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Metabolic abnormalities in obstructive sleep apnea patients

Abstract

Introduction: OSA is a well-recognized risk factor of cardiovascular disorders and is related to metabolic syndrome. The aim of this study was to evaluate the effect of BMI and AHI/RDI on metabolic disturbances in patients suspected of OSA.

Material and methods: Ninety-nine patients referred with suspected OSA underwent standard polysomnography or limited sleep study. AHI/RDI ≥ 10/hour was considered relevant for OSA diagnosis. Subjects with AHI/RDI < 10 were considered as controls. We assessed apnea-hypopnea index or respiratory disturbances index (AHI/RDI), Epworth sleepiness scale (ESS), body mass index (BMI), C-reactive protein (CRP, mg/l), glycosylated haemoglobin (HbA_{1c}, %), fasting serum total cholesterol, HDL-, LDL-cholesterol, triglycerides (TG), glucose (G), insulin (INS, IU/ml) and HOMA index.

Results: Data are presented as mean ± SD or median (interquartile range) for parametric and nonparametric data respectively. Twenty-two patients were included as controls (age 51.8 ± 10 *vs.* 55 ± 11in OSA; p = NS). AHI/RDI in the OSA group was 23 (16–31.3) and 7 (3.8–8.1) in controls (p < 0.001). BMI in OSA 32.2 ± 5.8 *vs.* 30.4 ± 4.6 in controls (p = NS). Patients with OSA had higher TG (160 ± 75.9 *vs.* 130.2 ± 51.9 mg/dl, p = 0.046), G (5.04 ± 0.6 *vs.* 4.47 ± 0.6, p = 0.0037), HOMA (2.31 ± 1.5 *vs.* 1.85 ± 1.7, p = 0.046). G correlated best with AHI/RDI (p < 0.001, r = 0.41). Significant differences were observed in OSA patients between obese (51 pts, BMI 35.2 ± 4.8) and non-obese (26 pts, BMI 26.61 ± 1.9) pts in: HDL-cholesterol (50.8 ± 13.2 *vs.* 60.9 ± 18.4 mg/dl; p = 0.02), TG (178.7 ± 69.9 *vs.* 124 ± 75.3 mg/dl, p < 0.001), G (5.15 ± 0.7 *vs.* 4.8 ± 0.5 mmol/l, p = 0.01), INS (11.7 ± 5.9 *vs.* 6.57 ± 4.7, p < 0.001), HOMA (2.7 ± 1.4 *vs.* 1.4 ± 1.2, p < 0.001), HbA_{1c} (5.89 ± 0.9 *vs.* 5.4 ± 0.8, p = 0.03), CRP (2.2 ± 2.9 *vs.* 1.09 ± 1.2, p = 0.01).

Conclusions: Our findings support the results of previous studies showing the influence of OSA alone on metabolic disturbances. However, BMI has major impact on metabolic variables.

Key words: OSA, metabolic abnormalities

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Introduction

Obstructive sleep apnea (OSA) is a significant problem in developed countries. The estimated frequency of OSA in the general population is about 4% in men and 2% in women [1]. The incidence of cardiovascular diseases and mortality associated with these diseases is higher in apneic subjects [2]. Obesity was considered the main factor responsible for this. Recent data suggest, however, that OSA might be associated with many cardiovascular risk factors independently of obesity. These factors might coexist in individual patients and are called metabolic syndrome. The present definition states that metabolic syndrome consists of [3] central obesity (waist ≥ 80 cm in women and ≥ 94 cm in men) or body mass index (BMI) > 30 kg/m^2 and 2 out of 4 of the following:

— raised triglycerides > 150 mg/dl (1.7 mmol/l) or specific treatment of this lipid abnormality,
— reduced HDL-cholesterol < 40 mg/dl (1.03 mmol/l) in men and < 50 mg/dl (1.29 mmol/l) in women, or specific treatment of this lipid abnormality,

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— raised systolic blood pressure ≥ 130 mm Hg or diastolic ≥ 85 mm Hg or treatment of previously diagnosed hypertension,
— fasting serum glucose ≥ 100 mg/dl (5.6 mmol/l) or previously diagnosed type 2 diabetes.

