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OBESITY AND SLEEP DURATION – INVESTIGATION OF DISORDERS OF GLYCOREGULATION AND SYSTEMIC INFLAMMATION

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Sleep quality and sleep duration are significantly associated with obesity onset and its progression. A prospective clinical study was conducted by analyzing 129 patients referred to polysomnography, out of whom 76 were obese. According to modified sleep quality survey ("National Health and Nutrition Examination Survey" - NHANES), patients were divided into two groups based on similar demographic and morphometric characteristics of sleep duration, so the group I comprised subjects with poor sleep quality, sleeping 4 hours or less on average, and group II enrolled subjects with moderate and good sleep quality, with 6 hours or more of sleep duration on average. It has been reported that all the subjects had elevated levels of C-reactive protein (CRP), and the subjects from group I with shorter sleep duration and poor sleep quality had statistically significant rise of CRP in comparison to the subjects from group II. It has also been proved that the subjects from both groups had elevated levels of glycated hemoglobin (HbA1c) as a parameter of poor glycoregulation. In obese persons, sleep duration and quality play a significant role in increasing inflammatory processes in the body. Obesity is a risk factor of impaired glycoregulation.

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Key words: *respiratory polygraphy, obesity, sleep duration, glycoregulation, systemic inflammation*

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Introduction

The World Health Organization (WHO) define overweight and obesity as abnormal or excessive fat accumulation that is a risk to health. The prevalence of overweight has significantly increased worldwide. In 2016 more than 1.9 billion adults over the age of 18 were overweight and out of them over 650 million were obese. Globally, 39% of adults (39% of men and 40% of women) were overweight, about 13% of adults (11% of men and 15% of women) were obese. Worldwide obesity has almost tripled between 1975 and 2016. Body mass index (BMI) is a simple index of body weight that is usually used for overweight and obesity classification in adults, and it is the same for both sexes and all ages of adults. It is defined as a person's weight in kilograms divided by the square of their height in meters (kg/m^2). As for adults, WHO defines overweight and obesity in the following way:

- overweight is a BMI 25 or greater;
- obesity is a BMI 30 or greater (1).

Short sleep duration has been increasing in many countries. The results from an analysis of 250,000 sleep questionnaires worldwide indicate that sleep duration on weekdays has dropped by about 37 minutes in the last decade (2). In the last 40 years sleep duration in the USA has declined for 1.5 to 2 hours. National Sleep Foundation of America survey in 2009 showed that American adults sleep 6h, 40 min on workdays on average, and 7h, 7 min at weekends, while in 1960 average sleep duration was 8h 30 min. The percentage of young people who sleep less than 7h a day has increased from 15.6% to 43% in the period from 1960 to 2009. In Brazil, sleep duration has declined for about 20 min in the period between 1987 and 2007 (3).

Experimental and clinical studies have recently demonstrated that sleep disorder and/or

sleep duration might affect glycoregulation and obesity onset and progression at one hand, and elevate levels of CRP, a marker of inflammation, on the other hand (4-6). Many of these studies are cohort, epidemiological, or cross-sectional ones enrolling large pools of participants, but very often these studies are inconsistent, conducted in inhomogeneous groups of participants, so this above mentioned association has not been clearly defined yet (7, 8). Sleep disorders and/or sleep duration are not the only factors responsible for obesity pandemic, but sleep affects energy balance and its effects should be taken seriously. Good sleep could be part of global approach in dealing with ongoing obesity pandemic (9). It has been proved in young, healthy volunteers that total sleep deprivation results in statistically significant increase in CRP levels at every 12-hour of total sleep deprivation, three-fold, or even four-fold in comparison to normal, average values in persons who sleep 7 hours a night (8, 10). It has also been undoubtedly confirmed that insomnia, obstructive sleep apnea/hypopnea syndrome (OSAHS), or 'restless leg syndrome' defined by reported symptoms and polysomnography are linked with disorders of metabolic and endocrine function, such as impaired glucose tolerance, leptin concentration levels decrease or increase, along with the development of leptin resistance, elevation of evening concentrations of cortisol, alterations in autonomic sympathetic activities, leading to increased appetite, body weight and its progression (11, 12).

The aim

The aim of this prospective clinical study was to establish HbA1c values as parameters of effective glycoregulation, and CRP values as markers of inflammation in obese individuals who sleep 4 hours or less in comparison to obese persons who sleep 6 to 7 hours per night.

Materials and methods

At the Clinic of Lung Diseases, University Clinical Center Niš, 129 patients underwent respiratory polygraphy from June 2016 to December 2017, aiming at confirming OSAHS. The procedures performed were as follows:

I. height and weight measurement, BMI calculation; individuals with BMI ≥ 30 were considered obese according to the WHO definition

II. modified NHANES survey on sleep quality in the last 12 months had 8 questions:

1. How often did you have trouble falling asleep?
2. How often did you wake up during night and did you find it difficult to fall asleep again?
3. How often did you wake up too early and were not able to fall asleep again?
4. How often did you feel tired during the day regardless the duration of sleep?
5. How often did you feel overly sleepy during the day?
6. How often did you not have enough sleep?
7. How often did you have leg twitching that woke you up?
8. How much sleep did you usually have at night?

The subjects who responded to any of 8 questions with 'almost always' (16 to 30 times a month) had poor sleep quality, in those who mostly responded 'often' (5-15 times a month) sleep quality was classified as moderate, and all the others had good sleep quality.

III. HbA1c values and CRP levels from blood samples were measured in all individuals.

Results

Out of 129 consecutive individuals, this study enrolled 76 obese ones with BMI ≥ 30, who were not diagnosed as diabetic patients before respiratory polygraphy, and who were divided into two groups according to average sleep duration and sleep quality based on given questionnaire. The first group comprised 40 individuals who slept 4 hours or less on average and assessed their sleep as poor quality, and the second group included 36 individuals with average sleep duration of 6 hours or more and who considered their sleep as moderately good and good sleep quality. Demographic and morphometric characteristics of all the subjects are given in Table 1.

Table 1. Demographic and morphometric characteristics of the subjects

Characteristics	Total - 76	I group – 40	II group – 36	p
Age	50.5 ± 7.1	51.7 ± 6.8	49.1 ± 9.4	p - n.s.
Men	49	20	19	p - n.s.
BMI	39.7 ± 10.6	40.1 ± 5.8	41.2 ± 4.9	p - n.s.
Smokers	38	17	21	p - n.s.
Alcohol consumption	40	18	22	p - n.s.
Marital	54	28	26	p - n.s.
Higher education	14	8	6	p - n.s.
Live in towns	48	25	23	p - n.s.

There was no statistically significant difference between the groups, both in morphometric and demographic characteristics. The groups were well homogenized according to obesity risk factors distribution and obesity itself in comparison to average sleep duration.

Statistical processing of systemic inflammation parameters, CRP levels and glycoregulation – HbA1c values in comparison to sleep duration in the groups of subjects are shown in Table 2.

Table 2. Values of systemic inflammation and glycoregulation parameters in both groups according to average sleep duration

	I group	II group	p
CRP (mg/l)	11.7 ± 9.4	7.92 ± 4.91	**p < 0.05**
HbA1c (%)	6.1 ± 4.8	5.9 ± 3.7	**n.s**

This study demonstrated statistically significant difference in the values of early systemic inflammation, CRP parameters, in obese patients with poor sleep quality and sleep duration of 4 hours or less in comparison to obese patients who slept 6 hours or more on average. In subjects of both groups statistically significant increase in CRP levels was registered in comparison to upper limit of the reference range for CRP of 5mg/l.

The results of this study have not confirmed statistically significant difference in HbA1c values between the groups of our obese patients in comparison to average sleep duration, but it has been proved that the subjects from both groups had elevated HbA1c values and poor glycoregulation, so further diagnostics and potential diabetes treatment is required.

Discussion

Sleep structure, duration and quality have been investigated for a long time, using different instruments, questionnaires, polygraphic recordings, polysomnography, aiming at better and more objective understanding of sleep influence in metabolic and endocrine body functions (11). Considering the fact that there are different sleep disorders, from obstructive and/or central sleep apnea, insomnia, narcolepsy, 'restless leg syndrome', 'jet lag', shift work disorder, 'Cheyne-Stokes' respirations, and alike, there are varieties of results and differences in examined populations that are still confusing (13). Black racial group, males over 65, obese, smokers, and heavy alcohol consumers are believed to be the most common risk factors for different sleep disorders, both in developed and developing countries (13, 14). The burden of modern times can be seen in disturbed sleep architectonics and sleep quality, consequently resulting in many cardiac, respiratory, endocrine and mental diseases (14). Knutson et al. found that sleep duration and quality were significant predictors of HbA1c, a key marker of glycemic control. In combination with existing evidence that link sleep loss with increased risk of diabetes onset, the authors suggest that optimizing sleep duration and sleep quality should be tested as a possible intervention for improving glucose metabolism control in patients with type 2 diabetes (15). Cappuccio et al. in their meta-analysis showed that a reduction of one hour sleep per day was associated with 0.35 kg/m^2 increase in BMI (16). Spiegel et al. found that six consecutive nights of sleep restrictions (4 hours sleep per night) resulted in a 30% reduction in acute insulin response to glucose (11). Irwin et al. Analyzed 72 studies (n-50000) by assessing CRP, interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF). They concluded that sleep disturbance was associated with higher levels of CRP. Shorter sleep duration, but not extremely short sleep duration, was associated with higher levels of CRP, but not IL-6. Extremely long sleep duration was associated with higher levels of CRP and IL-6. Sleep disorders and sleep duration were not associated with TNF-α alterations. Experimental sleep deprivation and restriction were not associated with CRP, IL-6, or TNF-α alterations (17). Patel et al. demonstrated in their study that an increase in usual sleep duration was associated with elevations in CRP levels and IL-6, while polysomnography revealed reduced sleep duration associated with elevated TNF-α levels. Activation of pro-inflammatory pathway may be a mechanism by which extreme sleep habits may affect our health (18). Dowd et al. examined association between inflammation and sleep characteristics in 1020 subjects from the Social Environment and Biomarkers of Aging Study from 2000 to 2006 in Taiwanese population aged 53 and over. They concluded that long sleep duration may be a cause of inflammatory diseases in older population (29).

Richardson et al. analyzed the sample of 5033 male and 4917 female individuals aged 20 and over in whom sleep duration was classified as short (6 or less hours a day), adequate (7-8 hours a day), or long (9 or more hours a day), the samples were homogeneous regarding age, race, smoking status, physical activity, and waist circumference. They concluded that short sleep duration was significantly associated with elevated serum CRP concentrations, regardless of the waist circumference and moderate physical activity in males, but not in females (20). Guilleminault et al. reviewed CRP levels in new

patients with OSAHS, upper airway resistance syndrome-UARS, and absence of important comorbidities, as well as in normal, healthy controls, in the period over 2 months and they concluded that obesity was a risk factor for high serum CRP levels in patients with sleep-disordered breathing and in general population as well, and that BMI was significantly associated with CRP levels in both genders (21). Having in mind the fact that sleep quality is one of the most important indicators of health and well-being, Nag and Pradhan concluded in their study that CRP level might be a marker of sleep disorder and excessive daytime sleepiness (22). Experimental studies have shown that there are distinct, not fully understood mechanisms of neuroendocrine system that determine metabolic effects of sleep deprivation (23), which can be seen as neurobehavioral outcomes, such as excessive appetite, constant sensation of hunger and need for additional energy intake, resulting in the onset and progression of obesity (17, 24). Our prospective study was conducted in adequately homogenous groups of respondents who were referred to polysomnography by doctors of different specializations, ENT doctors, endocrinologists, and chosen primary care physician. Obtained values of CRP levels were elevated in respondents from both groups, which is consistent with the results of many studies dealing with obesity (24). It actually confirms the hypothesis that adipose tissue stimulates and increases inflammatory processes in the body. Statistically significant difference was confirmed in early systemic inflammation parameters CRP between obese patients with poor sleep quality and sleep that usually lasted 4 hours or less and obese patients that slept 6 hours or more on average, suggesting the importance and impact of sleep duration and quality on the development of inflammatory processes in the body, as has been shown by other studies which were discussing this association as well. In all our respondents and within the groups as well, increased HbA1c values were reported in relation to sleep duration, suggesting that our obese respondents had long been suffering from metabolic disorder and poor glycoregulation, so type 2 diabetes mellitus diagnosis was warranted, which is consistent to the results of similar studies (17).

Conclusion

This prospective clinical study has confirmed that obese patients have elevated and statistically significant differences in values of CRP levels as a marker of inflammation, and elevated values of HbA1c as an indicator of prolonged poor glycoregulation, without statistically significant differences in relation to sleep duration and quality.

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GOJAZNOST I TRAJANJE SNA – ISTRAŽIVANJE POREMEĆAJA GLIKOREGULACIJE I SISTEMSKE INFLAMACIJE

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Kvalitet i dužina sna bitno utiču na nastanak i progresiju gojaznosti. Prospektivno kliničko istraživanje sprovedeno je na 129 bolesnika upućenih na polisomnografsko ispitivanje, od kojih je 76 bilo gojazno. Na osnovu modifikovanog upitnika o kvalitetu sna ("National Health and Nutrition Examination Survey" – NHANES upitnik) bolesnici su podeljeni u dve gupe sličnih demografskih i morfometrijskih karakteristika prema dužini sna, tako da I grupu čine oni sa lošim kvalitetom sna, koji prosečno spavaju 4 sata i kraće, a II grupu oni sa umereno dobrim i dobrim kvalitetom sna, koji spavaju prosečno 6 sati i duže. Nađeno je to da svi ispitanici imaju povećane vrednosti C-reaktivnog proteina (CRP), a ispitanici I grupe, sa kraćim snom lošeg kvaliteta, imaju statistički značajno veći CRP u odnosu na CRP ispitanika II grupe. Utvrđeno je to da ispitanici obe grupe imaju povećane vrednosti glikolizirajućeg hemoglobina (HbA1c), kao parametra loše glikoregulacije.

Kod gojaznih osoba dužina i kvalitet sna imaju značajnu ulogu u povećanju inflamatornih procesa u organizmu. Gojanost je faktor rizika za poremećaj glikoregulacije.

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Ključne reči: *respiratorna poligrafija, gojaznost, trajanje sna, glikortegulacija, sistemska inflamacija*