Original Article

Betatrophin association with serum triglyceride levels in obstructive sleep apnea patients

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Abstract:

BACKGROUND: Obstructive sleep apnea (OSA) is a common sleep problem, in which patients are at increased risk for metabolic and cardiovascular problems, including metabolic syndrome, diabetes mellitus (DM), and dyslipidemia. Betatrophin is a novel protein that regulates fatty acid and triglyceride (TG) metabolism and is related to obesity and metabolic abnormalities, including metabolic syndrome, DM, and dyslipidemia. Although OSA and betatrophin share common abnormalities, their relationship has not been investigated.

AIM: The aim of this study is to investigate the relationships among betatrophin, OSA, and the serum lipid profile.

METHODS: Ninety consecutive patients with suspected OSA underwent polysomnography (PSG) to confirm OSA. Plasma betatrophin, leptin, adiponectin, and the full lipid profile were analyzed. The patients were categorized as OSA or control based on the apnea-hypopnea index (AHI).

RESULTS: About 61% of patients had OSA, and 39% had normal PSG. The levels of betatrophin, leptin, and adiponectin were higher in patients with OSA (256.59 ± 29.35, 374.20 ± 37.93, and 17.86 ± 2.63 µg/mL, respectively) compared to the controls (141.86 ± 26.20, 205.53 ± 14.75, and 7.52 ± 1.02 µg/mL, respectively). Betatrophin levels were correlated with the AHI, leptin ($r = 0.413$, $P = 0.002$, $r = 0.782$, $P = 0.000$). TG levels were significantly higher, and high-density lipoprotein cholesterol (HDL-C) levels were lower, in OSA patients compared to controls (244 ± 20.33 vs. 138 ± 14.89, and 37.21 ± 1.26 vs. 43.78 ± 1.62, respectively). The TG level was correlated with betatrophin ($r = 0.353$, $P = 0.013$). Multiple regression analysis showed that the AHI, leptin, and arousals were independent predictors of betatrophin level (B = 1.70 $P = 0.046$ 95%, B = 0.56 $P < 0.005$, and B = 1, 2, $P = 0.003$, respectively).

CONCLUSIONS: Our results suggest a complex relationship between OSA, betatrophin, TG, and HDL, as well as other adipokines. Our results require further investigation to assess this complex association and re-evaluate previous related studies.

Keywords:
Apnea hypopnea index, betatrophin, sleep apnea, triglycerides

Obstructive sleep apnea (OSA) is a common chronic sleep-related disorder. It is characterized by repeated apnea, hypopnea, arousals, and intermittent hypoxemia during sleep that leads to oxidative stress, sympathetic activation, and inflammation.[1,2] Patients with OSA

have increased risks for metabolic and cardiovascular problems, including diabetes mellitus (DM) and serum lipid abnormalities. Betatrophin, also known as lipasin/RIFL/ANGPTL8, is a newly discovered protein mostly expressed in white/brown adipose tissues and the liver in humans. An increasing number of studies have shown a relationship

among obesity, DM, and abnormalities in serum lipid profiles.[3-5] Betatrophin interacts with ANGPTL3 and lipoprotein lipase (LPL) to regulate fatty acid and triglyceride (TG) metabolism.[6] Serum betatrophin may regulate nutritional status, as it increases after a meal in humans.[7]

The major adipokines, leptin, and adiponectin, which exert clinical and metabolic effects on adipose tissue, have shown differential associations in patients with OSA. Leptin increases with obesity and insulin resistance, and in response to hypoxia. Adiponectin is inversely associated with obesity and insulin resistance and increases in response to continuous positive airway pressure (CPAP) therapy in patients with OSA.[8,9] Conflicting reports point toward a complex association between OSA and adipokines. Little is known about the association between adipokines and serum lipid levels. Although OSA and betatrophin are related to serum lipid abnormalities, the associations among OSA betatrophin, and serum lipid levels have not been evaluated. We investigated the associations among OSA, betatrophin, and the serum lipid profile, as well as leptin and adiponectin, in patients with OSA and control subjects.

Methods

Patients
This prospective study enrolled 90 patients who were admitted to the sleep center of the Pulmonary Department of the University Medical Center with suspected OSA for polysomnography (PSG). PSG was performed between January 2014 and August 2015, and patients were selected consecutively. Health-related and demographic data, including age, sex, Epworth sleepiness scale score, Body Mass Index (BMI), and medical history were collected. Patients with metabolic diseases, including DM, metabolic syndrome, or cardiovascular, renal, or hepatic diseases were excluded from the study. The control group consisted of 35 individuals who were diagnosed with simple snoring. The local Ethics Committee approved this study protocol and written informed consent was obtained from all patients.

