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Free fatty acids and the metabolic syndrome in patients with obstructive sleep apnoea

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ABSTRACT: Obesity and metabolic syndrome (MS) occur frequently in patients with obstructive sleep apnoea syndrome (OSAS). We hypothesised that circulating free fatty acids (FFAs) are elevated in OSAS patients independently of obesity. This elevation may contribute to the development of MS in these patients.

We studied 119 OSAS patients and 119 controls. Participants were recruited and studied at sleep unit of our institution (Hospital Universitari Son Dureta, Palma de Mallorca, Spain) and were matched for sex, age and body mass index (BMI). The occurrence of MS was analysed by clinical criteria. Serum levels of FFAs, glucose, triglycerides, cholesterol, high-density lipoprotein–cholesterol, aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase, C-reactive protein and 8-isoprostanes were determined.

Prevalence of MS was higher in OSAS than in the control group (38 *versus* 21%; p=0.006). OSAS patients had higher FFAs levels than controls (mean±SD 12.2±4.9 *versus* 10.5±5.0 mg·dL^{-1}; p=0.015). Among subjects without MS, OSAS patients (OSAS+ MS-) showed higher levels of FFAs than controls (OSAS- MS-) (11.6±4.7 *versus* 10.0±4.4 mg·dL^{-1}; p=0.04). In a multiple regression model, after adjustment for age, sex, BMI and the presence of MS, FFAs were significantly associated with apnoea/hypopnoea index (p=0.04).

This study shows that FFAs are elevated in OSAS and could be one of the mechanisms involved in the metabolic complications of OSAS.

KEYWORDS: Free fatty acids, metabolic syndrome, sleep apnoea

Obstructive sleep apnoea syndrome (OSAS) is a common disorder defined by the occurrence of repeated episodes of upper airway obstruction and airflow cessation (apnoeas) that normally lead to arterial hypoxaemia and sleep disruption [1, 2]. A number of clinical features, such as obesity, insulin resistance and the metabolic syndrome (MS) are often, but not invariably, present in these patients [3].

The relationship between obesity and the development of the MS in patients with OSAS is complex and poorly understood [3–5]. Obesity is generally regarded as a risk factor for both OSAS and MS [4]. However, factors other than obesity appear to play a significant role in the development of metabolic disturbances in patients with OSAS [6, 7], including sleep fragmentation and intermittent hypoxia.

Circulating free fatty acids (FFAs) are mainly released from triglyceride stores of the adipose tissue and serve as physiologically important energy substrates [8]. Previous work suggests an important role of FFAs in the development of insulin resistance and various disturbances related to MS [9, 10]. Additionally, FFAs could also contribute to oxidative stress, inflammation and endothelial dysfunction [11–13]. Despite the evidently central role of FFAs in pathophysiological processes leading to MS, there exist no studies investigating the relationship between FFAs and MS in OSAS

In this study, we hypothesised that FFAs are elevated in OSAS patients independently of obesity, and that this elevation may contribute to the development of MS in these patients. To test this hypothesis, we compared their concentration in patients with OSAS (with and without MS) and matched controls (with and without MS).

METHODS

Subjects and ethics

In this case–control study, we included 119 patients with OSAS and 119 controls.

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Participants were recruited from subjects who attended the sleep unit of our institution between January 2008 and December 2009. Patients and controls were selected based on the diagnosis of OSAS and were matched for sex, age (±5 yrs) and body mass index (BMI) (±3 kg·m^{-2}). No participant suffered from any other chronic disease (chronic obstructive pulmonary disease, liver cirrhosis, thyroid dysfunction, rheumatoid arthritis, chronic renal failure and/or psychiatric disorders). There were no differences between the number of patients and controls taking hypoglycaemic, hypolipaemiant and/or antihypertensive agents. No participant was regularly taking anti-inflammatory medication. The study was approved by the Ethics Committee of our institution and all participants gave signed consent after being fully informed of its goal and characteristics.

