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Obstructive sleep apnea and metabolic bone disease: Insights in to the relationship between bone and sleep

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Abstract

Obstructive sleep apnea (OSA) and low bone mass are two prevalent conditions, particularly among older adults, a section of the U.S. population that is expected to grow dramatically over the coming years. OSA, the most common form of sleep disordered breathing, has been linked to multiple cardiovascular, metabolic, hormonal and inflammatory derangements and may have adverse effects on bone. However, little is known about how OSA (including the associated hypoxia and sleep loss) affects bone metabolism. In order to gain insight into the relationship between sleep and bone, we review the growing information on OSA and metabolic bone disease and discuss the pathophysiological mechanisms by which OSA may affect bone metabolism/architecture.

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Introduction

Low bone mass and sleep disturbances affect a significant portion of the population over 50 years of age and are associated with morbidity, mortality and economic burden. Based on National Health and Nutrition Examination Survey (NHANES) data, in 2010 approximately 54 million U.S. adults over the age of 50 were affected by low bone mass, 10 million of whom were in the osteoporotic range (1). In the U.S. in 2005, osteoporotic fractures cost an estimated $19 billion (2, 3). Such fractures are associated with pain, a decreased quality of life, an increased rate of institutionalization, and increased mortality (estimated at 20–40% in the first year after a hip fracture, with a persistently increased mortality risk up to 10 years after hip fracture) (2, 4).

Sleep disturbances are also common in U.S. adults. Obstructive sleep apnea (OSA) is the most common sleep disordered breathing problem in the U.S. (5). OSA affects nearly 1 in 7 adults, many of whom are undiagnosed (5, 6). OSA predominantly affects older, obese, males; some studies suggest that up to 1 in 4 older men are affected (6). Females and those with a normal BMI but who are anatomically predisposed to a narrow/collapsing airway are also affected (7). OSA is characterized by repeated episodes of airway collapse resulting from sleep-related changes in upper airway dilator muscle tone (5) leading to hypopneas (decreased airflow) and/or apneas (cessation of airflow). These events cause hypoxia and recurrent, apparently life-saving arousals that result in marked elevations in sympathetic nervous system (SNS) activity, which is often sustained beyond sleep throughout the waking hours. OSA is linked to increased inflammation, has the potential to disrupt melatonin secretion and is a risk factor for many cardiovascular disorders (hypertension, heart disease, stroke) (7) and endocrine disorders (metabolic syndrome, obesity, insulin resistance, diabetes mellitus type 2, hypogonadism) (7, 8). In addition, OSA has been associated with impaired motor function, cognitive function and memory which contribute to an increased risk of falls and accidents (9). OSA results in an estimated $3.4 billion in indirect medical costs related to co-morbid conditions and $15.9 billion in OSA-related motor vehicle accidents and decreased quality of life (10). The severity of OSA is generally expressed as the apnea-hypopnea index (AHI), a count of the number of apneas and hypopneas per hour of sleep, although this metric does not quantify the degree of hypoxemia experienced. Clinically, individuals with greater AHIs are more likely to report excessive daytime sleepiness, snoring, morning headaches and decreased libido (7). The treatment of choice for OSA is continuous positive airway pressure (CPAP) (11–13).

Evidence suggests an association between OSA and disorders of bone metabolism/architecture including fracture (14–16). Therefore, as the U.S. population ages and the prevalence of OSA and osteoporosis increase it is important to better understand how they may be linked. OSA can indirectly increase the risk of low bone mass and fracture through

metabolic changes and sleepiness (17) but also appears to directly affect bone health through other mechanisms. This review will focus primarily on OSA and its associated nocturnal hypoxia and sleep loss. However, the mechanisms by which OSA affects bone metabolism likely apply to other sleep disturbances since, for example, sleep loss, inflammation and alterations in melatonin are common to many abnormal sleep patterns and disorders.

We will provide a brief description of normal sleep, circadian and bone physiology; review the evidence relating OSA to bone turnover, BMD and fracture; examine the pathophysiological mechanisms by which OSA may affect bone biology via hypoxia, sleep loss, increased sympathetic tone, alterations in melatonin or co-morbid conditions; introduce the concept of skeletal chronotherapeutics; consider how osteoporosis may affect sleep; and propose future areas of OSA/bone research including exploring the skeletal implications of OSA in younger populations.

