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Contribution of impaired glucose tolerance in subjects with the metabolic syndrome: Baltimore Longitudinal Study of Aging

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Abstract

Background: In addition to fasting plasma glucose (FPG), we examined the contribution of the oral glucose tolerance test (OGTT) in the prevalence of subjects with the metabolic syndrome (MS).

Methods and Results: Study participants were white adults in the Baltimore Longitudinal Study of Aging who underwent a fasting 2-hour OGTT. In men between the ages of 20 to 39, 40 to 59, 60 to 79, and 80 to 95 years, the prevalence of the MS by Adult Treatment Panel (ATP) III criteria (which excludes OGTT) was 11%, 28%, 32%, and 15%, respectively; whereas in women the prevalence was 5%, 12%, 24%, and 16%, respectively. If the current ATPIII dysglycemia criteria also included a 2-hour postchallenge glucose (2hPG) of 7.8 mmol/L or higher, the prevalence of the MS increased from 25% to 33% in men and from 15% to 21% in women ($P < .0001$). In study participants with FPG less than 5.6 mmol/L, the prevalence of the MS increased from 16% to 23% in men and from 9% to 13% in women. In men between the ages of 20 to 39, 40 to 59, 60 to 79, and 80 to 95 years and FPG less than 5.6 mmol/L, the prevalence of the MS increased to 15%, 32%, 40%, and 29%, respectively ($P < .005$ for men between 40 and 95 years of age), with inclusion of an abnormal 2hPG. In women between the ages of 20 to 39, 40 to 59, 60 to 79, and 80 to 95 years and FPG less than 5.6 mmol/L, the prevalence of the MS increased to 7%, 14%, 33%, and 31%, respectively, with inclusion of an abnormal 2hPG ($P < .001$ for women between 60 and 95 years of age).

Conclusion: The prevalence of the MS is significantly underestimated when the current ATPIII criteria of FPG 6.1 mmol/L or higher is the only determinant of dysglycemia.

1. Introduction

The Adult Treatment Panel (ATP) III guidelines issued by the National Cholesterol Education Program defined the metabolic syndrome (MS) as the presence of 3 of the 5 determinants (abdominal adiposity, hypertension, low high-density lipoprotein cholesterol [HDL-C], elevated triglyceride levels, and abnormal fasting plasma glucose [FPG]) [1]. The importance of this classification was to highlight the association of these determinants with insulin resistance and its increased risk for atherosclerotic disease.

Inclusion of one of the components of the MS, FPG 6.1 mmol/L or higher (110 mg/dL), would identify patients not only with impaired FPG (6.1-6.9 mmol/L [110-125 mg/dL]) but also those with diabetes mellitus (DM) ($\geq$7.0 mmol/L [126 mg/dL]) [2]. The measurement of FPG is strongly encouraged by the American Diabetes Association (ADA) and remains the cornerstone of their clinical practice guidelines [3]. Reasons cited for its use are that it is easy to obtain and more reproducible than the oral glucose tolerance test (OGTT) [4]. However, the World Health Organization (WHO) has emphasized using FPG and 2-hour postchallenge glucose (2hPG) values in the classification of patients with abnormal glucose control [5].

There is ample evidence suggesting that impaired fasting glucose (IFG) is different from impaired glucose tolerance (IGT) [6-8], particularly for risk of DM and for development of atherosclerotic disease. Gabir et al [9] compared FPG and 2hPG as predictors for conversion to DM in Pima Indians using 3 criteria (ADA 1997 criteria; WHO 1985: DM diagnosed based on FPG $\geq$7.8 mmol/L [140 mg/dL] and 2hPG glucose $\geq$11.1 mmol/L [200 mg/dL]; WHO 1999:

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DM diagnosed with FPG ≥7.0 mmol/L [126 mg/dL] and 2hPG glucose ≥11.1 mmol/L). These investigators found that the overall prevalence and incidence rates of DM were lower with the ADA 1997 as compared with the WHO 1985 or WHO 1999 criteria. They also found that FPG of 5.7 mmol/L or higher (103 mg/dL) had virtually the same specificity and sensitivity as IGT in predicting conversion to DM [9].

The different effects of IFG and IGT on diabetic complications have also been studied. Barzilay et al [10] compared the prevalence and incidence of cardiovascular disease (CVD) in the Cardiovascular Health Study using the ADA 1997 and 1985 WHO criteria. These investigators found that the ADA criteria were less predictive of cardiovascular incidence than the WHO criteria, with individuals classified as normal by ADA having higher absolute number of incidents [10].

