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RESEARCH ARTICLE

Association of Serum Total Testosterone Levels with Obstructive Sleep Apnea Severity

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ABSTRACT

Objective: We aimed to investigate any associations between serum total testosterone (TT) levels and inflammation markers, carbohydrate-bone metabolic status, or other clinical/laboratory sleep variables in severe obstructive sleep apnea (OSA).

Materials and Methods: Seventy-four men who underwent polysomnography tests at the sleep laboratory were included in the study. The patient group consisted of 44 people with severe OSA with Apnea Hypopnea Index (AHI) score ≥30, and the control group consisted of 30 people with AHI score <5. Cases in the severe OSA group were divided into two subgroups based on the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) median value and evaluated statistically.

Results: Compared to the control group (395±101), TT was significantly lower in severe OSA (321±108), p=0.004. In severe OSA, TT was associated with biochemical parameters such as C-reactive protein (CRP), fibrinogen, HOMA-IR, and many sleep variables such as AHI, oxygen desaturation index, rapid eye movement (REM)-AHI, and Non-REM-AHI (p<0.05). After adjusting for body mass index and age variation, according to multiple linear regression analysis, TT was significantly related to the AHI score (β=−0.415, p=0.006). Compared to the control group, in the severe OSA group with HOMA-IR≥3.54, TT was found lower (p=0.001), systemic inflammatory response index, CRP, fibrinogen, Hemoglobin A1c, liver enzymes, and parathormone were found higher (p<0.05).

Conclusion: TT was associated with OSA severity, inflammation status, insulin resistance, and hypoxia. An independent relation was found between the severity of OSA and TT. Since testosterone deficiency could have a negative impact on sleep quality, it is important to measure TT level in OSA.

Keywords: Insulin resistance, obstructive sleep apnea, polysomnography, testosterone

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INTRODUCTION

Obstructive sleep apnea (OSA) is the most prevalent sleep-respiratory disorder characterized by a blockage of the upper airway during sleep.[1] OSA, the most important clinical cause of sleep disruption, impacts on cardiometabolic and male reproductive health.[2]

In a multi-center and randomized trial, Alvarenga et al.[3] showed a decreased proportion of healthy sperm cells and increased cortisol and thyroid-stimulating hormone (TSH) in patients with OSA and sleep-deprived individuals. OSA is associated with endocrine disorders and affects the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-gonadal axis, because it causes oxygen desaturation and sleep disruption.[4] OSA can cause chronic intermittent hypoxia (CIH) and sleep fragmentation, with ensuing rises in sympathetic activity, oxidative stress, insulin resistance, and these pathological alterations could impact men's testosterone metab-

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olism.[5] The increase in testosterone primarily depends on sleep integrity; decreased luteinizing hormone (LH) pulse frequency and total testosterone (TT) have been shown to be related to sleep disruption and CIH seen in OSA.[6]

The relationship between OSA and TT has not been clearly characterized. Testosterone levels are modulated by sleep duration, restriction, and sleep quality in men.[7] Serum testosterone levels in males with OSA may be mainly impacted by obesity.[8] Obesity, diabetes, testicular cancer, and metabolic syndrome cause decreased testosterone levels in adult men, and sleep apnea and other sleep-related disorders are common comorbidities with such diseases.[9] Due to insufficient or poor-quality sleep, OSA exacerbates obesity, creating a vicious cycle.[10]

We aimed to investigate possible changes in TT levels and any associations with inflammation markers, carbohydrate-bone metabolic status, or other clinical/laboratory sleep variables in men with severe OSA.

MATERIALS and METHODS

Study Design

This study's data was obtained retrospectively through the hospital/laboratory information system between January 2019 and June 2019. This study was carried out in compliance with the Helsinki Declaration. This study was approved by the Ethics Committee (Date: March 10, 2023, number: 66).

Subjects

This study included adult male patients with pre-diagnosed sleep apnea admitted to the ear nose throat or neurology outpatient clinics and underwent polysomnography (PSG) at the sleep laboratory.

The following inclusion criteria were used for selecting OSA patients: male, 18–65 years old, diagnosed with OSA based on overnight PSG evaluation with AHI above 30. The following were the exclusion criteria: (1) OSA patients in whom continuous positive airway pressure therapy was initiated, (2) cases with infectious and systemic inflammatory diseases, thyroid dysfunction, diabetes, severe liver failure, and chronic kidney disease, (3) cases with known hematological disorders, malignancy, and receiving immunosuppressive therapy, and (4) cases with body mass index (BMI) >40, 5) cases using any medication affecting serum testosterone levels such as 5-alpha reductase inhibitors, anti-androgens, and testosterone replacement therapy. Smoking status, alcohol consumption, anthropometric data, and comorbidities such as chronic obstructive pulmonary disease (COPD), hypertension, and coronary artery disease (CAD) were all recorded. Our patients were stratified into two groups, 30 males in the control group (first group) with an apnea hypopnea index (AHI) <5 events/hour and 44 males in the severe group with AHI> 30 events/hour. The severe OSA group was divided into two subgroups with respect to the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) median value: HOMA-IR<3.54 for the second group and HOMA-IR≥3.54 for the third group. BMI was determined through the formula [weight (kg)/height (m)^2].

