Introduction

Obesity is a common finding and a major pathogenetic factor in obstructive sleep apnea (OSA) [1]. OSA is characterized by recurrent episodes of absent or decreased airflow in the upper airway during sleep and most often arises in obese individuals who have a narrowing of the upper airway because of fatty deposits in the tongue and para-pharyngeal areas. Intermittent hypoxia, sleep fragmentation and increased cardiovascular risk are conditions associated with OSA [2,3]. Obesity is a risk factor for diabetes and cardiovascular events [4,5]. Adipocytes and inflammatory cells show a high degree of interaction in obesity and exert important endocrine functions, involving multiple cross talks with other tissues and different fat depots in the body [6,7]. Body mass index (BMI) is not an accurate indicator of body fat and thus is not a good predictor of comorbidities [8]. Most adult patients with OSA have central obesity and increased visceral fat [9], the latter being associated with neck adiposity, increased upper airway fat [10] and metabolic abnormalities [11]. Gender-related differences in the amount of visceral fat [12,13] could contribute to the higher prevalence of OSA in men. In recent years a number of studies have suggested a strong bidirectional association between OSA and metabolic syndrome (MetS), the commonly used term for the clustering of cardio metabolic risk factors including visceral obesity, hypertension, dyslipidaemia and type 2 diabetes mellitus [14]. The prevalence of MetS varies from 74 to 85% among patients with OSA [15]. Interestingly, it has been recently demonstrated that continuous positive airway pressure therapy lowers blood pressure and partially reverses metabolic abnormalities in MetS patients [16], further emphasizing the relationship between OSA and MetS.

Abstract

Background: Obstructive sleep apnea (OSA) and metabolic syndrome, both closely related to obesity, often coexist in affected individuals; however, body mass index is not an accurate indicator of body fat and thus is not a good predictor of OSA and other comorbidities. The aim of this study was to investigate whether the occurrence of OSA could be associated with an altered body fat distribution and a more evident cardio metabolic risk independently from obesity and metabolic syndrome.

Methods and Results: 171 consecutive patients (58 men and 113 women) were included in the study and underwent overnight polysomnography. Anthropometric data, blood pressure, lipid profile, glycaemic parameters were recorded. Body composition by DXA, two-dimensional echocardiography and carotid intima/media thickness measurement were performed. 67 patients (39.2%) had no OSA and 104 (60.8%) had OSA. The percentage of patients with metabolic syndrome was significantly higher among OSA patients (65.4%) that were older, heavier and showed a bigger and fatter heart compared to the control group. Upper body fat deposition index, the ratio between upper body fat (head, arms and trunk fat in kilograms) and lower body fat (legs fat in kilograms), was significantly increased in the OSA patients and significantly related to epicardial fat thickness. In patients with metabolic syndrome, multivariate regression analyses showed that upper body fat deposition index and epicardial fat showed the best association with OSA.

Conclusion: The occurrence of OSA in obese people is more closely related to cardiac adiposity and to abnormal fat distribution rather than to the absolute amount of adipose tissue. In patients with metabolic syndrome the severity of OSA is associated with increase in left ventricular mass and carotid intima/media thickness.
Methods

Objective
The aim of this study was to investigate whether the presence and severity of OSA associates with cardiovascular functional and structural changes and a more compromised metabolic phenotype than obesity and MetS per se by evaluating polysomnographic records, body fat distribution, echocardiographic findings and cardio metabolic risk factors in obese patients either healthy or affected by MetS.

Participants
171 consecutive obese patients of Caucasian origin (58 men and 113 women) were included in the study. All participants were asymptomatic outpatients admitted for routine check-up evaluations and underwent a detailed history, physical examination and overnight polysomnography at a hospital-based sleep laboratory [17]. Exclusion criteria were the presence of overt endocrinopathy, acute illnesses, heart diseases, and any respiratory disorder other than OSA, uncontrolled hypertension, craniofacial abnormalities, smoking status, current use of hypnotics or any treatment for breathing disorders.

Ethics
All subjects were enrolled after written consent and approval by the Ethic Committee of Sapienza, University of Rome, Italy.

