Tıkayıcı uyku apnesi sendromlu hastaların serum adiponektin düzeylerinin değerlendirilmesi

Evaluation of serum adiponectin levels in patients with obstructive sleep apnea syndrome

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ÖZET

Amaç: Serum adiponektin düzeylerinin obezite, hipertansiyon ve koroner arter hastalığı olan hastalarda daha düşük olduğu saptanmıştır. Çalışmamızda tıkayıcı uyku apnesi sendromunda (TUAS) serum adiponektin düzeyleri ve hastalığın şiddeti ile bu düzeylerin ilişkisi değerlendirildi. **Çalışma planı:** Polisomnografik yöntemle tanı konan TUAS'lı 62 hasta (39 erkek, 23 kadın) ve 32 olguluk kontrol (23 erkek, 9 kadın) grubunda serum adiponektin düzeyleri ELISA yöntemi ile ölçüldü. Hastalar apne- hipopne indeksine (AHİ) göre hafif (AHİ: 5-14), orta (AHİ: 15-29) ve ağır (AHİ ≥30) TUAS olarak sınıflandırıldı. Kontrol grubu AHİ <5 olarak tanımlandı. Açlık kan şekeri (AKŞ), total kolesterol (TK), trigliserid (TG), yüksek (HDL) ve düşük (LDL) molekül ağırlıklı kolesterol ölçümleri yapıldı ve sonuçlar gruplar arasında karşılaştırıldı. **Bulgular:** Hastaların ortalama yaşı (51,6±10,7 yıl) ve beden kütle indeksi (32,9±6,0 kg/m2), kontrol grubuna (48,3±10,8 yıl ve 31,±5,6 kg/m2) göre anlamlı bir fark oluşturmadı (p>0.05). Hasta ve kontrol grupları arasında hipertansiyonu ve diyabeti olanlar ile sigara içenlerin sayısı açısından da anlamlı bir fark saptanmadı. Serum TK, TG ve HDL kolesterol düzeyleri, hasta ve kontrol grubu arasında anlamlı bir fark oluşturmazken; serum adiponektin düzeyleri, hasta grubunda (3,0±3,4 µg/dl), kontrol grubuna (5.2±5.2 µg/dl) göre anlamlı olarak daha düşüktü (p=0,01). Serum adiponektin düzeyleri, AHİ ile anlamlı negatif korelasyon, (r= –0,221; p=0,03); minimum ve ortalama oksijen satürasyonları ile anlamlı olarak pozitif korelasyon gösterdi (r=0,213; p=0,04 ve r=0,205; p=0,05). **Sonuç:** TUAS'lı hastalarda, özellikle ağır TUAS grubunda, serum adiponektin düzeyleri anlamlı olarak azalmaktadır. Serum adiponektin düzeyleri, TUAS şiddeti ve arteriyel oksijen satürasyonları ile ilişkili bulunmuştur.

ABSTRACT

Objectives: Serum adiponectin levels have been found to be lower in patients with obesity, hypertension, and coronary artery diseases. In this study, we aimed to evaluate serum adiponectin levels in patients with obstructive sleep apnea syndrome (OSAS) and correlate these levels with the severity of OSAS. ***Study design:*** In 62 OSAS patients (39 males, 23 females) and 32 controls (23 males, 9 females) diagnosed by polisomnographic methods, serum adiponectin levels were analyzed by the ELISA method. Patients were classified as having either mild (apnea- hypopnea index, AHI: 5-14), moderate (AHI: 15-29) or severe (AHI >30) OSAS, and controls were defined as individuals with AHI <5. Plasma fasting glucose, total cholesterol (TC), triglyceride (TG), and high (HDL-C) and low-(LDL-C) density lipoprotein cholesterol levels were analyzed, and the results were compared between the groups. ***Results:*** There was no significant difference in mean age (51.6±10.7 years for patients, 48.3±10.8 years for controls) or body mass index (32.9±6.0 kg/m^2 for patients, 31.3±5.6 kg/m^2 for controls, p>0.05) in our study population. There was no significant difference in the number of hypertensive patients, diabetics, or smokers between the patients and the controls. While serum TC, TG, and HDL cholesterol levels were not significantly different between two groups, serum adiponectin levels of patients (3.0±3.4 pg/dl) were significantly lower than those of the controls (5.2±5.2 pg/dl, p=0.01). While serum adiponectin levels showed a significantly negative correlation with AHI (r=-0.221, p=0.03), there was a significantly positive correlation with minimum and mean oxygen saturations (r=0.213, p=0.04 and r=0.205, p=0.05). ***Conclusion:*** Serum adiponectin levels were significantly lower in patients with OSAS, especially for those in the severe OSAS group. Serum adiponectin levels are related to the severity of OSAS and arterial oxygen saturation