In this study we hypothesized that the prevalence of the MS would be significantly higher if a 2hPG of 7.8 mmol/L or higher (140 mg/dL) were included as a criterion of abnormal glucose control. Our results showed that abnormal 2hPG levels could be seen even in individuals with FPG less than 5.6 mmol/L (100 mg/dL) and that abnormal glucose tolerance increased markedly with aging and other determinants of the MS.

2. Methods

2.1. Study subjects

Community-dwelling healthy adult men and women were recruited as participants of the Baltimore Longitudinal Study of Aging (BLSA) [11]. They are middle- and upper-middle socioeconomic class volunteers 21 to 95 years old. Subjects included in the current analysis had visits between April 1984 and January 1999 (n = 1820). Exclusions for this report included nonwhites (n = 176), participants with current or past hypoglycemic therapy (n = 36), participants taking lipid-lowering medications (n = 10), and participants who did not have all of the requisite measurements (n = 195). Of the remaining 1403 participating subjects, 769 were men and 634 were women. The BLSA had continuing approval from the Institutional Review Board of Johns Hopkins Bayview Medical Center.

2.2. Clinical examination

Data were collected after an overnight fast; subjects wore a light hospital gown, were not permitted to smoke, and were at rest during the OGTT. Anthropometric measurements including height, weight, waist circumference, and blood pressure were recorded [12]. Fasting plasma glucose levels were obtained, an OGTT was administered to subjects not known to have diabetes, and 2hPG levels were measured. The glucose dose for the OGTT was 40 g/m^2 body surface area, corresponding to an average dose of 78 g in men and 68 g in women.

2.2.1. Glucose tolerance classification

The classification schema was based on the 2003 American Diabetes Association Guidelines [13]: normal FPG less than 5.6 mmol/L (100 mg/dL), IFG 5.6 to 6.9 mmol/L (100-125 mg/dL), and DM 7.0 mmol/L or higher (126 mg/dL); normal glucose tolerance (NGT) less than 7.8 mmol/L (140 mg/dL), IGT 7.8 to 11.0 mmol/L (140-199 mg/dL), and DM 11.1 mmol/L or higher (200 mg/dL).

2.2.2. Metabolic syndrome classification

Based on ATPIII, subjects were classified with the MS if there were 3 of the 5 determinants [1]; this meant that there were subjects classified with the MS who had normal FPG. We also analyzed the contribution of the OGTT to the MS in 2 ways: first, to classify subjects with the MS if either FPG of 6.1 mmol/L or higher (110 mg/dL) or 2hPG of 7.8 mmol/L or higher (140 mg/dL) was present, and the second was to classify subjects with the MS with FPG less than 5.6 mmol/L but with 2hPG of 7.8 mmol/L or higher.

Table 1
Characteristics of the BLSA study participants

	Men	Men	Women	Women
	MS(−)	MS(+)	MS(−)	MS(+)
n	579	190	539	95
Age (y)	63.4 ± 0.77	63.9 ± 1.1	57.7 ± 0.83[a]	65.0 ± 1.5[b]
BMI (kg/m^2)	25.3 ± 0.15	29.5 ± 0.30[b]	24.2 ± 0.15[a]	29.9 ± 0.43[b]
Abd. Circ. (cm)	91.1 ± 0.40	104.1 ± 0.78[b]	78.3 ± 0.42[a]	93.5 ± 1.02[bc]
SBP (mm Hg)	131.9 ± 0.79	140.2 ± 1.28[b]	127.8 ± 0.81[a]	143.4 ± 1.8[b]
DBP (mm Hg)	80.9 ± 0.43	85.3 ± 0.76[b]	76.7 ± 0.44[a]	84.9 ± 1.07[b]
HDL-C (mmol/L)	1.14 ± 0.01	0.86 ± 0.01[b]	1.43 ± 0.01[a]	1.07 ± 0.02[bc]
TG (mmol/L)	1.03 ± 0.02	2.21 ± 0.08[b]	0.95 ± 0.02[a]	2.03 ± 0.11[b]
FPG (mmol/L)	5.33 ± 0.02	6.06 ± 0.08[b]	5.06 ± 0.02[a]	5.74 ± 0.11[bc]
2hPG (mmol/L)	7.05 ± 0.08	10.01 ± 0.25[b]	6.69 ± 0.09[a]	9.43 ± 0.35[b]

Values are age-adjusted mean ± SE. Abd. Circ. indicates abdominal circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; and TG, triglyceride.

