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Discordance between insulin resistance and metabolic syndrome: features and associated cardiovascular risk in adults with normal glucose regulation

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Abstract

The aims of this study were to investigate the extent of concordance between metabolic syndrome (MS) and insulin resistance (IR), the features of discordance, and the magnitude of their independent association with cardiovascular disease (CVD) risk. After exclusion of individuals with diabetes and impaired fasting glucose, the population sample of 1534 men and women, representative of Turkish adults (mean age, 52.2 years), were evaluated cross-sectionally and at a mean 2 years' follow-up. Metabolic syndrome was identified by criteria of the Adult Treatment Panel III, except for male waist circumference (>94 cm). Insulin resistance was defined by the upper quartile in the sample (>2.245) of the homeostatic model assessment (HOMA) index. Clinical fatal and nonfatal CVD existed or developed in 165 subjects. Waist circumference proved to be by far the strongest significant determinant of HOMA in both sexes, followed by triglycerides. The cohort was categorized into 4 by the presence or absence of MS and IR. Each of the latter represented 34% and 25%, but together constituted 45% of the sample, thus disclosing concordance in a third of the conditions combined. The nonconcordant IR/NoMS group was less common than the MS/NoIR group and was distinct from the latter in having significantly lower waist girth, blood pressure, apolipoprotein B and triglyceride levels, and higher high-density lipoprotein cholesterol, glucose, and insulin levels and physical activity in both sexes. When adjusted for 5 important risk factors, although the excess risk in men with MS failed to attain significance, men with IR were associated with a significant 1.9-fold CVD risk. The IR/NoMS group had a 2.2-fold (95% confidence interval, 0.97-5.11) CVD likelihood compared with the large insulin-sensitive group, after adjustment for age, sex, log C-reactive protein, low-density lipoprotein cholesterol, smoking status, physical activity, and the 2 groups of MS with or without IR. Overlapping between MS and IR is limited in either sex, and MS/NoIR is more common than IR/NoMS. Overall, IR is more significantly associated with CVD risk than MS in men and in both sexes after adjustment for important confounders. Insulin resistance without MS tends to implicate in middle-aged and elderly Turkish men roughly a 2-fold CVD risk, corresponding to 50% excess risk per 1 SD in HOMA index, independent of MS and important covariates.

1. Introduction

The importance of hyperinsulinemia or insulin resistance (IR) in aggravating traditional cardiovascular risk factors and in contributing to the development of cardiovascular disease (CVD) is well recognized [1-3]. It has also been shown that the endothelium-dependent response of normal coronary arteries may be blunted by IR, thereby leading to coronary vascular endothelial dysfunction [4]. Hyperinsulinemia or IR has been emphasized as a coronary risk factor [5,6].

Although the gold standard as measure of IR is the euglycemic clamp method, because of its simplicity, hyperinsulinemia (10 mIU/L) or the homeostatic model assessment (HOMA) index has been widely used as a surrogate of IR and of beta-cell function in large clinical or population-based studies [6-8]. Estimates of IR with these measures have been demonstrated to be well correlated with the

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euglycemic clamp technique except in patients with marked hyperglycemia.

Although the clinical metabolic syndrome (MS) is closely related to IR, large consensus groups [9] are not willing to conclude that IR is a sine qua non of MS, and the extent to which the 2 conditions overlap is not well delineated. As Reaven [10] recently emphasized, neither the possibility that substantial numbers of subjects who do not satisfy the Adult Treatment Panel III (ATP III) criteria might have IR and are at increased CVD risk nor the ability of these criteria to identify insulin-resistant individuals has been adequately evaluated. Data in this regard have been available recently in 3 smaller studies [6,7,11], some partly addressing this issue directly. One quarter of 91 persons with MS were reported not to have true IR [11]. By contrast, evidence was also provided that measures of IR did add incremental value to the MS in association with coronary artery calcification, after controlling for multiple established risk factors [6].