Sleep Study

This study evaluated patients' sleep patterns with the Embla S4500 Software diagnostic device (Embla Systems Inc. Broomfield, USA) at the sleep laboratory. In PSG examination, brain activity with electroencephalogram recordings, bilateral eye movements with electrooculography, submental muscle and bilateral tibialis anterior muscle activity with electromyography, airflow with a thermistor and nasal cannula, abdominal and chest respiratory movements with plethysmography, lying position with position sensors, pulse oximeter arterial oxygen saturation (SpO_2), electrocardiography, and video recording with an infra-red-light camera were detected. PSG findings were recorded between 22.00 and 07.30 (full-night PSG). The same neurologist scored the data obtained.

Laboratory Analysis

Laboratory data including complete blood counts (XN9000; Sysmex Co., Kobe, Japan), fasting glucose, insulin, creatinine, alanine aminotransferase (ALT), gamma-glutaryl transferase (GGT), C-reactive protein (CRP), uric acid, ferritin, folate, parathormone (PTH), Vitamin B12, 25-hydroxyvitamin D (25(OH)D), TT, and TSH were retrieved from the records (AU5800 and Unicel DxI 800; Beckman Coulter Inc., Brea, California, US.). Moreover, plasma fibrinogen levels were studied using BCS-XP (Siemens Healthineers, Erlangen, Germany). Glycated hemoglobin (HbA1c) levels were measured through ADAMS A1c HA8180V (Arkray, Kyoto, Japan).

The estimated glomerular filtration rate was calculated through the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). HOMA-IR was calculated through the following equation: (fasting glucose [mg/dL] * fasting insulin [mIU/mL])/405. The equation calculates systemic immune-inflammation index (SII): (platelet count * neutrophil count)/lymphocyte count. Likewise, the equation calculates systemic inflammation response index (SIRI): (monocyte count * neutrophil count)/lymphocyte count.

Sample Size

Cohen's d effect size was 0.80; α value 0.05; the power (1-β) value was taken as 0.80, and the minimum number of samples required for statistical comparison of two independent groups was calculated as n=26 participants for each group through the G*Power version 3.1.9.4 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany).

Statistical Analysis

Kolmogorov–Smirnov or Shapiro–Wilk test was used to determine if the data fit the normal distribution. Continuous data were exhibited as mean and standard deviation or median (25^{th} and 75^{th} percentile), and discrete data as the ratio (per cent). Analysis for discrete variables was performed through Chi-square test. Mann–Whitney U or Student's t test was utilized to compare two independent groups according to the normal distribution fit. The one-way ANOVA or Kruskal–Wallis test was utilized to compare three independent groups according to the normal distribution fit. Pairwise comparisons for Kruskal–Wallis test were performed with the Bonferroni correction. The statistical significance level for Bonferroni correction was accepted as 0.017 for the p-value. The relationships between variables were evaluated with Spearman correlation analyses. AHI levels were adjusted to a normal distribution by logarithmic transformation. Multivariate linear regression was applied to assess the association between TT and AHI. The diagnostic performance of the laboratory parameters was assessed using Receiver Operating Characteristic (ROC). Using Youden's index, optimal cutoff values for the laboratory parameters were determined. All statistical evaluations were made in IBM SPSS version 26.0 (IBM Corp., Armonk, NY) and MedCalc version 20.115 (MedCalc Software Ltd, Ostend, Belgium). P significance level was accepted as <0.05.

RESULTS

Patients' Baseline Characteristics

There was no significant difference in age, alcohol/smoking intake, and comorbidities of COPD/CAD between the severe OSA and the controls (p>0.05). However, severe OSA patients had significantly higher BMI (p<0.001) and hypertension frequency (p=0.047). In addition, AHI, oxygen desaturation index (ODI), SpO_2<90%, rapid eye movement (REM)-AHI, Non-REM (NREM)-AHI (p<0.001), and N2-total sleep time (TST)% (p=0.012) parameters were found to be significantly higher, N3 (%TST), mean SpO_2, and minimum SpO_2 were found significantly lower; p<0.001 (Table 1).

