Two-Hour Insulin Determination Improves the Ability of Abdominal Fat Measurement to Identify Risk for the Metabolic Syndrome

FERNANDO F. RIBEIRO-FILHO, MD, PHD[1]
ALESSANDRA N. FARIA, MD, PHD[1]
NARCIA E.B. KOHLMANN, RN[2]
MARIA-TERESA ZANELLA, MD, PHD[1]
SANDRA R.G. FERREIRA, MD, PHD[3]

OBJECTIVE — Visceral obesity is shown to be a predictor of morbidity and mortality. We evaluated the association of measurements of generalized adiposity and visceral fat area (VFA), with abnormalities of metabolic syndrome (MS).

RESEARCH DESIGN AND METHODS — Seventy-six women (47.9 ± 9.2 years) with BMI of 38.7 ± 5.4 kg/m^2 underwent anthropometric measurements, laboratory procedures, bioeletrical impedance, and abdominal computed tomography (CT) scan. Diagnosis of MS was based on the presence of abdominal obesity and at least two of the following components: hypertension, dyslipidemia, and glucose intolerance and/or hyperinsulinemia.

RESULTS — BMI was correlated with both components of adipose tissue—subcutaneous ($r = 0.66$, $P < 0.01$) and VFA ($r = 0.33$, $P < 0.02$)—and leptin levels ($r = 0.38$, $P < 0.01$). In contrast, VFA was correlated with 2-h glucose and insulin levels ($r = 0.32$ and 0.35, $P < 0.05$, respectively), triglyceride, HDL cholesterol, and uric acid ($r = 0.33$, -0.34 and 0.24, $P < 0.05$, respectively). Subjects with high VFA, matched for BMI, showed greater plasma glucose area under the curve (621 ± 127 vs. 558 ± 129 mg · h^{-1} · dl^{-1}, $P < 0.05$), 2-h insulin (804 ± 599 vs. 579 ± 347 pmol/l, $P < 0.05$), and uric acid levels (0.33 ± 0.07 vs. 0.26 ± 0.06 mmol/l, $P < 0.05$) than subjects with low VFA. In logistic regression analysis, waist circumference, VFA, and 2-h insulin were identified as independent predictors of MS. Receiver operating characteristic curve analysis pointed out the values of 104 cm for waist circumference (58.1% specificity, 84.1% sensitivity), 158.5 cm^2 for VFA (78.1% specificity, 52.3% sensitivity), and 559.8 pmol/l for 2-h insulin (71.9% specificity, 69.8% sensitivity); the presence of at least two of the three variables resulted in a degree of concordance of 76%.

CONCLUSIONS — While BMI was unable to differentiate between obese people and those at higher risk for MS, abdominal fat was shown to be associated with its metabolic abnormalities. The usefulness of abdominal fat in the identification of high-risk subjects may be improved when combined with 2-h insulin determination.

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Obesity is considered a major public health problem due to its increasing prevalence and high morbidity and mortality, mainly attributed to abnormalities included in the spectrum of the metabolic syndrome (MS) (1–3). Particularly, upper-body obesity has been shown to be an important predictor of cardiovascular disease (4). The search for markers able to identify subjects at high risk to develop MS is motivated by the potential benefits of early interventions.

The simplicity of BMI assessment has made this widely used to classify subjects' risk of morbidity and mortality (1,5). However, BMI is not accurate to quantify body fat excess or the distribution of fatness. Recent studies have reported populations with low prevalence of obesity but high incidence of typical disturbances of MS (6,7), thereby raising the question of whether BMI plays a role in the identification of patients at high cardiovascular risk (8,9).

Since 1956, the impact of body fat distribution on the occurrence of metabolic abnormalities in obese people has received increased attention (10). Nowadays, abdominal fat accumulation is seen as key event for the pathogenesis of the MS (11,12). However, the impact of visceral fat on mortality of patients with MS is not completely known due to limitations, such as availability, radiation, high costs, and low specificity of the anthropometry (waist circumference or waist-to-hip ratio [WHR]), in the assessment of visceral fat by computed tomography (CT)—the gold standard. Also, data concerning the cutoff values for CT-determined intra-abdominal fat associated with high cardiovascular risk are not widely available (13,14).

