THREE MONTH FOLLOW UP OF THE EFFECTS OF CONTINUOUS POSITIVE PRESSURE DURING SLEEP (CPAP) ON THE VALUE OF GLYCATED HEMOGLOBIN HbA1c AND GLYCOREGULATION IN OBESE DIABETIC PATIENTS WITH CONFIRMED SEVERE OBSTRUCTIVE SLEEP APNEA

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Obstructive sleep apnea (OSA) is a serious disorder of breathing during sleep characterized by complete or partial interruption of breathing during sleep for 10 seconds and longer. In this prospective longitudinal clinical study in obese patients with diabetes mellitus type II which is determined by polysomnography heavy degree of OSA is accompanied by the application of positive pressure during sleep in the course of three months and evaluated its impact on the value of glycated hemoglobin HbA1c as an indicator of long-term glycoregulation.

A prospective clinical study in the quarterly monitoring included 98 patients (64 men and 34 women), who, after clinical, laboratory, spirometry and diffusion examination of lung function, underwent polysomnography testing on Philips Respironics Alice PDX device.

Out of 98 obese patients suffering from diabetes mellitus type II and severe OSA, average age 50.1, 23 of them were randomized in two groups: experimental - 11 patients with an average HbA1c of 9.9 %, the average BMI 37.1 and average AHI index of 36.7 (31 to 59) who used CPAP during sleep, and control group of 12 patients, with an average HbA1c was 9.1 %, average BMI 39.3 and AHI index was 39.7 (31 to 62). After three-month of using CPAP, the control of HbA1c in both groups was performed. Average HbA1c in the experimental group decreased with statistical significances (p < 0.01) from 9.9 % to 6.7 %, compared to the control group patients with no significant changes.

The results of this study indicated that in obese patients with diabetes mellitus II and severe OSA, long-term glycoregulation can be significantly improved using the CPAP during sleep.


Key words: obesity, diabetes mellitus type II, obstructive sleep apnea, CPAP

Introduction

Obstructive sleep apnea (OSA) represents a disease of the heterogenic group of breathing disorders during sleep characterised by recurring episodes of breathing cessations or episodes (apnea) of shallow breathing (hypopnea), and it is increasingly being recognized as an important health issue in the last two to three decades (1). OSA is a prevalent condition in close association with obesity epidemic globally, and it is characterized by the repetitive, partial or complete collapse of the upper airway during sleep, causing impaired gaseous exchange and sleep disturbance (2, 3).

It is the most common form of sleep-disordered breathing (SDB) worldwide as shown in different epidemiological studies. It is characterised by frequent episodes of upper airway collapse during sleep, causing recurrent arousals, intermittent hypoxemia, sleep fragmentation, and poor sleep quality.

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There is accumulating evidence that OSA is being considered as an independent risk factor for hypertension, glucose intolerance / diabetes mellitus, cardiovascular diseases and stroke, leading to increased cardiometabolic morbidity, and mortality (4, 5).

The prevalence rates of OSA have been estimated in the range of 2 to 10 per cent worldwide, and the risk factors for obstructive sleep apnea include advanced age, male sex, obesity, family history, craniofacial abnormalities, smoking and alcohol consumption. The common clinical presenting symptoms are heavy snoring, witnessed apneas and daytime hypersomnolence, which would help to identify the affected individuals (6).

With increasing awareness of this disease entity and associated complications in our society, there have been increased referrals to sleep physicians or expertise for further investigations and diagnostic evaluation.

Early recognition and treatment of obstructive sleep apnea may prevent from adverse health consequences. It has been associated with increased cardiovascular and cerebrovascular morbidity and mortality, although much of the causal role and mechanisms are still poorly understood. (6, 7, 8).

The interaction of obesity and sleep disorders, OSA typ, is presented in Figure 1.

**Figure 1.** The interaction of obesity and sleep disorders

### Aims

In this prospective, clinical, longitudinal study with three months of follow up, on consecutive obese patients with diabetes mellitus II in whom high degree of OSA by polysomography was confirmed, the authors examined the effects of using of continuous positive pressure CPAP during sleep on the value of glycated hemoglobin HbA1c as long-term indicator of glycoregulation.

### Material and methods

The examinations were conducted at the Clinic for lung diseases Clinical Center Niš from October 2016. to December 2017.

In all patients at rest spirometry, clinical, laboratory, and gas analyses of arterial blood were conducted, Epworth scale of sleepiness, Berlin and STOP BANQ questionnaire were used, and polysomnographic examination performed using the Philips respironics Alice PDx device.
The gold standard diagnostic test for OSA is the overnight in-laboratory polysomnography. It involves multi-channel continuous polygraphic recording from surface leads for electroencephalography, electrooculography, electromyography, electrocardiography, nasal pressure transducer (supplemented by thermistor) for nasal airflow, thoracic and abdominal impedance belts for respiratory effort, pulse oximetry, tracheal microphone for snoring, and sensors for leg and sleep position. These recordings will identify different types of apnoeas and hypopnoeas during sleep. An apnoea is defined as the complete cessation of airflow for at least 10 sec. There are three types of apnoeas: obstructive, central and mixed. In obstructive sleep apnoea, respiratory effort is maintained but ventilation decreases or disappears because of partial or total occlusion in the upper airway. Central sleep apnoea is defined as reduced respiratory effort resulting in reduced or absent ventilation. Mixed apnoea is often characterized by starting with central apnoeas and ending with obstructive events. A hypopnoea is defined as a reduction in airflow (30-50 %) that is followed by an arousal from sleep or a decrease in oxyhaemoglobin saturation (3-4 %) (5, 6). Sleep apnoea severity is assessed with apnoea-hypopnoea index (AHI), which is the number of apnoeas and hypopnoeas per hour of sleep. According to the American Academy of Sleep Medicine recommendations, OSA is defined with AHI > 5, and it is classified as mild OSA with AHI of 5 to 15; moderate OSA with AHI of 16 to 30; and severe OSA with AHI > 30.

The study included 98 obese patients with OSA. Out of that number, 23 obese diabetic patients with severe OSA were randomized and divided into two groups: an experimental group of 11 patients who used three months continuous positive pressure during sleep (CPAP) and control group of 12 patients who did not use CPAP because of various reasons.

Results

Polysomnographic examination was done to 98 consecutive obese patients, and 58 (60,2 %) of them had severe OSA with AHI index > 30. Out of 98 examined patients, 42 (42,85 %) had diabetes mellitus type II.

Out of 58 patients with high degree of OSA, diabetes mellitus type II had 37 patients (63,79 %), with average value of HbA1c of 11,7 %, indicating poor long-term glycoregulation in obese diabetic patients with severe OSA.

Out of 42 examined obese patients with diabetes mellitus type II, 37 of them had severe OSA (88 %).

In the experimental group of 11 obese diabetic patients with high degree OSA, we found an average HbA1c value of 8.9 %, average BMI value of 37.1 and an average AHI index of 36.7 (31 to 59) at the beginning of follow up period.

All of them 11 obtained devices for CPAP during sleep and its application began during sleep. After three months the results were summoned to control HbA1c values, just as for all patients from the control group.

In the control group consisting of 12 obese diabetic patients and high degree OSA in whom it was not possible to apply CPAP device during sleep, we found an average HbA1c value of 9.1 %, BMI of 39.3 and an AHI index of 39.7 (31 to 62).

There was no statistical difference between the examined groups in the value of glycated hemoglobin A1c as indicator of long term glycoregulation.

After three months of using CPAP devices during sleep statistically significant improvement in average values of HbA1c from 9.9 % to 6.7 % was found in the experimental group (p < 0.001).

In the control group we did not find any significant changes of average values of HbA1c from 9.1 to 9.7 %, Table 1.

<table>
<thead>
<tr>
<th>Experimental group (No 11)</th>
<th>Control group (12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI index</strong></td>
<td>37.1</td>
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<tr>
<td><strong>AHI index</strong></td>
<td>36.7</td>
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<tr>
<td><strong>Initial</strong></td>
<td>9.9%</td>
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<tr>
<td><strong>After 3 months of CPAPa</strong></td>
<td>6.7%</td>
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<tr>
<td><strong>The level of glycosylated hemoglobin HbA1c</strong></td>
<td>(p &lt; 0.001)</td>
</tr>
</tbody>
</table>