Normal Sleep (Figure 1)

In humans, the desire for, timing of, and ability to fall asleep are related to underlying interactions between homeostatic factors (e.g. prolonged wakefulness increases the drive to sleep), circadian factors (e.g. it is easier to sleep in the biological nighttime vs. daytime), as well as emotional and cognitive inputs (e.g. stress can interfere with sleep initiation or maintenance even after prolonged wakefulness and sleep loss) (9, 18). The reasons for sleep are not completely understood, but some primary mechanisms by which sleep occurs are known. At the neural level the balance between wake and sleep is governed, in part, by distinct groups of neurons, the tuberomammillary nucleus (TMN) and the ventrolateral preoptic nucleus (VLPO) (18). The firing rates of these two groups of neurons, relative to one another, tip the balance towards sleep (when VLPO dominates) or wakefulness (when TMN dominates) (Figure 1) (18). Hypothalamic release of the wake-promoting neurotransmitter orexin can stabilize this balance and prevent rapid transitions from wakefulness to sleep (18). On the other hand, the neurotransmitter adenosine accumulates in the basal forebrain during wakefulness and is thought to play a role in the homeostatic drive for sleep through actions on VLPO neurons. The circadian system affects many neural circuits and hormones that can modulate sleep and wakefulness. For instance, the circadian system helps promote sleep at night through neural projections to the pineal gland and release of melatonin, and helps promote wakefulness during the day via neural projections to the arousal areas of the brain, such as orexin neurons (18).

In humans, normal sleep consists of cycles of rapid eye movements (REM) and non-REM (NREM) stages; each stage is characterized by distinct patterns of brain, muscle and ocular activities (9). Slow wave sleep (SWS) (also known as N3 sleep), is the stage of NREM sleep that is considered the most restorative: it is when arousability is lowest and cortical activity is synchronized, presumably to facilitate some of the primary functions of sleep such as memory consolidation (19). SWS is also associated with increased parasympathetic activity, decreased sympathetic activity (9), and increased release of certain hormones including growth hormone (GH). SWS and total sleep time decrease with age (8).

OSA is more prevalent in older populations, can affect seemingly healthy elderly individuals (20), and can exacerbate these normal, age-associated, changes in sleep. Although the tiredness associated with OSA can result in more time spent in bed with greater total sleep time, it is considered to be non-restorative sleep perhaps due to the fact that VLPO neurons (the sleep promoters) are inhibited by noradrenergic input, which is increased in OSA. Increased sympathetic drive is an important feature of OSA that results from recurrent hypoxia, decreased SWS, and sleep loss (21, 22). In OSA, sleep restriction and disruption contribute to disorganized sleep architecture, disordered sleep-wake homeostasis and subsequent disturbances in normal hormonal rhythms. Acutely and over time, sleep deficiency and inefficiency contribute to increased mortality and disability related to cardiovascular and metabolic diseases, increased inflammation and impaired cognition and motor skills (9).

Normal Circadian Rhythm, Synchronization and Bone (Figure 2)

Approximately 10–20% of the genes in any tissue are expressed in a cyclic manner (23). The intrinsic central, or master, circadian clock is located in the hypothalamic suprachiasmatic nucleus (SCN). The SCN receives light/dark cycle input to synchronize its own activity and thereby orchestrate behavioral, physiologic and cellular rhythms optimally across the day and night, including the sleep/wake cycle (24–26). The SCN communicates and synchronizes with clock genes [*BMAL1, CLOCK, Period 1 and 2 (Per1 and Per2), Cryptochrome 1 and 2 (Cry1 and Cry2)]* located centrally and in the periphery via direct neural connections, the SNS, hormonal signals (such as melatonin and cortisol), and the regulation of body temperature (27–32). Clock genes, which have been identified in virtually all cells of the body, including bone cells (*Per1*, *Per2, Cry1, Clock*, and *BMAL1* in osteoblasts (33); *Cry2*, *Per1*, *Per2*, and *BMAL1* in osteoclasts (27)), contribute to the rhythmicity of numerous physiological systems by regulating gene expression (33, 34). *Per* genes in osteoblasts limit bone formation and *Cry2* genes in osteoclasts stimulate bone resorption (35–37). Female mice lacking either gene have a similar high bone volume phenotype (35). In *Per2* deficient mice the phenotype results from a higher bone formation rate and in *Cry2* deficient mice it results from decreased osteoclast activity.

