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The “Metabolic Syndrome” Is Less Useful than Random Plasma Glucose to Screen for Glucose Intolerance

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Abstract

Aims—To compare the utility of metabolic syndrome (MetS) to random plasma glucose (RPG) in identifying people with diabetes or prediabetes.

Methods—RPG was measured and an OGTT was performed in 1,155 adults. Test performance was measured by area under the receiver-operating-characteristic curve (AROC).

Results—Diabetes was found in 5.1% and prediabetes in 20.0%. AROC for MetS with FPG was 0.80 to detect diabetes, and 0.76 for diabetes or prediabetes – similar to RPG (0.82 and 0.72). However, the AROC for MetS excluding fasting plasma glucose (FPG) was lower: 0.69 for diabetes ($p < 0.01$ vs. both RPG and MetS with FPG), and 0.69 for diabetes or prediabetes. AROCs for MetS with FPG and RPG were comparable and higher for recognizing diabetes in blacks vs. whites, and females vs. males. MetS with FPG was superior to RPG for identifying diabetes only in subjects with age < 40 or BMI < 25 .

Conclusions—MetS features can be used to identify risk of diabetes, but predictive usefulness is driven largely by FPG. Overall, to identify diabetes or prediabetes in blacks and whites with varying age and BMI, MetS is no better than RPG – a more convenient and less expensive test.

Keywords

Screening; type 2 diabetes; prediabetes; impaired glucose intolerance; impaired fasting glucose

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CONFLICT OF INTEREST STATEMENT

The authors have no financial or personal relationships with other people or organizations that could inappropriately influence or bias this work.

Introduction

The prevalence of type 2 diabetes is growing rapidly, and by 2050 is expected to reach 50 million people in the U.S. [1]. Diabetes increases morbidity and mortality, impairs quality of life [2], and incurs substantial cost – estimated direct and indirect costs were \$132 billion in the U.S. in 2002 [3]. Since appropriate management of diabetes can reduce these problems [4–6], and treatment of prediabetes can reduce progression to diabetes [7], there is interest in early detection of diabetes and prediabetes.

The “epidemic” of type 2 diabetes is thought to be fueled by insulin resistance, which rises in response to increases in age, overweight, and inactivity [8–10], coupled with production of insulin which is inadequate to meet the challenge of insulin resistance [11]. Although assessment of insulin production generally requires procedures which are complex, costly, and inconvenient, insulin resistance can also be evaluated by alterations in measures which are within the reach of most patient care settings. The “metabolic syndrome” (MetS) is a cluster of abnormalities in blood pressure, triglycerides, HDL cholesterol, blood glucose, and/or visceral adiposity which individually and in combination reflect underlying insulin resistance [12,13], are associated with increased risk of cardiovascular disease [14], and are increasing in prevalence [15,16].

Although the presence of MetS abnormalities increases the risk of a subsequent diagnosis of diabetes [17], less is known about the potential utility of MetS (a) to identify prevalent glucose intolerance, (b) in subpopulations, and (c) in direct comparison with alternative approaches to screening. Subpopulation analyses are of particular importance because blacks are less likely than whites to exhibit abnormalities in HDL cholesterol or triglycerides, which has led some investigators to propose the use of racial/ethnic-specific cutoffs [18]. Moreover, since fasting plasma glucose (FPG) is a MetS component, but FPG is also used to diagnose glucose intolerance, the inclusion of FPG in the MetS risks circularity. We studied the ability of MetS – with and without inclusion of FPG – to identify glucose intolerance in subpopulations of blacks and whites stratified according to age and BMI. We also compared MetS to random plasma glucose (RPG) as a more convenient and less expensive screening test which can be performed at any time of the day and under any prandial condition.