This study aimed to evaluate the association of measurements of generalized (expressed by the BMI) and visceral adiposity (CT-determined visceral fat area) with typical abnormalities of MS.

RESEARCH DESIGN AND METHODS

— Patients aged 20–65 years with BMI ≥30 kg/m^2 were recruited from the Clinic of Obesity of the Federal University of São Paulo. Written informed consent was obtained from all participants, and the study was approved by the Institutional Ethics Committee. Exclu-

From the [1]Endocrinology Division, the Department of Internal Medicine, Federal University of São Paulo, São Paulo, Brazil; the [2]Nephrology Division, Department of Internal Medicine, Federal University of São Paulo, São Paulo, Brazil; and the [3]Department of Preventive Medicine, Federal University of São Paulo, São Paulo, Brazil.

Address correspondence and reprint requests to Fernando F. Ribeiro-Filho, Rua Loefgreen, 1543/33–CEP 04040-032, São Paulo, SP, Brazil. E-mail: fflexa@uol.com.br.

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Abbreviations: CT, computed tomography; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; MS, metabolic syndrome; NGT, normal glucose tolerance; ROC, receiver operating characteristic; SFA, subcutaneous fat area; VFA, visceral fat area; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Correlation coefficients of BMI, SFA, and VFA with anthropometric, metabolic, and hormonal parameters and percent body fat*

	BMI		SFA		VFA	
	r	*P*	*r*	*P*	*r*	*P*
Waist circumference	0.78	<0.01	0.55	<0.01	0.56	<0.01
Hip circumference	0.76	<0.01	0.60	<0.01	0.10	>0.10
WHR	0.34	<0.01	0.18	>0.10	0.58	<0.01
Fat mass	0.71	<0.01	0.48	<0.01	0.27	0.02
Subcutaneous fat by CT	0.66	<0.01	—	—	0.16	>0.10
Visceral fat by CT	0.33	<0.01	0.16	>0.10	—	—
Fasting plasma glucose	0.29	0.01	−0.01	>0.10	0.22	0.05
2-h plasma glucose	0.13	>0.10	−0.08	>0.10	0.32	<0.01
Glucose area under curve	0.15	>0.10	−0.08	>0.10	0.35	<0.01
Fasting insulin	0.16	>0.10	0.15	>0.10	0.30	<0.01
2-h insulin	0.12	>0.10	0.12	>0.10	0.35	<0.01
HOMA index	0.18	>0.10	0.12	>0.10	0.30	<0.01
Total cholesterol	−0.10	>0.10	−0.09	>0.10	0.09	>0.10
HDL cholesterol	−0.24	0.03	−0.07	>0.10	−0.34	<0.01
LDL cholesterol	−0.04	>0.10	−0.05	>0.10	0.09	>0.10
Apolipoprotein B	−0.02	>0.10	−0.10	>0.10	0.21	>0.10
Triglyceride	0.05	>0.10	−0.07	>0.10	0.33	<0.01
Uric acid	0.25	0.03	0.20	0.08	0.24	0.04
Leptin	0.38	<0.01	0.27	0.02	−0.03	>0.10
MS*	0.33	<0.01	0.14	>0.10	0.36	<0.01

*Presence of abdominal obesity and at least two of the following components: hypertension, dyslipidemia, and glucose intolerance and/or hyperinsulinemia.