Comparison of Severe OSA with the Controls

Serum TT levels were lower in the severe OSA (p=0.004). On the contrary, SIRI (p=0.026), CRP (p<0.001), fibrinogen (p=0.004), HOMA-IR (p<0.001), HbA1c (p<0.001), GGT (p=0.004), ALT (p=0.011), uric acid (p=0.012), and PTH (p=0.003) were found to be significantly higher (Table 2).

ROC Analysis of Severe OSA

In the ROC analysis for severe OSA, the HOMA-IR performed the highest area under the curve (AUC) value was 0.815 (95% confidence interval [CI]=0.708–0.896), presenting 70.5% of sensitivity and 90.0% of specificity at a cutoff value of 2.62, p<0.001. CRP performed the AUC value of 0.743 (95% CI= 0.628–0.838), presenting 63.6% of sensitivity and 73.3% of specificity at a cutoff value 2.35, p<0.001. HbA1c performed the AUC value was 0.711 (95% CI=0.594–0.811), presenting 47.7% of sensitivity and 83.3% of specificity at a cutoff value of 5.7%, p<0.001. PTH performed the AUC value of 0.703 (95% CI=0.586–0.804), presenting 77.3% of sensitivity and 56.7% of specificity at a cutoff value 43, p=0.001. GGT performed the AUC value of 0.700 (95% CI=0.583–0.801), presenting 50.0% of sensitivity and 83.3% of specificity at a cutoff value 31, p=0.002. TT performed the AUC value of 0.698 (95% CI=0.580–0.799), presenting 54.5% of sensitivity and 83.3% of specificity at a cutoff value of 311, p=0.001 (Fig. 1).

Comparison of Sub-groups for Severe OSA Separated According to HOMA-IR

The three groups had no statistical difference regarding SII, uric acid, ferritin, TSH, and Vitamin B12. While BMI, SIRI, CRP, fibrinogen, HbA1c, GGT, ALT, and PTH were higher in the third group, TT levels were lower in the third group (severe OSA with HOMA-IR≥3.54) compared to the first group; p= 0.001 (Table 3).

Association between TT and Other Variables

In the severe OSA, there was a significant negative association between TT and CRP (r=−0.319, p=0.004), fibrinogen (r=−0.400, p=0.007), HOMA-IR (r=−0.322, p=0.033), AHI (r=−0.531, p<0.001), ODI (r=−0.497, p=0.001), REM AHI (r=−0.414, p=0.005), NREM AHI (r=−0.464, p=0.002), SpO_2<90% (r=−0.358, p=0.002), but a positive relation (r=0.380, p=0.011) with SpO_2 minimum (Table 4). There was a significant relation between TT and HOMA-IR (r=−0.438, p=0.042), AHI (r=−0.633, p=0.002), ODI (r=−0.610, p=0.003), NREM AHI (r=−0.661, p=0.001), and SpO_2<90% (r=−0.440, p=0.041) in severe OSA group with HOMA-IR≥3.54 (Table 5).

Table 1. Comparison of demographic and polysomnographic findings between the severe OSA and control groups

Parameter	Control group (n=30)		Severe OSA (n=44)		p
	n	%	n	%	
Age (years)	42±10		45±10		0.157[a]
Body mass index (kg/m^2)	27.0±2.98		32.9±4.62		**<0.001[a]**
Alcohol consumption	8	26.7	6	13.6	0.270[b]
Smoking	10	33.3	13	29.5	0.928[b]
Hypertension	3	10	14	31.8	**0.047[b]**
COPD	0	0	2	4.5	0.511[b]
CAD	2	6.7	6	13.6	0.461[b]
ODI (events/h)	2.70 (1.60–4.00)		50.5 (38.2–67.8)		**<0.001[c]**
AHI (events/h)	3.35 (1.70–4.10)		49.9 (39.5–70.1)		**<0.001[c]**
TST (minutes)	414 (354–451)		431 (381–449)		0.409[c]
REM (TST%)	13.4±6.83		13.4±6.38		0.974[a]
N1 (TST%)	9.20 (7.20–10.4)		9.55 (5.25–14.8)		0.873[c]
N2 (TST%)	48.7 (44.7–52.4)		52.4 (47.7–70.9)		**0.012[c]**
N3 (TST%)	26.4±8.28		16.7±13.2		**<0.001[a]**
Sleep efficiency (%)	81.7 (74.5–87.9)		85.8 (76.2–92.6)		0.248[c]
NREM-AHI (events/h)	2.95 (1.20–4.10)		48.7 (38.3–72.3)		**<0.001[c]**
REM-AHI (events/h)	2.90 (0.00–6.00)		56.8 (42.5–72.8)		**<0.001[c]**
Mean SpO_2 (%)	95.0 (94.0–96.2)		93.7 (90.8–94.4)		**<0.001[c]**
Minimum SpO_2 (%)	90.0 (88.0–91.0)		79.0 (67.0–84.0)		**<0.001[c]**
SpO_2<90 (%)	0.00 (0.00–0.10)		6.05 (3.25–27.8)		**<0.001[c]**