Methods

Subjects

Beginning in January, 2005, participation in “Screening for Impaired Glucose Tolerance” study (SIGT) was offered to employees of the Grady Health System, Emory HealthCare, and Emory University and Morehouse Schools of Medicine, as well as members of the community. Inclusion criteria were no prior knowledge of diabetes, not pregnant or nursing, not taking glucocorticoids, and being well enough to be able to have worked during the previous week (without requiring employment). By 5/11/07, 2631 individuals had expressed interest, 2434 could be contacted, 1536 were scheduled for visits, and 1226 completed first visits. Of these, 43 declined second visits, 28 were scheduled for but had not had a second visit, 1,155 had completed both visits, and 1,139 (98.6%) had complete data.

Protocol

The study was approved by the Emory Institutional Review Board and was performed in General Clinical Research Centers at Emory University Hospital and Grady Memorial Hospital. Random plasma glucose (RPG) samples were obtained at the first visit, which did not require a prior overnight fast and was scheduled during the work day. The second visit was

scheduled within 3 weeks, and included a 75 g oral glucose tolerance test (OGTT) begun before 11 am following an overnight fast.

Height was measured with a stadiometer (to 0.1 cm) after shoes were removed. Weight was measured (to 0.1 kg) using digital scales with subjects in light clothing. Blood pressure was measured (to 1 mmHg) twice with digital manometers after subjects had been seated quietly for 5 minutes, and averaged. Waist circumference was measured (to 0.1 cm) halfway between the costal margin and the iliac crest by trained research interviewers, and sex-adjusted values were expressed relative to cutoffs for the “metabolic syndrome” (MetS) as defined by National Cholesterol Education Program [NCEP [19]] criteria. Subjects also reported their demographic information and family history of diabetes.

Measurements

Plasma glucose samples were obtained using sodium fluoride/oxalate preservative. These and fasting lipid samples were centrifuged, separated and frozen within 30 minutes. Analyses were performed in the clinical laboratory of the Grady Health System using the Beckman-Coulter LX-20 (Brea, CA). The glucose assay utilized glucose oxidase with an oxygen electrode and lipids were measured using liquid selective detergent separation. Sex-adjusted HDL cholesterol levels were expressed relative to “metabolic syndrome” cutoffs as above.

Analysis

Normal glucose tolerance (NGT) was defined by ADA criteria (fasting glucose <100, 2 hour glucose <140 mg/dl); impaired fasting glucose₁₀₀ (IFG₁₀₀) and impaired fasting glucose₁₁₀ (IFG₁₁₀) by fasting glucose 100–109 and 110–125 mg/dl, respectively, with 2 hour glucose <140 mg/dl; impaired glucose tolerance (IGT) by 2 hour glucose 140–199 with fasting glucose ≤125 mg/dl; and diabetes (DM) by fasting glucose ≥126 or 2 hour glucose ≥200 mg/dl. We focused particularly on diabetes and “high risk” prediabetes (diabetes or IGT or IFG₁₁₀), since such levels confer increased mortality [20,21]. Cutoffs for the “metabolic syndrome” were defined by National Cholesterol Education Program [NCEP [19]] criteria (with FPG₁₀₀).

Receiver operating characteristic (ROC) curve analysis was used to evaluate the discriminative effectiveness of MetS and RPG. The area under the ROC curve (AROC) was used as the index of effectiveness, with 1.0 indicating perfect discrimination and 0.5 chance discrimination. Bootstrap methodology was applied to assess the over-optimism of sample-calculated AROCs [22]. In this application, 200 bootstrap replicates were drawn (with replacement) to calculate a bias-corrected AROC. The method developed by DeLong, et. al. was used to compare AROCs [23]. Statistical analyses were conducted using S-Plus, version 7 (Insightful, Inc. Seattle, WA) and Stata, version 9 (Stata Corporation, College Station, Texas).

Results

The 1,155 study subjects had average age 48±12 years and BMI 30.3±6.8 kg/m²; 54% were black and 63% were female, and they had average random plasma glucose (RPG) 99±20 mg/dl (Table 1). Those with normal glucose tolerance (NGT) tended to be younger and less overweight, with average RPG 93±16 mg/dl. Those with abnormal glucose tolerance were older and heavier, but had similar distribution of gender and race. However, those with IFG only were less likely to be black or female, and those with IGT only were more likely to be female. The metabolic syndrome (MetS) was present in 27% overall – 10% of those with NGT, 25% with IGT alone, 76% with IFG_{110–125} alone, and 71% with diabetes.