Discussion

Obesity is a complex, multifactorial, and largely preventable disease (1), affecting, along with overweight, over a third of the world’s population today (3). If secular trends continue, by 2030 an estimated 38 % of the world’s adult population will be overweight and another 20 % will be obese (4).
Obstructive sleep apnea (OSA), a sleep-related breathing condition, is diagnosed based on a patient’s apnea-hypopnea index from a sleep study, and the presence or absence of symptoms. Diabetes mellitus (DM) and OSA share a significant common risk factor, obesity, with all three conditions contributing to the risk of developing cardiovascular diseases. The pathophysiological links between OSA and DM are still unclear, but intermittent hypoxia may be an important mechanism. (8) More awareness of the possible link between OSA and DM is needed, given their increasing prevalence locally and worldwide. Continuous positive airway pressure is the standard treatment for OSA, while weight loss through dietary and lifestyle modifications is important to holistically manage patients with either condition. (10, 11) There is currently insufficient evidence to support the benefits of screening every diabetic patient for OSA. However, diabetic patients with symptoms suggestive of OSA should be referred to a sleep specialist for further evaluation. Epidemiological evidence has demonstrated a high prevalence of OSA in patients with Type 2 DM. In a cross-sectional study, up to 23% of a diabetic population were found to have OSA(13). In another study by Einhorn et al., 48% of diabetic patients had OSA with AH1 ≥ 10/hr. (14) The most common reason of breathing cessation is OSA, while in 10-15% of patients the reason is the lack of impulse from the brain - central sleep apnea. It is considered that approximately 5% of general population suffers from sleep apnea and its frequency is considered to be approximately the one of asthma, obesity and DM in general population. The main difference is that OSA remains unrecognised for a long period of time and is not treated until its consequences occur - daytime sleepiness, depression, obesity, insulin resistance, DM2, hypertension, atherosclerosis, coronary disease and sudden cardiac death. It is acknowledged that OSA is the cause of many traffic accidents, and in the developed world it is regulated by law that professional drivers must be polysomnographically examined (14).

As a basic consequence of breathing cessation during sleep intermittent hypoxia followed by tachycardia and arterial pressure rise occurs as a compensatory mechanism. As a long-term and cumulative consequence, the rise of leptin, TNF-a, IL-6 levels occur which have a definitive glucose intolerance, insulin resistance and DM2 as a consequence. Also, hypoxemia induced sympathetic stimulation and hypothalamic-hypophysis homeostatic disorder which by adrenal gland and cortisol secretion lead to DM2. (15, 16)

Many studies were conducted in obese patients with a different level of disorder with or without DM. Some of them show that the application of CPAP device during sleep may lead to a significant improvement in fat metabolism, fat loss, downregulation of sleepiness measured by the Epworth scale, glycoregulation improvement and a lower risk of sudden cardiac death which is undoubtedly confirmed by our investigation. (11, 14, 17)

Based on the goals set, applied methods and gathered data, it is evident that in obese patients with OSA and DM, that application of CPAP during sleep significantly approves values of HbA1c. This confirms that OSA is pathologically connected to glucose blood homeostasis and that CPAP application can be a significant therapeutic approach in these patients.

The results of our research are different from some of the previous ones. The explanation for this is the fact that we studied obesity diabetics only with severe OSA, where the use of CPAP over 3 months had undoubtedly enhanced long-term glycoregulation. For example, in another study subjects were recruited via the Oxford Sleep Clinic between June 2004 and August 2005. Eligible subjects were men aged 18-75 years with established type 2 diabetes (on diet, oral hypoglycemc agents or insulin therapy). This double-blind randomized controlled trial of therapeutic and placebo CPAP for 3 months in men with type 2 diabetes and OSA did not show any significant improvement in glycosylated hemoglobin. According to this study therapeutic CPAP did not significantly improve measures of glycogenic control or insulin resistance in men with type 2 diabetes and OSA. (10, 15, 18) While there is great interest in the question of whether CPAP treatment improves DM, the data have, unfortunately, been mixed. Two recent meta-analyses, which included non-randomized trials as well as trials with non-diabetic and diabetic OSA patients, demonstrated that CPAP treatment improved insulin sensitivity. (12, 13) However, in the only randomized controlled trial by West et al, which specifically evaluated the impact of CPAP treatment on glycaemic control in known Type 2 diabetic patients with newly diagnosed OSA, three months of CPAP intervention did not reveal any significant benefit for insulin resistance or HbA1c. (12) It is possible that longer durations of CPAP usage per night may be required to achieve improvements in glycaemic control. Gou and his co. comment on possible numerous reasons for the different effects of CPAP on glycoregulation (19). A recent study by Grimaldi et al. found that poor glycaemic control was associated with the frequency of obstructive respiratory events during rapid eye movement (REM) sleep, but not non-REM sleep (20). As REM sleep predominates in the latter part of the sleep period, the majority of the REM sleep period would have been left untreated in patients who only had four hours of CPAP.