We aimed, therefore, to investigate (1) the extent of concordance between MS by National Cholesterol Education Program (NCEP) criteria and IR by HOMA, (2) differences in the clinical features in individuals with discordance in the 2 conditions, (3) the determinants of HOMA, and (4) the degree of independence and magnitude of the associations of IR and of subgroups of MS with risk of CVD in a population sample representative of middle-aged and elderly Turkish adults who have higher prevalences than Western populations of low high-density lipoprotein cholesterol (HDL-C) [12,13] and of the MS [14] and in whom fasting insulin levels were observed to be independently associated with coronary heart disease (CHD) [15].

2. Methods

2.1. Population sample

In the surveys in 2001 to 2002 and 2003 to 2004 of the cohort of the Turkish Adult Risk Factor Study, serum concentrations of insulin and glucose had been determined at least once in a total of 1803 different participants. 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 [13]. Details of sampling were described previously [16]. Excluded were 165 subjects with abnormal glucose regulation (91 diabetes and 74 impaired fasting glucose [IFG]) and 96 persons with nonfasting sera, leaving 1534 adults with normal glucose regulation who constituted the study sample. Individuals of the cohort were visited in their addresses on the eve of the examination and were requested to give written consent for participation after having read an explanatory note, manifesting by their voluntary participation the next morning. Data were obtained by history of the past years via a questionnaire, physical examination of the cardiovascular system, sampling of blood, and recording of a resting electrocardiogram.

2.2. Measurements and definitions

Blood samples were collected in a 11-hour or longer fasting state in all individuals in this study. Samples were spun at 1000*g* for 10 minutes and shipped within a few hours on cooled gel packs at 2°C to 5°C to Istanbul to be stored in deep-freeze at −75°C, until analyzed at the Yıldız Technical University in the same city. Concentrations of insulin were determined by the chemiluminescent immunometric method using kits from Roche Diagnostics (Mannheim, Germany) and Elecsys 1010 immunoautoanalyzer (Roche Diagnostics). Interassay coefficient of variation for insulin control was 2.9% and intra-assay coefficient of variation was 5.8%, and for glucose, 0.7% and 2.4%, respectively. Serum concentrations of apolipoprotein (apo) B and high-sensitivity CRP were measured by Behring kits and nephelometry (BN Prospec, Behring Diagnostics, Westwood, MA) using N Latex CRP mono reagent of Behring Diagnostics. Serum concentrations of total cholesterol, fasting triglycerides, glucose, and HDL-C (directly without precipitation) were determined by using enzymatic kits from Roche Diagnostics with a Hitachi 902 autoanalyzer (Roche Diagnostics). Low-density lipoprotein cholesterol (LDL-C) values were computed according to the formula by Friedewald et al [17].

Homeostatic model assessment was calculated with the following formula [18]: insulin (mIU/L) × glucose (in mmol/L)/22.5.

The upper quartile of HOMA emerged to be more than 2.245 and was considered to represent HOMA-IR for this sample, as previously proposed [18]. Homeostatic model assessment displayed the following diminishing brackets in the lower quartiles: 1.486 to 2.244, 1.01 to 1.485, 1.009 or less.

Blood pressure was measured in the sitting position on the right arm, and the mean of 2 recordings 3 minutes apart was recorded. Height was measured without shoes using a measuring stick and weight in light indoor clothes using scales. 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. Body mass index was calculated by the computer as the weight in kilograms divided by the square of height in meters. In regard to cigarette smoking, nonsmokers, past smokers, and current smokers formed the categories. Physical activity was graded by the participant himself into 4 categories of increasing order with the aid of a scheme [16]. All parameters reported and used in regression analyses, as well as the diagnosis of MS, refer to baseline data.

Individuals with MS were identified when 3 of the 5 criteria of the National Cholesterol Education Program (ATP III) [19] were met, and diabetes was diagnosed with criteria of the American Diabetes Association [20].