Circadian external synchrony (appropriate timing between an organism and its environment) and internal synchrony (appropriate timing between central and peripheral clocks) are important for efficiency, optimal metabolism and overall health (25, 38). Such synchrony likely evolved so that the cell/organism can prioritize metabolic processes and match energy supply with activity demands. For example, during the day metabolic processes in humans are optimized for energy intake and peak metabolic activity, while at night processes focus on repair, growth and consolidation (38). These circadian rhythms are disrupted when external cues are shifted (as occurs in jet lag or shift work). The central clock is capable of resynchronization. However, this process depends on the severity of the shift and can take many days (38). Peripheral clocks have different susceptibilities to environmental input (e.g. light/dark cycles, food intake, physical activity, etc.) and may resynchronize at a different speed than central clocks leading to internal desynchrony (26, 38). Desynchrony has been associated with the development and progression of metabolic/cardiovascular disease, cancer and even death (9) perhaps due to inefficient and uncoordinated cellular processes

and repair. For instance, internal desynchronization could result in a mismatch between protein production and receptor expression.

In humans, osteoblasts and osteoclasts seem to display circadian rhythmicity (*see next section*) and could be adversely affected by circadian disruption and/or poor sleep. The SCN communicates with osteoblasts via the SNS and glucocorticoids (36, 37, 39), while synchronization between the SCN and osteoclasts largely depends on glucocorticoids (27). This suggests that the SNS and glucocorticoids are important for internal synchronization despite their weak effect on the actual rhythm of bone turnover markers (BTMs).

There are several reasons to believe that OSA could cause circadian disruption. First, disturbed sleep may result in more nocturnal light exposure which can adjust the circadian system (40). Secondly, OSA can augment the transcription of circadian proteins (41). Thirdly, there is some evidence in humans and other animals to suggest that hypoxia impacts both the SCN and melatonin secretion (42). OSA has not been shown definitively to cause circadian disruption but it has the potential to cause internal desynchrony and disruption of the day/night rhythm of BTMs which could impact bone health.

Normal Diurnal Variation of Bone Turnover Markers (Figure 3)

Many hormones have day/night rhythms of secretion and pulsatility that are either endogenous circadian rhythms or are caused by the daily patterns of behavior, such as sleep/wakefulness or fasting/feeding. Such day/night rhythms are susceptible to disruption from sleep disturbance and nocturnal light exposure (8). BTMs have a clear day/night pattern in humans. Markers of bone resorption and, to a lesser degree, bone formation increase overnight with a peak in the early morning hours (a time period of predominantly REM sleep) and a nadir in the late afternoon (43). This rhythm is largely independent of posture (44), normal light/dark cycles (45), parathyroid hormone (PTH) (46), GH (47), sympathetic tone and cortisol (48, 49). As shown in Figure 3, CTX decreases with food intake while the *amplitude* of the diurnal rhythm is blunted during fasting (45, 50). Thus, the rhythm may be driven by food intake and associated endocrine and nutritional signals, including the release of glucagon-like peptide 2 (GLP-2) (45, 50). To a much lesser degree, the day/night patterns of BTMs are also influenced by sex, reproductive hormone status and use of osteoporosis-related medications such as bisphosphonates (51). Additional factors, such as leptin, may also be involved in BTM rhythmicity (52).

Little is known about any endogenous circadian rhythmicity of the osteocyte. A preliminary report suggested a day/night pattern of sclerostin is present in healthy young men with a peak around 1 AM but it did not distinguish if this peak was related to the occurrence of sleep or an internal circadian rhythm that would have persisted during constant behaviors (53). Intact but not C-terminal FGF-23 levels peak in the early morning (54) and skeletal FGF-23 levels appear to display a food-driven day/night pattern that is mediated by sympathetic activity (55). To our knowledge, peripheral clock genes have not been identified in the osteocyte, and it is unclear if an osteocyte's day/night pattern modulates the rhythms of other bone cells.

Bone Turnover and Bone Density in OSA

In 2008, Tomiyama et al found a positive correlation between AHI and urine CTX in men and urine CTX decreased after 3 months of OSA treatment with CPAP (16). To our knowledge, this is the only study of the relationship between OSA and BTMs and suggests an increased rate of bone turnover in OSA that can be normalized with OSA treatment.