Conclusion

In summary, there is strong epidemiological and pathophysiological evidence supporting the association between OSA and DM. The mechanism by which OSA impacts glucose homeostasis has yet to be fully elucidated, but multiple pathways are likely to play a role.

It is hoped that further research would be able to identify more specific pathophysiological pathways between the two diseases that may guide us in both the timing and nature of interventions to improve patient outcomes. Ultimately, it should be emphasized that diabetic medications are still the mainstay of treatment to achieve optimal glycaemic control, together with lifestyle modification and weight loss.
References


Three month follow up of the effects of continuous positive pressure...

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PRAĆENJE EFEKTA TROMESEČNE PRIMENE KONTINUIRANOG POZITIVNOG PRITISKA TOKOM SPAVANJA (CPAP) NA VREDNOSTI GLIKOZIRANOG HEMOGLOBINA HbA1c I DUGOTRAJNE GLIKOREGULACIJE KOD GOJAZNIH DIJABETIČARA SA DOKAZANOM TEŠKOM OPSEKREDITVOM APNEJOM TOKOM SPAVANJA

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Opstruktivna apnea u spavanju (OSA) predstavlja ozbiljan poremećaj disanja tokom sna koji karakterište potpuni ili delimični prekid disanja u trajanju od 10 sekundi i duže.

U ovoj prospективној клиничкој longitudinalној студији код гојацах пациенте са дијабетес мелитусом типа II којима је полисомнографским изследовањем утврђен тешак степен ОСА, праћен је ефекат примена положитивног притиска током сна (CPAP) у току три месеца на вредности гликозираног хемоглобина HbA1c као индикатора ефикасне дуготрајне дуготрајне гликорегулације.

У проспективну клиничку студију са тремеоносим, праћени укључено је 98 пациенте (64 мућара и 34 жене, тешке степености 50,1 године. /31- 66 година., и тешког BMI 39,1), којима је на конал клинике, лабораторије, спирометријско дифузиско ураде пулмне функције, највише гасних анализе респираторних гасова врежких у мину, испитивања Epworthove skale пропаности, начињена полисомнографско испитивање на Philips Respironics Alice PDx уређају.

Полисомнографско испитивање сprovedено је код 98 конекутивних гојацах пацијената од којих је 42 (42,8 %) пацијент имао дијабетес II. Од укупног броја испитаника код 58 (60,2 %) нађена је OSA тешког степена са AHl индексом већим од 30. Од укупног броја гојацах пацијената са тешким степеном OSA њих 37 (63,79 %) имало је дијабетес мелитус тип II са сеоносом HbA1c 11,7 %, што укључује на лошу дуготрајну гликорегулацију код дијабетицира са тешким степеном OSA.

Од 98 гојацах пацијената, који су имали дијабетес мелитус тип II и OSA тешког степена, рандомизован је њих 23, од чега је њих 11 са тешком вредношћу HbA1c 9,9 %, сеоснog BMI 37,1 и сеоносног AHl indeksa 36,7 (од 31 до 59), набавило апарата за приме порукиног-позитивног притиска (CPAP) током спавања, те су на том утврђено и примени CPAP обавиле контролу вредности гликозираног хемоглобина HbA1c као индикатора дуготрајне гликорегулације. Контролну групу испитанка чинило је њих 12 у експерименталној групи, чија је сеоносна HbA1c била 9,1 %, сеосна BМI 39,3 и AHl indeks bio је 39,7 (од 31 до 62), и без сташичка квалификације између група по степену тешке OSA и вредности HbA1c. Након тремеоносних примена порукиног положитивног притиска CODAP током спавања испитанци експерименталне групе постигли су сташичка квалитетно (p < 0,001) попраћивање вредности HbA1c са сеона 9,9 % на 6,7 %, што није утврђено код пацијената контролне групе који нису користиле CPAP током сна дијабетесом тип II и тешком OSA, примем порукиног положитивног притиска током спавања квалификације искажана кроз врежност HbA1c.


Klíjune reči: opstruktivna sleep apnea, dijabetes mellitus tip II, gojaznost, CPAP