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Original article

FRACTURE RISK AND OBSTRUCTIVE SLEEP APNOEA

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ABSTRACT

Obstructive Sleep Apnoea (OSA) with hypoxemia, oxidative stress, low-grade inflammation and multiple hormonal metabolic changes affect the bone metabolism. This leads to an increased fracture risk in patients with OSA.

Purpose: The aim of the study was to explore the connection between fracture riskand newly-diagnosed OSA.

Materials/methods: 130 patients with newly diagnosed OSA and 67 controls without OSA were included in the study. Anthropometric, laboratory, instrumental and study tests and fracture risk assessment under the FRAX program were performed.

Results: There isn't a statistical difference in the age and gender in the OSA group compared to the controls ($p>0.05$). A statistically significant difference between the OSA group and the control group was found with regard to the body mass index (BMI), visceral fat mass ratio (VFR), neck circumference, Epworth sleepiness scale (ESS), Vitamin D levels, beta-crosslaps and osteocalcin ($p<0.0001$ for all). Reduction of bone mineral density (BMD) was found in patients with OSA. On average, three risk factors for fracture were found in patients with OSA compared to an absence or only one risk factor in the control group ($p<0.0001$).

Conclusion: Patients with OSA are at an increased fracture risk due to disturbed bone metabolism. They have lower Vitamin D levels, reduction of BMD and 3 risk factors for high FR.This requiresan assessment of fracture risk and its eventual reduction in patients with OSA.

Keywords: Obstructive sleep apnoea, Vitamin D, bone mineral density, fracture risk,

INTRODUCTION

Obstructive sleep apnoea (OSA) syndrome is a systemic disease associated with high comorbidity (metabolic, endocrine and cardiovascular conditions)[1, 2]. Patients with OSA have impaired bone metabolism and an increased likelihood of fractures. Changes in bone metabolism are brought about through complex mechanisms. Repeated hypoxia in OSA causes acidosis, reduced vascular perfusion and leads to oxidative stress [3]. Hypoxia stimulates osteoclast activity and increases bone reabsorption [4]. On the other hand, acidosis and oxidative stress activate osteoclasts and inhibit osteoblast function, which leads to bone resorption and lower bone mass [5]. Lower night oxygen levels, characteristic of the OSA syndrome, can be responsible for the reduction of bone mineral density (BMD), which leads to osteopenia/osteoporosis [6]. Changes in sleep architectonics, melatonin secretion and other hormones, as well as an increased sympathetic tonus, all of which are associated with OSA, can affect bone metabolism [7]. The relation between OSA and bone metabolism is poorly elucidated and has contradictory findings.

The aim of this study was to explore the connection between fracture risk and newly-diagnosed OSA.

MATERIALS AND METHODS

A total of 197 participants aged over 18 were included in this prospective study.All of them gave their written informed consent totake part in this study.The protocols conformed to the guidelines of the 1975 Helsinki Declaration. The participants were divided into two groups – patients with newly diagnosed OSA and a control group without OSA.

Patients with OSA were randomly selected after an overnight polysomnography (PSG) test,which was conducted at the Sleep Laboratory in the Department of Propaedeutic of Internal Diseases, UMHAT Aleksandrovska, Medical University – Sofia, Bulgaria. All of them had newly diagnosed OSA, had not received any therapy with continuous positive airway pressure (CPAP) until then and had no supplementation with Vitamin D.

In the control group,OSA has been excluded by overnight pulse oximetry.

Patients with inflammatory or malignant respiratory system diseases; with previous CPAP therapy, patients receiving antiresorptive therapy or supplementation with Vitamin D;pregnant women; patients doing shift work; with cardiovascular diseases (heart failure class III or IV according to the New York Heart Association (NYHA), unstable angina pectoris, acute myocardial infarction, acute myo-, endo- or pericarditis), gastrointestinal diseases (autoimmune intestinal disorders, decompensated liver cirrhosis) or chronic kidney disease stage ≥3 awere excluded from the study.The exclusion criteria were also immunocompromised patients (with neoplasms, after organ transplantation, AIDS, haematological diseases, connective tissue diseases), patients with alcohol or drug abuse or dependence, severe mental disorders or refusal to sign an informed consent form.