[a]: Student's t test; [b]: Chi-square test; [c]: Mann–Whitney U test. OSA: Obstructive sleep apnea; COPD: Chronic obstructive pulmonary disease; CAD: Coronary artery disease; ODI: Oxygen desaturation index; AHI: Apnea-hypopnea index; TST: Total sleep time; REM: Rapid eye movement; N1 (TST%): Percent of non-rapid eye movement Phase 1 in TST; N2 (TST%): Percent of NREM Phase 2 in TST; N3 (TST%): Percent of NREM Phase 3 in TST, REM, (TST%): Percent of rapid eye movement phase in TST; NREM-AHI: Non-rapid eye movement phase AHI; REM-AHI: Rapid eye movement phase AHI; SpO_2: Arterial oxygen saturation

TT Was Independently Correlated with the AHI

In univariate linear regression analysis, TT was negatively related to logAHI (β=−0.521, p<0.001) in severe OSA. After adjusting covariates (age and BMI), using a multivariate linear regression model analysis, TT was independently correlated with the logAHI (β=−0.415, p=0.006).

Association between HOMA-IR and Other Parameters

In the severe OSA, there was a negative association between HOMA-IR and TT (r=−0.322, p=0.033), 25(OH)D (r=−0.334, p=0.027), N1 (%TST) (r=−0.382, p=0.011), mean SpO_2 (%) (r=−0.432, p=0.003), and minimum SpO_2 (%) (r=−0.398, p=0.007). However, there was a positive association between HOMA-IR and SIRI (r=0.383, p=0.010), ALT (r=0.452, p=0.002), PTH (r=0.405, p=0.006), AHI (r=0.389, p=0.009), ODI (r=0.396, p=0.008), sleep efficiency (r=0.304, p=0.045), TST (r=0.305, p=0.044), REM-AHI (r=0.376, p=0.012), NREM-AHI (r=0.337, p=0.025), and SpO_2<90% (r=0.453, p=0.002) (Table 6).

25(OH)D Levels Correlated with NREM Parameters

Serum 25(OH)D levels correlated with N2 stage sleep duration (r=−0.644, p=0.001) and N3 stage sleep duration (r=0.635, p=0.001) in severe OSA group with HOMA-IR≥3.54.

DISCUSSION

Although OSA affects a significant portion of the population, men are affected with a higher frequency than women, and patients with obesity have a higher prevalence than those with overweight, reaching 50–60%.[11] As expected, we had significantly higher BMI values in cases with severe OSA. Moreover, hypertensive patients were significantly more frequent in severe OSA.

Table 2. Comparison of laboratory findings between the severe OSA and control groups

Parameter	Control group (n=30)	Severe OSA (n=44)	p
SIRI	0.79 (0.60–0.92)	0.96 (0.72–1.41)	**0.026[b]**
SII	354 (277–430)	426 (321–572)	0.099[b]
CRP (mg/dL)	1.54 (0.88–2.51)	2.71 (1.95–7.41)	**<0.001[b]**
Fibrinogen (mg/dL)	292±59.4	340±73.1	**0.004[a]**
HOMA-IR	1.83 (1.14–2.26)	3.55 (2.27–4.74)	**<0.001[b]**
HbA1c (%)	5.43±0.36	5.73±0.38	**<0.001[a]**
eGFR (ml/dk)	107.2±15.13	106.0±16.93	0.756[a]
Uric acid (mg/dL)	5.72±1.13	6.47±1.27	**0.012[a]**
ALT (IU/L)	26.0 (18.0–30.0)	30.0 (24.0–48.0)	**0.011[b]**
GGT (IU/L)	23.0 (16.0–29.0)	31.0 (25.0–41.0)	**0.004[b]**
Ferritin (ng/mL)	50.1 (30.5–74.8)	59.1 (37.2–90.1)	0.344[b]
Folate (ng/mL)	7.08 (6.24–9.18)	8.17 (6.78–10.4)	0.062[b]
PTH (pg/mL)	40.4 (28.4–61.7)	60.7 (43.8–79.8)	**0.003[b]**
Total Testosterone (ng/dL)	395±101	321±108	**0.004[a]**
TSH (uIU/mL)	1.67 (1.16–2.50)	1.63 (0.91–2.38)	0.390[b]
25-hydroxyvitamin D (ng/mL)	19.2 (15.3–25.4)	17.9 (14.3–23.8)	0.636[b]
Vitamin B12 (pg/mL)	191 (155–221)	194 (166–265)	0.213[b]