Measurement of laboratory parameters
After PSG and a 12 h fasting period, morning blood samples were drawn from the antecubital vein of patients to measure lipid parameters. The blood was centrifuged at 2400 × g for 5 min, and the serum was stored at −80C. Fasting plasma betatrophin, adiponectin, and leptin levels were measured by commercially available enzyme-linked immunoassay kits (Hangzhou Eastbiopharm Co. Ltd., Hangzhou, China). Total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, and TG concentrations were measured by spectrophotometric assay with a commercial auto-analyzer (Architect Ci 6400; Abbott Laboratories, Chicago, IL, USA).

Polysomnography
Full night PSG was performed with a 16-channel Embla recording system (Medcare Inc., Reykjavik, Iceland) and continuous monitoring by a sleep technician. The system was comprised of four electroencephalogram channels (electrode placements at O1-A2, O2-A1, C4-A1, and C3-A2), submental electromyography (EMG), two electrooculography channels, oronasal airflow (nasal aperture), oxygen saturation, abdominal and thoracic movement, tibial EMG, electrocardiogram, a body position detector, and a tracheal sound detector. Sleep-disordered breathing events were scored manually by the same examiner according to the criteria of the American Academy of Sleep Medicine 2012. Complete cessation of airflow lasting more than 10 s was defined as apnea. A >30% decline in airflow for more than 10 s, accompanied by >4% desaturation, was defined as hypopnea. The average numbers of apnea and hypopnea episodes per hour of sleep were measured and compared with the apnea-hypopnea index (AHI). The OSA was determined by an AHI >5. Sleep stages were scored with standard criteria, and 30-s epochs were followed, verified, and reviewed by a certified sleep physician.

Statistical analysis
SPSS for Windows software (version 17.0; SPSS Inc., Chicago, IL, USA) was used for all analyses, and a value of $P < 0.05$ was accepted as significant. Data of continuous variables are presented as means ± standard deviation for normally distributed data and as median (interquartile range) for nonnormally distributed variables. The Kolmogorov–Smirnov test was run to assess the data distributions. The patients with OSA and control subjects were compared by Student's *t*-test or by Wilcoxon's test for nonnormally distributed variables. Spearman's correlation or Pearson's correlation was used to determine the associations among betatrophin, adiponectin, leptin, anthropometric measurements, and biochemical variables. A multiple linear regression analysis was used to determine whether age, sex, the AHI, BMI, leptin, arousals, mean SpO_2, minimum SpO_2, and adiponectin had independent effects on betatrophin levels.

Results

The characteristics of the population are listed in Table 1. The study contained 90 patients, 55 of whom had OSA; the remaining 35 were controls. The average age of the patients was 44 ± 1.53 years for the OSA group and 42 ± 1.89 years for the control group ($P > 0.05$). The patients with OSA had a significantly higher

Table 1: Anthropometric, sleep study and laboratory parameters characteristics of obstructive sleep apnea and control subjects

	OSA (*n*=55)	Control (*n*=35)	P
Age (years)	44.44±1.53	42.14±1.89	0.346
Weight (kg)	92.80±2.40	86.13±3.08	0.09
Height (cm)	169.70±1.30	170.66±1.47	0.637
BMI (kg/m^2)	32.4±6.7	29.5±5.5	0.087
Waist (cm)	103.93±3.26	98.72±2.26	0.234
Epwoth's scale	11.70±4.39	7.53±3.48	0.032
TST (h)	6.1±0.5	5.9±0.7	0.05
AHI (/h)	13.50 (6.35-28.22)	1.8 (1.2-3.7)	0.001
Arousol index	19.1 (11.8-20.04)	4.1 (2.7-8.5)	0.001
Minimum SpO$_2$	85 (83-90)	90 (87-94)	0.001
Mean SpO$_2$	93 (92-95)	96 (94-98)	0.001
Stage 3 (percentage TST)	8.4±1.3	20±1.9	0.03
REM (percentage TST)	9.7±1.5	18±3.1	0.04
TG (mg/dL)	193 (138-303)	117 (100-163)	0.001
HDL-C (mg/dL)	33 (27-42)	42 (36-52)	0.002
LDL-C (mg/dL)	121±6.67	125±6.97	0.688
Glucose (mg/dl)	102.87±2.77	95.03±2.001	0.038
Insulin (mIU/L)	13.94±1.43	14.77±2.47	0.76
HOMA-IR	3.43±0.23	3.27±0.33	0.697
Total cholesterol (mg/dL)	205.29±9.52	193.35±6.90	0.354
Adiponectin (µg/ml)	17.86±2.63	7.52±1.02	0.004
Leptin (µg/ml)	256 (225-526)	199 (159-222)	0.002
Betatrophin (µg/ml)	256.59±29.35	141.86±26.20	0.001