Diagnosis of CHD was based on the presence of angina pectoris, on a history of myocardial infarction with or

Table 1
Determinants of log HOMA in multiple linear regression (n = 1280)

	Men (n = 567)			Women (n = 713)		
	β Coefficient	SE	P	β Coefficient	SE	P
Waist circumference (cm)	.011	0.001	<.001	.0081	0.001	<.001
Triglyceride (mg/dL)	.00083	0.000	<.001	.00067	0.000	<.001
LDL-C (mg/dL)	.00033	0.000	NS	.000048	0.000	NS
Current smoking	−.05	0.02	<.001	−.009	0.014	NS
Log CRP	.02	0.02	NS	.049	0.022	.026
Physical activity grade 1-4	.03	0.02	.073	.015	0.017	NS

Model as a whole was significant (F = 35.9 in men, F = 27.3 in women; both P < .001) and explained 28% of HOMA variance in each.

without accompanying Minnesota codes of the electrocardiogram [21], or on a history of myocardial revascularization. Among women, typical angina and age of older than 45 years were prerequisite for a diagnosis. Isolated typical angina in women and atypical angina in men were considered as suspect diagnosis. "Ischemic type" electrocardiogram changes of greater than minor degree (codes 1.1-2, 4.1-2, 5.1-2, 7.1) were considered as myocardial infarct sequelae or myocardial ischemia, respectively. Coronary heart disease diagnosis in more than one quarter of patients was based on history of interventional procedures. Evidence of a sustained acute myocardial infarction existed in 23% of the patients.

The baseline sample was reexamined 2.2 years later, resulting in 2960 person-years of follow-up, during which 20 deaths were registered, 11 of which were of coronary and 1 of cerebrovascular origin. Moreover, 32 nonfatal CVD were diagnosed to have been newly developed, which along with those having CVD at baseline, resulted in a total of 165 participants with fatal or nonfatal CVD (10.8%). Cardiovascular disease at baseline was not excluded because, otherwise, outcome measure would have inadequate statistical power in this study.

2.3. Data analysis

Descriptive parameters were shown as mean ± SD and in percentages. Because of the skewed distribution of HOMA, insulin, and CRP values, these parameters were log-transformed for calculations. Two-sided t tests and Pearson χ^2 tests were used to analyze the differences in proportions between groups. Significance between multiple groups was assessed by analysis of variance and checked by Tukey post hoc test. Multiple linear regression analyses for HOMA were performed with continuous parameters. The contribution of a significant independent variable in association with log HOMA in linear regression analysis was calculated by multiplying the related mean value of the variable with the β coefficient and then log-transforming it. Estimates for CHD likelihood and 95% confidence intervals (CIs) were obtained by use of logistic regression analysis in models that controlled for age and other confounders. The increment corresponding to a 1 SD rise in HOMA by logistic regression analysis was calculated by dividing the log of the odds ratio (OR) value to the HOMA gradient across the groups per 1 SD, and then taking its anti-log. Statistical analyses were performed using SPSS-10 for Windows (SPSS, Chicago, IL, no. 9026510). A P value of less than .05 on the 2-tailed test was considered statistically significant.

3. Results

Metabolic syndrome was identified in 527 subjects (34.4%) in the study population (30.1% in men, 37.8% in women). Geometric mean HOMA index was similar in both sexes, 1.45 (±2.0) in men and 1.52 (±1.9) in women, exhibiting no significant change with aging in men, but increasing in women after menopause. Individuals with MS had significantly (P < .001) higher HOMA geometric mean values than those without MS in both sexes: 2.13 vs 1.22 in men, 2.06 vs 1.26 in women.

3.1. Determinants of HOMA

In a linear regression model comprising age, waist circumference, cigarette smoking status, physical activity, triglycerides, LDL-C, and CRP levels in 1280 subjects, waist circumference proved to be the strongest significant (P < .001) determinant of HOMA in both sexes, followed by triglycerides and, inversely, smoking in men and log CRP in women (Table 1). Taking into account the mean values of waist circumference, this variable contributed 1.02 (93 × 0.011) and 0.74 (91 × 0.0081) to HOMA in men and women, respectively, roughly 8-fold that of triglycerides.