Demographic and anthropometric data – age, gender, height, weight, body mass (BMI), neck circumference was collected for all included participants. BMI was determined using the following formula: *Body weight (kg)/ height^2 (m^2).* The following hematological and biochemical blood tests were performed: complete blood count, blood sugar on an empty stomach, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, uric acid, alkaline phosphatase, serum potassium.The tests of all the patients also included immunoreactive insulin (IRI), Vitamin D, parathyroid hormone (PTH), beta-crosslaps, osteocalcin. Laboratory tests were conducted at the Central Clinical Laboratory, UMHAT "Aleksandrovska", Sofia.

All patients in the OSA group had overnight polysomnography conducted using a Compumedics 64-channel polysomnography system. The record was taken from 21:00 in the evening to 6:00 on the next morning at the Sleep Laboratory. OSA has been diagnosed according to the criteria of the International Classification of Sleep Disorders (ICSD – 2), proposed by the American Academy of Sleep Medicine (AASM). In the control group, Overnight pulse oximetry was done for the exclusion of OSA. It was performed using a Medair LS1-9R monitor.

All participants received a quantitative evaluation of daytime sleepiness using the Epworth Sleepiness Scale (ESS). The questionnaire is standard and serves as a method to assess daytime sleepiness. The questionnaire consists of 8 statements. Each statement has a 4-point answer scale. The maximum number of points in the test is 24. A score above 10 points indicates excessive daytime sleepiness.

Dual energy X-ray absorptiometry (DXA) was performed using Stratos OR equipment. DXA is an X-ray method for measuring the absorption of X-rays in tissues with various densities. Two scales were used for the standardisation of the data obtained: T-score – the number of standard deviations from the reference value of a healthy 30-year-old person of the same gender; Z-score – the number of standard deviations from the reference value of a person of the same gender and the same age. BMD is measured at the proximal end of the femur and in the lumbar spine (L1-L4) with a coefficient of variation (CV) of 0.8% and < 1.2% and is expressed in g/cm^2.

The program Fracture Risk Assessment Tool (FRAX)was applied to all subjects in the study. The FRAX strategy for "individual case discovery" is based on the clinical risk factors for osteoporosis. They are divided into two major groups - fixed risk factors (age, female gender, family history, previous fracture, race, menopause, administration of systemic glucocorticoids, rheumatoid arthritis, and male hypogonadism) and variable risk factors (alcoholism, smoking, low BMI, malnutrition, Vitamin D deficiency, low intake of calcium in food, tendency to fall).The 10-year probability of hip fracture or major osteoporotic fracture (clinical spine, hip, forearm and shoulder fracture) is calculated, reflecting the risk factors and BMD/ Ò-score of the femoral neck from the osteometry testing (http://www.shef.ac.uk/FRAX).

The statistical data processing was carried out using SPSS for Windows, Version 19.0 (SPSS Inc., Chicago, IL, USA). The characteristics of the studied population are recorded as mean values ± standard deviation (SD). Categorical variables were summarized as frequency and percentage. Parametric and nonparametric tests were used for continuous variables and Student's t-test was for comparing normally distributed variables. A p-value of 0.05 was accepted as the significance level.

RESULTS

Patients were divided into two groups – a group of patients with newly diagnosed OSA (group with OSA) and a group without OSA (control group).

The group with OSA includes 130 patients, where the men/women ratio is 106/24 (81.5%/18.5%). The average age of the patients is 55.09 ± 9.61 years.

The control group includes 67 participants without OSAwith an average age of 53.16 ± 13.18 years and male to female ratioof 47 (70.1%) /20 (29.9%). There is no statistically significant difference between the two groups regarding gender and age ($p<0.05$ for both).

