original article

Serum levels of γ-glutamyl transferase are associated with cardiovascular disease in obstructive sleep apnea syndrome

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BACKGROUND AND OBJECTIVES: Obstructive sleep apnea syndrome (OSAS) significantly increases the risk of cardiovascular disease (CVD). γ-glutamyl transferase (GGT) is a new marker for predicting CVD. The aim of this study was to evaluate the relationship of serum GGT levels with cardiovascular event, severity of OSAS, and polysomnographic parameters in patients with OSAS.

DESIGN AND SETTINGS: This was a retrospective, cross-sectional study conducted between January 2011 and March 2013 (Gaziosmanpasa University, Faculty of Medicine, Tokat, Turkey).

METHODS: We performed a retrospective study. Patients were divided according to their apnea-hypopnea index (AHI) scores into OSAS negative (AHI< 5, Group 1), mild OSAS (AHI: 5-15, Group 2), moderate OSAS (AHI=15-30, Group 3), and severe OSAS (AHI > 30, Group 4) groups. The presence of heart failure, coronary artery disease, or arrhythmia was defined as CVD.

RESULTS: A total of 320 patients, with a mean age of 50.2 (10.8) years, were included in this study. There were 47, 68, 58, and 147 patients in Groups 1, 2, 3, and 4, respectively. Serum GGT levels were significantly different between groups (Group 1: 25.24 [14.95]; Group 2: 28.03 [11.92]; Group 3: 32.82 [18.18], and Group 4: 40.41 [31.90] mg/dL , *P*<.001). Besides, serum GGT levels were significantly correlated with AHI, oxygen desaturation index, and average and minimum O2 saturation values (*P*<.05). Serum GGT levels were significantly higher in patients with CVD compared with those without (*P*<.05). Multiple regression analysis demonstrated that independent predictors of CVD were serum GGT and low-density lipoprotein-cholesterol levels, age, and body mass index in patients with OSAS.

CONCLUSION: GGT level is an important predictor for CVD in patients with OSAS. The effectiveness of continuous positive airway pressure therapy on CVD and GGT levels should be investigated.

Obstructive sleep apnea syndrome (OSAS), characterized by repetitive complete or partial upper airway collapses occurring during sleep, is a common disorder affecting 4% of men and 2% of women in the general population.[1] The health impact of obstructive sleep apnea is enormous. OSAS significantly increases the risk of cardiovascular diseases (CVDs) and disorders, including hypertension, heart failure, arrhythmias, and coronary artery diseases.[2-4] Chronic intermittent hypoxia, sympathetic activation, inflammation, oxidative stress, and endothelial dysfunction are frequently seen in sleep apnea syndrome and may constitute etiologic mechanisms, linking OSAS to CVD.[5,6]

γ-glutamyl transferase (GGT) is a glycoprotein found predominantly in hepatocytes, and to a lesser extent in plasma membranes of vascular endothelium and also of cells and tissues of various organs as kidney and pancreas.[7,8] In addition to being a sensitive marker of hepatic inflammation, correlation between increases in serum GGT levels, and cardiac mortality, and nonfatal myocardial infarction has been demonstrated in various studies.[9,10] Still important roles played by GGT in the antioxidant system have been suggested, and increased serum GGT activity in human beings has been proposed as a potentially useful marker of enhanced oxidative stress.[11]

Based on this information, the aim of the study was to evaluate the correlation between serum GGT levels and cardiovascular events in patients with OSAS. We also investigated the correlations between serum levels of GGT, and the severity of OSAS polysomnographic (PSG) parameters, and the levels of serum alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and cholesterol subtypes.

