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CLINICAL RESEARCH

Metabolic Syndrome and Insulin Resistance in Subjects with Morbid Obesity

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Abstract
Background There is evidence that a group of subjects with obesity fits the characteristics of metabolically healthy but obese population. We aimed to assess the prevalence of the metabolic syndrome (MS) in nondiabetic subjects with morbid obesity (body mass index (BMI) ≥40 kg/m^2) and its correlation with insulin resistance.
Methods We analyzed the data of 211 patients (55 males and 156 females) with morbid obesity and without overt diabetes, consecutive referred for weight loss management. All subjects underwent an oral glucose tolerance test, and insulin resistance was calculated by the homeostasis model assessment (HOMA) at baseline and by the oral glucose insulin sensitivity (OGIS) during the glucose and insulin curve. Clinical and biochemical features of MS were also determined.
Results The criteria for MS were fulfilled in 74% of cases, and 10 patients had obesity as the sole feature. HOMA-R was normal in 26% of cases, whereas, OGIS was normal only in three females. HOMA-R and OGIS significantly differed in relation to the presence of MS, and a trend was observed in both tests as function of the number of factors of MS (P <0.001). At logistic regression analysis, after adjustment for age, sex, BMI at age 20 years, present BMI, and waist circumference, OGIS was the only parameter of insulin resistance significantly associated with MS (odds ratio, 2.42; 95% confidence interval, 1.63–3.60).
Conclusions A small number of metabolically healthy, but obese cases exist also in the subgroup of patients with morbid obesity in which insulin resistance maintains its pivotal role.

Keywords Insulin resistance · Hypertension · Lipid profile · Liver enzymes · Metabolic syndrome

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Introduction

The prevalence of obesity is increasing worldwide in both developed and developing countries at alarming rates of a few percent per decades [1], and overall prevalence data are subject to continuous updating. In some European countries, the prevalence of obesity is now about 20–30% [2], and it has been estimated that by 2015, two in five adults and one in four children in the United States will be obese [3]. In Italy, the percentage of overweight–obesity people over 20 years is about 43%; 34% is overweight and 9% is obese.

The increasing prevalence translates into an increased risk of overall mortality as well as mortality for a long series of specific diseases (diabetes, cardiovascular disease, respiratory, kidney and liver disease, and several cancers) [4]. Although the parameters of visceral obesity (waist circumference and waist-to-hip ratio) may be more closely associated with specific obesity-related events [5], the body mass index (BMI) remains a reasonably valid measure of general adiposity and a useful method to classify disease severity [6].

Obesity is the pivotal feature of the metabolic syndrome (MS) [7], a clustering of metabolic and clinical conditions associated with cardiovascular disease (CVD) [8]. In the Framingham study, the metabolic syndrome alone predicts

nearly 25% of all new-onset CVD [8]. The prevalence of the metabolic syndrome increases with obesity grade [9]; the strong associations between abdominal obesity and risk factors led to define the metabolic syndrome essentially as a clustering of complications of obesity [8].

In its original proposal, the metabolic syndrome was associated to insulin resistance [10]. Insulin resistance, generally, rises with increasing body fat content: most people with categorical obesity (BMI>30 kg/m²) have postprandial hyperinsulinemia and relatively low insulin sensitivity [11], but large variations in insulin sensitivities are present even within the obese population [12]. Insulin resistance is part of the metabolic profile associated with CVD risk through a variety of mechanisms mediated by the mitogen-activated protein kinase pathway [13]. Recent studies indicate that individuals' cardiovascular risk may depend jointly on their body size and metabolic profile led to an increasing recognition that the disease risk associated with obesity may not be uniform [14, 15]. This resulted in the investigation of body size phenotypes [16]. One type is the "metabolically healthy but obese" (MHO) phenotype, which is sometimes referred to as "uncomplicated obesity" [17, 18]: this subset of individuals, with BMI >30 kg/m^2, appears to be relatively resistant to the development of the adiposity-associated cardiometabolic abnormalities that increase CVD risk [19]. A second phenotype includes individuals with normal weight (BMI <25 kg/m^2) who express cardiometabolic abnormalities often associated with being overweight and obese ("metabolically obese, normal-weight" (MONW) individuals) [18, 20–22]. Different phenotypes possibly stem from differences in insulin resistance, which have been recently outlined [21].