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Abbreviations:
AHİ Apnea-hypopnea index
FBG Fasting blood glucose
BMI Body mass index
DM Diabetes mellitus
HDL High- density lipoprotein
HT Hypertension
CAD Coronary artery disease
CV Cardiovascular
LDL Low- density lipoprotein
MetS Metabolic syndrome
TG Triglyceride
TC Total cholesterol
OSAS Obstructive sleep apnea syndrome
HMW High molecular weight

Obstructive sleep apnea syndrome (OSAS) may frequently accompany metabolic syndrome (MetS) in which endothelial dysfunction plays an important role, type 2 diabetes mellitus (DM), hypertension (HT), and coronary artery disease (CAD),[1-7] In addition, MetS can cause cardiovascular (CV) complicationa in the long-term, and increase mortality, and morbidity.[8,9] The most prominent risk factors for OSAS are obesity, and male gender, and other risk factors include greater neck circumference, smoking, alcohol, and sedative usage.[1-4] However, main risk factors for coronary atherosclerosis are advanced age, male gender, HT, DM, dyslipidemia, obesity, and smoking.

Even though physiological role of adinopectin which is a biologically active peptide derived from adipose tissue is not fully disclosed yet, its potential association with CV risk factors has been reported. In recent years, antiatherogenic, and antiinflammatory effects of endothelial cells, and macrophages have been demonstrated.[10-12] In some studies investigators reported that serum levels of adinopectin decreased in the presence of CAD, DM, and MetS [13-17], and suggested that normal or even higher serum adinopectin levels in healthy individuals might prevent emergence of CV diseases, and complications.[18]

In this study, CV risk factors, and serum adinopectin levels were evaluated in various OSAS groups, and probable association (if any) between the severity of OSAS, and adinopectin levels were investigated.

PATIENTS AND METHODS

Hundred and twenty two patients (age range: 28-74 years) who referred to sleep clinic of our hospital with complaints of snoring, daytime sleepiness, and evidenced apnea complaints, and had undergone polysomnographic examination were evaluated. Medical history of the cases was obtained, physical, echocardiographic examinations were performed. Twenty eight patients with ischemic heart disease, peripheral artery disease, chronic heart failure, cor pulmonale or renal failure were excluded from the study.

Polisomnographic examination was conducted in a silent, dark, ambient temperature controlled one-person rooms without allowing any comnpany.[19] Elektroencefalographic (EEG), electrooculographic (EOG), chin electromyographic (EMG), examinations, and oronasal air flow measurements (using a oronasal thermistor and nasal cannula) were performed. Movements of thoracic, and abdominal walls were evaluated. Arterial oxygen saturation (using a pulse oximeter) measurements, and ECG recordings were obtained [19,20] All recordings were evaluated by a pulmonologist specialized in sleep medicine . Interruption of oronasal air flow for ≥ 10 seconds was defined as apnea, at least 50 % decrease in the velocity of air flow for ≥ 10 seconds together with 3 % drop in oxygen saturation or wakening was defined as hypopnea.[21] Total number of apnea and hypopnea episeodes per hour of sleep was termed apnea hypopnea index (AHİ). Patients with an AHI of ≥5 was evaluated as having sleep apnea, and in those with an AHI of < 5 this diagnosis was excluded.[21] Sixty two (39 men, and 23 women) patients with a diagnosis of obstructive sleep apnea syndrome, and as a control group 32 cases with an AHI of < 5 (simple snoring) were included in the study. Based on their AHI values, the patients were divided into mild (AHİ 5-14), moderate AHİ 15-29), and severe (AHİ ≥30) OSAS groups.