Description of procedures

Metabolic characterization. Metabolic characterization included: anthropometric measurements [weight, height, waist circumference (WC), hip circumference (HC)], measurement of systolic and diastolic blood pressure (BP) and heart rate (HR), lipid profile [triglycerides, total cholesterol (TOT-C), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)], glycaemic parameters [fasting plasma glucose (FPG), HbA1c], and fasting insulin. BP was measured twice in the sitting position after 5 min of rest (Omron-5M system). All laboratory specimens were drawn overnight polysomnography at a hospital-based sleep laboratory (OMRON-5M). All laboratory specimens were drawn according to the Ethic Committee of Sapienza, University of Rome, Italy.

Results

Statistical methods. Data were analyzed with the use of STATISTICA software, version 8.0 (Stat Soft Inc., Tulsa, Oklahoma). Results are expressed as mean±SD. Differences between groups were analyzed using ANOVA for continuous variables. Pearson correlation test was used to measure a linear association between variables. The roles of sex, age, BMI, body fat distribution, cIMT, EFT, glucose and serum lipids as associated variables with AH were tested by linear regression with the use of multivariate models. All P values presented are two-tailed, and values less than 0.05 are considered statistically significant.

Results
The baseline characteristics of the subjects studied are listed in Table 1. 67 patients (39.2%) had no OSA. Among the 104 apneic patients, 42 (24.6%) presented mild OSA, 26 (15.2%) and 36 patients (21.0%), moderate and severe OSA, respectively. Compared to control group, patients with OSA were older, heavier,
had higher BP, BMI, WC, HC, WHR, HbA1c, FPG, fasting insulin, HOMA-IR and triglycerides.

Table 2 shows the body composition data according to the severity of sleep disordered breathing. The percentage of fat mass was almost superimposable between the control and OSA groups, with the notable exception of the head and trunk fat and Upper body Fat Deposition Index (UFDI), the ratio between upper body fat (head, arms and trunk fat in kilograms) and lower body fat (legs fat in kilograms), that were significantly higher in the apneic patients.

Table 3 shows the body composition data according to the severity of sleep disordered breathing. The measures of EFT and of UFDI showed close co-linearity and were significantly related. Figure 1).

Table 4). This indicates a linear relationship between EFT and UFDI.

We then considered only MetS patients (92/171) and compared control and OSA patients within this group (Table 3). OSA patients were once again heavier but not fatter, showing a particular fat distribution pattern characterized by a significantly greater UFDI than control group. Systolic and diastolic BP values were higher in apneic patients that were also more insulin-resistant and showed higher levels of HbA1c than control ones. Increased ILVM, EFT and cIMT were present in MetS OSA patients compared with controls.

Discussion

OSA is frequently associated with obesity [26]. However, it is well known that BMI is not a good measure of body adiposity [8] and different factors beyond BMI are associated with OSA, with abdominal fat, gender and age being significant predictors of sleep disordered breathing [27, 28].

Sleep disordered breathing was identified as an independent, dose-dependent risk factor for hypertension [29] and for insulin resistance and diabetes development [30]; untreated severe OSA independently increases the odds of fatal and nonfatal cardiovascular events [31]. OSA and MetS, both closely related to obesity,
often coexist in affected individuals [32]. Accordingly, the parameters related to MetS, such as triglycerides, BP, FBG, WC, and other cardio metabolic risk factors, such as HbA1C, fasting insulin levels, HOMA-IR, were significantly increased in apneic patients and the prevalence of MetS was significantly higher in the severe OSA group (Figure 2).

It is thought that, in obese individuals, fat deposits in any part of the upper airway, increasing the total volume of soft tissue within the maxillomandibular enclosure, narrow the pharynx and increase the upper airways collapsibility [33], thereby predisposing to OSA. In addition, intramuscular fat content in the posterior tongue is significantly increased in obese patients and rat fed a high fat diet show an increase of the percentage of oil droplet areas in the genioglossus and geniohyoid muscles [34,35]. Interestingly, the amount of adipose tissue adjacent to the pharyngeal airway and in the intra peritoneal space directly associates with AHI, but