OSA has recently been discussed as a manifestation of metabolic syndrome [4, 5]. OSA is associated with obesity [1], moreover, most apneic patients suffer from hypertension [6–8] or diabetes [9, 10], which indicates that OSA and metabolic syndrome share similar clinical characteristics. The association of OSA and constituents of metabolic syndrome has been analysed. Nevertheless, previous studies on the relationship of OSA and insulin resistance (IR) have yielded conflicting results. Many of them suggest that OSA is independently associated with IR [11–14]. Other studies have shown that IR is related to obesity and not to OSA [15]. Similar controversies might be found regarding lipid metabolism [5, 15–17].

In this study we aimed to evaluate the prevalence of metabolic abnormalities in patients suspected of OSA referred to our sleep laboratory for sleep study. We also wanted to assess the possible influence of OSA and obesity on these abnormalities.

Material and methods

Subjects

Consecutive subjects suspected of OSA referred during a period of 4 months to the Sleep Laboratory of the 2nd Department of Lung Diseases at the National Institute of Tuberculosis and Lung Diseases were recruited. Patients with previously diagnosed diabetes and/or with self-reported use of lipid lowering treatment were excluded in order to eliminate subjects with very high IR (in the course of diabetes mellitus) and subjects with normal lipids achieved due to lipid lowering treatment. All subjects completed an Epworth sleepiness scale (ESS) and a questionnaire on sleep symptoms, medical history, current treatment and smoking status. Patients were referred to undergo full overnight polysomnography (PSG) or limited polysomnography depending on the clinical assessment of a specialist who calculated the probability of OSA diagnosis based on reported sleep disturbances, daytime symptoms and body habitus (BMI, neck circumference).

The study was approved by the local ethics committee. All patients gave their informed consent.

Assessments

The sleep study was performed with Sensor Medics Somno Star Alpha (CA, USA) or Poly-Mesam (MAP, Germany) in case of limited polysomnography. Sleep staging and respiratory events during PSG were scored manually using standard criteria [18]. The cut off point for the diagnosis of OSA for the purpose of this study was set at AHI/RDI ≥ 10/hour, which is the number used in some previously conducted studies [5, 19–22]. Patients with AHI/RDI < 10 were considered as controls. In the morning following sleep study, fasting blood samples were taken from all subjects. The following parameters were assessed: total cholesterol (TC), HDL-cholesterol, LDL-cholesterol, triglycerides (TG), glucose (G), insulin (INS), glycosylated haemoglobin (HbA_{1c}) and C-reactive protein (CRP). Lipids were considered abnormal if they exceeded the following values: TC > 190 mg/dl, HDL < 40 mg/dl (for the analysis, no separate normal values for women were considered), LDL > 115 mg/dl and TG > 150 mg/dl [23]. IR was calculated using the homeostasis model assessment (HOMA) score (fasting serum insulin (mIU/l) × fasting plasma glucose (mmol/l)/22.5) [24]. Biochemical measurements were conducted using a Hitachi autoanalyzer. Serum insulin was determined with an enzyme immunoassay.

Statistical analyses

Statistical analyses were performed using Statistica software (release 6.0 for Windows). Comparisons were made using the unpaired t test (parametric data) and the Mann Whitney U test or ANOVA (nonparametric data). Categorical parameters were compared by Chi-square test. Spearman's rank correlation coefficient was used to examine the association of two parameters. To assess the association between OSA and BMI and metabolic parameters a multiple linear regression model was used. Statistical significance was considered at $p < 0.05$.

Results

Ninety-nine patients were included. Six subjects in the non-OSA group and 39 in the OSA group underwent limited sleep study, the other subjects underwent PSG study. Cases and controls were similar in age, weight, BMI and ESS (tab. 1). Subjects with OSA presented a higher percentage of the night with oxygen saturation below 90%. Twenty-nine percent of all attendees were overweight (25 < BMI < 30) and 61% were obese (BMI ≥ 30).

