Prehypertension in dyslipidemic individuals; relationship to metabolic parameters and intima-media thickness

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Introduction. Like hypertension, prehypertension is associated with cardiovascular disease.

Aims. The aim of this study was to evaluate: a) the prevalence of prehypertension/hypertension in individuals with various dyslipidemic phenotypes; b) the relation between blood pressure (BP) and other risk factors for atherosclerosis; c) atherogenic potential of prehypertension by the assessment of intima-media thickness of the arteria carotis communis (IMT).

Methods. 667 clinically asymptomatic subjects were divided into four dyslipidemic phenotypes (DLP) according to apolipoprotein B (apoB) and triglycerides (TG): DLP1 (n=198, normo-apoB/normo-TG), DLP2 (n=179, normo-apoB/hyper-TG), DLP3 (n=87, hyper-apoB/normo-TG), DLP4 (n=203, hyper-apoB/hyper-TG). DLP1 served as a control group.

Results. There was significantly higher prevalence of prehypertension and hypertension in subjects with dyslipidemia (DLP2 43.0%, 41.3%; DLP3 42.5%, 29.9%; DLP4 42.4%, 47.8%) than in normolipidemic individuals (DLP1 32.8%, 20.2%). Systolic and diastolic blood pressure (SBP + DBP) correlated with age, total cholesterol, TG, non-HDL-cholesterol, body mass index and waist circumference; SBP additionally with C-peptide, fasting glycemia; DBP additionally with apoB, homeostasis model assessment (HOMA) and plasminogen activator inhibitor-1. The IMT of hypertensive and of prehypertensive subjects was higher than that of subjects with normal BP in all DLPs.

Conclusions. The prevalence of prehypertension was higher in all dyslipidemic patients. The common prevalence of prehypertension/hypertension was highest in the hypertriglyceridemic subjects. Prehypertensive and hypertensive patients had higher IMT than normotensive individuals in all DLPs.

Key words: prehypertension, hypertension, dyslipidemia, insulin resistance, intima-media thickness

Received: October 3, 2011; Accepted with revision: April 12, 2012; Available online: June 1, 2012
<http://dx.doi.org/10.5507/bp.2012.046>

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INTRODUCTION

Prehypertension has been defined as systolic blood pressure (SBP) 120 to 139 or diastolic blood pressure (DBP) 80 to 89 mm Hg, based on two or more properly measured seated blood pressure (BP) readings on each of two or more office visits¹. Prehypertension tends to increase in severity over time² and associates with increased incidence of cardiovascular disease (CVD), particularly in those with BP levels in the 130 to 139/85 to 89 mm Hg range^{3,4}. Compared with normal BP, prehypertension has been associated with a 27% increase in all-cause and 66% increase in CVD mortality⁵. A study of 1999 to 2000 NHANES data has suggested that 64% of prehypertensive subjects have ≥ 1 other abnormal CVD risk factors, the percentage increased to 94% in those ≥ 60 years of age⁶. The risk ratios for obesity, dyslipidemia, metabolic syndrome, and diabetes are all greater in prehypertensive than normotensive subjects^{7,8}. The dyslipidemias represent heterogenic metabolic disorders. Sniderman suggested an algorithm of dyslipidemia classification based on apolipoprotein B (apoB)

and triglyceride (TG) concentrations⁹. The classification divides dyslipidemias into four dyslipidemic phenotypes (DLP) on the basis of apoB and TG concentrations: DLP 1 (normo-apoB / normo-TG), DLP 2 (normo-apoB / hyper-TG), DLP 3 (hyper-apoB / normo-TG) and DLP 4 (hyper-apoB / hyper-TG). Assessment of ApoB used instead of LDL cholesterol (LDL-C) in this diagnostic algorithm is rational and fully justified. ApoB is a better predictor for the risk of coronary artery disease than total cholesterol (TC), LDL-C and non-HDL cholesterol (non-HDL-C). This has repeatedly been shown in a large number of prospective epidemiological studies dealing with lipids and apoB (ref.¹⁰).

The aims of the present study were to investigate: the prevalence of prehypertension and hypertension in dyslipidemic individuals without clinical manifestation of atherosclerosis; the relation between blood pressure and other risk factors for atherosclerosis-and the atherogenic capacity of prehypertension by assessment of the intima-media thickness of the arteria carotis communis (IMT), as a surrogate marker of subclinical atherosclerosis manifestation.

