Received: 29 October 2022 / Accepted: 11 February 2023 / Published online: 28 February 2023

DOI 10.34689/SH.2023.25.1.012

UDC 616.24-008.444-379-008.64

OBSTRUCTIVE SLEEP APNEA AND COGNITIVE FUNCTION WITH TYPE 2 DIABETES MELLITUS: A HOSPITAL-BASED CASE-CONTROL STUDY

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Abstract

The aim of our study is to examine the effect of obstructive sleep apnea syndrome (OSAS) on the cognitive functions of the brain in patients with type 2 diabetes.

Materials and methods. The study involved patients with clinically and laboratory proven type 2 diabetes mellitus. The cases group (Group 1) included patients with OSAS. The control group (Group 2) included patients without OSAS. Sleep duration and quality were assessed using respiratory monitoring. OSAS was screened using a portable night monitor. Cognitive assessment is performed using the Montreal Cognitive Test (MoCA). Three MoCA subscales were analyzed: visual-constructive function, executive function, and orienting function.

Results. A total of 94 patients (58 women and 36 men, 61.7% vs 38.3%) took part in the study. The age ranged from 45 to 59 years. The MoCA subscales - visual-spatial and executive functions, Clock and Orientation, were lower in the main group compared to controls ($p<0.05$). In the control group, significant correlation between the MoCA indicator and BMI ($r=0,39$; $p=0,015$), waist circumference ($r=0,48$; $p=0,002$), neck circumference (positive) ($r=0,33$; $p=0,040$) and Hba1c (negative) was found. In the main group, 32.7% of participants had MoCA score below 26, in the control group - only 67.3%

Conclusion. Lower sleep efficiency is associated with lower cognitive function in patients with abnormal glucose tolerance. Whether sleep optimization may improve cognitive function in these patients should be explored.

Key words: *obstructive sleep apnea, type 2 diabetes mellitus, respiratory monitoring, cognitive function, MoCa.*

Резюме

СИНДРОМ ОБСТРУКТИВНОГО АПНОЭ СНА И КОГНИТИВНОЙ ФУНКЦИИ ПРИ САХАРНОМ ДИАБЕТЕ 2 ТИПА: ИССЛЕДОВАНИЕ СЛУЧАЙ-КОНТРОЛЬ

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Цель: изучить влияние синдрома обструктивного апноэ сна (СОАС) на когнитивные функции головного мозга у больных сахарным диабетом 2 типа.

Материалы и методы: В исследование были включены пациенты с клинически и лабораторно подтвержденным сахарным диабетом 2 типа. В группу случаев (группа 1) вошли пациенты с СОАС. В контрольную группу (2-я группа) вошли пациенты без СОАС. Продолжительность и качество сна оценивали с помощью респираторного мониторинга. СОАС контролировали с помощью портативного ночного монитора. Когнитивное оценивание проводится с помощью Монреальского когнитивного теста (МоСА). Были проанализированы три подшкалы МоСА: зрительно-конструктивная функция, исполнительная функция и функция ориентировки.

Результаты: Всего в исследовании приняли участие 94 пациента (58 женщин и 36 мужчин, 61,7% против 38,3%). Возраст колебался от 45 до 59 лет. Подшкалы MoCA - зрительно-пространственные и исполнительные функции, Часы и Ориентация - были ниже в основной группе по сравнению с контролем (p<0,05). В контрольной группе выявлена достоверная корреляция между показателем MoCA и ИМТ (r=0,39; p=0,015), окружностью талии (r=0,48; p=0,002), окружностью шеи (положительная) (r=0,33); p=0,040) и Hba1c (отрицательный). В основной группе 37,2% участников имели балл MoCA ниже 26, в контрольной группе - только 67,3%.

Заключение. Более низкая эффективность сна связана с более низкой когнитивной функцией у пациентов с аномальной толерантностью к глюкозе. Следует изучить вопрос о том, может ли оптимизация сна улучшить когнитивные функции у этих пациентов.