More recent studies have examined the relationship between OSA and BMD in humans, with conflicting results. After adjusting for BMI, Uzkeser et al found that 21 Turkish men with OSA (average age 54 years), had lower BMD at the lumbar spine (L-spine) and femoral neck compared to 26 healthy age and sex matched controls (56). These differences in BMD were statistically but not clinically significant. Conversely, Mariani et al (57) performed a cross-sectional evaluation of the relationship between OSA and BMD in 115 obese men and women with OSA and found no association between the severity of OSA and L-spine, femoral neck or total hip BMD. Notably, this study lacked a control population and, likely due to obesity, the majority had normal BMD; < 5% were osteoporotic. The findings from Mariani et al were in line with those of Torres et al (58) who exposed orchiectomized mice to intermittent hypoxia, thereby to some extent mimicking OSA, and found that trabecular BMD in the femur did not differ between the normoxic and hypoxic rats. The authors suggested that the 32-day protocol used in the study was long enough to observe a change in BMD. However, it may not be an accurate translational model for humans since patients may be exposed to many years of undiagnosed or untreated OSA with cumulative effects. In 2013, Sforza et al (59) reported that OSA was associated with higher BMD (at the L-spine and proximal femur) in 833 elderly subjects in France and that worsening nocturnal hypoxemia appeared to be protective of BMD . The three studies in humans by Uzkeser et al (56), Mariani et al (57) and Sforza et al (59) differed in their patient populations, study designs and definition of OSA. Sforza et al used AHI ≥ 15, Mariani et al AHI ≥ 5 and Uzkeser et al did not specify. The American Academy of Sleep Medicine defines OSA as an AHI ≥ 15 or an AHI ≥ 5 with symptoms (60).

Most recently, Chen et al reported that 1377 people with OSA in a retrospective longitudinal cohort study in Taiwan were 2.7 times more likely to develop osteoporosis compared to 20,655 individuals without OSA over 6 years of follow-up (14). This study was the largest to date and had the longest follow-up. Another study from Taiwan corroborated these results and identified an increased risk of osteoporosis in those with apnea and non-apnea related sleep disturbance (61).

The contradictory results of OSA-BMD studies may be due to a number of factors, including study design and skeletal differences in susceptibility to OSA. For example, it may be that the *cumulative* effects of ongoing chronic injury are the most detrimental to bone and therefore can only be appreciated after many years of repetitive damage. In addition, the deleterious effects of OSA on bone may be most evident in bones more susceptible to imbalances in bone turnover, depending on age, sex hormone status and BMI (e.g. postmenopausal women, adolescents).

In sum, these studies utilized different study populations and had methodological inconsistencies that make it difficult to draw reliable conclusions. The study by Chen et al, which was longitudinal, larger, and studied more carefully identified OSA and control populations, interpreted together with the intervention study by Tomiyama et al, suggests that OSA is associated with increased bone resorption and subsequent BMD loss.

Sleep Disturbance and Fracture

Although no studies have specifically addressed OSA and fracture risk, a few have linked the physiological processes that occur in OSA to fracture. Additional literature suggests that other sleep disturbances are associated with increased fracture risk (15, 62).

Recent changes in the pattern of sleep were associated with an increased risk of hip fracture in Southern European men (63), although the nature of this sleep disturbance was not well characterized. The Nurses Health Study found an increased risk of hip and wrist fracture in postmenopausal women who reported working at least three rotating night shifts per month (62). The authors proposed that decreased melatonin secretion might have been responsible for the increased risk. However, the participants worked *rotating* night shifts therefore introducing several potential confounders to the proposed relationship (metabolic, hormonal, vitamin D related). In addition, the underlying pathophysiology may have been related to sleep loss and/or the inherent circadian shifts associated with the rotating schedule.

Individuals with daytime sleepiness from OSA are more likely to nap and Stone et al (64) identified more hip fractures in women who take naps. This was speculated to be due to decreased lower extremity strength in the napping population. Most convincingly, data from the MrOS study (15) indicates that nocturnal hypoxia (defined as $SaO_2 < 90\%$) was associated with an increased risk of falls and non-spine fractures in 2,900 men. This increased risk was independent of BMI, physical activity and age and might be due to the underlying inflammation associated with hypoxia (65–68). These analyses were unable to adjust for possible confounders such as vitamin D status, bone turnover or other hormonal factors. It is important that future prospective studies be designed to collect data to adequately investigate this relationship.