3.2. Metabolic syndrome and insulin resistance groups: proportions and features

The proportion of groups with insulin sensitivity, MS, and IR in men and women are presented in Table 2 and Fig. 1. Metabolic syndrome and/or IR combined were noted in 42.1% of men and 46.9% of women. Women tended to have

Table 2
Distribution of sex-specific groups of MS and IR in the study population with normal glucose regulation (references of comparisons provided)

	Total	NoMS/NoIR	IR/NoMS	MS/NoIR	MS + IR
Total (%)	1534	848 (55.3)	159 (10.4)	303 (19.8)	224 (14.6)
Men (%)	691	400 (57.9)	83 (12)	119 (17.2)	89 (12.9)
Women (%)	843	448 (53.1)	76 (9)	184 (21.8)	135 (16)
Reilly et al [6]	840	527 (62.7)	104 (12.4)	81 (9.6)	128 (15.2)
Cheal et al [11]	443	272 (61.4)	80 (18.1)	22 (5)	69 (15.6)
Egan et al [7]	141	65 (46.1)	23 (16.3)	23 (16.3)	30 (21.3)

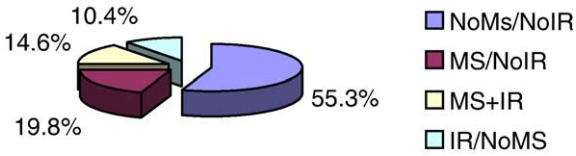

Fig. 1. Distribution of prevalences of the insulin-sensitive (NoMS/NoIR) group and the 3 subgroups of IR and MS is graphically illustrated.

MS unaccompanied by IR, men tended to have IR unaccompanied by MS slightly more often, whereas the proportions of HOMA-IR were similar with 25% in both sexes. Among persons with MS and/or IR, overlapping of the 2 conditions was encountered in 31% of men and 34% of women.

Characteristic features of the categories with and without MS or IR are summarized in Table 3. Parameters that lacked differentiating sex-specific features across groups are presented in a combined fashion, whereas age, current smoking status, levels of triglycerides, and HDL-C are provided separately because of sex-related intergroup differences.

For purpose of simplifying, salient features of the 3 groups involving IR and MS are summarized in Table 4. The following characteristics emerge from this tabulation. The IR-alone group (IR/NoMS) having a similar age distribution and blood pressure as the insulin-sensitive individuals lacks the dyslipidemia of MS and physical inactivity, but distinguishes itself significantly from the main category of NoMS/NoIR in wider waist girth, tendency to elevated CRP, a low proportion of male current smoking, and (by definition) high serum concentrations of fasting glucose and insulin. The MS/NoIR group distinguishes itself, on the other hand, from the IR category alone in having the dyslipidemia of MS (including high apoB), physical inactivity, significantly higher waist girth, CRP, and blood pressures in both sexes, and women being older, but in having normal glycemia and significantly lower insulin concentrations and HOMA. The MS + IR group differs additionally from the MS group only by still wider waist girth and higher serum concentrations of CRP, triglycerides,

Table 4
Synopsis of features in categories of IR and MS

	IR/NoMS	MS/NoIR	MS + IR
Waist circumference	High	Higher	Highest
Fasting glucose, insulin, HOMA	High	Normal (-high)	High
Triglycerides, CRP	Normal (-High)	High	Highest
Apo B, HDL-C, physical activity	Normal[a]	High, resp. low	High, resp. low
Blood pressures	Normal	High	High
Age	Normal	High in women	High in women
Current smoker prevalence	Low (men), high (women)	Low	Low
Prevalence of CV disease	Normal (-high)	Higher	Highest

[a] Normal denotes reference to the large insulin-sensitive group with no MS.

Table 3
Mean values and proportions of risk variables in men and women by categories of insulin sensitivity, MS, and IR

