Dyslipidemic Hypertension: Distinctive Features and Cardiovascular Risk in a Prospective Population-Based Study

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Background: The prevalence, features, and risk of cardiovascular disease (CVD) in dyslipidemic hypertension (DH) was investigated in a prospective population-based study. Dyslipidemic hypertension was defined in terms of blood pressure, plasma triglycerides, and HDL-cholesterol consistent with the metabolic syndrome criteria of the National Cholesterol Education Program guidelines. High-normal or hypertensive values not meeting the other two criteria were designated as "simple hypertensives" (SH).

Methods: A sample of 2225 men and women and free of CVD at baseline were followed up for a mean of 4.1 years. The proportions of DH, SH, and normotensives were 16%, 37%, and 47%, respectively. All persons with DH had metabolic syndrome by definition, whereas metabolic syndrome formed 44.6% of SH. Fatal and nonfatal CVD, diagnosed by clinical findings and Minnesota coding of resting electrocardiograms, developed in 166 subjects.

Results: Compared to SH, sex- and age-standardized individuals with DH had significantly higher body mass index, apolipoprotein B, fasting insulin, glucose, and C-reactive protein levels, had higher prevalence of impaired fasting glucose and metabolic syndrome. Cox regression analysis revealed a 1.57-fold higher (confidence interval 1.08–2.28) hazard ratio (HR) for CVD in DH than in SH, after adjustment for sex, age, LDL-cholesterol, and smoking status. The sex- and age-adjusted HR of DH was furthermore 1.45-fold higher than the remaining subjects with metabolic syndrome ($P = .096$). Among persons with DH, age, presence of diabetes, and pulse pressure proved to be independent predictors for CVD. High LDL-cholesterol levels and fasting hyperinsulinemia were associated with borderline significantly elevated relative risks among dyslipidemic hypertensives.

Conclusions: Dyslipidemic hypertension, prevailing in 1 of every 6 adults, implicates characteristic features, confers excess CVD risk compared to the remainder of hypertensives and carries half the attributable cardiovascular risk due to metabolic syndrome. Am J Hypertens 2005;18:409–416 © 2005 American Journal of Hypertension, Ltd.

Key Words: Cardiovascular disease, dyslipidemic hypertension, hypertension, insulin resistance, metabolic syndrome.

Hypertension and dyslipidemia are established risk factors of prime importance, as well as constituting two of the three components of the metabolic syndrome as defined by the National Cholesterol Education Program (NCEP) guidelines (Adult Treatment Panel III).[1] In the broad sense dyslipidemia includes abnormality in LDL-cholesterol apart from that in plasma HDL-cholesterol or triglyceride levels. The term dyslipidemic hypertension (DH) was first used by Williams and associates[2] in 1988 in the context of familial DH, which they proposed as a genetic syndrome found in approximately 12% of patients with essential hypertension and 48% of the hypertensive sibships. The LDL-cholesterol abnormality was encountered half as frequently as the dyslipidemia of the insulin syndrome.[3] It has been stated that insulin resistance coexists in up to 50% of hypertensive individuals.[4] Nonfamilial forms of DH are more common than the familial ones; in fact, in a cross-sectional

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survey of two New England communities, the conjoint frequency of DH was reported as 15% of the participants, which was 1.49 times the frequency expected by chance.[5]

The extent of distingushing features of and the cardiovascular disease (CVD) risk involved with hypertension developing in the setting of insulin resistance, compared to that without this setting, is not well known. Hence, characteristic features of DH as defined in a standard way by the NCEP Adult Treatment Panel III [1] need to be explored further, as well as the CVD risk conferred by it in a prospective population-based study.

This article reports our findings with respect to DH among Turkish adults who have a higher prevalence of hypertension (46% of adults aged ≥30 years),[6] of low HDL-cholesterol,[7,8] and of the metabolic syndrome[9] than Western populations. The aims of this study are to evaluate prospectively 1) the relative prevalence of the hypertension groups, 2) the distinguishing features of DH, 3) the relative risks for fatal and nonfatal CVD of DH with respect to the remaining hypertensive and normotensive groups, and 4) the independent predictors of CVD within the DH group in a population sample representative of middle-aged and elderly Turkish adults.