METHODS

Subjects

We performed a retrospective evaluation of the patients studied in our sleep disorders center (Gaziosmanpasa University, Faculty of Medicine, Tokat, Turkey). The patients were selected sequentially. From file archives arranged according to the order of the referrals to our sleep laboratory, polysomnography records, medical reports, and other medical information were obtained. Polysomnographic (PSG) tests of all the patients were performed in the same unit and scored by the same physician. Patients were categorized as cases with OSAS negative (apnea-hypopnea index [AHI] <5, Group 1), mild OSAS (AHI: 5-15, Group 2), moderate OSAS (AHI=15-30, Group 3), and severe OSAS (AHI > 30, Group 4) according to the American Academy of Sleep Medicine (AASM) Task Force criteria.[12] Apart from OSAS, patients with central sleep apnea syndrome, upper airway resistant syndrome, and narcolepsy or movement disorders were excluded from the study. Patients with chronic alcoholism, chronic liver disease, hepatobiliary disease, viral hepatitis, elevated liver enzymes, lung disease characterized by hypoxemia, such as chronic obstructive pulmonary diseases, interstitial lung disease, asthma, were also excluded. Data related to demographic characteristics, sleep, and medical history, including cardiovascular and metabolic diseases, medication use, and habits, were obtained using a standardized questionnaire before the sleep study. Routine blood tests (fasting blood glucose, liver enzymes, lipid profile) and respiratory function tests were performed. As for the purpose of the study the term "cardiovascular disease" referred only to the presence of heart failure, coronary artery disease, or arrhythmia. The diagnosis of CVD had been made by a physician. As a medical treatment, the patients were receiving 1 or more than 1 antiaggregant, antiischemic agents, beta-blocker, angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and calcium antagonist. Hyperlipidemia was defined as follows: serum low-density lipoprotein-cholesterol (LDL-C) >160 mg/dL, total cholesterol (TC) > 240 mg/dL , triglyceride (TG) >200 mg/dL or high-density lipoprotein-cholesterol (HDL-C) <40 mg/dL.[13] Informed consents were obtained from the patients, and this study was approved by the ethics committee of our university.

Polysomnographic evaluation

Overnight PSG was performed in all patients using a 55-channel polysomnograph (ALICE Sleepware, Philips Respironics, USA, and included the following variables: electrooculograms (2 channels), electroencephalograms (4 channels), electromyograms of the submental muscles (1 channel), anterior tibialis muscle of both legs (2 channels), electrocardiograms, airflow measurements (with oro-nasal thermistor and nasal cannula pressure transducer), changes in the body position during sleep (body position sensor), and snoring vibrations (snore sensor). Chest and abdominal efforts (2 channels) were recorded using piezo-electric belts, and arterial oxyhemoglobin saturation (SaO_2: 1 channel) by pulse oximetry with a finger probe. The recordings were scored according to the standard criteria of AASM. Apnea was defined as ≥90% decrease in the airflow persisting for at least 10 seconds relative to the baseline amplitude. AASM provided 2 definitions for hypopnea. The recommended one is a ≥30% decrease in the airflow amplitude relative to the baseline values with associated ≥4% oxygen desaturation, all sustaining for at least 10 seconds. An alternative definition is formulated as ≥50% decrease in the airflow amplitude relative to the baseline values with associated ≥3% oxygen desaturation or arousal, all sustaining for at least 10 seconds. In our study, hypopnea was determined according to the alternative definition.[14] Arousals were scored according to accepted definitions.[15] AHI was calculated as the number of apneas and hypopneas per hour of sleep. Patients with AHI ≥5 events/h were diagnosed as having OSAS. Oxygen desaturation index (ODI) was defined as the total number of oxyhemoglobin desaturation of ≥4% within ≥10 seconds ≤3 minutes from the immediate baseline, divided by the total sleep time.

Laboratory analysis

Serum GGT levels were measured by the enzymatic calorimetric test, and L-γ-glutamyl-3-carboxy-4-nitroanilide was used as substrate. L-γ-glutamyl-3-carboxy-4-nitroanillidine transfers a γ-glutamyl group to glycylglycine. The amount of 5-amino 2-nitrobenzoate released is in direct proportion with GGT activity in the sample. An increase in the absorbance was measured and determined at 409 nm. For the evaluation of the measurements, COBAS

INTEGRA γ-glutamyltransferase ver. 2 (GGT-2) (Roche Diagnostics GmbH, Mannheim, Germany) diagnostic kit was used. The detection range of the kit was between 3 and 1200 U/L. In our laboratory, the normal reference value of the GGT level for a healthy individual was 5 to 61 U/L.[16]