The impact of insulin resistance and its surrogate estimates on the metabolic syndrome has been studied in the general population and in obesity [23], but only a few data are available on the role of different obesity grades. This is mainly the case of subjects with class III obesity (BMI>40 kg/m^2), in which excess visceral adiposity may be masked by the very large amount of peripheral fat tissue. The aim of this study was to assess the prevalence of factors of the metabolic syndrome in patients with the more severe grade of obesity, independently of diabetes and its correlation with insulin resistance.

Patients and Methods

Patients

We extracted from our database the data of obese patients who were referred to our center for weight loss management between January 2000 and July 2008. Per protocol, all subjects without overt diabetes are submitted to an oral glucose tolerance test (OGTT) as an initial screening. After excluding cases with incomplete data (less than 5%) and subjects with less severe obesity (grade I and II, BMI between 30 and 39.9 kg/m^2), 211 cases were available for analysis. Fifty-five were males, 156 were females, in the age range of 19 to 76 years. Their pertinent laboratory data are presented in Table 1.

All subjects had an anthropometric assessment (including the measurement of waist circumference), a measurement of blood pressure, and an evaluation of routine biochemical tests. Any pharmacologic treatment was also registered so as to individuate subjects with previous diagnosis and treatment for hypertension and diabetes. The protocol of present analysis was submitted to and approved by the Institutional Review Board of the Department, an organ responsible for noninterventional studies.

Methods

Body weight was measured in subjects in light clothing to the nearest 0.5 kg; height was measured by a stadiometer in subjects without shoes. The data were used to calculate BMI as weight (kg) divided by squared height (in meters). Waist circumference was measured (to the nearest centimeter) midway, between the lower rib and the iliac crest. Blood pressure was measured in the sitting position; as a routine, three values are obtained at a 1-min distance, and the average is recorded.

Biochemical tests included fasting glucose, triglycerides, HDL-cholesterol, as well as basal insulin, creatinine, total cholesterol, uric acid, and aminotranferase activity (alanine and aspartate aminotransferase—ALT and AST). The upper limit of normal for alanine aminotransferase in our institution is set at 37 U/l.

Subjects without overt diabetes were submitted to an oral glucose tolerance test (OGTT; 75 g of glucose in 200 ml of water). Samples were obtained at 0, 30, 60, 90, and 120 min. Plasma glucose, both in the fasting state and in response to a standard glucose load, was measured in duplicate with an automated analyzer. The coefficient of variation for any single determination was ±1.5%. Insulin was determined by an immunoenzymometric assay (AIA-PACK IRI, AIA-1200 system, Tosoh Co., Tokyo, Japan) with intra- and interassay coefficients of variation for the quality control <7%. Cholesterol, HDL-cholesterol, and triglycerides were measured by enzymatic and colorimetric methods using CHOL, HDL-C plus (2nd generation), and TG assays (Roche Diagnostics Co, Indianapolis, Indiana, USA).

All patients had a waist circumference exceeding 102 cm in men and 88 cm in women; accordingly, the diagnosis of the metabolic syndrome was based on the presence at least of two

Table 1 Clinical and biochemical characteristics of our population with class III obesity, in relation to gender (mean±SD

