Obstructive sleep apnea as a risk factor for osteopenia and osteoporosis in the male population.

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Running Head: OSA and Bone Mineral Density in Men

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Take home message

This report proposes the clinical potential of monitoring bone mineral density in male obstructive sleep apnea patients.

Obstructive sleep apnea (OSA) is a sleep disorder featured by recurrent apnea events leading to hypoxia, hypercapnia and sleep disruption.[1] OSA represents a growing health problem mainly affecting men; in fact, its prevalence in the adult male population is between 4 and 24%.[1-3]

It was recently demonstrated that OSA may lead to a deficient vitamin D status inducing a secondary hyperparathyroidism, which may produce the demineralization of the skeleton and the reduction of the bone mineral density (BMD).[3] In keeping with this observation, recent studies documented reduced BMD in OSA patients, thus speculating that OSA may represent a risk factor for bone resorption.[4-6] However, the evidence proposed so far is controversial due to differences in patients' populations, study designs, definition of OSA; principally, since physical activity and body mass index (BMI) can negatively influence BMD, major limitations of the previous studies are the lack of physical activity assessment and absence of BMI-matched controls.[7-8]

Therefore, the aim of the present study was to evaluate bone homeostasis in a large cohort of male OSA patients compared to male controls matched for age, BMI and physical activity, also investigating and correlating the measured BMD to both polygraphic parameters, Epworth Sleepiness Scale (ESS) scores and serum biomarkers levels, such as vitamin D, parathormone (PTH), calcium, fibrinogen and C-reactive protein (CRP).

We screened 240 consecutive male severe OSA (Apnea-Hypopnea Index –AHI- >30/h) patients undergoing polygraphic cardiorespiratory monitoring from October 2014 to March 2015; 148 patients were excluded and 92 patients (age 51.17±11.82; BMI 30.90±5.87; ESS 10.73±6.03) were included in the study. We compared OSA population to a sample of 50 controls (age 51.00±11.68; BMI 30.78±1.93; ESS, 5.67±2.29) matched for age and BMI with OSA patients. Exclusion criteria for OSA patients and controls were: concomitant neurologic and/or psychiatric diseases; chronic liver disease or chronic renal failure; chronic obstructive pulmonary disease; diabetes; thyroid dysfunction; malignancies; use of corticosteroids or antibiotics over the 4 weeks preceding recruitment in the study; autoimmune disorders; symptoms or signs of acute or chronic

inflammatory disorders or recent infections; calcium or vitamin D supplements; diuretic treatments; heavy smoking; alcohol abuse; hypogonadism; history of immobilization or fractures.

All patients and controls underwent: demographics, medical history and medication assessment; a venous blood sample between 08:00 and 09:00 am after overnight fasting; the dual-energy x-ray absorptiometry (DEXA) measurement of BMD in lumbar spine and femur. DEXA results are expressed as absolute BMD values and as T-scores. T-score evaluates how the examined value is different from that of the standard population (healthy subjects of the same sex at the bone mass peak). We referred to "osteopenia" when the T-score value was less than -1 standard deviation (SD), and to "osteoporosis" when it was less than -2.5 SD.[9]

Using Student T test to compare data between group, we documented that OSA patients showed significantly lower vitamin D (18.62±8.02 vs 31.64±15.03, $p<0.0001$), higher PTH (62.74±23.63 vs 54.32±12.19, $p<0.05$) and increased fibrinogen (404.41±101.89 vs 316.74±43.72, $p<0.001$) and CRP serum levels (3.69±4.29 vs 1.82±0.97, $p<0.001$) compared to controls. We found the significant reduction of BMD in all the regions analysed of both lumbar spine and femur in OSA patients with respect to controls (Figure 1A). Moreover, χ-square analysis with correction for continuity showed that T scores consistent with osteopenia/osteoporosis were more frequent in OSA patients compared to controls at all regions of lumbar spine and at femur neck, upper femur neck, and Ward triangle (Figure 1B).