Patients with OSA have statistically significant higher BMI and VFR compared to the control group (42.260 ± 7.9083 kg/m^2 vs. 27.48 ± 3.56 kg/m^2 for BMI and 24.04 ± 8.364 vs. 11.1 ± 4.46 for VFR, $p<0.0001$ for both). The mean muscle mass for the OSA group is 70.1 ± 11.9 kg and is significantly higher than in the control group (48.8 ± 13.7kg, $p<0.0001$). Neck circumference also differs significantly between the two groups (48.37 ± 5.023 cm for OSA vs. 39.6 ± 2.98cm. in controls, $p<0.0001$).

Patients with OSA have significantly higher scores in the ESS test than the control group ($p<0.0001$).

The main laboratory results in both groups are presented in Table 1. A statistically significant difference is found between the OSA group and the control group with regard to Vitamin D levels,Beta-crosslaps and Osteocalcin ($p<0.0001$ for all)(Tabl. 1).

Table 1. Main laboratory results in the OSA group and the control group

parameter	Group with OSA (n=130)	Control group (n=67)	P
Vitamin D – nmol/L, ± SD	19.8 ± 11.67	36.13 ± 21.65	<0.0001*
PTH – pg/ml, ± SD	3.93 ± 2.427	3.92 ± 1.86	0.71
Beta-crosslaps – ng/ml, ± SD	0.22 ± 0.174	0.42 ± 0.274	<0.0001*
Osteocalcin – ng/ml, ± SD	7.46 ± 6.647	22.59 ± 11.589	<0.0001*
Calcium – mmol/l, ± SD	2.22 ± 0.174	2.37 ± 0.127	0.320
AP – U/l, ± SD	72.19±23.195	87.36±41.713	0.234

Note: PTH – Parathormone, AP – Alkaline phosphatase, Beta-crosslaps – bone resorption marker, Osteocalcin – bone formation marker; * – presence of statistically significant difference

BMD in tested patients with OSA is statistically significantly lower than in the control group. BMD of the lumbar vertebrae in the OSA group was 0.915 ± 0.182 g/sm^{2}compared to 1.1 ± 0.166 g/sm^2 in the control group (p<0.0001), while BMD of the hip was 0.849 ± 0.128 g/sm^2 compared to 1.11 ± 0.144g/sm^2 (p<0.0001).

On average 2.3 ± 1.3 risk factors for fracture are found in the patients with OSA. Seventeen patients have only one risk factor (13.07%). Twenty-seven patients (20.76%) have two risk factors, 56 patients (43.07%) – 3 risk factors and 4 risk factors are found in 24 (18.5%) patients. 5 risk factors are present in 5 patients (3.84%),and one patient (0.76%) has six risk factors.

In the control group, 25 participants (37.31%) are without risk factors, and 23(34.33%) have only one risk factor for fracture. Fourteencontrols (20.90%) have 2 risk factors, and 3 risk factors are found in 4(5.97%) controls. Five risk factors are found in one participant in the control group (1.49%).

The distribution of different risk factors for fracture in the OSA group and in the control group is presented in Table 2.

Table 2. Distribution of patients according to the type of risk factors

Risk factors	Group with OSA (n=130)	Control group (n=67)	P
Without risk factors	-	25	0.001
Previous fracture	70	14	0.001
Family fractures	32	10	0.030
Smoking	76	24	0.001
Alcohol use	91	10	0.001
Rheumatologic	28	23	0.001

DISCUSSION

OSA can changebone metabolism and is a risk factor for the development of osteoporosis[6, 7, 8]. Low bone mineral density (BMD) screening using DXA is an adopted strategy for the identification of people at an increased fracture risk. However, mass screening with DXA in the general population is not usually recommended [9]. A great number of fractures occur in women with BMD within the osteopenic range [10]. Therefore, it is important to identify the risk factors for fractures. Adding clinical risk factors for fracture, irrespective of BMD, improves the ability to predict fracture risk [11].

Uzkeser H, et al. studied 26 men with OSA and 21 without OSA and found that spine and femoral neck BMD values were significantly lower in the patients with OSA compared with the control group[12].