	All cases (n=211)	Males (n=55)	Females (n=156)	P value
Age (years)	47.1±12.6	42.6±11.0	48.6±12.8	0.335
Weight (kg)	120.9±18.2	135.2±4.14	115.9±16.1	<0.001
Body mass index (kg/m^2)	44.8±4.14	44.4±4.40	44.9±4.04	0.789
Body mass index (BMI; kg/m^2) at age 20 years	28.4±5.3	28.7±5.5	28.1±5.2	0.226
BMI class at age 20 years (Normal/overweight/obes I/obes II/obes III; %)	28/39/21/9/3	23/30/32/11/4	30/41/18/8/3	0.252
Basal glucose (mg/dl)	100.5±14.2	100.7±14.5	100.4±14.1	0.886
120-min OGTT glucose (mg/dl)	132.0±50.5	126.8±44.8	133.8±52.4	0.378
Glucose regulation				0.753
Normal glucose tolerance (number (%))[a]	141 (67%)	39 (71%)	102 (65%)	
Impaired glucose tolerance (number (%))[a]	48 (23%)	11 (20%)	37 (24%)	
Diabetes (number (%))[a]	22 (10%)	5 (9%)	17 (11%)	
Basal insulin (μU/ml)	22.8±12.6	25.7±15.9	21.7±11.0	0.047
OGIS (ml×min^{-1}×m^{-2})	6.82±1.30	6.52±1.25	6.93±1.30	<0.001
HOMA (%)	5.74±3.44	6.55±4.54	5.45±2.92	0.042
Total cholesterol (mg/dl)	208.2±38.7	202.7±42.2	210.1±37.4	0.239
HDL-cholesterol (mg/dl)	50.3±12.1	41.7±7.34	53.3±12.0	<0.001
Triglycerides (mg/dl)	160.4±85.1	193.9±118.8	148.6±66.2	<0.001
Creatinine (mg/dl)	0.92±0.22	1.06±0.33	0.87±0.15	<0.001
Uric acid (mg/dl)	5.88±1.51	6.90±1.36	5.54±1.40	<0.001
Aspartate aminotransferase (UI/l)	25.4±11.9	29.5±11.8	24.0±11.7	0.009
Alanine aminotranferase (UI/l)	36.0±25.3	48.4±29.5	31.8±22.2	<0.001
Alanine aminotraferase ≥38 U/l (%)	34 (27–41)	21 (11–34)	39 (30–48)	<0.001
Systolic blood pressure (mm Hg)	137.2±13.9	138.0±13.3	136.8±14.2	0.601
Diastolic blood pressure (mm Hg)	87.4±10.3	88.5±10.3	87.0±10.3	0.370
Waist circumference (cm)	124.6±14.0	134.4±14.8	120.9±11.8	0.026
Features of metabolic syndrome				
Blood glucose ≥100 mg/dl (% (CI))[b]	48 (41–55)	46 (32–57)	47 (39–55)	0.876
Triglycerides ≥150 mg/dl (% (CI))[b]	56 (49–62)	55 (41–66)	42 (35–50)	0.149
HDL-cholesterol <40 mg/dl (M), <50 (F) (% (CI))[b]	41 (35–48)	36 (24–48)	43 (35–51)	0.621
Arterial pressure ≥130/85 mm Hg (% (CI))[b]	83 (77–87)	83 (75–88)	83 (70–90)	>0.999
Number of features (1/2/3/4/5; %)	4/22/37/27/10	2/18/49/27/4	5/23/32/28/12	0.186
Prevalence of metabolic syndrome (% (CI))[b]	74 (67–79)	80 (65–88)	72 (63–78)	0.346

CI 95% confidence interval, *HOMA* homeostasis model assessment, *OGIS* oral glucose insulin sensitivity, *OGTT* oral glucose tolerance test, *M* males, *F* females

[a] Number of cases (%)

[b] Percent of cases (95% confidence interval)

parameters of National Cholesterol Education Program—Adult Treatment Panel III (ATPIIIR) [24] or International Diabetes Federation classification [25] of the Metabolic Syndrome, which are coincident in this population.

Measurement of Insulin Sensitivity/Resistance

The homeostasis model assessment (HOMA) was used to estimate insulin resistance in the basal state as: HOMA – R : (basal glucose (mmol/l) × basal insulin (μU/ml))/22.5 [26]. In our laboratory, the cutoff of the upper quartile of HOMA, selected as indicative of insulin resistance, is set for the general population in our laboratory at 2.7 [27].

Insulin sensitivity in response to the oral glucose tolerance test was calculated by the oral glucose insulin sensitivity (OGIS), using a web-derived formula as described by Mari et al. [28]. The cutoff point to indicate insulin resistance (<9.8) has been previously identified [27]. HOMA and OGIS have been suggested to identify hepatic and peripheral insulin sensitivity/resistance [29], respectively.

Finally, the insulin sensitivity on lipid metabolism was assessed in the fasting state as the ratio of triglyceride to

HDL-cholesterol levels, as suggested by McLaughlin et al. [30]. The ratio has been extensively validated [30] and values above 3.0 mg/dl identify insulin resistance in people of Caucasian origin [31].