Finally, we performed a functional evaluation of performance status and physical activity through the Physical Activity Scale for the Elderly (PASE) test, which is a brief, easily scored, reliable and valid instrument for the assessment of physical activity in young-old populations over a 1-week period.[10] On the basis of PASE test scores, OSA patients and controls did not differ in terms of physical activity (83.90±35.41 vs 86.38±35.86).

The Paerson correlation test documented significant correlations between lower BMD in lumbar spine and femur and lower mean oxygen saturation (SaO2) level and SaO2 nadir, and higher time

spent with a SaO2 <90%. Moreover, lower BMD in several lumbar spine and femur regions also correlated with higher ESS scores and higher BMI.

Therefore, this study documented that male OSA patients are affected by reduced BMD in lumbar spine and femur, thus suffering more frequently from osteopenia and osteoporosis in those regions with respect to age, BMI and physical activity matched male controls. Since BMD reduction in several lumbar and femur segments significantly correlated with the alteration of night oxygen saturation indices, hypoxia seems to be the main candidate in reducing BMD in male severe OSA patients. In agreement with this observation, hypoxia has been closely related to changes in bone turnover, and recent in vitro studies have shown that hypoxia promotes osteoclast formation and activity whereas inhibits osteoblast function, thus determining bone resorption.[11-12] Indeed, we hypothesized that lower nocturnal oxygen levels, featuring OSA syndrome, could be responsible for the reduction of BMD in OSA patients, which arranges to osteopenia/osteoporosis.

However, the etiology of bone resorption, and then osteopenia/osteoporosis, in OSA patients could be complex and multifactorial, also including alteration in vitamin D homeostasis, chronic systemic inflammation, and reduced physical activity related to sleepiness and obesity. Accordingly, we documented vitamin D insufficiency coupled with secondary hyperparathytoidism and increased systemic inflammation, featured by higher CRP and fibrinogen levels, in OSA patients. Nevertheless, the lack of correlations between BMD and serum biomarkers data does not propose a reciprocal link among systemic chronic inflammation, alteration in vitamin D status and bone metabolism derangement in OSA patients. Furthermore, since OSA patients and control population did not differ in terms of physical activity, age and BMI, we can exclude insufficient physical activity, obesity and ageing as putative factors of reduced BMD in OSA patients. Although reduction of BMD could also be influenced by the disease duration, sleep-disordered breathing can occur without awareness thus making difficult the quantification of the disease duration.[13]

Absence of an interventional treatment, such as positive airway pressure (PAP), is the major limitation of this study, since we cannot test the possible restorative effect of PAP therapy on BMD in OSA patients.

Finally, although we are aware that osteoporosis is more frequent in women,[14] we did not include in this study female OSA patients since they already show changes in sexual hormones due to postmenopausal condition, which primary influences bone turnover and metabolism, and because prevalence of OSA in women is low. Hence, considering that osteoporosis is a growing concern in the male population, in which a more complete picture of osteoporosis prevalence and etiopathogenesis is needed, we selectively conducted this study in men.

In conclusion, taking into account that bone diseases are rarely considered in the evaluation of OSA patients, this report proposes the clinical potential of performing DEXA in male patients, since OSA could be a detrimental factor on BMD leading to osteopenia and osteoporosis and thus giving susceptibility to bone fractures. On these bases, we encourage clinicians in assessing BMD especially in male OSA patients, in consideration of the possibility to start early intervention opportunities required to reduce the future fracture risk.

Figure legend

Figure 1. *Panel A* shows the significant reduction of BMD in all the lumbar spine and femur regions of OSA patients compared to controls ($p<0.001$ for all regions apart from trochanter $p<0.05$). *Panel B* shows the comparison between T scores of OSA patients and controls, which is significant at all regions of lumbar spine and at femur neck, upper femur neck, and Ward triangle ($p<0.01$ for all regions).