	NoMS/NoIR	IR/NoMS	MS/NoIR	MS + IR
Adults (N = 1534)				
Waist circumference (cm)	86.6 ± 10.1	93[a] ± 11.2	97.9[a] ± 8.9	100.5[a] ± 8.9
Systolic blood pressure (mm Hg)	123.6 ± 22	127.1 ± 21.6	142.7 ± 26.3	140[a] ± 22
Diastolic blood pressure (mm Hg)	77.7 ± 12	80.4 ± 11.1	88.6 ± 13.3	87[a] ± 12.8
Fasting glucose (mg/dL)	81.3 ± 12	94.9[a] ± 18.5	83.7 ± 15.4	97.8 ± 18.9
LDL-C (mg/dL); n = 1428	115.9 ± 34.4	113.4 ± 34.9	120 ± 36.5	120.8 ± 36
Apolipoprotein B (mg/dL); n = 1202	105.6 ± 35.7	106.5 ± 37.4	123.7[a] ± 45.6	127.4 ± 41.6
Physical activity grade	2.35 ± 0.73	2.33[a] ± 0.71	2.18 ± 0.75	2.13 ± 0.69
Log CRP (mg/L)[b] n = 1458	1.67 ± 3.26	2.06 ± 2.7	2.52[c] ± 2.85	3.30[a] ± 2.74
Log fasting insulin[b] (mIU/L)	5.35 ± 1.75	13.0[a] ± 1.74	7.09[a] ± 1.49	14.5 ± 1.67
Log HOMA index[b]	1.01 ± 1.77	3.25[a] ± 1.49	1.4[a] ± 1.42	3.57 ± 1.66
Hypertension[d] (%)	27.7	35.2	76.2[a]	76.3
CVD, n (%)	67 (7.9)	17 (10.7)	43 (14.2[c])	38 (17.0[c])
Men (n = 691)				
Age (y)	52.3 ± 12.5	53.1 ± 10.7	53.1 ± 10.8	52.6 ± 10.9
Fasting triglycerides (mg/dL)	143.1 ± 82	166.4 ± 105	205.5[a] ± 106.2	248[a] ± 117.5
HDL-C (mg/dL)	40.1 ± 9.5	40[a] ± 11.5	34.3 ± 7.3	32.7 ± 6.6
Current smoker (%)	51[a]	33.7[c]	39.5	40.4
Women (n = 843)				
Age (y)	49.8 ± 11.9	49.7 ± 10.5	54.6[a] ± 11.5	55.5 ± 10.1
Fasting triglycerides (mg/dL)	107.8 ± 49.3	114 ± 39.4	171.8[a] ± 74	202[a] ± 93
HDL-C (mg/dL)	48.4 ± 11.3	47.8[a] ± 10.1	40.9 ± 7.5	40.2 ± 7.8
Current smoker (%)	20.1[c]	17.1	10.9	11.1

[a] Significantly higher than the category with the next lower mean value; hence, categories with still higher values are automatically significantly different as well. For example, the geometric mean of insulin in the IR/NoMS category (13.0) and automatically 14.5 are significantly higher than 7.09, and 7.09 is significantly higher than 5.35 in the NoIR/NoMS group.

[b] Log-transformed mean ± SD.

[c] Significantly higher than the category with second next lower mean value.

[d] Includes high normal blood pressure.

fasting glucose, and insulin. Cardiovascular disease prevailed increasingly stronger as the categories changed from NoMS/NoIR to IR alone, MS alone, and MS + IR, although significantly elevated prevalence related only between the NoMS/NoIR and the 2 MS groups.

3.3. Cardiovascular disease risk with respect to MS and IR in 2 different models

In logistic regression analysis for CVD in a model with 1348 subjects having normal glucose regulation, participants with IR (HOMA >2.245)—compared with those without—conferred a borderline significant 43% excess risk in all adults and a significant 89% excess risk in men (OR, 1.89; 95% CI, 1.03-3.47) when controlled for MS, log CRP, LDL-C, smoking status, physical activity grade, sex, and age (Table 5). In this model, in which MS did not attain significance, 1 SD increment in HOMA (gradient 3.07-fold = 1.51 SD) implicated among men a 47% increase in CVD risk, independent of the confounders. This increment was with reference to all insulin-sensitive adults with or without MS. Among the covariates, age, LDL-C, CRP, and physical inactivity remained independently significant in men and women combined. The association of IR for CVD likelihood did not reach significance in women.

We analyzed a second model comprising the 4 groups of MS and IR, along with the identical 6 further variables, namely, sex, age, smoking, LDL-C, physical activity grade, and log CRP. The referent here was the large NoMS/NoIR group, and again 1348 participants were included (Table 6). In all adults, the MS + IR group (OR, 1.80) was associated with significantly higher CVD likelihood, whereas the MS/NoIR group (OR, 1.43) reached only borderline significance. The IR/NoMS group also exhibited a borderline significant OR, which with 1.71 was at least in the order of that in the 2 MS groups. In men, the adjusted OR in the IR/NoMS group exceeded 2.2 (95% CI, 0.97-5.11; P = .06), whereas the association in the MS/NoIR group did not reach significance (P = .16) because of a small sample (153 subjects) being encoded. In women, none of the MS-IR groups had a significant association; rather, age and physical activity remained significant.