HOMA-IR = Homeostasis model assessment of insulin resistance, HDL-C = High density lipoprotein cholesterol, LDL-C = Low density lipoprotein cholesterol, TG = Triglycerides, OSA = Obstructive sleep apnea, TST = Total sleep time, BMI = Body mass index, AHI = Apnea hypopnea index, REM = Rapid eye movement
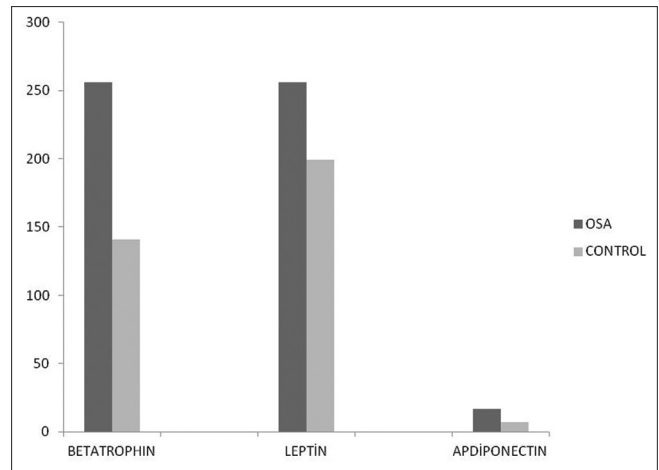

Figure 1: The serum levels of betatrophin, leptin adiponectin in obstructive sleep apnea and controls
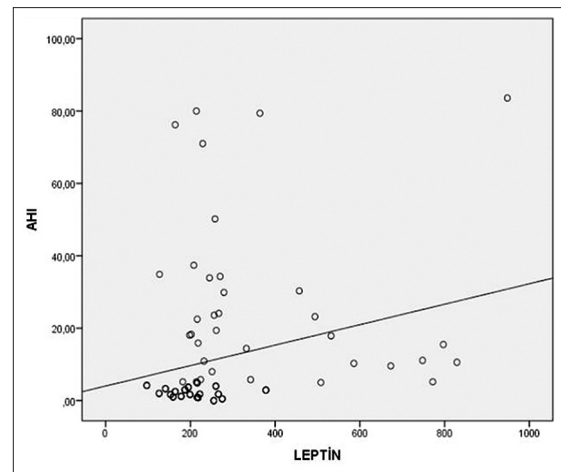

Figure 2: The correlation between serum adiponectin levels and apnea hypopnea index index (*r* = 0.280, *P* = 0.041)
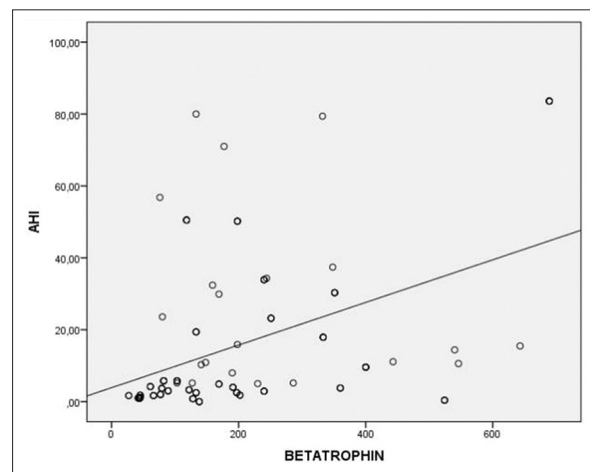

Figure 3: The correlation between serum betatrophin levels and apnea hypopnea index index (*r* = 0.413, *P* = 0.002)

