Introduction: Obstructive sleep apnea (OSA) is a common sleep-related respiratory disorder. It is associated with many endocrinopathies including hypogonadotropic hypogonadism, hypercortisolism, and glucose intolerance that may lead to bone loss with secondary osteoporosis.

Methods: We report the case of a 41-year-old man who presented with bilateral 9th rib fractures and was found to have obstructive sleep apnea and osteoporosis. We also present a literature review on this topic.

Results: OSA can lead to bone loss through various mechanisms. Some are shared with obesity, including hypogonadism, altered adrenergic tone, inflammation, oxidative stress, vitamin D deficiency and diabetes mellitus; others are specific to OSA, such as hypoxia and altered glucocorticoids regulation.

Conclusion: There are no guidelines on screening for osteoporosis in OSA. Further research is needed to assess the incidence of bone loss and fractures in OSA.

Keywords: obstructive sleep apnea, bone loss, fracture, hypoxia, obesity

Clinical Significance of Rib Fractures in Men

Rib fracture is one of the most common clinical fractures in older men. It predicts more than two-fold increased risk of future fracture of the rib, hip, or wrist, independent of other covariates, and is considered as an osteoporotic fracture. However, in the European prospective osteoporosis study, rib fracture predicted incident limb fractures only in women. Based on the possibility of increased fracture risk, it is suggested to perform a bone density scan and an osteoporosis work-up in men presenting with a rib fracture in the absence of trauma.

Causes of Bone Loss in Men

Osteoporosis is defined by the NIH as “a skeletal disorder characterized by compromised bone strength, predisposing a person to an increased risk for fracture.” It affects not only women but also men, a frequently under-recognized fact. Osteoporotic fractures in men, although less frequent than in women, are associated with a higher mortality. Following the diagnosis of an osteoporotic fracture, in addition to clinical evaluation and risk factors assessment (e.g. smoking), a work up should be done based on the most common etiologies. In men, 50% of cases are secondary to one of three conditions: endogenous or exogenous glucocorticoid excess, hypogonadism, and excessive alcohol consumption. In addition to these, idiopathic hypercalciuria—defined as urinary calcium > 3–4 mg/kg/day or 300 mg/24 h—is present in 8% of men with osteoporosis. At a minimum, measurement of serum calcium, phosphate, creatinine (with estimated glomerular filtration rate), alkaline phosphatase, liver function, 25-hydroxyvitamin D [25(OH)D], total testosterone, TSH, complete blood count, and 24-hour urinary calcium, creatinine, and sodium is recommended.

Potential Causes of Bone Loss in Men with OSA

Chronic respiratory diseases, mostly COPD, are becoming increasingly known as secondary causes of osteoporosis. OSA, another chronic respiratory disorder, is not a known cause of osteoporosis, but could lead to bone loss and increased risk of fracture through multiple mechanisms, including hypogonadism, sympathetic activation, systemic inflammation, oxidative stress, hypercortisolism, and hypoxemia, as discussed next. Obesity and OSA are tightly related, as about 70% of people with OSA are obese. Conversely, more than one-third of obese people have OSA, the prevalence of which increases with increasing BMI. Since obesity is also associated with most of the factors that could link OSA to bone loss, it is difficult to distinguish the individual effects of obesity and OSA. We will therefore examine the potential mechanisms of bone loss common to both obesity and OSA, and the potential mechanisms specific to OSA separately.

