Metabolic Signature and Obstructive Sleep Apnea in Nepalese Patients

Avatar Verma[1] Narendra Bhatta[1] Deebya Raj Mishra[1] Rejina Shahi[1] Augraj Uprety[1] Prakash Aryal[1] Devesh Kumar Yadav[1] Urmila Lama[2]

[1] Department of Pulmonary, Critical Care and Sleep Medicine, B. P. K.I.H.S, Dharan, Nepal
[2] Department of Pediatrics and Adolescent Medicine, BPKIHS, Dharan, Nepal

ABSTRACT

Introduction: Untreated Obstructive Sleep Apnea (OSA) causes sleep related symptoms and also causes increased incidence of RTA, cardiovascular diseases and all cause mortality. Currently OSA has been recognized as the consequence of number of interrelated metabolic and oxidative pathologies. As there are limited data of association of OSA with metabolic stress and its correlation with severity of OSA, study of metabolic profile of these patients in view of defining the Metabolic signature of OSA was carried out in eastern Nepal.

Objectives: To study metabolic profile of OSA and its association with clinical severity.

Methods: Hospital based descriptive cross-sectional study. Biochemical profile results related to metabolic –oxidative pathway of the OSA patients were obtained. Quantitative and qualitative data were obtained. Quantitative data were compared using Mann–Whitney test while qualitative variables compared using Pearson $\chi 2$. Correlation was carried out using Pearson and Spearman's test. P-value<0.05 considered significant.

Results: 33 patients of OSA were enrolled. Majority of patients had deranged metabolic and oxidative parameters despite mild OSA. Among metabolic stress parameters, most commonly deranged were decreased high density lipoprotein (HDL), increased mean arterial pressure (MAP), waist circumference (WC) and raised fasting blood sugar (FBS). Increased MAP and increased WC was significantly corelated with severity.

Conclusion: Besides symptom complex, OSA is also harbinger of metabolic stress that can lead to various cardiometabolic diseases and premature mortality thus early recognition and treatment can mitigate these consequences.

Keywords: Metabolic parameters; Stress; Obstructive Sleep Apnea

INTRODUCTION

OSA is most common Sleep Related Breathing Disorders (SRBD).[1] Untreated OSA contributes towards increased incidence of cardiovascular disease, stroke, hypertension, diabetes, cognitive dysfunction, motor vehicle accident and all-cause mortality.[2] Patients with OSA often have co-existent risk factors for cardiovascular disease such as obesity, hypertension, dyslipidemia, and impaired glucose tolerance.[3] Many diseases with abnormalities related to metabolic stress result in characteristic biochemical changes prior to development of clinical symptoms.[4] These biochemical changes of the specific disease can be described as the metabolic signature of that particular disease. These signatures improve identification of early, easier diagnosis and also aid in predicting prognosis of disease.[5] Since at present we cannot apply the perfect metabolic signature, combining different biochemical test results will provide information compensating for the shortcoming of individual metabolic signature.

Therefore, within this background, we studied the metabolic profile of patients with OSA and attempted to describe the Metabolic signature of OSA by combining different biochemical test and also explored the relationship of Metabolic signature with severity of OSA.

Corresponding author:
Avatar Verma
Department of Pulmonary, Critical Care and Sleep Medicine, BPKIHS
Sunsari, Province no.1, Nepal
avatar4ktm@yahoo.com

METHODS

Hospital based cross sectional study carried out in the Department of Critical Care and Sleep Medicine at B.P. Koirala Institute of Health Sciences (BPKIHS), a tertiary care university teaching hospital in Dharan, Nepal. 33 patients diagnosed as OSA according to AASM sleep criteria by standard PSG and giving informed consent were enrolled in the study, and was conducted from July 2nd 2021 to April 1st 2022 after informed consent from patient and approval from Institute's Ethical Review Board. Inclusion Criteria: a) Adults > 18 years; b) OSA according to AASM Sleep Criteria; c) History of OSA based on laboratory PSG; d) Patients not using continuous positive airway pressure (CPAP) therapy, oral appliances or any other treatment for OSA. Patients who were known case of ischemic heart disease and poorly controlled chronic respiratory disease were excluded from study.

Detailed history including risk factors and comorbidities was taken and examination was done. Waist circumference (WC) and Blood pressure (BP) was measured during the time of enrolment. Biochemical parameters such as Fasting blood sugar (FBS) and lipid profiles including Total Cholesterol (TC), High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL) was measured in BPKIHS laboratory. Measured WC, BP, FBS as well as lipid profile in combination was considered as metabolic signature. Waist circumference of 102 cm for male and 88 cm for female was cut off value for increased waist circumference. Patients were considered as hypertensive or having raised blood pressure when mean arterial pressure (MAP) ≥ 92 mmHg.[6] Deranged lipid profiles were considered when TC ≥200 mg/dl; HDL <40 mg/dL in males and <50 mg/dL in females; LDL ≥130 mg/dl; TG ≥150 mg/dl; Fasting blood sugar was considered normal when below 100 mg/dl, impaired when between 100 and 124.9 mg/dl and deranged when above or equal to 125 mg/dl. Sleep study was conducted at sleep laboratory using a digital system (EMBLA S 4500; Embla Systems, Broomfield, CO) at the sleep laboratory during the subject's habitual sleep time. Apnea, Hypopnea, Obstructive apnea or central apnea were diagnosed according to AASM criteria. Quantitative and qualitative data were expressed as frequencies and percentages, respectively. Quantitative data were compared using Mann–Whitney U test while qualitative variables were compared using Pearson Chi square test. Correlation of variables with normal distribution was carried out using Pearson Correlation test, whereas Spearman's rho test was used for variables without normal distribution. For inferential statistics Mc Nemar $\chi 2$ test and paired t-test were utilized with a confidence interval of 95%, and a p value of <0.05 inferring statistical significance. The results were illustrated in tabular and graphical formats. Data were analysed using SPSS version 20.0.

RESULTS

A. Baseline characteristics of study population:

During the study period of one year, we enrolled 33 patients of polysomnography confirmed OSA. Among our study subjects 16 (51.5%) were female and 17 (48.5%) were male. Mean age of patients in our study was 47.97±16.47 years. The baseline characteristics of the study population are displayed in Table 1. Age and gender distribution of patients presenting with OSA are depicted in Figure 1 and Figure 2.

Table 1. Baseline characteristics of the patients presenting with OSA

Characteristics	Category	Number	Percentage (%)
Age (years)	<45	12	36.4
	45-59	12	39.4
	≥60	8	24.2
Gender	Male	16	48.5
	Female	17	51.5
Occupation	Agriculture	5	15.2
	Business	12	36.4
	Student	3	9.1
	Household	13	39.4
Residence	Non-plain area	8	24.2
	Plain area	25	75.8
Education	Formal	19	57.6
	Informal	14	42.4

Figure 1. Age distribution of patients presenting with OSA

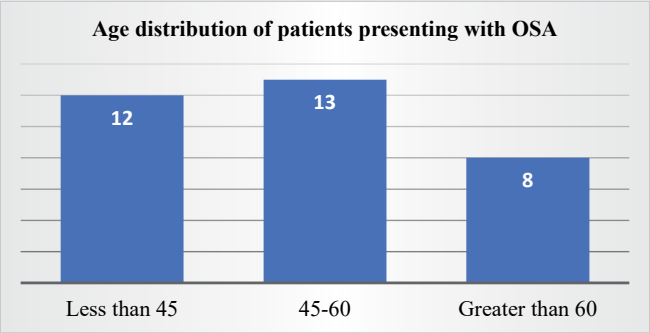
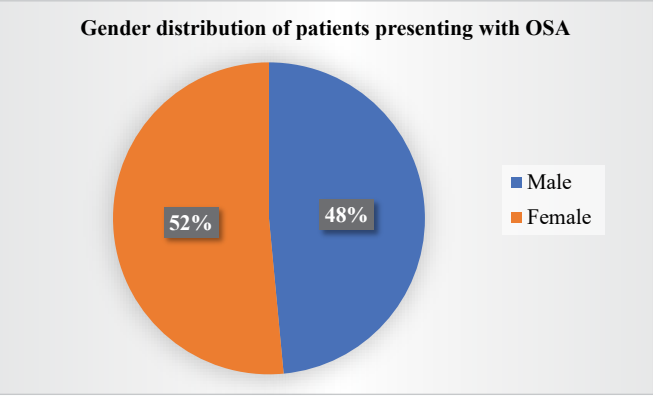


Figure 2. Gender distribution of patients presenting with OSA



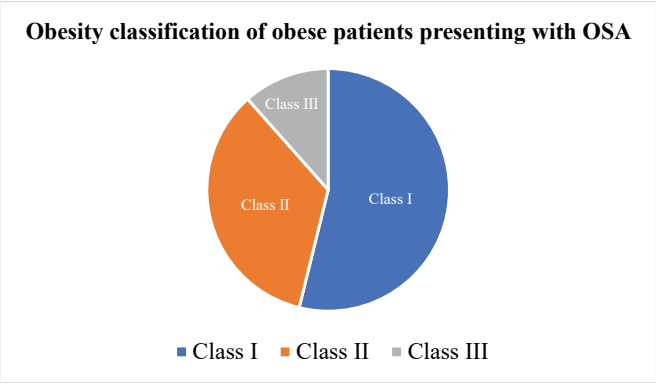
B. Risk characterisation of patients presenting with OSA

Most of our patients, 26 (78.8 %) were obese with BMI of 30 kg/m^2 and average BMI of patients presenting with OSA was 33.42±5.77 kg/m^2. Male patients presenting with OSA had lower BMI (30.16±3.65 kg/m^2) compared to female patients (36.49±5.78 kg/m^2) which was statistically significant (p=0.001). 69.7% also had increased waist circumference and average waist circumference of the patients presenting with OSA was 104.55±10.66 cm. Average waist circumference of female patients with OSA were larger than male patients and was also statistically significant (p=0.18). Increased waist circumference was also corelated significantly with severity of OSA (r=0.377, p=0.015). Risk characterization of patients presenting with Obstructive Sleep Apnea is illustrated in Table 2. Similarly, obesity classification is represented by Figure 3.

Table 2. Risk characterization of patients presenting with OSA

Characteristics	Category	Number	Percentage (%)
Obesity	Class I	14	42.4 (53.8)
	Class II	9	27.3 (34.6)
	Class III	3	9.1 (11.5)
	Total	26	78.8
Increased waist circumference		23	69.7
Smokers	Current	4	12.1
	Former	10	30.3
	Total	14	42.4
Alcohol consumption		14	42.4
Indoor Air Pollution		14	42.4

Figure 3. Obesity classification of patients presenting with OSA



C. Sleep related complaints among the Patients Presenting with OSA

Most common sleep related presenting complaint among patients presenting with OSA in our study was snoring which was present in 31 (93.9%) patients followed by excessive daytime sleepiness seen in 28 (84.8%), 18 (54.5%) patients also complaints of restlessness during sleep and/or sleep fragmentation. Sleep related complaints among the patients presenting with OSA is depicted in Table 3.

Table 3. Sleep related complaints among the Patients Presenting with OSA

Sleep related complaints	Frequency	Percentage
Snoring	31	93.9 %
Excessive daytime sleepiness	28	84.8%
Restlessness during sleep and/or Sleep fragmentation	18	54.5%
Cessation of breathing during sleep	10	30.3%

D. Severity characterization of Patients Presenting with OSA based upon Polysomnography:

Based upon sleep study results, we subcategorise the patients presenting with OSA in different severity grade. Majority of patients had mild OSA, followed by moderate and severe respectively. Mean level of AHI observed was 18.22±16.93. Comparing gender difference in OSA severity, mild and moderate OSA was more common in female however severe OSA was more common in male though this difference was not statistically significant (p=0.343). Severity categorization of OSA based upon polysomnography and categorisation of OSA severity in relation with gender is represented by Figure 4. and Figure 5.

Figure 4. Severity categorization of patients presenting with OSA based upon polysomnography

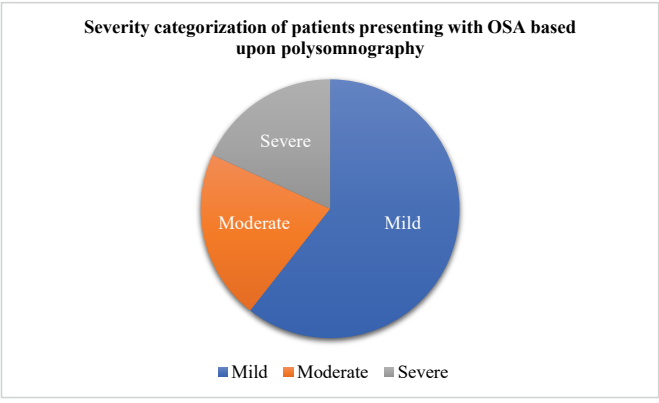
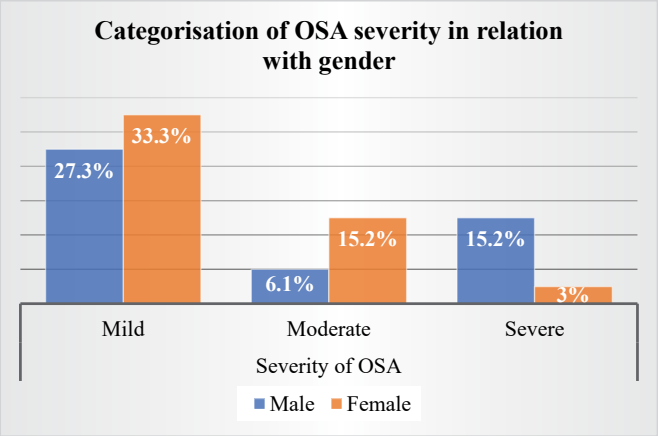


Figure 5. Categorisation of OSA severity in relation with

gender



E. Abnormalities in the parameters of Metabolic Profile among the Patients Presenting with OSA

Our study research revealed deranged metabolic parameters in most of the OSA patients. Most of them, 25 (75.8%) of patients had decreased HDL level with mean value of 38.72±10.21 mg/dl. MAP was increased in 24 (72.7%) respectively with average value of 100.57±14.98 mg/dl which was significantly corelated with severity of OSA (r=0.579, p=0.001). Other metabolic parameters were also deranged as depicted in above table such as TG, FBS, LDL and TC level. Abnormalities in the parameters of metabolic profile among the patients of OSA is represented by table 4.

Table 4. Abnormalities in the parameters of metabolic profile among the patients presenting with OSA

Parameters of Metabolic Profile	Frequency (%)		Mean±S.D.	Range	r	p-value
HDL (mg/dl)	Decreased	25 (75.8%)	38.72±10.21	13-69	0.200	0.265
MAP (mmhg)	Elevated	24 (72.7%)	100.57±14.98	73-137	0.579	0.001
TG (mg/dl)	Elevated	20 (60.6%)	186.58±95.39	80-512	0.011	0.475
FBS (mg/dl)	Impaired	13 (39.4%)	120.48±73.97	63-437	**-0.176**	0.327
	Deranged	6 (18.2%)				
LDL (mg/dl)	Elevated	8 (24.2%)	110.90±41.50	13-205	-0.**166**	0.356
TC (mg/dl)	Elevated	6 (18.2%)	188.48±52.31	84-295	**-0.204**	0.255

DISCUSSION

We have described the contemporary clinical presentation and demographics of patients presenting with OSA in Nepal with their divergent clinical characteristics as well as unique and specific sleep abnormality in sleep studies and metabolic profile. We also combined certain anthropometric measurement, MAP and different biochemical profile results related to metabolic pathway of these patients and expressed it as a distinct Metabolic signature of OSA in Nepal. This signature revealed important clinical utility in subcategorizing OSA into different severity sub groups in combination with sleep studies and clinical symptoms among Nepalese patients.

Majority (75.8%) of patients presenting with OSA in our study were from geographical area of plain terrain in Nepal which has hotter and more humid climate in most of the time in year. Recent studies indicate that ambient temperature may modulate OSA severity.[7]

Our study reveals interesting gender-related aspects in the clinical presentation of OSA. The difference can be observed in all aspects of the presentation of OSA right from symptoms, PSG features, to the treatment. The typical patient present at our study center in need of evaluation of OSA is quite different from the classical picture of the male, obese, and sleepy patient, suggesting that different clinical faces of OSA exist in Nepalese population. Furthermore, female patients with sleep apnea in Nepal tend to present differently from male patients and they are harder to diagnose. Female patients with OSA in Nepal predominantly present with nonspecific symptoms such as fatigue and sleep fragmentation, insomnia, depressive symptoms, and discordant results exist regarding the reporting of snoring, apneas, and excessive daytime sleepiness. Due to this "atypical" clinical presentation, female patients are likely to be misdiagnosed and treated for other diseases, such as depression and are diagnosed with OSA later, when they are older and have more severe OSA.

One of the remarkable finding in our study was higher prevalence of OSA among women of age 60 years. The severity of OSA in Nepalese women seem to be attenuated in the postmenopausal years that is in fifth to sixth decade of life as menopause may influence the sleep architecture. It is also worth noting menopausal status in female patients needs to be taken into account during clinical evaluation for OSA risk, as well as in the diagnosis and treatment of OSA among Nepalese patients. This new information and evidence of these gender-related differences in clinical presentation of OSA in female patients and especially searching for surrogate features of insomnia, poor sleep quality, in female patients may contribute to an increased awareness of this condition among clinicians and improved screening of OSA and referrals for diagnosis. It is also important to point out that despite less severe OSA in terms of AHI; female patients in our study population were not less symptomatic compared to males. It is also plausible to state that sex differences in aging, hormones, upper airway anatomy, fat distribution, and respiratory stability in OSA may also play a role. The upper airways in female patients are less collapsible and more stable during sleep than in male patients, as a result of various complex mechanisms, including the modulating effects of sex hormones.[8]

78.8 % of our patients presenting with OSA were obese with BMI of 30 kg/m^2 or more, of which majority of them around were class I obese. Obesity is a well-recognized risk factor for OSA. Higher body mass index (BMI) is associated with greater severity of OSA for both sexes, for the same AHI, women tend to be more obese than men. Hormones may also play a role in the distribution of body fat. Postmenopausal women have a higher fat mass compared to the period prior to menopause, and fat distribution is more likely to be in the upper body and trunk area compared with the lower body. Fat distribution has physiological as well as mechanical effects in patients with OSA.[8] Obese women, especially those with moderate OSA, have significantly increased hypercapnic and hypoxic responses; there may also be gender differences in the arousal response to apneas. One possibility is that the long-term effects of REM sleep disruption contribute to greater symptomatology at lower AHI values in women compared with men.[9]

Besides increased BMI, around 70% of our study patients had increased waist circumference, a central obesity marker and was also significantly corelated with severity of OSA proving itself as better severity and obesity marker in Nepalese population. Already there are numerous studies considering increased waist circumference as better marker for increased metabolic and cardiovascular risk.[10] Adding to it there are studies which considered increased waist circumference as better marker of presence as well as severity markers of OSA and was proven in our study as well.[11] This could be important finding while screening for OSA as well as aid in developing newer risk or severity score in OSA patients even in Nepalese population.

Result of polysomnography, among the patients presenting with OSA were characteristically unique in our study. Interestingly Men with OSA reported higher Apnea/Hypopnea Index (AHI) compared to female. An interesting finding is that women are symptomatic at lower AHI cut-off values compared with men with the same AHI. Women with moderate OSA may be more symptomatic because they have more episodes of upper airway resistance during sleep. Obstructive events can be thought of as a continuum from partial to complete upper airway obstruction. Upper airway resistance alone, without complete obstructive apnea or respiratory disturbance, has been shown to produce clinical symptoms such as daytime fatigue and which are symptoms reported by women with OSA. Sleep architecture is another aspect that has been shown to differ between males and females. The occurrence of multiple episodes of upper airway resistance without frank apneas means that an AHI value may not provide a physician with a true indication of the degree of sleep fragmentation being experienced by patients.[9] Our study also reveals that female OSA patients with milder OSA displayed significant number of hypopneas associated with arousal from sleep, they contribute towards significant daytime fatigue to the point where treatment may be of benefit. Growing evidence suggests that mild OSA is associated with reduced quality of life, including general tiredness, fatigue, daytime impairment, difficulty concentrating and completing tasks, depressed mood, poor sleep quality and poor psychomotor performance. Therefore, it is important to correctly diagnose and treat OSA before the disease becomes more severe.

Risk characterization of patients presenting with OSA revealed interesting findings that nearly 50% of the patients presenting with OSA had history of tobacco smoking and significant exposure with indoor air pollution. Reports revealed prevalence of male smoker is about 27.2 % and that of female is around 8.4 % in Nepal.[12] However there are no studies revealing prevalence of smoking among patients presenting with OSA. There are studies from other countries revealing increased OSA and its severity among smokers.[13] Plausible explanation of which could be increased risk of respiratory diseases among smokers which is already are established risk factors of OSA. Indoor air pollution is common in Nepal due to increased use of biomass fuels and woods while cooking and poor ventilation that too led to increased respiratory disease burden and ultimately increase odds of OSA.[14] Though most of the patients were not suffering from any respiratory morbidity suggesting smoking and indoor air pollution as independent risk factor among OSA patients. This relation also highlights importance of newer disease burden among older risk factor and also will help to advocate screening of OSA among such group of patients and proceeding for polysomnography even with low screening score in these sorts of patients. It also provides opportunity to modify existing screening OSA scoring system or adding a newer score system encompassing these risk factors.

Patients presenting with OSA revealed interesting sleep related complaints, majority of them snores however excessive daytime sleepiness and sleep fragmentation

during sleep were also reported by substantial number of patients. Though commonly only snoring in Nepalese social construct is considered as symptoms of OSA that too when it is loud and disturbs his/her bed partner and most of the patients of our study came for the same. Though there are studies from Nepal where other symptoms were also seen in patients of OSA such as choking during sleep and excessive sleepiness however most of them only presented when they had snoring.[15] In our study substantial number of patients had excessive daytime sleepiness and sleep fragmentation suggesting that other symptoms should also be enquired during OSA patients screening.

Interestingly majority of our patients had mild OSA, mild and moderate OSA was more common in female however severe OSA was more common in male. Majority of study done in OSA usually comprise of moderate to severe OSA but in our study majority of patients were having mild OSA. This could indicate that facial abnormalities, obstructive causes or obesity is not so much prevalent in Nepalese patients especially in eastern part. It is well known form other studies also that female patients had lower AHI compared to male one for same BMI or other risk factors.[9] Same finding was seen in our study also despite fact that majority of mild to moderate OSA patients were female.

The metabolic parameters were deranged in most of the OSA patients. Most of them, 25 (75.8%) of patients had evidence of abnormalities in their lipid profiles. As OSA is generally considered only disease leading to increase sleepiness and snoring, many studies have revealed deranged metabolic parameters in OSA patients.[16,17,18] Same finding was reflected in our patients as well where most of the patients had deranged lipid profile and raised fasting blood sugar level from prediabetic level to overt diabetes. The most surprising was that it was seen in population where most of the patients were suffering from milder disease suggesting greater impact of OSA in causing metabolic derangements in Nepalese population.

Thus, based upon these findings of our study, we conclude that OSA in Nepalese population is a complex multifactorial disease with distinct phenotypes and exhibits a phenotypic shift, from a "local" to a "systemic" disease, the association of OSA and metabolic dysfunction represents a harmful background, which has a profound Cardio-Metabolic-Hyperinflammatory-Endocrinological consequences.

OSA in Nepal presents with divergent clinical characteristics as well as unique and specific sleep abnormality in sleep studies and metabolic-oxidative profile. Results from our study also provide the evidence and basis for recommending the use of targeted sleep history among the patients presenting specific Metabolic signature even in the absence of specific sleep related symptom in order to diagnose OSA, especially in females in Nepal.

We believe that information generated from this study might also have the prognostic and public health relevance as OSA although highly prevalent in Nepal, is largely undetected and undetectable using a symptom based strategy. Yet, even mild forms are associated with clinical, cardio-metabolic and pulmonary derangements. OSA is an increasing major health concern affecting a large number of middle aged subjects in Nepal and contributes to the etiologies of a wide range of health effects that extend far beyond the one specific domain.

One of the major limitation in our study was small sample size and inclusion of limited number of biochemical tests and other measurement denoting metabolic stress which on inclusion would have given more clarity regarding association of these signatures with OSA in Nepalese patients.

CONCLUSIONS

OSA is not uncommon disease because of increasing obesity, sedentary lifestyle, unhealthier feeding habits and poor sleep hygiene. It is harbinger of large number of metabolic and cardiovascular disease as well as major cause of unintended road traffic accidents leading to significant morbidity and mortality. There are scarce data on its prevalence and characteristic features among OSA patients of Nepal. Different biochemical profile results related to metabolic pathway of patients were combined to express distinct Metabolic signatures of OSA in Nepalese patients that also had utility in subcategorizing these patients into severity level. Based, upon findings of our study, we conclude that OSA in Nepalese population is a complex multifactorial disease with distinct phenotypes and association of OSA with metabolic dysfunction represent a harmful background, which has profound Cardio-Metabolic-Hyperinflammatory-Endocrinological consequences. The consequences of undiagnosed and untreated OSA are serious, and medical and societal costs are very high. Early identification of those patients with yet undiagnosed OSA and treating them is therefore vital. This will assist clinicians with the development of clinical care protocol for local contextual setting for identification and treatment of even mild forms of OSA and sleep related breathing disorders and assure that these are implemented in routine pulmonary practice.

Conflict of Interest: None

REFERENCES

1. Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc. 2008;5(2):136-43. [Pubmed]
2. Kim J, Tran K, Seal K, Fernanda A, Glenda R, Messier R, et al. Interventions for the Treatment of Obstructive Sleep Apnea in Adults: A Health Technology Assessment. Canadian Agency for Drugs and Technologies in Health; 2017;6(1b):1-22. [Pubmed]

3. Soneja M, Singh V. Metabolic abnormalities in obstructive sleep apnea: A double whammy. Lung India. 2012;29(2):107-8. [Pubmed]
4. Hutcheson R, Rocic P. The Metabolic Syndrome, Oxidative Stress, Environment, and Cardiovascular Disease: The Great Exploration. Exp Diabetes Res. 2012;2012: 271028. [Pubmed]
5. Sharifi-Rad M, Anil Kumar N V., Zucca P, Varoni EM, Dini L, Panzarini E, et al. Lifestyle, Oxidative Stress, and Antioxidants: Back and Forth in the Pathophysiology of Chronic Diseases. Front Physiol. 2020;11:694. [Pubmed]
6. Melgarejo JD, Yang WY, Thijs L, Li Y, Asayama K, Hansen TW, et al. Association of Fatal and Nonfatal Cardiovascular Outcomes with 24-Hour Mean Arterial Pressure. Hypertension. 2020;77:39–48. [Pubmed]
7. Valham F, Sahlin C, Stenlund H, Franklin KA. Ambient temperature and obstructive sleep apnea: effects on sleep, sleep apnea, and morning alertness. Sleep. 2012;35(4):513-7. [Pubmed]
8. Wellman A, Redline S. Sleep Apnea. In: Jameson JL, Kasper DL, Longo DL, Anthony S. Fauci, Hauser SL, Loscalzo J et al., editors. Harrison's Principles of Internal Medicine. 20th ed. New York: Mc Graw Hill; 2018:2013-9. [Internet]
9. Wimms A, Woehrle H, Ketheeswaran S, Ramanan D, Armitstead J. Obstructive Sleep Apnea in Women: Specific Issues and Interventions. Biomed Res Int. Biomed Res Int. 2016;2016:1764837. [Pubmed]
10. Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. Am J Clin Nutr. 2004;79(3):379–84. [Google Scholar]
11. Young T, Skatrud J, Peppard PE. Risk Factors for Obstructive Sleep Apnea in Adults. J Am Med Assoc. 2004;291(16):2013-6. [Pubmed]
12. Khanal GN, Khatri RB. Burden, prevention and control of tobacco consumption in Nepal: a narrative review of existing evidence. Int Health. 2021;13(2):110–21. [Pubmed]
13. Bielicki P, Trojnar A, Sobieraj P. The impact of smoking status on obstructive sleep apnea (OSA) severity. Eur Respir J. 2018;52(62):4356. [Google Scholar]
14. Ghimire S, Mishra SR, Sharma A, Siweya A, Shrestha N, Adhikari B. Geographic and socio-economic variation in markers of indoor air pollution in Nepal: evidence from nationally-representative data. BMC Public Health. 2019;19(1):195. [Pubmed]
15. Chokhani R, Pathak V, Kanth R. Sleep apnoea syndrome in Nepal. Nepal Med Coll J. 2005;7(1):32–5. [Pubmed]
16. Wu WT, Tsai SS, Shih TS, Lin MH, Chou TC, Ting H, et al. The association between obstructive sleep apnea and metabolic markers and lipid profiles. PloS one. 2015;10(6):e30279. [Pubmed]
17. Silva LOE, Guimarães TM, Luz GP, Coelho G, Badke L, Almeida IR, et al. Metabolic Profile in Patients with Mild Obstructive Sleep Apnea. Metab Syndr Relat Disord. 2018;16(1):6–12. [Pubmed]
18. Togeiro SM, Carneiro G, Ribeiro Filho FF, Zanella MT, Santos-Silva R, Taddei JA, et al. Consequences of obstructive sleep apnea on metabolic profile: A Population-Based Survey. Obesity. 2013;21(4):847–51. [Pubmed]