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Elevated LDL-Cholesterol Level Predicts Diabetes in Centrally Obese Women but Not Men

—— Relative Roles of Insulin Resistance and Central Obesity ——

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Background The aim was to investigate the sex-specific effect of hypercholesterolemia interacting with abdominal obesity (AO) in predicting Type 2 diabetes mellitus (DM). The 3,048 participants (aged ≥28 years) were free of DM at baseline, a representative sample of Turkish adults and were evaluated prospectively.

Methods and Results As cut-off points for AO were used ≥95 cm in men and ≥91 cm in women, and for hypercholesterolemia ≥5.2 mmol/L. Diabetes was diagnosed using criteria of the American Diabetes Association. Four groups were formed at baseline: Group I subjects had neither AO nor hypercholesterolemia (33.3%), Group II subjects had AO only (27.6%), Group III subjects had hypercholesterolemia only (17.8%), and Group IV subjects had AO combined with hypercholesterolemia (21.3%). Over a mean of 5.9 years, DM developed in 103 women and 116 men. An age-adjusted relative risk (RR) by logistic regression for DM in the 4 groups, using AO as a reference group, disclosed an RR of 1.88 (95% confidence interval 1.14; 3.09) in women and an insignificant RR 1.29 in men (women were predicted to be 1.46 times more likely to develop DM). Hypercholesterolemia alone did not differ significantly from Group I in its ability to predict diabetes. An elevated level of low-density lipoprotein (LDL)-cholesterol (C) (≥3.4 mmol/L) was delineated as the element associated with diabetes in hypercholesterolemia by multiple logistic regression. The identification of 48 participants with familial-combined hyperlipidemia phenotypes alone could not account for most of the centrally obese and hypercholesterolemic women developing DM.

Conclusion It was suggested that a diminished effectiveness of insulin resistance in centrally obese Turkish women (but not men) might predispose them to an elevation in LDL concentrations, while other features of visceral adiposity still predispose them to DM. In summary, an elevated LDL-C level interacts with AO in Turkish women to enhance the development of diabetes. (*Circ J* 2007; **71:** 1463 – 1467)

Key Words: Abdominal obesity; Diabetes type 2; Familial-combined hyperlipidemia; Hypercholesterolemia; Insulin resistance; Sex difference

Hypertriglyceridemia, low high-density lipoprotein (HDL)-cholesterol (C) levels and small-dense low-density lipoprotein (LDL) particles characterize the dyslipidemia associated with increased amounts of visceral adipose tissue, metabolic syndrome (MS) and Type 2 diabetes mellitus (DM). An elevated level of LDL-C is not a feature of the dyslipidemia seen with abdominal obesity (AO)[1–3] but has been observed in some diabetic groups.[4,5] A higher prevalence of hypercholesterolemia has been reported in upper compared with lower brackets of waist circumference[6] without elaborating specifically on this issue. The major link between hypercholesterolemia, AO and diabetes is familial-combined hyperlipidemia (FCH). Underlying this most common genetic form of hyperlipidemia, is the overproduction of apolipoprotein (apo) B in lipoproteins, not observed in other forms of hypertriglyceridemia. FCH has been described as a subtype of MS with higher apo B levels.[7]

Genetic susceptibility to hyperlipidemia in FCH was shown to interact with AO.[8] In studying 618 FCH relatives and 297 spouses, age- and gender-corrected odds for the prevalence of hyper apoB and hypertriglyceridemia were dependent on (abdominal) obesity in FCH but not in hypercholesterolemia. Increments in measure of central obesity were a determinant of the expression of hypertriglyceridemia alone in FCH.[8]

Possibly because of a higher prevalence of FCH among Turks than in most Western populations, Turks have a higher prevalence also of MS, among whom hypercholesterolemia is significantly associated with AO. However, there is an excess of this association in women than in men; the underlying factor for which is unknown. Our hypothesis is that this association predicts the development of DM in Turkish women.