As shown in figure 1, abnormal lipid profile was very common in the studied group.

Participants with OSA had higher levels of TG than the non-OSA group (tab. 2). No difference in other lipid parameters was observed. HOMA-IR and G were significantly higher in the group with

Table 1. Study population characteristics

	Non-OSA AHI < 10 (22 pts)	OSA AHI ≥ 10 (77 pts)	p
Men, n/%	12/54.5%	57/74%	NS
Women, n/%	10/45.5%	20/26%	NS
Age, years	51.8 ± 10	55 ± 11	NS
BMI, kg/m^2	30.4 ± 4.6	32.3 ± 5.8	NS
AHI, n/hour (Me(IQR))	7 (3.8–8.1)	23 (16–31.3)	< 0.001
Sat < 90%, % night (Me(IQR))	0.55 (0–2.3)	5.5 (1.75–25.4)	< 0.001
ESS, points	10.4 ± 5	10.6 ± 5.6	NS
Current smokers, n (%)	11 (50%)	47 (61%)	NS

BMI = body mass index; Sat < 90% = percentage of night with oxygen saturation below 90%
The mean (± SD), median (interquartile range (IQR)) and number are presented for parametric, nonparametric and categorical data respectively

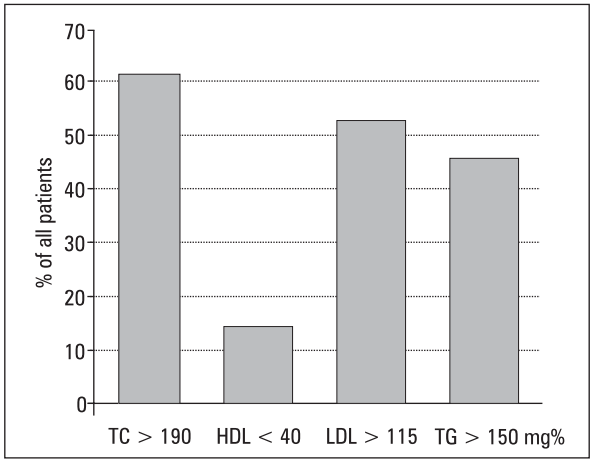


Figure 1. Prevalence of serum lipid abnormalities in the studied population

OSA; however, fasting insulin levels did not differ between the groups (tab. 2).

To compare the effects of sleep apnea and body mass on metabolic abnormalities, patients were divided, according to BMI, into an obese and a non-obese group. When patients within OSA group were analyzed we found that they had similar AHI, but the obese patients were significantly younger (tab. 3).

In the non-OSA group, a significant difference between obese and non-obese subjects was observed in the case of HOMA and CRP. Analysis of the relationship between BMI and lipid profile and glucose metabolism showed statistically significantly higher levels of G, INS, HOMA, HbA_{1c} and CRP in OSA group (tab. 3).

A predominant effect of body mass on metabolic abnormalities was also present in the linear regression analysis. In the multiple regression models with metabolic parameters used as dependent variables, BMI was significantly related to TG

Table 2. Comparison of metabolic parameters and CRP in OSA and non-OSA patients

	Non-OSA AHI < 10 (22 pts)	OSA AHI ≥ 10 (77 pts)	p
TC, mg/dl	206.5 ± 26.9	204.6 ± 41.4	NS
HDL, mg/dl	58.8 ± 13.7	54.3 ± 15.8	NS
LDL, mg/dl	120.8 ± 26.9	117.2 ± 40.8	NS
TG, mg/dl	130.2 ± 51.9	160.03 ± 75.9	0.046
G, mmol/l	4.47 ± 0.6	5.04 ± 0.6	0.0037
INS, μIU/ml (Me(IQR))	5.7 (3.8–11.7)	8.1 (5–14.4)	NS
HOMA (Me(IQR))	1.14 (0.7–2.7)	1.84 (1.1–3.4)	0.046
HbA_{1c} (%) (Me(IQR))	5.5 (5.3–5.7)	5.5 (5.3–6.3)	NS
CRP, mg/l (Me(IQR))	0.9 (0.5–4.1)	1.1 (0.4–2.6)	NS

The mean (± SD), median (interquartile range (IQR)) and number are presented for parametric, nonparametric and categorical data respectively

(R^2 0.17, β = 0.44, p < 0.001), HDL (R^2 0.11, β = –0.35, p = 0.002), G (R^2 0.18, β = 0.34, p = 0.01), INS (R^2 0.19, β = 0.46, p < 0.001), HOMA-IR (R^2 0.24, β = 0.49, p < 0.001) and CRP (R^2 0.1, β = 0.30, p < 0.001). AHI, after adjustment for BMI, was significantly related to G (R^2 0.18, β = 0.3, p < 0.01) and HbA_{1c} (R^2 0.09, β = 0.2, p = 0.04) (fig. 2, 3). The interaction of obesity and AHI was significant (R^2 0.1, β = 0.33, p < 0.001) (fig. 4).

To evaluate the possible modifying effect of gender we analyzed the material with respect to sex. Results are shown in table 4 and figure 5. Women with OSA were older than men with OSA. Non-apneic women had higher BMI than non-apneic men.

Women with OSA had higher TC (219.9 ± 38.7 *vs.* 199.2 ± 41.3, p = 0.03), higher HDL (67.2 ±

Table 3. Comparison of obese and non-obese patients within the OSA and non-OSA groups

	Non-OSA AHI < 10		p	OSA AHI ≥ 10		p
	BMI < 30 (n = 13)	BMI ≥ 30 (n = 9)		BMI < 30 (n = 26)	BMI ≥ 30 (n = 51)	
Age (years)	58.6 ± 9	49.5 ± 11	NS	58.6 ± 10	53.1 ± 11	0.04
BMI [kg/m^2]	26.3 ± 3	34 ± 2.8	< 0.001	26.6 ± 1.9	35.2 ± 4.8	< 0.001
AHI [n/hour]	5.9 ± 2.9	6.3 ± 2.4	NS	21.6 ± 10	28.7 ± 16	NS
ESS [points]	9.4 ± 5.2	11.7 ± 4.7	NS	8.26 ± 4.9	11.4 ± 5.6	0.03
TC [mg/dl]	212 ± 28,4	199.9 ± 24.7	NS	209.7 ± 43.7	202 ± 40.4	NS
HDL [mg/dl]	63.1 ± 13.5	53.6 ± 12.7	NS	60.9 ± 18.4	50.8 ± 13.2	0.006
LDL [mg/dl]	125.1 ± 28.3	115.1 ± 25.3	NS	124.8 ± 42.7	113.7 ± 40.1	NS
TG [mg/dl]	119.3 ± 55.3	143 ± 46.8	NS	124.07 ± 75.3	178.7 ± 69.9	0.003
G [mmol/l]	4.34 ± 0.4	4.64 ± 0.7	NS	4.79 ± 0.5	5.16 ± 0.67	0.02
INS [μIU/ml]	6.2 ± 4.3	12.4 ± 11.1	NS	6.57 ± 4.7	11.7 ± 5.9	< 0.001
HOMA	1.19 ± 0.8	2.57 ± 2.1	0.04	1.4 ± 1.2	2.7 ± 1.4	< 0.001
HbA_{1c} (%)	5.5 ± 0.7	5.69 ± 0.6	NS	5.4 ± 0.8	5.89 ± 0.9	0.01
CRP [mg/l]	3.4 ± 7	7.3 ± 10	0.02	1.09 ± 1.2	2.2 ± 2.89	0.02

Data presented as mean (±SD)