Statistical analysis

Chi-square tests were used to compare the categorical variables used in the study. In 2×2 tables, Fisher exact chi-square test was used when the expected value was smaller than 5. Categorical data were expressed as count and percentages. Shapiro-Wilks test was used to evaluate whether the distributions of continuous variables were normal. According to continuous variables with normal distribution or not, two independent sample *t* tests and Mann-Whitney U tests were used to compare continuous variables between patients without CVD and patients with CVD groups. According to continuous variables with normal distribution or not, 1-way analysis of variance (ANOVA) and Kruskal-Wallis ANOVA were used to compare continuous variables among diagnosis groups. In 1-way ANOVA for post hoc multiple comparison, lysergic acid diethylamide test was used. Multiple comparisons in Kruskal-Wallis ANOVA were made using Bonferroni test. In 1-way ANOVA or 2 independent sample t tests, continuous variables were expressed as mean (standard deviation) (SD). In Kruskal-Wallis ANOVA and Mann-Whitney U test, continuous variables were expressed as median (interquartile range). According to continuous variables with normal distribution or not, Pearson and Spearman correlation coefficients were used for correlation coefficient between variables. A multivariate logistic regression model was implemented to determine the relationtionship among selected variables and CVD. Significant univariate variables with $P<.10$ and risk factors for CVD were included in the multiple logistic regression analysis. *P* values below .05 were considered statistically significant. Statistical analysis was performed by using commercial software SPSS, vesion 19.0 (SPSS inc., an IBM Co., Somers, NY USA).

RESULTS

The records of 371 patients were evaluated. The patients who had chronic obstructive pulmonary diseases (n=15), asthma (n=18), central sleep apnea (n=1), narcolepsy (n=1), chronic liver disease, chronic alcoholism, or elevated liver enzymes (n=16) were not included in the study. So the results presented herein belong to 320 participants. A total of 273 patients were classified as having OSAS, while 47 patients with an AHI <5 constituted the OSAS negative group.

Demographic and clinical characteristics are presented in **Table 1**. Patients in the severe OSAS group prevalence of CVD and hypertension were statistically significantly higher compared with the moderate and mild OSAS and OSAS negative groups ($P=.005$ for CVD; $P=.019$ for hypertension). PSG study results are shown in **Table 2**. Apnea-hypopnea index, ODI, average oxygen saturation, minimum oxygen saturation, desaturation levels (%), and distribution of sleep stages were significantly different between groups ($P<.001$).

When 4 groups were compared as for biochemical parametres, serum levels of GGT and HDL-C differed significantly between groups ($P<.05$) (**Table 3**). There was no difference between groups with regard to levels of AST, ALT, ALP, LDL-C, TC, and TG. Correlations between PSG and biochemical parameters were evaluated. AHI values were positively correlated with GGT, and negatively correlated with HDL-C levels ($P<.05$). Besides, serum GGT levels were positively correlated with desaturation percentages and ODI values, and negatively correlated with average O2 saturation and minimum O2 saturation values (**Table 4**). There was no correlation between PSG parameters and other biochemical parameters.

The cases were divided into 2 groups as those with or without CVD. Only GGT levels demonstrated a statistically significant intergroup difference (mean GGT values were 44.33 [31.26] U/L and 34.29 [20] U/L in patients with and without CVD, respectively ($P=.003$)]. Serum GGT levels in patients with and without CVD in study groups demonstrated in **Figure 1**.

The median value of GGT was 32 U/L. In 41 (68.3%) of 66 cases with CVD, the GGT value was >32 U/L. However, in cases with GGT values of >32 and <32 U/L, CVD was seen at a rate of 25.9 and 15.4%, respectively ($P=.020$).

Potential determinants for the CVD were investigated. The final regression model analyzed the variables as age, body mass index (BMI), AHI, ODI, serum GGT, and LDL-C levels. The independent predictors of CVD were age, BMI, and serum GGT and LDL-C levels in patients with OSAS (**Table 5**).

DISCUSSION

The most important outcomes of this study where serum GGT levels were investigated are the detection of significantly higher levels of GGT in OSAS patients with CVD relatively to those without, and a significant correlation between the AHI, which is the indicator of severity of OSAS, hypoxemia, and GGT levels.

Table 1. Demographic and clinical characteristics of the study group.