[a] $P < .001$, MS(−) women compared with MS(−) men.

[b] $P < .001$, MS(+) men or women compared with MS(−) men or women.

[c] $P < .02$, MS(+) women compared with MS(+) men.

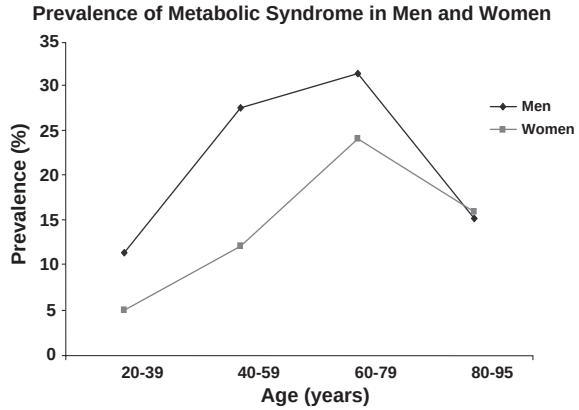

Fig. 1. Prevalence of the MS in the BLSA based on current ATPIII criteria. Subjects were classified with the MS based on the presence of 3 of the 5 determinants. The number of subjects per age and sex were the following: men—ages 20 to 39 years (n = 96), 40 to 59 years (n = 188), 60 to 79 years (n = 327), and 80 to 95 years (n = 158); women—ages 20 to 39

2.3. Analytical procedures

The glucose oxidase method was used to measure plasma glucose levels (Abbott Laboratories ABA 200 ATC Series II Biochromatic Analyzer 1983-1992, Irving, Tex; Abbott Spectrum CCX 1992-1999). Plasma triglyceride and total cholesterol concentrations were determined by enzymatic method (Abbott Laboratories ABA-200 ATC Biochromatic Analyzer). High-density lipoprotein cholesterol was determined by dextran sulfate–magnesium precipitation procedure [14]. Low-density lipoprotein cholesterol concentrations were estimated by the Friedewald formula [15].

2.4. Statistical analysis

All data were analyzed using SAS version 8.2 (SAS Institute Inc, Cary, NC). Standard methods were used to compute means and standard deviations. Unpaired *t* tests were used to detect differences in age, blood pressure,

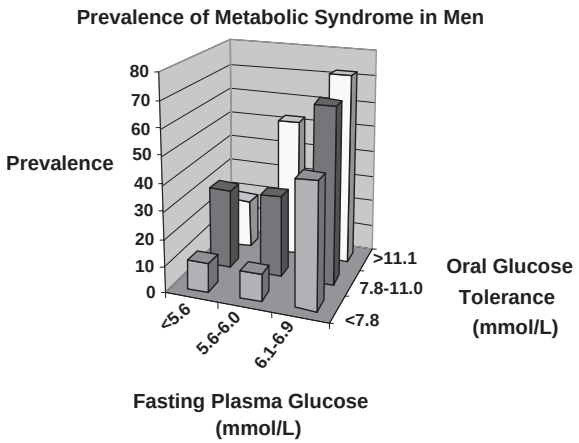

Fig. 2. Prevalence of MS in men stratified by FPG and OGTT (2hPG) levels.

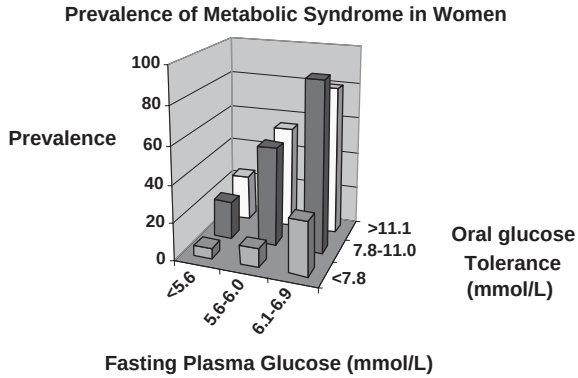

Fig. 3. Prevalence of MS in women stratified by FPG and OGTT (2hPG) levels.

lipids, glucose levels, and obesity between men and women. The Cochran-Armitage test was used to detect an age trend in the prevalence of the MS. McNemar test was used to measure the agreement between the ATPIII criteria for the MS and the modification of the criteria to include the OGTT. *P* values below .05 were regarded as statistically significant.

