Vitamin D status in obstructive sleep apnea patients

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Diploma thesis

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I would firstly like to thank my mother and father for their continuous support and love throughout my medical studies. I would also like to thank my sisters Elena & Emilija for always being there for me and being the role models that I needed.

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1. INTRODUCTION

1.1. Obstructive sleep apnea

1.1.1. Definition

Obstructive sleep apnea (OSA) is a chronic disorder characterized by repeated episodic collapse of the upper airways during sleep. If this collapse is complete the condition is then called apnea and if it is partial the condition is called hypopnea. As a consequence, OSA can lead to disturbances in gas exchange such as oxygen desaturation, hypercapnia and sleep fragmentation (1). This can lead to manifestation of OSA complications amongst other systems including metabolic (diabetes, metabolic syndrome, osteoporosis), cardiovascular (hypertension, coronary artery disease) and neurocognitive (depression) effects (2-4).

Furthermore, OSA has a significant impact on the quality and quantity of sleep which results in fatigue, diminished cognitive and psychomotor functions and sleepiness during the day which significantly impacts the quality of life of patients with OSA. The definition of OSA is an apnea-hypopnea index (AHI) ≥15 with disregarding the level of oxygen desaturation, or 5 ≤ AHI ≤14.9 with oxygen saturation being ≤88% for ≥10 seconds (5-8).

1.1.2. Epidemiology

The prevalence of OSA in the USA in adults, mostly white aged 30-60 years, is estimated at 24% in men and 9% in women (9). In Europe, particularly in Spain, 26% of men and 28% of women aged 30-70 had an AHI≥5, and a 14% of men and 7% of women had and AHI≥15 (10). In Hong Kong, the male population, aged 30-60, the prevalence of OSA at an AHI≥5 were 9% in males and 4% in females, and at an AHI≥15, 5% in males and 3% in females (11).

1.1.3. Risk factors

Individuals with a pharynx that is abnormally narrowed and collapsible have a greater risk of developing OSA syndrome (12). OSA has been found to be more common in men than in women, two-three times more to be exact, and it is more common in older individuals (65 years of age or more) than middle aged individuals (30-64 years of age). Risk for developing OSA raises

with body weight: a 10 % increase in body weight increases the risk by 6 six times for developing OSA (14). Obesity can cause accumulation of fat in the neck, which in turn can narrow the lumen of the pharynx, that can cause collapse during sleep. There are also other factors that contribute to pharyngeal collapsibility in normal weight individuals which include macroglossia and adeno tonsillar hypertrophy (13).

Individuals with craniofacial anomalies such as Pierre Robinson syndrome or retrognathia, that can cause posterior displacement of the tongue which in turn can block the pharynx are one of the other important causes of OSA in non-obese patients (14, 15). Moreover, lifestyle habits like smoking and nasal congestion can also increase the risk for developing OSA by causing pharyngeal narrowing through inflammation (16).

1.1.4. Pathophysiology

There are several different factors that contribute to pharyngeal collapse, these include a negative vacuum pressure from within the airway that occurs during inspiration and a positive pressure from structures on the outside, such as fat. Conversely, increase in lung volume and activation of pharyngeal dilator muscles preserves the patency of the airway, which by longitudinal traction keep the airway open (6).

Considering all of these variables there is a complex interaction between collapsing forces and negative pressure in the airway and dilating forces. The patency of the pharynx in healthy individuals is delicately protected by the pharyngeal dilator muscles, the most important stimulus being negative airway pressure also known as collapsing pressure for their activation (7,8).

These muscles maintain the airway patency, even when the central respiratory modulation is absent. In order to compensate pharyngeal anatomy that has become compromised, the dilator muscles in patients with apnea have to be far more active when patients are awake as opposed to healthy controls. Significantly more genioglossal activity was observed in patients afflicted with sleep apnea compared to healthy individuals. (18).

Additionally, there is a requirement for a greater amount of intrapharyngeal pressure in order to maintain enough airflow in apnea patients. The slope of the relation between muscle

activation and negative pressure is similar in controls and patients. The increase in negative pressure causes the increased muscle activation. Secondly, the basal tonus of the muscle groups was also increased in patients. The mechanisms at play are yet to be understood, however the plasticity of the neural system likely plays a roll. Moreover, the airway muscle compensation for the deficiency in the anatomy is very precise. Even in the most severe cases the compensation was such that these patients only suffered from apnea episodes during sleep. This highlights the importance of sleep in the pathogenesis of the disorder. Potentially, this is stated effect is mediated by a loss of neuromuscular reflexes (18).

It has been known for several decades that the postural neuromuscular reflexes are decreased or missing during sleep. Furthermore, in healthy subjects the pharyngeal dilator muscles have an attenuated ability to respond to negative pressures. Though the neurochemistry is still unknown, there may be a role played by neuromodulators (cholinergic, serotonergic, orexinergic and adrenergic). The loss of excitatory inputs sent by the hypoglossal motor neurons could significantly reduce the genioglossus and other upper dilator airway muscles ability to respond to negative pressures (amongst other stimuli) that can otherwise reliably activate these muscles when patients are awake (19).

A loss of the reflex driven activation of muscles occurs during sleep in apnea patients and as a result causes the closure of the airway. Therefore, if an individual's pharyngeal anatomy requires reflex activation of the dilator muscles to stay patent during wakefulness, this same individual is vulnerable to have their airway collapse during sleep. Aside from the important dilator muscle control, other factors are also significant. Increased lung volume can also contribute to pharyngeal patency. Sleep induced decrease in the volume of the lungs can cause significant reductions in the longitudinal traction of the airway, subsequently increasing the likelihood of pharyngeal collapse (19, 20).

Theoretically, some people could be fairly dependent on the mechanism mentioned to maintain the patency in wakefulness and then lose it during sleep. Until 2001, the importance of individual ventilatory control mechanisms has been controversial. Younes and colleagues created a technique of proportional assisted ventilation to assess loop gain (ventilatory control stability) during sleep (21).

Loop gain is the affinity of feedback controls to become unstable and oscillate based on intrinsic properties. The following all increase loop gain and thus make apnea more likely, extended circulation time, high ventilatory drive (responsiveness to hypercapnia, hypoxia) and smaller volume in lungs. Results have shown that independently of the upper airway collapse, the loop gain of individuals with obstructive sleep apnea was increased when compared to controls, this indicated that the ventilatory control systems in patients was intrinsically less stable than in controls. Admittedly, the relationship between cause and effect is yet to be established, the implication of the observation is that there may be some contribution from unstable ventilatory control during sleep in the pathogenesis of apnea in certain patients (21).

1.1.5. Clinical Presentation

The main signs and symptoms of sleep apnea are snoring, obesity, hypertension, excessive daytime sleepiness, family history, previous tonsillectomy and witnessed apneas or gasping during sleep. The strongest associations include snoring, obesity and witnessed apneas. Patients with one or more of these signs and symptoms should be highly suspected of having a sleep disturbance, despite the fact that OSA is found usually in older obese men, some patients diagnosed with OSA are not obese. With that being said physicians should look for subtler signs and symptoms in order to correctly diagnose OSA in the future (17).

1.1.6. Diagnosis

An often used diagnostic approach for OSA is overnight polysomnography which is performed in a sleep laboratory, that includes recordings of electroencephalo-gram, electro-oculogram, chin electromyogram, snoring (microphone), airflow measuring device, electrocardiogram, pulse oximetry, and tibialis anterior electromyogram (22). Nasal pressure recordings are useful in identifying high inspiratory resistance and more discrete respiratory events (23). As it now stands polysomnography is the gold standard for the diagnosis of OSA, however there are new techniques and equipment that are evolving (23, 24).

Split night studies have increased in popularity. They are characterized by a combination of diagnosis and treatment throughout the same night. With this strategy the patient is being monitored for the first 3 hours, if an apnea is detected a nasal CPAP titration is promptly undertaken. This modality has its own pros and cons. Firstly, the time that the patient has to attend in the sleep lab is substantially decreased. With that being said the cost is also decreased. Second in order for the patients to adhere to long term treatment with CPAP the first impression is of high importance (24).

Hence there has been different opinions for this approach some say half- night treatment leads to poorer sleep consolidation than full night therapeutic approach. However, from the data that is available there is no important evidence that suggest a significant difference in adherence to CPAP when comparing split versus full night treatment. Third, on rare occasions the therapeutic effects of CPAP might not be achieved during split night titration because of the shorter treatment time, which may lead to an additional night in the sleep laboratory for further treatment. Fourth, if auto-titrating positive pressure devices become well developed and readily available in people's homes, there will be less need of split night studies, which may lead to people preferring home-based treatment. However, during this time split-night studies remain an effective approach. Many methods for diagnosis at home are under investigation (25).

The current home system differs significantly from two-channel which include snoring and oximetry to four-channel which include oximetry, airflow, effort and position, to full polysomnogram. The accuracy from these diagnostic test it’s around 80% with more channels improving the accuracy, but at the same time adding complexity. Nonetheless, the use of these devices and their role is not without its controversies (26, 27).

The approaches vary from country to country and regions within that country. Some clinicians prefer the most cost-effective approach and some prefer the most qualitative approach. In many regions polysomnography remains the standard diagnostic approach, although in some regions home diagnosis and treatment is preferred more. Lastly some physicians only use respiratory monitoring for the diagnosis of sleep apnea and CPAP titration(26, 27).

1.1.7. Metabolic disorders in OSA patients

Multiple studies in the last few decades have shown that patients with OSA have a number of risk factors for developing metabolic syndrome (28, 29). Metabolic syndrome is associated with multiple conditions occurring together and is marked by the existence of three or more of the following listed: hyperglycemia, hypertension, abdominal obesity, low plasma high-density lipoprotein (HDL) levels and hypertriglyceridemia (30). One of the main manifestations of metabolic syndrome is insulin resistance (31). A study conducted by Gabric *et al*. in 2018 acquired data from patients with type 2 diabetes mellitus and found that these patients have high risk of developing OSA and their health-related quality of life (HRQoL) was substantially decreased (32). It is believed that OSA affects metabolism through multiple pathways including tissue hypoxia, oxidative stress, sympathetic nervous system activation and sleep fragmentation. (Figure 1).