Mechanisms of Bone Loss Common to Obesity and OSA

Hypogonadism

Hypogonadism in obesity: There is good evidence for a link between obesity and hypogonadism. Obese patients have...
The decreased androgen level in obese individuals is potentially mediated through alteration in the pituitary secretion of gonadotropin. The mean diurnal LH levels, mean diurnal LH pulse amplitude, and the sum of all diurnal LH pulse amplitudes and secretory mass were all significantly lower in obese individuals than controls, although the LH pulse frequency was similar. The amplitude of the cortisol and ACTH secretory pulse was also decreased, suggesting a general alteration of hypothalamic-pituitary function in obese men. In another study, the mean baseline serum LH and the magnitude of the pituitary response to exogenous GnRH measured by the secretory burst mass, secretory amplitude, and half-duration of the LH pulses were similar in 7 obese and control subjects. Nevertheless, the apparent endogenous half-life of LH was significantly shorter in the obese group than in the control. Obesity is also associated with insulin resistance, which is in turn associated with decreased testosterone secretion in men. In fact, insulin receptors are present on Leydig cells, and a negative correlation was observed between testosterone and fasting insulin levels. In addition, hyperestrogenemia in obese individuals may be responsible for an inhibitory effect on pituitary gonadotropin secretion, leading to low testosterone. Finally, excess circulating leptin is thought to be an important contributor to the development of reduced androgen levels, including total and free testosterone, in obese males. In fact, leptin receptors are highly inversely correlated with BMI. Conversely, weight loss leads to a significant increase in gonadotropic hormone levels.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal range</th>
<th>Patient level</th>
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<tbody>
<tr>
<td>WBC</td>
<td>4,000–11,000/mm³</td>
<td>8,400/mm³</td>
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<tr>
<td>Hemoglobin</td>
<td>13–18 g/dL</td>
<td>16.2 g/dL</td>
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<tr>
<td>Platelets</td>
<td>150,000–400,000/mm³</td>
<td>270,000/mm³</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.6–1.2 mg/dL</td>
<td>0.9 mg/dL</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.5–10.5 mg/dL</td>
<td>9.3 mg/dL</td>
</tr>
<tr>
<td>Ionized calcium</td>
<td>1.13–1.4 mmol/L</td>
<td>1.29 mmol/L</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>2.7–4.8 mg/dL</td>
<td>3.6 mg/dL</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.6–2.5 mg/dL</td>
<td>2 mg/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>36–53 g/L</td>
<td>48</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>&gt; 21 IU/L</td>
<td>135</td>
</tr>
<tr>
<td>GGT</td>
<td>10–50 IU/L</td>
<td>73</td>
</tr>
<tr>
<td>AST</td>
<td>0–50 IU/L</td>
<td>28</td>
</tr>
<tr>
<td>FBS</td>
<td>76–110 mg/dL</td>
<td>101</td>
</tr>
<tr>
<td>HbA1c</td>
<td>4–6%</td>
<td>5.5%</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>15–76 pg/mL</td>
<td>60.7 pg/mL</td>
</tr>
<tr>
<td>Vitamin D (25OH)</td>
<td>&gt; 25 ng/mL (desirable)</td>
<td>20 ng/mL</td>
</tr>
<tr>
<td>TSH</td>
<td>0.27–4.2 mIU/mL</td>
<td>0.668</td>
</tr>
<tr>
<td>FT4</td>
<td>0.93–1.7 ng/dL</td>
<td>1.47</td>
</tr>
<tr>
<td>Prolactin</td>
<td>4.1–18.4 ng/mL</td>
<td>12.4 ng/mL</td>
</tr>
<tr>
<td>Total testosterone</td>
<td>249–836 mg/dL</td>
<td>281 mg/dL</td>
</tr>
<tr>
<td>Free testosterone (RIA)</td>
<td>8.7–54 pg/mL</td>
<td>8.3 pg/mL</td>
</tr>
<tr>
<td>LH</td>
<td>5–12 mIU/mL</td>
<td>1.4 mIU/mL</td>
</tr>
<tr>
<td>FSH</td>
<td>1–12 mIU/mL</td>
<td>2.9</td>
</tr>
<tr>
<td>24h urine calcium</td>
<td>&lt; 300 mg/24 h</td>
<td>253 mg/24 h (volume = 920 mL)</td>
</tr>
</tbody>
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The results have been inconsistent: some showed increased LH with CPAP therapy, while another study did not. Conversely, most OSA patients with pronounced erectile dysfunction experience some improvement with CPAP treatment. Despite the evidence linking OSA and hypogonadism, screening with testosterone level in patients with OSA has not been recommended. Screening for chronic respiratory disease is recommended in patients with unexplained secondary hypogonadism and osteoporosis in men. The latter may be important in view of the linking mechanisms and the potential worsening of OSA with testosterone replacement, even though this effect is small.

**Altered Adrenergic Tone**

OSA and obesity are associated with increased activity of the sympathetic nervous system (SNS) through variable mechanisms, including stimulation of baroreceptors and chemoreceptors and recurrent arousals. It has been demonstrated that SNS—directly or through leptin—plays a role in the regulation of bone remodeling. In fact, sympathetic and sensory nervous fibers are present in bone tissue, and adrenergic and neuropeptide receptors have been detected on
Vitamin D Deficiency

Vitamin D deficiency, leading to secondary hyperparathyroidism while it inhibits osteoclasts through osteoprotegerin (OPG), resulting in increased bone resorption. Centrally, leptin has dual and antagonistic effects; it inhibits bone loss through Cocaine Amphetamine Regulated Transcript (CART) regulated pathway and conversely activates the sympathetic nervous system, which stimulates bone loss through osteopontin mediated inhibition of osteoblasts and RANKL activation of osteoclast.

