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SCIENCE DIRECT

Metabolism Clinical and Experimental 54 (2005) 800–808

Metabolism
Clinical and Experimental

www.elsevier.com/locate/metabol

Sex difference in development of diabetes and cardiovascular disease on the way from obesity and metabolic syndrome
Prospective study of a cohort with normal glucose metabolism

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Received 19 August 2004; accepted 19 January 2005

Abstract

Aim: The objective of this study was to investigate sex-specific differences existing on the way from (abdominal) obesity and metabolic syndrome (MS) to type 2 diabetes mellitus (DM) and cardiovascular disease (CVD).

Methods: A population sample of 1974 men and women, representative of Turkish adults (mean age, 48 years), with normal glucose metabolism (GM) and free of CVD at baseline, was prospectively evaluated at a mean 4.1 years of follow-up. The term abnormal GM designated both DM and impaired fasting glucose (IFG). Metabolic syndrome was identified in 29% of men and 40% of women by the criteria of the National Cholesterol Education Program guidelines. Fatal and nonfatal CVD, diagnosed by clinical findings and Minnesota coding of resting electrocardiograms, developed in 121 subjects.

Results: The cohort was dichotomized by the presence or absence of MS and of obesity defined by a body mass index of 30 kg/m^2 or greater. Compared with the major female group with no obesity or MS, women with MS, regardless of the presence of obesity, predicted highly significantly the development of abnormal GM with relative risks exceeding 2, whereas no independent significant association was noted in men with MS. Similar divergence of sexes pertained to the prediction of diabetes. When age, smoking status, grade of physical activity, IFG, DM, and the 4 groups with obesity and MS were analyzed for the prediction of CVD by logistic regression, men with MS, regardless of the presence of obesity, predicted highly significantly CVD (with relative risks ranging from 2 to 4), but neither DM nor IFG contributed independently. Conversely, in women, abnormal GM predicted CVD independent of age, smoking status, and grade of physical activity, but the groups with obesity and MS failed to significantly contribute independently.

Conclusions: In populations with prevalent MS, whereas women with normal GM are prone to DM within the context of MS and are exposed to CVD risk primarily by way of DM, men are prone to visceral adiposity, less susceptible to DM, and run CVD risk primarily by the intermediary of MS, largely independent of the DM component.

1. Introduction

A main pathophysiological road from obesity and adverse body fat distribution goes over insulin resistance and type 2 diabetes mellitus (DM) to cardiovascular disease (CVD). A known major sex difference is that men have unfavorable body fat distribution and higher vulnerability to CVD. Type 2 diabetes mellitus has been assessed to prevail equally in most populations (with some evidence of male preponderance in early middle age), although having exhibited a pronounced preponderance in women in the first half of the last century [1]. A recent study of known diabetes in 8 European countries reported no consistent sex differences in national prevalence rates [2]. Diabetic women, however,

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0026-0495/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2005.01.025

generally have a greater relative risk (RR) for CVDs than diabetic men, and newly diagnosed diabetic women showed higher RR for cardiovascular death than diabetic men in the recent large DECODE Study [3]. Equal prevalence in sexes holds true also for the metabolic syndrome (MS) in the United States, but not among African and Hispanic Americans [4] as well as in Turkish adults [5] among whom female preponderance exists. We have the impression that Turkish postmenopausal women who are generally very prone to obesity tend to develop DM more than men and thereby sustain CVD, whereas Turkish men (who have a greater susceptibility to visceral adiposity than women [6]) sustain CVD primarily by the intermediary of the MS.

We tested the latter hypothesis among Turkish adults who have higher prevalences than do Westerners of low high-density lipoprotein cholesterol (HDL-C) [7,8] and MS [5]. The aims of this study are to evaluate prospectively (*a*) the sex-specific predictors of abnormal glucose metabolism (GM) (defined below) and (*b*) the sex-specific determinants of fatal and nonfatal CVD after accounting for DM and MS in a population sample representative of middle-aged and elderly Turkish adults.

2. Methods

2.1. Population sample

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 all 7 geographical regions of the country [8,9]. Because HDL-C measurements had not been performed before the follow-up visit in 1997-1998, the latter examination formed the baseline. Further follow-ups were carried out in 2000, 2001-2002, and in 2003. Participants were aged 28 years or older at baseline examination. The survey was representatively stratified for sex, age, geographical regions, 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 2000. The study was approved by the committee of the Turkish Society of Cardiology (Istanbul). Data were obtained by history of the past years via a questionnaire, physical examination of the cardiovascular system, recording of a resting electrocardiogram (ECG), and laboratory analyses. After exclusion of participants with 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 but were 1 year younger. A total of 2225 men and women was prospectively examined in this study. Mean age of the 1091 men included in the study was 48.8 (±12.8) years at baseline and of the 1134 women was 48 (±12.5) years. Participants were traced for a mean of 4.1 (±1.31) years (total follow-up being 9070 person-years). Of these, 251 participants with abnormal GM (140 with DM and 111 with impaired fasting glucose [IFG]) at baseline examination were also excluded, leaving 1974 adults (992 men and 982 women) with normal GM at onset of study who were followed up for a mean of 4.1 years.