Direct and indirect mechanisms by which OSA may affect bone

OSA may affect bone metabolism and architecture via hypoxia, sleep restriction, increased sympathetic tone, alterations in melatonin and/or other hormonal or co-morbid conditions.

Hypoxia and bone

Nocturnal hypoxia is a cardinal feature of OSA, but the skeletal response to OSA-induced hypoxia in humans is not known. Many studies on the effects of hypoxic conditions have been performed in human cell cultures or animal (mouse) models with different degrees of hypoxia severity, often not simulating OSA (in which there is nocturnal recurrent hypoxemia of variable severity with periods of desaturation and re-oxygenation). Additionally, a skeletal response to hypoxia likely differs based on bone age, the severity/chronicity of the hypoxia, and whether the hypoxia is local and physiologic (as occurs in a

growing skeleton and at fracture sites) vs. diffuse and pathologic (e.g. OSA, bone metastases).

Hypoxia affects bone through a family of transcription factors [Hypoxia-Inducible Factor (HIF)] (69, 70). There are 3 HIF proteins that share a common β subunit and have unique α subunits (70). HIFs are essential for cells to adapt and survive in a hypoxic environment (69). Osteoblasts express HIF-1α and HIF-2α (69) which regulate angiogenic osteogenic coupling (69, 70). HIF-1α accumulates in response to hypoxia. HIF-1α directly stimulates osteoclast activity (71), directly inhibits MSC osteogenic and adipogenic differentiation (70) and blocks the osteoanabolic effects of PTH in mature mouse bone (72). HIF-1α also induces production of vascular endothelial growth factor (VEGF). In humans, VEGF stimulates MSCs, their osteogenic differentiation and the subsequent proliferation and survival of osteoblasts (70). VEGF also stimulates hematopoietic stem cell differentiation into osteoclasts and bone resorption in humans (73, 74). Thus, HIF-1α and VEGF both stimulate osteoclasts but have opposing effects on osteoblasts. It is possible that regulation of this balance allows the HIF-1α/VEGF pathway to be beneficial in physiological periods of bone growth or in fracture repair, but may become disregulated in mature, remodeling bones and in hypoxic conditions produced by disease (e.g. bone metastases, OSA).

Hypoxia is harmful to bone by inducing acidosis and inflammation. The episodic nocturnal hypoxia seen in OSA (throughout the night and over years if untreated) can cause recurrent ischemic injury, which creates inflammation and a hypoxic, acidotic microenvironment in bone. In humans, inflammation has been associated with fractures (75, 76). In animal (rat and elephant) bone, acidosis activates osteoclasts and inhibits mineral deposition by osteoblasts (67, 68).

Hypoxia favorably affects the osteocyte in animal models. Hypoxemia promotes osteoblast differentiation into the osteocyte in mice (77) and decreases sclerostin expression in rats (66).

Oxidative stress is often present with hypoxia. It occurs when there is insufficient antioxidant capacity for a given free radical burden. Oxidative stress is associated with increased bone resorption and low bone mass. Low antioxidant levels have been associated with osteoporosis and an increased fracture risk (78–80). Although the mechanisms for this association are unclear, it may be related to altered collagen structure (15, 81), osteoclast stimulation (via increased production of RANKL) and inhibition of osteoblast differentiation and function (80).

Much of this data comes from simulated hypoxia in rats and the effect of hypoxia on bone cells in humans may ultimately depend on the duration, severity, frequency and chronicity of the hypoxia (82).

Sleep fragmentation, sleep deficiency and bone

Recurrent awakenings occur throughout the night in those affected by OSA, resulting in the build-up of sleep loss or sleep “debt”. Although the amount of sleep required by an individual varies, evidence suggests physiologic and neurobehavioral deficits are more

likely with less than 7 hours of sleep per night (83, 84). The Centers for Disease Control and Prevention estimate that 1 in 3 U.S. adults are below this threshold (85). Sleep fragmentation resulting in sleep loss over time is an important component of OSA and may have additional direct effects on bone that may act synergistically with hypoxia to structurally weaken bone.