	Group 1 OSAS negative (n=47)	Group 2 Mild OSAS (n=68)	Group 3 Moderate OSAS (n=58)	Group 4 Severe OSAS (n=147)	*P*
Age (y)[a]	44.89 (11.2)[b]	50.94 (8.84)	50.33 (11.43)	51.47 (10.97)	.003
Gender, male, n (%)	16 (34)	45 (66.2)	44 (75.9)	111 (75.5)	<.001
BMI (kg/m^2)[a]	28.91 (4.66)[c]	30.21 (4.74)	31.84 (5.731)	35.15 (7.26)	<.001
Medical History					
Hypertension, n (%)	8 (17)	14 (20.6)	18 (31)	54 (36.7)d	.019
Diabetes mellitus, n (%)	4 (8.5)	14 (20.6)	7 (12.1)	24 (16.3)	.293
CVD, n (%)	3 (6.4)	11 (16.2)	10 (17.2)	42 (28.6)d	.005
Hyperlipidemia, n (%)	18 (39.1)	24 (35,3)	26 (44.8)	71 (48.3)	.303
Smoking, n (%)	10 (21.3)	12 (17.6)	13 (22.4)	34 (23.1)	.836

BMI: Body mass index, CVD: cardiovascular disease.

[a]Mean (standard deviation); Multiple comparison test results: [b]There were statistically significant differences from Group 2, Group 3, Group 4. [c]There was statistically significant difference from Group 4. [d]There were statistically significant differences from Group 1, Group 2, Group 3.

Table 2. Polysomnographic findings.

	Group 1 OSAS negative (n=47)	Group 2 Mild OSAS (n=68)	Group 3 Moderate OSAS (n=58)	Group 4 Severe OSAS (n=147)	*P*
Stage 1 (%)[a]	7 (3.8)	7.9 (5.1)	10.3 (7.8)	14.4 (11.2)[b]	<.001
Stage 2 (%)[a]	42.5 (8.5)	41.2 (9.8)[c]	43.2 (10.2)	46.8 (13.2)	<.001
Stage 3 (%)[a]	33.1 (10.4)	31.8 (9.1)	29.8 (10.2)	24.9 (12.0)[d]	<.001
REM (%)[a]	17.4 (6.2)	18.7 (5.9)	16.6 (5.9)	13.8 (6.5)[d]	<.001
SE (%)	80.0 (12.6)	82.4 (10.6)	82.4 (10.0)	81.4 (11.2)	.838
AHI events/hr	2.7 (2.3)[e]	10.8 (8.3)[f]	22.0 (3.7)[d]	58.5 (24.4)	<.001
Average O_2 sat (%)	95.4 (2.4)[e]	94.6 (1.6)[f]	93.2 (3.3)[d]	90.7 (5.2)	<.001
Minimum O_2 sat (%)	90.3 (5.5)[e]	85.6 (5.6)[f]	80.9 (7.5)[d]	71.2 (14.7)	<.001
Desaturation (%)[b]	2.1 (14.3)[f]	1.0 (2.4)[f]	7.2 (16.6)[d]	23.2 (28.6)	<.001
ODI	2.9 (4.2)[f]	8.2 (4.8)f	19.0 (6.8)[d]	54.1 (28.1)	<.001

REM: Rapid eye movement, SE: sleep efficiency, AHI: apnea hpopnea index, sat: saturation, ODI: oxygen desaturation index.

[a]Sleep stages are given as per cent of total sleep time, bsleep time of SpO_2< 90%. Multiple comparison test results: bThere were statistically significant differences from Group 1, Group 2. [c]There was statistically significant difference from Group 4. [d]There were statistically significant differences from Group 1, Group 2, Group 3. [e]There were statistically significant differences from Group 2, Group 3, Group 4. [f]There were statistically significant differences from Group 3, Group 4.

Another important outcome of the study is the demonstration of GGT as an independent predictor for OSAS cases with CVD.

Cardiovascular complications are the most serious complications of the patients with OSAS. These complications include hypertension, coronary artery disease, cardiac failure, cardiac arrhythmia, ventricular dysfunction, and pulmonary hypertension.[17-19] Although the mechanism of impairment in myocardial contraction and relaxation seen in patients with OSAS has not been fully understood, OSAS may increase cardiac risk due to the derangement of the relation between myocardial oxygen demand and supply as a result of hypoxia, hypercapnia, increased sympathetic activation occurring during apnea, and oxygen desaturation periods associated with apnea triggered by myocardial ischemia at night.[20,21] Recent evidence suggests that OSAS could be considered as a pro-atherosclerotic disease,

Table 3. The results of biochemical analysis.

