Accessible at: http://jkb.ub.ac.id/index.php/jkb/article/view/2235
Jurnal Kedokteran Brawijaya Vol. 30, No. 2, Agustus 2018, pp. 133-137
Article History: Received 27 Februari 2018, Accepted 24 April 2018
Translated Version

Original Research

Hubungan Tingkat Risiko *Obstructive Sleep Apnea* dan Sindroma Metabolik dengan Fungsi Kognitif Global

The Correlation of Obstructive Sleep Apnea Risk level and Metabolic Syndrome with Global Cognitive Functions

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ABSTRAK

Obstructive sleep apnea (OSA) berhubungan dengan peningkatan risiko gangguan fungsi kognitif, dan gangguan fungsi kognitif tersebut juga terkait dengan komponen sindrom metabolik (hipertensi, diabetes melitus, obesitas sentral, dan dislipidemia). Penegakan diagnosis penyakit tersebut membutuhkan keahlian khusus, waktu pemeriksaan yang lama, dan mahal, oleh karena itu penapisan tingkat risiko OSA dengan instrumen sederhana sangat diperlukan. Penelitian ini bertujuan untuk menginvestigasi tingkat risiko OSA dan sindroma metabolik dengan fungsi kognitif global. Desain potong lintang dilakukan dengan melibatkan 89 subjek yang datang dalam acara *Car Free Day* dan memenuhi kriteria inklusi. Data yang dikumpulkan meliputi usia, jenis kelamin, riwayat hipertensi, dislipidemia, diabetes melitus, indeks massa tubuh (IMT), obesitas sentral, tingkat risiko OSA, dan fungsi kognitif global. Tingkat risiko OSA dinilai dengan menggunakan instrumen *STOP-BANG Questionnaire* dan fungsi kognitif global menggunakan instrumen *Clock Drawing Test* (CDT). Hasil penelitian menunjukkan terdapat perbedaan bermakna dalam hal frekuensi subjek dengan tingkat risiko tinggi OSA (p=0,042) dan subjek dengan diabetes melitus (p=0,04) antara kelompok subjek dengan status fungsi kognitif global normal dan menurun. Hasil penelitian juga menunjukkan bahwa hanya satu komponen sindroma metabolik, yaitu hipertensi yang berhubungan dengan tingkat risiko OSA (p<0,001), sedangkan diabetes melitus, obesitas sentral dan dislipidemia tidak. Dapat disimpulkan bahwa tingkat risiko OSA berhubungan dengan status fungsi kognitif global dan komponen sindroma metabolik yang berperan adalah diabetes melitus dan hipertensi.

Kata Kunci: Fungsi kognitif global, *obstructive sleep apnea,* penapisan, sindrom metabolik, tingkat risiko

ABSTRACT

Obstructive sleep apnea (OSA) is related to an increased risk of cognitive function impairment, and cognitive impairment is also associated to metabolic syndrome components (hypertension, diabetes mellitus, central obesity, and dyslipidemia). The diagnosis of the disease requires special skills, long examination time, and is expensive; therefore, OSA risk screening with simple instruments is necessary. This study aimed to investigate the OSA risk level and metabolic syndrome with global cognitive function. Cross-cut design was carried out by involving 89 subjects who came in a Car Free Day event and met the inclusion criteria. Data collected included age, gender, hypertension history, dyslipidemia, diabetes mellitus, body mass index (BMI), central obesity, OSA risk level, and global cognitive function. OSA risk level was assessed using STOP-BANG Questionnaire while global cognitive function by using Clock Drawing Test (CDT) instrument. The results show a significant difference in the frequency of subjects with high risk OSA (p=0.042) and subjects with diabetes mellitus (p=0.04) between the subjects with normal and declining global cognitive function status. The results also show that only one component of metabolic syndrome, i.e. hypertension, is associated with OSA risk level (p<0.001), whereas diabetes mellitus, central obesity, and dyslipidemia are not. It can be concluded that OSA risk level is related to the status of global cognitive function and the acting components of metabolic syndrome are diabetes mellitus and hypertension.

Keywords: *Global cognitive function, metabolic syndrome, obstructive sleep apnea, risk level, screening*

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DOI: http://dx.doi.org/10.21776/ub.jkb.2018.030.02.10

INTRODUCTION

Obstructive sleep apnea (OSA) is a form of sleep disorder that is associated with an increasing risk of metabolic syndrome, cardiovascular diseases, and cognitive function disorders (1-3). The prevalence of OSA varies greatly in various countries in the world, ranging from 9% to 38%, and is higher among male population (4). OSA prevalence data in Indonesia is currently not available, but one study in a normal population in Jakarta shows that the prevalence of OSA in that particular region was 49.5% (5).

OSA diagnosis using polysomnographic examination requires special expertise, long examination time, and is expensive (6). Therefore, although screening for the initial level of OSA risk in individuals is highly needed at the population level, confirmation of the diagnosis can only be done in individuals with high risk levels. Screening the OSA risk level requires an instrument that is simple, easy to apply, and validated. The STOP-BANG Instrument Questionnaire is the right instrument for that purpose. This instrument has been validated in the general population and in hospital patients (7-9). This instrument has also been used in Asian populations (10).

Impaired cognitive function related to OSA, theoretically, is closely related to the occurrence of intermittent hypoxia in OSA patients which triggers cerebral vascular endothelial dysfunction. This results in the formation of free radicals and the occurrence of an inflammatory response in the brain that leads to the neurodegeneration process (11). The brain structures that are most susceptible to the neurodegeneration process are mainly hippocampus and frontal lobes, which are important structures for cognitive function formation (12). One study showed that the neurodegeneration process associated with OSA increased the presence of the metabolic syndrome (13).

Metabolic syndrome is one of the risk factors for OSA. In addition, several components of the metabolic syndrome, i.e. hypertension and obesity, are the constituent components of the STOP-BANG Questionnaire (7,14). Impaired cognitive function in OSA patients can be a result of OSA disease or associated with OSA risk factors, including metabolic syndrome components. Studies in sub-population in Mataram found that among the components of the metabolic syndrome, hypertension had the highest prevalence (15). This study aimed to investigate the influence of OSA factors and risk levels on global cognitive function in subjects who have never been diagnosed with OSA before in Mataram.

METHOD

This research was a cross-sectional study involving subjects who came to Car Free Day activities that are routinely held every Sunday in Mataram, West Nusa Tenggara. Subjects were selected using a non-probability sampling technique with inclusion criteria, namely men or women aged ≥40 years, fully aware, and willing to participate as research subjects. Subjects were excluded if they had a history of being diagnosed with OSA or decided not to continue their participation in the study. This research was carried out for 3 months, February-April 2017, after obtaining approval from the ethics commission. The implementation of this research was approved by the Health Ethics Research Commission University of Mataram through Ethics Approval No. 81/UN18.8/ETIK/2017.

Data collected in this study included demographic characteristics (age and sex) and clinical characteristics (hypertension, diabetes mellitus, body mass index (BMI), central obesity, dyslipidemia, OSA risk level, and global cognitive function status) of the subjects. The data were obtained through structured interviews, physical examination of the subject, and laboratory examinations. Subjects were categorized as having central obesity if the waist circumference measurement was ≥90cm for men and ≥80cm for women and categorized as dyslipidemia if serum HDL cholesterol levels were <40 mg/dl for men and <50 mg/dl for women (16).

OSA risk levels were measured using the STOP-BANG Questionnaire instrument. The instrument consisted of 8 questions that confirmed whether the subject was snoring at night, had tiredness, episodes of not breathing during sleep that can be seen by the partner (observed apnea), hypertension, body mass index (BMI) >35 kg/m^2, age > 50 years, result of neck circumference >40cm, and male. Each question was given a score of 1 if it was answered "yes" and a score of 0 if it was answered "no". OSA risk levels were categorized into 2 groups, i.e. high risk level if the score was 4-8 and low if the score was 0-3 (7).

Evaluation of global cognitive function was carried out using the Clock Drawing Test (CDT) instrument, a simple validated instrument for screening global cognitive functions and its application is not influenced by the education level (17,18). On CDT examination, the subjects were asked to draw a circle of a wall clock complete with the numbers in the correct position and draw clock hands that showed ten minutes past eleven. Scores were given on four assessment components, including a closed circle shaped image, numbers starting from 1 to 12, correct position of numbers, and the clock shows ten minutes past eleven. Each component of the assessment was given a value of 1 if the answer was true and 0 if wrong. Subjects were categorized into 2 groups, i.e. group with normal global cognitive function status if having a total CDT score of 4 and decreasing if they had a total CDT score of 0-3 (19).

Data on clinical characteristics and demographic of subjects were presented in the form of mean values and percentages. The difference in mean of subjects' age in the two groups of global cognitive function status was analyzed using the independent parametric t test, while the mean difference in BMI was analyzed using the Mann-Whitney non-parametric test. Differences in gender frequency, hypertension, dyslipidemia, diabetes mellitus, central obesity, dyslipidemia, neck circumference, and OSA risk levels in both groups of global cognitive function status were analyzed using the Kai-square test. The differences in the frequency of the components of the metabolic syndrome in both OSA risk groups was analyzed using the Kai-square test.

RESULTS

Overview of Demographic Characteristics, Metabolic Syndrome, OSA Risk Levels, and Global Cognitive Functions

This study involved 89 subjects with an average age of 53.7±8.2 years, BMI 25.6±4.7 kg/m^2, and balanced sex proportions. The frequency of subjects with hypertension, dyslipidemia, and diabetes mellitus was low, while the frequency of subjects with central obesity was quite high. The frequency of subjects with high risk levels of OSA and decreasing global cognitive function status was relatively parallel to the frequency of normal subjects (Table 1).

Table 1. Overview of demographic characteristics, metabolic syndrome components, OSA risk levels, and global cognitive functions

Characteristic	Result (n=89)
Demographic	
• Age in year (mean±SD)	53,7±8,2
• Male, n(%)	42 (47,2)
metabolic syndrome component	
• Hypertension, n(%)	32 (35,0)
• Dyslipidemia, n(%)	12 (13,6)
• Diabetes mellitus, (n%)	11 (12,4)
• BMI in kg/m^2 (mean±SD)	25,6±4,7
• Central Obesity, n(%)	59 (66,3)
High risk level for OSA, n(%)	39 (43,3)
Low cognitive functions (score CDT=0-3), n(%)	47 (52,2)

Note: BMI = Body Mass Index, OSA = Obstructive Sleep Apnea, CDT = Clock Drawing Test.

Correlation among Demographic Characteristics, Metabolic Syndrome Components, OSA Risk Level with Global Cognitive Function

In this study, there were significant differences in the frequency of diabetes mellitus and OSA risk levels between groups of subjects with normal global cognitive function status and decreasing global cognitive function status ($p < 0.05$). There were no differences in age and BMI, gender frequency, hypertension, dyslipidemia, and central obesity between the two groups of global cognitive function status (Table 2).

Table 2. Effects of clinical and demographic characteristics of subjects on global cognitive function

Characteristic	Global Cognitive Functions		p-value
	Normal	Low	
Age in year (mean±SD)	52.5±8.2	54.7±8.2	0.205*
Gender, n(%)			
Male	20 (22.5)	22 (24.7)	0.939
Female	22 (24.7)	25 (28.1)	
Hypertension, n(%)			
Yes	11 (12.4)	21 (23.6)	0.070
No	31 (34.8)	26 (29.2)	
Dyslipidemia, n(%)			
Yes	5 (5.6)	7 (7.9)	0.680
No	37 (41.6)	40 (44.9)	
Diabetes mellitus, n(%)			
Yes	2 (2.3)	9 (10.1)	0.040
No	40 (44.9)	38 (42.7)	
BMI in kg/m^2 (mean±SD)	25.6±5.4	25.6±4.0	0.551**
Central obesity, n(%)			
Normal weight	15 (16.9)	15 (16.9)	0.705
Obese	27 (30.3)	32 (35.9)	
OSA risk level, n(%)			
Low	29 (32.6)	21 (23.6)	0.021
High	13 (14.6)	26 (29.2)	

Note: * Independent t test, ** Mann Whitney test

Correlation of Metabolic Syndrome Components and OSA Risk Level

The results showed that there were significant differences in the hypertension frequency between the high and low risk groups to the OSA occurrence ($p < 0.001$). There were no significant differences in the frequency of dyslipidemia, central obesity, and diabetes mellitus between the two groups of OSA risk level (Table 2).

Table 2. Correlation between metabolic syndrome components and OSA risk level

Characteristic	OSA Risk level		p-value
	Low	High	
Hypertension, n(%)			
Yes	9 (10.1)	23 (25.8)	0,000
No	41 (46.1)	16 (18.0)	
Dyslipidemia, n(%)			
Yes	7 (7.9)	5 (5.6)	0,872
No	43 (48.3)	34 (38.2)	
Central obesity, n(%)			
Normal	17 (13.5)	13 (18.0)	0,947
Obese	33 (42.7)	26 (25.8)	
Diabetes mellitus, n (%)			
Yes	4 (4.5)	7 (7.9)	0,138
No	46 (51.7)	32 (35.9)	

Note: Kai-square test

DISCUSSION

This study was aimed at investigating the correlation of factors and levels of OSA risk on the global cognitive function. The results showed that in the group of subjects with high OSA risk, the frequency of subjects with decreasing global cognitive function significantly was higher than the frequency of subjects with normal global cognitive function. Obstructive Sleep Apnea (OSA) is associated to a decreasing cognitive function (3,20,21). The pathophysiology of decreasing cognitive function in OSA patients begins with the occurrence of intermittent hypoxia which induces an increase in sympathetic nervous system activity (24). The increased activity of the sympathetic nervous system will induce a series of processes that in sequence are vasoconstriction of cerebral vessels, endothelial vascular dysfunction, excessive inflammatory response, and blood-brain barrier damage (3). Damage to the blood-brain barrier causes structural and functional changes in brain tissue, including brain

tissue that carries cognitive function, which leads to the neurodegeneration process (25). The most important brain parts for the formation of cognitive functions that are prone to decreasing volume and function due to the process are the hippocampus, frontal, parietal, and temporal lobes (24). Neuron populations in all three parts of the brain are sensitive to hypoxic conditions, so intermittent hypoxic conditions that last for a long time will damage the population of these neurons.

The results of this study indicate that in subjects with diabetes mellitus as OSA risk factors, the frequency of subjects with declining global cognitive functions was significantly higher compared to subjects with normal cognitive function. The proportion of other metabolic syndrome components, namely hypertension, dyslipidemia, and central obesity, are not significantly different according to global cognitive function. Obstructive Sleep Apnea has a two-way relationship with the metabolic syndrome, i.e. the metabolic syndrome components increase the risk of OSA, and vice versa (1). Increased sympathetic nervous system activity found in OSA can also be found in the metabolic syndrome which can occur independently or be enhanced by OSA (26,27). Based on several previous studies, the metabolic syndrome also has a connection with the incidence of declining cognitive function (28-30). Therefore, increasing OSA risk due to the presence of the metabolic syndrome components can also cause a decline in cognitive function.

The role of diabetes mellitus on decreasing cognitive function can be an influence of diabetes mellitus independently or through its influence on the increasing risk of OSA (31-34). To determine the role of diabetes mellitus on the OSA risk level, in this study an analysis of the correlation between diabetes mellitus and the four other components of the metabolic syndrome on the increasing risk of OSA was also conducted. The results of this study indicate that the proportion of diabetes mellitus, dyslipidemia, and central obesity did not differ significantly according to the OSA risk level. These results confirm that diabetes mellitus independently plays a role in the decreasing global cognitive function. On the other hand, the results of this study indicate that hypertension is not independently associated with cognitive function, but through its role in increasing the risk of OSA occurrence.

Early management of decreasing cognitive function associated with OSA will provide satisfactory results compared to management in the later stages (22). Given that the diagnosis of OSA has limitations, the prevalence of OSA in the general population is quite high but rarely diagnosed (23), screening the OSA risk level and decreasing cognitive function associated with the risk of OSA level is important. Further studies need to be carried out using polysomnographic examination in high-risk OSA subjects to enforce the diagnosis of OSA as a basis for examining the correlation among OSA risk level, OSA diagnosis, and global cognitive function status.

It can be concluded that the OSA risk level is associated with a decreasing global cognitive function in the subjects of a sub-population in Mataram. The metabolic syndrome components, which are comorbid in subjects with high-risk OSA in causing a decreasing cognitive function, are diabetes mellitus and hypertension.

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