholesterol esters were progressively depleted and replaced by triglyceride molecules. In addition, the production of large triglyceride-rich VLDL 1 is dependent on triglyceride availability and VLDL 1 is associated with smaller, denser LDL particles (reviewed in Ref. [5]).

The atherogenic lipoprotein phenotype resembles dyslipidemia in diabetes type 2. It has been demonstrated that a predominance of small, dense LDL is associated with a 2- to 4-fold increased cardiovascular risk (reviewed in Ref. [5]). Several reasons have been suggested for the atherogenicity of small, dense LDL: Smaller, denser LDLs are taken up more easily by arterial tissue than larger LDLs [36], suggesting greater transendothelial transport of smaller particles. In addition, smaller LDL particles have decreased receptor-mediated uptake and increased proteoglycan binding [37-40]. Several studies reported that LDL subfractions differ in susceptibility to in vitro oxidative stress, a factor of significance in atherogenesis [41-43]. Altered properties of the surface lipid layer associated with reduced content of free cholesterol [42], diminished antioxidant content [44], and increased content of polyunsaturated fatty acids [41] might contribute to enhanced oxidative susceptibility of small, dense LDL.

It is concluded that LDL size in diabetes type 2 is a marker of clinical apparent (CHD) and non-apparent (IMT) atherosclerosis. Hence, LDL size is a promising parameter for estimating individual cardiovascular risk in diabetes type 2.

Acknowledgments

KB was supported by an unrestricted research grant from AstraZeneca AG, 6301 Zug, Switzerland, and from the FAG, Basel, Switzerland. We wish to thank Dr Ronald M. Krauss from Lawrence Berkeley National Laboratories, California, for providing lipoprotein calibrators of previously determined particle size for gradient gel electrophoresis and for his scientific advice.

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