	Group 1 OSAS negative (n=47)	Group 2 Mild OSAS (n=68)	Group 3 Moderate OSAS (n=58)	Group 4 Severe OSAS (n=147)	*P*
AST level (U/L)	21.9 (12.1)	23.5 (11.8)	24.24 (11.1)	25.8 (13.4)	.248
ALT level (U/L)	23.2 (17.3)	26.9 (20.4)	26.5 (16.3)	30.2 (20.8)	.151
GGT level (U/L) Median (IQR)	25.2 (15.0) 23.5 (16-31)[b]	28.0 (11.9) 24.5 (18-32)[c]	32.8 (18.2) 26 (18-37)	40.4 (31.9) 31 (21-47)	<.001[a]
ALP level (U/L)	71.5 (24.4)	72.7 (16.9)	72.0 (19.9)	73.6 (21.7)	.140
HDL-C level (mg/dL)	48.5 (12.31)[c]	48.9 (13.4)[c]	43.4 (13.2)	42.3 (12.0)	.001
LDL-C level (mg/dL)	130.4 (34.8)	132.7 (30.0)	130.8 (31.9)	133.7 (34.5)	.913
TG level (mg/dL)	161.5 (60.1)	161.7 (110.8)	174.8 (84.9)	187.9 (101.2)	.186
TC level (mg/dL)	194.9 (36.0)	200.8 (35.6)	198.3 (35.2)	200.4 (39.1)	.826

Data were expressed as means (standard deviation).

[a]Kruskal–Wallis analysis of variance was used. Multiple comparison test results: [b]There were statistically significant differences from Group 2, Group 3, Group 4. [c]There were statistically significant differences from Group 3, Group 4. AST: Aspartate aminotransferase, ALT: alanine aminotransferase, GGT: γ-glutamyl transferase, IQR: Interquartile range ALP: alkaline phosphatase, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TG: triglyceride, TC: total cholesterol.

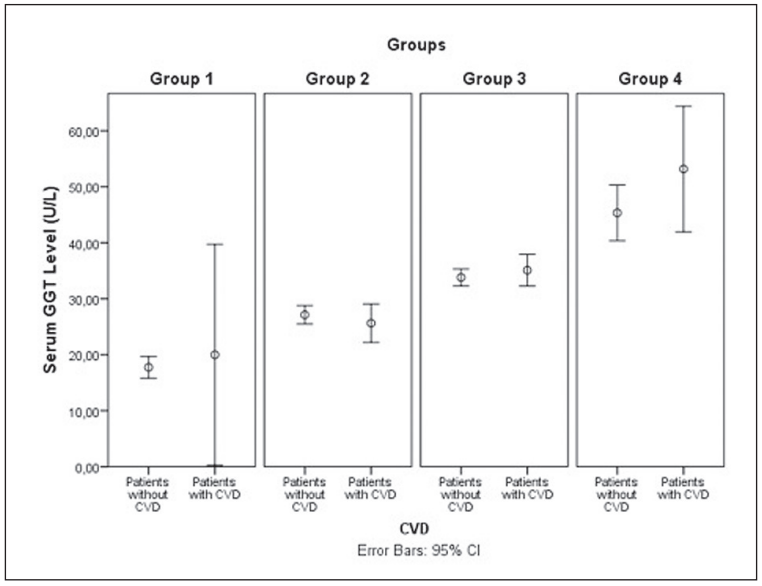

Figure 1. Serum GGT levels in patients with and without cardio-vascular disease (CVD) in study groups.

Table 4. Correlation between polysomnographic parameters with GGT.

	GGT	
	r	*P*
AHI events/h	0.260	<.001
Average O_2 sat (%)	-0.149	.008
Minimum O_2 sat (%)	-0.136	.016
Desaturation (%)	0.131	.020
ODI	0.253	<.001

AHI: Apnea- hypopnea index, sat: saturation, ODI: oxygen desaturation index, GGT: γ-glutamyl transferase.

independent of the visceral fat amount.[22] Intermittent episodes of hypoxia as a result of transient cessation of breathing during sleep are major physiologic characteristics of OSAS and resemble ischemia–reperfusion injury. Intermittent nocturnal hypoxemia induces the production of oxygen-free radicals and therefore causes a state of low-grade circulation and local inflammation.[23] Foresi et al revealed the development of airway inflammation during the sleep by measuring airway inflammation and oxidative stress markers in the exhaled air of OSAS patients.[24] Karamanli et al demonstrated that nitrotyrosine, IL-6, TNF-α, and 8-isoprostane levels in texhaled breathing condensate were decreased significantly with continuous positive airway pressure (CPAP) treatment.[25] These results demonstrate that inflammation and oxidative stress are important factors in the development of cardiovascular complications in cases with OSAS, and effective treatment of OSAS can decrease the incidence of these complications.