| Table 2. Body composition (upper) echocardiographic findings and cIMT measurements (lower) according to the severity of sleep disordered breathing. |
|-------------------------------------------------|
| Body Fat (%) | All (n = 155) | No OSA (n = 66) | Mild OSA (n = 33) | Moderate OSA (n = 24) | Severe OSA (n = 32) |
| Head fat (%) | 20.34 ± 1.67 | 20.81 ± 1.54 | 21.21 ± 1.57 | 21.80 ± 0.87 | 22.43 ± 2.17 |
| Trunk Fat (%) | 38.42 ± 7.43 | 37.12 ± 7.11 | 39.49 ± 9.05 | 37.90 ± 5.91 | 40.42 ± 6.18 |
| Left arm fat (%) | 46.73 ± 10.33 | 45.09 ± 9.66 | 48.47 ± 11.75 | 47.53 ± 8.94 | 49.05 ± 10.65 |
| Right arm fat (%) | 45.32 ± 10.84 | 43.46 ± 10.21 | 46.92 ± 12.17 | 45.49 ± 9.77 | 47.90 ± 11.25 |
| Left leg fat (%) | 39.20 ± 8.57 | 39.70 ± 7.89 | 39.84 ± 9.46 | 39.27 ± 8.83 | 36.77 ± 8.88 |
| Right leg fat (%) | 40.18 ± 8.66 | 40.51 ± 8.21 | 40.54 ± 9.35 | 40.31 ± 9.23 | 38.60 ± 8.65 |
| UFDI | 1.91 ± 0.64 | 1.75 ± 0.44 | 1.97 ± 0.63 | 1.81 ± 0.65 | 2.36 ± 0.88 |
| EFT (mm) | 8.41 ± 1.62 | 7.62 ± 0.92 | 8.23 ± 1.12 | 8.75 ± 0.85 | 9.23 ± 1.39 |
| LVMI (g/m²) | 112.44 ± 22.45 | 105.20 ± 22.56 | 110.00 ± 17.32 | 124.68 ± 19.04 | 121.32 ± 25.15 |
| c IMT (mm) | 0.77 ± 0.18 | 0.71 ± 0.16 | 0.77 ± 0.14 | 0.78 ± 0.19 | 0.85 ± 0.22 |

Values represent mean ± standard deviation unless otherwise indicated.

*ap < 0.05 vs no OSA.

bp < 0.01 vs no OSA.

cp < 0.001 vs no OSA.

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Figure 1. Linear regression analysis between epicardial fat thickness (EFT) and upper body fat deposition index (UFDI). r = 0.51223; p < 0.001

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not with BMI [36]. These data reinforce the assumption that BMI is not a good predictor of OSA, whether abdominal fat and truncal obesity indices are more sensitive parameters for prediction [27,37].

Various measures of fat distribution by DXA can predict insulin resistance and MetS [38]. We found a specific pattern of adiposity in OSA patients consisting in increased arms, trunk and head fat in the presence of superimposable legs adipose tissue content. This is the first time to our knowledge that the arms adipose tissue content is included in the evaluation of central obesity, although an increased arms fat content in post-menopausal women and in Cushing syndrome has been found but never associated with metabolic derangement [39,40]; UFDI strictly correlates with both AHI and EFT suggesting that this new parameter might have the property to highlight in obese patients the risk to develop OSA and cardiovascular diseases.

Sleep-disordered breathing is prevalent among the population with heart failure and preserved LVEF [41,42] and can impair LV diastolic function [43]. Furthermore, a link between OSA and atherosclerosis has been demonstrated [44]. EFT strongly and independently reflects the intra-abdominal visceral fat as measured by magnetic resonance imaging [24] and intra-myocardial lipid content, as measured by proton magnetic resonance spectroscopy [45]. A growing number of studies indicate that EFT measurement may play a role in the stratification of the cardio-metabolic risk [46] and that is also significantly and independently related to MetS and other traditional cardiovascular risk factors [47].

In our patients, echocardiographic evaluation showed a bigger and fatter heart: LVMI and EFT were significantly increased in severe OSA group, suggesting a worsening of cardiac structural changes in relation to AHI progression. OSA patients also showed an increased cIMT, a marker of subclinical atherosclerotic disease.

A significant number of our patients had both OSA and MetS, a condition that has been defined as a new pathological entity termed syndrome Z [48]. We found that patients with syndrome Z, although had a higher BMI, were not fatter than MetS patients without OSA and showed a clear alteration in body fat distribution. In fact, supporting the data of McLaughlin T et al. [49], the UFDI values were higher in these patients who had also higher levels of HbA1C and were more insulin-resistant. Furthermore, OSA patients with MetS showed higher BP, more pronounced heart modifications and an increased cIMT. Thus, OSA severity seems to worsen the cardio metabolic risk expected from MetS per se.