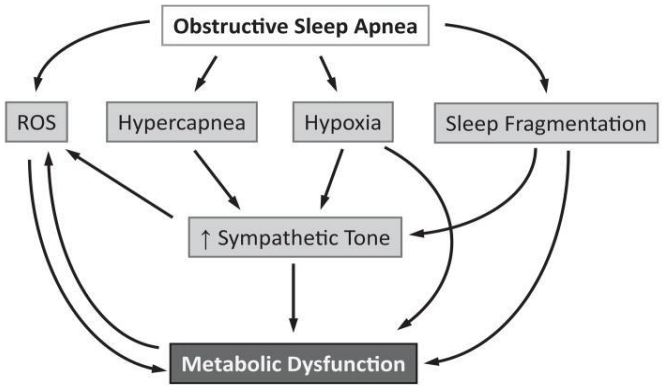

Figure 1. A diagram demonstrating mechanisms that may play a key role in metabolic dysfunction in obstructive sleep apnea (31).

ROS, reactive oxygen species.

Reactive oxygen species (ROS) production from leukocytes is increased in patients with OSA, however after treatment with CPAP this phenomenon is attenuated (33, 34). OSA induces oxidative stress via mechanism that are not well understood, however have commonly been attributed to hypoxia. OSA is marked by transient decrease in the saturation of hemoglobin during flow-limited or obstructed breathing. The term intermittent hypoxia (IH) is characterized by a cyclic pattern of hypoxia and re-oxygenation. The main theory regarding IH causing oxidative

stress suggests that "the oscillations of oxygen concentrations during chronic IH drastically mimics the processes of ischemia/re-oxygenation and therefore could increase cellular production of ROS (35)

Other pathways exist in which OSA may induce oxidative stress. Circulating substrate levels (glucose and free fatty acids, FFA) increase dynamically in patients with OSA during (36-37). These dynamic increases may be related to stimulation of the autonomic nervous system which is hypoxia-induced, leading to generation of ROS via previously mentioned pathways. In particular, an increase in FFA has shown to cause endothelial dysfunction trough development of vascular ROS. In addition to this it has also shown to play a role in skeletal muscle insulin resistance and inflammation (38).

Intermittent hypoxia is one of the key characteristics of OSA. One study has shown that intermittent hypoxia can cause increase in blood pressure mediated trough the activation of the renin angiotensin system (39). This was observed in a study where muscle sympathetic activity was measured alongside plasma and urine catecholamines and following treatment with CPAP levels were within normal range (40). Multiple studies have observed the role of acute sleep fragmentation and its role in developing metabolic dysfunction in humans. One particular study used a combination of auditory and mechanical stimuli to fragment sleep over a period of two nights in healthy, non-obese volunteers. Following sleep fragmentation, volunteers demonstrated poorer insulin sensitivity and glucose handling following an oral glucose tolerance test (41).

Other studies with similar results have been observed using different modes of inducing sleep fragmentation. One study used slow wave sleep deprivation, while the other used auditory sleep deprivation. The latter study observed that the physiological decrease of blood pressure normally seen during sleep was not recorder in the control subjects. The role of sleep fragmentation inducing these physiologic changes is not well understood but it has been postulated that the changes in autonomic tone could be connected with the sleep and wake states (42-44).

1.1.8. Treatment

Uvulopalatopharyngoplasty (UPPP) is the most common surgical procedure for obstructive sleep apnea (OSA). In this procedure the uvula and redundant soft tissue of the soft palate is

resected. Success rates are variable with this procedure and are even miniscule in improperly selected patients. Nonetheless patients with substantial hypertrophy of the tonsils (size 3,4), BMI less than 40 and a Friedman palate position of 1 or 2, the rate of success advances to 80% (45). Besides, patient selection for surgery is a difficult decision as imaging or physical examination procedures generally have not been shown to improve patients' selection for surgery. Therefore, treatment of OSA is rather limited using UPPP procedure.

Three or four months after surgery; overnight polysomnography is clearly indicated in these patients. Snoring will stop after the operation, in many cases, but disordered breathing continues, leading to silent apnea and can makes the surgery less favorable. More aggressive surgery (eg. genioglossal advancement and maxillomandibular advancement) has been reported to be more successful. However, one of the most effective surgeries in adults is maxillomandibular advancement surgery, with 73% rate of success respectively. Nevertheless, these procedures are not widely accepted as the results are debatable and unclear (46).

To further elucidate these outcomes randomized control trials are needed. More recent surgical approaches such as laser-assisted palatal procedures, and radiofrequency ablation techniques have been disappointing in many cases as well. In OSA, none of neither of these modern techniques have been satisfactory (47,48).

Long- term improvements in AHI after gastric stapling has been reported by several studies. Others, however, have reported recurrence of apnea after weight loss surgery in the absence of weight gain. Even though the role of surgery for obesity in management of OSA is unclear, it is increasingly becoming more popular (49,50). Mechanical devices such as mandibular advancing and tongue retaining devices are designed to prevent retroglossal collapse. Oral appliances have a role in the treatment of OSA but CPAP is more effective, especially in more severe disease (51).

In a four year follow up study, researchers randomly assigned patients to receive oral appliances versus UPPP in the treatment of mild OSA and oral appliances was seemingly better. However, due to a large number of dropouts, no definitive conclusion can be made (52). Oral appliances should be considered, therefore, for patients who have failed or refused CPAP treatment, and for those patients with snoring or mild OSA, as well as those who do not respond favourably to surgery. Retropalatal collapse is probably reduced by surgery, whereas the oral

appliance decreases retroglossal collapse. However, data for neurocognitive and cardiovascular outcomes are insufficient after treatment with oral appliances (53-55)

Treatment with Continuous positive airway pressure (CPAP) is still the therapy of choice for sleep apnea due to its effectiveness. The results of multiple studies have illustrated significant improvements in neurocognitive performance and daytime sleepiness on patients treated with CPAP compared to controls. Additionally, blood pressure lowered with CPAP use. One limitation with CPAP is adherence, with the best adherence being among the patients with the most severe forms of apnea and significant daytime sleepiness. The following strategies are aimed at improving adherence; heated humidification, nasal decongestants and regular follow ups (56-58).

There are three different situations where non CPAP therapies should be considered. Firstly, patients with reversible apneas caused my anatomical deformities should instead be candidates for surgery. Obesity is a reversible risk factor; however significant weight loss is still associated with a low success rate in curing OSA (59). Secondly, patients who refuse CPAP should be considered for other therapies. Finally, whether or not patients with mild apnea should be treated with CPAP is still controversial. Instead, these patients could be candidates for conservative therapy, including avoiding depressants like alcohol, maintain nasal patency, advice to sleep on the back and aiming for 7-8 hrs of sleep a night. Despite the aforementioned methods CPAP should also be considered for these patients with the mild form of OSA. The results that came from randomized control trials have been that patients who received CPAP treatment showed improvements in daytime symptoms (60).

1.2. Vitamin D

Vitamin D is a vitamin which is fat soluble that can be found in two forms: ergocalciferol/vitamin D2, found in dietary plant sources and cholecalciferol/vitamin D3 found in animal sources (61). Vitamin D3 can also be synthesized from the sun by a process of isomerization. UVB radiation from the sun converts 7-dehydrocholesterol located in the epidermal cells to pre – vitamin D which later isomerizes into vitamin D3. Both of these vitamins are biologically inactive and they need to be converted into their active forms trough enzymatic

activity. This process starts in the liver and the vitamin undergoes 25-hydroxilation into 25(OH)D (calcidiol), which is one of the main forms of circulating vitamin D and it has a half-life of 2-3 weeks. Then calcidiol can be further converted in the kidneys trough 1-alpha-hydroxylation to 1,25(OH)2D (calcitriol) which is the most active circulating form of the vitamin with a half-life of 4-6 hours (62, 63).

Hence the best indicator for the status of vitamin D is Serum 25-hydroxyvitamin D (25(OH)D) (64). One of the most important functions of vitamin D is bone homeostasis regulation (65). Some studies have found vitamin D receptors in multiple brain areas which one of them includes the hypothalamus that has been found to regulate changes in the sleep-wake cycle, which may be responsible for daytime sleepiness and night time sleep fragmentation. However, further research is required to elucidate this link (66).

2. OBJECTIVES

The aim of the presented study was to compare 25-dihydroxy vitamin D concentrations and other laboratory parameters between OSA patients and healthy control group.

Hypothesis

1. The concentration of 25-dihydroxy vitamin D will be lower in OSA patients.
2. There will be no difference in iPTH, calcium or phosphorus levels between OSA patients and control group.
3. There will be a negative correlation between apnea-hypopnea index and serum vitamin D levels in OSA patients.

3. SUBJECTS AND METHODS

3.1. Subjects

Study included 30 male patients that were diagnosed with OSA at the Split Sleep Medicine Centre (University Hospital of Split, University of Split School of Medicine) in Croatia between May 2018 and January 2019. OSA was diagnosed according to the guidelines of the American Academy of Sleep Medicine (AASM) and European Sleep Research Society (ESRS) (67, 68).

The subjects were excluded from the study if they met one of the following exclusion criteria: malignancy, previous continuous positive airway pressure (CPAP) therapy, chronic renal, pulmonary, cardiovascular, and endocrine disorders, prolonged immobilization, history of repeated fractures, diabetes mellitus, usage of calcium or vitamin D supplements and other medications that could affect bone homeostasis, age under 20 or over 65 years. Medical history, assessment of daily habits and demographic data were obtained from all subjects.