The aim of the study is to investigate prospectively the association between hypercholesterolemia and abdominally obese women in the prediction of Type 2 diabetes, in comparison with men, in a representative sample of Turkish adults.[9]

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Table 1 Baseline Characteristics in Men and Women With AO (n=1,464)

	Men						Women					
	n	AO		AO + H		p value	n	AO		AO + H		p value
		Mean	SD	Mean	SD			Mean	SD	Mean	SD	
Age, years	*733*	*49.6*	*11.1*	*49.8*	*11.1*	*0.7*	*731*	*50.8*	*11*	*51.3*	*11.2*	*0.5*
WC, cm	*733*	*101.5*	*3.7*	*102.7*	*4.1*	*0.2*	*731*	*99.5*	*3.8*	*100.4*	*4.1*	*0.15*
Log f. insulin, ml U/L*	*389*	*8.87*	*2.0*	*10.8*	*2.07*	*0.01*	*441*	*94.5*	*1.94*	*9.43*	*1.77*	*0.98*
*Log HOMA**	*322*	*1.68*	*1.9*	*2.07*	*1.98*	*0.006*	*365*	*1.86*	*1.79*	*1.82*	*1.69*	*0.63*
SBP, mmHg	*733*	*130.7*	*21.1*	*137.4*	*25.7*	*0*	*731*	*137.6*	*25.3*	*143.5*	*26.9*	*0.003*
DBP, mmHg	*733*	*83.8*	*12.6*	*86.9*	*14.9*	*0*	*731*	*86.2*	*13.8*	*88.4*	*14.9*	*0.046*
Fasting glucose, mmol/L	*425*	*5.3*	*1.1*	*5.4*	*1.1*	*0.46*	*493*	*8.35*	*1.1*	*5.5*	*25.4*	*1.4*
TC, mmol/L	*733*	*4.26*	*0.6*	*5.93*	*0.6*	*0*	*731*	*4.4*	*0.55*	*6.0*	*0.68*	*0*
F. triglyceride, mmol/L	*577*	*1.67*	*0.95*	*2.58*	*1.4*	*0*	*611*	*1.45*	*1.0*	*2.0*	*1.1*	*0*
LDL-C, mmol/L	*602*	*2.66*	*0.6*	*3.72*	*0.7*	*0*	*638*	*2.7*	*0.6*	*3.9*	*0.78*	*0*
HDL-C, mmol/L	*723*	*0.89*	*0.25*	*0.98*	*0.29*	*0*	*709*	*1.1*	*0.32*	*1.22*	*0.33*	*0*

**Geometric means.*

AO, abdominal obesity; H, hypercholesterolemia; WC, waist circumference; HOMA, homeostatic model assessment; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol.

Methods

Population Sample

Participants of the nationwide survey conducted in 1997/1998 of the Turkish Adult Risk Factor Study were followed up until 2004/2005. This is a prospective survey on the prevalence of cardiac disease and risk factors in a representative sample of adults in Turkey carried out periodically almost biennially since 1990 in 59 communities scattered throughout all geographical regions of the country.[9] Details of sampling were described previously.[10] As the combined measurements of waist circumference, HDL-C and apo B were first perfomed at the follow-up visit in 1997/1998, the latter examination formed the baseline. Participants were 28 years of age or older at baseline examination, and those with no missing values for serum total cholesterol and waist circumference numbered 3,229, of which 1,631 were women. Of the survivors, 8% were examined up to the survey period of 2001/2002, 14% up to 2003, and the remainder having been examined last in the survey period of 2004/2005. Exclusion of cases of diabetes limited the study sample to 1,509 men and 1,529 women. Individuals of the cohort were visited at their addresses on the eve of the examination and were requested to give written consent for participation after having read an explanatory note, which was manifested by their voluntary participation the next morning. The survey conformed to the principles embodied in the Declaration of Helsinki. Data were obtained by history of the past years via a questionnaire, a physical examination of the cardiovascular system, sampling of blood and recording of a resting electrocardiogram.

Measurements of Risk Variables

Blood pressure was measured in the sitting position on the right arm after 5 min of rest, and the mean of 2 recordings 3 min apart was recorded. Weight was measured without shoes in light indoor clothes using scales. Waist circumference was measured with a tape (Roche LI95 63B 00) – the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest. Body mass index was calculated as weight divided by height squared (kg/m^2).