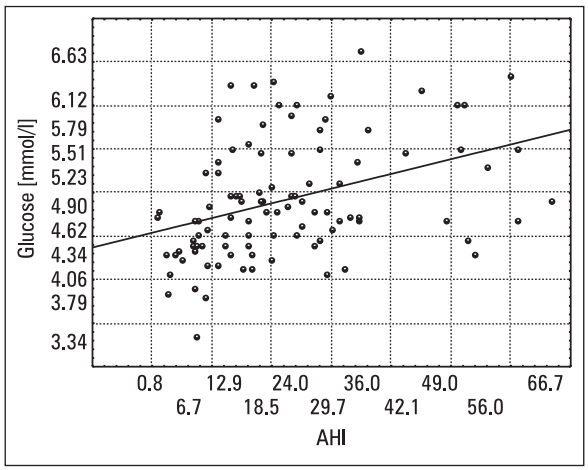


Figure 2. Correlation between AHI and glucose (R^2 0.18, b = 0.3, p < 0.01)

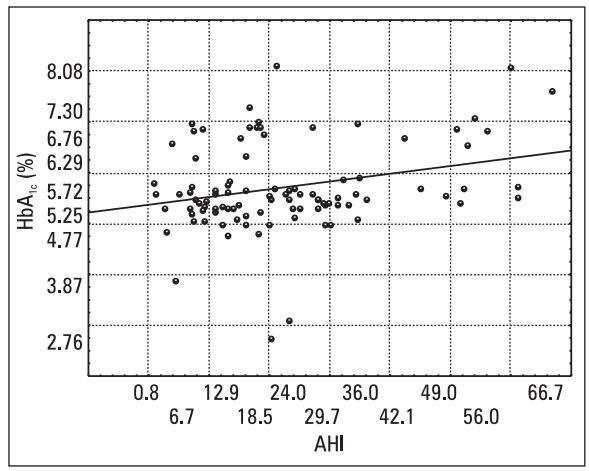


Figure 3. Correlation between AHI and HbA_{1c} (R^2 0.09, β = 0.2, p = 0.04)

17.5 *vs.* 49.7 ± 12.3, p < 0.001) and lower TG (136.7 ± 86.1 *vs.* 167.7 ± 71.4, p = 0.03) than men (fig. 5). In turn, men with OSA had higher G when compared to women with OSA (5.1 ± 0.6 *vs.* 4.8 ± 0.7, p = 0.03) and non-apneic men (5.1 ± 0.6 *vs.* 4.4 ± 0.4, p = 0.03). No other significant differences between men and women were observed.

Discussion

One of the factors contributing to impaired glucose metabolism in OSA is sleep deprivation and sleep fragmentation [25–27] which acts by activation of sympathetic nervous system and hypothalamic-pituitary-adrenal axis leading to increased cortisol levels [28], and raised free fatty acid thus promoting IR and elevation of TG [29].

Some studies a showed correlation between sleepiness and IR [4]. No such dependence was observed in our population (R^2 0.002, β = 0.051, p = 0.62).

In our study, sleep apnea influenced glucose metabolism independently of BMI; however, body mass had a major impact on metabolic disturbances. In our study, we found that abnormal lipids were present in about 50% of patients suspected of OSA (similar to the apneic group). Current data on

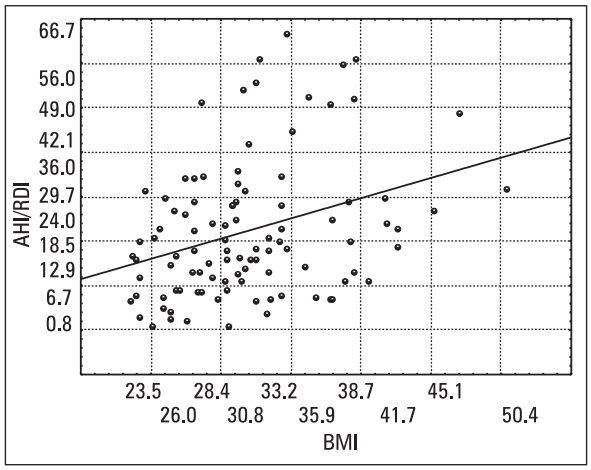


Figure 4. Relation between AHI and BMI (R^2 0.1, β = 0.33, $p < 0.001$)

