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

To the Editor:

Obstructive sleep apnoea (OSA) is a sleep disorder characterised by recurrent apnoea 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 demineralisation of the skeleton and a 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 patient populations, study designs and 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 polygraphic parameters, Epworth Sleepiness Scale (ESS) scores and serum biomarker levels, such as vitamin D, parathormone (PTH), calcium, fibrinogen and C-reactive protein (CRP).

We screened 240 consecutive, male, severe OSA (apnoea–hypopnea index >30 per h) patients undergoing polygraphic cardiorespiratory monitoring from October 2014 to March 2015; 148 patients were excluded and 92 patients (mean±SD age 51.17±11.82 years, BMI 30.90±5.87 kg·m⁻² and ESS score 10.73±6.03) were included in the study. We compared the OSA population to a sample of 50 controls (age 51.00±11.68 years, BMI 30.78±1.93 kg·m⁻² and ESS score 5.67±2.29) matched for age and BMI with the OSA patients. Exclusion criteria for OSA patients and controls were: concomitant neurological 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; and a history of immobilisation or fractures.

All patients and controls underwent: demographic, medical history and medication assessment; a venous blood sample between 08:00 and 09:00 h after overnight fasting; and dual-energy X-ray absorptiometry (DEXA) measurement of BMD in the 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 <-1 SD and to “osteoporosis” when it was <-2.5 SD [9].

Using Student’s t-test to compare data between groups, we documented that OSA patients showed significantly lower vitamin D (18.62±8.02 versus 31.64±15.03 ng·mL⁻¹, p<0.0001), and higher PTH (62.74±23.63 versus 54.32±12.19 pg·mL⁻¹, p<0.05), fibrinogen (404.41±101.89 versus 316.74±43.72 mg·dL⁻¹, p<0.001) and CRP serum levels (3.69±4.29 versus 1.82±0.97 mg·L⁻¹, p<0.001) than controls. We found a significant reduction of BMD in all the regions analysed of both the lumbar spine and femur in OSA patients with respect to controls (figure 1a). Moreover, Chi-squared analysis with correction for continuity showed that T-scores consistent with osteopenia/osteoporosis were more frequent in OSA patients than controls at all regions of the lumbar spine, and at the femur neck, upper femur neck and Ward triangle (figure 1b).

Finally, we performed a functional evaluation of performance status and physical activity using 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 versus 86.38±35.86).

The Pearson correlation test documented significant correlations between lower BMD in the lumbar spine and femur, lower mean arterial oxygen saturation (SaO₂) and SaO₂ nadir, and higher time spent with an 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 the 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