AHI, arousals, and lower mean SpO$_2$ and minimum SpO$_2$ (all *P* < 0.01). The betatrophin level was higher in the patients with OSA (256.59 ± 29.35 µg/mL) compared to the controls (141.86 ± 26.20 µg/mL) [Figure 1]. The leptin level was also higher in the patients with OSA (374.20 ± 37.93 µg/mL) compared to the controls (205.53 ± 14.75 µg/mL), as was the level of adiponectin (17.86 ± 2.63 µg/mL vs. 7.52 ± 1.02 µg/mL, respectively). In addition, the TG level was significantly higher in patients with OSA compared to the controls (244 ± 20.33 vs. 138 ± 14.89, respectively). In contrast, the HDL-C level was significantly lower in the patients with OSA compared to the controls (37.21 ± 1.26 vs. 43.78 ± 1.62, respectively) [Table 1]. Betatrophin levels were positively correlated with the AHI (*r* = 0.413, *P* = 0.002) [Figure 2], and leptin levels (*r* = 0.782, *P* = 0.000). TG levels were correlated with betatrophin levels (*r* = 0.353, *P* = 0.013). Leptin was positively correlated with the AHI (*r* = 0.280, *P* = 0.041) [Figure 3], betatrophin (*r* = 0.782, *P* = 0.000), adiponectin (*r* = 0.542, *P* = 0.000), TG (*r* = 0.296, *P* = 0.037), and the arousal index (0.363 *P* = 0.003), and HDL-C levels were negatively correlated with leptin levels (*r* = −0.278, *P* = 0.044). Adiponectin was positively correlated with leptin (*r* = 0.542, *P* = 0.000), the arousal index (*r* = 0.351 *P* = 0,001), and the AHI

(r = 0.288, P = 0.027) [Figure 4 and Table 2]. A multiple regression analysis showed that AHI, leptin, and arousals were independent predictors of the betatrophin level (B = 1.70 P = 0.046, B = 0.56 P < 0.005, B = 1.2, P = 0.003, respectively). Betatrophin and adiponectin were independent predictors of leptin (B = 1 P < 0.005 95% confidence interval [CI] =0.7–1, 2, B = 4.9 P = 0.001 95% CI = 2.3–7.5), and leptin and BMI were independent predictors of adiponectin (B = 0.04 P < 0.005 95% CI = 0.03–0.6, B = −0.7 P = 0.043 95% CI = −1.5 to − 0.27).

Discussion

The main observation in this study was that betatrophin levels were significantly higher in patients with OSA
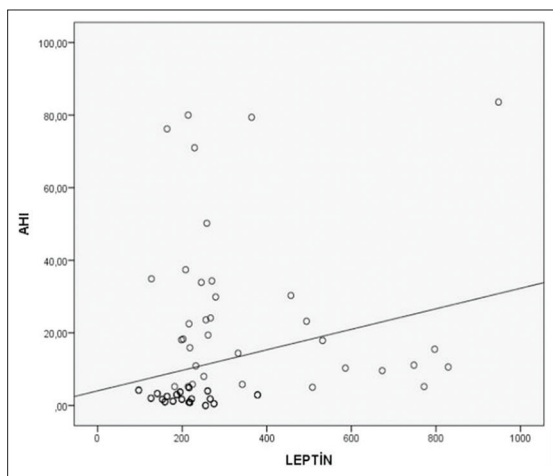

Figure 4: The correlation between serum leptin levels and apnea hypopnea index index (r = 0.288, P = 0.027)

Table 2: Correlations of betatrophin, leptin and adiponectin with clinical parameters and polysomnographic variables

	Betatrophin	Adiponectin	Leptin
BMI (kg/mm²)	0.096 (0.500)	−0.162 (0.220)	0.041 (0.771)
Age (years)	0.038 (0.793)	0.100 (0.458)	0.052 (0.712)
Adiponectin (µg/ml)	0.297 (0.050)	1.000	0.542** (0.000)
Leptin (µg/ml)	0.782** (0.000)	0.542** (0.000)	1.000
Betatrophin (µg/ml)	1.000	0.297(0.05)	0.782** (0.000)
AHI (per/h)	0.413** (0.002)	0.288*(0.027)	0.280* (0.041)
LDL-C (mmol/L)	−0.044 (0.759)	−0.093 (0.486)	−0.066 (0.640)
HDL-C (mmol/L)	−0.244 (0.081)	−0.190 (0.153)	−0.278* (0.044)
TG (mmol/L)	0.353* (0.013)	0.196 (0.151	0.296* (0.037)
Total cholesterol (mmol/L)	0.043 (0.765)	−0.020 (0.88)	−0.060 (0.674)
Arousol index	0.147 (0.228)	0.351** (0.001)	0.363* (0.003)
Minimum SpO₂	−0.23 (0.19)	−0.11 (0.2)	−0.16 (0.1)
Mean SpO₂	−0.21 (0.2)	−0.11 (0.2)	0.8 (0.2)

*Correlation is significant at the 0.01 level, **Correlation is significant et the 0.05 level. AHI = Apnea hypopnea index, HDL-C = High density lipoprotein cholesterol, LDL-C = Low density lipoprotein cholesterol, TG = Triglycerides, BMI = Body mass index

than controls. Pearson's correlation analysis revealed that betatrophin levels were correlated with the AHI and leptin. Multiple regression analysis showed that AHI, leptin, and arousals were independent predictors of the betatrophin level.

