

Very severely obese patients have a high prevalence of type 2 diabetes mellitus and cardiovascular disease

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Abstract The prevalence of very severe obesity has increased progressively and faster than other classes of obesity over the last years. It is unclear whether the prevalence of obesity-related complications and health risks increases progressively or reaches a plateau above a certain degree of obesity. The aim of our study was to investigate whether the severity of obesity was correlated with the prevalence of type 2 diabetes mellitus (T2DM), impaired fasting glucose, impaired glucose tolerance (IGT), metabolic syndrome (MS), and cardiovascular diseases (CVDs) in a large cohort of patients with different degrees of obesity. A cross-sectional study was conducted in 938 obese patients without a previous diagnosis of diabetes. Patients were assigned to different categories of obesity: mild-moderate obesity (BMI 30–39.9 kg/m²), morbid obesity (BMI 40–49.9 kg/m²), and super-obesity (SO, BMI ≥50 kg/m²). The prevalence of IGF, IGT, screen-detected T2DM, MS, and CVD was higher in SO patients than in the other groups. Interestingly, the association between SO and either MS or CVD was independent of glucose tolerance status, indicating that factors other than glucose metabolism also favor cardio-metabolic complications in obese patients. In patients

without screen-detected T2DM ($n = 807$), insulin sensitivity and secretion OGTT-derived indexes indicated that SO patients had the worst glucose homeostasis relative to the other categories of obesity, which was indicated by the most reduced disposition index in these patients, a predictor of future T2DM. In conclusion, SO patients have an extremely high prevalence of glucose metabolism deterioration, and cardio-metabolic complications are more prevalent in these patients compared to less obese patients.

Keywords Obesity · Super-obesity · Severe obesity · Type 2 diabetes · Metabolic syndrome · Cardiovascular diseases · Cardio-metabolic diseases

Introduction

Obesity is dramatically increasing throughout the world. A recent study showed that more than one-third of US adults are obese [1]. Similarly, almost half of Italian men and approximately one-third of Italian women are overweight or obese. From 2001 to 2008, the age-standardized prevalence of overweight and obesity increased in Italy by 1.4 and 1.9 % in men and 0.4 and 0.5 % in women, respectively [2]. Obesity increases mortality from all causes and cardiovascular risk. In particular, obesity is associated with insulin resistance and other metabolic complications such as type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension. Obesity is also a major component of metabolic syndrome, a cluster of metabolic and clinical conditions associated with elevated cardiovascular disease risk [3, 4]. The T2DM prevalence increases with age [5] and BMI, reaching 18.3 % in obese individuals (over 35 kg/m²) [6]. Data on the prevalence of these metabolic diseases in very morbidly obese patients are scarce.

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Very morbid obesity (BMI >50 kg/m²), also defined as super-obesity, has increased significantly and faster than any other class of obesity [7]. Its prevalence increased by 52 % in the USA between 2000 and 2005 [8]. It is unclear whether the prevalence of obesity-related metabolic complications and health risks increases progressively with BMI or reaches a plateau above a certain degree of obesity [9, 10]. While some data indicate that the risk of developing complications is proportional to the degree of obesity [11], the presence of metabolic abnormalities varies widely among obese individuals of the same category.

The aim of our study was to define the prevalence of cardio-metabolic risk factors (such as impaired fasting glucose, impaired glucose tolerance, T2DM, and metabolic syndrome) and cardiovascular events in a continuous series of obese patients with different degrees of obesity.

Patients and methods

A total of 1,258 obese (BMI ≥ 30 kg/m²) patients (387 males, 871 females; mean age = 40.2 ± 13.4 years, range 18–75 years; mean BMI 44.7 ± 9.4 kg/m², range 30.0–84.2 kg/m²) referred to our Obesity Center (University of Catania Medical School, Garibaldi Hospital Medical Center, Catania, Italy) for weight loss management were consecutively recruited from January 2009 to December 2010. The exclusion criteria were pregnancy ($n = 24$) and the presence of acute and/or severe organ disease ($n = 73$). To evaluate the effect of obesity on cardio-metabolic complications, patients with known T2DM were excluded (223 out of a total of 1,258 patients screened, 17.7 %) from the study to avoid the confounding effect of hyperglycemia on the parameters examined. In total, 938 obese patients were included in the study (270 males, 668 females).