Plasma concentrations of cholesterol, fasting triglycerides, HDL-C and glucose were determined at baseline examination by the enzymatic dry chemistry method using a Reflotron apparatus (Roche Diagnostics, Mannheim, Germany). External quality control was performed with a reference laboratory in a random selection of 5–6% of participants. LDL-C values were computed according to the Friedewald formula. Blood samples were spun at 1,000 g for 10 min and also shipped within a few hours on cooled gel packs at 2–5°C to Istanbul to be stored in deep-freeze at –75°C, until analyzed at a central laboratory. Concentrations of insulin were determined by the chemiluminescent immunometric method using Roche kits and an Elecsys 1010 immunautoanalyzer (Roche Diagnostics, Mannheim, Germany). A homeostatic model assessment (HOMA) was calculated with the following formula:[11] insulin (mIU/L)× glucose (in mmol/L)/22.5.

Definitions and Outcomes

Individuals with diabetes were diagnosed using criteria from the American Diabetes Association,[12] namely by self report or when the plasma fasting glucose was ≥7.0 mmol/L or when the 2-h postprandial glucose level was >11.1 mmol/L. The same criteria were utilized for the diagnosis of new diabetes that had developed over the follow-up period. Hypercholesterolemia was defined as a serum total cholesterol level of ≥5.2 mmol/L. AO was defined in this study in terms of waist circumference in agreement with this anthropometric measure emerging as the most appropriate one to reflect visceral adiposity among Turks;[13] ≥95 cm in males[14] and ≥91 cm in females were cut-off points selected for AO based on results of receiver operating characteristics related to CHD, DM, and MS.

Data Analysis

Four groups were formed, depending on the presence or absence of AO and hypercholesterolemia. Values of the baseline examination were used to evaluate prospective developments. Descriptive parameters were shown as mean ± SD. Because of the skewed distribution of concentrations of insulin and HOMA, these were log-transformed for calculations. Two-sided t-tests and Pearson's chi-square tests were used to analyze the differences in means and proportions between groups. Estimates (and 95% confidence intervals (CI)) for relative risk (RR) of a dependent variable were obtained by use of logistic regression analysis in models that controlled for sex and age. A value of $p<0.05$ on the 2-sided test was considered statistically significant.

Table 2 Interaction in Women of H With AO for the Prediction of New Diabetes

Women n	Men n		Women		Men	
			RR	95% CI	RR	95% CI
366	472	AO (≥91/95 cm) only	1		1	
503	510	None	0.29	0.14; 0.60	0.37	0.22; 0.65
299	242	H only (≥200)	0.69	0.36; 1.33	0.56	0.3; 1.06
361	285	AO + H	1.88	1.14; 3.09	1.29	0.81; 2.05
1,529	1,509	Age (years)	1.024	1.006; 1.042	1.034	1.019; 1.050
29	17	Statin usage	0.32	0.043; 2.437	1.323	0.294; 5.949

Diabetes developed in 103 women and 116 men.
RR, relative risk; CI, confidence interval. Other abbreviations see in Table 1.

Table 3 Adjusted Risks of Diabetes for LDL-C, Non-HDL-C and Apolipoprotein B, by Gender

	n	Women				Men			
		Model 1		Model 2		Model 1		Model 2	
		RR	p value	RR	p value	RR	p value	RR	p value
LDL-C >130 mg/dl	2,647	1.55	0.045	1.47	0.096	1.05	NS	1.08	NS
Non-HDL-C >160 mg/dl	2,979	1.51	0.064	1.41	0.14	1.24	NS	1.33	NS
Apolipoprotein B >120 mg/dl	2,268	1.42	0.13	1.41	0.16	1.05	NS	1.09	NS

Model 1, adjusted for age and AO; Model 2, adjusted for age, AO and log high-sensitivity C-reactive protein.
High low-density lipoprotein existed in 28.7% of men, 34.2% of women.
Abbreviations see in Tables 1,2.