Ключевые слова: *обструктивное апноэ сна, сахарный диабет 2 типа, респираторный мониторинг, когнитивные функции, MoCa.*

Түйіндеме

ОБСТРУКТИВТЫ ҰЙҚЫ АПНОЭ СИНДРОМЫНЫҢ ЖӘНЕ КОГНИТИВТЫ ФУНКЦИЯСЫ 2 ҚАНТ ДИАБЕТ ТҮРІНДЕ: АУРУХАНАЛЫҚ КЕЙС-БАҚЫЛАУ

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Зерттеу мақсаты: 2 типті қант диабетімен ауыратын науқастардың обструктивті ұйқы апноэ синдромының (ҰОАС) мидың когнитивті қызметіне әсерін зерттеу.

Материалдар мен әдістер: зерттеуге клиникалық және зертханалық расталған 2 типті қант диабеті бар науқастар енгізілді. Істер тобына (1-топ) ҰОАС бар науқастар кірді. Бақылау тобына (2-ші топ) ҰОАС жоқ пациенттер кірді. Ұйқының ұзақтығы мен сапасы респираторлық бақылау арқылы бағаланды. ҰОАС портативті түнгі монитормен басқарылды. Когнитивті бағалау Монреаль когнитивті тесті (MoCA) арқылы жүзеге асырылады. MoCa-ның үш ішкі шкаласы талданды: визуалды-конструктивті функция, атқарушы функция және бағдарлау функциясы.

Нәтижелері және талқылауы: зерттеуге барлығы 94 пациент қатысты (58 әйел және 36 ер адам, 61,7% қарсы 38,3%). Жасы 45 пен 59 жас аралығында болды. MoCa ішкі шкалалары-визуалды-кеңістіктік және атқарушы функциялар, сағат және бағдар-бақылаумен салыстырғанда негізгі топта төмен болды (p<0,05). Бақылау тобында MoCA және Дене салмағының индексі көрсеткіші (r=0,39; p=0,015), бел шеңбері (r=0,48; p=0,002), мойын шеңбері (оң) (r=0,33) арасындағы сенімді корреляция анықталды; p=0,040) және Hba1c (теріс). Негізгі топта қатысушылардың 37,2% - MoCa ұпайы 26-тен төмен болса, бақылау тобында тек 67,3% болды.

Қорытынды. Ұйқының төмен тиімділігі глюкозаға төзімділігі қалыптан тыс науқастарда когнитивті функцияның төмендеуімен байланысты. Ұйқыны оңтайландыру осы науқастардың когнитивті қызметін жақсарта ала ма деген сұрақты зерттеу керек.

Түйінді сөздер: *ұйқының обструктивті апноэ синдромы, 2 типті қант диабеті, тыныс алуды бақылау, когнитивті функция, MoCa.*

Bibliographic citation:

Shinalieva K.A., Kasenova A.S., Zhumabayev M.B., Abdrakhmanova M.G., Bekenova A.O., Madirova S.E. Obstructive sleep apnea and cognitive function with type 2 diabetes mellitus: a hospital-based case-control study // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2023, (Vol.25) 1, pp. 94-99. *doi 10.34689/SH.2023.25.1.012*

Шиналиева К.А., Касенова А.С., Жумабаев М.Б., Абдрахманова М.Г., Бекенова А.О., Мадирова С.Е. Синдром обструктивного апноэ сна и когнитивной функции при сахарном диабете 2 типа: исследование случай-контроль // Наука и Здравоохранение. 2023. 1(Т.25). С. 94-99. *doi 10.34689/SH.2023.25.1.012*

Шиналиева К.А., Касенова А.С., Жумабаев М.Б., Абдрахманова М.Г., Бекенова А.О., Мадирова С.Е. Обструктивты ұйқы апноэ синдромының және когнитивты функциясы 2 қант диабет түрінде: ауруханалық кейс-бақылау // Ғылым және Денсаулық сақтау. 2023. 1 (Т.25). Б. 94-99. *doi 10.34689/SH.2023.25.1.012*

Introduction

Type 2 diabetes mellitus (DM-2) is a major medical and social health problem in most countries of the world. According to the International Diabetes Federation (IDF), in 2021the number of patients with diabetes in the world exceeded 536 million people, which is about 10% of the adult population of the world [6]. The number of patients with diabetes mellitus is expected to reach 642 million people by 2040 [1].

Obstructive sleep apnea (OSA) is a common sleep disorder in patients with type 2 diabetes mellitus. The incidence of OSAS among patients with obesity and type 2 diabetes is higher than in the general population. The prevalence of OSAS in the general population varies between 23 and 49% [16]. While, according to the Sleep Action for Health in Diabetes (AHEAD) study, the prevalence of this disorder in patients with obesity and type 2 diabetes reaches 88% [7].

OSA is a condition in which recurrent episodes of complete or partial obstruction of the upper airways develop, resulting in a decrease in blood oxygen saturation [11]. Oxygen deficiency as a result of repeated episodes of upper airway obstruction leads to intermittent hypoxia, which, in turn, leads to activation of the hypothalamic-pituitary-adrenal system and a shift in the balance of the autonomic nervous system in favor of its sympathetic division.

Current evidence suggests that OSAS can contribute to the development of carbohydrate metabolism disorders, including type 2 diabetes mellitus and increased insulin resistance. [15] Intermittent hypoxemia and sleep fragmentation are cardinal features of OSAS and are likely in the causal pathway leading to metabolic dysfunction. A number of studies have shown that nocturnal hypoxemia in OSAS contributes to the development and progression of non-alcoholic fatty liver disease (NAFLD), which potentiates insulin resistance by reducing the activity of the insulin signaling pathway and subsequent disruption of intracellular glucose functioning transporters (GLUTs) [2]. Several cross-sectional studies demonstrated an independent association between the severity of OSAS and insulin resistance in individuals without type 2 diabetes [8]. In healthy volunteers, exposure to 5 hours of intermittent hypoxia during wakefulness led to a 17% reduction in insulin sensitivity without a simultaneous increase in insulin secretion. In another experiment, however, exposure to 3 hours of intermittent hypoxia resulted in an increase in plasma glucose levels without changes in insulin secretion. Therefore, there may be a threshold regarding the intensity of hypoxemia or duration of exposure that may lead to an adverse impact on insulin sensitivity. The sleep fragmentation using acoustic stimuli to suppress non-rapid eye movement (REM) slow-wave sleep or to fragment non-REM sleep reduced insulin sensitivity by 20% to 25%.

Cognitive decline is another important consequence of OSAS. Cognitive functions help us to process the complex knowledge about the world. These include perception, psychomotor functions, speech, attention, memory, control functions, social intelligence.

R.S. Bucks et al. proposed two possible mechanisms of the OSAS effect on cognition. First, cognitive decline may be the result of daytime sleepiness, followed by impaired concentration. Secondly, OSAS can lead to remodeling of the vascular system of the brain [3]. In addition, it was found that in people with OSAS the hippocampus, which plays a significant role in learning and memory, is also involved in the pathological process [19].

At the same time, type 2 diabetes mellitus itself is a significant risk factor for the development and progression of cognitive impairment. It has been established that dementia in patients with type 2 diabetes is diagnosed on average 2.5 years earlier than in the general population. In turn, in patients with type 2 diabetes with an apnea/hypopnea index (AHI) ≥15 had the 1.9 times higher risk of dementia [7]. The cognitive abilities also correlate with snoring activity, and this association differs between age groups. This means that the children are more vulnerable for snoring influence on cognitive abilities rather than older groups of people.

Cognitive impairment is a socially significant complication of type 2 diabetes that largely determines the prognosis and quality of life. We suggest that there might be a relationship between snoring and cognitive dysfunction in a way that snoring tends to negatively alter the cognitive thinking. Dementia is mainly manifested by a decrease in memory and cognitive functions, as well as personality changes, which lead to serious consequences for social interaction, professional development and life of patients. Therefore, timely detection of risk factors for cognitive impairment, including OSAS, in patients with type 2 diabetes can have a positive effect on the rate of development and progression of cognitive dysfunction and dementia.

The aim of our study is to study the effect of obstructive sleep apnea on the cognitive functions of the brain in patients with type 2 diabetes.

Materials and Methods

Study design and participant selection.

This study was performed in 2021 at the Department of Neurology of the NAO Medical University of Astana, in the Endocrinological department, the 1st city clinical hospital in Nur Sultan. In working with patients, the ethical principles presented by the Helsinky declaration of the World Medical Association “Ethical Principles of Scientific and Medical Research with the Participation of Human (with the amendments of 2008) were observed. All examined persons gave informed consent to participate in the study and publishing its results in print media, were familiarized with the aim of this work and the design of the study. The research plan was approved by the local bioethical committee at the Astana Medical University No.3 dated 16.01.2020).

Selection criteria: disease duration of at least 1year, glycosylated hemoglobin index (HbA1C) >6.5, the presence of hypoglycemic conditions. *Exclusion criteria*: the presence of severe or unstable concomitant somatic pathology, strokes and transient ischemic attacks, traumatic brain injuries, CNS tumors, CNS diseases (inflammatory, degenerative, epilepsy, cerebral palsy), as well as mental disorders, depression, dementia, alcoholism or drug addiction.

Outcomes

The diagnosis of type 2 diabetes was established by an endocrinologist.

Sleep parameters were assessed using respiratory monitoring with a portable apparatus of Somnocheck Micro,

Cardio, Germany [5]. This device allows you to assess the severity of the degree of apnea, hypopnea, the level of blood saturation with oxygen, the intensity of snoring, the frequency and duration of breathing stops in a dream. The results of the assessment were evaluated in accordance with the recommendations of the American Academy of Sleep Medicine guidelines [9]. During the respiratory monitoring we recorded nasal breathing during the night, saturation of hemoglobin with oxygen (SPO2), and heart rate. The pulse waves obtained using photoplethysmography were analyzed jointly with the respiratory flow signals to differentiate obstructive and central apnea and provide information about the degree of fragmentation of sleep [10].

The Apnea-Hipopnea (AHI) index was calculated as a ratio obtained by dividing the total duration of Apnea and hypopnea observed during sleep, for the total duration of sleep[13], [14]. Based on the level of IAG, 5-15, 15-30 and> 30 epizodes per hour, a preliminary diagnosis of OSAS of mild, medium and severe degree, respectively.

The ratio of utility (ID) was calculated as the number of desaturation over time. Respiratory disorders were also recorded when a decrease in the saturation of hemoglobin with oxygen by 3% (desaturation) with a holding of breathing at least 10 s (apnea) or a reduction in the amplitude of the respiratory intensity curve (hypopnea) was coincided. In addition, we recorded the levels of minimal, medium and maximum saturation.

Cognitive Testing

Montreal Cognitive Assessment is a one-page 30-point test administered in 10-20 minutes. Details on the specific MoCA items are as follows. The short-term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately 5 minutes. Visuospatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point). Multiple aspects of executive functions are assessed using an alternation task adapted from the Trail Making B task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2points). Attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each). Language is assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points), and the aforementioned fluency task. Finally, orientation to time and place is evaluated (6 points). The MoCa test according to meta-analysis data at ≤26, the sensitivity for moderate cognitive impairment is 90%, and the specificity is 87% [12].

All patients underwent following assessments: height, weight, BMI, neck circumference, waist/hip ratio. Overweight and obese categories were defined according to the World Health Organization classification based on the following BMI cutoffs: BMI (kg\m^2) <18,5 - underweight; 18,5-24,9 normal weight; 25-29,9 – overweight; 30-34,9-obesity I grade; 35-39,9 obesity II grade; >40 obesity III grade[15].

Statistical analysis.

Statistical analysis was performed using SPSS 26 (IBM, USA) program. To compare the mean value of the main group (patients with type 2 diabetes with OSA) and the control group (patients with type 2 diabetes without OSA), a t-test was performed, as well as the Mann-Whitney test. Pearson's correlation analysis was used to assess the relationship between MoCA and clinical and laboratory data and to assess its strength and statistical significance. In order to assess the distribution of the number of observed respondents by groups with low and acceptable MoCA scores in the context of the two compared groups, Pearson's chi-square test was used.

Results

Study population

A total of 94 patients (58 women and 36 men, 61.7% vs 38.3%) took part in the study. Comparison of the main and control groups showed that there was no difference between groups in age, neck circumference, and Hba1c. The average age of respondents suffering from OSA was 55 years. Patients with type 2 diabetes with OSA had significantly higher BMI, larger waist circumference and lower MoCA results ($p<0.05$). According to the gender structure, there were more males the main group (61.5%), while only 31.6% the control group. The age ranged from 45 to 59 years. Baseline characteristics of study participants are presented in Table 1.

Table 1.

Baseline characteristics of study participants.

	patients with OSA (n=45)	p - value	patients without OSA (n=49)
AHI, mean (SD)	12.73(10.44)	<0.000	2,30(1.16)
Age, mean (SD)	55.49 (8.63)	0.435	57.13 (9.70)
Sex:			
Male	61.50%	0.012*	31.60%
Female	38.50%		68.40%
Body mass index, mean (SD)	31.36 (7.14)	0.050	28.51 (5.16)
Waist circumference, mean (SD)	112.23 (18.62)	0.018*	101 (22.01)
Hip circumference, mean (SD)	109.56 (16.63)	0.692	108.24 (12.37)
Neck circumference, mean (SD)	46.07 (19.26)	0.057	40.64 (4.72)
MoCAscore, mean (SD)	22.07 (3.17)	0.007**	24.21 (3.57)
Hba1c, mean (SD)	11.24 (3.00)	0.924	11.17 (3.13)

*Note. Statistical significance: * $p < 0.05$, ** $p < 0.01$.*

Frequency analysis according to MoCA results.

As part of this analysis, the number of people with MoCA scores below ≥26 and over 26 were compared for each group. In the main group, 66.7% of participants had MoCA score below 26, in the control group - only 67.3% (Table 2). The difference in frequency distribution presented in the table had statistical significance according to Pearson's chi-square test ($p<0.05$).

Table 2.

MoCA results in the main and control group.

		MoCA score ≥26	MoCA score < 26	Result
group 2 without OSA	Frequency	16	33	49
	% instatus	32,7%	67,3%	100,0%
group 1 - with OSA	Frequency	15	30**	45
	% instatus	33,3%	66,7%	100,0%

*Note. Suggested statistical significance:** p<0.05*

Comparison of MoCA indicators between the two groups.

The MoCA subscales - Visuospatial and executive functioning Clock and Orientation were significantly lower in the main group compared to controls (p<0.05), (Table 3). For other indicators, there were no significant differences (p>0.05) between the compared groups.

Tables 3.

Comparison of MoCA scores among (score).

Ability, mean (SD)	group 1 - patients with type 2 diabetes with OSA(n=45)	p -value	group 2 –patients with type 2 diabetes without OSA (n=49)
MoCA Visuospatial and executive functioning Create Alternating Path 1 (n-1)	0.67 (0.48)	0.680	0.71 (0.46)
MoCA Visuospatial and executive functioning Cube (n-1)	0.49 (0.51)	0.109	0.68 (0.53)
MoCA Visuospatial and executive functioning Clock (n-1)	1.97 (0.74)	0.024*	2.29 (0.96)
Animal naming (n-3)	2.97 (0.16)	0.543	2.95 (0.23)
Attention (n-6)	4.15 (1.41)	0.376	4.45 (1.41)
Language (n-3)	2.18 (0.94)	0.316	2.42 (0.76)
Abstraction (n-2)	1.62 (0.63)	0.380	1.71 (0.61)
Delayed recall (short-term memory) (n-5)	2.56 (1.79)	0.120	3.18 (1.66)
Orientation (n-6)	5.46 (0.55)	0.001**	5.82 (0.51)
MoCA score	**22.07 (3.17)**	**0.007****	**24.21 (3.57)**

*Note. Statistical significance: * p < 0.05, ** p < 0.01.*

Correlation analysis between the MoCA indicators and clinical and laboratory data (Table 4).

In the main group there was no correlation between studied parameters. However, in the control group, significant correlation between the MoCA indicator and BMI, waist circumference, neck circumference (positive) and Hba1c (negative) was found.

Table 4.

Correlation the MoCA indicators and clinical and laboratory data.

	MoCA (with OSA)		MoCA (without OSA)	
	Pearson's correlation coefficient:	p-value	Pearson's correlation coefficient:	p-value
Age	-0,11	0,493	-0,17	0,311
AHI	-0,099***	0,516	-0,23	0,876
Body mass index	-0,15	0,351	0,39	0,015*
Sex	0,00	0,988	-0,28	0,087
Neck circumference	-0,16	0,329	0,33	0,040*
Waist circumference	0,04	0,826	0,48	0,002**
Hip circumference	0,30	0,063	0,21	0,207
Hba1c	0,19	0,256	-0,39	0,016*

*Note. Statistical significance: * p < 0.05, ** p < 0.01, *** - Spearman correlation*

Discussion

The results of this study showed that: 1) patients with type 2 diabetes with OSAS have lower MoCA scores, especially in visual-spatial and executive functions, Clock and Orientation subscales; 2) In the main group 82.1% of participants had MoCA score below 25 compared to 47.4% in controls; 3) in the control group there was a significant correlation between the MoCA indicator and BMI, waist circumference, neck circumference (positive) and Hba1c (negative) was found.

Our results are in line with the results from a meta-analysis that showed that OSA was associated with an increased risk of cognitive impairment (relative risk 2.37) [18], [20]. Our study confirmed that patients with OSA have the worst indicators of cognitive functions: MOCA, executive functions, orientation. The severity of OSA is associated with deterioration in cognitive functions: visual constructive function, executive function, orientation. However, not all studies have found such associations [4].

Our study had several limitations. Firstly, sample size was one of the limiting factors of this study. Therefore the results may not be extrapolated to the larger population. Secondly, all participants in this study had decompensated type 2 diabetes. Possibly this was one of the reasons why all participants had poor sleep. Therefore, the results could not be readily generalized to all people with type 2 diabetes,

especially those with good glycemic control. Thirdly, the results of this cross-sectional study can not confirm the direction of the association and causality. Further large prospective studies with people at different levels of compensations are warranted.

Conclusion

Lower sleep efficiency is associated with lower cognitive function in patients with abnormal glucose tolerance. Whether sleep optimization may improve cognitive function in these patients should be explored.

Disclosure: *The authors declare no conflict of interest. All authors have seen and approved the manuscript. Informed consent was obtained from all patients for being included in the study.*

Role of the Funder/Sponsor: *Center for the Department of Medicine "Senim", "Astana Medical University", provided financial support in the form of a device for diagnosing respiratory disorders during sleep "Somnocheck Micro" and a research fund.*

Acknowledgements: *The authors would like to thank of the participants for taking the time to participate in this study, Sarmanova Aliya for her valuable comments and help with the manuscript.*

Conflict of inerest: *Authors did not have conflict of interests, including specific financial interests and relationships and affiliations relevant to the subject of this manuscript. The principal author "had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis".*

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