Statistical Analysis

Data were analyzed with StatView 5.0™ (SAS Institute Inc., Cary, North Carolina, USA). A descriptive analysis of clinical parameters was carried out by means±standard deviation or number of cases with categorical data (percent and 95% confidence interval). Comparison between groups and correlation analysis were carried out by means of parametric and nonparametric tests, as appropriate (Student's *t* test, Mann–Whitney and Kruskall–Wallis test, and Spearman's test).

Finally, logistic regression analysis was carried out to determine the parameter(s) of insulin resistance independently associated with the metabolic syndrome in our populations. The dependent variable was the ATPIII-identified metabolic syndrome; all estimated values of insulin resistance in the fasting state and in response to oral glucose were tested as independent variables, after correction for age, sex, weight history, BMI, and waist circumference. The significance limit was set at P values <0.05.

Results

Our middle-aged population was characterized by similar BMI between males and females. In both groups, the excess fat mass was the result of either progressive weight gain from early adulthood or childhood overweight/obesity. Laboratory data indicated higher fasting insulin and higher HOMA values in males, whereas, OGIS was markedly lower. Among the parameters of the metabolic syndrome, male gender was characterized by higher triglycerides and lower HDL-cholesterol. Also, the levels of aminotransferases were remarkably higher in comparison to females, but a higher proportion of females had enzyme levels exceeding the upper limit of normality.

Over 80% of the cohort had blood pressure levels above the cutoffs of ATPIII proposal. The prevalence of the other features of the metabolic syndrome was on average around 40–50%, and three quarter of cases were identified as metabolic syndrome by three or more ATPIII criteria, with a slight prevalence in males.

The majority of subjects were characterized by insulin resistance. HOMA-IR values within the normal range were present only in 20 females (12.8%) and eight males (14.6%), whereas, OGIS values above the selected cutoff were present in only three females (1.9%) and no males.

When data were grouped as function of the presence/absence of the metabolic syndrome, one quarter of cases did not have the metabolic syndrome (Table 2) and nearly 5% of cases were left without any additional feature of the metabolic syndrome but obesity (see further discussion). Age did not differ in relation to either the presence of metabolic syndrome or to the number of positive features of ATPIII criteria (P=0.125, Kruskall–Wallis test). Differences in HOMA-IR and OGIS were highly significant between groups, and a progressive decrease of OGIS and increase in HOMA-IR values was present as function of the number of factors of the metabolic syndrome (P<0.001; Fig. 1). However, not all cases were identified as having insulin resistance by HOMA-IR also in cases with the metabolic syndrome. The sensitivity on lipid metabolism (TG/HDL-cholesterol) was consistent with the definition criteria of the metabolic syndrome. A higher proportion of cases with the metabolic syndrome also had elevated levels of alanine aminotransferase.

In logistic regression analysis, after adjustment for age, sex, BMI at age 20 years, present BMI, and waist circumference, OGIS was the only parameter of insulin resistance significantly associated with the presence of the metabolic syn-

Table 2 Parameters of insulin resistance and its clinical correlates in our obese population, according to the presence of the metabolic syndrome (mean±SD)

	Without MS (n=56)	With MS (n=155)	P value
Male gender (% (CI))[a]	20 (11–33)	28 (21–36)	0.345
Age (years)	48.1±12.7	45.6±12.1	0.237
Body mass index (BMI; kg/m^2)	44.7±3.9	44.8±4.1	0.899
Change in BMI from age 20 years (kg/m^2)	16.0±5.6	16.8±5.7	0.433
Basal insulin (μU/ml)	17.6±7.3	24.4±12.8	<0.001
Alanine aminotransferase>37 U/l (% (CI))[a]	21 (11–34)	39 (30–48)	0.039
HOMA (%)	3.98±1.71	6.33±3.60	<0.001
HOMA≥2.7 (% (CI))[a]	73 (51–87)	91 (84–94)	0.007
OGIS (ml×min^{-1}×m^{-2})	7.72±1.02	6.54±1.29	<0.001
OGIS <9.8 (% (CI))[a]	100 (91–100)	98 (93–99)	0.565
TG/HDL-cholesterol	2.02±0.78	4.11±2.67	<0.001
TG/HDL-cholesterol≥3(% (CI))[a]	8 (3–18)	59 (50–67)	<0.001