Measurements and definitions

The diagnosis of OSAS was established by full polysomnography (E-Series; Compumedics, Abbotsford, Australia) that included recording of oronasal flow, thoracoabdominal movements, ECG, submental and pretibial electromyography, electro-oculography, electroencephalography, and transcutaneous measurement of arterial oxygen saturation (S_{a,O_2}). Apnoea was defined by the absence of airflow for >10 s. Hypopnoea was defined as any airflow reduction that lasted >10 s and resulted in arousal or oxygen desaturation. We considered desaturation a decrease in S_{a,O_2} >4%. The apnoea/hypopnoea index (AHI) was defined as the sum of the number of apnoeas plus hypopnoeas per hour of sleep. The case or control status was defined by the AHI threshold of ⩾10 events·h^{-1}. Patients were classified into three groups according to their AHI as mild (AHI 10–20 events·h^{-1}), moderate (AHI 21–40 events·h^{-1}) and severe OSAS (AHI >40 events·h^{-1}).

Excessive daytime sleepiness was quantified subjectively by the Epworth Sleepiness Scale.

The occurrence of the MS was analysed according to the National Cholesterol Education Program Adult Treatment Panel III clinical criteria: 1) waist circumference ⩾102 cm in males and ⩾88 cm in females; 2) fasting glucose ⩾100 mg·dL^{-1} or patient on specific drug treatment; 3) triglycerides ⩾150 mg·dL^{-1} or patient on specific treatment; 4) high-density lipoprotein-cholesterol (HDLc) <40 mg·dL^{-1} in males and < 50 mg·dL^{-1} in females or patient on specific drug treatment; and 5) systolic blood pressure ⩾130 mmHg or diastolic blood pressure ⩾85 mmHg, or patient on specific drug treatment. MS was diagnosed if three out of these five factors were present.

After fasting overnight, venous blood samples were obtained between 08:00 and 10:00 h. Blood was centrifuged, and serum was immediately separated into aliquots and stored at -80°C until analysis.

Glucose, triglycerides, total cholesterol, HDLc, aspartate aminotransferase, alanine aminotransferase, γ-glutamyltransferase (GGT), uric acid and FFAs were determined by standard enzymatic methods on a Hitachi Modular analyser (Roche Diagnostics, Indianapolis, IN, USA). The plasma concentration of C-reactive protein (CRP) was measured by a commercial chemiluminiscent assay on a Immulite 2000 analyser (Siemens Medical Solutions Diagnostics, NY, USA). 8-isoprostanes were measured with an 8-isoprostane EIA kit (Cayman Chemicals Company, Ann Arbor, MI, USA).

Statistical analysis

Results are presented as %, median or mean±SD. Comparisons of group means were performed using unpaired t-tests (for comparison between any two groups) and using one-way ANOVA (for multiple-group comparison), followed by *post hoc* contrast when appropriate.

To determine the effect of sleep apnoea on FFAs, we used a multiple regression analysis, including all subjects, with study group, age, sex, BMI and AHI as the independent variables, and FFAs as the dependent variable.

The study was powered to detect a difference of 2.0 mg·dL^{-1} in FFAs, assuming a within-subject standard deviation of 2.0 in healthy subjects [13], at a significance level of 5% and with a power of 90%, which required 20 subjects in each group.

Correlations between variables were explored using the Spearman rank test. A p-value <0.05 was considered significant.

RESULTS

Characteristics of the study population are summarised in table 1. By design, sex, age and BMI were similar in patients and controls.

The prevalence of the MS was higher in the OSAS group than in the control group (p=0.006).

Metabolic and biochemical parameters are presented in table 2. Tables 3 and 4 show these parameters according to the presence or absence of the MS.

TABLE 1 Subject characteristics

	Controls	OSAS	p-value
Subjects n	119	119	
Age yrs	45±11	46±12	0.635
Males	87 (73)	88 (74)	0.883
BMI kg·m^{-2}	28±4	28±4	0.727
Waist circumference cm	101±11	101±11	0.889
Hypertension	22 (21)	26 (22)	0.470
Diabetes	4 (4)	9 (8)	0.169
Current smoker	36	36	0.951
MS	21%	38%	0.006
AHI events·h^{-1}	3.2 (1.8–4.5)	39 (23.2–53.5)	<0.001
Arousal index events·h^{-1}	22±13	47±18	<0.001
S_{a,O_2} %			
Mean	94±3	93±2	<0.001
Minimum	86±9	83±8	0.061
ESS score	7 (5–10)	11 (6–14)	<0.001

Data are presented as mean±SD, n (%) or median (interquartile range), unless otherwise stated. OSAS: obstructive sleep apnoea syndrome; BMI: body mass index; MS: metabolic syndrome; AHI: apnoea/hypopnoea index; S_{a,O_2}: arterial oxygen saturation; ESS: Epworth Sleepiness Scale.

TABLE 2 Metabolic and biochemical markers

	Controls	OSAS	p-value
Subjects n	119	119	
Glucose mg·dL^{-1}	94±4	103±22	0.001
Triglycerides mg·dL^{-1}	124±51	147±94	0.079
Cholesterol mg·dL^{-1}	207±41	212±39	0.398
HDLc mg·dL^{-1}	56±15	55±16	0.505
Creatinine mg·dL^{-1}	0.88±0.2	0.96±0.3	0.692
Uric acid mg·dL^{-1}	6.2±4.7	6.1±3.2	0.336
AST U·L^{-1}	22±7	21±7	0.387
ALT U·L^{-1}	27±15	27±13	0.809
GGT U·L^{-1}	32±27	37±29	0.048
CRP U·L^{-1}	1.4 (0.5–3.2)	2.0 (0.9–3.6)	0.01
8-isoprostanes U·L^{-1}	4.3 (1.2–9.1)	11.4 (6.1–22.5)	0.001
FFAs mg·dL^{-1}	10.5±5	12.2±5	0.015

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. OSAS: obstructive sleep apnoea syndrome; HDLc: high-density lipoprotein-cholesterol; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: γ-glutamyltransferase; CRP: C-reactive protein; FFA: free fatty acid.

Compared with controls subjects, OSAS patients showed abnormal plasma levels of glucose, GGT, CRP and 8-isoprostanes (table 2).

Plasma levels of FFAs were significantly higher in OSAS patients than in subjects without OSAS (p=0.015). No significant differences in FFAs were detected between OSAS patients with MS (OSAS+ MS+) and controls with MS (OSAS- MS+) (p=0.271) (table 3). Nevertheless, among subjects without MS, OSAS patients (OSAS+ MS-) show higher levels of FFAs than controls (OSAS- MS-) (p=0.04) (table 4).

TABLE 3 Metabolic and biochemical markers in patients and controls with metabolic syndrome

	Controls	OSAS	p-value
Subjects n	23	45	
Glucose mg·dL^{-1}	101±15	116±27	0.013
Triglycerides mg·dL^{-1}	147±51	195±128	0.123
Cholesterol mg·dL^{-1}	218±45	217±32	0.981
HDLc mg·dL^{-1}	57±25	51±10	0.380
Creatinine mg·dL^{-1}	0.85±0.07	0.89±0.14	0.607
Uric acid mg·dL^{-1}	5.8±1.8	6.3±1.4	0.523
AST U·L^{-1}	23±8	21±8	0.349
ALT U·L^{-1}	30±15	30±15	0.789
GGT U·L^{-1}	43±35	44±35	0.957
CRP U·L^{-1}	1.3 (0.5–3.8)	2.0 (0.9–3.5)	0.894
8-isoprostanes U·L^{-1}	4.2 (2.3–7.6)	10.6 (4.7–24.0)	0.228
FFAs mg·dL^{-1}	11.5±5	13.1±5	0.271

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. OSAS: obstructive sleep apnoea syndrome; HDLc: high-density lipoprotein-cholesterol; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: γ-glutamyltransferase; CRP: C-reactive protein; FFA: free fatty acid.

TABLE 4 Metabolic and biochemical markers in patients and controls without metabolic syndrome

	Controls	OSAS	p-value
Subjects n	86	74	
Glucose mg·dL^{-1}	92±15	95±12	0.204
Triglycerides mg·dL^{-1}	114±42	118±47	0.599
Cholesterol mg·dL^{-1}	201±37	207±43	0.313
HDLc mg·dL^{-1}	56±16	55±15	0.767
Creatinine mg·dL^{-1}	0.88±0.15	0.89±0.15	0.811
Uric acid mg·dL^{-1}	4.8±1.5	5.5±1.3	0.023
AST U·L^{-1}	21±6	21±7	0.723
ALT U·L^{-1}	26±15	25±11	0.676
GGT U·L^{-1}	29±25	33±25	0.358
CRP U·L^{-1}	1.4 (0.5–3.2)	2.0 (0.8–3.8)	0.01
8-isoprostanes U·L^{-1}	4.8 (1.4–9.4)	12.0 (6.7–21.2)	0.001
FFAs mg·dL^{-1}	10.0±4.4	11.6±4.7	0.04

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. OSAS: obstructive sleep apnoea syndrome; HDLc: high-density lipoprotein-cholesterol; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: γ-glutamyltransferase; CRP: C-reactive protein; FFA: free fatty acid.

In the OSAS group, FFA levels were significantly related to AHI (r=0.210, p=0.026; fig. 1a) and the arousal index (r=0.236, p=0.010; fig. 1b). FFAs were also significantly related to GGT (r=0.274, p=0.003; fig. 2a) and HDLc levels (r=0.305, p=0.001; fig. 2b).

Associations between FFA levels and nocturnal oxygenation indices did not reach the level of statistical significance (mean S_{a,O_2} r=0.189 (p=0.083) and minimum S_{a,O_2} r=0.139 (p=0.141)).

In a multiple regression model, after adjustment for age, sex, BMI and the presence of MS, FFAs were significantly associated with AHI (p=0.028).

In addition, FFAs were significantly different between the three groups with mild, moderate and severe OSAS (ANOVA p=0.004) and higher in the severe OSAS group (13.3±5.2 mg·dL^{-1}) than in the moderate (11.4±4.2 mg·dL^{-1}; p<0.004) and the mild OSAS groups (10.5±4.0 mg·dL^{-1}; p<0.004).

In OSAS without MS, FFA levels were higher in the severe group (12.4±5.0 mg·dL^{-1}) than in the mild-to-moderate group (11.0±4.1 mg·dL^{-1}; p<0.01), but the correlation analysis between FFAs and AHI did not reach statistical significance (r=0.154; p=0.191). In this group, FFAs were also related to GGT (r=0.274; p=0.01) and HDLc (r=0.305; p=0.037).

DISCUSSION

The strengths of this study include assessment of associations between FFAs and OSAS, and the presence of the MS without the potential influence of confounding factors.

This study shows that: 1) the prevalence of the MS is higher in OSAS patients than subjects without OSAS of similar age, sex and BMI, suggesting that OSAS itself is a risk factor for the MS; 2) FFAs are elevated in patients with OSAS; and 3) AHI is independently associated with FFAs levels. These observations

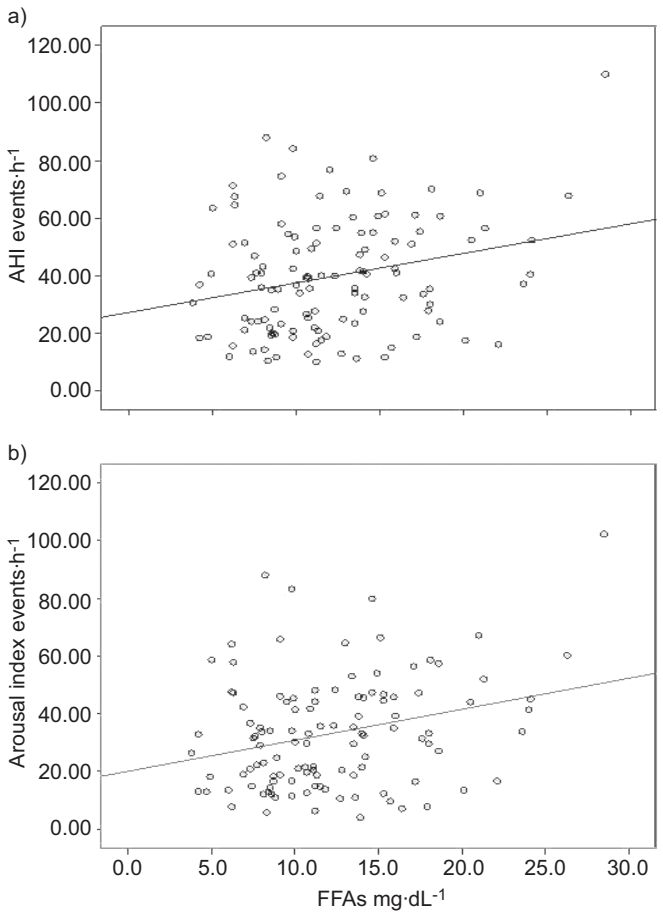

FIGURE 1. Relationship between free fatty acid (FFA) levels, and a) apnoea/hypopnoea index (AHI) (r=0.204, p=0.026) and b) arousal index (r=0.210, p=0.026) in the obstructive sleep apnoea syndrome population studied.

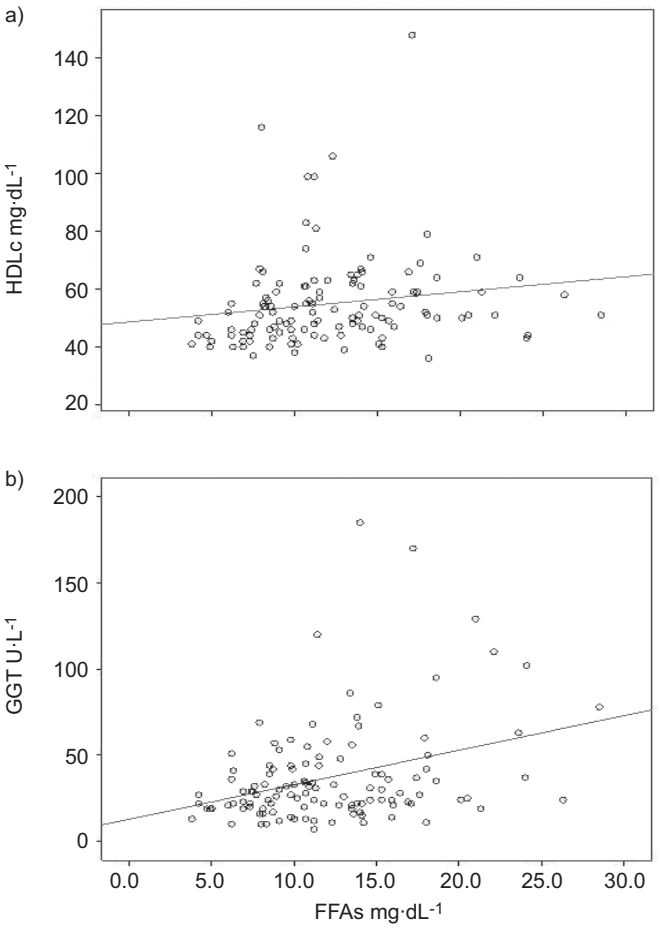

FIGURE 2. Relationship between free fatty acid (FFA) levels and a) high-density lipoprotein/cholesterol (HDLc) (r=0.305, p=0.001) and b) γ-glutamyltransferase (GGT) (r=0.274, p=0.003) in the obstructive sleep apnoea syndrome population studied.

suggest that FFA elevation could be one of the mechanisms involved in the metabolic complications of OSAS patients.

The relationship between OSAS, obesity and the MS is complex and unclear [3].

Prevalence of the MS is higher in OSAS patients than in the general population [14, 15]. However, both OSAS and MS are associated with obesity, which is an important confounder for the independent effects of OSAS on metabolic variables [5, 16]. In our study, the prevalence of the MS was higher in OSAS patients than subjects without OSAS of similar age, sex and BMI, suggesting that OSAS itself is a risk factor for the MS. The MS is associated with increased risk for cardiovascular events, diabetes and non-alcoholic fatty liver disease [17–19]. The high prevalence of the MS in OSAS patients raises the possibility that some of the complications associated with the MS may be attributable to OSAS. In this sense, recent observations have shown that obstructive sleep apnoea has an incremental effect on markers of atherosclerosis in patients with metabolic syndrome [20].

The search for additional factors that may contribute to better a understanding of the links between OSAS and the MS is highly desirable. In this study, we evaluated whether FFAs may play a role in the development of the MS in OSAS.

Experimental studies in healthy subjects have demonstrated that an elevation in FFAs induces insulin resistance [21] . In addition, increased levels of FFAs in obese subjects were reported to contribute in the development of various disturbances related to the MS, such as insulin resistance, hypertension, dyslipidaemia and others [10, 11, 22].

Increased FFA supply in the liver is an initial step for the development of the characteristic disorders of the MS [12]. FFAs are released principally from adipose tissue through lipolysis of triglycerides [23]. Release of FFAs is regulated by the action of insulin and modulated by adrenergic activity [23, 24]. FFA concentrations are higher in obese individuals [8]. Nevertheless, there appears to be limited interindividual variability in plasma FFAs levels between people with similar BMI [10]. In our study, despite the similar anthropometric characteristics between OSAS and controls, FFAs were higher in the OSAS group, suggesting a high FFA flux originating from lipolysis in adipose tissue in these patients.

There are several mechanisms that support a relationship between OSAS and a dysfunctional adipose tissue, such as increased sympathetic activity, oxidative stress or adipose tissue inflammation [25–28] . Compared with controls subjects,

OSAS patients showed abnormal plasma levels of markers of inflammation and oxidative stress, such as CRP and 8-isoprostanes levels. However, these differences were independent of the presence of the MS. In our study, FFA levels were higher in OSAS patients without MS than in controls without MS. By contrast, despite the fact that FFA levels were higher in OSAS patients with MS than in controls with MS, the difference did not reach statistical significance. It is possible that the high variability in FFAs levels detected both in controls and patients with MS may explain the lack of significance.

We found a significant correlation between FFAs levels and AHI and arousal index, suggesting that sleep fragmentation and repetitive arousals may be involved in the FFA release into the circulation. However, the relationships between these mechanisms in OSAS and the regulation of FFAs, and their mediating role between OSAS and the MS needs further investigation. FFAs levels were different between the three groups with severe, moderate and mild OSAS. In OSAS patients without MS, FFA levels were also higher in the severe group than in mild-to-moderate group. Our results are concordant with a study by LAM *et al.* [29]. Those authors found that adipocyte fatty acid-binding protein levels correlated with obstructive sleep apnoea independently of obesity [29]. Multiple linear regression controlling for BMI, sex, age and the presence of MS confirmed an independent association between AHI and FFA levels.

Several lines of evidence support an independent association between OSAS and dysregulation of lipid metabolism [30, 31]. In our study, we observed a relationship between FFAs and HDLc, suggesting that the increased flux of FFAs to the liver may represent an important factor for the presence of dyslipidaemia in patients with OSAS. We speculate that elevated plasma FFAs could be one of the mechanisms involved in the metabolic and cardiovascular complications of OSAS patients.

Limitations

Some potential confounding factors, such as nutritional status, physical activity or the interaction between genetic variants, were not taken into account in our analysis.

Analyses were not adjusted for albumin. Since FFAs travel in serum bound to albumin, this may affect the results [32].

Increases of plasma FFAs cause endothelial dysfunction in healthy subjects [33]. Future studies should examine the role of FFAs using techniques to assess endothelial function and evaluate their long-term effect on the vascular bed in patients with OSAS.

However, we did not measure the levels of FFAs after continuous positive airway pressure treatment. Normalising plasma levels of FFAs levels can be expected to improve insulin resistance and other features of the MS. We think that future studies including these measurements are needed to determine the impact of all these observations on metabolic dysfunction of OSAS patients.

Conclusions

This study shows that FFAs are elevated in OSAS and may play a role in the pathogenesis of the MS in patients with OSAS.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

None declared.

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