MATERIALS AND METHODS

Study design and subjects

The study was carried out as a cross-sectional study on subjects who had been examined at the Lipid Center of the 3rd Department of Internal Medicine, University Hospital Olomouc, Czech Republic in the period October 2005 to June 2011. All subjects (patients with dyslipidemia, their spouses, relatives and healthy volunteers; $n=828$) filled out a questionnaire on their medical history, especially cardiovascular status, medication and smoking habits. All subjects were tested for an underlying cause of secondary hyperlipidemia: diabetes mellitus, hypothyroidism, hepatic or renal impairment and nephrotic syndrome. Subjects with these diagnoses were not enrolled in the study. Other exclusion criteria were history of clinically manifest atherosclerosis (coronary artery disease, cerebrovascular ischemic disease and peripheral arterial disease), hypolipidemic treatment in the previous 8 weeks, hormone therapy with estrogens and clinical presence of acute infectious disease or trauma. The study was reviewed and approved by the institutional Ethics Committee of the Faculty of Medicine and Dentistry and University Hospital and informed consent was obtained from all participants. Individuals who met the above mentioned criteria ($n=667$), were divided into four dyslipidemic phenotypes (DLP) based on apolipoprotein B and triglycerides: DLP 1 ($n=198$, apoB<1.2 g/L and TG<1.5 mmol/L), DLP 2 ($n=179$, apoB<1.2 g/L and TG $\geq$ 1.5 mmol/L), DLP 3 ($n=87$, apoB $\geq$ 1.2 g/L and TG<1.5 mmol/L), DLP 4 ($n=203$, apoB $\geq$ 1.2 g/L and TG $\geq$ 1.5 mmol/L). The use of TG value in this algorithm is justified as well. It had been proved that the amount of small dense LDL increases with TG concentration 1.5 mmol/L (ref.^{9,11}). A value 1.2 g/L for apoB was chosen, because at this level the cardiovascular risk rapidly increased^{9,12}. This value corresponds to the 75th percentile of the North American population, the level chosen to define an elevated LDL-C (ref.^{13,14}). Subjects with DLP 1 - who were normolipidemic (normo-apoB / normo-TG) - served as a control group. The presence of metabolic syndrome was assessed according to National Cholesterol Education Program Adult Panel III (ref.¹⁵). The ten-year risk of having a heart attack using risk assessment tool based on information from Framingham Heart Study was estimated in all participants¹⁶.

Blood pressure measurement

Body mass index (BMI), waist circumference, SBP and DBP were determined. The auscultatory method of BP measurement with a properly calibrated and validated mercury sphygmomanometer was used. Persons were seated quietly for at least 5 min in a chair, with feet on the floor, and arm supported at heart level. An appropriate-sized cuff was used to ensure accuracy. The first and fifth Korotkoff sounds were used to identify SBP and DBP (ref.¹). At least three sitting BP measurement with a 30-second interval were taken and the mean from the last two was calculated. Subjects with SBP $\geq$ 120 and

< 140 or DBP $\geq$ 80 and < 90 mmHg were defined as prehypertensive. Patients treated by antihypertensive drugs, or with SBP $\geq$ 140 or DBP $\geq$ 90 mmHg were taken as hypertensive¹. There was a substantial part of treated patients within the hypertensive group. Hypertensive patients with DLP 1 ($n=40$) were treated by ACE inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs) in 37.5%, by calcium channel blockers (CaCBs) in 5.0%, by beta blockers (BBs) in 35.0%, and by diuretics in 12.5%. Patients with hypertension and DLP 2 ($n=74$) were treated by ACE-I or ARBs in 48.6%, by CaCBs in 18.9%, by BBs in 36.5%, by diuretics in 18.9%, and by imidazoline-1 receptor ligands (IRLs) in 9.5%; one patient was treated by alfa-metyldopa. Hypertensive patients ($n=26$) with DLP 3 were treated by ACE-I or ARBs in 26.9%, by CaCBs in 11.5%, and by BBs in 11.5%. Patients with hypertension and DLP 4 ($n=97$) were treated by ACE-I or ARBs in 50.5%, by CaCBs in 17.5%, by BBs in 35.0%, by diuretics in 20.6%, and by IRLs in 4.1%; one patient was treated by doxazosine.