2.2. Definitions of IFG, glucose tolerance, DM, GM, and MS

In addition to subjects identified by self-report and in accordance with the American Diabetes Association/World Health Organization criteria [10], those with a fasting plasma glucose level of 126 mg/dL or greater and/or a 2-hour plasma glucose level of 200 mg/dL or greater were considered to have diabetes. Subjects with a fasting plasma glucose level between 110 and 125 mg/dL were considered to have IFG. Two men and one woman who showed a 2-hour plasma glucose level between 140 and 200 mg/dL during follow-up were considered to have impaired glucose tolerance (GT) and were grouped together with 76 subjects who had IFG. Subjects who had a fasting glucose level below 110 mg/dL or a 2-hour postprandial glucose level below 140 mg/dL were considered to have normal GM. The term *abnormal GM* was used to encompass both DM and IFG.

Identification of MS conformed to the definition recommended by the National Cholesterol Education Program guidelines [11], namely when 3 or more of the following 5 risk determinants were present: waist circumference (men, >102 cm; women, >88 cm), triglyceride levels of 150 mg/dL or greater, HDL-C (men, <40 mg/dL; women, <50 mg/dL), blood pressure (BP) of ≥130/≥85 mm Hg, and a fasting glucose level of 110 mg/dL or greater.

2.3. Measurement of risk factors and validation

Blood pressure was measured twice in the sitting position on the right arm using a sphygmomanometer (Erka, Germany), after at least 5 minutes of rest. First appearance and disappearance (phase V) of Korotkoff's sounds were used to define the pressures. Readings were recorded to the nearest even number, and the mean of 2 recordings 3 minutes apart was computed. Waist circumference was measured—with the subject standing and wearing only an underwear—at the level midway between the lower rib margin and the iliac crest, whereas that of the hip 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. Physical activity was graded by the participants themselves into 4 categories of increasing order with the aid of a scheme [9].

Serum concentrations of cholesterol, fasting triglycerides, HDL-C, and glucose were determined by the enzymatic dry chemistry method using a Reflotron apparatus (Böhringer Mannheim, Mannheim, Germany). Glucose was sampled in the postabsorptive state in 82% of the participants and

2 hours postprandially in the remaining 18%. Low-density lipoprotein cholesterol (LDL-C) values were computed according to the Friedewald formula. Concentrations of insulin were determined by the chemiluminescent immunometric method using Roche kits and an Elecsys 1010 immunoautoanalyzer (Roche Diagnostics, Mannheim, Germany). Concentrations of C-reactive protein (CRP) were measured by the Behring nephelometry using an N Latex CRP mono reagent (Behring Diagnostics, Marburg, Germany), as were serum apolipoprotein (apo) AI and B values. Plasma fibrinogen levels (from citrated blood) were measured by the modified Clauss method using a Behring Fibrintimer II coagulometer and Multifibren U kit. External quality control was performed with a reference laboratory in a random selection of 5% to 6% of the participants.

2.4. Ascertainment of cause of death and diagnosis of coronary heart disease

Information on cancer, stroke, accidents, sudden death, and others were elicited from first-degree relatives and local health center staff, and cause of death was assigned in the survey with the consideration of the preexisting clinical and laboratory findings elicited during the biennial follow-ups. Sudden death was defined in this study as death arising within 24 hours of onset of symptoms and was considered of cardiovascular origin in the absence of further information. In women, death at an age younger than 45 years was considered of noncoronary origin. Coronary heart disease death included death from heart failure 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, on a history of myocardial infarction with or without accompanying Minnesota codes of the ECG [12], or on a history of myocardial revascularization in the course of biennial examinations. Retrosternal or precordial distress coming on exertion, lasting 2 to 15 minutes and relieved by rest, was designated as typical angina. Among women, typical angina at an age younger than 45 years 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. Cardiovascular disease diagnosis in nearly one quarter of patients was based on history of interventional procedures (12 aortocoronary bypass surgeries, 6 coronary angioplasties with or without stenting, 9 coronary angiograms). A cerebrovascular accident was diagnosed when a new stroke occurred or when death followed such an event.

In a total of 92 subjects in this study, nonfatal CVD was considered to have developed during the follow-up of the survey among subjects with normal GT at baseline. Furthermore, 66 deaths of which 29 were identified as resulting from CVD (men, 18; women, 11) occurred. Cardiovascular disease occurred at a mean age of 65.5 years in men and 65.8 years in women.