[a]: Student's t test; [b]: Mann–Whitney U test. OSA: Obstructive sleep apnea; SIRI: Systemic inflammatory response index; SII: Systemic inflammatory index; CRP: C-reactive protein; HOMA-IR: Homeostatic model assessment of insulin resistance; HbA1c: Glycated hemoglobin; eGFR: Estimated glomerular filtration rate; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; PTH: Parathyroid hormone; TSH: Thyroid-stimulating hormone

The results of studies investigating the association between testosterone levels and OSA showed that OSA was significantly related with low TT levels in males. Because OSA patients had lower REM sleep, less deep sleep time, more fragmented sleep, more nighttime awakenings, and decreased sleep efficiency.[12] Moreover, apnea severity was negatively related to testosterone level; a lower serum testosterone level was correlated with higher AHI, ODI scores.[6,13,14] In another study, OSA was linked to low total and free testosterone levels in males with severe obesity.[14] In ROC analysis for TT, the AUC value was 0.748 (95% CI: 0.648–0.849, p<0.001) with cutoff = 412 ng/dL (Sensitivity = 80.6%; Specificity = 64.9%).[14] Even though there were non-obese male patients in our study group, our cutoff value was close to the one in this study.[14] In our study, TT was lower in the severe OSA and was found to be related to many sleep variables (AHI, ODI, NREM-, REM-AHI, and SpO_2 levels). In addition, for TT, the AUC value was 0.698 (95% CI: 0.580–0.799; p= 0.001) with cutoff=311 ng/dL (Sensitivity = 54.5%; Specificity = 83.3%). In a meta-analysis, serum testosterone levels in men were negatively correlated with OSA, regardless of BMI and age. Furthermore, OSA severity also correlated with serum testosterone levels, similar to our findings.[5]

A significant reduction in the amount of deep sleep developed in mouse, which underwent gonadectomy, was shown to be improved by testosterone replacement therapy.[15] Male patients with OSA have an increased risk of infertility, the risk increases with the duration of OSA exposure.[16,17] Sexual dysfunction and hypogonadism can be improved with OSA treatment.[18] Furthermore, a recent case report highlighted the possible usage of testosterone supplementation in treating OSA.[16,17] Nevertheless, some randomized controlled studies showed that testosterone medication might acutely create sleep-disordered breathing; therefore, the issue of testosterone effects on OSA should not be disregarded.[19,20] The negative impact of testosterone deficiency on sleep quality could be ameliorated by testosterone replacement. However, using large amounts of exogenous testosterone and androgenic steroids was linked to sleep length and structure abnormalities. Current guidelines state that testosterone treatment is contraindicated in patients who have untreated OSA.[21] Testosterone re-

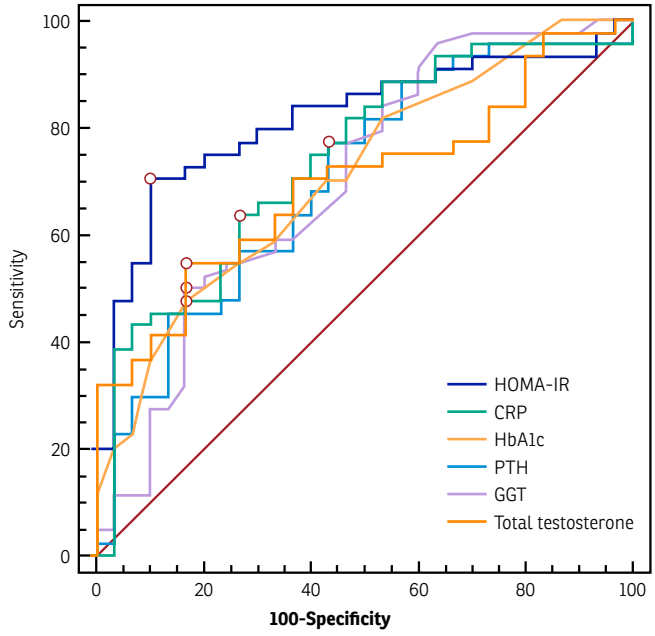

Figure 1. Receiver operating curve analysis of laboratory parameters in identifying severe OSA

HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; CRP: C-reactive protein; HbA1c: Glycated hemoglobin; PTH: Parathormone; GGT: Gamma-glutaryl transferase; OSA: Obstructive sleep apnea

placement worsens OSA through a variety of physiological reasons, such as neuromuscular alterations to the airways, modifications to metabolic needs, and adjustments to the body's physiological reaction to hypoxia and hypercapnia.[18] It has been shown in many studies that TT levels were not investigated before testosterone treatment, and it is understood that testosterone levels were not measured after treatment in a larger proportion of cases.[22]

There is a two-way interaction between obesity and testosterone. Low testosterone levels trigger obesity due to insulin resistance, adipocyte dysfunction, and sleep disturbance. Obesity triggers inflammation, primarily by releasing cytokines, adipokines, and cortisol secretion. Low testosterone may develop due to increased aromatase expression, especially in the inflamed and insulin-resistant adipose tissue. In addition, obesity decreased sex hormone binding globulin (SHBG) due to hyperinsulinemia. Just as obesity leads to a decrease in TT, low testosterone may also promote obesity.[18] Supporting these findings, we found a significant relationship between TT and CRP, fibrinogen, and HOMA-IR. In severe OSA, inflammation and impaired glycometabolism might have an impact on the reduction of TT levels.

Steatosis, ALT elevation, and metabolic syndrome were among the seven outcomes, having a high quality of evidence, and they presented significant associations with OSA through an umbrella review.[23] Moreover, HOMA-IR and fasting plasma insulin in the severe OSA were shown to be higher than the controls in another study.[24] We found HOMA-IR, ALT, GGT higher in the severe OSA, so our findings supported the literature.[23,24] Higher systemic inflammatory parameters such as sedimentation, fibrinogen, and CRP levels could arise from the combined interplay of nocturnal hypoxia, metabolic syndrome, and obesity.[25] We found inflammation parameters such as SIRI, fibrinogen, and CRP higher in the severe OSA. In ROC analysis for severe OSA, of all the variables we studied, the HOMA-IR had the highest diagnostic performance. Moreover, CRP, HbA1c, and GGT showed similar diagnostic performances (Fig. 1). While statistically examining the importance of TT levels in OSA cases, we also showed the effect of HOMA-IR values in this study. When we had two sub-groups of severe OSA, due to a HOMA-IR median value of 3.54, we had significantly lower TT levels in severe OSA with higher HOMA-IR compared to the controls, as shown in Table 3.

The microarousal index and ODI were shown to be independently associated with HOMA-IR.[26] Hyperinsulinemia and an elevated HOMA-IR were independently linked to REM-AHI. Furthermore, the length of REM sleep was independently linked to hyperinsulinemia.[27] In our study, similar to these studies, HOMA-IR was related to sleep duration, NREM-AHI, REM-AHI, AHI, ODI, mean SpO_2, minimum SpO_2, and SpO_2<90% in severe OSA.

In a study, patients with severe OSA had significantly longer stage N1(%TST) sleep, shorter N3(%TST), and shorter REM sleep than the control group.[28] In our study, REM did not differ in severe OSA, but N3 was shorter, supporting this study.[28] Furthermore, N2 (%TST), NREM AHI, REM AHI parameters, and the ratio of patients with SpO_2<90% were significantly higher, mean SpO_2, and minimum SpO_2 parameters were significantly lower in the severe OSA.

Dorr et al.[29] tested testosterone pellet therapy on a patient with severe osteoporosis and observed a reversion of osteoporosis diagnosis and improved sleep quality. It was shown that there was a relation between OSA and low 25(OH)D and high PTH levels.[30] Apart from bone metabolism, 25(OH)D has pleiotropic effects that modulate numerous metabolic processes in many tissues in the body.[30] High PTH levels and/or 25(OH)D deficiency were linked to insulin resistance, diabetes, metabolic syndrome, and inflammation, which

Table 3. Comparison of body mass index and laboratory findings between the controls, severe OSA with lower HOMA-IR, and severe OSA with higher HOMA-IR