Biochemical analyses

Venous blood samples were drawn in the morning after a 12 h fast. Total cholesterol, triglycerides and HDL-cholesterol were determined enzymatically on Modular SWA analyzer (Roche, Basel, Switzerland) using commercially available kits (Cholesterol SYS 917, Triglycerides GPO-PAP and HDL cholesterol plus, 3rd generation kits, Roche, Basel, Switzerland). Determination of HDL-C was made by a direct method without precipitation of apo B containing lipoproteins. LDL-C levels were calculated according to the Friedewald formula (for TG < 4.5 mmol/L). We also calculated non-HDL cholesterol (non-HDL-C = TC - HDL-C). Concentration of apoB and apolipoprotein A1 (apoA1) was determined immunoturbidimetrically on Modular SWA analyzer (TinaQuant Apo A1, TinaQuant Apo B kits, all Roche, Basel, Switzerland). High-sensitivity C-reactive protein (hs-CRP) was assessed by means of an ultra sensitive latex immunoturbidimetric method on Modular SWA analyzer (CRP latex TinaQuant kit, all Roche, Basel, Switzerland). Glycemia was determined by enzymatic-colorimetric method (Glucose GOD-PAP kit) on Modular SWA analyzer. Insulin was determined using the commercially available kits - Insuline (Immunotech, Marseille, France) using specific antibodies by IRMA (immunoradiometric assay) method. The result obtained was then used for calculation of the parameter of insulin resistance HOMA [homeostasis model assessment, described by Matthews et al.: fasting glycemia (mmol/L) * fasting insulin (mU/L) / 22.5] (ref.¹⁷). C-peptide and intact proinsulin were determined using the commercially available kits - C-peptide (Immunotech, Marseille, France) and Proinsulin (DRG Instruments GmbH, Marburg, Germany) using specific antibodies by IRMA method for C-peptide and radioimmune assay (RIA) method for proinsulin. Concentrations of insulin, proinsulin, C-peptide and hs-CRP were measured in the serum stored at -80° C. Serum levels of the soluble intercellular cell adhesion molecule-1 (s-ICAM-1) and plas-

minogen activator inhibitor-1 (PAI-1) were measured by enzyme-linked immunosorbent assay (ELISA) using commercially available standard kits s-ICAM-1 (Immunotech, Marseille, France) and PAI-1 (Technoclone, Vienna, Austria). These markers of endothelial damage were used because we previously found significant differences in their levels between individual DLPs (ref.^{18,19}).

IMT measurement

Ultrasound scanning of IMT was performed with a 10 MHz linear array transducer (Philips Sonos 5500, 2004). All measurements were performed with subjects in a supine position. The head was tilted to the one side at an angle of 45°. The longitudinal B-mode image of the common carotid artery (CCA) was displayed just before the widening of the bulb. When an optimal longitudinal image of the far wall of the CCA in the region of 1 cm proximally from the bulb was obtained, it was frozen on the R wave according to a simultaneous ECG and videotaped. Three video records were made on both CCA. IMT measurements were processed off-line using the software Image-Pro Plus (Version 4.0, Media-Cybernetics, Silver Spring, USA). The region under evaluation was the CCA wall 1-2 cm distant proximally from the mentioned border. The average of all mean IMT of three frozen images of both sides was chosen as the outcome variable. The measurement of IMT was made without knowledge of laboratory results.

Statistical analyses

All values are expressed as means $\pm$ SD or as median with 25 and 75 percentiles for variables with non-normal distribution. The Kolmogorov-Smirnov test was used to test for normal distribution. Variables with non-normal distribution (TG, proinsulin, insulin, C-peptide, HOMA, hs-CRP, PAI-1) were log transformed to normalize their distribution before statistical analysis. Differences in

means between groups were analyzed using ANOVA after adjustment for age, sex, BMI, and smoking. Differences in categorical variables were analyzed by χ^2 test. For statistical evaluation of correlations between parameters we used a univariate Pearson correlation analysis. Multivariate regression analysis was used for testing for an independent association between dependent and independent variables. Statistical analysis was performed using SPSS for Windows version 12.0 (Chicago, Illinois, USA). Probability values of $P < 0.05$ were considered as statistically significant.

RESULTS

Basic characteristics

Table 1 shows the biochemical and anthropometric characteristics in individual DLPs. Individuals with hyperapoB DLPs (DLP 3 and 4) had significantly increased total cholesterol and LDL-C; individuals with hyper-TG DLPs (DLP 2 and 4) had decreased HDL-C and apoA1 compared to normolipidemic subjects (DLP 1). Non-HDL-C and apoB/apoA1 significantly rose from DLP 1 to DLP 4. Subjects with hyper-TG DLPs (DLP 2 and 4) showed increased markers of insulin resistance (HOMA, C-peptide, insulin, proinsulin), obesity (BMI, waist circumference) and also increased prevalence of metabolic syndrome. They had higher blood pressure (SBP, DBP) and levels of PAI-1. Patient with DLP4 had significantly increased IMT and s-ICAM-1 levels.

Prevalence of hypertension and prehypertension in individual dyslipidemic phenotypes

Fig. 1 shows the prevalence of hypertension, prehypertension, and normal BP in DLPs. The prevalence of prehypertension and of hypertension was significantly higher in all dyslipidemic patients (DLP 2, 3, and 4) com-

Fig. 1. Prevalence of normal blood pressure, prehypertension and hypertension in individual dyslipidemic phenotypes.

DLP = dyslipidemic phenotype; DLP 1: apoB < 1.2g/L + TG < 1.5 mmol/L, DLP 2: apoB < 1.2 g/L + TG $\geq$ 1.5 mmol/L, DLP 3: apoB $\geq$ 1.2g/L + TG < 1.5 mmol/L, DLP 4: apoB $\geq$ 1.2g/L + TG $\geq$ 1.5 mmol/L.

Differences in hypertension and prehypertension between subgroups were analyzed with χ^2 test. Significant difference $P < 0.05$ at least – ^a vs. DLP 1; ^b vs. DLP 2; ^c vs. DLP 3; ^d vs. DLP 4.

Table 1. Basic characteristics in dyslipidemic phenotypes.

	DLP 1	DLP 2	DLP 3	DLP 4
n/men	198/67	179/102	87/36	203/108
Age (years)	39.5±15.5 ^{β,γ,δ}	43.6±14.0 ^{α,δ}	45.1±14.4 ^α	49.0±12.7 ^{α,β}
TC (mmol/L)	5.14±1.0 ^{b,c,d}	5.84±1.36 ^{a,c,d}	7.26±0.99 ^{a,b,d}	7.72±1.82 ^{a,b,c}
TG †(mmol/L)	1.0[0.77-1.2] ^{b,d}	2.28[1.76-3.73] ^{a,c}	1.27[1.01-1.44] ^{b,d}	2.57[2.01-3.76] ^{a,c}
HDL-C (mmol/L)	1.67±0.42 ^{b,d}	1.3±0.39 ^{a,c}	1.64±0.42 ^{b,d}	1.33±0.38 ^{a,c}
LDL-C (mmol/L)	3.02±0.84 ^{c,d}	3.14±0.79 ^{c,d}	5.04±1.01 ^{a,b}	4.97±1.3 ^{a,b}
non-HDL-C (mmol/L)	3.48±0.88 ^{b,c,d}	4.55±1.34 ^{a,c,d}	5.63±1.01 ^{a,b,d}	6.39±1.81 ^{a,b,c}
apoB (g/L)	0.87±0.19 ^{c,d}	1.0±0.15 ^{c,d}	1.39±0.19 ^{a,b}	1.50±0.28 ^{a,b}
apo A1 (g/L)	1.66±0.33 ^{b,d}	1.47±0.32 ^a	1.61±0.3	1.52±0.33 ^a
apoB/apoA1	0.54±0.16 ^{b,c,d}	0.69±0.18 ^{a,c,d}	0.9±0.24 ^{a,b,d}	1.05±0.38 ^{a,b,c}
glycemia (mmol)	4.86±0.56	5.14±0.71	4.92±0.65	5.24±0.87
Insulin †(mIU/L)	6.4[4.2-8.8] ^{b,d}	8.8[6.2-12.7] ^{a,c}	6.3[3.9-8.5] ^{b,d}	8.4[5.9-11.5] ^{a,c}
HOMA † (mIU*mmol/L ²)	1.4[0.9-2.0] ^{b,d}	1.9[1.4-3.0] ^{a,c}	1.4[0.9-1.9] ^{b,d}	1.8[1.3-2.8] ^{a,c}
C-peptide †(mg/L)	1.8[1.4-2.4] ^{b,d}	2.5[1.9-3.3] ^{a,c}	1.7[1.4-2.4] ^{b,d}	2.6[1.8-3.4] ^{a,c}
Proinsulin †(mIU/L)	9.3[7.1-12.5] ^{b,d}	12.9[9.8-18.1] ^{a,c}	10.5[7.6-13.8] ^b	12.0[9.4-17.6] ^a
hs-CRP † (mg/L)	1.0[0.5-2.3] ^d	1.3[0.7-3.2]	1.3[0.7-3.0]	1.8[1.0-3.5] ^a
SBP (mm Hg)	122.5±13.6 ^{b,d}	130.2±15.9 ^a	126.2±17.0	131.7±14.7 ^a
DBP (mm Hg)	75.8±9.2 ^{b,d}	80.0±9.4 ^a	78.7±7.8	81.7±8.0 ^a
BMI (kg/m ²)	24.0±4.0 ^{β,δ}	27.5±6.1 ^{α,γ}	24.8±2.9 ^{β,δ}	27.1±4.1 ^{α,γ}
Waist (cm)	79.8±11.7 ^{b,d}	91.1±13.3 ^{a,c}	83.3±9.9 ^{b,d}	91.4±11.8 ^{a,c}
MS ATP III (%)	3.0 ^{b,d}	45.8 ^{a,c}	2.3 ^{b,d}	49.3 ^{a,c}
IMT (mm)	0.59±0.12 ^d	0.66±0.14	0.67±0.11	0.72±0.14 ^a
PAI-1†(ng/ml)	57.5[35.0-82.9] ^{b,d}	74.7[46.4-99.4] ^a	69.2[44.0-92.0]	81.1[50.7-106.8] ^a
s-ICAM-1 (ng/ml)	490.1±143.2 ^d	521.4±213.3 ^d	482.1±148.3 ^d	567.1±202.0 ^{a,b,c}

DLP = dyslipidemic phenotype; DLP 1: apoB < 1.2g/L + TG < 1.5 mmol/L, DLP 2: apoB < 1.2 g/L + TG ≥ 1.5 mmol/L, DLP 3: apoB ≥ 1.2g/L + TG < 1.5 mmol/L, DLP 4: apoB ≥ 1.2g/L + TG ≥ 1.5 mmol/L

TC = total cholesterol, TG = triglycerides, HDL-C = HDL cholesterol, LDL-C = LDL cholesterol, non-HDL-C = non-HDL cholesterol (TC - HDL-C), apoB = apolipoprotein B, apoA1 = apolipoprotein A 1, HOMA = homeostasis model assessment [fasting glycemia (mmol/L) fasting insulin (mU/L) / 22.5], hs-CRP = high sensitivity C reactive protein, SBP = systolic blood pressure, DBP = diastolic blood pressure, BMI = body mass index, MS ATP III = metabolic syndrome diagnosed according to National Cholesterol Education Program Adult Panel III, IMT = intima-media thickness, PAI-1 = plasminogen activator inhibitor-1, s-ICAM-1 = soluble intercellular cell adhesion molecule-1

Values are expressed as mean ± S.D., for † (parameters with skewed distribution) median [25 and 75 percentiles].

Differences in variables between subgroups were analyzed with ANOVA after adjustment for age, sex, BMI and smoking. Significant difference p<0.05 at least – ^a vs. DLP 1; ^b vs. DLP 2; ^c vs. DLP 3; ^d vs. DLP 4. Significant differences in age and BMI (without adjustment) P<0.05 at least – ^α vs. DLP 1; ^β vs. DLP 2; ^γ vs. DLP 3; ^δ vs. DLP 4.

Parameters with skewed distribution (TG, proinsulin, insulin, C-peptide, HOMA, hs-CRP, PAI-1) were log transformed to normalize their distribution before statistical analysis.

pared to normolipidemic subjects (DLP 1). The odds ratio of the presence of prehypertension or hypertension in dyslipidemic subjects versus normolipidemic subjects are presented in Table 2. The cumulative prevalence of prehypertension/hypertension was also significantly higher particularly in hyper-TG DLPs (DLP 2 and 4). Subjects with DLP 1 had hypertension or prehypertension in 53.0% (105/198). Prehypertension or hypertension was found in 84.4% (151/179) of DLP 2 subjects and in 72.4% (63/87) of subjects with DLP 3. The highest prevalence of hypertension or prehypertension - 90.1% (183/203) was found in DLP 4.

Relationship of blood pressure with other parameters

As a substantial percentage of hypertensive patients were being treated by anti-hypertensive drugs (see above), which influence the level of BP, only normotensive and prehypertensive subjects were enclosed in the subsequent analysis. SBP correlated with age ($r=0.33$; $P<0.01$), total cholesterol ($r=0.14$; $P<0.01$), TG ($r=0.16$; $P<0.01$), non-HDL-C ($r=0.13$; $P<0.01$), fasting glycemia ($r=0.14$; $P<0.01$), C-peptide ($r=0.10$; $P<0.05$), BMI ($r=0.23$;

$P<0.01$) and waist ($r=0.32$; $P<0.01$). By using multivariate backward stepwise regression analysis SBP was independently predicted by total cholesterol, non-HDL, waist circumference in all dyslipidemic subjects (DLP 2+3+4) and additionally by fasting glycemia in hypertriglyceridemic individuals (DLP 2+4) - see table 3. DBP correlated with age ($r=0.25$; $P<0.01$), total cholesterol ($r=0.12$; $P<0.05$), TG ($r=0.13$; $P<0.01$), non-HDL-C ($r=0.12$; $P<0.05$), apoB ($r=0.16$; $P<0.01$), HOMA ($r=0.10$; $P<0.05$), BMI ($r=0.21$; $P<0.01$), waist ($r=0.26$; $P<0.01$) and PAI-1 ($r=0.20$; $P<0.01$). By using backward stepwise regression analysis DBP was independently predicted by total cholesterol, non-HDL-C, waist circumference, and PAI-1 in hypertriglyceridemic subjects (DLP 2+4), in addition by apoB in subjects with DLP2, and only by waist circumference and PAI-1 in subjects with DLP 3 - see Table 3.

IMT according to blood pressure in individual dyslipidemic phenotypes

IMT rose from DLP 1 to DLP 4 (see Table 1). The highest elevation of IMT was observed in patients with simultaneously elevated levels of TG and of apoB (DLP

Table 2. Odds ratios (95% confidence interval) of presence of prehypertension or hypertension in dyslipidemic subjects (DLP 2,3,4) versus normolipidemic subjects (DLP 1).

	Prehypertension	Hypertension
DLP 2 vs. DLP 1	1.545 (1.016-2.348)*	2.784 (1.763-4.397)**
DLP 3 vs. DLP 1	1.514 (0.902-2.543)*	1.684 (0.947-2.993)*
DLP 4 vs. DLP 1	1.504 (1.001-2.259)*	3.615 (2.321-5.523)***

DLP = dyslipidemic phenotype; DLP 1: apoB < 1.2g/L + TG < 1.5 mmol/L, DLP 2: apoB < 1.2 g/L + TG ≥ 1.5 mmol/L, DLP 3: apoB ≥ 1.2g/L + TG < 1.5 mmol/L, DLP 4: apoB ≥ 1.2g/L + TG ≥ 1.5 mmol/L.

* ~ $P<0.05$, ** ~ $P<0.01$, *** ~ $P<0.001$... statistical significance level

Table 3. Predictive values of independent predictors on the levels of systolic and of diastolic blood pressure by multivariate backward stepwise regression analysis in dyslipidemic individuals.

	DLP 2		DLP 3		DLP 4	
	SBP	DBP	SBP	DBP	SBP	DBP
TC	$\beta=0.878$ $P<0.001$	$\beta=0.522$ $P<0.001$	$\beta=1.351$ $P<0.001$	n.s.	$\beta=0.854$ $P<0.001$	$\beta=0.988$ $P<0.001$
non-HDL-C	$\beta=-0.655$ $P<0.001$	$\beta=-0.422$ $P<0.001$	$\beta=-0.946$ $P<0.001$	n.s.	$\beta=-0.625$ $P<0.001$	$\beta=-0.813$ $P<0.001$
apoB	-	$\beta=0.269$ $P<0.001$	-	n.s.	-	n.s.
glycemia	$\beta=0.242$ $P<0.001$	-	n.s.	-	$\beta=0.287$ $P<0.001$	-
waist	$\beta=0.528$ $P<0.001$	$\beta=0.368$ $P<0.001$	$\beta=0.587$ $P<0.001$	$\beta=0.580$ $P<0.001$	$\beta=0.482$ $P<0.001$	$\beta=0.498$ $P<0.001$
PAI-1	-	$\beta=0.259$ $P<0.001$	-	$\beta=0.416$ $P<0.001$	-	$\beta=0.322$ $P<0.001$

DLP = dyslipidemic phenotype, SBP = systolic blood pressure, DBP = diastolic blood pressure, TC = total cholesterol, non-HDL-C = non-HDL cholesterol (TC - HDL-C), apoB = apolipoprotein B, PAI-1 = plasminogen activator inhibitor-1, β (beta) = standardized coefficient of regression, P = statistical significance level

IMT (mm)

	DLP 1	DLP 2	DLP 3	DLP 4
IMT NBP (mm)	0.54±0.08 ^{c,d}	0.55±0.07	0.62±0.11 ^a	0.65±0.14 ^a
IMT PHN (mm)	0.62±0.12 ^d	0.64±0.13	0.67±0.10	0.71±0.15 ^a
IMT HN (mm)	0.71±0.14	0.73±0.13	0.72±0.10	0.75±0.12

Fig. 2. Intima-media thickness according to blood pressure in individual dyslipidemic phenotypes.

DLP = dyslipidemic phenotype; DLP 1: apoB < 1.2 g/L + TG < 1.5 mmol/L, DLP 2: apoB < 1.2 g/L + TG ≥ 1.5 mmol/L, DLP 3: apoB ≥ 1.2 g/L + TG < 1.5 mmol/L, DLP 4: apoB ≥ 1.2 g/L + TG ≥ 1.5 mmol/L.

IMT = intima-media thickness, NBP = normal blood pressure, PHN = prehypertension, HN = hypertension. Values are expressed as mean ± S.D. Differences in IMT between subgroups were analyzed with ANOVA after adjustment for age, sex, BMI and smoking. Significant difference $P < 0.05$ at least – ^a vs. DLP 1; ^b vs. DLP 2; ^c vs. DLP 3; ^d vs. DLP 4.

4). In the whole group of all participants IMT was thicker in prehypertensive (IMT=0.67±0.14; $P < 0.05$) and in hypertensive (IMT=0.73±0.12; $P < 0.05$) patients respectively than in normotensive individuals (IMT=0.57±0.10) after adjustment for age, sex, BMI and smoking. Fig. 2 shows differences of IMT in various groups according to BP and the presence of various DLP. IMT of hypertensive and of prehypertensive subjects respectively was higher than of subjects with normal BP within all DLPs. By comparison between DLPs the significant differences were found between IMT of normotensive (DLP 1 versus DLP 3, and DLP 4 respectively) and prehypertensive subjects (DLP 1 versus DLP 4). Because anti-hypertensive drugs could influence BP and IMT, only untreated subjects were enrolled in the further analysis. IMT correlated with age ($r=0.69$; $P < 0.001$), SBP ($r=0.35$; $P < 0.001$), DBP ($r=0.21$; $P < 0.01$), total cholesterol ($r=0.46$; $P < 0.001$), LDL-C ($r=0.39$; $P < 0.001$), non-HDL-C ($r=0.45$; $P < 0.001$), TG ($r=0.23$; $P < 0.01$), apoB ($r=0.36$; $P < 0.001$), C-peptide ($r=0.15$; $P < 0.01$), BMI ($r=0.23$; $P < 0.01$) and waist ($r=0.29$; $P < 0.01$). IMT correlated with 10-year coronary heart disease risk in the whole group ($r=0.48$, $P < 0.001$) and also in individual DLPs (DLP1 $r=0.52$; $P < 0.001$, DLP2 $r=0.47$; $P < 0.001$, DLP3 $r=0.38$; $P < 0.01$, DLP4 $r=0.36$; $P < 0.001$). By using multivariate backward stepwise regression analysis IMT was independently predicted only by age (beta=0.22±0.02; $P < 0.001$), total cholesterol (beta=0.15±0.02; $P < 0.001$), SBP (beta=0.38±0.05; $P < 0.001$) and waist circumference (beta=0.26±0.05; $P < 0.001$).

DISCUSSION

The results showed significantly higher prevalence of prehypertension/hypertension in clinically asymptomatic subjects with dyslipidemia (DLP 2, 3, and 4) than in normolipidemic individuals (DLP 1) even after adjustment for age, sex, smoking and body mass index. Cumulative prevalence of prehypertension or hypertension was the highest in the hypertriglyceridemic subjects (DLP 2 and 4). They had significantly increased blood pressure. SBP correlated with age, total cholesterol, TG, non-HDL-C, C-peptide, fasting glycemia, BMI and waist circumference. DBP correlated with age, total cholesterol, TG, non-HDL-C, apoB, HOMA, BMI, waist circumference and PAI-1.

Many cross-sectional studies of different populations demonstrated that prehypertensive individuals had higher total cholesterol, LDL-C, TG and lower HDL-C than normotensive subjects^{6-8,20-30}. Some prospective studies also showed that dyslipidemia could predict occurrence of incident hypertension by years³¹⁻³³. The mechanism by which dyslipidemia leads to BP elevation is only partially understood. Dyslipidemia causes endothelial dysfunction, the loss of vasomotor reactivity and arterial stiffness³⁴. We found total cholesterol, and non-HDL-C independent predictors for BP elevation. PAI-1 as a maker of endothelial dysfunction was independently associated with DBP in all dyslipidemic patients of this study, too. These findings may be explained by the suggesting pathogenetic mechanism. Lipid particles could activate recently identified liver X receptor, which is a potential regulator of renin expression^{32,35}. The activation of renin-angiotensin-aldosterone system (RAAS) increases BP and also leads (via angiotensin II) to PAI-1 expression³⁶. PAI-1 can promote

fibrosis, vascular remodeling, arterial stiffness and BP increase by preventing the activation of matrix metalloproteinases and the degradation of extracellular matrix by plasminogen activators and plasmin³⁷. The significant increase of blood pressure and the highest cumulative prevalence of prehypertension/hypertension were detected in hypertriglyceridemic subjects and the levels of PAI-1 were significantly elevated in these patients too.

Hypertriglyceridemic subjects also showed increased markers of insulin resistance and of abdominal obesity. Many papers found the association between insulin resistance and prehypertension^{8,38,39} or hypertension⁴⁰. Hyperinsulinemia directly increases sodium re-absorption in renal tubules and may lead to fluid retention^{41,42}. Insulin activates sympathetic nervous system, increases catecholamine levels and the activity of RAAS (ref.⁴³⁻⁴⁵). However, not insulinemia alone but insulin resistance is usually related to blood pressure in prehypertensive and hypertensive patients and it is able to predict incident hypertension⁴⁶⁻⁴⁸. There was not found correlation between insulin levels and BP in the present study, too. Only C-peptide and fasting glycemia correlated with SBP, HOMA with DBP. However, in multivariate regression analysis no more specific marker of insulin resistance (except fasting glycemia) rested to predict BP levels. SDP and DBP were independently predicted by waist circumference. Abdominal obesity seems to play an independent role in BP elevation of all dyslipidemic patients. Among various anthropometric measurements waist circumference was detected the best predictor for incidence of hypertension⁴⁹ and waist circumference was also independent predictor for progression of prehypertension to hypertension⁵⁰. The possible mechanism linking abdominal obesity with BP elevation is production of adipokines. Visceral fat produces more angiotensinogen and PAI-1 than subcutaneous fat⁵¹. The activation of RAAS leading to vasoconstriction and increase sodium re-absorption, together with chronic inflammation and endothelium dysfunction are probably the main causes of prehypertension and hypertension in patients with abdominal obesity.

The present study also showed increased IMT of prehypertensive, hypertensive patients respectively compared to normotensive individuals in all dyslipidemic phenotypes. IMT was independently predicted by age, total cholesterol, SBP, and waist circumference. It was closely related to 10-year coronary heart disease risk estimated using Framingham Risk Score¹⁵. Several papers also found IMT of the common carotid artery in patients with prehypertension or borderline hypertension thicker compared to normotensive controls^{52,53}. Many studies detected the increase of IMT in patients with dyslipidemia. Our findings showed cumulative effect of dyslipidemia and BP increase on IMT. We found significant differences between IMT of prehypertensive subjects according to DLPs after adjustment for age, sex, smoking and BMI. Prehypertensive patients with DLP 4 had the same IMT as normolipidemic patients with hypertension. While the second group should be treated by antihypertensive drugs, the pharmacological treatment for prehypertension has been still recommended only in patients with

diabetes mellitus, chronic kidney disease or coronary artery disease¹. Also assessment of global cardiovascular risk in clinically asymptomatic dyslipidemic middle-aged patients with prehypertension only by SCORE(ref.⁵⁴) or by Framingham Risk Score¹⁵ may not result to recommendation for hypolipidemic treatment. And thus measurement of IMT could constitute useful diagnostic tool for cardiovascular risk prediction and making decision on pharmacological treatment in these people. This non-invasive examination should be considered especially in asymptomatic dyslipidemic individuals with hyperapoB/hyperTG phenotype, who have not reached the level of risk for initiation of therapy based on clinical and laboratory data only.

CONCLUSION

The prevalence of prehypertension was significantly higher in all dyslipidemic patients compared to normolipidemic subjects. Common prevalence of prehypertension and hypertension was the highest in the hypertriglyceridemic subjects. Prehypertensive and hypertensive patients had higher IMT than normotensive individuals in all dyslipidemic phenotypes. Dyslipidemia and blood pressure have cumulative effect on IMT. IMT measurement should be considered in asymptomatic individuals with hyperapoB/hyperTG phenotype to improve estimation of their cardiovascular risk.

ABBREVIATIONS

ANOVA, Analysis of variance; ACE-I, Angiotensinogen-converting enzyme inhibitors; ApoA1, Apolipoprotein A1; ApoB, Apolipoprotein B; ARBs, Angiotensin II receptor blockers; BBs, Beta blockers; BMI, Body mass index; BP, Blood pressure; CaCBs, Calcium channel blockers; CCA, Common carotid artery; CVD, Cardiovascular disease; DBP, Diastolic blood pressure; DLP, Dyslipidemic phenotype; ELISA, Enzyme-linked immunosorbent assay; HDL, High density lipoprotein; HDL-C, HDL cholesterol; HOMA, Homeostasis model assessment; Hs-CRP, High sensitivity C reactive protein; IMT, Intima-media thickness; IRMA, Immunoradiometric assay; IRLs, Imidazoline-1 receptor ligands; LDL, Low density lipoprotein; LDL-C, LDL-cholesterol; NHANES, National Health and Nutrition Examination Survey; Non-HDL-C, Non-HDL cholesterol; PAI-1, Plasminogen activator inhibitor-1; RAAS, Renin-angiotensin-aldosterone system; RIA, Radioimmune assay; SBP, Systolic blood pressure; SPSS, Statistical package for the social sciences; S-ICAM-1, Soluble intercellular cell adhesion molecule-1; TC, Total cholesterol; TG, Triglycerides.

ACKNOWLEDGEMENTS

This work was supported by grant IGA MZCR NS/10284-3.

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