All patients gave informed consent, and investigations were performed in accordance with the principles of the Declaration of Helsinki. The Ethical Committee of the hospital approved the study.

All participants underwent a physical examination and were maintained on a weight-maintaining diet for 4 days before performing the metabolic study. The age of obesity onset was recorded from self-reports. Height was measured to the nearest 0.1 cm, and body weight was measured with a 0.1 kg precision with the subjects wearing light indoor clothing without shoes. Blood pressure was measured twice with the subject in a sitting position after a minimum of 5 min of acclimatization and before blood sampling. The mean of the two blood pressure measurements was used in the analysis.

Blood specimens were obtained after an overnight fast as previously described, and glucose, insulin, triglycerides,

and total and HDL cholesterol levels were measured using commercially available kits [12].

Classification of obesity

BMI was calculated as weight (kg) divided by height \times height (m²). Obesity was defined as BMI ≥ 30 kg/m². The patients were assigned to three categories according to BMI: mild-moderate obesity (MMO, $n = 306$, BMI 30–39.9 kg/m²), morbid obesity (MO, $n = 374$, BMI 40–49.9 kg/m²), and super-obesity (SO, $n = 258$, BMI ≥ 50 kg/m²).

Glucose tolerance status and metabolic syndrome

All patients with fasting plasma glucose (FPG) <7 mmol/l (889 out of 938) underwent an oral glucose tolerance test (OGTT), measuring glucose and insulin values before and 30, 60, 90, and 120 min after glucose load (75 g). T2DM, impaired fasting glucose (IFG), and impaired glucose tolerance (IGT) were defined according to the ADA criteria [13]. Individuals who had not been diagnosed as diabetic but who had a fasting plasma glucose level ≥ 7 mmol/l and/or 2 h plasma glucose ≥ 11.1 mmol/l were classified as having screen-detected T2DM ($n = 131$).

Metabolic syndrome was defined according to the ATP-III classification [3], which requires three or more of the following five components: large waist circumference (>102 cm in men and >88 cm in women), hypertriglyceridemia (≥ 1.7 mmol/l) or antihyperlipidemia treatment, low HDL cholesterol level (<1.0 mmol/l in men or <1.3 mmol/l in women), elevated blood pressure (systolic ≥ 130 mmHg and/or diastolic ≥ 85 mmHg and/or antihypertensive treatment or a history of hypertension), and elevated fasting plasma glucose (≥ 5.5 mmol/l).

Insulin sensitivity and secretion

Insulin sensitivity and secretion were evaluated by OGTT-derived indexes in patients who had not been classified as having screen-detected T2DM ($n = 807$). Insulin sensitivity was calculated according to Matsuda's index (insulin sensitivity index, ISI), as previously described [14]. Insulin secretion was calculated according to the insulinogenic index (IGI) [15]. The disposition index (DI) was calculated as $IGI \times ISI$ [15, 16]. Of note, potential violations of the hyperbolic shape ($IGI \times ISI = k$, where k is a constant value) were excluded using a goodness-of-fit test for the following nonlinear model $IGI = k/ISI$ ($R^2 = 0.41$, $p < 0.0001$).

Cardiovascular disease

The recorded cardiovascular comorbidities included a documented history of myocardial infarction (MI) or

stroke, heart failure (HF), atrial fibrillation (AF), or deep vein thrombosis (DVT) [17].

Statistical analysis

Values are provided as the mean \pm SD (text and table) or as the mean \pm SEM (figures). No normally distributed variables (plasma insulin, triglycerides, IGI, and DI) were log transformed for analysis.

Continuous variables were compared between groups using an unpaired t test or an analysis of variance (ANOVA). After adjusting for several covariates, differences between groups were evaluated by a covariance analysis (ANCOVA) followed by a post hoc analysis with Fisher's protected least-significant difference test (PLSD). Simple and multiple regression models were used to test for correlations between continuous variables.

Categorical variables were compared by the chi-square test. Multivariate logistic regression models were applied to assess the risk of cardio-metabolic diseases in the different categories of obesity. The dependent variable in this model was the binary status of cardio-metabolic disease (T2DM, prediabetes, metabolic syndrome, and cardiovascular disease). The degree of obesity was the main predictor included as a continuous variable (MMO category = 0, MO = 1, SO = 2). Analyses were adjusted for age and gender, and the results are presented as adjusted odds ratios (ORs) with 95 % confidence intervals (CIs).

The significance limit was set at p values <0.05 . Data analyses were performed using the StatView 5.01 (SAS

Institute, Cary, North Carolina, USA) and SPSS (version 15; SPSS Inc., Chicago, IL, USA) statistical packages.

Results

Obesity, age of onset, and gender

The anthropometric and clinical characteristics of the 938 patients included in the study are shown in Table 1 stratified in three categories according to BMI.

The male/female ratio decreased progressively with the increasing severity of obesity from MMO (76/230 subjects, 33 %) to MO (103/271, 38 %) and SO (91/167, 54 %) patients (p for trend ≤ 0.01 after adjusting for age). Super-obese patients were slightly but significantly older (39.5 ± 12.3 years) than MMO (35.6 ± 11.8 years) and MO patients (37.0 ± 12.0 years) ($p \leq 0.01$ for both after adjusting for gender). Interestingly, patients with more severe obesity (MO and SO) reported an earlier onset of obesity than MMO patients (mean age at onset 14.1 ± 10.5 and 14.4 ± 10.3 vs. 21.7 ± 12.0 years, respectively; $p < 0.0001$ after adjusting for age and gender). Additionally, a longer disease duration was observed from MMO (13.9 ± 8.9 years) to MO (23.0 ± 11.5 years) and SO (25.1 ± 11.1 years) patients ($p < 0.0001$ after adjusting for age and gender). In the post hoc analysis, the obesity duration was significantly higher in SO individuals compared with MO ($p < 0.005$) and MMO ($p < 0.0001$) individuals; the difference between the MO and MMO categories was also highly significant ($p < 0.0001$).

Table 1 Characteristics of patients according to the degree of obesity

	Total	MMO	MO	SO
Number (n)	938	306	374	238
Gender (M/F)	270/668	76/230	103/271	91/167*
Age (years)	37.3 ± 12.1	35.6 ± 11.8	37.0 ± 12.0	$39.5 \pm 12.3^\circ$
BMI (kg/m^2)	45.3 ± 9.6	35.6 ± 2.8	44.7 ± 2.8	57.7 ± 7.0
Age of obesity onset (years)	16.7 ± 11.5	21.7 ± 12.0	$14.1 \pm 10.5^\#$	$14.4 \pm 10.3^\#$
Obesity duration (years)	20.6 ± 11.6	13.9 ± 8.9	$23.0 \pm 11.5^\#$	$25.1 \pm 11.1^\#\wedge$
Fasting glucose (mmol/l)	5.5 ± 1.0	5.3 ± 0.8	$5.5 \pm 0.9^+$	$5.8 \pm 1.2^\#\S$
Fasting insulin (mU/l)	18.7 ± 9.7	16.3 ± 8.4	$18.5 \pm 9.4^+$	$21.9 \pm 10.8^\#\S$
Total cholesterol (mmol/l)	5.05 ± 1.0	5.01 ± 1.1	5.04 ± 1.0	5.09 ± 1.0
HDL (mmol/l)	1.12 ± 0.3	1.12 ± 0.3	1.14 ± 0.3	1.10 ± 0.3
Triglycerides (mmol/l)	1.42 ± 0.8	1.31 ± 0.7	$1.44 \pm 0.8^\dagger$	$1.53 \pm 0.8^\#\P$
SBP (mmHg)	124.5 ± 13.0	121.3 ± 12.9	$124.8 \pm 12.6^+$	$127.8 \pm 12.9^\#\wedge$
DBP (mmHg)	79.8 ± 9.0	78.5 ± 9.5	79.6 ± 8.9	$81.8 \pm 8.2^\#\wedge$

Data are expressed as the mean \pm SD

* p for trend ≤ 0.01 after adjusting for age; $^\circ p \leq 0.01$ versus MO and MMO in the post hoc analysis after adjusting for gender; $^\# p < 0.0001$ versus MMO; $^\wedge p < 0.005$ versus MO; $^\S p < 0.0001$ versus MO; $^+ p < 0.0005$ versus MMO; $^\dagger p < 0.005$ versus MMO; and $^\P p < 0.05$ versus MO in the post hoc analysis after adjusting for age and gender

Moreover, a significant linear correlation ($r = -0.23$, $p < 0.0001$) was found between the individual BMIs and the age of obesity onset. Together, these data suggest that the most severe degrees of obesity are associated with an increasing percentage of male patients with an earlier onset of obesity.

Prevalence of glucose metabolism abnormalities and metabolic syndrome

The fasting blood glucose, serum insulin and triglycerides, and systolic and diastolic blood pressure progressively increased from MMO to MO and SO patients (differences between groups in the post hoc analysis after adjusting for age and gender are shown in Table 1).

The prevalence of screen-detected T2DM was 14 % in the entire cohort and progressed significantly from MMO (6.5 %, 20/230 subjects) to MO (15.5 %, 58/271) and SO (20.5 %, 53/167) patients (p for trend <0.0001) (Table 2). In the multivariate logistic regression analysis, the risk of having screen-detected T2DM significantly increased from MMO to MO and SO patients (OR 1.67; CI 1.30–2.16; $p < 0.0001$ after adjusting for age and gender). Similarly, the prevalence of prediabetes (IFG and/or IGT) was 41.4 % in the entire cohort and progressed significantly from MMO (34.3 %) to MO (41.2 %) and SO (50.0 %) patients (p for trend <0.0001) (Table 2). The multivariate logistic regression analysis confirmed that the risk of having prediabetes was significantly increased in MO and SO patients compared to MMO patients (OR 1.34; 95 % CI 1.13–1.60; $p \leq 0.001$ after adjusting for age and gender).

The prevalence of metabolic syndrome was 58.2 % in the entire cohort and progressed significantly from MMO (47.1 %) to MO (56.7 %) and SO (73.6 %) patients (p for trend <0.0001). The risk of this syndrome increased significantly and progressively from MMO to MO and SO patients (OR 1.60; 95 % CI 1.33–1.93; $p < 0.0001$ after adjusting for age and gender). Interestingly, the association between the prevalence of metabolic syndrome and the degree of obesity remained significant after adjusting for glucose tolerance status (OR 1.28; 95 % CI 1.05–1.57; $p \leq 0.01$ after adjusting for age, gender and glucose tolerance status).

Table 2 Prevalence of comorbidities

	Total	MMO	MO	SO
IFG and/or IGT (%)	41.4	34.3	41.2	50.0*
T2DM (%)	14.0	6.5	15.5	20.5*
MS (%)	58.2	47.1	56.7	73.6*
CVD (%)	2.4	0.3	1.9	5.8*

T2DM screen-detected type 2 diabetes mellitus, MS metabolic syndrome, CVD history of cardiovascular diseases

* p for trend <0.0001 adjusted for age and gender

Insulin sensitivity and secretion in non-diabetic obese patients

Insulin sensitivity, evaluated by the ISI value, significantly decreased in the different obesity categories (higher in MMO, lower in SO, $p < 0.0001$ after adjusting for age and gender) (Fig. 1a). In the post hoc analysis, the ISI value was significantly ($p < 0.0001$) reduced in SO individuals (2.50 ± 1.18) compared with MO (3.16 ± 1.69) and MMO (3.67 ± 2.18) individuals; moreover, ISI was significantly lower in MO individuals compared to MMO individuals ($p < 0.0005$) (Fig. 1a). Additionally, insulin secretion, as indicated by the insulinogenic index (IGI) values, progressively decreased from MMO to MO and SO patients ($p < 0.05$ after adjusting for age and gender) (Fig. 1b). In the post hoc analysis, the IGI value was significantly ($p \leq 0.001$) reduced in both SO (27.4 ± 18.3) and MO (27.9 ± 20.0) individuals compared to MMO (30.7 ± 18.8) individuals. Finally, the disposition index (DI; i.e., the product of the IGI and the ISI values) significantly differed across the three groups ($p < 0.0001$ after adjusting for age and gender) (Fig. 1c). In the post hoc analysis, the DI was reduced in SO (61.7 ± 47.5) individuals when compared with MO (84.9 ± 76.8 ; $p < 0.005$) and MMO (110.1 ± 108.3 ; $p < 0.0001$) individuals. The difference between the MO and MMO categories was also highly significant ($p \leq 0.005$, Fig. 1c).