Parameter	Control group (n=30)	Severe OSA with HOMA-IR <3.54 (n=22)	Severe OSA with HOMA-IR ≥3.54 (n=22)	p
Body mass index (kg/m^2)	26.3 (24.7–28.4)	31.1 (27.8–33.0)[a=0.002]	35.7 (30.8–39.0)[a=<0.001, b=0.010]	**<0.001[c]**
SIRI	0.790 (0.600–0.920)	0.875 (0.640–1.340)	1.175 (0.830–1.470)[a=0.005]	**0.017[c]**
SII	353.8 (276.5–430.4)	383.3 (244.6–496.9)	461.8 (359.9–610.0)	0.071[c]
CRP (mg/dL)	1.54 (0.88–2.51)	2.38 (1.54–4.77)	3.58 (2.10–10.0)[a=<0.001]	**0.001[c]**
Fibrinogen (mg/dL)	292.3±59.38	328.1±59.79	352.9±83.94[a=0.006]	**0.007[d]**
HOMA-IR	1.83 (1.14–2.26)	2.27 (1.73–2.78)	4.74 (4.08–7.91)[a=<0.001, b=<0.001]	**<0.001[c]**
HbA1c (%)	5.43±0.36	5.72±0.34[a=0.024]	5.75±0.43[a=0.010]	**0.004[d]**
Uric acid (mg/dL)	5.60 (5.20–6.40)	6.45 (5.40–7.20)	6.55 (5.70–7.70)	0.037[c]
GGT (IU/L)	23 (16–29)	30 (21–41)	32 (25–41)[a=0.005]	**0.012[c]**
ALT (IU/L)	26 (18–30)	27 (19–45)	41 (27–52)[a=0.001]	**0.004[c]**
Ferritin (ng/mL)	50.1 (30.5–74.8)	62.9 (38.0–87.60)	52.6 (31.8–98.0)	0.620[c]
Folate (ng/mL)	7.08 (6.240–9.180)	9.535 (7.250–12.94)[a=0.009]	7.680 (6.080–9.220)	**0.028[c]**
PTH (pg/mL)	40.4 (28.4–61.7)	53.3 (37.2–71.3)	67.6 (50.9–108)[a=<0.001]	**0.002[c]**
Total Testosterone (ng/dL)	394.8±100.8	351.7±102.2	290.5±106.1[a=0.001]	**0.002[d]**
TSH (uIU/mL)	1.67 (1.16–2.50)	1.53 (0.83–2.28)	1.69 (0.94–2.57)	0.605[c]
25-hydroxyvitamin D (ng/mL)	19.2 (15.3–25.4)	23.4 (15.7–28.3)	16.8 (11.9–20.3)[b=0.003]	**0.011[c]**
Vitamin B12 (pg/mL)	191 (155–221)	217 (158–274)	189 (175–255)	0.448[c]

[a]: Comparison with control group; [b]: Comparison with severe OSA group with HOMA-IR<3.54; [c]: Kruskal–Wallis test; [d]: One-way ANOVA test. OSA: Obstructive sleep apnea; HOMA-IR: Homeostatic model assessment of insulin resistance; SIRI: Systemic inflammatory response index; SII: Systemic inflammatory index; CRP: C-reactive protein; HbA1c: Glycated hemoglobin; GGT: Gamma-glutamyl transferase; ALT: Alanine aminotransferase; PTH: Parathyroid hormone; TSH: Thyroid-stimulating hormone

were also present in OSA patients. Supplemental Vitamin D could decrease systemic inflammation and enhance insulin sensitivity.[24] Differences in blood 25(OH)D levels between ethnic groups in OSA patients might be caused by metabolic and Vitamin D receptor gene polymorphisms. Furthermore, PTH mutations were found to be highly related to OSA in Asian Indians.[31] As OSA patients have a greater amount of adipose tissue, the store of Vitamin D also increases, but decreased release of Vitamin D into the bloodstream results in less bioavailability.[10] Another study showed that PTH and Vitamin D levels did not differ statistically among OSA subgroups. As Vitamin D was independently associated with HOMA-IR in OSA, it was stated that Vitamin D deficiency might play a role in the pathogenesis of insulin resistance in OSA.[24] Unlike other studies,[10,32,33] 25(OH)D levels did not differ between severe OSA and the controls in our study. In both controls and severe OSA, we found serum 25(OH)D median values <20 ng/mL, considered as deficient. However, 25(OH)D levels were lower in the third group compared to the second group. Moreover, our study found a relationship between 25(OH)D, PTH, and HOMA-IR. Furthermore, we found higher PTH levels in the severe OSA with higher HOMA-IR.