In a study from Norway, insomnia, which is self-reported poor sleep quality, was associated with an increased risk of osteoporosis in unadjusted and adjusted models (OR 1.52, 95% CI: 1.14–2.01 adjusted for age, gender, education, anxiety, depression) (86). Specker et al (87) performed a cross-sectional analysis of over 1100 healthy adults in South Dakota and found no difference in areal bone density (at the L-spine, femoral neck or total hip) in the 19% of the population identified as being sleep deficient (average < 6.5 hours of sleep/weekday night) compared to those who had adequate sleep. However, using peripheral quantitative computed tomography (pQCT), cortical (not trabecular) volumetric BMD (vBMD) was lower in sleep-deficient women but higher in sleep-deficient men, compared to sleep-replete individuals, both before and after adjustment for covariates. After multiple covariate adjustments including height and weight, torsional bending strength, as estimated by polar stress strain index (pSSI), was lower in sleep deficient men compared to men with normal sleep (pSSI 358 mm^3 vs. 382 mm^3 $p < 0.05$) which may have been due to lower cortical area in the sleep deprived men. This clinically small difference was attributed to a trend towards smaller periosteal circumference and cortical area. It is unclear why the differences in this study were seen in cortical, but not trabecular bone.

Similarly, in a study from China, there was a trend towards lower total and regional BMD in women sleeping < 7 hours per night with the largest difference in those who had ≤ 5 hours vs. those with ≥ 8 hours of sleep/night (β for total BMD = −0.11, 95% CI −0.07 to −0.01, p <0.01; β for spine BMD = −0.09, 95% CI −0.08 to −0.01, p <0.05) (88). Rat models also suggest that sleep loss is a risk factor for low bone mass. Compared to controls, osteoid thickness, osteoblast number/activity and femoral areal BMD (aBMD) were decreased in sleep-deficient rats while TRACP5b, a bone resorption marker, was elevated (89).

In general, the effect sizes of sleep disturbance on skeletal measures were small in these studies. However, clinically significant differences may accumulate over time and/or when sleep loss occurs at vulnerable times for bone, such as during bone modeling or gonadal deficiency. For instance, sleep loss is common in peri- and postmenopausal women and may accelerate the rapid estrogen-deficient bone loss that occurs during this time. Military training (90) and space flight also represent overlapping periods of sleep disturbance and alterations in bone turnover with accelerated bone loss. There may be additional skeletal implications for these groups.

Overall, evidence suggests that sleep loss is detrimental to bone but the exact mechanism (lower BMD vs. microarchitectural changes), the clinical significance of these seemingly small differences, and their implications for fracture risk are unknown.

Leptin, sympathetic tone and bone

Overall leptin is a powerful inhibitor of bone mass accrual. Leptin's rhythm of secretion is affected by the circadian system and by the sleep/wake and fasting/feeding cycles. In

humans, leptin levels typically peak at night when fasting (26, 91). Although pharmacological experiments previously found that leptin directly signals bone cells, all subsequent *in vivo* cell lineage tracing and cell-specific gene deletion experiments have demonstrated only indirect effects of leptin on bone. Indeed, the main mediator of leptin's inhibition of bone mass accrual is the sympathetic nervous system that inhibits bone formation and favors bone resorption (33, 92, 93). Leptin deficient mice have a high bone mass phenotype, which can be corrected by intracerebroventricular infusion of leptin (94, 95). Similarly, bone mass is affected when the leptin receptor is deleted in the brain, but not in the osteoblast (96, 97). Leptin inhibits serotonin synthesis in the brain as the first step in a pathway that culminates in stimulation of sympathetic tone (96, 97). The fact that leptin regulates bone mass by enhancing sympathetic tone is particularly relevant in OSA, when SNS activity is already increased. Although inconsistent, the majority of the literature suggests that leptin levels are increased in OSA (independent of OSA severity and BMI) (91) and levels decrease with CPAP (98). High levels of leptin and SNS activity favor a low bone mass phenotype. Therefore, if leptin stimulates sympathetic tone in OSA then lower bone mass should result.

Sympathetic tone is increased in OSA. Murine osteoblasts express adrenergic receptors (99). Excess noradrenergic tone leads to bone loss through suppression of bone formation and increased bone resorption (99). The chronicity of increased noradrenergic tone may attenuate the skeleton's response. In chronic stress, release of neuropeptide-Y (NPY) protects bone by inhibition of corticotropin-releasing hormone (CRH) and catecholamines (99). Acutely, NPY has the opposite effect. Therefore, the effects of increased sympathetic tone in OSA on bone may depend on its chronicity. BTMs peak overnight, a time when sympathetic tone is usually low. The increased sympathetic tone in OSA may disrupt the normal nocturnal peak in bone remodeling and therefore bone structure, density and strength.