In the study group after 12 hours of fasting period, blood glucose (FBG), total cholesterol (TC), triglyceride (TG), low (LDL) , and high- density lipoprotein cholesterol (HDL) levels were measured, and all other routine biochemical tests were performed in venous

blood samples. Venous blood samples drawn to measure adiponectin levels were centrifuged at 4000 rpm for 7 minutes. Serum samples obtained were equally divided into aliquots, and kept at -20°C in the laboratory. Adinopectin levels were measured using an ELISA kit (Adiponektin ELISA BioVendor, BioVendor lab. Medicine, Inc., Czech Rep)

Undersigned informed consent forms were obtained from all patients, and our study was approved by the local ethics committee of our hospital

Statistical analysis

Statistical analysis was performed using "Statistical Package for Social Sciences version 15.0" (SPSS-15.0, for Windows vista) package program. Continuous variables were expressed as mean ± standard deviation, and quantitative variables as numbers, and percentages. For the comparisons of numerical data, and evaluation of the groups with or without OSAS, Student's *t*-test, and for intragroup comparisons of OSAS groups Kruskal- Wallis test were used. Pairwise comparisons of the control, and OSAS groups were performed using Mann-Whitney U-test. Qualitative variables were compared using *chi*-square test. In the analysis of correlations between serum adiponectin levels, and some parametres, Pearson correlation test was used. P<0.05 was considered as statistically significant.

RESULTS

Comparisons between basic characteristics of the patient, and the control groups are shown in Table 1. Mean ages of the patient (51.6±10.7 years) , and the control (48.3±10.8 yıl) did not differ significantly (p>0.05). Besides, any significant difference was not detected between the patient, and the control groups as for body mass index (BMI), diastolic blood pressure, and number of patients with HT, diabetes, and smokers (p>0.05). However mean systolic blood pressure in the patient group was significantly higher (p=0.001). Mean AHI index score of the patient group was 33.0±27.6. (Table 1).

Table 1. Comparison of demographic, and polysomnographic characteristics, and cardiovascular risk in patients with obstructive sleep apnea syndrome, and the control group

	Patient group (n=62)			Control group (n=32)			
	n	%	mean ± SD	n	%	mean ± SD	*p*
Gender							
Male	39	62		23	72		AD
Female	23	38		9	28		AD
Age			51.6±10.7			48.3±10.8	AD
Body mass index (kg/m²)			32.9±6			31.3± 5.6	AD
Systolic blood pressure (mm Hg)			127.4±17.7			115.6±14.5	**0.001**
Diastolic blood pressure (mm Hg)			80.8±11.6			78.5±12.7	AD
Hypertensives	24	39		12	38		AD
Diabetics	13	21		6	19		AD
Smokers	18	29		6	19		AD
Drug usage							
Antihipertensives	24	39		12	38		AD
Statins	10	16		4	13		AD
Oral antidiabetics	13	21		6	19		AD
Apnea-hypopnea index (pts)			33.0±27.6			1.8±1.4	–
SaO_2 (%)							
Minimal SaO_2 (%)			90.3±5.3			94.6±1.9	–
Sleeping hours (h)			76.3±9.9			87.0±5.6	–
			6.8±1.1			5.5±1.34	AD

SaO_2: Mean oxygen saturation; AD: not significant

Mean serum adinopectin level was significantly lower in the OSAS group (OSAS group: 3.0±3.4 µg/dl; control group: 5.2±5.2 µg/dl) (p=0.01) (Table 2). Any significant difference in TC, TG, and HDL-C levels between OSAS, and control groups was not observed, while LDL-C values in the patient group were significantly lower (Table 2). However FBG levels were significantly higher in the patient group (OSAS group: 111.2±24.7 mg/dl; control group (100.7±17.7 mg/dl) (p=0.04).