Statistical analyses were performed using SPSS-10 for Windows (SPSS Inc, Chicago, IL, USA).

Results

The mean age of the study sample was 48.2 ±11.9 years at baseline.

Sex-Specific Prevalence of Hypercholesterolemia and Central Obesity in a Non-Diabetic Sample

At baseline, 510 men and 503 women had neither AO nor hypercholesterolemia (33.3%), 472 men and 366 women had AO alone (27.6%), 242 men and 299 women had hypercholesterolemia alone (17.8%; 16.0% men vs 19.6% women), and 285 men and 361 women had AO combined with hypercholesterolemia (21.3%; 18.9% men vs 23.6% women).

Over a mean follow-up period of 5.9 years (total 18,000 person-years), incident Type 2 diabetes developed in 103 women (11.4 per 1,000 person-years) and 116 men (13.0 per 1,000 person-years).

Age-Adjusted Baseline Characteristics in Groups by Gender

Table 1 shows the mean estimates of baseline risk parameters (and SD) in the group with AO and AO combined with hypercholesterolemia, separately in women and men. In both genders, insulin concentrations and the HOMA index is slightly raised, but although the men in the group with hypercholesterolemia had significantly higher insulin concentrations and a higher HOMA index than those patients with AO alone, the results for both groups involving women are similar. Thus, elevated levels of lipids and blood pressure are significantly higher than in the group with AO alone in both genders, but while these rises are accompanied by significant rises in insulinemia and HOMA in men, they are not among women.

Seventeen men and 29 women were taking statins and 10.3% of men and 21.3% of women were taking antihypertensive medication.

Prediction of Diabetes by Hypercholesterolemia

Hypercholesterolemia was by one-quarter more common in women than men (43.2% vs 35%).

Age- and statin usage-adjusted RR in the 4 groups of the sample in logistic regression analysis is presented in Table 2. The group in which AO was used as reference, disclosed for diabetes an RR of 3.45 (95% CI 1.67; 7.14) in women and an RR 2.7 (95% CI 1.54; 4.55) in men compared with the group that had neither of the 2 abnormalities. Hypercholesterolemia alone did not differ significantly from the reference group in its ability to predict diabetes, although the RR of 0.56 in men approached significance. Males with AO combined with hypercholesterolemia did not significantly predict diabetes (RR 1.29), whereas females did so significantly (1.88; 95% CI 1.14; 3.09). Women with AO combined with hypercholesterolemia were 1.46 times more likely to have the development of diabetes predicted for them.

Screening for FCH

Based on the proposition by Veerkamp et al,[15] we have attempted to identify FCH by using sex- and age-adjusted 90th percentile values of plasma fasting triglycerides (usually >7.2 mmol/L in males, >6.3 mmol/L in females), total cholesterol (usually >6.3 mmol/L in males, >6.5 mmol/L in females), and apo B values >120 mg/dl. None of the 3 criteria existed in 62.2% of the sample; the selection by triglyceride or total cholesterol identified 576 of 2,220 persons, the selection by triglyceride and total cholesterol identified 216 persons, and all 3 criteria identified 48 subjects (2.2%), which were considered as participants with FCH phenotypes. These comprised 21 men and 27 women.

Logistic regression for DM in a model comprising 2,103 men and women with no dyslipidemia formed the referent group, while FCH phenotype and the remaining group with elevated triglyceride and/or total cholesterol levels formed Groups 3 and 2. Sex- and age-adjusted odds ratio for 174

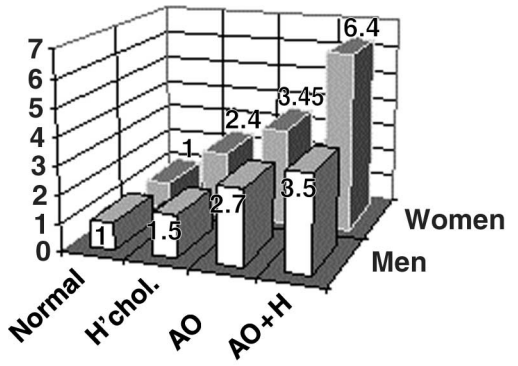


Fig 1. Risk of developing diabetes in groups of abdominal obesity (AO) and hypercholesterolemia (H) (compared with the group having none) in men and women. Note that males and females in the group with AO only had a significantly higher risk than the "normal" group, but only women with AO and H exhibited a significantly higher risk than if they had AO only.