lipid abnormalities in the general population in Poland indicate that about 20% of people have elevated LDL-cholesterol, 20% — triglycerides, 3.7% — reduced HDL-cholesterol and 69% — raised total cholesterol [30]. In our group, more patients than in the general population presented with elevated triglycerides. This might result from the higher prevalence of obesity than in the general population (61% *vs.* 32%) [30], since an association between obesity and OSA and elevation of triglycerides has been previously established [5, 11, 31–33].

Attendees with sleep apnea had higher triglycerides, glucose and HOMA insulin resistance index when compared to subjects without OSA. A study on a similar population was conducted by Ip et al. [13]. Two hundred and seventy subjects suspected of OSA referred for polysomnography were included. OSA subjects had higher insulin resistance index, but they were older and more obese than the non-OSA group. Nevertheless, the independent influence of sleep apnea on insulin resistance was present. However, BMI was a major determinant of insulin resistance. Despite the fact that patients in the above study were younger than in our group (42 and 45 years *vs.* 52 and 55 in non-apneic and apneic patients, respectively) and had lower BMI (24 and 28 *vs.* 30 and 32) the value of the HOMA index in both groups was similar. These results are consistent with results of another large study — the Sleep Heart Study [12], in which sleep disordered breathing was independently associated with glucose intolerance and insulin resistance. Conversely, a study by Gruber et al. [15] on a far smaller population (n = 79) showed that OSA patients (similar age and BMI as our subjects) had elevated triglycerides and glucose, but insulin resistance index (HOMA) after adjustment for age and BMI was not associated with a diagnosis of OSA. HOMA was, however, significantly higher in the OSA group than in the non-OSA group.

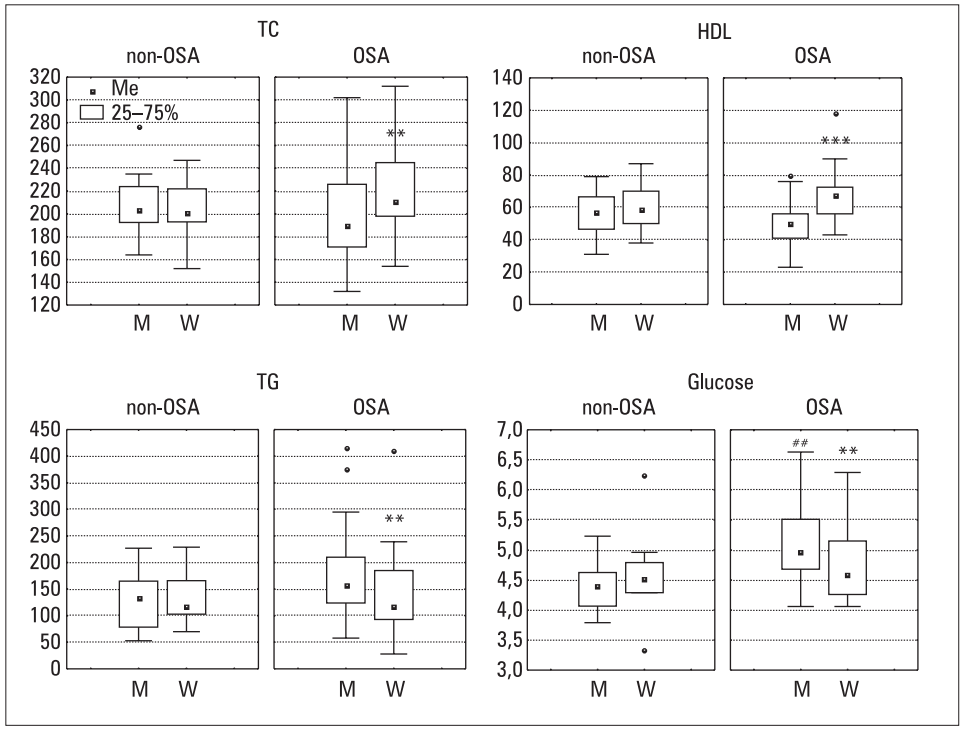
In the study population, 30% of subjects were female, of which about 66% were apneic. They were older than the apneic men, which is consistent with previous studies [1, 21]. The high number of female participants had a modifying effect on the results. The only significant difference between patients with OSA and non-OSA observed after the elimination of women from the analysis occurred in their glucose, which was higher in apneic subjects. It also indicates that sleep apnea influenced glucose metabolism most severely from all the analyzed parameters.

In our study, we included patients suspected of OSA whose obesity accompanied by snoring, reported sleep disturbances and daytime sleepiness (resulting in similar daytime sleepiness in compared groups) prompted their physicians to diagnose OSA. Subjects with AHI < 10/hour

Table 4. Comparison of women and men in the study population

	Men (n = 69)		p	Women (n = 30)		p	p	p
	OSA– (n = 12)	OSA+ (n = 57)		OSA– (n = 10)	OSA+ (n = 20)		OSA– M *vs.* W	OSA+ M *vs.* W
Age (years)	50.5 (47–58)	52 (46–60)	NS	53.5 (50–63)	61 (55–67.5)	NS	NS	0.003
BMI [kg/m^2]	27.6 (26–30.4)	31.4 (28.5–36.2)	0.01	33.5 (27.9–35.9)	30.8 (26.5–33.7)	NS	0.05	NS
AHI [n/hour]	7.3 (5.8–8.8)	24 (16–34.4)	< 0.001	7.1 (2.3–10)	20.6 (16.6–28)	< 0.001	NS	NS
ESS [points]	11 (8.5–16.5)	10.5 (6–16)	NS	11 (8–14)	7 (4–14)	NS	NS	NS

M = men; W = women
The mean (± SD), median (interquartile range (IQR)) and number are presented for parametric, nonparametric and categorical data, respectively



**p = 0.03 women *vs.* men in OSA group
***p ≤ 0.001 women *vs.* men in OSA group
##p = 0.03 men in OSA group *vs.* men in non-OSA group

Figure 5. Differences in metabolic parameters in men and women

were considered as controls for the purpose of the study. The control group was relatively small and patients presented similar clinical characteristics as OSA patients, which might have affected the results. The differences between apneic and non-apneic patients in our study might be minimized due to a high cut off limit (AHI/RDI = 10/hour). Nonetheless, clear differences between the two groups were present. To avoid this type of bias, Sharma et al. [20] compared 40 obese apneic patients to 40 non-apneic obese and 40 non-apneic normal weight subjects and found that there was no difference in metabolic status between obese apneic and non-apneic patients. Significantly lower insulin and HOMA when compared to these patients was noted in normal weight controls. This reflects the importance of obesity in the development of insulin resistance in the OSA population.

There are conflicting results regarding concentrations of triglycerides in OSA. Schäfer et al. [22] found no relationship between OSA and concentration of lipoproteins in 81 male subjects. Similarly, there was no difference in triglyceride concentrations between OSA and non-OSA controls in a study conducted previously in our department [34] and studies by McArdle [16] and Sharma [20]. However, the patients in those studies [16, 20] were younger and had lower BMI than in our study. In populations studied by Coughlin and Makino, which were closer in age and BMI to our group, OSA subjects had significantly higher triglycerides than non-OSA subjects [5, 11].

In our study, only glucose levels were associated with sleep apnea independently of BMI. Moreover, BMI influenced most of the studied metabolic parameters. Our findings support the results of previous studies showing the influence of OSA alone on metabolic disturbances. However, BMI has a major impact on metabolic variables.

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