sion criteria were patients with self-reported diabetes, severe dyslipidemia (total cholesterol >9.0 mmol/l and/or triglyceride >4.5 mmol/l), weight loss ≥3 kg in the last 3 months, cause-specific obesity, use of medication that could potentially affect lipid or glucose metabolism, and systolic and diastolic blood pressure >160/110 mmHg. In this cross-sectional study, patients were submitted to anthropometric measurements and clinical examination, and data were taken by the same investigator. BMI was calculated as weight (kilograms) divided by height (meters) squared. WHR was calculated as the ratio of waist (measured at the midpoint between the lateral iliac crest and lowest rib) to the hip (at the level of the trochanter major) circumferences. Blood pressure was taken after a 5-min resting in the sitting position by standard sphygmomanometry. Hypertension was defined by systolic or diastolic blood pressure ≥130/85 mmHg or by the use of antihypertensive medications (15). Body fat mass was estimated with a single-frequency (50 kHz) battery-operated bioimpedance analyzer (model BIA 101Q; RJL System, Clinton, MI). A tetrapolar placement of electrodes was used according to the manufacturer's instructions. Fasting subjects rested supine on a couch for 15 min in a thermoneutral (24–26°C) room, without touching any metallic object. Weight, height, age, and sex were entered into the bioimpedance analyzer (BIA) machine for analysis with the measured bioelectrical impedance to calculate body composition from the manufacturer's equations. Subcutaneous (SFA) and visceral fat areas (density –50 –250 HU) were obtained by CT scan in a single tomographic slice at the L_4-L_5 level, expressed as centimeters squared. Laboratory evaluation included a 75-g oral glucose tolerance test for plasma glucose and insulin determinations, lipid profile (total cholesterol and fractions, triglyceride, and apolipoprotein B), uric acid, and leptin concentrations. Given that there is no internationally agreed upon definition for MS, in the present study MS was based on the presence of abdominal obesity and at least two of the following components: hypertension, dyslipidemia, and glucose intolerance and/or hyperinsulinemia (fasting insulin >145 pmol/l). Because all patients were obese and had waist circumference >88 cm for women, such measurement was not used as a diagnostic parameter. Both fasting and 2-h plasma glucose values were used to diagnose the glucose tolerance status. Serum lipids and blood pressure cutoffs follow National Cholesterol Education Program (NCEP) criteria (15). Insulin resistance index was estimated by homeostasis model assessment (HOMA) and glucose area under the curve.

Plasma glucose was determined by the glucose-oxidase method. Cholesterol contents of lipoprotein fractions and serum triglyceride were measured enzymatically. Insulin was determined by monoclonal antibody-based immunofluorimetric assay (Delfia) and leptin by radioimmunoassay (Linco).

Statistical analysis included unpaired Student's *t* test to compare means of clinical and laboratory data between groups of subjects stratified by BMI and visceral fat area (VFA). Data were given as the mean and standard deviation. Pearson and Spearman coefficients were used to test correlation between variables. Independent associations of variables with MS were analyzed by logistic regression. Receiver operating characteristic (ROC) curve analysis was used to establish cut points for a number of variables associated with the occurrence of MS. κ statistics were used to assess the concordance with the diagnosis of MS. Level of significance was set at $P < 0.05$. Data analysis was performed using software SPSS 10.0.

Table 2—*Anthropometric, hemodynamic, and metabolic parameters of groups of patients with matched BMI or VFA*