Table 2. Evaluation of fasting blood sugar, lipid, and serum adinopectin levels in the obstructive sleep apnea syndrome, and control groups

	Patient (n=62)	Control (n=32)	p
FBG (mg/dL)	111.2±24.7	100.7±17.7	**0.04**
TC (mg/dL)	202.5±40.0	217.7±32.3	AD
TG (mg/dL)	179.2±118.0	190.3±90.2	AD
HDL-C (mg/dL)	43.2±15.0	41.8±9.7	AD
LDL-C (mg/dL)	123.5±35.6	140±31.3	**0.02**
Adinopectin (µg/dL)	3.0±3.4	5.2 ± 5.2	**0.01**
(Min & max	0.42 - 36.0	0.40 - 24.2	

FBG: fasting blood glucose; TC: total cholesterol; TG: triglyceride; HDL; high-density cholesterol; LDL: low-density lipoprotein

Comparisons between OSAS subgroups, and the control group with respect to basic characteristics, variables of sleep recordings, and laboratory test values are shown in Table 3. Serum adinopectin levels in OSAS subgroups, and the control group were significantly different (p=0.01) (Figure 1 and Table 3). Besides, significant intergroup differences existed as for systolic blood pressure, and fasting blood glucose levels (p=0.01, and p=0.03).

A significant difference was not found between subgroups of OSAS (mild, moderate, severe) as for systolic blood pressure, and fasting blood glucose levels. All of these parametres differed significantly between the control group, and each of the subgroup of OSAS. (p values for adinopectin in comparisons between control/mild OSAS, and control/severe OSAS were 0.03, 0.01, and 0.007; corresponding p values for systolic blood pressure 0.04, 0.02, and 0.003, and for FBG were 0.04, 0.04, and 0.004, respectively).

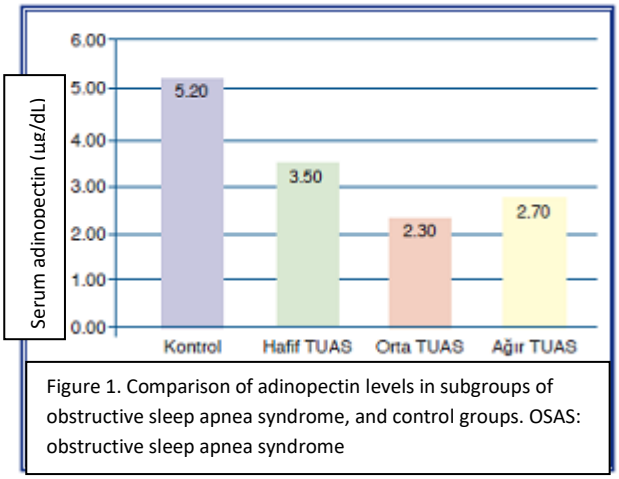

Figure 1. Comparison of adinopectin levels in subgroups of obstructive sleep apnea syndrome, and control groups. OSAS: obstructive sleep apnea syndrome

Table 3: Comparison of demographic characteristics, sleep study variables, and laboratory test values in subgroups of obstructive sleep apnea syndrome, and the control group

	Control AHI <5	Mild OSAS AHI 5-14	Moderate OSAS AHI 15-29	Severe OSAS AHI ≥ 30)