Methods

Population Sample

A total of 2225 men and women were prospectively examined in this population-based study. Participants are from the cohort of the Turkish Adult Risk Factor Study, a prospective survey on the prevalence of cardiac disease and risk factors in adults in Turkey carried out periodically since 1990 in seven geographic regions of the country.[8] Because measurement of HDL-cholesterol levels had not been perfomed before the follow-up visit in 1997/1998, the latter examination formed the baseline. Further follow-ups were carried out in 2000/2001 and in 2002/2003. Participants were 28 years of age or older at baseline examination. The survey was stratified for sex, age, geographic region, and for rural–urban distribution. Informed consent was obtained from each individual, and the survey conformed to the principles embodied in the Declaration of Helsinki. Data were obtained by history of the past years by way of a questionnaire, physical examination of the cardiovascular system, and recording of a resting electrocardiogram (ECG). After exclusion of participants with coronary heart disease (CHD) at onset, the cohort numbered 2460 at baseline examination; nearly 9.5% of the enrolled subjects did not show up for examination when contacted in the subsequent biennial surveys or were lost to follow-up. Those not followed up were not significantly different (1 year younger). Mean age of 1091 men included in the study was 48.8 ± 12.8 years at baseline and of 1134 women 48 ± 12.5 years. Participants were traced for a mean of 4.1 years (total follow-up, 9070 person-years).

Measurement of Risk Factors and Validation

Blood pressure (BP) was measured twice in the sitting position on the right arm using a sphygmomanometer (Erka, Germany), after at least 5 min of rest. First appearance and disappearance (phase V) of Korotkoff sounds were used to define the pressures. Readings were recorded to the nearest even number, and the mean of two recordings 3 min apart was computed. Waist circumference was measured, with the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest, and the hip circumference was measured at the level of the great trochanters. Body mass index (BMI) was calculated by the computer as weight divided by height squared (kg/m^2). With regard to cigarette smoking, nonsmokers, past smokers, and current smokers formed the categories.

Blood samples were collected as a rule in an 11-h or longer fasting state. Serum concentrations of cholesterol, triglycerides, HDL-cholesterol, and glucose were determined by the enzymatic dry chemistry method using a Reflotron apparatus (Roche Diagnostics, Mannheim, Germany). Glucose was sampled in the postabsorptive state (in 82%), and 2 h postprandially (in 18%) of participants. Triglycerides and insulin determinations were carried out only in sera of fasting persons. Individuals with diabetes mellitus or impaired fasting glucose were identified by self-report or by adhering to the criteria of the American Diabetes Association. The LDL-cholesterol values were computed according to the Friedewald formula. Concentrations of insulin were determined by the chemiluminescent immunometric method using Roche kits and Elecsys 1010 immunautoanalyzer (Roche Diagnostics, Mannheim, Germany). Concentrations of C-reactive protein (CRP) were measured by means of particle-enhanced immunonephelometry with the Behring nephelometer method using N Latex CRP mono reagent (Behring Diagnostics, Marburg, Germany). Serum apolipoprotein (apo) AI and B values were measured by the nephelometric method (Behring), whereas plasma fibrinogen levels were measured by the modified Clauss method using Behring Fibrintimer II coagulometer and Multifibren U kit. Mean values given for concentrations of insulin and CRP are geometric means calculated from the log-transformed distribution. External quality control was performed with a reference laboratory in a random selection of 5% to 6% of participants.

