Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2022;11(3):1060-2

The relationship between serum gamma glutamyl transferase levels and obtructive sleep apnea severity

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Received 30 December 2021; Accepted 30 March 2022
Available online 11.05.2022 with doi: 10.5455/medscience.2021.12.414

Abstract

Obstructive sleep apnea (OSA) can cause local and systemic inflammation due to hypoxia, asphyxia, hypercapnia, respiratory acidosis. Searching for new inflammatory markers in OSA may facilitate the prediction of OSA-related conditions. Therefore, we aimed to investigate the relationship between OSA severity and serum gamma-glutamyl transferase (GGT) levels. In the study, the GGT levels of the patients were compared according to the degree of OSA determined by polysomnography. The patients' demographic, polysomnographic, and laboratory parameters were evaluated with SPSS 25 program. A total of 500 patients, 299 (59.8%) male and 201 (40.2%) female, were included in the study. The mean age of the patients was 47.9±13.1, and body mass index (BMI) was 32.2±6.6. There were 98 (19.6%) patients in the control group, 100 (20%) in the mild OSA group, 103 (20.6%) in the moderate OSA group, and 199 (39.8%) in the severe OSA group. When the BMI and desaturation index of the groups were compared, there was a statistical difference (respectively, $p<0.001$, $p<0.001$). When the serum GGT values of the groups were compared, the GGT values of the moderate and severe OSA groups were higher than the control group (respectively, $p=0.011$, $p=0.001$), and there was a statistically significant difference between the groups ($p=0.001$). There was a positive correlation between GGT levels and BMI ($r=0.151$, $p=0.010$). There was a positive correlation between GGT levels and age ($r=0.615$, $p=0.029$). As a result of our study, a relationship was found between high GGT levels and the severity of OSA. Serum GGT level may be a promising biomarker to identify OSA patients at high risk.

Keywords: Gamma glutamyl transferase, inflammation, body mass index

Introduction

Obstructive sleep apnea (OSA) is a disease characterized by complete or partial obstruction of the upper airway during sleep [1]. In OSA, biomarkers showing systemic inflammation increase at mild and moderate levels, mostly in correlation with the severity of the disease. Apnea scores, complaints and some complications can be improved in OSA with an effective continuous positive airway pressure (CPAP) treatment.

Gamma glutamyl transferase (GGT), is an enzyme found in serum and on the outer surface of many cells [2]. Hanes et al. were the first to describe GGT in human tissues [3]. Szczeklik et al. were the first to report its use for diagnostic purposes [4]. Although the liver is the most important source of GGT in serum, kidney, pancreas and small intestine are tissues that contribute to its activity in serum, albeit in small amounts [5].

GGT is a widely used laboratory test, especially in the diagnosis of alcohol-related liver diseases. Increases in serum GGT activity are also closely associated with diabetes mellitus, obesity, and cardiac problems [6]. It has been reported that GGT activity exceeding 25 U/L in men is a risk factor for the development of diabetes [7]. It has been reported that increased levels of GGT within normal limits are associated with an increased incidence of both coronary heart diseases and strokes [8]. In addition, it is observed that serum GGT levels are increased in many diseases which are caused by oxidative stress in the pathogenesis. In systemic inflammation, while circulating oxidants increase,

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antioxidant capacity decreases. Increased GGT activity in serum causes oxidative stress in humans [9]. The possible mechanism here is explained as follows: Increasing oxidative stress due to risk factors increases the need for glutathione. It is stated that decreased intracellular glutathione levels can induce GGT activity. Increased GGT can be released into the circulation, and thus cell stressors can cause increases in serum GGT levels [10].

Since systemic inflammation is one of the important mechanisms in OSA, searching for new inflammatory markers in OSA may make it easier to predict related conditions. More studies are needed on the place of inflammation in the diagnosis and treatment process of OSA, whether how inflammatory markers can be used in diagnosis and treatment follow-up [1]. Therefore, we aimed to investigate the relationship between OSA severity and serum GGT levels.

Materials and Methods

Patients who underwent polysomnography in the Sleep Disorders Center of Turgut Özal Medical Center in 2017 were included in the study. In the study, patients over 18 years of age who did not have a circulatory system, respiratory system, central nervous system disease, liver and gallbladder disease, liver enzyme elevation, and alcohol history were evaluated retrospectively. The GGT levels of the patients, which were determined by laboratory devices (ARCHITECT, Toshiba, Abbott Park, USA), were compared according to the degree of OSA determined by the polysomnography system (Alice 6® Sleepware, Philips Respironics, PA, USA). The normal reference value of GGT level for healthy individuals was accepted as 9-36 U/L.

Polysomnographic Evaluation: Polysomnography recordings were analyzed according to guidelines published by the American Academy of Sleep Medicine (AASM) [11]. Sleep efficiency, sleep stages (REM stage and non-REM stages; N1, N2, N3), apnea-hypopnea index (AHI), and desaturation index were evaluated. The AHI result was calculated by dividing the apnea and hypopnea numbers by the sleep duration. Patients with AHI ≥5 were diagnosed with OSA. AHI of 5-15 was graded as mild OSA, 16-30 as moderate OSA, and patients with AHI >30 were graded as severe OSA. The number of oxygen desaturations per hour observed during sleep was considered desaturation index.

Ethical approval: The study application was approved by the İnönü University Ethics Committee (issue: 2021/1730).

Statistical Analysis: SPSS (IBM SPSS Statistics 25, NY, USA) program was used. The patients' demographic, polysomnographic, and laboratory parameters were evaluated with ANOVA test and Pearson's correlation test. The obtained values were given as the mean ± SD, $p<0.05$ were considered statistically significant.

