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FREE FATTY ACIDS AND THE METABOLIC SYNDROME IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA. [1,2,3,4]

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ABSTRACT

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[4] Running title: FFAs levels in OSAS

Keywords: Sleep apnea, Free fatty acids, Metabolic syndrome

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

Methods: We studied 119 OSAS patients and 119 controls. Participants were recruited and studied at sleep unit of our institution and were matched for gender, age and BMI. The occurrence of the MS was analyzed by clinical criteria. Serum levels of FFAs, glucose, triglycerides, cholesterol, HDL cholesterol, aspartate-aminotransferase, alanine-aminotransferase, gamma-glutamyltransferase, C-reactive protein and 8-isoprostanes were determined.

Results: Prevalence of MS was higher in OSAS than in the control group (38 vs 21%, p= 0.006). OSAS patients had higher FFAs levels than controls (12.2±4.9 vs 10.5±5.0mg/dL, p=0.015). Among subjects without MS, OSAS patients (OSAS+ MS-) showed higher levels of FFAs than controls (OSAS- MS-) (11.6±4.7 vs 10.0± 4.4mg/dL, p=0.04). In a multiple regression model, after adjustment for age, gender, BMI and the presence of metabolic syndrome, FFAs were significantly associated with AHI (p=0.04).

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

Abstract word count: 200

INTRODUCTION

The obstructive sleep apnea syndrome (OSAS) is a common disorder defined by the occurrence of repeated episodes of upper airway obstruction and airflow cessation (apneas) that normally lead to arterial hypoxemia 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 metabolic syndrome 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, other factors 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 suggest an important role of FFAs in the development of insulin resistance and various disturbances related to metabolic syndrome [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 the MS, there exist no studies investigating the relationship between FFAs and the MS in OSAS

In this study we hypothesized that FFAs are elevated in OSAS patients independently of obesity, and that this elevation may contribute to the development of the 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. Participants were recruited from subjects who attended our 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 gender, age (± 5 years) and BMI (± 3 $Kg.m^{-2}$). No participant suffered from any other chronic disease (chronic obstructive pulmonary disease (COPD), 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 hypoglycemic, hypolipemiant 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 signed their 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, electrocardiography, submental and pretibial electromyography, electrooculography, electroencefalography and trancutaneous measurement of arterial oxygen saturation. Apnea was defined by the absence of airflow for more than 10 seconds. Hypopnea was defined as any airflow reduction

that last more than 10 seconds and resulted in arousal or oxygen desaturation. We considered desaturation a decrease in SaO_2 greater than 4%. The apnea-hypopnea index (AHI) was defined as the sum of the number of apneas plus hypopneas per hour of sleep. The case or control status was defined by the AHI threshold of 10 or greater. Patients were classified into three groups according to their AHI as mild OSAS (AHI = 10-20), moderate OSAS (AHI = 21-40) and severe OSAS (AHI >40). Excessive daytime sleepiness (EDS) was quantified subjectively by the Epworth sleepiness scale (ESS).

The occurrence of the MS was analyzed according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) clinical criteria: (1) waist circumference ≥ 102 cm in men and ≥ 88 cm in women, (2) fasting glucose ≥ 100 mg/dL or patient on specific drug treatment, (3) triglycerides ≥ 150 mg/dL or patient on specific treatment, (4) HDL cholesterol (HDLc) <40 mg/dL in men and < 50 mg/dL in women or patient on specific drug treatment, (5) systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or patient on specific drug treatment. The MS was diagnosed if 3 of these 5 factors were present.

After fasting overnight, venous blood samples were obtained between 8 and 10 am. Blood was centrifuged and serum was immediately separated in aliquots and stored at –80ºC until analysis.

Glucose, triglycerides, total cholesterol, HDL cholesterol (HDLc), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT), uric acid and FFAs were determined by standard enzymatic methods on a Hitachi Modular analyzer (Roche Diagnostics, Indianapolis, USA). The plasma concentration of hs-C-reactive protein (hs-CRP) was measured

by a commercial chemiluminiscent assay on a Immulite 2000 analyzer (Siemens Medical Solutions Diagnostics, NY, USA). 8-isoprostanes were measured with 8-isoprostane EIA kit (Cayman Chemicals Company, USA)

Statistical analysis

Results are presented as percentages, median or mean ± standard deviations. 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 apnea on FFAs we used a multiple regression analysis, including all subjects, with study group, age, gender, BMI, and AHI as the independent variables, and FFAs as the dependent variable.