	Kontrol AHİ <5 (n=32)	Hafif TUAS AHİ 5-14 (n=25)	Orta TUAS AHİ 15-29 (n=12)	Ağır TUAS AHİ ≥30 (n=25)	p*
Age (years)	49.4±10.2	48.8±10.6	58.7±8.6	50.0±11.7	AD
Body mass index (kg/m^2)	31.0±5.6	32.1±6.6	32.7±5.8	34.0±5.5	AD
Systolic blood pressure (mm Hg)	116.0±14.5	124.4±19.0	129.2±16.2	129±17.7	**0.01**
Diastolic blood pressure (mm Hg)	78.5±12.7	79.0±11.0	84.2±15.0	81.2±10.5	AD
Apnea-hypopnea index (pts)	1.8±1.4	9.0±2.6	23.4±4.6	61.6±20.4	**0.0001**
SaO_2 (%)	94.6±1.9	94.0±2.0	90.6±3.8	86.6±5.8	**0.0001**
Minimal SaO_2 (%)	87.0±5.7	83.0±5.9	76.4±7.3	69.7±10.1	**0.0001**
Total cholesterol (mg/dL)	218.0±32.4	210.0±43.0	196.3±31.3	197.8±40.4	AD
Triglyceride (mg/dL)	193.0±90.2	189±73.4	170.0±69.4	174.0±167.0	AD
HDL-C (mg/dL)	41.8±10.0	47.0±20.9	42.3±9.4	40.0±8.0	AD
LDL-C (mg/dL)	140.0±31.3	124.0±43.7	123.8±36	123.0±27.0	AD
Fasting blood glucose (mg/dL)	103.4±27.4	107.9±23.2	111.8±32.3	114.2±22.5	**0.03**
Adinopectin (µg/dL)	5.2±5.2	3.5±4.2	2.3±1.2	2.7±3.2	**0.01**
Min & max	0.40 - 24.2	0.42 - 15.8	0.56 - 36	0.58 - 28.1	

* Related to the comparison of all groups: OSAS: obstructive sleep apnea syndrome; SaO_2: oxygen saturation; HDL; high-density lipoprotein cholesterol; LDL-C: low- density lipoprotein cholesterol

In our study a significant correlation between serum adinopectin levels, BMI, and lipid parametres was not detected (p>0.05). However serum adiponectin levels demonstrated a significantly negative correlation with AHİ (r= -0.221, p=0.03) (Figure 2a), and a significantly positive correlation with minimal, and mean oxygen saturations (r=0.213, p=0.04) (Figure 2b), (r =0.205, p=0.05) (Figure 2c).

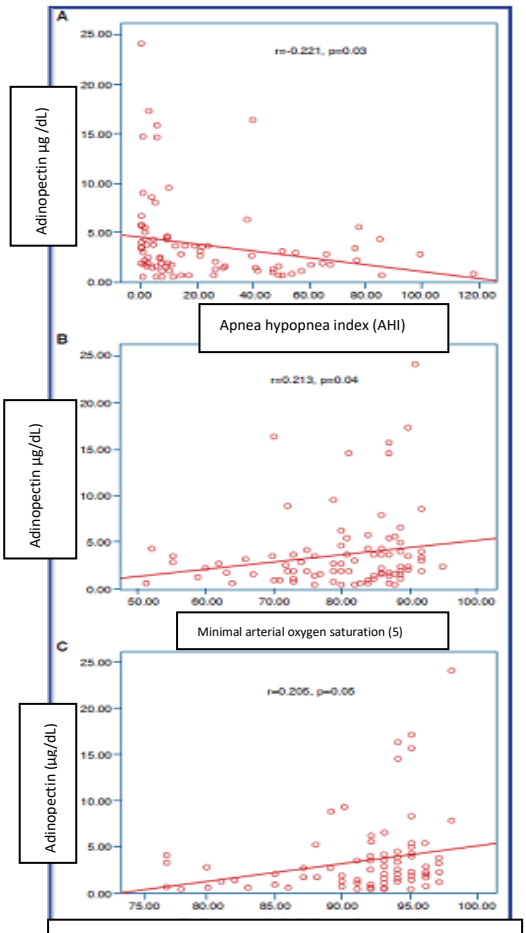

Figure 2. Correlation between serum adinopectin levels and (A) apnea-hypopnea index, (B) minimal oxygen saturation (C) mean oxygen saturation