Table 2 shows the areas under the ROC curve (AROCs) for identification of diabetes (DM), diabetes or IGT (DM/IGT), and diabetes or IGT or IFG_{110–125} (DM/IGT/IFG, or any glucose

intolerance₁₁₀, AGI₁₁₀). Bias-corrected AROCs were very similar to the observed AROCs, differing only in the third and fourth decimal places, and are not shown. For all categories of glucose intolerance, the AROC for identification by MetS with fasting plasma glucose (FPG) was uniformly greater than that for MetS without FPG; the average difference in AROC was 0.078 ($p < 0.05$). The difference in AROC was also uniform in subgroup analyses of Blacks and Whites, and females and males ($p < 0.05$ only for Blacks and males, not shown), across ages <40 , 40–55, and >55 years (all $p < 0.05$), and BMI <25 , 25–35, and >35 kg/m² ($p < 0.05$ only for BMI <25 and >35). However, for the entire group of subjects, the identification of glucose intolerance by MetS with FPG was no better than that for RPG alone; the average difference in AROC was 0.012, neither clinically nor statistically significant.

MetS appeared to be useful mainly for identifying diabetes as opposed to other categories of glucose intolerance; as shown in Figure 1, the AROCs for identifying diabetes were generally higher than those for identifying DM/IGT or for AGI₁₁₀. MetS was also useful mainly in 10 subjects who were younger or slim. The AROCs were 0.98 (95% CI 0.95–1.00) for MetS with FPG and 0.93 (0.85–1.00) for MetS without FPG to identify diabetes in subjects <40 years old, both significantly higher than the AROCs for subjects 40–55 and >55 years old ($p < 0.01$ for all). Such discrimination appears to reflect the tendency of the diabetes subjects <40 years to have a lower HDL (average 30 mg/dl, adjusted to be comparable to a male standard [see Methods]) and higher triglycerides (226 mg/dl) compared to diabetes subjects 40–55 and >55 years old (Table 3). The ability of MetS with FPG to identify diabetes in those with BMI <25 was also high (AROC 0.91, 95% CI 0.83–0.99), significantly greater than that for subjects with BMI >35 (AROC 0.74, 95% CI 0.66–0.83) and also greater than that for subjects with BMI 25–35 (AROC 0.76, 95% CI 0.68–0.85), all $p < 0.005$. Although the ability of MetS without FPG to identify diabetes in those with BMI <25 was lower (AROC 0.83, 95% CI 0.75–0.92), it was also significantly greater than that for subjects with BMI 25–35 or >35 , $p < 0.01$ for both. Identification of the diabetes subjects with BMI <25 appears to reflect their tendency to have a higher systolic blood pressure (136 mmHg), and higher triglycerides (172 mg/dl) than diabetes subjects with BMI 25–35 or >35 .

Use of RPG for diabetes screening requires choice of a cutoff which balances sensitivity and specificity appropriately. In our population, a cutoff of 125 mg/dl provided 41% sensitivity, 92% specificity, and 22% positive predictive value (PPV) for detection of diabetes, and 19% sensitivity, 94% specificity, and 52% PPV for detection of any glucose intolerance₁₁₀; over half of those followed up with an OGTT would have a “high-risk” glucose abnormality. Sensitivity would be increased with lower cutoffs, but specificity and PPV would fall.