The control group was adjusted for gender, age, waist circumference and body mass index (BMI) as the study group, and it enrolled 30 healthy volunteers. Two screening tools were used for determining the risk of OSA development in control group - the *Snoring, Tiredness, Observed apnea, high blood Pressure-Body mass index, Age, Neck circumference, and Gender* (STOP-BANG) questionnaire, and Epworth Sleepiness Scale (ESS) validated in the Croatian language. Subjects with a STOP-BANG questionnaire score ≥ 3, and subjects with ESS score >9 were not enrolled due to increased risk of undiagnosed OSA (69). Control group performed all measurements by the same protocol as the study group.

Ethics Committee of the University of Split School of Medicine approved this study. Procedures were undertaken in accordance with the Declaration of Helsinki. Informed consent was obtained from all enrolled subjects.

3.2. Anthropometric measurements

All study subjects underwent physical examination and anthropometric measuring. Body height and weight was measured with calibrated scale (Seca, Birmingham, UK). Waist and neck circumference were measured while subjects were standing in upright position with a tape measure. Place of measuring waist circumference was midway between the lower rib margin and the upper aspect of the iliac crest, while neck circumference was measured at the midpoint of the

neck, between mid-cervical spine and the mid-anterior neck (0,5 cm below the laryngeal prominence).

3.3. Daily habits

In detailed interview, information regarding physical activity was taken. We defined physical activity as minimally 30 minutes of activity with weariness and sweating.

For purposes of assessment of total daily calcium intake, 72-hour recall method was used. Sunday, Monday and Tuesday were days of recall. Serving information from participants was put into International Osteoporosis Foundation calcium calculator, and results were processed and recorded.

3.4. Sleep assessment

Polysomnographic recording (PSG) was used on all study group participants. It included electroencephalography, electrooculography, mental and tibial electromyography, electrocardiography, snoring intensity, nasal airflow, thoracic and abdominal movements and finger pulse oximetry (Alice 5LE, Philips Respironics, Eindhoven, Netherlands). Recordings were validated in accordance with the AASM and ESRS guidelines (67, 68).

If subjects attended sleep study less than 6 hours, recording was rejected and another PSG was performed. We defined apnea as complete cessation of respiratory airflow for at least 10 s, and hypopnea as a 50% reduction of airflow for more than 10 s, in combination with downgrade of saturation for minimally 3%. Finally, we defined apnea-hypopnea index (AHI) as a number of apnea or hypopnea episodes per hour during the sleep recording time.

3.5. Biochemical analysis

Venous blood samples were taken after a 12 hour fasting time. Routine laboratory techniques were used for calcium and phosphorus analysis. Furthermore, automated Chemiluminescence Sandwich Immunoassay (CLIA) method was used to assess 25-dihydroxy vitamin D (Immunodiagnostic Systems, Frankfurt, Germany) levels. Intact parathyroid hormone

(iPTH) was analyzed with the electrochemiluminescence immunoassay (ECLIA) method on Roche Cobas e601 (Roche Diagnostics, Mannheim, Germany), while calcium and phosphorus concentrations were determined using standard laboratory procedures.

3.5. Statistical analysis

Statistical analysis was performed with statistical program IBM® SPSS Statistics for Windows® (version 25.0, IBM, Armonk, NY, USA). Continuous and categorical variables were shown as mean ± standard deviation and whole numbers (N) with percentages (%). Kolmogorov-Smirnov test was used for testing the normality of distribution for continuous variables. Differences between continuous variables were assessed with t-test for independent samples, while Chi-squared (χ^2) was used for categorical variables. Correlations between polysomnographic, anthropometric and laboratory parameters were tested with Pearson's correlation analysis. Statistical significance was set at $P<0.05$.

4. RESULTS

Baseline anthropometric characteristics of the study participants are presented in Table 1. Difference between OSA and control group was not observed in any of the parameter, except in neck circumference (41.4 ± 3.5 vs. 38.3 ± 2.2, P<0.001).

Table 1. Baseline anthropometric characteristics of study population

Parameters	**OSA group (N=30)**	**Control group (N=30)**	***P****
Age (years)	52.5 ± 8.4	51.5 ± 8.1	0.608
Body height (cm)	183.8 ± 7.4	182.1 ± 5.7	0.322
Body weight (kg)	104.2 ± 15.0	99.9 ± 11.1	0.207
Body mass index (kg/m^2)	30.8 ± 3.4	30.1 ± 3.0	0.425
Neck circumference (cm)	41.4 ± 3.5	38.3 ± 2.2	<0.001
Waist circumference (cm)	107.6 ± 10.2	104.9 ± 12.5	0.359

Data are presented as mean ± standard deviation or as stated otherwise.
* t-test for independent samples

Table 2 shows daily habits of study participants. There was no difference in total daily calcium intake (P=0.667) or physical activity (P=0.755) between the two groups.