Inflammation

Inflammatory markers including IL-1β, IL-6, and TNF-α are elevated in OSA and in obesity; these markers are known regulators of the RANK/RANKL/OPG system and induce osteoclast differentiation and/or activation.

Oxidative Stress

OSA is characterized by intermittent hypoxia followed by re-oxygenation. Those repeated oxyhemoglobin desaturation episodes have been associated with increased oxidative stress and production of reactive oxygen species (ROS). On the other hand, oxidative stress has been also associated with increased adiposity. The effect of oxidative stress on bone has been widely studied. Free oxygen radicals enhance bone resorption by directly stimulating osteoclasts and indirectly facilitating the resorptive effect of PTH, IL-1 and TNF on bone. Furthermore, oxidative stress inhibits bone formation by antagonizing Wnt signaling in osteoblasts, a known important pathway in osteoblast activation. In fact, urinary excretion of the F2-isoprostane, a biomarker of oxidative stress, correlates negatively with BMD, after adjustment for many confounders including sex, age, BMI, and smoking.

Vitamin D Deficiency

Although serum 25-hydroxy vitamin D level was significantly lower in women with increasing OSA severity, obesity could have been a confounder. Obesity is a risk factor for vitamin D deficiency, leading to secondary hyperparathyroidism. Low serum 25-hydroxy vitamin D in obese subjects is due to feedback inhibition of hepatic synthesis of the metabolite by increased circulating 1,25(OH) vitamin D. Another explanation is decreased bioavailability of vitamin D from cutaneous and dietary sources because of its deposition in adipose tissue.

Altered Glucose Metabolism, Insulin Resistance, and Diabetes Mellitus

Obesity is a known predisposing factor for insulin resistance and diabetes mellitus. On the other hand, cross-sectional studies have found that 20% to 30% of OSA patients have diabetes. Diabetes mellitus is a condition characterized by discrepant bone characteristics; despite an increased BMD, there is an increased risk of fracture, probably related to altered bone composition, hormonal changes, microvascular complications, and high prevalence of vitamin D deficiency.

Mechanisms Specific to OSA

Altered Glucocorticoid Regulation in OSA:

OSA had a mild but significant nocturnal elevation in cortisol levels, compared with non-apneic obese controls, independent of cortisol binding globulins levels. Excessive cortisol leads to increased osteoclast-mediated bone resorption and decreased osteoblast-mediated bone formation. This could in part explain the increase in the serum/urinary levels of bone resorption markers in OSA patients.

Although the enzyme 11-hydroxysteroid dehydrogenase type I, which activates cortisol into cortisone in adipose tissue may be over-expressed in obese individuals resulting in local cortisol excess, systemic cortisol levels have not been consistently found to be elevated in obese individuals.

Direct Effect of Hypoxia on OSA on Bone

Oxygen tension acts as a key regulator of osteoclastic bone resorption. In vitro studies have shown that hypoxia stimulates bone resorption directly by increasing the formation of large osteoclasts, and indirectly by increasing ATP release from osteoblasts which stimulates osteoclast activity. Furthermore, hypoxia decreases bone formation through an inhibitory effect on osteoblasts. This effect is mediated through stimulation of Notch signaling, a known inhibitor of mesenchymal progenitor differentiation into osteoblasts. Finally, hypoxia reduces collagen production, alkaline phosphatase, and osteocalcin gene expression, all of which are mediators of bone formation.

CONCLUSIONS

OSA has been associated with several endocrinopathies which lead to bone loss and osteoporosis. Several potential mechanisms mediate this association, some shared with obesity such as hypogonadism and increased inflammation, and others specific to OSA, including hypoxia, sleep fragmentation, and altered HPA axis.

While chronic respiratory diseases, specifically COPD, are important secondary causes of osteoporosis, bone disease is rarely taken into consideration in the approach to patients with OSA. There are no guidelines on screening for osteoporosis or risk factors such as hypogonadism or vitamin D deficiency in OSA. Further studies are needed to assess the incidence of bone loss and fractures in OSA patients in order to guide future recommendations.

ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
CART, cocaine amphetamine regulated transcript
OPG, osteoprotegerin
OSA, obstructive sleep apnea
25(OH)D, 25-hydroxyvitamin D
ROS, reactive oxygen species
SNS, sympathetic nervous system
REFERENCES


DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.