Table 5
Cardiovascular disease risk of HOMA-IR adjusted for MS and 6 other variables

	β Coefficient	SE	OR	95% CI	P
Adults					
HOMA-IR	.36	0.21	1.43	0.94-2.17	.092
MS	.26	0.20	1.30	0.87-1.94	.20
Physical activity	−.37	0.15	0.69	0.51-0.93	.015
Log CRP	.50	0.20	1.65	1.13-2.43	.01
LDL-C (mg/dL)	.006	0.003	1.006	1.001-1.011	.022
Age (y)	.065	0.009	1.068	1.049-1.087	.001
Men					
HOMA-IR	.64	0.31	1.89	1.03-3.47	.039
MS	.40	0.30	1.49	0.83-2.67	.18
Physical activity	−.24	0.20	0.78	0.53-1.16	.22
Log CRP	.65	0.28	1.92	1.12-3.30	.018
LDL-C (mg/dL)	.006	0.004	1.006	0.998-1.014	.144
Current smoker	.38	0.39	1.47	0.68-3.16	.33
Age (y)	.056	0.013	1.057	1.03-1.085	.092

Model included sex and 596 men and 752 women having 68 and 79 cases of CVD. Referents were 1022 insulin-sensitive and 875 men and women without MS, respectively. Smoking status not significant in adults.

Table 6
Cardiovascular disease risk of IR/MS groups adjusted for 6 other variables

	β Coefficient	SE	OR	95% CI	P
Adults					
IR/NoMS	.54	0.32	1.71	0.91-3.20	.096
MS/NoIR	.36	0.24	1.43	0.89-2.29	.139
MS + IR	.59	0.25	1.80	1.10-2.95	.019
Physical activity	−.38	0.15	0.69	0.51-0.93	.015
Log CRP	.51	0.20	1.66	1.13-2.44	.01
LDL-C (mg/dL)	.006	0.003	1.006	1.001-1.011	.022
Age (y)	.066	0.009	1.068	1.049-1.087	.001
Men					
IR/NoMS	.80	0.42	2.22	0.97-5.11	.060
MS/NoIR	.52	0.37	1.68	0.81-3.48	.161
MS + IR	.99	0.37	2.70	1.30-5.62	.008
Physical activity	−.24	0.20	0.78	0.53-1.15	.22
Log CRP	.66	0.28	1.93	1.12-3.31	.018
LDL-C (mg/dL)	.006	0.004	1.006	0.998-1.014	.145
Current smoker	.38	0.39	1.47	0.68-3.16	.33
Age (y)	.056	0.013	1.058	1.03-1.085	.001
Women					
IR/NoMS	.31	0.51	1.36	0.50-3.68	.54
MS/NoIR	.14	0.32	1.15	0.61-2.17	.66
MS + IR	.30	0.35	1.34	0.68-2.67	.40
Physical activity	−.51	0.25	0.60	0.37-0.97	.037
LDL-C (mg/dL)	.006	0.004	1.006	0.999-1.013	.083
Age (y)	.076	0.013	1.079	1.05-1.11	.001

Model included sex, smoking, and 596 men and 752 women having 68 and 79 cases of CVD, respectively. Referents were 748 insulin-sensitive men and women without MS.

4. Discussion

In a middle-aged and elderly population sample in which participants with diabetes and IFG were excluded, this large cross-sectional study with a brief follow-up found that HOMA-IR, mainly determined by waist circumference, and the NCEP-defined MS had limited overlapping. Although the IR as well as MS groups disclosed elevated CVD risk, the nonconcordant "IR/NoMS" group distinguished itself from the "MS/NoIR" category in having significantly lower waist girth, blood pressures, apoB and triglyceride levels, and higher HDL-C, glucose, and insulin levels and physical activity in both sexes, and women being younger. In men and in both sexes, IR, overall, was more significantly associated with CVD likelihood than MS, after adjustment for salient covariates. Insulin resistance without MS implicated in men roughly a 2-fold risk compared with the NoMS/NoIR group, independent of MS and important confounders.