Discussion

In a mixed population of whites and blacks, male and female, our findings show that the presence of the metabolic syndrome (MetS) can be used to identify individuals with increased risk of glucose intolerance. The recognition of diabetes was better than that for prediabetes, but still statistically significant both for the entire group and for subgroups of males and females, and whites and blacks. Usefulness as a screening test was due substantially to the inclusion of elevated levels of fasting plasma glucose (FPG), and screening performance was generally no better than that of random plasma glucose (RPG) – a less expensive and more convenient test. MetS was more effective than RPG in identifying the likelihood that diabetes is present only in individuals who in general have low risk – those with BMI <25 kg/m², or who are <40 years old. Since many individuals with diabetes and prediabetes are unrecognized, but screening is infrequent [24], the presence of MetS features could be used to signal the need for glucose tolerance tests in such subpopulations.

The development of glucose intolerance reflects a reduction in insulin secretion rather than an increase in insulin resistance [11]. However, the inconvenience of measuring β -cell function, and the low prevalence of diabetes in insulin-sensitive individuals even if genetic risk is high [25], have led to a focus on insulin resistance to identify risk of unrecognized glucose intolerance. Insulin resistance is more common in individuals who are older or overweight [26], or have increased abdominal adiposity [27]. And elevated FPG, low HDL cholesterol, and/or high triglycerides can indicate that insulin secretion is inadequate to suppress hepatic production of glucose and/or VLDL cholesterol [28]. Accordingly, it is reasonable to hypothesize that the combined presence of such abnormalities in MetS would predict glucose intolerance. Consistent with this hypothesis, the ability of MetS to identify glucose intolerance was statistically significant both for the group as a whole, and for subgroups of men and women, blacks and whites, and groupings by BMI and age. However, the screening characteristics of MetS to identify diabetes alone or diabetes + prediabetes were little better than those of RPG alone, except for individuals with age <40 or BMI <25.

There have been previous studies of the ability of MetS and glucose measurements both to identify *prevalent* and predict *incident* glucose intolerance. Phenotypic risk scores which excluded glucose values provided poor identification of *prevalent* HbA1c $\geq 6.5\%$ [AROC 0.71 [29]] and T2DM [AROC 0.58–0.69 [30]] and were poorly generalizable across diverse populations [30]. Meigs et al [31] reported the AROC for detection of *prevalent* T2DM/IGT to be 0.62–0.80 using IFG alone or in combination with other MetS traits, but 0.62–0.72 with trait combinations not including IFG. Nelson and Boyko [32] reported the AROC for detection of *prevalent* T2DM/IGT to be 0.76 using a risk score of clinical variables with FPG. Schmidt et al [33] also found the AROC for detection of *prevalent* T2DM/IGT to be 0.73 using a risk function of clinical variables with FPG, but 0.64 for MetS variables excluding FPG.

Schmidt et al [34] reported the AROC for prediction of *incident* T2DM to be 0.78 using clinical variables with FPG, 0.74 with FPG alone, 0.71 with clinical variables excluding FPG, and 0.75 with MetS traits including FPG₁₀₀ or FPG₁₁₀. Meigs et al found the age- and sex-adjusted AROC for prediction of *incident* T2DM by MetS (including FPG) to be 0.78 in the Framingham Offspring Study [17]. In the San Antonio Heart Study [35], the AROC for predicting *incident* T2DM was 0.76–0.78 using the MetS including FPG, and 0.80 with the 2-hour OGTT glucose alone, similar to our findings with RPG alone; prediction with a more extensive model including FPG was more robust [36], although not always generalizable to separate populations [37]. Adding FPG to MetS-type risk factors improved the AROC for prediction of *incident* T2DM from 0.74 to 0.78 in Thai subjects [38], and from 0.71 to 0.78 in the ARIC study [34]. *Incident* T2DM was also predicted more strongly by FPG than by other risk factors in Beaver Dam subjects [39], in the Framingham Offspring Study [17], in the Bruneck study [40], and in the Hong Kong Cardiovascular Risk Factor Prevalence Study [41], and *incident* T2DM was predicted comparably by 2-hr OGTT glucose alone vs. MetS in San Antonio subjects [42]. These earlier reports are consistent with our findings that excluding FPG weakens the ability of the other MetS traits to identify glucose intolerance, and that the MetS with FPG is generally comparable to identification with glucose values alone. However, these studies did not include either subgroup analyses or direct comparisons with RPG.