Definition of DH and Metabolic Syndrome

Individuals with a systolic BP <130 mm Hg, a diastolic BP <85 mm Hg, and not being on antihypertensive medication were designated as normotensive. Of the remaining hypertensive participants, DH was considered in those having values of BP, plasma triglyceride, and HDL-cholesterol consistent with the metabolic syndrome criteria of the NCEP guidelines (Adult Treatment Panel III),[1]

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whereas those exhibiting high-normal or hypertensive values but not meeting criteria of both triglycerides and HDL-cholesterol were designated as "simple hypertensives" (SH). Distinction of DH in a minority of subjects with no fasting triglyceride values at baseline was made by taking into account fasting values in the subsequent survey in year 2000.

Identification of metabolic syndrome conformed to the definition used by the NCEP guidelines,[1] namely when three or more of the following five risk determinants were present: waist circumference (men >102 cm, women >88 cm), triglycerides ≥ 150 mg/dL, HDL-cholesterol (men <40 mg/dL, women <50 mg/dL), BP (≥130/≥85 mm Hg), and fasting glucose ≥110 mg/dL.

Ascertainment of Cause of Death and Diagnosis of CHD

Cause of death was assigned based on information on cancer, stroke, accidents, sudden death, and so on elicited from first-degree relatives and local health center staff. In four individuals who had an unclear cause, the preexisting clinical and laboratory findings elicited during the biennial follow-ups helped define the cause. Sudden death was defined in this study as death arising within 24 h of onset of symptoms and was considered of cardiovascular origin in the absence of further information. In instances where the only risk factor was hypertension, sudden death was considered to be of cerebrovascular origin. In women, death at less than 45 years of age was considered of noncoronary origin. Coronary heart disease death comprised death from heart failure of coronary origin and fatal coronary event.

Diagnosis of a CHD event among participants free of CHD at baseline was based on the new development of angina pectoris, of a history of myocardial infarction with or without accompanying Minnesota codes of the ECG,[10] or on a history of myocardial revascularization in the course of biennial examinations. Retrosternal or precordial distress resulting from exertion, lasting 2 to 15 min and relieved by rest was designated as typical angina, whereas in the absence of the last feature this was considered as atypical angina. Among women typical angina before age 45 years and atypical angina at any age precluded the diagnosis. Isolated typical angina in women and atypical angina in men were considered as suspect diagnosis. These criteria resulted in the fact that ECG changes of "ischemic type" of greater than minor degree (codes 1.1–2, 4.1–2, 5.1–2, 7.1) were associated in more than three-fifths of all patients. A cerebrovascular accident was diagnosed when a new stroke occurred, or when death followed such an event.

Data Analysis

Due to the skewed distribution of CRP and fasting insulin values, these parameters were log-transformed for calculations. Continuous risk variables by BP groups were standardized for sex and age groups. Two-sided *t* tests and Pearson's χ^2 tests were used to analyze the differences in proportions between groups. Significance between multiple groups was assessed by ANOVA and checked by Tukey's post hoc test. The independent associations between risk variables and CVD morbidity and mortality on prospective analysis were evaluated by Cox regression taking into account the exposed time. Hazard ratio (HR) estimates and 95% confidence intervals (CI) were obtained. Regression models were adjusted for confounding variables (age, sex, and so on). A value of $P < .05$ was considered statistically significant. Multiple regression analyses of the data were carried out using SPSS-10 for Windows package (SPSS, Inc., Chicago, IL).

Results

Characteristics of the sample population at baseline examination in 1997/1998, which are representative of Turkish adults aged ≥28 years, are presented in Table 1 separately for men and women. Tendency to abdominal obesity is evident among women and suggested in men. This is accompanied by high serum triglyceride levels in both genders. Compared to Western populations, striking features of the study sample are the low mean levels of total cholesterol (around 185 mg/dL), LDL-cholesterol (around 116 mg/dL), and especially of HDL-cholesterol (about 41 mg/dL). In addition, smoking is prevalent among men.

Prevalence and Features of DH and Cardiovascular Disease

At baseline examination, 360 men and women (16.1% of the sample) were identified as having DH. This was roughly half as common as simple hypertensives, which made up 812 adults (36.5%). Normotensives constituted 47.3% of the cohort (1053 men and women). Although metabolic syndrome formed only 12.3% of the normotensive population, 44.6% of simple hypertensives had metabolic syndrome simultaneously, and all individuals with DH had the metabolic syndrome by definition.

Men were significantly younger (49.0 years) than in the simple hypertensive group (55.3 years), whereas women alone had significantly larger waist circumference. Mean cardiovascular risk variables, standardized for sex and age, are presented in Table 2 according to the BP groups. Compared to simple hypertensives, individuals with DH had significantly higher measures of (abdominal) obesity, higher concentrations of total cholesterol, LDL-cholesterol, apo B, fasting glucose, insulin, and CRP. Systolic BP and pulse pressure were similar in the two groups. Women in DH alone had significantly higher LDL-cholesterol levels (129.9 mg/dL) than men (119 mg/dL), even after age standardization.

Nearly half of simple hypertensives had metabolic syndrome, this being generally a consequence of asso-

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Table 1. Characteristics of sample population (n = 2225) at baseline, by gender

	Men (n = 1091)			Women (n = 1134)		
	n	**Mean**	**SD**	***n***	**Mean**	**SD**
Age (y)		48.8	12.8		48.0	12.5
Waist circumference (cm)		93.9†	10.9		90.5	12.5
Systolic blood pressure (mm Hg)		127.8	22.2		134.0†	26.9
Diastolic blood pressure (mm Hg)		81.6	13.2		83.8†	14.4
Pulse pressure (mm Hg)		46.2	14.7		50.2†	17.0
Fibrinogen (g/L)	832	2.9	1.12	870	3.12†	1.1
Log C-reactive protein (mg/L)*	933	1.8	3.13	993	2.07†	3.2
Log fasting insulin (mIU/L)*	567	7.2	2.06	657	7.5	1.9
Total cholesterol (mg/dL)		182.0	37		188.4†	39.0
HDL-cholesterol (mg/dL)		37.3	12.1		45†	12.9
LDL-cholesterol (mg/dL)		114.4	31.9		117.6†	34.4
Triglycerides (mg/dL)		154.9†	97.7		131.5	82.7
Glucose (mg/dL)	863	99.7	26.5	928	101.6	26.9
Apolipoprotein A (mg/dL)	334	122.3	29.9	336	140.1†	34.7
Apolipoprotein B (mg/dL)	766	114.6	40.6	831	114.5	45.3
Total/HDL-cholesterol ratio		5.3†	1.8		4.5	1.6
Current smoker (%)		52.8†			18.3	
Former smoker (%)		19.9†			3.3	
Diabetes/Imp. fasting glucose (%)		4.6/0.6%			5.8/1.6%†	
Metabolic syndrome (%)		31.5			44.7†	

* Values derived from log transformed means and SD; † Significantly higher.

Table 2. Sex- and age-standardized means of risk parameters, events and follow-up, by blood pressure status