Prevalence of cardiovascular disease

The prevalence of cardiovascular disease also increased with increasing obesity (Table 2) with 0.3 % in MMO patients, 1.9 % in MO patients, and 5.8 % in SO patients (p for trend <0.0001), and the risk progressively increased in the different obesity categories (OR 3.4; 95 % CI 1.65–7.08; $p < 0.001$ after adjusting for age and gender). Interestingly, this association remained significant after adjusting for glucose tolerance status (OR 3.4; 95 % CI 1.61–7.05; $p \leq 0.001$ after adjusting for age, gender, and glucose tolerance status).

Discussion

Our data indicate that SO patients have a younger age at obesity onset and higher prevalence of metabolic alterations and cardiovascular disease compared to MMO patients.

The inverse correlation between BMI and age at obesity onset supports the previously reported role of childhood overweight and obesity as a risk factor for the development of severe obesity later in life [18, 19]. Both a longer exposure of these patients to the causative factors of

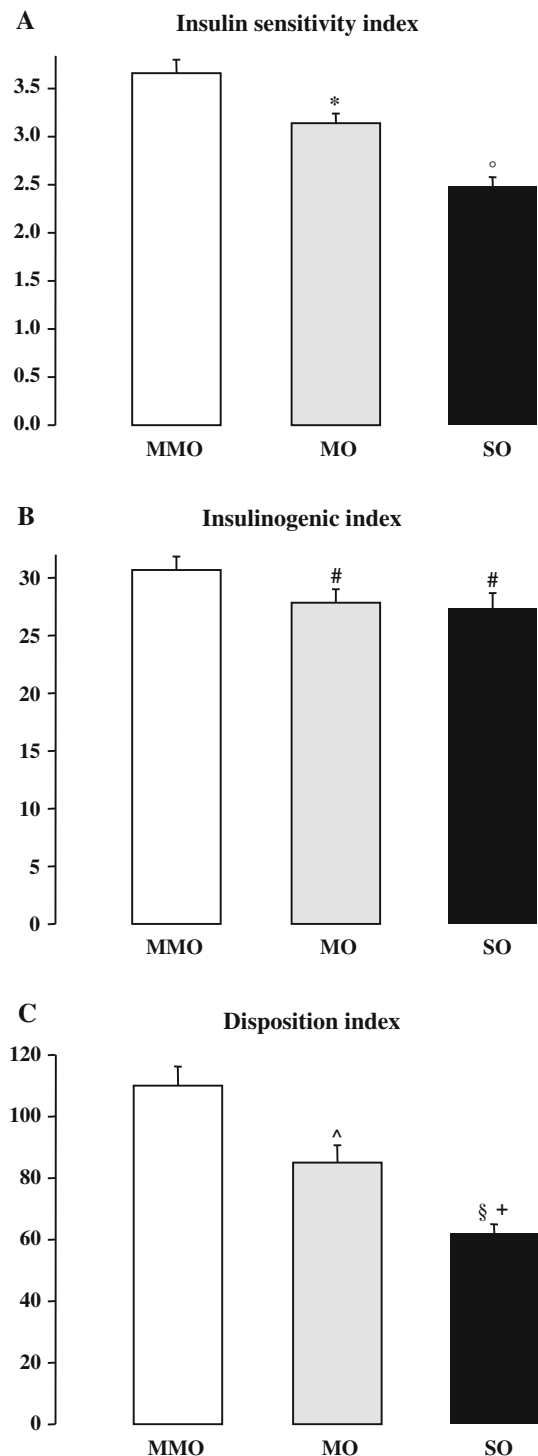


Fig. 1 OGTT-derived indexes in the different obesity categories. Insulin sensitivity index (a), insulinogenic index (b), and disposition index (c) values in MMO (mild-moderate obesity, white bars), MO (morbid obesity, gray bars), and SO (super-obesity, black bars) patients. All data were adjusted for age and gender. **a** * $p < 0.0005$ versus MMO; ° $p < 0.0001$ versus MO and MMO; **b** # $p \leq 0.001$ versus MMO; **c** ^ $p \leq 0.005$ versus MMO; § $p < 0.005$ versus MO; + $p < 0.0001$ versus MMO

obesity and a genetic background favoring fat accumulation can explain this association. Patients with very morbid obesity ($\text{BMI} \geq 50 \text{ kg/m}^2$) have a more abnormal metabolic profile than less obese patients. The risk of having metabolic abnormalities such as undiagnosed diabetes, prediabetes, and metabolic syndrome increased significantly and progressively from mild to severe obesity.