cases of DM was 1.52 (95% CI 1.10; 2.09) in Group 2, and 1.82 ($p<0.23$) in Group 3; this was only based on 5 of 41 cases. Thus, the FCH phenotype alone could not account for most of the centrally obese and hypercholesterolemic women developing DM.

With the purpose of better identifying the element associated with diabetes in hypercholesterolemia, logistic regression analyses were performed with elevated levels of LDL-C (>130 mg/dl, ≥3.4 mmol/L), non-HDL-C (>160 mg/dl, ≥4.1 mmol/L) and apo B (>120 mg/dl) in 2 models (Table 3). Adjustment for age and AO was carried out in the first model, additional adjustment for log high-sensitivity C-reactive protein (hsCRP) in the second. AO was the significant main predictor of diabetes in both sexes in each model, and log hsCRP was not independently significant in men but was so in women in each model. Though the lipoprotein fractions were not significant in men, elevated LDL-C was the only significant parameter in predicting diabetes among women (RR 1.55). The association was attenuated to a borderline significant level when also adjusted for log hsCRP.

Discussion

In this prospective study on a representative sample of non-diabetic Turkish adults, for both centrally obese men and women, the prediction to develop diabetes was significant, as anticipated, however, in contrast to men, only centrally obese women with hypercholesterolemia had diabetes predicted with a nearly 2-fold likelihood of occurrence than women with AO alone. An enhanced prediction of diabetes was delineated to be caused by elevated LDL-C levels.

Our findings indicate that both AO and hypercholesterolemia are determining factors for the development of Type 2 diabetes in both genders (Fig 1). Of these, AO conferred a greater magnitude of RR (roughly 3 and 2.5-fold in women and men, respectively) than hypercholesterolemia (2.1 and 1.4, respectively), and in this model, women (3-fold for AO and 2.1-fold for hypercholesterolemia) experienced stronger increments for diabetes than men did for these 2 parameters (2.5- and 1.46-fold, respectively).

A main potential link between AO combined with hypercholesterolemia, specifically in terms of elevated LDL-C levels, and diabetes is FCH. Individuals with a FCH genotype are recognized to tend strongly to AO and DM, concomitantly exhibiting often elevated levels of total cholesterol[16,17] The identified 48 participants with FCH phenotype in the present study, although displaying an elevated age-adjusted RR for DM, could account for no more than 3% of incident DM cases. AO combined with hypercholesterolemia prevailed in nearly one-quarter of Turkish women; thus, shear commonness of this phenomenon necessitated the search for another mechanism.

Before proposing a mechanism, it is pertinent to recall relevant information regarding lipoprotein metabolism in diabetes and/or insulin resistance (IR) and to state certain related features of Turkish women. In DM, an increased influx of free fatty acids and glucose to the liver leads to increased production of (large) very LDL (VLDL) particles, along with elevated apo B production, especially in obese subjects. The proportion of VLDL converted to LDL is decreased (by augmented direct removal by the liver), and LDL levels remain often normal[5] In contrast to Turkish men who at age 50 years or over have lower total cholesterol levels and in whom IR plays an anticipated role as a determinant of DM, postmenopausal women exhibit higher total cholesterol concentrations than men[9] and, rather than IR per se, it is central obesity that mainly determines the development of atherogenic dyslipidemia[18] and of DM.