Melatonin

It is not known if melatonin levels or rhythms are different in OSA. Individuals with OSA are more likely to have nocturnal light exposure that can theoretically disrupt melatonin secretion. Disturbances in melatonin may have skeletal implications.

Melatonin, secreted by the pineal gland at night in humans, plays an important role in the regulation of sleep and in circadian synchronization. The relationship between melatonin and bone metabolism is complex and was recently reviewed comprehensively by Amstrup et al (80). Melatonin receptors have been identified on human osteoblasts (100, 101), human monocytes (102) and on osteoclasts in goldfish (80, 103, 104). Some rat models show an inverse correlation between bone formation markers and melatonin (105). Conversely, in mice, melatonin impairs osteoclast function by scavenging free radicals produced by local bone resorption (decreasing oxidative stress), promotes mesenchymal stem cell (MSC) differentiation into osteoblasts, decreases RANKL and increases osteoprotegerin (OPG) (80, 106). Oxidative stress is associated with decreased bone formation (by inhibiting osteoblast differentiation and function) and enhanced bone resorption (by unknown mechanisms) (80). Some evidence suggests that continuous, not intermittent, exposure to melatonin is

responsible for the beneficial effects on bone formation (80, 107). Therefore, OSA's interference with continuous nocturnal melatonin secretion could have deleterious skeletal effects.

Melatonin receptor expression is increased at night and may have similar rhythmic expression on osteoblasts (80, 101). This may indicate a role for melatonin in the regulation of the rhythm of BTMs. Levels of melatonin and its receptor decline with age, particularly after menopause (80, 101). Therefore, lower levels of melatonin and decreased sensitivity to melatonin due to decreased receptor availability may exacerbate post-menopausal bone loss. The effects of melatonin on bone appear to be modulated by estrogen status. In animal studies, melatonin can work synergistically with estrogen to positively impact bone (80, 108). However, melatonin also has anti-estrogenic effects (109). Melatonin is low in night shift workers (110). Low levels of melatonin are speculated to explain the epidemiological association between increased cancer rates and shift work/jet lag (38). The anti-estrogenic effects of melatonin may play an important role since these associations are strongest for estrogen and hormone-dependent cancers (breast, prostate, endometrial) (38). The relationship between melatonin, estrogen and bone remains unclear but may have implications for those with OSA (particularly if it is present during and after menopause) and those with occupation related sleep disorders.

Slow wave sleep is decreased in OSA. Cardinali suggested that melatonin could help prevent age-related bone loss by increasing SWS and GH (111). The only randomized controlled trial of melatonin for bone health and quality of life in humans showed no difference in BTMs or bone density by calcaneal ultrasound (112). This trial was small (18 peri-menopausal women) and of short duration (6 months). Further research in this area is needed.

Effects of sleep disturbance on bone via other mechanisms (Figure 4)

Sleep disturbance and OSA may indirectly affect bone via associated co-morbidities such as vitamin D deficiency, hypogonadism, obesity, insulin resistance and cognitive/physical impairments.

Serum 25-hydroxyvitamin D levels, which correlate with BMD (113, 114) and hip fracture (115), are lower in those with OSA vs. controls. This relationship appears to be proportional to OSA severity but is not conclusively independent of BMI (116, 117). In addition, OSA has been linked to a causal role in central hypogonadism (118, 119) that impairs bone density by increasing bone resorption and therefore may mediate part of the relationship between sleep and bone.

A cyclic relationship exists between metabolic dysregulation and sleep disturbances. Sleep restriction has been shown to increase appetite (120), decrease satiety (120), decrease resting metabolic rate (121), and contribute to insulin resistance thereby promoting weight gain, obesity and diabetes mellitus type 2. Moreover, obesity is a risk factor for OSA and other sleep disturbances (122) which can perpetuate the cycle. Osteoblasts express insulin and IGF-1 receptors (123). Therefore, insulin resistance and GH suppression seen in sleep restriction and OSA (8) may mediate some of the effects of sleep disturbance on bone

metabolism. Although obesity has traditionally been thought to be protective of bone density, it appears that type 2 diabetes mellitus and obese phenotypes fracture despite a higher BMD (124). