ORIGINAL ARTICLE

PLASMA ADIPONECTIN LEVELS IN OBSTRUCTIVE SLEEP APNEA: A CROSS SECTION STUDY

Ambreen Qamar, Shazia Nazar*, Fareeha Butt*, Farah Iqbal, Shumaila Rehmani***, Zeba Haque†**

Department of Physiology, Dr. Ishrat-ul-ebad Khan Institute of Oral Health Sciences, *Dow Medical College, Dow University of Health Sciences, **Department of Radiology, Dallah Hospital, Riyadh, KSA, ***Fellow MSPH Public Health, AAPNA Institute, Jinnah Sindh Medical University, †Department of Biochemistry, Dow International Medical College, Dow University of Health Sciences, Karachi, Pakistan

Background: Obstructive sleep apnea (OSA) is a disorder of airway obstruction during sleep with multisystem implications and associated complications, while mostly underdiagnosed and undertreated. It has drawn more attention in recent years with a substantial increase in its prevalence. Studies reported inconclusive results for the association of adiponectin with OSA as a reliable biomarker. The present study aimed to evaluate this association. **Methods:** A total of 88 participants, including 44 apnea subjects and 44 controls, fulfilling the inclusion and exclusion criteria, were selected for this cross-sectional study performed from Dec 2018 to Jan 2020. Apnea subjects were selected after confirmation of their OSA by overnight polysomnography, and classified into mild, moderate, and severe OSA groups based on their Apnea-Hypopnea Index (AHI). Blood samples were collected in EDTA-containing tubes and Enzyme-link immune-sorbent assay (ELISA) was done for plasma levels of adiponectin. SPSS-20 was used for analysis of the data. **Results:** Mean adiponectin level was significantly higher in controls as it was 9.16±3.54 µg/ml for controls and 3.47±2.03 µg/ml for OSA. Comparison between different OSA sub-group revealed mean adiponectin as 3.99±1.69, 2.73±1.65, and 3.64±2.30 µg/ml in mild, moderate, and severe OSA groups respectively. **Conclusion:** Lower plasma adiponectin levels were identified among OSA subjects as compared to controls. Lower levels of adiponectin are associated with the presence of OSA and could be helpful to identify subjects who are at risk for OSA-related comorbidities.

Keywords: Obstructive sleep apnea, OSA, Biomarker, Adiponectin, Sleep-related breathing disorder

Pak J Physiol 2023;19(1):17–20

INTRODUCTION

Obstructive sleep apnea (OSA) is an underrated but common chronic condition with repetitive episodes of complete or partial upper airway obstruction during sleep. This complete (apnea) or partial (hypopnea) airway obstruction causes deficient oxygen supply to the blood and leads to intermittent hypoxia and hypercapnia. Breathing efforts against a collapsed airway may lead to awakening and sleep fragmentation.[1] The prevalence of OSA in the general population has been reported as 9–38%. OSA has been identified as a risk factor for the development of cardiovascular diseases, hypertension, neurocognitive issues, insulin resistance, daytime sleepiness, road traffic, and other occupational accidents. OSA along with its comorbidities is a well-known reason for the excessive burden on healthcare resources.[2]

Disruption of sleep due to episodes of arousal and negative intra-thoracic pressure is reported to be responsible for the sympathetic and parasympathetic imbalance. Increased sympathetic tone has also been reported during wakefulness in these subjects. It can be correlated with enhancing the risk for cardiovascular disorders in OSA.[3] Studies suggested that the presence of systemic inflammation and intermittent hypoxia-related free radicals are related to the progression of metabolic deregulations, insulin resistance, neurodegenerative diseases, obesity, and multiple cardiovascular complications.[4]

Polysomnography is the gold standard diagnostic test for OSA.[5] The severity of OSA, based on the number of apnea and hypopnea in one hour of sleep called as Apnea-Hypopnea Index (AHI).[1] Continuous positive airway pressure (CPAP) therapy is considered as gold standard treatment for OSA, helpful to decrease/ mitigate respiratory obstruction and hypoxemia during sleep.[6] OSA has been considered a global health issue and numerous research studies are carried out to identify its etiology and its association with the progression of several pathophysiological feathers related to a large spectrum of comorbid conditions.

Adipose tissue is a central player in our body with its role in metabolic regulation. It is related to the production and release of multiple peptide hormones collectively known as adipokines. These adipokines are bioactive molecules that act in a paracrine and endocrine manner. One of the most important adipokines is adiponectin. Adiponectin is known to have antiatherogenic, anti-inflammatory, antidiabetic, and cardioprotective properties. Low level of adiponectin has been reported to have an association with multiple diseases such as metabolic disorders, type-2 diabetes, obesity, cardiovascular diseases, coronary artery

diseases, hypertension, etc.[4,7,8] Low level of adiponectin is commonly found in various states of insulin resistance as well.[4] Due to its antiatherogenic and insulin-sensitizing properties, it protects against type 2 diabetes and atherosclerosis.[9] Its dwell role as an anti-inflammatory molecule as well as a pro-inflammatory molecule, multiple physiological functions, and its relation with many diseases make it an attractive target for research studies.

The incidence and prevalence of OSA are likely to be increased dramatically with the conditions of obesity, CVDs, and insulin resistance. Thus, it is clinically significant to analyse the potential biomarkers with the presence of OSA and its related comorbidities. Studies have examined the association of adiponectin with OSA. Some epidemiological studies demonstrated that levels of adiponectin among OSA patients were found to be lower as compared to non-OSA patients. A recent study suggested that it is the presence of oxidative stress in OSA which is responsible for the low level of this adipokine. Study described that OSA causes oxidative damage to plasma proteins and lipids that led to reduced levels of adiponectin.[4] Some studies described adiponectin as an independent indicator of OSA severity and mentioned the role of intermittent hypoxia in mitochondrial damage and disruption in adiponectin secretion.[10] However, the association of adiponectin in OSA still has contradictory results. Some studies demonstrated its lower levels among OSA patients while contrary to it, some studies didn't find any association of adiponectin with OSA or any sleep parameter. Neither any change in adiponectin levels after apnea treatment (CPAP).[11,12] The association between adiponectin and OSA could be multidirectional and complicated. Studies that are in favour of a causal relationship between adiponectin and OSA also proposed the intermediate role of adiponectin for OSA related comorbidities. The aim of this study was to assess the association between adiponectin levels and OSA.

MATERIAL AND METHODS

A total of 88 participants were included in this cross-sectional study performed in the Polysomnography Laboratory of Dow University of Health Sciences Karachi from December 2018 to January 2020. Ethical approval was granted by the Ethical Review Board of the University. Case subjects were selected from subjects coming to the sleep laboratory, for the diagnosis of their apnoea. Referral of patients was from sleep OPD Dow University as well as from different hospitals/clinics of Karachi and other cities due to their signs and symptoms of sleep-related breathing disorders.

Inclusion criteria were the presence of snoring, excessive daytime sleepiness (EDS) with an Epworth Sleepiness Scale (ESS) Score of more than 9, witnessed apnea, and an indication of Polysomnography. The ESS is a questionnaire with 8 questions about different life situations, which can indicate daytime sleepiness if the score is more than 9.[13] Exclusion criteria were pregnancy, recent surgery, and current active illness.

Each suspected case of OSA reached the Sleep laboratory between 9 to 10 PM on their respective booked night for polysomnography. Along with a verbal explanation of the procedure, written permission was signed by the patient or accompanied relative, on approved consent forms prepared in Urdu and English. Medical and personal history, anthropometric measurements, medical examination, and all relevant information were recorded on an approved Performa. All subjects were monitored in a dark comfortable room temperature by a sleep lab technician through a fixed camera. No drug was used to induce sleep. A multichannel polysomnographic machine system (Philips Respironic Alice 5 and Alice 6) was used to perform split night polysomnography. The results provided details for apnea-hypnea index (AHI), gas exchange parameters, the percentage of the total sleep time, electrocardiogram, electromyogram, electroencephalogram, chest and abdominal wall movement, sleep efficiency, the spontaneous arousal index and the respiratory arousal index.[14] Based on AHI they were categorized as mild apnea group (AHI=5–15), moderate apnea group (AHI 15–30), and severe apnea group (AHI >30). This categorization was based on criteria specified by the American Academy of Sleep Medicine (AASM).[15]

Polysomnographically diagnosed OSA subjects gave a blood sample in the next morning for Plasma Adiponectin measurement, in a vacutainer tube containing ethylene diamine tetra acetic acid (EDTA). Subjects without any signs and symptoms of OSA and ESS score less than 9 (n=44) were selected as the control group. To extract plasma from the samples, centrifugation was performed and the extracted plasma samples were stored at -80 °C up to further processing.

Enzyme-link immune-sorbent assay (ELISA) kit (DIA source, S.A. Belgium) was used and standard protocol was followed for sample handling, temperature maintenance, and all working procedures. Dichromatic readings were used after calculation of the mean of duplicate determinations.

SPSS-20 was used for analysis of the data. Descriptive statistics were used to describe the frequencies. Independent sample *t*-test was used to compare the means between cases and controls, and $p \leq 0.05$ was considered statistically significant.

RESULTS

Study results described the gender distribution as 61.3% (n=54) males and 38.7% (n=34) females. The mean age (47.76±13.71 years), mean BMI (29.976±6.9947), and

mean plasma adiponectin level (6.3179±4.05360) for the study group are tabulated in Table-1. The mean age comparison in cases and controls (49.89±15.07 *vs* 45.64±11.99) showed no significant difference (p=0.146) between groups. Mean ESS score, BMI, and adiponectin are tabulated as Table-2. Mean Adiponectin level for the control group was 9.16±3.54 µg/ml and it was 3.47±2.03 µg/ml for the OSA group (p=0.000) (Table-2). Comparison between groups of different OSA severity showed mean adiponectin in mild apnea group as 3.99±1.69, in moderate apnea as 2.73±1.65, and in severe apnea group as 3.64±2.30 µg/ml, showing comparatively higher plasma adiponectin levels in mild apnea group as compared to moderate and severe apnea group. Study results describe significantly lower levels of adiponectin in OSA subjects as compared to controls.

Table-1: Age, anthropometric parameters, and serum adiponectin level of the subjects (n=88)

Variables	Minimum	Maximum	Mean±SD
Age	21	85	47.76±13.71
BMI	13.4	45.8	29.98±6.99
Weight	36	164	82.27±21.33
Height	143.0	210.7	165.34±10.18
Adiponectin (µg/ml)	0.62	17.54	6.32±4.05

Table-2: Baseline characteristics of the subjects (Mean±SD)

Characteristics	Controls	Cases	*p*
Age (Years)	45.64±11.99	49.89±15.07	0.146
Height (Cm)	164.73±9.91	165.95±10.37	0.574
Weight (Kg)	70.83±14.60	93.70±20.95	0.000*
BMI	26.23±5.46	33.71±6.36	0.000*
ESS Score	3.27±2.70	13.16±4.40	0.000*
Plasma Adiponectin (µg/ml)	9.160±3.54	3.4755±2.03	0.000*

Independent samples *t*-test was applied. *Significant

Table-3: Comparison of mean baseline characteristics between controls and OSA cases (Mean±SD)

	Controls (n=44)	Mild OSA (n=10)	Moderate OSA (n=12)	Severe OSA (n=22)	*p*
Age (Years)	47.76±13.71	48.30±13.53	52.58±19.70	49.14±13.32	0.433
BMI	26.23±5.46	30.89±5.55	31.67±7.26	36.15±5.41	0.000*
ESS Score	3.27±2.70	9.00±2.98	11.67±2.74	15.86±3.85	0.000*
AHI score	0.00±0.00	8.67±3.57	24.50±5.79	52.65±15.04	0.000*
Plasma Adiponectin (µg/ml)	9.160±3.54	3.99±1.69	2.73±1.65	3.64±2.30	0.000*

ANOVA was applied. *Significant

DISCUSSION

This study assessed the plasma level of adiponectin in OSA patients as compared to the control subjects. The frequency of male subjects was higher as compared to females. There were no significant differences in age among the study participants. The adiponectin levels were significantly low in OSA patients in comparison to the controls. The plasma adiponectin levels in the mild apnea group were found higher as compared to the moderate and severe apnea groups. Similar results were reported by Vatansever *et al*[4] who examined their Turkish population and described low adiponectin levels in mild and moderate-severe apnea cases as compared to control subjects, although their sample size was small as compared to the current study. Mutairi *et al*[10] also described similar results in their study population in Kuwait. Their study emphasized that adiponectin should be considered a protective hormone whose plasma levels are supposed to be inversely related to many diseases. Similar results were also demonstrated by Bingol *et al*[16] with lower adiponectin levels in OSA patients. They reported that adiponectin levels have a significant role in OSA and could also have an association with OSA-related comorbidities.

Contrary to our findings, De Lima *et al*[11], and Zhang *et al*[12] described no significant association between adiponectin and OSA. Both studies also evaluated the effect of OSA treatment and described no effect of treatment on adiponectin levels.

Different mechanisms have been proposed to explain the association of adiponectin with OSA. It is suggested that the recurrent hypoxia with reoxygenation episodes, arousals, and sleep fragmentations in OSA subjects might be responsible for the activation of oxidative stress and higher sympathetic activity which may lead to decreased levels of adiponectin. OSA has been identified as the reason to elevate inflammatory cytokine as well. It is also proposed that higher levels of some inflammatory cytokines like TNF-α have an inhibitory effect on the synthesis and secretion of adiponectin.[4]

Mutairi *et al* described that intermittent hypoxia in OSA is responsible for mitochondrial dysfunction, imbalance in some regulatory hormone secretions, and alteration in adiponectin release. All these factors could have a strong association with different clinical and metabolic perturbations that lead to the risk of diabetes and CVDs in OSA subjects.[10] Lu *et al*[9] also explained that hypoxia could be the main factor, responsible for this association. They emphasized that OSA induced-hypoxia reduces the levels of adiponectin through disruption of the mechanism that is responsible for adiponectin secretion. However, Sanchez-de-la-Torre *et al*[17] suggested that obesity is also a major factor that could contribute significantly to a reduced level of adiponectin among OSA patients. Their study described no independent association between adiponectin levels and OSA.

Zhang DM *et al*[12] mentioned obesity as an important factor for the presence of OSA as well as for

lower adiponectin levels. Their study emphasized that hypoxia, insulin resistance, inflammation, and obesity are the major factors or proposed mechanisms that are associated and interlinked with reduced plasma levels of adiponectin in OSA.[12]

Low plasma adiponectin levels were also reported by Lavie *et al*[18] who explained that low levels of adiponectin are associated with OSA because OSA develops oxidative damage to plasma proteins and lipids, leading to reduced levels of adiponectin. However, Li X *et al*[19] emphasized that the association between plasma levels of adiponectin and OSA is multidirectional and could be dependent on several confounding factors.

CONCLUSION

Adiponectin could be a useful circulatory biomarker in OSA subjects. Its low levels could be helpful for diagnosis and to recognize those who are at higher risk for OSA-related comorbidities. It can also be used as a feasible marker in OSA treatment follow-ups, especially in setups where polysomnography is not easily available. Association between adiponectin and OSA should be verified given the number of several confounding factors. Further study on a large sample size might be a future implication of this work that will expand the scope of this study.

ACKNOWLEDGMENTS

We are thankful to the team of Polysomnography Laboratory, Dow University of Health Sciences, Karachi for their valuable support in this study.