In super-obese patients, the prevalence of undiagnosed diabetes is higher than expected in the adult Italian population [20, 21], and our data demonstrated that it was also 1.3-fold higher in SO patients than in MO patients and 3.1-fold higher when compared to MMO patients. Similar results were observed for the presence of prediabetes (IFG or IGT), with a significant increase from the lowest to the highest degree of obesity. Considering diabetes and prediabetes together, these abnormalities were present in 55 % of obese individuals and reached 70 % in SO patients. Moreover, such a high prevalence of glucose homeostasis abnormalities in the most severe categories of obesity suggests that appropriate screening tools should be used in all these patients, including foremost the OGTT, which can identify both diabetes and IGT.

Additionally, the prevalence of metabolic syndrome increased progressively with the degree of obesity. The observation that the frequency of cardiovascular events increased with increasing obesity independently of the level of glucose metabolism derangement in a multivariate logistic regression analysis suggests that other factors, such as the level of dyslipidemia, increased blood pressure, and increased cardiac effort due to body mass, are major contributors to cardiovascular damage in severely obese patients.

Super-obesity is clearly associated with an increased risk of death due to many chronic diseases. At a BMI of 40–45 kg/m^2 , median survival is reduced by 8–10 years; for a BMI between 25 and 50 kg/m^2 , each 5 kg/m^2 BMI increase is associated with approximately 40 % higher mortality due to ischemic heart disease, stroke, and other vascular causes [22].

Non-diabetic SO patients also had a more abnormal glucose homeostasis during OGTT due to an inefficient interplay between insulin secretion and insulin sensitivity (i.e., a reduced disposition index), the best predictor of future T2DM. In hyperglycemic individuals, the disposition index may be reduced because of decreased insulin secretion, increased insulin resistance, or both. Our data indicate that higher degrees of obesity are associated with both impaired insulin secretion and increased insulin resistance in non-diabetic patients. Therefore, these individuals have a very high risk of developing T2DM. The insulinogenic index, the ratio of the increment in insulin

concentration to the increment in glucose concentration during OGTT, however, is a surrogate measure of insulin secretion. The circulating levels of insulin, indeed, reflect both insulin secretion and clearance and C-peptide concentrations after the OGTT would be preferable to calculate the insulin secretion rate through C-peptide deconvolution. Nevertheless, the OGTT-derived indexes used in this study (insulinogenic index, insulin sensitivity index, and disposition index) have been validated for large-scale and epidemiologic studies [15, 16, 23, 24].

Several previous studies investigated the metabolic abnormalities associated with obesity, but few data are available in super-obese patients. Some of these studies reported that certain parameters of metabolic status worsen as the severity of SO increases, whereas others found that the metabolic situation remains the same or even improves with more severe stages of obesity [9–11, 25]. The reasons for the conflicting results in the various studies are unknown but may occur secondarily to the limited numbers of study subjects in some of these reports. A recent study showed that both pre- and postmenopausal severely obese women had a better lipid profile than moderately obese women [26]. Nevertheless, the use of medications for diabetes and hypertension was significantly higher in the severely obese women when compared to the moderately obese women.

Conclusions

In conclusion, our data demonstrated that the prevalence of metabolic abnormalities (diabetes, prediabetes, and metabolic syndrome) and cardiovascular disease substantially increased with increasing BMI, suggesting that super-obese patients have a higher cardiovascular risk than the moderately obese patients.

These findings have important public health implications for the prevention (which has to begin during childhood with specific educational intervention programs), management (which requires an adaptation of structures designed to accommodate this type of patient), and treatments (surgical and non-surgical) of morbid and very morbid obesity.

Conflict of interest None.

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