2.5. Data analysis

Because of the skewed distribution of CRP and fasting insulin values, these parameters were log transformed for calculations. 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 analysis of variance and checked by Tukey's post hoc test. The independent associations between the groups with (abdominal) obesity, MS, and the end point of combined CVD morbidity-mortality on prospective analyses were evaluated by logistic regression. Relative risk estimates and 95% CIs were obtained. Regression models were adjusted for age and sex. A P value less than .05 was considered statistically significant. Multiple regression analyses of the data were carried out using SPSS-10 for Windows package (SPSS Inc, Chicago, Ill).

3. Results

Metabolic syndrome was identified in 31.5% (344/1091) of men before exclusion of those with abnormal GM and in 29.1% (289/992) of men with normal GM. The corresponding proportions in women were 44.7% (507/1134) and 40% (393/982).

3.1. Features of the 4 groups with normal GM

Characteristics of the sample population with normal GM and free of CVD at baseline examination in 1997-1998 are presented in Table 1, separately for men and women and by dichotomized groups of obesity (BMI, ≥ 30 kg/m^2) and MS. The main category with no obesity and no MS reveals a tendency toward abdominal obesity among women accompanied by high serum triglyceride levels in men, and especially of low HDL-C (39.5 and 48 mg/dL in men and women, respectively). In addition, most men were smokers. The obese-only category differed from the latter group in both sexes by waist circumference, BP measures, and total cholesterol. The MS-only category distinguished itself from the obese-only group obviously by lower waist circumference and fasting insulin but also by higher systolic BP, triglycerides, apo B and TC/HDL-C ratio, lower HDL-C levels in both sexes, and pulse pressure in women. Subjects with both obesity and MS differed significantly from the MS-only group by waist circumference, diastolic BP, pulse pressure, and CRP concentrations in both sexes. Nonobese women with MS had significantly higher CRP levels than nonobese women without MS. Geometric mean values for CRP were significantly higher in women with MS (3.00 mg/L) than in men with MS (2.09 mg/L).

3.2. Incidence of newly developing abnormal GM

New DM and new IFG developed in the follow-up in 36 and 32 men, respectively, and in 46 and 47 women, respectively. These correspond to annual incidences of IFG and DM of 8.9 and 7.9 per mille, respectively, in men, and to

Table 1
Baseline characteristics of participants with normal GM and free of CVD by groups and sex

	Men (n = 992)								Women (n = 982)							
	Nonobese, no MS (n = 643)		Obese only (n = 60)		MS only (n = 197)		MS + obese (n = 92)		Nonobese, no MS (n = 479)		Obese only (n = 110)		MS only (n = 157)		MS + obese (n = 236)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (y)	47.2	12.9	49	11.2	48.9	11.8	50.3	12.2	44	12.1	49.4	11.8	51.5	12.2	49.3[a]	11.2
Waist circumference (cm)	89.2	8.8	103[a]	8.4	96.6[a]	8	109[a]	8	81.5	9.3	98.8[a]	9.1	90.8[a]	8	100.6	9.2
Systolic BP (mm Hg)	120.2	17.8	131[a]	21.6	138[a]	20.7	142.4	25.7	120.8	20.8	131[a]	22.2	142[a]	25.7	152[a]	27.2
Diastolic BP (mm Hg)	77	10.6	85.4[a]	13.9	88.7	12.3	90.7[a]	14.6	77.3	11.9	83.7[a]	13.9	87.4[a]	14.6	93.1[a]	13.9
Pulse pressure (mm Hg)	43.2	12.8	45.9[a]	13.5	49.4	15.1	51.7[a]	17.6	43.5	13.4	47.3[a]	12.9	54.1[a]	17.6	58.5[a]	18.2
Fibrinogen (g/L)	2.85	1.1	2.76	0.78	2.88	1.07	2.95	1.18	2.99	1	3.28	1.27	2.98	1.18	3.14	1
Log CRP[b] (mg/L)	1.63	2.9	2.32	3.1	1.83	2.7	2.66[a]	3	1.33	3	2.4	2.5	2.13[a]	3	3.57[a]	2.5
Log fasting insulin[b] (mIU/L) n = 521/569	6.36	2.1	9.77	2	7.71[a]	1.6	9.87	1.6	6.03	2	9.35	1.6	8.09[a]	1.6	8.86	1.6
Total cholesterol (mg/dL)	175.5	34.2	187[a]	37.3	195.6	39.4	190.9	37.4	175.5	35	192[a]	37.2	197.9	37.4	196.7	38.7
HDL-C (mg/dL)	39.4	12.8	38.3	13.1	32.5[a]	8.9	32.9	8.8	47.9[a]	13	52.6	15.4	39.4[a]	8.8	39	8.6
LDL-C (mg/dL)	110.9	29.5	122.5	34.8	119.8	35.4	119[a]	31.3	107.8	31.7	120[a]	33.3	126.4	31.3	125.2	34.4
Triglycerides (mg/dL)	127.4	79.8	132.8	64.7	221.3	102.7	209[a]	128	100	48	95.6	34	168.2	128	166[a]	95.7
Glucose (mg/dL)	93	11.5	95.8	13.9	94.7	11.6	97.4	13.7	94.9	11.2	94.1	10.6	94	13.7	96.5	11.8
Apo AI (mg/dL)	120.9	37	122.3	39.3	120.6	42.2	131	43.3	143.1	38.6	145	37.9	136.6	43.3	132.1	50
Apo B (mg/dL) n = 695/711	108.2	30.1	117.1	34.1	128.1	27.5	125[a]	30.1	101.7	37.4	108.2	36.2	124.3	30.1	123[a]	26.5
Total/HDL-C ratio	4.84	1.64	5.36[a]	1.7	6.37	1.87	6.06[a]	1.54	3.92	1.24	3.87	1.18	5.23	1.54	5.21[a]	1.37
Physical activity grade (1-4)	2.54	0.8	2.42	0.76	2.37	0.74	2.35	0.74	2.34	0.74	2.25	0.7	2.08	0.66	2.14	0.67
Current smokers (%)	58.7		34.7		51.6		43.5		16.9		7.8		17.8		7.8	
Past smokers (%)	17.3		26.4		22.3		22.8		3.4		4.9		2.2		2.6	