The risk of developing diabetes increases in the presence of certain risk factors. In non-diabetic Finnish subjects, this risk was elevated in subjects with high triglyceride, low HDL-C levels, high body mass index, high fasting insulin, and in those having hypertension[19] Fasting insulin and the waist-to-hip ratio, postload and fasting glucose levels and serum insulin predicted diabetes in factor analysis among Chinese subjects[20] They concluded that IR alone did not underlie all features of MS. Different physiological processes associated with various components of the MS contained unique information about diabetes risk. In the Insulin Resistance Atherosclerosis Study, risk factors for developing Type 2 diabetes included PAI-1, hypertension, high triglycerides, low levels of HDL-C, and impaired glucose tolerance (but not hypercholesterolemia). Each of these sex- and age-adjusted risk factors increased the risk of diabetes after further adjustment of IR and waist circumference. Thus, individuals with multiple risk factors are at an increased risk of diabetes, which is only partially mediated by IR or central obesity[21] Specific adjustment was not made in multivariate analysis in approximately 15% of study subjects in whom antihypertensive medication was received. Although antihypertensive drugs might reduce the risk of future diabetes, it is unlikely that this might preferentially enhance the prediction of diabetes by elevated LDL-C levels.

Modulation by IR and obesity has been observed also in lipid phenotype expression concerning high apo B and small, dense LDL in FCH[22] And sex does matter in regard to the actions of insulin, susceptibility to develop IR, and the response to stimuli that enhance or impair sensitivity to the effects of insulin[23] Also, C-reactive protein levels are more strongly related to MS in women than in men[24] and impaired glucose tolerance and diabetes are closely associated with small, dense LDL particles[25] The mediation of diabetes risk by elevated levels of LDL-C in centrally obese women might be explained by their inherent diminished effectiveness of IR whereby the proportion of the increased VLDL converted in the liver to LDL might not be decreased. This might explain the observed elevation in LDL concentrations in postmenopausal women, while other features of

visceral adiposity (atherogenic dyslipidemia, including diminished LDL size, reduced adiponectin, little expanded subcutaneous fat mass[26] mediated by low sex hormone-binding globulin (SHBG)) still predispose them to DM. We hypothesize that diminished LDL size contributes to the development of DM in Turkish women, enhanced by low SHBG levels in which the action on triglycerides seems to operative in both genders while that in women additionally involves apo B, the LDL composition and presumably the regulation of dysglycemia.