References

1. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. American Journal of Respiratory and Critical Care Medicine. 2002;165(9):1217:1239.
2. Placidi F, Diomedi M, Cupini LM, Bernardi G, Silvestrini M. Impairment of daytime cerebrovascular reactivity in patients with obstructive sleep apnoea syndrome. Journal of sleep research. 1998;7(4):288-292.
3. Liguori C, Romigi A, Izzi F, Mercuri NB, Cordella A, Tarquini E, Giambrone MP, Marciani MG, Placidi F. Continuous Positive Airway Pressure Treatment Increases Serum Vitamin D Levels in Male Patients with Obstructive Sleep Apnea. J Clin Sleep Med. 2015 Jun 15;11(6):603-7.
4. Uzkeser H, Yildirim K, Aktan B, Karatay S, Kaynar H, Araz O, Kilic K. Bone mineral density in patients with obstructive sleep apnea syndrome. Sleep Breath. 2013 Mar;17(1):339-42.
5. Chen YL Weng SF, Shen YC, Chou CW, Yang CY, Wang JJ, Tien KJ. Obstructive sleep apnea and risk of osteoporosis: a population-based cohort study in Taiwan. The Journal of clinical endocrinology and metabolism. 2014;99(7):2441-2447.
6. Terzi R and Yılmaz Z. Bone mineral density and changes in bone metabolism in patients with obstructive sleep apnea syndrome. J Bone Miner Metab. 2015 Jul 24. [Epub ahead of print]
7. Rosen CJ. The Epidemiology and Pathogenesis of Osteoporosis. In: De Groot LJ, Beck-Peccoz P, Chrousos G, et al., eds. Endotext. South Dartmouth (MA)2000.
8. Chilibeck PD, Sale DG, Webber CE. Exercise and bone mineral density. Sports medicine. 1995;19(2):103-122.
9. Orimo H, Hayashi Y, Fukunaga M, Sone T, Fujiwara S, Shiraki M, Kushida K, Miyamoto S, Soen S, Nishimura J, Oh-Hashi Y, Hosoi T, Gorai I, Tanaka H, Igai T, Kishimoto H;

Osteoporosis Diagnostic Criteria Review Committee: Japanese Society for Bone and Mineral Research.Diagnostic criteria for primary osteoporosis: year 2000 revision. Journal of bone and mineral metabolism. 2001;19(6):331-337.

10. Washburn RA, McAuley E, Katula J, Mihalko SL, Boileau RA. The physical activity scale for the elderly (PASE): evidence for validity. J clin epidemiol. 1999 Jul;52(7):643-51.
11. Arnett TR, Gibbons DC, Utting JC, Orriss IR, Hoebertz A, Rosendaal M, Meghji S. Hypoxia is a major stimulator of osteoclast formation and bone resorption. Journal of cellular physiology. 2003;196(1):2-8.
12. Utting JC, Robins SP, Brandao-Burch A, Orriss IR, Behar J, Arnett TR. Hypoxia inhibits the growth, differentiation and bone-forming capacity of rat osteoblasts. Experimental cell research. 2006;312(10):1693-1702.
13. Gooneratne NS and Vitiello MV. Sleep in older adults: normative changes, sleep disorders, and treatment option. Clin.Geriatr.Med 2014;30:591-627.
14. McClain JJ, Lewin DS, Laposky AD, Kahle L, Berrigan D. Associations between physical activity, sedentary time, sleep duration and daytime sleepiness in US adults. Preventive medicine. 2014;66:68-73.

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Claudio Liguori and Fabio Placidi have full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Authors Contribution

Claudio Liguori: study concept, acquisition of data, data analysis and interpretation, statistical analysis, drafting the manuscript.

Andrea Romigi: critical revision of the manuscript for important intellectual content.

Francesca Izzi: critical revision of the manuscript for important intellectual content

Alberto Cordella: literature search

Eleonora Piccirilli: acquisition of data

Salvatore Viola: acquisition of data

Silvio Costa: acquisition of data

Paolo Sbraccia: acquisition of data

Maria Grazia Marciani: study supervision

Umberto Tarantino: study supervision, critical revision of the manuscript for important intellectual content

Nicola Biagio Mercuri: study supervision, critical revision of the manuscript for important intellectual content

Fabio Placidi: study concept and supervision, data analysis and interpretation, statistical analysis, drafting the manuscript.