Table 2. Daily habits of study population

Parameter	**OSA group (N=30)**	**Control group (N=30)**	***P****
Total daily calcium intake / mg	1103.1 ± 705.3	1030.9 ± 582.1	0.667
Physical activity (N, %)			
Not physically active	9 (30.0)	9 (30.0)	0.755
1-4 x / month	8 (26.7)	10 (33.3)	
> 4 x / month	13 (43.3)	11 (36.7)	

Data are presented as mean ± standard deviation or as stated otherwise.
* t-test for independent samples or chi-square test

OSA patients' polysomnographic parameters are presented in Table 3. The mean value of AHI was 45.3 ± 13.3 events per hour and oxygen desaturation index (ODI) 42.4 ± 14.1 events per hour.

Table 3. Polysomnographic parameters in OSA patients (N=30)

Parameter	**Value**
AHI (events/h)	45.3 ± 13.3
ODI (events/h)	42.4 ± 14.1
Mean SpO_2 (%)	92.9 ± 2.6
Minimum SpO_2 (%)	73.2 ± 9.2
Total sleep time (h)	6.4 ± 1.3
Obstructive apnea[a]	156.9 ± 141.5
Central apnea[a]	32.9 ± 39.7
Hypopnea[a]	127.5 ± 74.5

Data are presented as mean ± standard deviation
Abbreviations: AHI-apnea-hypopnea index; **ODI**-oxygen desaturation index; **SpO_2**-arterial oxygen saturation;
[a] Number of events per total sleep time

Laboratory parameters of both OSA and control group are shown in Table 4. There was no significant difference observed in serum values of iPTH, calcium and phosphorus between OSA patients and healthy controls. However, all of the measured values were higher in OSA group.

Table 4. Laboratory parameters of study population

Parameter	OSA group (N=30)	Control group (N=30)	*P**
iPTH (pmol/L)	5.82 ± 1.8	5.56 ± 1.75	0.583
Calcium (mmol/L)	2.41 ± 0.08	2.39 ± 0.09	0.328
Phosphorus (mmol/L)	0.99 ± 0.17	0.95 ± 0.20	0.380

Data are presented as mean ± standard deviation
Abbreviations: i**PTH**- intact parathyroid hormone
* t-test for independent samples

Concentrations of 25-dihydroxy vitamin D in OSA and control group were 49.3 ± 15.8 nmol/L and 48.2 ± 17.6 nmol/L, respectively. However, the difference in concentrations was not observed (*P*=0.744), as presented in Figure 2.

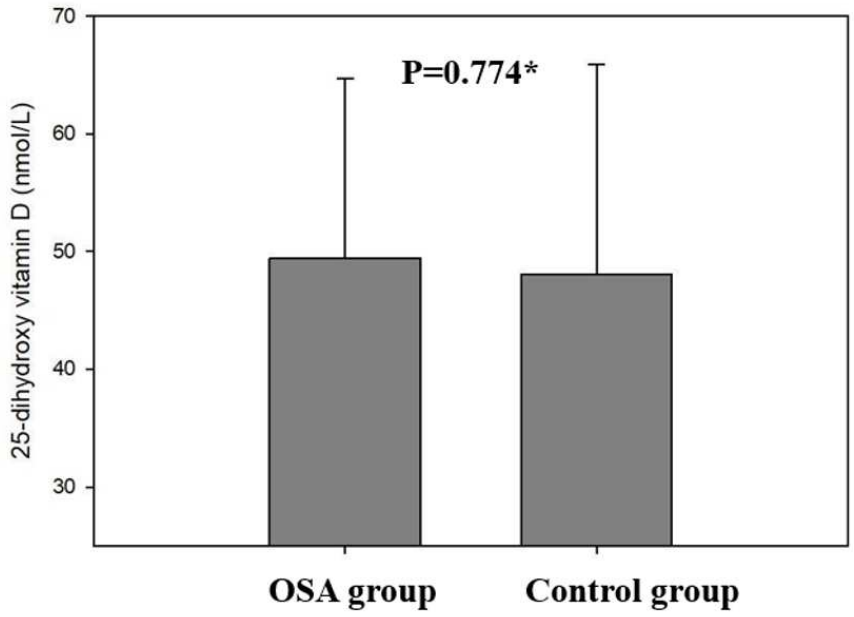

Figure 2. Concentrations of 25-dihydroxy vitamin D in OSA and control group

* t-test for independent samples
Data are presented as mean ± standard deviation.

The correlation of AHI, and 25-dihydroxy vitamin D between selected polysomnographic, anthropometric and laboratory parameters are presented in Table 5. There was a significant negative correlation between BMI and 25-dihydroxy vitamin D concentration (r=-0.304, P=0.018), and waist circumference and 25-dihydroxy vitamin D concentration (r=-0.359, P=0.004). There was no significant correlation between the studied parameters (age, BMI, neck and waist circumference) and AHI.

Table 5. Correlation of AHI, and 25-dihydroxy vitamin D between selected polysomnographic, anthropometric and laboratory parameters

Parameter	**25-dihydroxy vitamin D (nmol/L)** ***r* (*P**)**	**AHI (events/h)** ***r* (*P**)**
Age (years)	-0.017 (0.899)	0.043 (0.822)
BMI (kg/m^2)	-0.304 (0.018)	0.201 (0.287)
Neck circumference (cm)	-0.054 (0.684)	0.233 (0.215)
Waist circumference (cm)	-0.359 (0.004)	0.144 (0.446)
AHI (events/h)	0.024 (0.900)	/

Abbreviations: AHI- apnea-hypopnea index, **BMI**- body mass index.
***** Pearson's correlation test

5. DISCUSSION

The main finding of the presented study was that patients with obstructive sleep apnea had similar concentrations of 25-dihydroxy vitamin D as healthy controls. However, this finding should be carefully interpreted. Previous studies have documented that vitamin D levels in individuals at Mediterranean are lower than expected that may even call for adjustment of standard cut-off levels (70). Furthermore, the association between concentrations of 25-dihydroxy vitamin D and obstructive sleep apnea has been studied extensively. Studies show that there is a decrease in vitamin D among patients with risk for developing OSA, however with no connection of vitamin D levels and OSA severity (71). Furthermore, a large study that included 2827 men showed that patients with lowest levels of 25-dihydroxy vitamin D did have greatest odds of severe sleep apnea, however this finding was most likely confounded with neck circumference and BMI (72). The agreement on association between concentrations of 25-dihydroxy vitamin D and obstructive sleep apnea has not been reached to date.

Furthermore, as this association has been extensively studied, the systematic review with meta-analysis has been conducted in order to clarify the aforementioned association. The study by Neighbors *et al.*, published in 2018, included 14 studies and 4937 subjects, of whom the 3424 were patients with diagnosed obstructive sleep apnea. The patients with obstructive sleep apnea included in the review were categorized as mild, moderate and severe obstructive sleep apnea patients. Moreover, the mean differences in serum concentrations of 25-dihydroxy vitamin D, when compared to control group were -2.7% for mild, -10.1% for moderate and -17.4% for severe obstructive sleep apnea. The authors concluded that decrease in concentrations of 25-dihydroxy vitamin D was exacerbated with increasing severity of the disease. Interestingly, it was uncertain whether a low serum concentration of 25-dihydroxy vitamin D was a risk factor for obstructive sleep apnea, or if the obstructive sleep apnea was a risk factor for 25-dihydroxy vitamin D serum concentration decrease (73).

Several studies included in the systematic review concluded that body mass index was a confounding factor in the research of association between 25-dihydroxy vitamin D concentrations and obstructive sleep apnea. Therefore, the authors stated that the association between 25-dihydroxy vitamin D concentrations and obstructive sleep apnea could be due to the body mass index, and not obstructive sleep apnea per se. Although there was no difference between our OSA

patients and control group in vitamin D status, interestingly vitamin D was also decreased in patients with higher body mass index values, and waist circumference.

Taking all mentioned into consideration there are two possible explanations. It is possible that our OSA patients indeed did not differ from control group in vitamin D status, and that the low serum levels were somewhat expected. Evidence for this in provided in the fact that the 25-dihydroxy vitamin D concentrations were in significant correlation with BMI and waist circumference for all included subjects. However, considering previous research it may be possible that a study including greater population could identify lower vitamin D levels in OSA patients, regardless of generally low levels in Mediterranean population.

Furthermore, a statistically significant correlation between 25-dihydroxy vitamin D concentrations and apnea-hypopnea index was not observed in our study. This finding is in accordance with previously published data on adult obstructive sleep apnea patients. However, the mentioned correlation has previously been observed in paediatric patients (70-73).

Difference in physical activity of obstructive sleep apnea patients and control group was not observed and thirty percent of the obstructive sleep apnea group participants reported that they were not physically active. It is encouraging that OSA patients maintain the same level of physical activity as their healthy counterparts. Moreover, they may be further encouraged to engage in even more physical activity as obstructive sleep apnea patients who are involved in regular and aerobic exercise programs have shown a reduction in the severity of the disease and in daytime sleepiness have improved sleep efficiency and an increase in peak oxygen consumption (74).

It should be acknowledged that our study, however, has some limitations. The first limitation is a small number of the participants included in this study, and the participants were not divided in groups based on the obstructive sleep apnea severity. Moreover, the study was conducted as a single center study and involved only participants from Split-Dalmatia County. Furthermore, some of the collected data could be influenced by recall or even reporting bias. For instance, physical activity is recommended in majority of the disease, and in obstructive sleep apnea, so this could lead to over reporting of this positive behavior in study participants. Moreover, as for the calcium intake assessment the recall method was used, the quality of data presented in this study is determined on the participants' ability to accurately remember the exposure. Additionally, other factors commonly related to 25-dihydroxy vitamin D deficiency were not

assessed, such as sunlight exposition, seasonality, alcohol intake and others. However, even with the presented limitations, our study results are in accordance with previously published research and could add to this field.

6. CONCLUSION

1. There was no difference in serum concentrations of 25-dihydroxy vitamin D in OSA patients and healthy controls.
2. The statistically significant negative correlation was observed between 25-dihydroxy vitamin D concentrations and BMI and waist circumference.
3. The correlation between AHI and 25-dihydroxy vitamin D levels was not observed.
4. Average 25-dihydroxy vitamin D levels were low in both OSA patients and control group.
5. There was no difference in iPTH, calcium or phosphorus levels between OSA patients and controls.

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8. SUMMARY

Objectives: Obstructive sleep apnea is pathological condition characterized by recurrent episodes of upper airway collapse during sleep and is associated with multiple metabolic conditions including metabolic syndrome and osteoporosis. The aim of the presented study was to compare 25-dihydroxy vitamin D concentrations and other laboratory parameters between OSA patients and healthy control group.

Patients and methods: The study included 30 male patients that were diagnosed with OSA and a control group with 30 gender and BMI matched healthy volunteers. All study subjects underwent physical examination and anthropometric measuring. In detailed interview, information regarding physical activity was taken. Polysomnographic recording (PSG) was used on all study group participants. Automated Chemiluminescence Sandwich Immunoassay (CLIA) method was used to assess 25-dihydroxy vitamin D (Immunodiagnostic Systems, Frankfurt, Germany) levels. Intact parathyroid hormone (iPTH) was analyzed with the electrochemiluminescence immunoassay (ECLIA) method on Roche Cobas e601 (Roche Diagnostics, Mannheim, Germany), while calcium and phosphorus concentrations were determined using standard laboratory procedures.

Results: There was no difference in serum concentrations of 25-dihydroxy vitamin D in OSA patients and healthy controls, however aaverage 25-dihydroxy vitamin D levels were low in both groups (49.3 ± 15.8 nmol/L vs. 48.2 ± 17.6 nmol/L, *P*=0.744). There was a significant negative correlation between 25-dihydroxy vitamin D concentrations and BMI (r=-0.304, P=0.018) and waist circumference (r=-0.359, P=0.004). The correlation between AHI and 25-dihydroxy vitamin D levels was not observed (r=0.024, P=0.900). There was no difference in iPTH, calcium or phosphorus levels between OSA patients and controls.

Conclusion: There was no difference in serum concentrations of 25-dihydroxy vitamin D in OSA patients and healthy controls, however serum concentrations of 25-dihydroxy vitamin D were low in both groups. Further studies with a larger number of OSA patients are needed to investigate the relationship between OSA and 25-dihydroxy vitamin D levels.

9. CROATIAN SUMMARY

Naslov diplomskog rada: Razine vitamina D u pacijenata s opstrukcijskom apnejom u spavanju

Cilj: Opstrukcijska apneja tijekom spavanja (OSA) je patološko stanje karakterizirano ponavljajućim epizodama kolapsa gornjih dišnih putova tijekom spavanja i povezano je s više metaboličkih stanja uključujući metabolički sindrom i osteoporozu. Cilj ovog istraživanja bio je usporediti koncentracije 25-dihidroksi vitamina D i druge laboratorijske parametre između OSA bolesnika i zdrave kontrolne skupine.

Ispitanici i metode: Istraživanje je uključilo 30 muških bolesnika kojima je dijagnosticirana OSA i 30 zdravih dobrovoljaca uparenih prema spolu i indeksu tjelesne mase (ITM). Svi ispitanici su podvrgnuti fizikalnom pregledu i antropometrijskim mjerenjima. Detaljnim intervjuom su prikupljene informacije o tjelesnoj aktivnosti. Svi ispitanici su podvrgnuti polisomnografskom snimanju (PSG). Kemiluminiscencijska imunokemijska analiza (CLIA) metoda je korištena za procjenu razine 25-dihidroksi vitamina D (Immunodiagnostic Systems, Frankfurt, Njemačka). Intaktni paratiroidni hormon (iPTH) analiziran je metodom elektrokemiluminiscencijskog imunotesta (ECLIA) na Roche Cobas e601 (Roche Diagnostics, Mannheim, Njemačka), dok su koncentracije kalcija i fosfora određene standardnim laboratorijskim postupcima.

Rezultati: Nije bilo razlike u serumskim koncentracijama 25-dihidroksi vitamina D u OSA bolesnika i zdravih kontrola, međutim, prosječne vrijednosti 25-dihidroksi vitamina D bile su niske u obje skupine (49,3 ± 15,8 nmol/L naprema 48,2 ± 17,6 nmol/L, P=0,744). Opažena je značajna negativne korelacija između koncentracija 25-dihidroksi vitamina D i indeksa tjelesne mase (r =-0,304, P=0,018) i opsega struka (r=-0,359, P=0,004). Korelacija između AHI i razina 25-dihidroksi vitamina D nije uočena (r=0,024, P=0,900). Nije bilo razlike u razinama iPTH, kalcija ili fosfora između bolesnika s OSA-om i kontrola.

Zaključci: Nije bilo razlike u serumskim koncentracijama 25-dihidroksi vitamina D u OSA bolesnika i zdravim kontrolama, međutim serumske koncentracije 25-dihidroksi vitamina D bile su niske u obje skupine. Potrebna su daljnja istraživanja s većim brojem OSA pacijenata kako bi se istražio odnos između OSA-e i razine 25-dihidroksi vitamina D.

10. CURRICULUM VITAE

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