Results

A total of 500 patients, 299 (59.8%) male and 201 (40.2%) female, were included in the study. The mean age of the patients was 47.9±13.1, and body mass index (BMI) was 32.2 ±6.6. There were 98 (19.6%) patients in the control group, 100 (20%) in the mild OSA group, 103 (20.6%) in the moderate OSA group, and 199 (39.8%) in the severe OSA group. Demographic data, polysomnographic data, and serum GGT levels of the groups were compared. When the age of the groups were compared, there was no difference between the groups (p=0.088). When the BMI and desaturation index of the groups were compared, there was a statistical difference ($p<0.001$, $p<0.001$). When the serum GGT values of the groups were compared, the GGT values of the moderate and severe OSA groups were higher than the control group (respectively, p=0.011, p=0.001), and there was a statistically significant difference between the groups (p=0.001). There was no statistically significant difference in terms of age, sleep efficiency, and sleep stages, the results are summarized in Table 1. There was a positive correlation between GGT levels and BMI (r=0.151, p=0.010). There was a positive correlation between GGT levels and age (r=0.615, p=0.029).

Table 1. Demographic, polisomnografic and laboratory parameters of the study groups

	Control Group(n=98)	Mild OSA(n=100)	Moderate OSA(n=103)	Severe OSA(n=199)	p
Age (year)	46.8±13.5	44.1±12.8	48.0±11.9	52.2±11.5	0.088
BMI (kg/m²)	29.2±5.9	30.0±6.2	32.4±5.7	35.5±16.2	<0.001
Sleep efficiency (%)	82.3±11.7	79.7±14.0	76.6±15.5	74.5±14.8	0.540
N1(%)	8.9±6.4	9.6±10.7	11.5±10.5	12.0±10.9	0.158
N2(%)	51.3±16.5	53.9±11.3	53.9±13.4	58.8±15.2	0.083
N3(%)	31.3±14.4	27.7±13.2	25.4±12.4	26.8±14.7	0.097
REM (%)	14.3±9.6	14.7±7.0	13.6±5.8	11.7±6.1	0.705
Desaturation Index	13.7±29.1	16.0±27.4	19.3±26.0	31.6±27.1	<0.001
GGT (U/L)	22.9±14.0	31.1±16.1	35.6±24.7	41.1±38.8	0.001

BMI: Body mass index, REM: Rapid eye movement, N1: Non-REM stage 1, N2: Non-REM stage 2, N3: Non-REM stage 3, GGT: Gamma glutamyl transferase

Discussion

In our study, a significant relationship was found between GGT levels, the severity of OSA, and BMI. A positive correlation was found between GGT levels and BMI and age.

OSA, can cause local and systemic inflammation due to hypoxia, asphyxia, hypercapnia, respiratory acidosis. In OSA patients, hypoxia deepens in proportion to AHI, and deterioration in respiratory parameters and oxygen desaturation occur. In our study, it was determined that GGT levels increased proportionally with hypoxia, depending on the increase in AHI, that is, the severity of OSA. In the study of Norman et al., serum GGT levels were associated with nocturnal hypoxemia in OSA patients [12]. A comprehensive study showed that serum concentrations of GGT

correlated with mean oxygen saturation during sleep and markers of nocturnal hypoxemia [13]. In the study of Bozkuş et al., serum GGT levels were found to be associated with the degree of OSA, and it was reported that GGT activities increased with age [14]. Similarly, in our study, a positive correlation was found between GGT levels and age. Kanbay et al. determined that GGT level is an indicator for heart diseases in OSA patients, independent of all known risk factors in OSA [15]. Similarly, Köseoğlu et al; found that GGT level was a predictor for heart diseases in OSA patients [16]. Considering the relationship between serum GGT activity and cardiovascular diseases, it has been shown that there is a GGT relationship, especially in diseases with underlying atherosclerosis [8]. A doubling of serum GGT activity was found to increase the probability of coronary artery disease by 58% [17]. In another study conducted with 6-year follow-up of 469 patients with ischemic syndrome and coronary artery disease, serum GGT was found to be a predictor of mortality. Two different threshold values (25-40U/L) were determined within normal limits for increased risk [18].

Obesity is one of the most fundamental health problems of today. Along with the increasing degree of obesity, a parallel increase is observed in the rates of various end-organ damage. There is a relationship between obesity and many metabolic, hormonal, neuroendocrinological, hemostatic and inflammatory abnormalities [20]. Aktaş et al found that non-diabetic obese individuals had higher GGT and uric acid levels than overweight non-diabetic individuals [20]. In our study, the relationship between GGT levels and BMI was statistically significant. This relationship seems to be due to the coexistence of other related factors, including respiratory disorders and central obesity. Barcelo et al. showed in their study that GGT decreased without any change in BMI after CPAP therapy. This supports the hypothesis that the increase in GGT is directly related to OSA [21].

OSA has a direct effect on oxidative imbalance and activation of the inflammatory cascade through intermittent hypoxia [22]. The results of our study may be associated with increased underlying inflammation and obesity in patients with OSA. It is very important to monitor the levels of biomarkers that play a role in OSA. The most important limitation of our study is that it is a cross-sectional study. More comprehensive studies investigating the effect of CPAP treatment on GGT activity are needed.

Conclusion

As a result of our study, a relationship was found between the severity of OSA and high GGT levels. Serum GGT level may be a promising biomarker to identify OSA patients at high risk. There is a need to evaluate the results in prospective controlled studies with more patients.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
Ethics approval was obtained from the Inonu University Faculty of Medicine Ethics Committee (issue: 2021/1730).

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