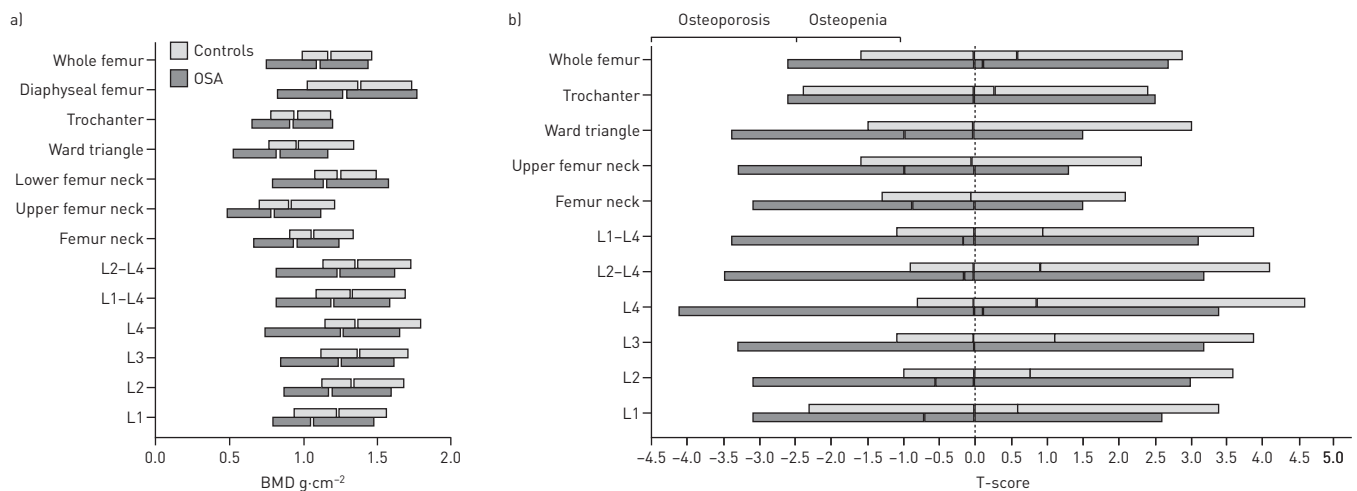


FIGURE 1 a) Significant reduction of bone mineral density [BMD] in all the lumbar spine (L) and femur regions of obstructive sleep apnoea [OSA] patients compared to controls [p<0.05 for trochanter; p<0.001 for all other regions]. b) Comparison between T-scores of OSA patients and controls, which is significant at all regions of the lumbar spine, and at the femur neck, upper femur neck and Ward triangle [p<0.01 for all regions].

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 hypothesised that lower nocturnal oxygen levels, a characteristic of OSA syndrome, could be responsible for the reduction of BMD in OSA patients, which results in osteopenia/osteoporosis.

However, the aetiology of bone resorption, and then osteopenia/osteoporosis, in OSA patients could be complex and multifactorial, also including alterations 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 hyperparathyroidism and increased systemic inflammation, characterised by higher CRP and fibrinogen levels, in OSA patients. Nevertheless, the lack of correlations between BMD and serum biomarker 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 disease duration [13].

The 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 female OSA patients in this study as they already show changes in sexual hormones due to post-menopausal 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 aetiopathogenesis 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 to assess BMD especially in male OSA patients, in consideration of the possibility of starting early interventions to reduce the future risk of fracture.



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This report proposes the clinical potential of monitoring bone mineral density in male OSA patients <http://ow.ly/Voe47>

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Deficient interleukin-17 production in response to *Mycobacterium abscessus* in cystic fibrosis



To the Editor:

The respiratory tract of patients with cystic fibrosis (CF) is colonised with a high diversity of micro-organisms. Nontuberculous mycobacteria (NTM) show a high and increasing prevalence. 40% of these positive NTM cultures are caused by *Mycobacterium abscessus* [1], one of the rapidly growing NTMs present in the environment. Patients with *M. abscessus* infection are difficult to treat, due to natural and acquired antibiotic resistance [2, 3], and an infection with *M. abscessus* is controversially discussed as a contraindication for lung transplantation [4].

Immune-modulatory treatment strategies might contribute to overcome this problem. For their development, a better understanding of the defective immune response explaining the higher susceptibility of CF patients to *M. abscessus* is needed. Here we present three CF patients with *M. abscessus* infection, in whom we describe the pathogen-specific innate and adaptive cytokine production and compare this with non-CF patients with pulmonary infection caused by various NTMs: *M. abscessus* (n=1), *M. avium* (n=3), *M. kansasii* (n=2) and *M. intracellulare* (n=1).

Case 1 is a 24-year-old female patient with CF (dF508del/dF508del) with pancreatic insufficiency and *Pseudomonas* colonisation since 2003. In 2004, she presented with allergic bronchopulmonary aspergillosis (ABPA) which was successfully treated with corticosteroids. After years of infectious exacerbations she presented with an episode of haemoptysis in 2010. Shortly thereafter, *M. abscessus* was cultured from her sputum. In 2011, haemoptysis and clinical deterioration led to hospitalisation and several courses of antimycobacterial regimens (combinations of amikacin, clarithromycin, tigecycline, meropenem and clofazimine) were given without successful *M. abscessus* eradication.

Case 2 is a 23-year-old male patient with CF (dF508del/dF508del), pancreatic insufficiency and *Staphylococcus aureus* and *Aspergillus* colonisation who presented with ABPA. After a course of corticosteroids and itraconazole, he improved and serological markers for ABPA have remained at low levels ever since. After this episode, *M. abscessus* was consistently cultured and although he had no physical complaints, his pulmonary function deteriorated, and a computed tomography thorax scan showed several subpleural and intraparenchymatous nodular lesions compatible with mycobacterial disease. No clearance of *M. abscessus* was achieved, despite two courses of treatment with combination regimens of amikacin, meropenem, clarithromycin and clofazimine.

Case 3 is a 15-year-old male patient with CF (dF508del/G551D), pancreatic insufficiency and *Pseudomonas* colonisation. Since 2011 *M. abscessus* has been consistently cultured and he experienced several exacerbations in 2014, in which his pulmonary function deteriorated, despite several NTM regimens (including tigecycline,