3. Results

The characteristics of the group, with and without the MS, are outlined in Table 1. Women with the MS had higher HDL-C, lower FPG, and smaller abdominal waist circumferences, but were similar in age, body weight, 2hPG, systolic and diastolic blood pressure compared to men with the MS. In comparison to men without the MS, men with the MS had all of the following defining characteristics: larger abdominal waist circumference, higher body mass index (BMI), higher systolic and diastolic blood pressure, lower HDL-C and higher TG

Table 2
Prevalence of IGT and DM in different determinants of the MS

FPG	WC	HDL	TG	HTN	
Men					
<5.6	33.0	49.5	25.7	78.0	IGT
	25.0	43.8	12.5	75.0	DM
5.6-6.0	30.6	55.6	33.3	81.9	IGT
	40.0	66.7	46.7	100	DM
6.1-6.9	38.1	52.4	23.8	81.0	IGT
	42.4	60.6	45.5	75.8	DM
Women					
<5.6	26.7	33.3	21.3	62.7	IGT
	31.2	56.2	31.2	93.8	DM
5.6-6.0	64.7	67.6	38.2	82.4	IGT
	66.7	66.7	66.7	88.9	DM
6.1-6.9	63.6	63.6	27.3	9.1	IGT
	60.0	60.0	60.0	100	DM

WC indicates waist circumference >102 cm (40 in for men), >88 cm (35 in for women); HDL, <1.04 mmol/L (40 mg/dL) for men and <1.29 mmol/L (50 mg/dL) for women; TG, ≥1.7 mmol/L (150 mg/dL); HTN, ≥130 mm Hg systolic/≥85 mm Hg diastolic.

levels, higher FPG (6.1 vs 5.3 mmol/L [109 vs 96.2 mg/dL]), and higher 2hPG (10 vs 7.2 mmol/L [180 vs 130 mg/dL]). In comparison to women without the MS, women with the MS also had all of the following defining characteristics: larger abdominal waist circumference, higher BMI, higher systolic and diastolic blood pressure, lower HDL-C and higher TG levels, higher FPG (5.7 vs 5.1 mmol/L [103.5 vs 91 mg/dL]), and higher 2hPG (9.5 vs 6.6 mmol/L [170.7 vs 118.5 mg/dL]).

Based on ATPIII criteria, without the contribution of the OGTT results, the prevalence of the MS significantly increased in men ($P < .0003$) and women ($P < .0001$) up to 79 years of age, but then decreased in the oldest age group (Fig. 1). When we then considered the contribution of an abnormal OGTT (IGT and DM) to the prevalence of the MS stratified by FPG in men (but not including DM by FPG), the results showed a even greater prevalence of the MS with increasing FPG (Fig. 2). Similar trends were found in women (Fig. 3). We included the values for DM based on the 2hPG levels in these figures because this additional information would not have been obtained had the OGTT not been performed.

We then examined the prevalence of IGT and DM, based on 2hPG levels, in different determinants of the MS. In men, the presence of low HDL-C and hypertension (HTN) was associated with a high prevalence of IGT and DM, even in the presence of absolutely normal FPG (Table 2). As compared to WC or TG, the prevalence of IGT was 2.4× and 2.9× higher, whereas the prevalence of DM was 2.3× and 2.4× higher, respectively, in men with HTN. In comparison, in women, the prevalence of IGT and DM was highest in those with HTN. Across the different determinants (WC, HDL, TG, and HTN), the prevalence of IGT and DM increased with IFG compared to normal FPG.

The results from the OGTT showed the contribution of abnormal 2hPG levels to the prevalence of MS even in the presence of normal FPG based on 2003 ADA criteria. We examined the effect of an abnormal OGTT on the prevalence of the MS across the varying age groups using the standard ATPIII criteria and in subjects with FPG less than 5.6. As shown in Table 3, in comparison to current ATPIII criteria (FPG >6.1 mmol/L), the inclusion of an abnormal 2hPG (≥7.8 mmol/L) significantly increased the prevalence of MS in men and women in the total population and even in the group with an FPG less than 5.6 mmol/L. A profound effect of age on the contribution of an abnormal 2hPG in men and women was seen when the participants were stratified into age groups. The prevalence of MS increased significantly with the addition of an abnormal OGTT in men beginning in middle age, whereas for women the effects of an abnormal OGTT on increased prevalence of OGTT were seen in those older than 60 years; this trend was seen in both sexes regardless of FPG.