[a] Significantly higher than the category with the next lower mean value; hence, categories with still higher values are automatically significantly different as well (unless they are also significantly higher than the category marked by *a*). For example, in men, total/HDL-C ratio in the obese-only category (5.36) is significantly higher than 4.84, and 6.06 is significantly higher than 5.36, and 6.37 is significantly higher than the first 2 categories but not higher than 6.06.

[b] Log-transformed mean values.

Table 2
Distribution of diabetes and IFG developed in follow-up

	Nonobese, no MS	Obese	MS only	MS + obese	Total	Follow-up (y)	Incidence per 1000 population
Men							
New diabetes/IFG %	22/19	0/1	9/6	5/6	36/32	4041	
	3.4/3.0	0/1.7	4.6/3.0	5.4/6.5	3.6/3.2		8.9/8.0
Women							
New diabetes/IFG %	12/11	5/4	8/11	21/21	46/47	4017	
	2.5/2.3	4.5/3.6	5.1/7.0	8.9/8.9	4.7/4.8		11.5/11.7

11.5 and 11.7 per mille, respectively, in women. The distribution in each of the 4 categories is presented in Table 2.

It is also noteworthy that, whereas among 289 men with MS and normal GM at baseline, 26 (9%) developed new DM/IFG, among 393 women with MS and normal GM at baseline, 61 (15.5%) developed new DM/IFG.

3.3. Predictors of abnormal GM

Among 992 men and 982 women who had initially normal GM, predictors of newly developing DM and abnormal GM (DM plus IFG combined) were sought in logistic regression analyses that included the 4 groups with obesity and MS and were adjusted for age. In each model, the referent was the major group with no obesity or MS that exhibited crude annual incidences of abnormal GM of 10 and 5.6 per mille in men and women, respectively. The group that had obesity alone demonstrated no significant independent association with diabetes or abnormal GM either in men or women and is therefore not mentioned in Table 3. It is to be noted that women with MS, regardless of the presence of obesity, predicted highly significantly abnormal GM with RRs exceeding 2 whereas men with MS failed to have a significant association. A similar divergence held true also in the prediction of diabetes. Whereas obese women with MS showed a highly significant RR of 3.59 in predicting new DM, (even) obese men with MS did not attain a significant association.

We tested as to what extent the relationships became modified when the measure of abdominal obesity was substituted for obesity. The lower half of Table 3 discloses essentially no change in RRs among women. In men, however, a waist circumference cutpoint of 102 cm served better than a BMI limit of 30 kg/m^2 in the prediction of abnormal GM: abdominally obese men with MS attained a significant age-adjusted RR of 2.1 (95% CI, 1.14-3.89).

3.4. Predictors of CVD

Again among persons initially having normal GM, multiple logistic regression analyses were performed to assess independent predictors of subsequent fatal and nonfatal CVD, separately in men and women. (The annual incidence of CVD in this cohort with normal GM was 16.2 and 13.5 per mille.) Age, smoking status, grade of physical activity, IFG, DM, and the 4 groups with obesity and MS were included as independent variables in the model. The group that had obesity alone demonstrated no significant independent association with CVD in either sex and is thus not mentioned in Table 4. Worthy of note is that MS in men, regardless of the presence of obesity, predicted highly significantly CVD with RRs ranging from 2 to 4. Neither DM or IFG nor physical inactivity contributed independently to the prediction whereas smoking did. Conversely, in women, IFG—although not DM—predicted CVD independent of age, smoking status, and grade of physical

Table 3
Logistic regression analysis of age-adjusted groups with MS, obesity/abdominal obesity as predictors of diabetes and abnormal GM, by sex

	Men			Women		
	P	RR[a]	95% CI	*P*	RR[a]	95% CI
For diabetes	n = 36/960			n = 46/935		
Age (y)	.012	1.031	1.007; 1.057	.011	1.031	1.000; 1.036
MS + BMI <30 kg/m^2	NS	1.30		NS	1.75	
MS + BMI >30 kg/m^2	NS	1.56		.001	3.59	1.72; 7.48
For abnormal GM	n = 68/992			n = 93/982		
Age (y)	.000	1.033	1.014; 1.052	.047	1.018	1.000; 1.036
MS + BMI <30 kg/m^2	NS	1.16		.008	2.40	1.25; 4.59
MS + BMI >30 kg/m^2	.093	1.84		.000	3.95	2.30; 6.79
For diabetes						
MS + waist circumference <102/<88 cm	NS	1.38		.064	2.88	
MS + waist circumference >102/>88 cm	NS	1.92		.010	2.77	1.28; 5.98
For abnormal GM						
MS + waist circumference <102/<88 cm	NS	1.07		.003	3.46	1.51; 7.92
MS + waist circumference >102/>88 cm	.018	2.10	1.14; 3.89	.000	3.54	2.00; 6.29

All RRs of groups with obesity/abdominal obesity alone were nonsignificant in both sexes.

[a] Referent: participants with a BMI less than 30 kg/m^2 and no MS (643 men, 479 women).

Table 4
Metabolic syndrome with or without obesity/abdominal obesity as independent predictors of CVD, adjusted for age, smoking, physical activity, and GM status, by sex (n = 1747)

	Men			Women		
	P	RR[a]	95% CI	*P*	RR[a]	95% CI
n	59/878			52/869		
Age (y)	.000	1.076	1.051; 1.101	.000	1.067	1.04; 1.095
MS + BMI <30 kg/m^2	.031	2.15	1.07 ; 4.29	NS	1.39	
MS + BMI >30 kg/m^2	.000	4.04	1.93; 8.47	NS	1.78	
IFG	NS	0.31		.030	2.83	1.11; 7.23
DM	NS	0.57		NS	1.50	
Smokers vs nonsmokers	.013	2.64	1.23; 5.67	NS		
Physical activity grade	NS	trend 0.46		NS		
n	66/992[b]			55/982[b]		
MS + waist circumference <102/<88 cm	.005	2.62	1.33 ; 5.16	.118	2.34	
MS + waist circumference >102/>88 cm	.001	3.16	1.68; 5.95	.137	1.75	
IFG	NS	0.29		.019	2.98	1.23; 7.20
DM	NS	0.74		NS	1.26	

RRs of groups with obesity/abdominal obesity alone were nonsignificant in both sexes.
[a] Referent: participants with a BMI less than 30 kg/m^2 and no MS (570 men, 420 women).
[b] Referent: participants with a waist less than 102/88 cm and no MS (660 men, 408 women).

activity, but the groups with obesity and MS failed to significantly contribute independently.

We tested the extent of the modifications of the relationships by substituting for obesity the measure of abdominal obesity. The lower half of Table 4 reveals no essential change in RRs among men or women.

We analyzed by logistic regression the excluded 251 subjects with IFG/DM at baseline regarding sex differences for subsequent CVD in models that included age, smoking status, and grade of physical activity as covariates. In men with IFG/DM, the presence of MS plus obesity was the only variable significantly associated with subsequent CVD (RR, 6.08 [95%CI 1.07-34.6]). In 142 women with IFG/DM, obesity with or without MS predicted CVD (RR, 11.1 and 37.7; P = .036 and .022, respectively); in addition, smoking (RR, 9.4; P = .006) was significant and physical activity grade exhibited a borderline significant trend (P = .097).

4. Discussion

In addressing sex-specific associations with DM and CVD in a middle-aged and elderly population sample having normal GM and a high prevalence of the MS at baseline, this study found, by assessing the relative roles of (abdominal) obesity and MS, that women are likely to develop abnormal GM followed by CVD whereas men are likely to develop CVD directly after developing MS. A further salient finding was that obesity alone, unaccompanied by MS, was an independent predictor neither of abnormal GM nor of CVD in either sex and that, even in predicting abnormal GM in women, the weighting of BMI was less than that of MS.