REFERENCES

1. Unnikrishnan D, Jun J, Polotsky V. Inflammation in sleep apnea: an update. Rev Endocr Metab Disord 2015;16(1):25–34.
2. Shiffman HS, Khorsandi J, Cauwels NM. Minimally invasive combined Nd:YAG and Er:YAG laser-assisted uvulopalatoplasty for treatment of obstructive sleep apnea. Photobiomodul Photomed Laser Surg 2021;39(8):550–7.
3. Kheirandish-Gozal L, Bhattacharjee R, Gozal D. Autonomic alterations and endothelial dysfunction in pediatric obstructive sleep apnea. Sleep Med 2010;11(7):714–20.
4. Vatansever E, Surmen-Gur E, Ursavas A, Karadag M. Obstructive sleep apnea causes oxidative damage to plasma lipids and proteins and decreases adiponectin levels. Sleep Breath 2011;15(3):275–82.
5. Hussain I, Hossain MA, Jany R, Bari MA, Uddin M, Kamal ARM, *et al*. Quantitative evaluation of EEG-biomarkers for prediction of sleep stages. Sensors (Basel) 2022;22(8);3079.
6. Bock JM, Vungarala S, Karim S, Somers VK. Obstructive sleep apnea as a cardiovascular risk factor—beyond CPAP. Can J Cardiol 2021;37(5):756–65.
7. da Silva Rosa SC, Liu M, Sweeney G. Adiponectin synthesis, secretion and extravasation from circulation to interstitial space. Physiology (Bethesda) 2021;36(3):134–49.
8. Najafi A, Mohammadi I, Sadeghi M, Bruhl AB, Sadeghi-Bahmani D, Brand S. Evaluation of plasma/serum adiponectin (an anti-inflammatory factor) levels in adult patients with obstructive sleep apnea syndrome: A systematic review and meta-analysis. Life (Basel) 2022;12(5);738.
9. Lu M, Fang F, Wang Z, Wei P, Hu C, Wei Y. Association between serum/plasma levels of adiponectin and obstructive sleep apnea hypopnea syndrome: a meta-analysis. Lipids Health Dis 2019;18(1):30.
10. Al Mutairi S, Mojiminiyi OA, Al Alawi A, Al Rammah T, Abdella N. Study of leptin and adiponectin as disease markers in subjects with obstructive sleep apnea. Dis Markers 2014;2014:706314.
11. de Lima AM, Franco CM, de Castro CM, Bezerra Ade A, Ataide L Jr, Halpern A. Effects of nasal continuous positive airway pressure treatment on oxidative stress and adiponectin levels in obese patients with obstructive sleep apnea. Respiration 2010;79(5):370–6.
12. Zhang DM, Pang XL, Huang R, Gong FY, Zhong X, Xiao Y. Adiponectin, omentin, ghrelin, and visfatin levels in obese patients with severe obstructive sleep apnea. Biomed Res Int 2018;2018:3410135.
13. Guo Q, Song WD, Li W, Zeng C, Li YH, Mo JM, *et al*. Weighted Epworth sleepiness scale predicted the apnea-hypopnea index better. Respir Res 2020;21(1):147.
14. Molero-Ramirez H, Tamae Kakazu M, Baroody F, Bhattacharjee R. Polysomnography parameters assessing gas exchange best predict postoperative respiratory complications following adenotonsillectomy in children with severe OSA. J Clin Sleep Med 2019;15(9):1251–9.
15. McNicholas WT. Diagnostic criteria for obstructive sleep apnea: time for reappraisal. J Thorac Dis 2018;10(1):531–3.
16. Bingol Z, Karaayvaz EB, Telci A, Bilge AK, Okumus G, Kiyan E. Leptin and adiponectin levels in obstructive sleep apnea phenotypes. Biomark Med 2019;13(10):865–74.
17. Sanchez-de-la-Torre M, Mediano O, Barcelo A, Pierola J, de la Pena M, Esquinas C, *et al*. The influence of obesity and obstructive sleep apnea on metabolic hormones. Sleep Breath 2012;16(3):649–56.
18. Lavie L. Oxidative stress in obstructive sleep apnea and intermittent hypoxia--revisited--the bad ugly and good: implications to the heart and brain. Sleep Med Rev 2015;20:27–45.
19. Li X, He J. The association between serum/plasma leptin levels and obstructive sleep apnea syndrome: A meta-analysis and meta-regression. Front Endocrinol (Lausanne) 2021;12:696418.

Address for Correspondence:

Dr Ambreen Qamar, Associate Professor of Physiology, Dr. Ishrat-ul-ebad Khan Institute of Oral Health Sciences, Dow University of Health Sciences, Karachi, Pakistan. **Cell:** +92-300-0200277
Email: ambreen.qamar@duhs.edu.pk

Received: 16 Jun 2022 **Reviewed:** 28 Dec 2022 **Accepted:** 31 Dec 2022

Contribution of Authors
AQ: Concept, Design,Drafting and literature review
SN: Aqeusition of data and revising critically
FB: Aqeusition of data and accountable on all aspect of the work
FI: Data analysis, interpretation of data and tabulation
SR: Aqeusition of data and referencing
ZH: Final approval

Funding: None
Conflicts of interest: None