	Matched BMI		Matched VFA	
	Less centralized ($n = 38$)	More centralized ($n = 38$)	Less generalized ($n = 38$)	More generalized ($n = 38$)
Age (years)	45.1 ± 10.7	50.7 ± 6.3*	48.0 ± 9.6	47.8 ± 8.9
BMI (kg/m^2)	38.4 ± 5.9	39.1 ± 4.9	36.8 ± 4.0	40.7 ± 5.9*
Waist circumference (cm)	105.5 ± 13.5	114.9 ± 11.3*	107.0 ± 12.0	113.6 ± 13.8*
WHR	0.90 ± 0.09	0.99 ± 0.07*	0.95 ± 0.09	0.95 ± 0.10
Fat mass (%)	42.5 ± 5.4	44.0 ± 4.4	41.7 ± 4.8	44.8 ± 4.7*
Visceral fat by CT (cm^2)	101.0 ± 34.2	182.9 ± 47.0*	143.3 ± 60.5	140.6 ± 56.1
Subcutaneous fat by CT (cm^2)	374.0 ± 124.7	383.3 ± 128.7	332.3 ± 110.8	424.9 ± 124.3*
Systolic blood pressure (mmHg)	147.0 ± 21.2	152.5 ± 19.5	151.4 ± 23.4	148.0 ± 17.0
Diastolic blood pressure (mmHg)	93.6 ± 10.6	96.0 ± 10.0	93.9 ± 10.8	95.7 ± 9.9
Heart rate (bpm)	79.0 ± 6.4	77.7 ± 8.0	78.3 ± 7.7	78.4 ± 6.8
Fasting plasma glucose (mmol/l)	5.2 ± 0.7	5.4 ± 0.6	5.2 ± 0.5	5.4 ± 0.7
2-h plasma glucose (mmol/l)	6.8 ± 2.2	7.8 ± 2.4*	7.2 ± 2.4	7.3 ± 2.3
Glucose area under curve ($mg \cdot h^{-1} \cdot dl^{-1}$)	557.8 ± 129.3	621.1 ± 126.6*	583.1 ± 118.3	595.8 ± 144.0
Fasting insulin (pmol/l)	113.7 ± 64.3	132.1 ± 65.9	120.3 ± 57.4	125.6 ± 73.2
2-h insulin (pmol/l)	578.7 ± 346.7	804.2 ± 599.1*	757.8 ± 609.6	620.3 ± 341.8
HOMA index	3.7 ± 2.4	4.4 ± 2.2	3.9 ± 2.0	4.2 ± 2.6
Total cholesterol (mmol/l)	5.3 ± 1.0	5.3 ± 1.0	5.3 ± 1.0	5.3 ± 1.0
HDL cholesterol (mmol/l)	1.1 ± 0.3	1.0 ± 0.2*	1.0 ± 0.3	1.1 ± 0.3
LDL cholesterol (mmol/l)	3.4 ± 0.9	3.5 ± 0.9	3.5 ± 0.9	3.4 ± 0.9
Apolipoprotein B (g/l)	1.22 ± 0.27	1.36 ± 0.29†	1.30 ± 0.28	1.31 ± 0.30
Triglyceride (mmol/l)	1.4 ± 0.6	2.0 ± 0.8*	1.7 ± 0.8	1.7 ± 0.7
Uric acid (mmol/l)	0.29 ± 0.06	0.33 ± 0.07*	0.30 ± 0.50	0.31 ± 0.11
Leptin (ng/ml)	26.3 ± 19.3	26.3 ± 13.3	20.9 ± 13.0	31.3 ± 14.0*

Data are means ± SD. *$P < 0.05$ vs. group less centralized or generalized; †$P = 0.07$ vs. group less centralized or generalized.

RESULTS — Seventy-six patients aged 47.9 ± 9.2 years, with a predominance of Caucasians (66%), having a BMI of 38.7 ± 5.4 kg/m^2 were included. Eighty-seven percent ($n = 66$) were hypertensive, glucose intolerance was diagnosed in 41%, 82% had dyslipidemia, and 35% had hyperinsulinemia. Fifty-eight percent ($n = 44$) fulfilled criteria for MS.

Correlation coefficients between BMI, SFA, or VFA and a number of variables are shown in Table 1. VFA was found to be correlated with metabolic parameters characteristic of MS, such as triglyceride, HDL cholesterol, and uric acid levels, as well as 2-h post–glucose load glycemia, insulinemia, and insulin resistance index. BMI showed significant correlation with fasting plasma glucose, HDL cholesterol, uric acid levels, leptin, percent of body fat mass, waist and hip circumferences, and VFA and SFA determined by CT scan. Multiple linear regression indicated that both visceral and subcutaneous fat, but mainly the latter, were independent predictors of BMI ($r^2 = 0.48$, $P < 0.001$).

Patients were then stratified into groups defined by "matched BMIs" or "matched VFAs" (Table 2). For stratification by matched BMIs, from each pair of subjects, the individuals with the higher VFAs comprised the subgroup "more centralized adiposity"; for stratification by matched VFAs, the individuals with higher BMIs comprised the subgroup of "more generalized adiposity." Therefore, groups divided according to BMI showed similar VFAs, and those divided according to VFA showed similar BMIs. Comparing groups of subjects with matched VFAs, those with higher BMI (more generalized adiposity) also had significantly higher waist circumference, percent of body fat mass, and SFA. When groups with matched BMIs were compared, those with higher VFA (more centralized adiposity) showed higher waist circumference, 2-h plasma glucose and insulin levels, glucose area under the curve, and triglyceride and uric acid levels. The contrast in glycemic curves and insulin values obtained for subjects with matched VFAs and matched BMIs is depicted in Fig. 1. Forty-four patients with MS showed higher BMI and adipose depots in the abdominal region (reflected by the waist circumference and WHR), fasting and 2-h insulin, HOMA index, and VFA, but not SFA, determined by CT (Table 3).

When patients were categorized according to normal glucose tolerance (NGT, $n = 45$), impaired glucose tolerance (IGT, $n = 25$), or diabetes ($n = 6$), the VFAs (129.0 ± 54.4, 153.0 ± 59.3, and 192.5 ± 48.7, for NGT, IGT, and diabetes, respectively, $P < 0.05$) but not BMIs (37.8 ± 5.0, 40.6 ± 6.0, and 38.1 ± 4.0) were higher in those with disturbances of glucose metabolism.

In the logistic regression analysis, age, BMI, VFA, SFA, waist circumference, fasting and 2-h insulin, and leptin were entered into the model as variables of interest in the association with MS. Waist circumference, VFA, and 2-h insulin were shown to be independently associated with MS. Using the ROC curve, the values of 104 cm for waist circumference (58.1% specificity, 84.1% sensitivity, positive predictive value of 74.0%, and negative predictive value of 72.0%), 158.5 cm^2 for VFA (78.1% specificity, 52.3% sensitivity, positive predictive value of 76.7%, and negative predictive value of 54.3%),

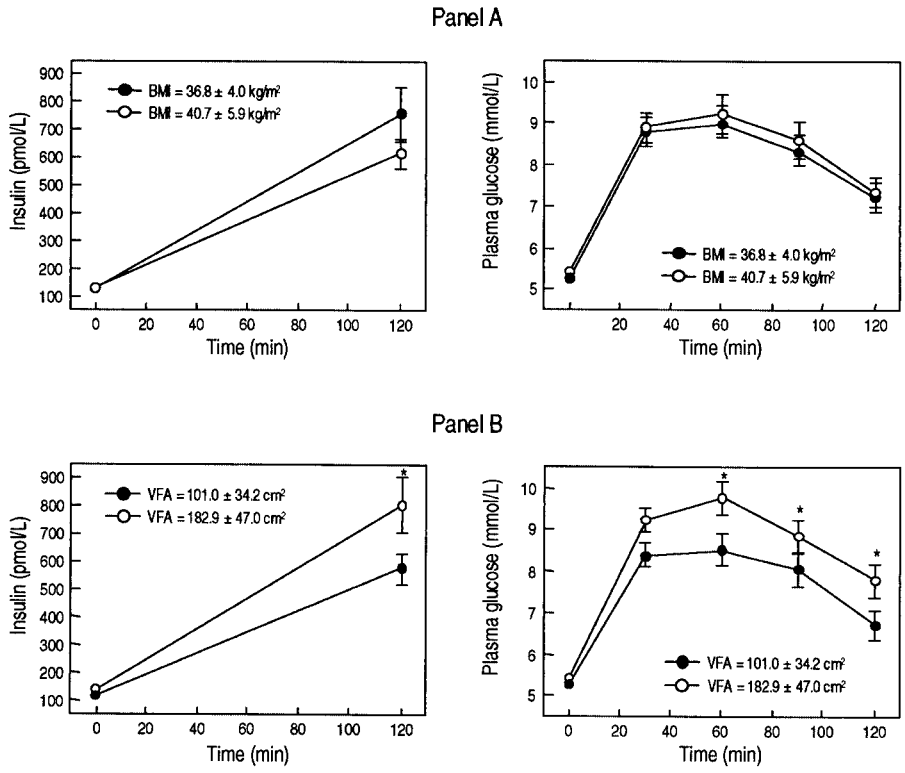

Figure 1—*Glycemic curves and insulin values obtained for subjects with matched VFA (A) and for those with matched BMI (B). P < 0.05 vs. lower VFA group.*

and 559.8 pmol/l for 2-h insulin (71.9% specificity, 69.8% sensitivity, positive predictive value of 76.9%, and negative predictive value of 63.9%) were found to be the best indicators of MS. Insulin levels and waist circumference were concordant with MS diagnosis in 71% of patients (κ 0.41 and 0.43, respectively, $P < 0.01$, for both), whereas the concordance of VFA was 63% (κ 0.29, $P < 0.01$). Taken into consideration the three variables, the presence of at least two resulted in a degree of concordance of 76% (κ 0.50, $P < 0.001$).

CONCLUSIONS — Obesity is a well-known risk factor for diabetes, hypertension, and dyslipidemia, all of which elevate cardiovascular mortality (1,2,5). The benefits of intervening in obesity have been shown (1), particularly in regard to the prevention of diabetes (16). Among obese subjects, the identification of those at higher risk to develop such diseases would improve effectiveness of prevention strategies. Despite the association of elevated body fatness, as reflected by high BMI, with morbidity and cardiovascular mortality (1,5), reports of populations at high risk for cardiovascular disease but with low prevalence rates of obesity are also found in literature (6,7). In addition, the findings of obese people without metabolic disturbances raise questions concerning the role of BMI as an isolated marker of risk (8,9).

Insulin resistance has been shown as the link between intra-abdominal adiposity and metabolic and hemodynamic abnormalities (3,8). Arner (17) proposed the "portal theory," in which free fatty acids released from the visceral adipose tissue could be a trigger factor to reduce insulin sensitivity, elevate insulin levels, and provoke a number of typical disturbances of the MS. Several lines of evidence have supported a more deleterious role of visceral fat relative to subcutaneous fat (3,8,18). However, a causal relationship of visceral adiposity with the insulin resistance syndrome is not a consensus (11,19). A recent study indicated that subcutaneous adipose tissue is the main source of free fatty acids (19). Goodpasteur et al. (20) found correlation of the subcutaneous abdominal fat with characteristic features of the insulin resistance. Thus, the assessment of adipose tissue distribution and its relationship with morbidity is of great interest in order to identify subjects at high cardiovascular risk.

In the present study, VFA determined by CT, but not the BMI or SFA, was associated with metabolic abnormalities such as reduced HDL cholesterol; elevated triglyceride, apolipoprotein B, and uric acid levels; and disturbed insulin sensitivity expressed by the HOMA index. Our findings are in agreement with others who emphasized the importance of visceral adipose tissue for the genesis of insulin resistance syndrome (3,7,18,21). Strong correlation was detected between BMI and leptin, the levels of which are known to be proportional to the subcutaneous fat (22). This may suggest that BMI is inap-

Table 3—*Anthropometric and hormonal characteristics according to the presence of MS*

	Without MS (n = 32)	With MS (n = 44)
Age (years)	47.2 ± 10.6	48.4 ± 8.1
BMI (kg/m^2)	36.9 ± 5.0	40.1 ± 5.4*
Waist circumference (cm)	103.4 ± 13.5	115.1 ± 10.8*
WHR	0.91 ± 0.09	0.97 ± 0.09*
Fat mass (%)	42.6 ± 5.1	43.7 ± 4.9
Fasting insulin (pmol/l)	88.3 ± 32.3	147.9 ± 71.8*
2-h insulin (pmol/l)	450.2 ± 251.7	868.1 ± 558.6*
HOMA index	2.8 ± 1.0	5.0 ± 2.5*
Leptin (ng/ml)	25.0 ± 19.6	27.2 ± 13.8
Subcutaneous fat by CT (cm^2)	357.2 ± 136.6	394.2 ± 116.7
Visceral fat by CT (cm^2)	119.7 ± 56.0	158.1 ± 54.5*

Data are means ± SD. *$P < 0.01$ vs. without MS. MS was defined by presence of abdominal obesity and at least two of the following components: hypertension, dyslipidemia, and glucose intolerance and/or hyperinsulinemia.

propriate to reflect the intra-abdominal fat depots.

After stratifying subjects according to similar BMI or similar VFA, we found that the discriminatory power of VFA was markedly better than BMI since the former identified patients with worse lipid profile and higher uric acid and postchallenge glucose levels, which are well-recognized cardiovascular risk factors (23–25). In agreement with others (4,9,12), our data support the indication of measurements of fat distribution to assess cardiovascular risk.

Our findings in the patients with MS, i.e., elevated BMI accompanied by higher VFA and insulin levels, corroborate the hypothesis that insulin may be the factor underlying the metabolic abnormalities (2,3). In contrast, the involvement of leptin in this syndrome, as suggested by some investigators (26), was not supported in our study.

Waist circumference, VFA determined by CT, and postchallenge insulin levels were found to be independent predictors of MS. Hyperinsulinemia was previously reported as an independent cardiovascular risk factor (27). More recently, the importance of altered postprandial glycemia was demonstrated in epidemiological study (23). Our findings supported the investigation of the impact of 2-h insulinemia for the cardiovascular risk. Such factor seemed to be relevant even more than BMI and leptin levels in our regression model. We propose that much of the importance of BMI for morbidity and mortality should be attributed to the visceral component of the body fatness. Such a hypothesis is reinforced by the fact that the proportion of the visceral component increases as BMI elevates (28,29). The inclusion of only obese subjects limited to test this hypothesis in our sample. Additional evidence on the relevance of fatness distribution was reported by Egger (9), who showed that nonobese subjects with abdominal adiposity are at higher cardiovascular risk than those obese subjects with gluteal-femoral adiposity.

Cut points for anthropometric parameters associated with increased risk of morbidities have been suggested (30,31). Despite the significant correlations between waist circumference and WHR with VFA observed in this study, a number of limitations of these measurements can be identified. The technical procedure includes quantification of also the subcutaneous adipose tissue located in the abdominal wall. Additionally, such measurements are related to high interethnic variation and considerable inter- and intra-examiner variation, which limits the applicability of the measurements in clinical evaluation of visceral fat depots (32). On the other hand, scant studies are available that suggest cut points for CT-determined visceral fat, which is associated with cardiovascular risk factors (13,14). This study proposes that a combination of an anatomical measurement, such as waist circumference (high sensitivity) and/or VFA (high specificity), with a metabolic parameter, such as the 2-h insulin determination, which improves the diagnostic concordance, could be useful to identify subjects at high risk for developing MS. High cutoff points found in this study may be explained by the inclusion of obese subjects only.

In conclusion, isolated BMI measurement is not a precise marker of risk in obese subjects, in contrast with abdominal fat, which shows significant correlations with typical abnormalities of the MS. When associated with the 2-h insulin level, abdominal fat may be useful to more precisely identify patients at high cardiovascular risk. Longitudinal studies are needed to define VFA and waist circumference cutoffs predictive of mortality. Considering the high costs of CT scan, alternative methods with high specificity to assess visceral fat are desirable.

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