Table 4. Significant correlations between total testosterone and the other variables in the severe OSA group

Parameter	Total testosterone	
	r	p
CRP (mg/dL)	−0.319	**0.004**
Fibrinogen (mg/dL)	−0.400	**0.007**
HOMA-IR	−0.322	**0.033**
REM-AHI (events/h)	−0.414	**0.005**
NREM-AHI (events/h)	−0.464	**0.002**
SpO_2 minimum (%)	0.380	**0.011**
SpO_2<90 %	−0.358	**0.002**
AHI (events/h)	−0.531	**<0.001**
ODI (events/h)	−0.497	**0.001**

OSA: Obstructive sleep apnea; r: Spearman correlation coefficient; CRP: C-reactive protein; HOMA-IR: Homeostatic model assessment of insulin resistance; REM-AHI: Rapid eye movement phase AHI; NREM-AHI: Non-rapid eye movement phase AHI; AHI: Apnea-hypopnea index; SpO_2: Arterial oxygen saturation; ODI: Oxygen desaturation index

Vitamin D status related to overtime changes in patterns of sleep (sleep duration and quality) in a longitudinal study of

Table 5. Significant correlations between total testosterone and the other parameters in the severe OSA group with HOMA-IR≥3.54

Parameter	Total testosterone	
	r	p
HOMA-IR	−0.438	**0.042**
NREM-AHI (events/h)	−0.661	**0.001**
SpO_2<90 %	−0.440	**0.041**
AHI (events/h)	−0.633	**0.002**
ODI (events/h)	−0.610	**0.003**

OSA: Obstructive sleep apnea; HOMA-IR: Homeostatic model assessment of insulin resistance; r: Spearman correlation coefficient, NREM-AHI: Non-rapid eye movement phase AHI; SpO_2: Arterial oxygen saturation; AHI: Apnea-hypopnea index; ODI: Oxygen desaturation index

Table 6. Significant correlations between HOMA-IR and the other variables in the severe OSA group

Parameter	HOMA-IR	
	r	p
SIRI	0.383	**0.010**
ALT (IU/L)	0.452	**0.002**
PTH (pg/mL)	0.405	**0.006**
Total Testosterone (ng/dL)	−0.322	**0.033**
25-hydroxyvitamin D (ng/mL)	−0.334	**0.027**
AHI (events/h)	0.389	**0.009**
ODI (events/h)	0.396	**0.008**
Sleep efficiency (%)	0.304	**0.045**
TST (minutes)	0.305	**0.044**
N1 (TST%)	−0.382	**0.011**
REM-AHI (events/h)	0.376	**0.012**
NREM-AHI (events/h)	0.337	**0.025**
Mean SpO_2 (%)	−0.432	**0.003**
Minimum SpO_2 (%)	−0.398	**0.007**
SpO_2<90 (%)	0.453	**0.002**

HOMA-IR: Homeostatic model assessment of insulin resistance; OSA: Obstructive sleep apnea; r: Spearman correlation coefficient; SIRI: Systemic inflammatory response index; ALT: Alanine aminotransferase; PTH: Parathyroid hormone; AHI: Apnea-hypopnea index; ODI: Oxygen desaturation index; TST: Total sleep time; N1 (TST%): Percent of non-rapid eye movement Phase 1 in TST; REM-AHI: Rapid eye movement phase AHI; NREM-AHI: Non-rapid eye movement phase AHI; SpO_2: Arterial oxygen saturation

urban middle-aged adults.[34] Short sleep duration and OSA were shown to be independently linked to the risk of 25(OH)D deficiency.[35] In our study, 25(OH)D was moderately linked to (negatively) N2 in the severe OSA with higher HOMA-IR, so the previous report supports our finding.

The fact that this study, in which we investigated the effect of hypoxia and inflammation on metabolic processes, took place before the pandemic period should be considered as an aspect that strengthens the study. Furthermore, the groups did not differ in age, alcohol/smoking intake, comorbidities, renal/thyroid function, and serum levels of ferritin, folate, Vitamin B12, and 25(OH)D. Among the limitations, mild and moderate OSA patients were not included in our research. Moreover, TT levels might show deviations due to inflammation and metabolic status, and we could not use SHBG, free testosterone, follicle-stimulating hormone, and LH levels through our hospital records. We used serum TT levels measured by a chemiluminescence method; it could be better to serum free testosterone levels measured by mass spectrometer methods in this patient group. If it was a prospective design, it could add value to the questionnaire about ageing male symptoms and the international index of erectile function.

CONCLUSION

In severe OSA, TT was found significantly decreased. Moreover, TT was associated with inflammation status, insulin resistance, OSA severity, and hypoxia. OSA severity was inversely related with serum TT levels, regardless of BMI and age. Furthermore, HOMA-IR correlated with PTH and 25(OH)D in the severe OSA. Both inflammation and impaired glycometabolism might have an impact on the reduction of serum TT levels in OSA. Measurement of testosterone level is important in patients with OSA. Since testosterone deficiency could have a negative impact on sleep quality, it could be useful to monitor serum TT levels and to question about erectile/sexual dysfunction to improve the routine treatment process, especially based on the relationship with sleep parameters.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences İstanbul Training and Research Hospital Clinical Research Ethics Committee (No: 66, Date: 10/03/2023).

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