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
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throughout all geographical regions of the country.9 Details almost biennially since 1990 in 59 communities scattered valence of cardiac disease and risk factors in a represen-

tion of the cardiovascular system, sampling of blood and

population of sampling were described previously.10 As the combined difference was measured with a tape (Roche LI95 63B 00) –

out shoes in light indoor clothes using scales. Waist circum-

ings 3 min apart was recorded. Weight was measured with-

the right arm after 5 min of rest, and the mean of 2 record-

cohort were visited at their addresses on the eve of the

survey period of 2001/2002, 14% up to 2003, and the remain-

waist circumference numbered 3,229, of which 1,631 were

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 0.8 2.0 10.8 2.07 0.01 441 9.45 1.94 9.45 1.94 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 733 133.9 21.1 137.4 25.7 0 731 137.6 25.3 145.5 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 5.31 0.6 0 731 4.4 0.55 6.0 0.6 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 722 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 pre-

fined in this study in terms of waist circumference in agree-

tions of insulin and HOMA, these were log-transformed

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. Concentra-
tions of insulin were determined by the chemiluminescent

methoRoche kits and an Elecsys 1010 immunoa

A 1010 immunoanalyzer (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 Association12 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 ≥2.5 mmol/L. AO was de-

fined in this study in terms of waist circumference in agree-

ment with this anthropometric measure emerging as the

methods that controlled for sex and age. A value of p<0.05

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 concentra-
tions 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 propor-
tions between groups. Estimates (and 95% confidence intervals (CI)) for relative risk (RR) of a dependent vari-
able 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.
Hypercholesterolemia Predicts Diabetes

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 antihypercholesterolemic 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 al15 we have attempted to identify FCH by using sex- and age-adjusted 90th percentile values of plasma fasting triglycerides (usually >1.7 mmol/L in males, >1.3 mmol/L in females), total cholesterol (usually >6.3 mmol/L in males, >5.5 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, 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
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. 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. 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 and, rather than IR per se, it is central obesity that mainly determines the development of atherogenic dyslipidemia 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. Fasting insulin and the waist-to-hip ratio, postload and fasting glucose levels and serum insulin predicted diabetes in factor analysis among Chinese subjects. 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. 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. 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. Also, C-reactive protein levels are more strongly related to MS in women than in men and impaired glucose tolerance and diabetes are closely associated with small, dense LDL particles. 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 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 operate 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