DISCUSSION

In recent years adinopectin which is released from adipose tissue has been associated with cardiovascular risk factors.[12-17] If potential development of long-term cardiovascular complications in OSAS is considered,[1,8,9] assessment of serum adinopectin levels and investigation of possible correlation (if any) between severity of the disease, and arterial oxygen saturations in these patients, convey importance. Significant decrease in serum adiponectin levels in patients with OSAS relative to controls, and detection of a correlation between its levels, and the severity of the disease are fundamental outcomes of our study. Positive correlation between minimal, and average serum adinopectin levels with arterial oxygen saturation is another important consequence of our study. In a study, authors demonstrated relatively decreased serum adinopectin levels in patients with OSAS when compared with simple snorers, and suggested that OSAS might induce a decrease in adinopectin levels.[22] Similarly, in a study performed by Kanbay et al [23] markedly decreased adinopectin levels were found in the OSAS group independent from obesity. In a separate study conducted by Masserini et al .[24] , OSAS group of 46 obese patients were compared with 37 healthy control subjects with normal body weights, and apparently decreased serum adinopectin levels were revealed in OSAS group independent of BMI, and insulin resistance. However in another study, although a positive correlation was detected between the severity of OSAS (AHI index scores), and serum leptin levels, Any significant correlation between serum adinopectin levels, and AHI was not detected. The authors also suggested that serum adinopectin levels are regulated independently from the presence of OSAS.[25]

In an *in vivo* and *in vitro* experimental model realized by Nagakawa et al.[26], the authors demonstrated that hypoxic stress leads to a significant decrease in serum adinopectin levels. In their study, investigators asserted that nocturnal decrease in serum adinopectin levels might constitute a risk factor for cardiovascular events in patients with OSAS.[26]

Obstructive sleep apnea syndrome is a cardiovascular risk factor independent from age, gender, habit of cigarette smoking.[8,27] In a study where the association between serum adiponectin levels, and severity of angiographically established coronary disease was evaluated, decrease in serum adinopectin levels which became more prominent as the severity of the coronary lesion increased was demonstrated . It was also asserted that decrease in serum adiponectin levels might indicate multivessel disease, rather than a single vessel disease.[28] In our review article where cardiovascular biomarkers were evaluated in patients with sleep apnea syndrome, we emphasized that serum adinopectin levels decrease in patients with OSAS which might be a predictive marker for future cardiovascular events.[29]

Even though multivariate analysis was not performed in our study, inability to detect a statistically significant difference between the patient, and the control groups as for age, BMI, blood pressure values, and number of diabetics, hypertensives, and smokers, suggest the presence of a direct relationship between a decrease in serum adinopectin levels of the patients, and OSAS. Significantly positive correlation between serum adiponectin levels, and AHI also supports this outcome.In other words, AHI scores which indicate severity of the disease increase, serum adinopectin levels decrease. Besides, detection of significantly positive correlations between serum adiponectin levels, and minimal, and average arteriial oxygen saturations is another consequence of our study. In conditions of decreased arterial oxygen saturations (hypoxia), serum adinopectin levels also decrease, and also concomitant increases are observed in both parametres.