It is not clear why the presence of MetS is particularly useful to detect glucose intolerance in individuals who would be expected to be at low risk because of relatively young age (<40 years) or normal BMI (<25 kg/m²). The prevalence of MetS is increasing in younger individuals [43], reflecting underlying increases in central adiposity and triglycerides, along with low HDL cholesterol. In our study, subjects with diabetes who were <40 years old also had such a phenotype (Table 3). The lipid accumulation product (waist circumference $\times$ triglycerides) is a strong predictor of glucose intolerance [44], and in our study, subjects with diabetes who had BMI <25 tended to have high triglycerides. Alternatively, it is possible that the good screening

performance of MetS in low-risk subjects is due simply to the lower background of insulin resistance in individuals with age <40 years or BMI <25.

The strengths of our study include evaluations of MetS with/without inclusion of FPG, extensive subgroup analyses, and direct comparisons with RPG as an alternative screening strategy; such comparisons were generally not present in previous examinations (above). Our study also has limitations. Although several aspects of our results are consistent with previous work (above), the study subjects were self-selected (potentially because of a family history of diabetes), and the findings need to be confirmed in unselected populations. Also, the FPG values used to meet MetS criteria were part of the diagnostic OGTT. However, this should have reduced some of the variability for MetS as a screen, and thus makes the performance of RPG relatively more robust, since RPG samples were obtained at a separate visit. Finally, although we found that there was no effect of the race on the predictive performance of MetS and RPG, our study was limited to whites and blacks. The findings also need to be confirmed in other racial/ethnic groups, because the distribution of obesity, MetS, and insulin resistance varies substantially in different populations [31].

Because of the magnitude of the “diabetes epidemic”, our findings have important implications for application to clinical practice. Since the presence of MetS confers a high risk of undetected glucose intolerance, healthcare systems should consider ways to prompt a diagnostic OGTT in patients who have MetS if they have BMI <25 or age <40 years. However, except for such low-risk patients, it should be most useful for practitioners to consider screening based on an RPG value such as 125 mg/dl, which constitutes an equally effective but more convenient and less expensive screen, and deserves greater emphasis in programs aimed at early detection and aggressive management of glucose intolerance.

LIST OF ABBREVIATIONS

AGI₁₁₀, any glucose intolerance₁₁₀ (diabetes or IGT or IFG_{110–125})
 ARIC, Atherosclerosis Risk in Communities study
 AROC, area under the ROC curve
 DETECT-2, “international data pooling collaboration specifically addressing issues related to screening for type 2 diabetes”
 dysglycemia, type 2 diabetes or IGT or IFG₁₁₀
 EPIC-Norfolk, European Prospective Investigation of Cancer-Norfolk
 FPG, fasting plasma glucose
 GCRC, General Clinical Research Center
 Health ABC, Health, Aging, and Body Composition study
 HDL, high density lipoprotein
 IFG, impaired fasting glucose
 IFG₁₁₀ or IFG_{110–125}, IFG with fasting plasma glucose 110–125 mg/dl
 IGT, impaired glucose tolerance
 NCEP, National Cholesterol Education Program
 NHANES-III, National Health and Nutrition Examination Survey III
 Prediabetes, IGT and/or IFG₁₁₀
 ROC, receiver-operating-characteristic
 RPG, random (nonfasting) plasma glucose
 T2DM, type 2 diabetes mellitus
 WHO, World Health Organization

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IDENTIFYING GLUCOSE INTOLERANCE

Figure 1.

AROC for identifying categories of glucose intolerance by screening with RPG, MetS with FPG, and MetS without FPG – diabetes alone (DM), diabetes or IGT (DM/IGT), and any glucose intolerance₁₁₀ (DM/IGT/IFG) – in categories of age (above) and BMI (below).