Given the overlapping of the conditions (abdominal) obesity and MS, the latter—in the context of subjects with normal GM and when opposed to (abdominal) obesity—connotes mainly dyslipidemia and hypertension. In agreement with this statement is the fact that significant differences in the MS-only group compared with the obese-only group were higher BP measures, triglycerides and apo B concentrations, TC/HDL-C ratio (but not LDL-C), and lower HDL-C levels in both sexes. Hypertriglyceridemia with elevated apo B, the lipoprotein manifestation of a condition presumably caused by impaired fatty acid trapping by adipose tissue that Sniderman et al [13] recently coined *the Medusa Hypothesis*, may be the link in this cohort to excess risk both for CVD and for abnormal GM. In a population sample of obese postmenopausal Turkish women, we have recently reported evidence for a complex risk profile among those with hypertriglyceridemia and elevated apo B [14].

4.1. Sex difference related to MS prevalence and CVD risk in a population with normal GM

The reason why a divergence between sexes had not been uncovered earlier may not only be related to the characteristics of the population sampled but may also stem from the fact that few studies investigated samples with normal GM, as was done here. Evidence exists, namely, apart from the present study, that in the general population including persons with abnormal GM, the greater propensity to DM/IFG in obese women (than in men) raises the prevalence of MS and its share within MS more in the female sex and consequently abolishes (and perhaps reverses) the gradient in risk for abnormal GM existing between nonobese men and women free of MS. Isomaa et al [15], in investigating the prevalence and cardiovascular risk associated with MS in a large family study of type 2 diabetes in the Botnia study, tabulated their data by the status of GT. Hypertension and dyslipidemia, with or without obesity, were present in the normal GT group in 15% of men vs 8% of women, whereas they existed in 31% and 24%, respectively, of those with IFG/IGT and in 60% and 67%, respectively, among diabetic individuals. This is consistent with a shift from male to

female prevalence of the high-risk MS components as GM status evolves toward DM.

In a population study in Mauritius, the prevalence of DM as well as that of coexisting IFG and IGT were similar among the sexes [16]. Nevertheless, men were twice as likely as women to have isolated IFG and significantly less likely to have isolated IGT. The authors concluded that the distribution of impaired GM differed according to sex and questioned the ability of the current glucose thresholds to equally identify men and women at high risk of developing diabetes. Moreover, contribution of risk for the hypertension-diabetes comorbidity in various obesity phenotypes has been reported to be greater in black and Hispanic women than in black and Hispanic men [17].

Our finding on the incidence of newly developing abnormal GM should be commented upon to give a perspective of the insulin resistance underlying the population. Annual incidences of DM in men and women with normal GM were estimated to be 8.9 and 11.7 per mille, respectively, and of IFG were 8.0 and 11.9 per mille, respectively. Our DM incidence lies in between the age-adjusted 6.3 per 1000 adults for white Americans and the 10.1 figure for Hispanic Americans [18]. In the middle-aged white male nondiabetic participants of the PROCAM study, the annual incidence of DM may be estimated as 8.5 per mille [19]. Our DM incidence is thus comparable with that of Western populations.

4.2. Sex difference in developing obesity or MS relative to the incidence of abnormal GM

The fact that the annual incidence of abnormal GM was by a third more common in men than in women (15.8 vs 12 per mille) among nonobese participants without MS suggests that the inherent greater susceptibility of men to abnormal GM (perhaps via reduced insulin sensitivity or enhanced visceral adiposity [6] despite lack of obesity) is minimally modified by the acquisition of obesity or MS; in contrast, women almost quadruple this risk by acquiring the 2 features. It has been stated that metabolically obese, normal-weight individuals are common in the general population and that central fat distribution and inactivity are among the main factors predisposing them to insulin resistance [20]. Hazard ratios for diabetes increasing with the number of components of the MS [21,22] and the possibly prevailing 1 or 2 MS components among our male cohort with no MS and no obesity might account for the higher incidence of abnormal GM in men.

Sex differences have been observed in postprandial lipemia. Examining the response of postprandial TRL to a standardized meal, men were characterized not only by a greater visceral adipose tissue accumulation but also by a greater plasma triglyceride response, postprandial insulin, and free fatty acid levels compared with women, suggesting that sex difference in visceral adipose tissue accumulation is an important contributing factor involved in the response in men [23].