Table 3
Contribution of OGTT to the prevalence of the MS in relation to FPG

	MS(+) %, all subjects FPG <7.0 mmol/L			
	ATPIII	ATPIII and OGTT	% Increase	*P*
Men	24.7	32.6	32	<.001
Women	15.0	21.1	41	<.001
Men				
20-39	11.5	14.6	27	.083
40-59	27.7	31.9	15	.005
60-79	31.5	40.4	28	<.001
80-95	15.3	28.7	88	<.001
Women				
20-39	5.1	6.8	33	.157
40-59	12.2	13.6	12	.083
60-79	24.3	33.3	37	<.001
80-95	16.1	31.4	95	<.001
	MS(+) %, subjects with FPG <5.6 mmol/L			
Men	15.9	23.3	47	<.001
Women	8.5	13.3	57	<.001
Men				
20-39	9.3	12.0	29	.157
40-59	22.2	26.9	21	.025
60-79	21.7	29.5	36	<.001
80-95	4.2	17.7	321	<.001
Women				
20-39	4.6	4.6	0	–
40-59	8.3	9.4	13	.157
60-79	12.0	20.0	67	<.002
80-95	8.6	22.6	163	<.001

4. Discussion

The goal of this study was to quantify the effect of adding an abnormal 2hPG level on the prevalence of the MS. The clinical relevance in identifying more subjects with the MS by adding an abnormal 2hPG level is twofold: identification of subjects [1] at increased risk of developing DM and [2] at increased risk for CVD because of undiagnosed IGT and/or DM by postglucose challenge. Results from the Hoorn study showed that those persons with IFG at baseline had a 38% increased risk for developing DM over a period of 6 years [16]. In those subjects with IGT, the risk was 32% for conversion to DM. In those subjects who were found to have IFG and IGT the risk increased to 65% for conversion to DM. The participants in the Hoorn study are comparable to our elderly cohort, in that the population was white, elderly, and included both men and women.

The prevalence of coronary heart disease (CHD) risk factors and incident CHD events was studied in the BLSA with IFG and IGT using the 1997 ADA criteria as well as the recent 2003 recommendation of the ADA lowering the cut-point of FPG to 5.6 mmol/L (100 mg/dL) [17]. Subjects with IGT alone or IFG and IGT had higher triglyceride, lower HDL-C levels, higher BMI, larger waist circumferences, and higher prevalence of the MS compared with

subjects with NGT or IFG alone. Incident CHD rates (cardiac death or nonfatal myocardial infarction) were also higher in subjects with IGT or IFG and IGT compared with subjects with NGT or IFG alone.

Other investigators have found that IGT is a risk factor for CVD [18-20]. Results from the Funagata Diabetes Study showed that subjects with IGT had lower survival rates from CVD compared with those with NGT, whereas no difference was seen in survival rates in subjects with IFG compared with individuals with NGT [21]. Similar findings of increased fatal CVD in those with abnormal glucose tolerance were as also shown in the Rancho Bernardo Study [22]. The increased risk was seen in women, but not in men, and was independent of age, hypertension, central obesity, cigarette smoking, HDL cholesterol, and triglycerides [22].

Increased all-cause mortality was shown in subjects found to have IGT in the DECODE (Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe) study, a prospective study of 13 European centers that performed the OGTT [23]. The results showed that study participants with IGT had the highest absolute number of excess deaths, with the largest contribution coming from those individuals with normal FPG [23]. Based on 1997 ADA criteria, subjects with IFG had survival curves slightly worse than subjects with normal fasting glucose. However, based on 2-hour glucose criteria, the survival curves for those with newly diagnosed DM were comparable to those with known DM; for those with IGT the survival curves were intermediate between those with known DM and those with NGT.

In our study participants, the OGTT results also demonstrated increasing glucose intolerance with aging. This observation was seen even in the presence of normal FPG (<5.6 mmol/L [110 mg/dL]) using the 2003 ADA criteria. Our observation of increased glucose intolerance with aging was consistent with results reported by Resnick et al [24] for the Health, Aging, and Body Composition Study. These investigators found that the prevalence of undiagnosed DM in a study of African American and white men and women between the ages of 70 to 79 years was 8.5% by WHO criteria as compared with 3.8% by ADA criteria [24]. Although the results showed a significant underestimation of DM using ADA criteria, in contrast to our results, this study did not examine the prevalence of abnormal glucose tolerance in elderly subjects with normal FPG.