Decreased secretion of some cytokines, like adinopectin induced by activation of the sympathetic system, might trigger cardiovascular outcomes of obstructive sleep apnea syndrome. Association between severity of OSAS, and risk of CAD might stem from unfavourable effects of hypoxia observed on endothelial function, sympathetic hyperactivation, increase in inflammatory response and /or classical risk factors (obesity, HT, insulin resistance, and hyperlipidemia) frequently associated with OSAS. .[30] Hyperactivation observed in patients with OSAS, induce insulin resistance even in non-obese patients, and insulin resistance augment the effects of oxidative stress on vascular wall contributing to the development of HT, and vascular remodelling.[31] In a study, decrease in serum adinopectin levels (hypoadiponectinemia) had been associated with activation of the sympathetic system, and severity of OSAS.[32]

Although important role of inflammation at the onset, and progression of an atherosclerotic disease is already recognized, all of biochemical, and cellular events leading to induction, and progression of an atherosclerotic disease have not been fully elucidated, yet. Also, mechanisms

triggering inflammation have not been defined, so far. Some studies demonstrated decreased levels of adiponectin in the presence of CAD, DM, and MBS..[30-32] ıt was suggested that in healthy individuals normal or even higher serum adiponectin levels might prevent emergence of cardiovascular diseases, and complications.[18] However many studies revealed that as a paradoxal finding, in patients with heart failure, serum adinopectin levels were significantly higher than those encountered in healthy individuals. However, this condition remains to be fully explained.[33-35]

Some investigations revealed a negative correlation between serum adinopectin levels, and fasting plasma insulin, fasting blood glucose, and glucose levels at postprandial 2. hour glucose tolerance test, systolic, and diastolic blood pressure, total, and LDL cholesterol, TG, and uric acid levels, and a positive correlation between serum adinopectin levels, insulin sensitivity, and HDL-C concentrations.[36,37] However, in our study, a significant correlation between serum adinopectin levels, and the abovementioned parametres could not be demonstrated. Inability to disclose such a correlation might be attributed to scarce number of our study population. Even though, a significant difference could not be detected between the patient, and the study groups as for HT, mean systolic blood pressure in cases with OSAS systolic blood pressure was significantly higher than controls.

High molecular weight (HMW) adinopectin is the active form of adinopectin, and constitutes most of the intracellular adinopectin. HMW adinopectin plays a more active role in glucose, and lipid metabolism relative to total adinopectin..[12] Inoue et.al.[38] found a correlation between levels of HMW adinopectin, and vasospastic angina pectoris, stable angina pectoris, and myocardial infarction in their study group of 149 patients. They demonstrated that, relative to cases with single vessel CAD, multivessel CAD patients had relatively lower HMW adinopectin levels, and decreased HMW levels had predictive value for DM, insulin resistance, hs- CRP, and cardiovascular events [38] However, in our study, serum adinopectin levels were measured, but its molecular forms were not evaluated. Still, in our study decreased total adinopectin levels in patients with OSAS relative to controls, also suggest the possibility of lower HMW adinopectin levels in cases with OSAS

Limitations of the study

Scarce number of our cases constitute an important limitation of our study. As another limitation of our study, though diabetic cases were included in our study, those with insulin resistance, and MetS were not evaluated separately. In our study, the effects of serum adinopectin levels on potential development of cardiovascular events in the future were not investigated either. . This limitation of our study obviously needs further experimental studies, and prospective, long-term investigations to be performed. Lack of any multivariate analysis conducted between serum adiponectin levels, and age, gender, BMI, HT, and DM. İs another limitation of our study. Since as a recognized fact, serum adiponectin levels change with age, and a positive correlation exists between age and adiponectic levels[39], decrease in serum adinopectin levels in patients with OSAS relative to younger control patients is noteworthy which partly compensates for lack of multivariate comparisons.

Conclusion

Serum adinopectin levels of the patients with obstructive sleep apnea decrease significantly, and this decrease is more prominent in patients with severe OSAS. Serum adinopectin levels is associated with arterial oxygen saturations, and AHI which reflects the severity of OSAS. Relatively lower serum adiponectin levels in the OSAS group might be result of nocturnal hypoxemia, and excessive sympathetic activation. Indeed, significant, and positive correlation between serum adinopectin levels, and arterial oxygen saturation supports this argument. In patients with OSAS, serum adinopectin levels can be a new marker just like major cardiovascular risk factors as HT, obesity, MetS, and dyslipidemia

Conflict of interest: None declared

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