Contrasted to the finding of exquisite prediction of DM/IFG by MS in women, the poor prediction in men in the present paper is at apparent variance with the finding of MS as an effective predictor of diabetes in the exclusively male cohort of the West of Scotland Study [21]. In multivariate analysis incorporating conventional risk factors, however, MS was reported not to be predictive of diabetes. C-reactive protein has been also linked with the prediction of diabetes in the mentioned study consistent with the notion of an inflammatory element in type 2 diabetes. In line with this finding were concentrations of CRP in the present study significantly higher in the MS and obese group than in the obese-only group in both sexes.

With regard to future development of DM/IFG, an MS diagnosis in men with or without obesity was not helpful in predicting, whereas waist girth greater than 102 cm in men with an MS was indeed a significant predictor, independent of age. This observation underlines that waist girth is the parameter to be watched in men, with respect both to CVD risk and to abnormal GM. It was reported in the 4-year follow-up of 1005 Finnish middle-aged men that the National Cholesterol Education Program definition of MS (including waist >102 cm) identified persons at high risk for developing diabetes, yet that it was less sensitive in predicting diabetes than the World Health Organization definition, although being more specific [24].

4.3. Hypothesis that men and women have divergent pathways supported

Our findings in individuals with abnormal and normal GM were essentially consistent with each other, namely MS components other than the combination of obesity and IFG contributed little to the development of subsequent CVD in women, whereas the components of MS other than obesity determined subsequent CVD in men. This suggests that our

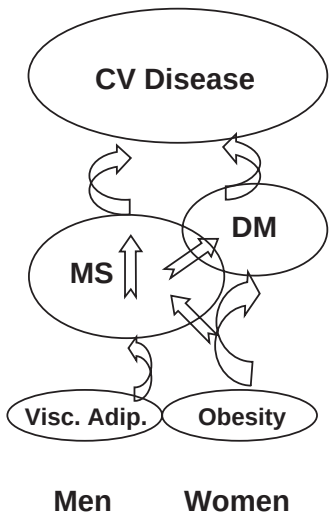

Fig. 1. Schematic representation of preferential pathways leading from (abdominal) obesity via the MS to abnormal GM (DM) and CVD among men and women.

conclusion on subjects with normal GM was not biased by the exclusion of persons with IFG/DM.

Based on this set of observations, the hypothesis that men and women diverge in their pathways from (abdominal) obesity to DM and CVD is supported. As schematically illustrated in Fig. 1, among adults with normal GM, obese or abdominally obese women are prone to develop MS and, in particular, DM; in addition, unless they primarily develop DM, they run little risk of CVD. In contrast, among men with normal GM, susceptibility to abdominal obesity reflecting visceral adiposity, via the development of MS, rather than obesity per se predicts CVD, with little regard to the concurrence of DM. In the recent NHANES III study, MS was indeed found much more important than DM with regard to the likelihood of coronary disease [25], but sex difference was not separately evaluated. The working hypothesis may be accounted for by postulating a weaker insulin resistance but—as existed in this study—a greater inflammation in obese women with MS than obese men with MS. Men, owing to a greater susceptibility to visceral obesity [6], bear the consequences of developing MS and cardiovascular events, yet with little further impact on DM. A higher degree of inflammation in obese women with MS, encountered in other studies [26,27] as well, enhances the emergence of abnormal GM, which may then be detrimental for the heart and vessels. It was suggested that inflammation might have a greater effect on insulin resistance in women than in men [26,27] and that higher levels of insulin resistance were observed in men than in women [26].

The validity of our hypothesis needs to be tested in other populations in which MS is highly prevalent. Whether these dynamics might also apply to lean population strata having elevated LDL-C and normal HDL-C concentrations would be interesting to learn. The proposed hypothesis is highly relevant from the viewpoint of preventive cardiology.

Our findings, furthermore, implicate that, given the current global epidemics of obesity, the proportion of women with MS who have abnormal GM will rapidly rise in the foreseeable future, a development that is unlikely to be approached in men.

Possible limitations of the study include that soft end points such as newly developed angina pectoris have been included as outcome measures. Yet, any potential bias in inaccuracy in the diagnosis of CVD or death would tend to dilute rather than augment the association between clinical events and the sex-specific metabolic groups. The just more than 4 years' duration of mean follow-up, although being limited, was adequate to allow the accumulation of abnormal GM and CVD events in sufficient individuals. The fact that confounders such as cigarette smoking and physical inactivity as well as abnormality of GM have been assessed points to the strength of the study.

We conclude that, among middle-aged and elderly adults having a high prevalence of MS but normal GM, whereas women within the context of MS are prone to DM and are exposed to CVD risk primarily by way of DM, men are prone to abdominal obesity (a surrogate of visceral adiposity), less susceptible to DM, and exposed to CVD risk primarily by the intermediary of MS, independent of the DM component. The validity of this hypothesis needs to be tested in other populations in which MS is highly prevalent.