Table 1

Subject demographics

Group	N	Age yr	BMI kg/m ²	Black (%)	Female (%)	RPG mmol/l mg/dl	MetS (%)
All	1155	48±12	30.3±6.8	54	63	5.5±1.1 99±20	27
NGT	705 (61%)	46±12	29.2±6.7	55	70	5.2±0.9 93±16	10
IFG ₁₀₀₋₁₀₉ only	160 (14%)	51±10	30.7±5.9	42	44	5.8±1.0 104±18	51
IFG ₁₁₀₋₁₂₅ only	38 (3%)	54±10	32.7±7.8	39	45	6.0±1.0 108±17	76
IGT only	92 (8%)	52±10	30.8±6.3	58	67	5.7±1.2 102±21	25
IGT + IFG ₁₀₀₋₁₀₉	61 (5%)	53±11	33.4±6.5	64	51	6.0±0.8 109±15	70
IGT + IFG ₁₁₀₋₁₂₅	40 (3%)	53±9	34.2±4.7	55	50	6.4±1.2 115±22	67
Diabetes	59 (5%)	55±10	34.1±6.9	63	51	7.0±1.8 127±32	71
Any IGT or any IFG ₁₁₀ or diabetes (any glucose intolerance ₁₁₀₊ AGI ₁₁₀)	290 (25%)	53±10	32.8±6.6	57	55	6.2±1.3 111±24	57

Table 2
The predictive ability of RPG, MetS with FPG, and MetS without FPG in all subjects:

Test	Glucose intolerance	Sensitivity	Specificity	AROC	95% CI	N
RPG	DM	78	71	0.815	0.762–0.868	1152
MetS w/ FPG	DM	76	70	0.796	0.748–0.844	1155
MetS w/o FPG	DM	54	70	0.694	0.637–0.751	1155
RPG	DM/IGT	62	71	0.714	0.678–0.750	1152
MetS w/ FPG	DM/IGT	63	70	0.733	0.701–0.766	1155
MetS w/o FPG	DM/IGT	53	70	0.675	0.641–0.710	1155
RPG	DM/IGT/IFG	63	70	0.725	0.692–0.758	1152
MetS w/ FPG	DM/IGT/IFG	68	70	0.760	0.730–0.790	1155
MetS w/o FPG	DM/IGT/IFG	55	70	0.685	0.652–0.717	1155

Table 3

Metabolic characteristics of subjects with/without diabetes:

Subjects	N	SBP	HDL	Trig	Waist	HI Waist	FPG	Fam hx	BMI
All	58	129	37	127	115.0	79%	123	67%	34.4
Black	1081	121	43	90	103.9	51%	94	48%	30.1
	36	131	36	115	117.1	83%	125	69%	36.0
White	574	123	42	76	105.3	56%	93	55%	31.4
	22	126	38	147	111.4	73%	122	64%	31.7
Female	507	118	50	106	102.2	45%	95	39%	28.7
	30	128	36	95	116.2	83%	123	77%	35.1
Male	691	118	43	81	106.2	58%	92	50%	30.6
	28	130	37	161	113.7	75%	125	57%	33.6
Age < 40	390	125	43	107	99.7	38%	97	43%	29.3
	5	127	30	226	114.6	100%	127	80%	36.8
40-55	247	116	43	77	99.9	38%	89	41%	29.4
	20	127	37	107	116.8	80%	121	70%	35.0
> 55	513	121	43	89	105.0	52%	94	50%	30.6
	33	131	37	124	113.9	76%	126	64%	33.6
BMI < 25	321	124	44	103	105.0	58%	97	49%	30.0
	5	136	44	172	93.0	0%	113	60%	23.8
	246	112	49	67	87.1	2%	89	36%	22.6
25-35	26	128	37	128	107.6	77%	125	65%	30.2
	605	123	43	95	102.7	52%	95	49%	29.4
> 35	27	129	35	118	126.1	96%	125	70%	40.3
	230	124	37	103	124.7	99%	96	56%	40.3