	Normotensives (n = 1053)		Simple Hypertensives (n = 812)		Dyslipidemic HT (n = 860)	
	Mean	**SE**	**Mean**	**SE**	**Mean**	**SE**
Body mass index (kg/m^2)	26.1	0.15	28.8	0.17	30.2	0.26**
Waist circumference (cm)	88.6	0.35	94.1	0.39	97.9	0.57**
Apolipoprotein B (mg/dL) [n = 1597]	111.5	1.59	107.8	1.76	136.1	2.47**
Triglycerides (mg/dL)	130.6	2.46	111.8	2.79	249.2	4.07**
HDL-cholesterol (mg/dL)	41.5	0.38	44.7	0.43	32.7	0.62**
LDL-cholesterol (mg/dL)	113.7	1.03	115.9	1.17	123.1	1.71**
Total cholesterol (mg/dL)	181	1.15	182.6	1.3	203.6	1.9**
Total/HDL cholesterol ratio	4.73	0.05	4.39	0.06	6.48	0.08**
NonHDL-cholesterol (mg/dL)	139.5	1.14	137.9	1.3	170.9	1.9**
Glucose (mg/dL) [n = 1791]	98.2	0.94	100.4	1.04	108.7	1.57**
Fasting insulin (mIU/L)¶ [n = 1224]	6.5	1.03	8.02	1.04	9.4	1.05*
C-reactive protein (mg/L)¶ [n = 1926]	1.69	1.04	2.09	1.05	2.57	1.07*
Fibrinogen (g/dL) [n = 1702]	3.04	0.04	2.9	0.04	3.07	0.07 ns
Systolic blood pressure (mm Hg)	114.2	0.54	145.3	0.6	147.6	0.89 ns
Pulse pressure (mm Hg)	41.1	0.41	54.5	0.46	55.3	0.67 ns
Current/past smoker (%)	45.3/10.4		23.2/13.2		32.9/10.3	*
Presence of diabetes mellitus (%)	2.3		6.8		10.3	*
Impaired fasting glucose (%)	0.9		1.1		1.9	*
Presence of metabolic syndrome (%)	12.3		44.6		100	*
Cardiovascular events (n and %)	29	2.75	85	10.5	52	14.4*
Noncardiovascular deaths (n and %)	10	0.95	31	3.82	8	2.22 ns
Total follow-up (person-years)	4302		3340		1428	

* $P < .05$ between simple HT and dyslipidemic HT, ** $P < .001$.
¶ log-transformed values.

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Table 3. Sex- and age-adjusted univariate hazard ratios of some risk factors

	Hazard Ratio	95% Confidence Intervals
Age (y)	1.078	1.064–1.092
Body mass index (kg/m^2)	1.071	1.034–1.109
Waist circumference (cm)	1.028	1.013–1.042
Systolic blood pressure (mm Hg)	1.019	1.013–1.026
Diastolic pressure (mm Hg)	1.025	1.013–1.036
Glucose (mg/dL) $n = 1746$	1.012	1.007–1.016
Total cholesterol (mg/dL)	1.008	1.004–1.012
LDL-cholesterol (mg/dL)	1.007	1.003–1.012
Apolipoprotein B (mg/dL) $n = 1574$	1.005	1.002–1.009
Triglycerides (mg/dL)	1.003	1.002–1.005
HDL-cholesterol (mg/dL)	0.981	0.966–0.995
Fibrinogen (g/dL)	1.025	NS
Log fasting insulin (mIU/L) $n = 1218$	2.137	1.00–4.57
Log C-reactive protein (mg/L) $n = 1912$	2.201	1.532–3.162
Current smokers versus nonsmokers	1.696	1.083–2.656

$n = 2174$; 165 cases of coronary heart disease.

ciation with low HDL-cholesterol or abdominal obesity (54% and 48%, respectively), whereas hypertriglyceridemia (11%) and impaired fasting glucose (8%) accompanied hypertension uncommonly. Among simple hypertensives with metabolic syndrome, coexistent low HDL-cholesterol and abdominal obesity accounted for metabolic syndrome in 62%, four times more common than did the coexistence of high triglycerides and abdominal obesity.

Of the 84 deaths that occurred during the follow-up period, 35 were identified as resulting from CVD (22 men, 13 women). Of the 35 deaths from CVD and 131 nonfatal CVD, cardiovascular events developed in 52 individuals with DH (14.4%) as compared to 85 in subjects with simple hypertensives (10.5%) ($P = .08$) and 29 in normotensives (2.8%) ($P < .001$). Noncardiovascular deaths were encountered in the three groups in 8 (2.22%), 31 (3.8%), and 10 persons (0.95%), respectively (Table 2); the difference between the hypertensive groups did not reach significance.

Relative Risks for Cardiovascular Disease

For overview, the sex- and age-adjusted hazard ratios for CVD risk of various risk factors are presented in Table 3, all of which (except fibrinogen levels) were significant.