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References

1. Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR. Diabetes, blood lipids and the role of obesity in coronary heart disease risk for women. *Ann Intern Med* 1977; **87:** 393–397.
2. Barrett-Connoe E, Grundy SM, Holdbrook MJ. Plasma lipids and diabetes mellitus in an adult community. *Am J Epidemiol* 1982; **115:** 657–663.
3. Uusitupa M, Siitonen O, Voutilainen E, Aro A, Hersio K, Pyörälä K, et al. Serum lipids and lipoproteins in newly diagnosed non-insulin-dependent (type II) diabetic patients, with special reference to factors influencing HDL-cholesterol and triglyceride levels. *Diabetes Care* 1986; **9:** 17–22.
4. Howard BV, Knowler WC, Vasquez B, Kennedy AL, Pettitt DJ, Bennett PH. Plasma and lipoprotein cholesterol and triglyceride in the Pima Indian population: Comparison of diabetics and nondiabetics. *Arterioclerosis* 1984; **4:** 462–471.
5. Howard BV. Lipoprotein metabolism in diabetes mellitus. *J Lipid Res* 1987; **28:** 613–628.
6. Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal obesity and overall obesity in predicting type 2 diabetes among men. *Am J Clin Nutr* 2005; **81:** 555–563.
7. Carr MC, Brunzell JD. Abdominal obesity and dyslipidemia in the metabolic syndrome: Importance of type 2 diabetes and familial combined hyperlipidemia in coronary artery disease risk. *J Clin Endocrinol Metab* 2004; **89:** 2601–2607.
8. van der Kallen CJH, Voors-Pette C, de Bruin TWA. Abdominal obesity and expression of familial combined hyperlipidemia. *Obes Res* 2004; **12:** 2054–2061.
9. Onat A. Risk factors and cardiovascular disease in Turkey. *Atherosclerosis* 2001; **156:** 1–10.
10. Onat A, Avcı GŞ, Şenocak M, Örnek E, Gözükara Y. Plasma lipids and their interrelation in Turkish adults. *J Epidem Commun Health* 1992; **46:** 470–476.
11. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001; **285:** 2486–2497.
12. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, et al; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus: The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2003; **26:** 3160–3167.
13. Onat A, Avcı GŞ, Barlan MM, Uyarel H, Uzunlar B, Sansoy V. Measures of abdominal obesity assessed for visceral adiposity and relation to coronary risk. *Int J Obes* 2004; **28:** 1018–1025.
14. Onat A, Uyarel H, Hergenç G, Karabulut A, Albayrak S, Can G. Determinants and definition of abdominal obesity as related to risk of diabetes, metabolic syndrome and coronary disease in Turkish men: A prospective cohort study. *Atherosclerosis* 2007; **191:** 182–190.
15. Veerkamp MJ, de Graaf J, Hendriks JCM, Demacker PNM, Stalenhoef AFH. Nomogram to diagnose familial combined hyperlipidemia on the basis of results of a 5-year follow-up study. *Circulation* 2004; **109:** 2980–2985.
16. McNeely MJ, Edwards KL, Marcovina SM, Brunzell JD, Motulsky AG, Austin MA. Lipoprotein and apolipoprotein abnormalities in familial combined hyperlipidemia: A 20-year prospective study. *Atherosclerosis* 2001; **159:** 471–491.
17. Hopkins PN, Heiss G, Ellison RC, Province MA, Pankow JS, Eckfeldt JH, et al. Coronary artery disease risk in familial combined hyperlipidemia and familial hypertriglyceridemia: A case-control comparison from the National Heart, Lung, and Blood Institute Family Heart Study. *Circulation* 2003; **108:** 519–523.
18. Onat A, Hergenç G, Türkmen S, Yazıcı M, Sarı İ, Can G. Discordance between insulin resistance and metabolic syndrome: Features and associated cardiovascular risk in adults with normal glucose regulation. *Metabolism* 2006; **55:** 445–452.
19. Mykkänen L, Kuusisto J, Pyörälä K, Laakso M. Cardiovascular disease risk factors as predictors of type 2 (non-insulin-dependent) diabetes mellitus in elderly subjects. *Diabetologia* 1993; **36:** 553–559.
20. Wang JJ, Qiao Q, Miettinen ME, Lappalainen J, Hu G, Tuomilehto J. The metabolic syndrome defined by factor analysis and incident type 2 diabetes in a Chinese population with high postprandial glucose. *Diabetes Care* 2004; **27:** 2429–2437.
21. D'Agostino RB Jr, Hamman RF, Karter AJ, Mykkänen L, Wagenknecht LE, Haffner SM; Insulin Resistance Atherosclerosis Study Investigators. Cardiovascular disease risk factors predict the development of type 2 diabetes: The Insulin Resistance Atherosclerosis Study. *Diabetes Care* 2004; **27:** 2234–2240.
22. Veerkamp MJ, de Graaf J, Stalenhoef AF. Role of insulin resistance in familial combined hyperlipidemia. *Arterioscler Thromb Vasc Biol* 2005; **25:** 1026–1031.
23. Mittendorfer B. Insulin resistance: Sex matters. *Curr Opin Clin Nutr* 2005; **8:** 367–372.
24. Nakanishi N, Shiraishi T, Wada M. C-reactive protein concentration is more strongly related to metabolic syndrome in women than in men: The Minoh Study. *Circ J* 2005; **69:** 386–381.
25. Ban Y, Koba S, Tsunoda F, Yokota Y, Ezumi H, Kondo T, et al. Predominance of small dense low-density lipoproteins and abnormal glucose regulation in patients with acute coronary syndrome. *Circ J* 2006; **70:** 393–401.
26. Virtanen KA, Iozzo P, Hallsten K, Huupponen R, Parkkola R, Janatuinen T, et al. Increased fat mass compensates for insulin resistance in abdominal obesity and type 2 diabetes: A positron-emitting tomography study. *Diabetes* 2005; **54:** 2720–2726.