EFT and UFDI were analyzed separately by multiple regression analysis because, being the 2 parameters highly correlated, they both convey essentially the same information and neither may contribute significantly to the model after the other one is included. The multivariate regression analysis performed only in patients with MetS and involving BMI and fat distribution...
Table 3. Characteristics of patients with metabolic syndrome according to the severity of sleep disordered breathing.

| Parameters             | No OSA (n = 23) | OSA (n = 67) | Mild OSA (n = 22) | Moderate OSA (n = 18) | Severe OSA (n = 27) |
|------------------------|-----------------|--------------|-------------------|-----------------------|---------------------|
| AHI (events/h)         | 1.47±1.46       | 30.2±22.12   | 8.83±2.91         | 20.483±7.57          | 51.98±15.72        |
| Gender (F/M)           | 17/6            | 41/26        | 17/5              | 10/8                  | 14/13               |
| Age (years)            | 44.71±15.18     | 50.46±12.05  | 47.74±13.88       | 54.61±10.91          | 50.06±10.89        |
| BMI (kg/m²)            | 36.72±5.64      | 44.23±9.54   | 40.68±7.65        | 42.01±6.48           | 48.14±10.97        |
| WC (cm)                | 113.39±20.75    | 131.05±18.19 | 121.35±12.67      | 129.17±12.82         | 140.24±20.71       |
| HC (cm)                | 123.43±12.92    | 127.75±12.15 | 123.70±18.16      | 128.78±7.24          | 130.50±14.71       |
| WHR                    | 0.96±0.08       | 1.02±0.13    | 1.01±0.22         | 1.025±0.09           | 1.005±0.06         |
| Head fat (%)           | 21.31±1.53      | 21.68±1.76   | 20.72±1.28        | 21.64±0.80           | 22.73±2.30         |
| Body Fat (%)           | 36.26±7.67      | 38.64±7.18   | 40.14±8.42        | 36.93±6.07           | 38.59±6.69         |
| Trunk Fat (%)          | 36.11±7.35      | 39.58±7.38   | 41.02±9.47        | 36.72±5.11           | 40.62±6.65         |
| Left arm fat (%)       | 44.06±8.08      | 48.35±9.03   | 49.38±11.63       | 46.23±9.43           | 50.04±11.07        |
| Right arm fat (%)      | 42.06±9.80      | 46.56±11.48  | 47.78±12.62       | 44.10±10.00          | 49.26±11.58        |
| Left leg fat (%)       | 36.99±7.16      | 37.92±9.91   | 40.21±10.26       | 37.82±8.95           | 36.22±9.56         |
| Right leg fat (%)      | 38.09±7.88      | 39.15±9.71   | 40.94±9.73        | 38.97±9.44           | 38.03±9.32         |
| UFIDI                  | 1.85±0.32       | 2.14±0.53    | 2.07±0.70         | 1.86±0.70            | 2.51±0.90          |
| Systolic BP (mmHg)     | 129.69±16.50    | 136.34±12.72 | 134.78±10.39      | 138.69±14.10         | 136.13±13.08       |
| Diastolic BP (mmHg)    | 80.22±10.82     | 85.49±8.48   | 83.70±8.15        | 86.94±8.77           | 86.71±9.07         |
| TOT-C (mmol/L)         | 4.81±1.29       | 5.21±1.13    | 4.81±0.9          | 5.43±1.32            | 5.46±1.11          |
| LDL-C (mmol/L)         | 3.15±1.03       | 3.23±0.97    | 2.77±0.64         | 3.43±1.10            | 3.44±0.99          |
| HDL-C (mmol/L)         | 1.09±0.28       | 1.12±0.23    | 1.07±0.26         | 1.15±0.24            | 1.18±0.24          |
| Triglycerides (mmol/L) | 1.7±0.75        | 1.97±1.26    | 1.99±1.4          | 1.98±1.5             | 1.94±0.99          |
| FPG (mmol/L)           | 5.72±1.29       | 6.40±2.21    | 6.2±1.11          | 6.97±3.58            | 6.03±1.55          |
| Insulin (pmol/L)       | 166.61±105.91   | 267.45±160.22 | 264.79±171.33  | 258.03±176.02        | 305.06±164.62      |
| HOMA-IR                | 6.31±4.66       | 11.50±9.42   | 9.99±5.97         | 12.46±11.69          | 12.05±10.04        |
| HbA1c (%)              | 5.79±0.54       | 6.52±1.25    | 6.22±0.91         | 6.85±1.64            | 6.41±1.07          |
| EFT (mm)               | 8.22±0.97       | 8.97±1.13    | 8.38±1.00         | 8.83±0.88            | 9.40±1.41          |
| ILVM (g/m²)            | 111.80±20.80    | 119.68±22.75 | 110.80±16.89      | 124.08±18.52         | 123.88±22.17       |
| cIMT (mm)              | 0.74±0.22       | 0.79±0.18    | 0.76±0.13         | 0.76±0.20            | 0.84±0.12          |

Values represent mean±standard deviation unless otherwise indicated.