A study by Stern et al addressed the use of the OGTT, among other variables, including age, in predicting future CVD. These investigators studied participants in the San Antonio Heart Study and developed predictive models for CVD, which included variables such as age, sex, ethnicity, blood pressure, low-density lipoprotein cholesterol, BMI, first-degree relative with DM, current cigarette smoking, and 2hPG [25]. These investigators found that incorporation of 2hPG in multivariate analysis did not significantly increase prediction of CVD incidence as compared to fasting lipids, blood pressure, BMI, smoking history, and family history of CVD [25]. Age was also found to increase the odds ratios significantly for CVD risk in both univariate and multivariate analysis. The lack of effect with 2hPG values on CVD mortality contrasted with those found in the DECODE study. The authors attribute these differences to end point measurement, the inclusion of older subjects in the DECODE study (as they are also present in our cohort), and to the lack of receiver operator characteristic curves. Although our results showed that inclusion of an abnormal OGTT significantly increased the prevalence of the MS, in agreement with Stern et al, it was also clear that the prevalence of abnormal glucose tolerance, particularly in subjects with FPG less than 5.6 mmol/L, was higher in subjects with abnormal fasting lipids (low HDL-C) and hypertension. Among the different determinants, the prevalence of IGT or DM did not significantly increase with deteriorating FPG.

Lorenzo et al [26] found that the MS (modified 1999 WHO criteria) predicted the incident rate of DM in participants of the San Antonio Heart Study. These investigators found that the addition of IGT to the National Cholesterol Education Program guidelines increased the sensitivity in the prediction of incident DM and IGT had a higher positive predictive value [26]. Our cross-sectional data showed that the prevalence of IGT and DM increased with increasing FPG; in fact, the prevalence of IGT and DM was increased even in subjects with FPG of less than 5.6 mmol/L.

The limitations of our study merit discussion. Our population is middle- and upper-class whites, who on average were close to the upper limit of desirable body weight (although, as expected, subjects with the MS were overweight and closer to being defined as obese). The dose of 40 gm/m^2 was based, in part, on varying doses of glucose used for the OGTT and from the recommendations of the Committee on Statistics of the American Diabetes Association Standardization of the Oral Glucose Tolerance Test [27]. We did not directly compare the effects of 75 vs $40g/m^2$ in each of the study subjects; however, the average glucose dose was 68 g in women (9% less than the 75 g) and was 78 g in men (4% more than the 75 g). These differences are small and would, especially in women, underestimate the prevalence of IGT and/or DM. Nonetheless, we suspect that given the high prevalence of IGT and DM based on 2hPG values in our study cohort, the prevalence rates for the MS would be even higher in populations at risk. Ford et al did indeed find that the prevalence of the MS was significantly higher in African American men with the use of the WHO criteria for the MS (which includes 2hPG) as compared with the ATPIII criteria [28].

There are differences between the WHO and the ATPIII in each of the 4 “domains” defining the MS (glucose/insulin, obesity/fat distribution, dyslipidemias, and blood pressure). Our report discusses one aspect in the first of these domains, whether to include an oral glucose tolerance criterion in the diagnostic rubric. It should be noted that there are other differences between the 2 sets of criteria: the WHO system includes an abnormality in insulin sensitivity in the glucose

domain [1] and the WHO system demands an abnormality in this domain to diagnose the MS [2]. Resolving these multiple differences between the 2 sets of criteria in glucose domain alone is beyond the scope of this report. We do, however, recommend, on the basis of the analyses presented, that an impaired glucose tolerance test be added to the criterion of an impaired fasting glucose concentration for the ATPIII classification system. We do not recommend including a quantification of insulin sensitivity by the glucose clamp method as an additional criterion; it is clearly not a technique applicable to clinical use.

In summary, FPG alone as one component of the MS underestimated the prevalence of the MS in our study subjects. The importance of correctly identifying those subjects with the MS is highlighted by the studies of Isomaa et al [29] and Lakka et al [30] who showed that cardiovascular morbidity and mortality was associated with the MS. The results from our study, and that of others, suggest the need to combine fasting and 2hPG levels in assessing the prevalence of the MS, a population not only at risk for incident DM and but also for CVD.

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