Tomiyama H, et al. have reported that bone resorption markers are significantly higher in patients with OSA compared with the control group [13].

A study of 1377 patients with OSA and 20 655 controls conducted in Taiwanfound that the risk of osteoporosis is 2.52 times higher in patients with OSA than in the control group [14].

Yen et al. measured incidents of osteoporosis in 44,690 patients (846 with apnea and 43,844 without) with newly diagnosed sleep disorders and 89,380 comparisons without sleep disorders. They found that apnea sleep disorder was associated with the highest risk of osteoporosis without fracture (HR=2.98;95% CI=2.36–3.74) compared with both the nonapnea sleep disorders and comparisons without sleep disorders [15].

The results of our study are similar to the mentioned

above. We found statistically lower BMD in patients with OSA than in the control group (p<0.0001).

Wang C, et al. reported that compared with the control group, the OSA group has a higher incidence of osteoporosis (OR = 2.03, 95% CI: 1.26~3.27, Z = 2.90, P = 0.004). The lumbar spine BMD is significantly lower (MD = -0.05, 95% CI: -0.08 ~ -0.02, Z = 3.07, P = 0.002), and the lumbar spine T-score is significantly decreased (MD = -0.47, 95% CI: -0.79~-0.14, Z = 2.83, P = 0. 005) in the OSA group [6].

Vitamin D deficiency is found among patients with OSA [16,17]. Serum levels of Vitamin D correlate with nighttime desaturations (mean and minimum saturation during sleep, time spent with oxyhaemoglobin saturation <90%) [18]. Vitamin D levels have a high prognostic value for the probability of fracture in patients with OSA.

In our study, the level of Vitamin D differs significantly in the two groups (19.8 ± 11.67 nmol/L in the OSA group vs 36.13 ± 21.65 nmol/L in the control group; p<0.0001) and a Vitamin D deficiency was found in the patients with OSA. Calcium levels are similar in both of the studied groups (p=0.320), while beta-crosslaps and osteocalcin are significantly lower in the OSA group (p<0.0001 for both).

In the cohort of patients with OSA studied by us, on average 2.3 ± 1.3 risk factors for fracture are found. Almost half of the patients – 56 (43.1%), have three risk factors. The main risk factors that we found are alcohol use, smoking and previous fracture.

Choi SB, et al. studied 2969 men and 3220 women over 40 years of age. Patients were followed up for 10 years. They found that the risk of fracture is 1.68 times higher (p =0.006, CI 95% 1.16-2.43) among women with severe sleep apnoea when compared with the control group (p <0.001). The risk factors for osteoporosis and fractures for women with a severe degree of OSA are height (p=0.014,HR 0.966, 95% CI 0.939-0.993), waist circumference (p=0.039, HR 0.978, 95% CI 0.957-0.999), hip circumference (p=0.014, HR 1.047, 95% CI 1.009-1.086), family history of osteoporosis or fracture (p=0.029, HR 1.658, 95% CI 1.052-2.612), rheumatoid arthritis (p=0.020, HR 1.563, 95% CI 1.073-2.278) [19]. In another prospective study, Huang T, et al. examined the relationship between OSA and the risk of incident vertebral fracture and hip fracture. They found that ahistory of OSA is independently associated with a higher risk of confirmed vertebral fracture, with the strongest association observed for OSA with daytime sleepiness (HR 2.86; 95%CI 1.31, 6.21). On the other hand,the authors did not find a statistically significant association between OSA history and self-reported hip fracture in women [20]. The study of Matlen LB, et al. demonstrated that both girls and boys with untreated sleep apnoea, in comparison to those without diagnosed sleep apnoea, have increased odds of lower extremity fracture [21].

CONCLUSIONS

Patients with OSA are at an increased fracture risk due to disturbed bone metabolism. They have lower levels of Vitamin D and BMD. Most frequently, 3 risk factors are found to be conducive to fractures. This requires an assessment of fracture risk and its eventual reduction in patients with OSA.

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