As criterion of abdominal obesity, more than 94 cm rather than more than 102 cm as recommended by the ATP III was selected for men after having tested both. As yet unpublished analysis of the Turkish Adult Risk Factor Study male cohort namely showed that the higher (as compared with the lower)

threshold failed to detect one third of the total number of patients with diabetes, most abdominally obese men (in contrast to women), and the significant associations between waist girth on the one hand and total cholesterol or smoking, and the likelihood of CVD on the other. Because in women, more than 88 cm of waist circumference appeared appropriate, this criterion was retained in identifying MS.

When controlled for concentrations of triglycerides, LDL-C (or apoB; not reported in Results), and log CRP, waist circumference proved to be the strongest *determinant* of the HOMA index. This is in agreement with the findings obtained with HOMA-IR in 542 Arab Americans [22] and with HOMA index being positively correlated with CRP among Koreans [23].

4.1. Degree of concordance between MS and IR

Cheal et al [11] evaluated the ability of the ATP III criteria to identify individuals with IR. Body mass index was substituted for waist circumference, and the top tertile of steady-state plasma glucose was used for IR. They concluded that the ATP III criteria (which had a predictive value of 76%) do not provide a sensitive approach to identifying insulin-resistant individuals. Examining the association of IR and NCEP-defined MS in 840 asymptomatic, nondiabetic men and women with a family history of premature CVD, Reilly et al [6] recently reported that both MS and HOMA index were associated with coronary atherosclerosis independent of established factors, including CRP. They concluded that biomarkers of IR provided (in addition to NCEP criteria for MS) incremental value in assessing CVD risk.

Concordance between MS and IR existed in one third of men or women involved in these 2 conditions, somewhat lower than overall in the 3 US studies [6,7,11] in which this was calculated by us to be 40%, stressing that overlapping is limited. Moreover, although in samples of US adults, the MS/NoIR constituted with 9% of the total the smallest of the 3 abnormal groups, this group had the greatest proportion (19.8%) among Turkish adults. The comparative high prevalence of MS/NoIR among Turks raises the question whether the highly prevailing low HDL-C levels, considered to be predominantly of genetic origin [24], might largely contribute to its high proportion. This is unlikely according to Table 3, wherein it can be noted that, in this category as well, the mean value of HDL-C retains its reciprocality to plasma triglycerides and its relationship with other components of MS (with little regard to an association with IR).

It has been previously expressed that the NCEP-defined MS, which does not include a measure of insulin, might not detect the totality of IR, as compared with that defined by World Health Organization criteria [6,25-27]. In the 3 US study samples [6,7,11] of subjects designated to have IR, 47.7% were categorized to that without NCEP-defined MS, a figure close to our 42%. With respect to IR, the sensitivity of the ATP III criteria in our study was calculated as 58%, the specificity 74%, and the positive predictive value 43%. These indicate a higher sensitivity, but a slightly lower specificity than in the study of Cheal et al [11].

4.2. Differences between MS without IR and IR without MS

The MS/NoIR group had normal glycemia and significantly lower insulin concentrations and HOMA than individuals with IR/NoMS; on the other hand, they had the anticipated dyslipidemia of MS (including high apoB), physical inactivity, significantly higher waist girth and blood pressures in both sexes, and women were older. A substantial share of men and of younger centrally obese women, despite having IR, were not qualified for ATP III–defined MS due to the lack of dyslipidemia and as yet "low" blood pressure. Hypertension is known to be a covariate accompanying MS later in the course, as is diabetes, which was excluded in this study sample. Cardiovascular disease prevalence progressively increased from NoMS/NoIR to IR alone, MS alone, and MS + IR; and risk appeared to be paralleled chiefly by waist circumference, triglycerides, and CRP, all independent predictors or determinants of CVD in Turkish men [28,29]. A lower threshold of waist girth seems to be required for IR to develop than for dyslipidemia and hypertension, which may have also alternate pathways other than IR, perhaps mediated by physical inactivity. A smaller waist circumference was observed in persons with IR than in patients with MS also in the study of McLaughlin et al [30].