The study was powered not to miss a difference of 2.0 mg/dL in FFAs assuming a within subject SD 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 lower than 0.05 was considered significant.

RESULTS

Characteristics of the study population are summarized in Table 1. By design, gender, 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. Table 3 and 4 showed these parameters according to the presence or absence of the MS.

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

FFAs plasma levels 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).

In the OSAS group, FFAs levels were significantly related to AHI (r= 0.210, p= 0.026) and to the arousal index (r=0.236, p= 0.010), (Figure1, panels a and b, respectively). FFAs were also significantly related to GGT (r= 0.274, p= 0.003) and HDL cholesterol levels (r= 0.305, p= 0.001), (Figure 2, panels a and b, respectively). Associations between FFAs levels and nocturnal oxygenation indices did not reach the statistical level of significance (mean and minimum oxygen saturation: r= 0.189, p= 0.083; and r= 0.139, p=0.141 respectively).

In a multiple regression model after adjustment for age, gender, BMI, and the presence of metabolic syndrome 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) than in the moderate (11.4 ± 4.2 mg/dL, p< 0.004) and the mild OSAS group (10.5 ± 4.0, p< 0.004).

In OSAS without metabolic syndrome, FFAs were higher in the severe group (12.4±5.0 mg/dL) than in the mild to moderate group (11.0 ±4.1 mg/dL, 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 HDL cholesterol (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 metabolic syndrome 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, gender and BMI, suggesting that OSAS itself is a risk factor for the MS; *(2)* FFAs are elevated in patients with OSAS;*(3)* AHI is independently associated with FFAs levels. These observations suggest that FFAs 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]. On the other hand, 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, gender 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 apnea has an incremental role on markers of atherosclerosis in patients with metabolic syndrome [20].

The search for additional factors that may contribute to better understand 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 metabolic syndrome such as insulin resistance, hypertension, dyslipidaemia and others [10;11;22].

Increased FFAs supply of the liver is an initial step for the development of the characteristic disorders of the metabolic syndrome [12]. FFAs are released principally from adipose tissue through lipolysis of triglycerides [23]. Release of FFAs is regulated by action of insulin and modulated by adrenergic activity [23;24]. FFAs concentrations are higher in obese individuals [8]. Nevertheless, there appears to be limited inter-individual 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 FFAs 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 to controls subjects, OSAS patients showed abnormal plasma levels of inflammation markers and oxidative stress such as hs-C reactive protein and 8-isoprostanes levels. However these

differences were independent of the presence of the MS. In our study FFAs levels were higher in OSAS patients without MS than in controls without MS. By contrast, despite the fact that FFAs 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 FFAs 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 metabolic syndrome needs further investigation. FFAs levels were different between the three groups with severe, moderate and mild OSAS. In OSAS patients without MS, FFAs levels were also higher in the severe group than in mild to moderate group. Our results are concordant with a study from Lam et al. These authors have found that adipocyte-fatty acid binding protein levels correlated with obstructive sleep apnea independently of obesity [29]. Multiple linear regression controlling for BMI, gender, age and the presence of metabolic syndrome confirms an independent association between AHI and FFAs 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 HDL cholesterol 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 FFASs 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. Analysis were not adjusted for albumin. Since FFAs travel in serum bound to albumin, this may interact with 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.

On the other hand we did not measure the levels of FFAs after CPAP treatment. Normalizing plasma levels of FFAs levels can be expected to improve insulin resistance and others 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 metabolic syndrome in patients with obstructive sleep apnea. OSAS.