The Cox proportional HR for subsequent CVD was 1.57-fold higher in individuals with DH than in simple hypertensives (95% CI 1.08–2.28; $P < .02$) after adjustment for sex, age, LDL-cholesterol, and smoking status. The latter three confounders too were significantly associated with CVD risk, as was the HR of normotensives significantly lower (0.50) than SH (95% CI 0.32–0.80).

Risk of DH Within Metabolic Syndrome The relative CVD risk of DH within individuals having the metabolic syndrome was tested in a logistic regression model in which persons with metabolic syndrome and DH were contrasted against the remaining persons with metabolic syndrome. The sex- and age-adjusted risk ratio (RR) of DH was 1.45-fold higher (95% CI 0.94–2.24) than the remaining metabolic syndrome subjects ($P = .096$).

Table 4. Relative risk induced by risk factors among dyslipidemic hypertensives (DH) for incident cardiovascular disease, adjusted for sex and age ($n = 306$)

	β Coefficient	SE	RR	Confidence Intervals
Pulse pressure (mm Hg)	0.055	0.013	1.056	1.03–1.08
LDL-cholesterol (mg/dL)			1.001	NS
Past smoking			2.48	NS
Current smoking	0.88	0.50	2.41	0.90–6.47
Impaired fasting glucose			2.04	NS
Diabetes mellitus	1.60	0.47	4.64	1.98–12.33
Age (y)	0.067	0.021	1.07	1.03–1.11
Gender (M)			0.75	NS

Model excluded noncardiovascular deaths, included 46 cases of fatal and nonfatal cardiovascular disease among 150 men and 156 women with DH.

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Table 5. Relative risk induced by risk factors among dyslipidemic hypertensives (DH) for incident cardiovascular disease, adjusted for sex and age (n = 153)

	β Coefficient	SE	RR	Confidence Intervals
LDL-cholesterol >130 mg/dL	1.002	0.553	2.723	0.92–8.05
Fasting insulin >10 mIU/L	0.76	0.51	2.14	0.79–5:81
Apolipoprotein B (apoB) >120 mg/dL			1.09	NS
Waist circumference >102/88 cm			0.50	NS
C-reactive protein (CRP) >3 mg/L			1.12	NS
Age (y)	0.079	0.024	1.08	1.03–1.13
Gender (M)			0.87	NS

Model excluded noncardiovascular deaths, included 23 cases of fatal and nonfatal cardiovascular disease. Among 60 men and 93 women with DH, cutoff met in 81 with respect to insulin, in 57 to apo B, in 95 to LDL-cholesterol, in 50 to waist girth, and 81 to CRP.

CVD Risk Induction in DH Table 4 reveals findings of a logistic regression analysis for CVD which comprised six independent variables (used as continuous variables); age, presence of diabetes, pulse pressure, and, at a borderline significance, current smoking proved to be independent predictors of CVD among persons with DH.

Another model of determinants for CVD risk in DH was sought (Table 5), which comprised all 168 persons with DH who had no missing values for fasting insulin, LDL-cholesterol, apo B, CRP, and waist circumference. These variables were dichotomized and evaluated in DH across the cut points of LDL-cholesterol >130 mg/dL to indicate high levels,[1] apo B >120 mg/dL as a surrogate of high number of small dense LDL particles,[11] CRP >3 mg/L reflecting high chronic inflammation,[12] fasting insulin >10 mIU/L indicating insulin resistance,[13] and waist girth >102/88 cm as an index of abdominal obesity.[1] Only high LDL-cholesterol and fasting hyperinsulinemia were associated with borderline significantly elevated RRs among dyslipidemic hypertensives.

Seeking the relationship between serum lipoproteins and measures of obesity in the entire cohort, in a linear regression model that included gender, age, triglycerides, HDL-cholesterol, LDL-cholesterol, and apo B, both waist circumference and BMI were highly significantly ($P <$ .001) associated with each of the four serum variables, whereby triglycerides were the greatest contributant to the variance. Apo B contributed independently only in the model with waist circumference as dependent variable, but not in that with BMI.