Comprising the ten cases classified as metabolically healthy but obese—MHO (see text)

[a] Percent of cases (95% confidence interval)

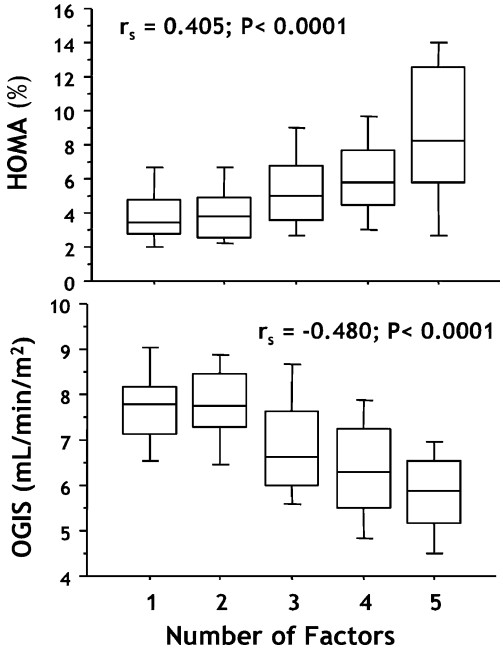

Fig. 1 Correlation between the number of parameters of the metabolic syndrome and insulin resistance measured by the homeostasis global assessment (HOMA) method (*upper panel*) and the oral glucose insulin sensitivity (OGIS) value (*lower panel*). Note that HOMA and OGIS values for each group are represented as *box plots* where the *bold horizontal line* corresponds to median values, the *boxes* stretch from 25° to 75° percentile and the *vertical lines* reach the 5° and the 95° percentile

drome, more than doubling the risk for any 1-point decrease (odds ratio (OR), 2.42; 95% confidence interval, 1.63–3.60). Interestingly, OGIS maintained its predictive value also after correction for the TG/HDL ratio (OR, 2.23; 95% CI, 1.39–3.57), even if the parameter of insulin resistance on lipid metabolism was highly associated with the metabolic syndrome (OR, 3.76; 95% CI, 2.15–6.58), being based on two of the parameters included in the ATPIII criteria.

Metabolically Healthy, but Obese Cohort

On the basis of ATPIII criteria, we identified a small subgroup of ten patients having obesity as the sole abnormality among the criteria of the metabolic syndrome. They were characterized by a BMI (45.1±4.7 kg/m^2) and a BMI at age 20 (30.5±5.8) not different from the total population, but were relatively younger (41.8±4.7 years; *P* versus subjects with metabolic syndrome, 0.175); including increase in BMI, since the age 20 years was not different (14.5±5.6 kg/m^2). They were, nonetheless, insulin resistant (HOMA, 3.85±1.72%; OGIS, 7.72±0.91 ml/min/m^2), but had normal triglycerides (98.7±.7 mg/dl) and HDL-cholesterol (57.5±8.6 mg/dl) and a normal TG/HDL-cholesterol ratio. Aminotransferase levels were within normal limits in all cases, as was arterial pressure (systolic, 117±6 mm Hg; diastolic, 75±6 mm Hg).

Discussion

Our study documents that the metabolic syndrome is highly prevalent in subjects with morbid obesity, also in the absence of overt diabetes, but approximately 20% of males and nearly 30% of females do not fulfill the accepted criteria. In addition, approximately 5% of total cases have obesity as the sole criterion. These individuals fit the current definition of MHO because despite having a BMI exceeding 30 kg/m^2, they exhibit a healthy metabolic and lipid profile. However, HOMA-IR and OGIS were indicative of insulin resistance in the majority of these cases, and both tests were associated with a higher risk of metabolic syndrome.