Similar to MS and IR, poor concordance was observed between IFG and impaired glucose tolerance (IGT) [31]. A progressive decline in insulin sensitivity was noted when moving from normal glucose tolerance to IGT and to subjects with diabetes, whereas insulin secretion followed an inverted U-shaped form. In was concluded in the Botnia Study [31] that IFG is characterized by basal IR and other features of the MS, whereas subjects with IGT have impaired insulin secretion in relation to glucose concentrations. It is unlikely that MS/NoIR, constituting one fifth of the present study sample, would represent occult IGT and impaired insulin secretion, because levels of fasting glucose were not significantly elevated.

In the NHANES III, 1938 persons with the MS—as opposed to those without the MS—had a 5.25-fold HOMA index, 1.46-fold CRP, and 2.97-fold apoB levels after adjustment for age, sex, body mass index, physical inactivity, smoking, and alcohol intake [32]. The proportion of overlap between MS and IR was not reported. Significantly higher nearly 2-fold log CRP and more than 2-fold log HOMA values existed in our sample in individuals with MS, compared with the insulin-sensitive group.

4.3. Cardiovascular disease risk in IR and MS

Our study shows that in middle-aged and elderly Turkish men, overall IR independently confers high excess risk, and IR without evidence of NCEP-defined MS tends to confer high excess risk independent of MS and other established risk factors. The magnitude of the multiadjusted borderline significant excess risk in IR/NoMS was 52% for an

increment of 1 SD in HOMA index, compared with the NoIR/NoMS. This was additive to the significant association of MS with CVD likelihood. In its CVD association, waist circumference mediated HOMA index, partly in men and largely in women. Individual risk factors were reported to predict subsequent CVD in the Strong Heart Study, in which 2283 nondiabetic American Indians were examined, of whom 35% had the ATP III–defined MS; risk of CVD did not increase as a function of either baseline IR or MS [8] with which our findings are at some variance.

Every fourth or fifth person with MS and/or IR had IR without meeting criteria for MS and, yet, proved to be associated with independently raised CVD. This finding supports the recent observation by Reilly et al [6] that biomarkers of IR provided incremental value in assessing CVD risk, in addition to NCEP criteria for MS, and extends their observation on coronary artery calcification to clinical CVD and to the involved risk in men being higher than that of MS.

Limitations of the study include the largely cross-sectional nature with follow-up yielding about one quarter of outcome and that a soft end point such as angina pectoris has been included as outcome measure. Any potential bias due to inaccuracy in the diagnosis of CVD, however, would tend to dilute rather than augment the association between CVD likelihood and the IR groups. The strength of the study resides in its being the largest to date, being based on a representative population sample and having also excluded persons with IFG.

The present study's findings do not contest the clinical utility of the MS as defined by ATP III. In fact, by pointing out that MS without IR has a *global* CVD likelihood comparable to that of IR without MS, they support the concept that IR is not a prerequisite for a cluster of related abnormalities that increase CVD risk, which led to the adoption of the name MS rather than IR syndrome. Our findings, however, demonstrate that MS is heterogeneous as to CVD risk and IR adds to the CVD risk of MS, as they conversely suggest that the presence of IR in men is associated with greater independent CVD risk than MS as a whole and that IR/NoMS imparts a CVD risk comparable to overall MS. This runs against arguments cited by Cheal et al [11] as to the possible lack of importance to identify insulin-resistant individuals in the absence of dyslipidemia and hypertension. Thus, search for a more appropriate definition of this MS that would incorporate the element of IR might be beneficial, at least for certain populations. It should be pointed that in this sample population, the descendants of a crossbreed of races are whites, and not Asians.

In conclusion, a substantial proportion of obese men and women, despite having IR, is not detected as ATP III–defined MS due to a less widened waist circumference, lack of associated atherogenic dyslipidemia, and/or relatively low blood pressure. MS/NoIR is more common than IR/NoMS. Insulin resistance implicates an associated 50% excess CVD risk (per 1 SD HOMA index) in men independent of MS and several MS-unrelated established risk factors.

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