Discussion

The DH as herein defined proved to have distinctive features related to insulin resistance, a significantly higher CVD risk than the remaining hypertensives, and some standard risk factors independently elevated the CVD risk among dyslipidemic hypertensives in this population-based prospective study.

The definition differed from conventional usage in limiting dyslipidemia to the dyslipidemia of the metabolic syndrome, hence in excluding isolated abnormality of LDL-cholesterol. The group of SH included subjects with high-normal BP with the purpose of using the same criteria in both hypertension groups. In this context, the finding in the Framingham Study that 1.6- to 2.5-fold risk of CVD was associated in persons with high-normal BP than with optimal BP[14] supports the rationale of using these criteria. The designation of "simple" for the remaining group of hypertensives should not mislead in the sense of a homogeneous or a totally separate group, as 45% of them had associated metabolic syndrome, mostly due to low levels of HDL-cholesterol or abdominal obesity. The Olivetti Heart Study[15] showed that increased BP may be associated with central obesity, independently of insulin resistance. Nonetheless, the definitions here conform with that used by NCEP Adult Treatment Panel III for metabolic syndrome[1] and the present article is, to our knowledge, the first prospective population-based study to examine this issue.

That the covered subject is of great clinical relevance is indicated by the fact that DH existed in 1 of every 6 adults in this population sample, appeared to be responsible of 31% of all fatal and nonfatal CVD. Moreover, half of all CVD events attributable to metabolic syndrome stemmed from DH, although DH made up no more than 42% of individuals with metabolic syndrome. That DH defines a group at higher risk within metabolic syndrome is also suggested by our finding of a borderline significantly higher sex- and age-adjusted CVD risk than the remaining subjects with metabolic syndrome. Nonfamilial forms of DH are apparently encountered several times more frequently than the familial DH described by Williams and co-workers.[2] In fact, in a cross-sectional survey of two New England communities, the conjoint frequency of DH was reported as 15% of the participants.[5] Our finding of 16% is similar to the latter prevalence, although the definition used herein is a somewhat narrower one.

Distinctive Features

Among hypertensive men, DH developed 6 years before, which is probably related to the comparatively early onset of metabolic syndrome in men.[9] Features of DH distinguishing it from SH were sought after sex and age stan-

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dardization, and these included indices of (abdominal) obesity, higher levels of total cholesterol, apo B, fasting insulin, glucose, and CRP, which are all related to the coexisting metabolic syndrome. The LDL-cholesterol levels between the two hypertensive groups were similar in men, but significantly higher in women in DH. However, no interaction was found between gender and LDL-cholesterol on the risk of CVD. Thus, DH distinguished itself from SH by features of the insulin-resistance syndrome, which rendered these individuals to have a higher CVD risk.

Elevated LDL-cholesterol concentrations were observed not uncommonly in familial DH,[16,17] which led to considering the familial combined hyperlipidemia as the leading cause of dyslipidemia in familial DH.[17] Allayee and associates[18] reported that age, familial combined hyperlipidemia status, and waist circumference significantly contributed to systolic BP in female relatives of familial combined hyperlipidemia, underlining the importance of abdominal obesity in the development of DH.

More recently, the same group of genetic researchers found a locus on chromosome 4 that was associated with a fourfold increase in the likelihood of developing systolic high BP as well as with a concomitant increase in plasma free fatty acid concentrations.[18] Moreover, a locus on chromosome 19p was detected in Dutch adults that provided a link between systolic BP and high apo B levels.[18] Sprecher et al[19] observed that 38 individuals heterozygous for lipoprotein lipase (LPL) mutations not only had elevated triglycerides and lower HDL-cholesterol compared to 95 family members without the LPL gene defect, but also higher BP levels, suggesting that LPL gene defect may contribute to the expression of systolic BP. These genetic observations indicate that multiple genetic factors exist that may affect both the BP and plasma lipids.