Serum GGT levels used as an indicator of hepatic inflammation increase in cases with cholestatic liver disease, non-alcoholic fatty liver disease, intoxication of alcohol, and various drugs.[26] The relationship of GGT with cardiovascular mortality was first described by Wannamethee et al.[27] In a cohort including 163 944 individuals, GGT was reported as a risk factor for

cardiovascular mortality, and a positive correlation was observed between serum GGT, and serum triglyceride, total cholesterol, blood glucose levels, systolic, and diastolic blood pressures.[28] In various studies, a correlation has been reported between increased serum GGT levels, and increased incidence of CVD, non-fatal myocardial infarction, and cardiac mortality.[29-34]

In the coronary artery risk development in young adults study in which the predictive value of GGT levels in the development of diabetes and hypertension in young adults was investigated, a strong correlation was detected between baseline serum GGT levels, diabetes, and hypertension. A correlation was observed between serum GGT levels and fibrinogen values at the end of 5 years of follow-up, while GGT levels demonstrated correlations with uric acid, C-reactive protein, and F2 isoprostane only at the end of 15 years of the the follow-up period. More importantly, this correlation was detected to be independent of alcohol consumption. As a concluding remark, after observation of all these outcomes, GGT was proposed as an early-stage biochemical marker for both oxidative state and other stress-inducing conditions.[35]

Many studies have investigated GGT levels in OSAS so far. Barcelo et al evaluated the antioxidant capacity in cases with OSAS and demonstrated decreases in total antioxidant capacity (TAC), levels of vitamin A and E, and increases in GGT values. They also asserted that with CPAP therapy levels of TAC and GGT returned to their normal ranges.[36] This result is important in that it implicates oxidative stress as a contributing factor in the development of cardiac complications in cases with OSAS. In a study performed by Gude et al, a relationship between serum GGT levels and nocturnal hypoxemia was demonstrated.[37] Norman et al. found a correlation between serum aminotransferase levels and hypoxemia in patients with OSAS, while AHI scores did not correlate with serum concentrations of this enzyme.[38] In our study, serum GGT levels were positively correlated with AHI, desaturation percentages, and ODI values and negatively correlated with average O_2 saturation and minimum O_2 saturation values. In other words, the levels of GGT increased in proportion with the severity of OSAS and decreases in oxygen saturation. These observations might explain the higher incidence of cardiovascular complications in cases with severe OSAS. In fact, detection of significantly higher levels of GGT in cases with CVD relative to those without is the most important outcome of this study. Besides, the median GGT value in 68.3% of the cases with CVD was relatively higher. As another important outcome of the study, in multiple regression analyses, the GGT level was revealed to be an independent predictor for CVD in cases with OSAS.

Our study yielded important outcomes in that it was conducted in a relatively larger patient population and emphasized the importance of GGT in the prediction of CVD in cases with OSAS. However, the most important limitation of our study is the lack of long-term follow-up periods, which prevented us to reveal any change in the levels of GGT, especially, in cases who had undergone CPAP therapy. The effectiveness of CPAP therapy on GGT levels, and recovery from CVD should be investigated with prospective studies.

Table 5. Risk factors for cardiovascular diseases in patients with obstructive sleep apnea syndrome (multivariate analysis).

	Odds ratio	Confidence interval 95%	P
Age (y)	1.052	1.022-1.083	.001
BMI (kg/m^2)	1.057	1.003-1.114	.040
GGT (U/L)	1.015	1.002-1.028	.027
LDL-C	0.990	0.981-0.999	.030
AHI	1.005	0.992-1.018	.432
ODI	1.023	0.942-1.112	.584

BMI: Body mass index, LDL-C: low-density lipoprotein cholesterol, GGT: γ-glutamyl transferase, AHI: apnea-hypopnea index, ODI: oxygen desaturation index.

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