*p≤0.05 vs no OSA.

*0.00000).

Table 4. Evaluation of effects of age, sex, BMI, WC, HC, WHR and UFIDI on AHI with multivariate regression analysis in patients with metabolic syndrome (adjusted $R^2=52483790$; $p<0.00002$).

| Parameters | β     | ES    | p value |
|------------|-------|-------|---------|
| Age        | −0.18624 | 0.758620 | 0.808453 |
| Sex        | 0.40259  | 0.530958 | 0.456732 |
| BMI        | 3.47049  | 0.570903 | 0.124839 |
| WC         | −2.94049 | 2.318892 | 0.218656 |
| HC         | −0.61747 | 1.547565 | 0.694126 |
| WHR        | −3.13552 | 1.718780 | 0.083879 |
| UFIDI      | 0.73746  | 0.137864 | 0.000017 |

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parameters (Table 4) showed that UFIDI was the only parameter significantly associated with AHI. A further model designed to evaluate which cardiovascular parameter showed the best

Table 5. Evaluation of effects of age, sex, BMI, EFT, LVMI, cIMT on AHI with multivariate regression analysis in patients with metabolic syndrome (adjusted $R^2=59617544$ $p<0.00000$).

| Parameters | β     | ES    | p value |
|------------|-------|-------|---------|
| Age        | 0.421418 | 0.580703 | 0.473836 |
| Sex        | 0.177947 | 0.509540 | 0.729439 |
| BMI        | 0.136449 | 0.735003 | 0.854016 |
| LVMI       | −0.337980 | 0.610544 | 0.584114 |
| cIMT       | 0.664158 | 0.822765 | 0.426107 |
| EFT        | 0.762926  | 0.1109871 | 0.000000 |

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association with AHI, revealed that EFT, a marker of fat storage in myocardial tissue, was the most reliable (Table 5).

Considering that echocardiography is safer than a radiation involving technique like DXA, and that UFDI and EFT can provide the same information, or the association with OSA severity, we suggest to measure EFT in patients with MetS.

It is well known that hepatic, epicardial, skeletal and myocardial muscle fat accumulation increases cardio metabolic risk [50]. Ectopic fat deposition associates with insulin resistance and mitochondrial defects [51,52] and occurs when subcutaneous adipose tissue is unable to store energy excess [53]. In our patients, UFDDI directly associates with both AHI, a parameter related to the amount of adipose tissue adjacent to the upper airway and EFT, a measure of cardiac ectopic fat. Thus UFDDI could be an indirect index of ectopic fat deposition and of reduced subcutaneous fat accumulation. Altered lipid partitioning within muscle and myocardial triglyceride stores were independently associated with carotid atherosclerosis, insulin resistance and type 2 diabetes [54,55]. Interestingly, HbA1c levels and cIMT were significantly associated with cumulative fat mass per se, and the presence and severity of OSA seem to worsen the cardio metabolic risk already established by MetS. The phenotype of obesity characterized by increased UFDDI may be suggestive on one side of OSA and on the other can reflect cardiac structural changes and adiposity. Myocardial steatosis, as measured by EFT, may mirror the ectopic fat deposition in upper airway muscles that plays an important role in disordered breathing.

Conclusions

The major strength of this study is the highlighting of the close relationship between UFDDI and echocardiographic abnormalities with sleep disordered breathing in obese patients.

In conclusion, the occurrence of OSA in obese people relates to abnormal fat distribution and to EFT, rather than to the amount of adipose tissue per se, and the presence and severity of OSA seems to worsen the cardio metabolic risk already established by MetS. The phenotype of obesity characterized by increased UFDDI may be suggestive on one side of OSA and on the other can reflect cardiac structural changes and adiposity. Myocardial steatosis, as measured by EFT, may mirror the ectopic fat deposition in upper airway muscles that plays an important role in disordered breathing.

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Author Contributions

Conceived and designed the experiments: CL LG. Performed the experiments: MS GB PS EA DC MT. Analyzed the data: LMD AL. Contributed reagents/materials/analysis tools: GDL GG. Wrote the paper: CL LG.

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