It had been previously demonstrated in the population-based Paris Prospective Study that high free fatty acid concentrations were a risk factor at 3 years' follow-up for the development of hypertension, after controlling for risk factors and other abnormalities of the insulin-resistance syndrome.[20] Factors contributing to the development of DH include the diminution of nitric oxide (NO) synthesis or release due to insulin resistance.[21] Obese hypertensive persons exhibit high levels of nonesterified fatty acids such as oleic and linoleic acids, which are resistant to suppression by insulin. This leads to inhibition of NO synthase activity in endothelial cells with a consequent blunting in the endothelium-dependent vasodilation.[22]

We found persons with DH to have significantly higher CRP concentrations than simple hypertensives. It has been suggested that endothelial inflammation caused by dyslipidemia—among other metabolic abnormalities—may lead to an increase in arterial BP.[23] Evidence was recently provided in a cross-sectional study in elderly persons that serum interleukin-1β and IL-1 receptor antagonist are significant predictors of BP.[24]

CVD Risk in DH Higher Than in SH

Among adults free of CVD at onset, DH conferred a substantially higher CVD risk than simple hypertensives when age, sex, and the two other major risk factors, LDL-cholesterol and current smoking, were adjusted. Concentrations of insulin appeared to be involved in this context, as they attenuated the independent contribution of RR in DH. In a cross-sectional study of our cohort, hyperinsulinemia was observed by us to contribute twofold to the coronary heart disease risk, independently of the classic risk factors including HDL-cholesterol.[25]

Markers of Elevated Risk in DH

Of practical interest is the issue as to which parameters may be regarded as markers of high risk within the DH group of individuals. Age, presence of diabetes, and pulse pressure proved to be significant determinants of further elevated risk. These proved to be—apart from TC/HDL-cholesterol ratio—the main significant predictors of coronary heart disease risk in previous analyses of the cohort of the Turkish Adult Risk Factor Study.[6,8] Elevated levels of fasting insulin and, in Turkish women, of LDL-cholesterol, which are frequently inherently associated with DH, lend these individuals a higher risk that, in turn, may be augmented by diabetes and increased pulse pressure.

Each lipid and (apo)lipoprotein in this cohort study proved to be significantly and independently associated with waist circumference or BMI on multivariate analyis, but triglycerides had the greatest impact. This underlines the strong interrelationship between dyslipidemia—which is linked to hypertension—and (abdominal) obesity. As recently reported[26] for a limited sample of this cohort, apo B and HDL-cholesterol in men, and HDL-cholesterol in women, were independently associated with computed tomographically identified visceral adipose tissue area in linear regression models that also comprised triglycerides, fasting insulin, and CRP concentrations.

Distinction between subjects with DH and SH is compounded by the presence of metabolic syndrome in 4 of each 9 persons with SH. Elderly men (with hypertension) tend to lose their hypertriglyceridemia, and are categorized into DH, whereas their coexistent abdominal obesity and low HDL-cholesterol levels keep their status as metabolic syndrome. This situation likely leads to an attenuation of the apparent gradient of CVD risk between the two hypertensive groups. Using apo B rather than triglyceride measurements to define dyslipidemia conceiveably might be of value in this distinction.

Among possible limitations of the study is that soft end points such as newly developed angina pectoris has been included as outcome measures. Yet, noteworthy is that any potential bias in terms of inaccuracy in the diagnosis of cardiovascular disease or death would tend to dilute rather than augment the association between clinical events and the hypertension groups.

Taken together, our results indicate that dyslipidemic

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hypertensives, encountered very commonly, are distinguished from simple hypertensives by measures of (abdominal) obesity, higher levels of total cholesterol, apo B, fasting insulin, and CRP. Dyslipidemic hypertension, carrying approximately half of the population-attributable risk due to metabolic syndrome, confers to the individual a hazard ratio for CVD 1.57-fold higher than SH, after adjustment for sex, age, LDL-cholesterol, and smoking status. In persons with DH, age, presence of diabetes, and pulse pressure are independent predictors of higher risk for CVD. This knowledge has relevance for risk assessment in clinical practice and a potential in therapeutic decision making.

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