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Table 1. Subject characteristics

	Controls (n=119)	OSAS (n=119)	p value
Age (years)	45 ± 11	46 ± 12	0.635
Men (%)	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
Metabolic Syndrome (%)	21 %	38 %	0.006
AHI ($hour^{-1}$)	3.2 (1.8-4.5)	39 (23.2-53.5)	< 0.001
Arousal index ($hour^{-1}$)	22 ± 13	47 ± 18	< 0.001
Mean Sat O_2 (%)	94±3	93 ± 2	< 0.001
Minimal Sat O_2 (%)	86±9	83±8	0.061
Epworth scale	7 (5-10)	11 (6-14)	< 0.001

Table 2. Metabolic and biochemical markers

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

Table 3. Metabolic and biochemical markers in patients and controls with MS

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

Table 4. Metabolic and biochemical markers in patients and controls without MS

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

FIGURE LEGEND

Figure 1: Relationship between FFAs levels and apnea-hypopnea index (panel a) and arousal index (panel b) in the OSAS population studied.

Figure 2: Relationship between FFAs levels and HDL cholesterol (panel a) GGT (panel b) in the OSAS population studied.

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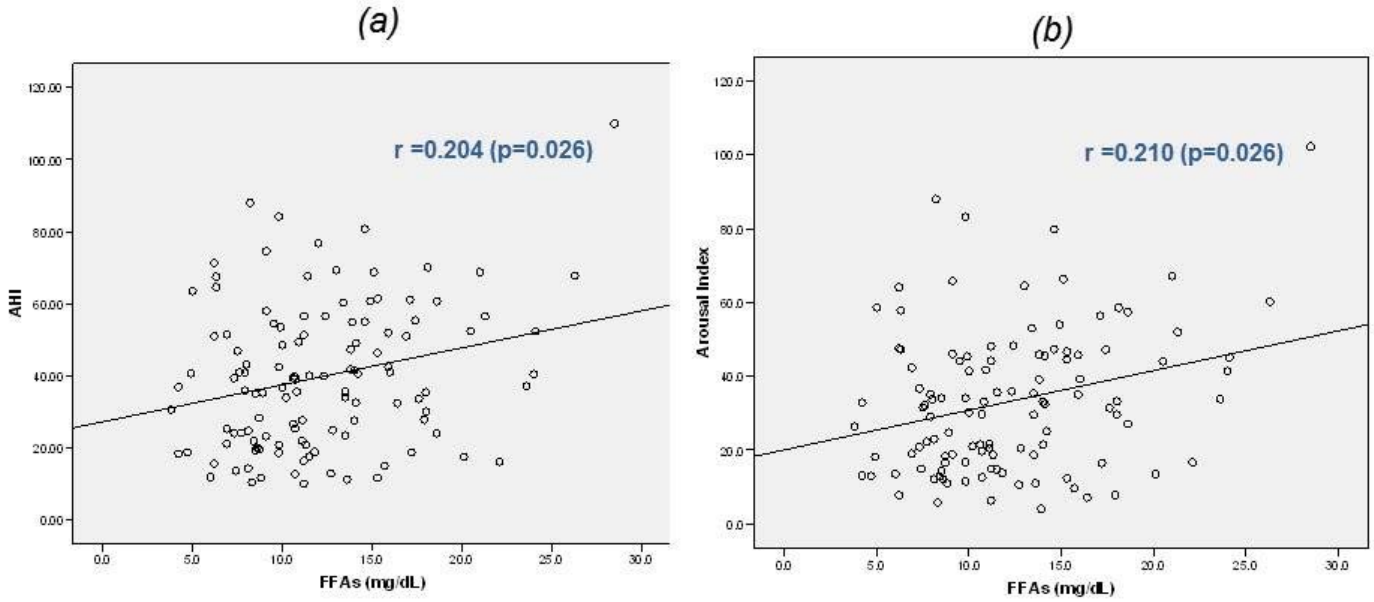
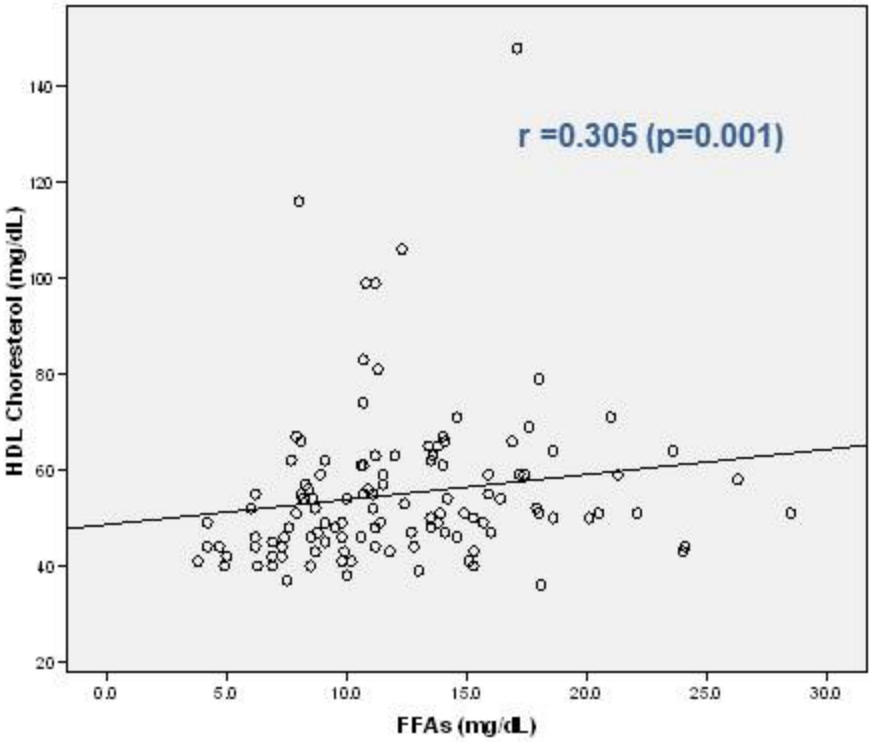
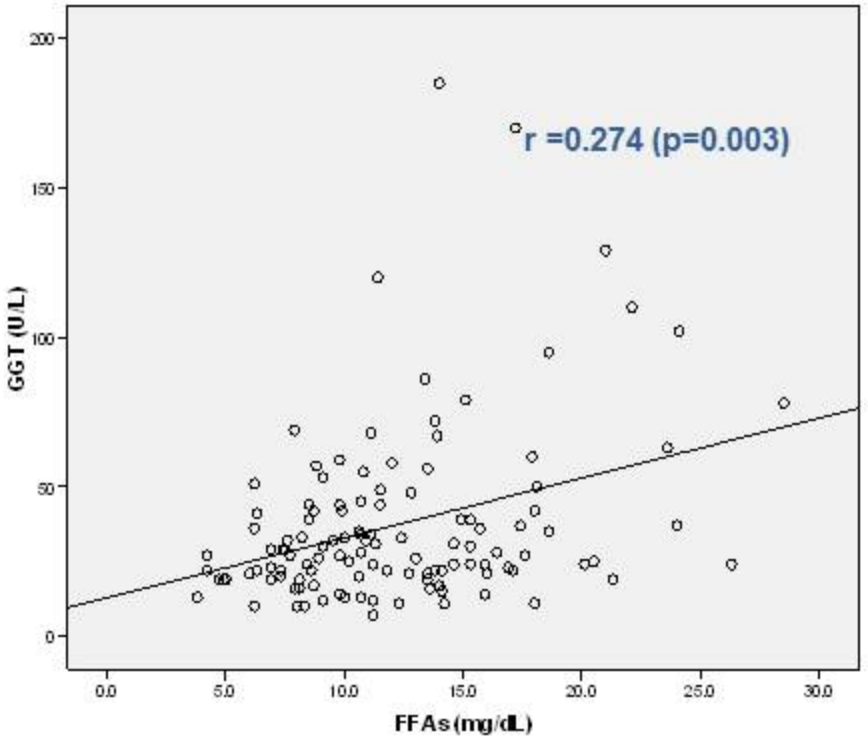

(a)
r =0.204 (p=0.026)
AHI
FFAs (mg/dL)
(b)
r =0.210 (p=0.026)
Arousal Index
FFAs (mg/dL)

(a)


r =0.305 (p=0.001)
HDL Choresterol (mg/dL)
FFAs (mg/dL)
20
40
60
80
100
120
140
0.0
5.0
10.0
15.0
20.0
25.0
30.0

(b)


r =0.274 (p=0.003)
GGT (U/L)
FFAs (mg/dL)
0
50
100
150
200
0.0
5.0
10.0
15.0
20.0
25.0
30.0