The two tests (HOMA and OGIS) explore different aspects of insulin sensitivity/resistance. HOMA is calculated as the product of the OGTT glucose and insulin concentration at time 0; this simple test is appropriate for epidemiological studies and demonstrates a good correlation with hyperinsulinemic euglycemic clamp [32]. In the fasting state, the contribution of hepatic gluconeogenesis to the maintenance of glucose levels and the suppression of hepatic glucose production by insulin are at their top levels, and as such, HOMA is considered a surrogate of hepatic insulin sensitivity. By contrast, OGIS is based on the dynamic of glucose and insulin in response to the glucose load, when the action of the periphery in insulin-stimulated glucose uptake is highest and is considered a surrogate of peripheral (muscle tissue) sensitivity to insulin [28]. Both insulin actions are altered in the presence of morbid obesity, although the hepatic defect seems more closely associated with the metabolic syndrome and abdominal obesity. Recent studies pointed out the importance of the liver in the pathogenesis of the metabolic syndrome and diabetes [33] via steatosis-associated hepatic insulin resistance extending to peripheral organs [34].

The definition of metabolic syndrome includes an enlarged waist circumference, not a high BMI, as diagnostic feature [8, 25]. In subjects with the most severe grades of obesity, waist circumference is not a reliable parameter of abdominal obesity, being above the accepted cutoff in all cases. In severe obesity, the evaluation of central fat size should be more properly based on imaging technique, not available in our study, and a correct classification of our cases as "metabolically healthy" but central versus peripheral obese individuals remains unsettled.

The history of obesity was of no help in defining the risk of metabolic syndrome. In agreement with a previous study on a larger population [35], the BMI class at age 20 years was extremely variable in this population, and severe obesity could be the result of either progressive weight gain from a condition of normal BMI/overweight in early adulthood or derived from childhood obesity. These conditions did not produce any different effect on metabolic parameters.

In general, the definition of MHO remains uncertain. Karelis and Coll extensively studied the MHO phenotype in women [36], but they considered only the lipid profile (total cholesterol, HDL cholesterol, triglycerides, and LDL cholesterol) and HOMA-R to define subjects as MHO [18]. In particular, they identified MHO on the basis of normal insulin sensitivity, and when MHO obese women were compared with those with altered metabolic profile, this metabolically normal profile was associated with a lower accumulation of visceral adipose tissue and an earlier age-related onset of obesity [37]. Morbid obesity is also characterized by a high rate of impaired glucose regulation, associated with hypoadiponectinemia [38], which makes OGTT mandatory to fully define the metabolic profile [39]. Also, in our experience, the assessment of glucose regulation may be a critical issue in the presence of morbid obesity, and either impaired glucose tolerance or type 2 diabetes were present in one third of cases, with fasting glucose below the diagnostic threshold for diabetes. This is also supported by the larger prevalence of insulin resistance measured in response to OGTT by the OGIS calculator than by the HOMA algorithm in the fasting state, as abovementioned.

In a study where subjects were defined MHO on the basis of normal insulin sensitivity during the euglycemic hyperinsulinemic clamp, the maintenance of a normal lipid profile was related to higher-than-normal insulin secretion and higher disposition index, an adaptive mechanism to compensate for increased body surface demands [21].

Karelis et al. showed that MHO postmenopausal females are also characterized by a more favorable inflammatory profile [40], namely lower CRP levels, which may be the reason for a lower-than-expected cardiovascular risk. Whether this also applies to morbid obesity and specifically to males, remains to be determined.

Finally, subjects with metabolic syndrome were characterized by a higher prevalence of liver enzyme abnormalities in keeping with the accepted evidence linking high liver enzyme, insulin resistance, and the metabolic syndrome [41]. Although drinking habits were not specifically recorded in our patients, elevated liver enzymes in the general population are largely due to nonalcoholic fatty liver disease [42], which is considered the hepatic expression of the metabolic syndrome [43]. Several studies have shown that subjects with morbid obesity are at great risk of liver abnormalities [44–47], which should be considered before patients may be labeled as "metabolically healthy, but obese." In the present series, liver enzymes were normal in all cases having obesity as the sole feature of the metabolic syndrome, confirming the importance of the liver in metabolic imbalance.

In summary, our study underlines the existence of a small fraction of the population with class III obesity without metabolic alterations. These cases were, however, relatively younger than total population, and follow-up studies are needed to define whether MHO is related to a shorter exposure to obesity or is a peculiar (genetic?) characteristics of individual patients. The possible late development of metabolic abnormalities, as well as, the assessment of long-term risk of cardiovascular events are of major importance in planning therapeutic interventions.

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