OSA is a common sleep-related breathing disorder characterized by repeated apnea, hypopnea, arousals, and intermittent hypoxemia, which induces oxidative stress and inflammation and activates the sympathetic nervous system. OSA is an independent contributor to the pathogenesis of metabolic and cardiovascular disorders, including serum lipid abnormalities, which are related to serum betatrophin level.[1-3,5] Our results revealed increased serum betatrophin levels in patients with OSA compared with controls. A significant positive correlation was detected between serum betatrophin level and the AHI.

Betatrophin is a new member of the ANGPTL family of proteins. Some studies have suggested that this family of proteins plays important roles in metabolic and cardiovascular diseases as well as obesity.[10-13] It is well known that betatrophin has a significant role in lipid metabolism,[3-6,14,15] as it interacts with ANGPTL3 to regulate LPL activity; LPL hydrolyzes TGs by binding to the surface of capillary endothelial cells, and TG is taken up by peripheral tissues. Overexpression of betatrophin leads to increased serum TG, while knockout reduces fatty acid uptake by adipose tissues and increases LPL activity.[4,15] Studies have shown lower serum TG levels in betatrophin-null mice in response to refeeding, and a significant relationship was detected between betatrophin level and the atherogenic lipid profile.[16-18] Ambrosi *et al*. reported that betatrophin levels were significantly lower in dyslipidemic subjects with higher TG and lower HDL-C levels.[19] Some studies have suggested elevated dyslipidemia in OSA cases.[20-22] A meta-analysis that included 18,116 subjects (control n = 10,145, OSA n = 7,071) showed that TG and HDL abnormalities were correlated with the AHI.[23] The study revealed an increase in both betatrophin and TG levels in patients with OSA and a significant positive correlation between them. Betatrophin and HDL-C tended to be negatively correlated in our study. Low HDL-C levels and high TG levels are characteristic features of atherogenic dyslipidemia.[24] Our results also suggest that betatrophin has a role in the atherosclerotic process, along with other adipokines, in patients with OSA. We speculate that high levels of betatrophin have a central role in dysregulating serum lipid levels. An elevated betatrophin level may indicate the development of serum lipid abnormalities. Thus, the betatrophin level is an important target marker for diagnosing and treating dyslipidemia in patients with OSA.

Leptin and adiponectin are major adipocytokines. Some studies have reported conflicting results regarding the

association between adiponectin, leptin levels, and OSA, suggesting complexity in the associations among OSA, obesity, and adipocytokines.[25-27] Plasma leptin is high, and adiponectin is low, in obese patients. Leptin was the first adipocytokine to be associated with OSA. In the majority of studies, leptin levels were higher in patients with OSA independent of BMI and OSA severity, compared to BMI-matched non-OSA controls.[28,29] The study showed high leptin levels in OSA cases compared with controls. Leptin was also positively correlated with the AHI. TG level was positively correlated, and HDL-C level was negatively correlated, with leptin. There are conflicting results regarding the relationship between adiponectin and OSA. Some studies have found lower levels of adiponectin in patients with OSA, whereas others have not.[26,30] The study showed an elevated adiponectin level in OSA cases, compared with the controls. Adiponectin level was also correlated with the AHI, arousal index, and leptin level.

CPAP therapy can correct serum lipid abnormalities. However, some studies have reported inconsistent results due to the heterogeneous characteristics of the study population, small size of the study population, short follow-up duration, or insufficient treatment adherence.[7,31] A large, randomized, controlled study with better treatment adherence would likely show the expected results. Future CPAP treatment studies should investigate serum lipid and betatrophin levels simultaneously.

Our study had potential limitations. First, our sample size was small, and we did not investigate the effects of CPAP treatment on serum betatrophin or lipid levels.

Conclusions

We showed that betatrophin levels were higher, correlated with the AHI, and had important effects on serum TG levels in patients with OSA. The results suggest a complex relationship between betatrophin and serum lipid levels, particularly TG and HDL-C, as well as with the AHI, leptin, and adiponectin. These results require further studies for validation and a re-evaluation of previous studies.

Conflicts of interest
There are no conflicts of interest.

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