Acknowledgments

The financial support over the years of the Turkish Society of Cardiology and that of pharmaceutical firms in Istanbul (Pfizer, AstraZeneca, MSD, Roche, and Unilever) are gratefully acknowledged. We are indebted to Dr G Can for statistical assistance and appreciate the dedicated work of H Uyarel, MD, B Uzunlar, MD, and M Özmay, the coworkers in the survey teams.

References

[1] Gale EA, Gillespie KM. Diabetes and gender. Diabetologia 2001;44:3-15.
[2] Fleming DM, Schellevis FG, van Casteren V. The prevalence of known diabetes in eight European countries. Eur J Public Health 2004;14:10-4.
[3] Hu G, DECODE Study Group. Gender difference in all-cause and cardiovascular mortality related to hyperglycemia and newly-diagnosed diabetes. Diabetologia 2003;46:608-17.
[4] Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults. Findings from the Third National Health and Nutrition Examination Survey. JAMA 2002;287:356-9.
[5] Onat A, Ceyhan K, Başar Ö, Erer B, Sansoy V. Metabolic syndrome: major impact on coronary risk in a population with low cholesterol levels—a prospective and cross-sectional evaluation. Atherosclerosis 2002;165:285-92.
[6] 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;28:1018-25.
[7] Mahley RW, Palaoğlu E, Atak Z, et al. Turkish Heart Study: lipids, lipoproteins, and apolipoproteins. J Lipid Res 1995;36:839-59.
[8] Onat A. Risk factors and cardiovascular disease in Turkey. Atherosclerosis 2001;156:1-10.
[9] Onat A, Avc GŞ, Şenocak M, Örnek E, Gözükara Y. Plasma lipids and their interrelation in Turkish adults. J Epidemiol Community Health 1992;46:470-6.
[10] Alberti KGMM, Zimmet PZ, for the WHO Consultation. Definition, diagnosis and classification of diabetes mellitus, provisional report of a WHO Consultation. Diabet Med 1998;15:539-53.
[11] 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). National Heart, Lung, and Blood Institute, NIH Publication No. 01-3670, 2001.
[12] Rose GA, Blackburn H, Gillum RF, Prineas RJ. Cardiovascular survey methods. 2nd ed. Geneva: WHO; 1982. p. 124-7.
[13] Sniderman A, Williams K, Haffner S, Sattar N. Insights from apo B: from better diagnosis and therapy to the Medusa Hypothesis. Atherosclerosis Suppl 2004;5(2):19-24.
[14] Onat A, Yazıcı M, Can G, Sniderman A. Evidence for a complex risk profile in obese postmenopausal Turkish women with hypertriglyceridemia and elevated apolipoprotein B. Clin Sci 2004;170:97-104.
[15] Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24:683-9.
[16] Williams JW, Zimmet PZ, Shaw JE, et al. Gender differences in prevalence of impaired fasting glycemia and impaired glucose tolerance in Mauritius. Does sex matter? Diabet Med 2003;20:915-20.

[17] Okosun IS, Chandra KM, Choi S, Christman J, Dever GE, Prewitt TE. Hypertension and type 2 diabetes comorbidity in adults in the United States: risk of overall and regional adiposity. Obes Res 2001;9:1-9.
[18] Incidence of diabetes. http://www.cdc.gov/diabetes/statistics/incidence/index.htm, 2004.
[19] Von Eckardstein A, Schulte H, Assmann G. Risk for diabetes mellitus in middle-aged Caucasian male participants of the PROCAM study: implications for the definition of impaired fasting glucose by the American Diabetes Association. Prospective Cardiovascular Münster. J Clin Endocrinol Metab 2000;85:3101-8.
[20] Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S. The metabolically obese, normal-weight individual revisited. Diabetes 1998;47:699-713.
[21] Sattar N, Gaw A, Scherbakova O, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. Circulation 2003;108:414-9.
[22] Klein BE, Klein R, Lee KE. Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in Beaver dam. Diabetes Care 2002;25:1790-4.
[23] Couillard C, Bergeron N, Prud'homme D, et al. Gender difference in postprandial lipemia: importance of visceral adipose tissue accumulation. Arterioscler Thromb Vasc Biol 1999;19:2448-55.
[24] Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. Am J Epidemiol 2002;156:1070-7.
[25] Alexander CM, Landsmann PB, Teutsch SM, Haffner SMI. NCEP-defined metabolic syndrome, diabetes mellitus, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes 2003;52:1210-4.
[26] Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB, Wilson PWF. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring study. Circulation 2004;110:380-5.
[27] Han TS, Sattar N, Williams K, Gorales-Yillalpando C, Lean MEJ, Haffner SM. Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study. Diabetes Care 2002;25:2016-21.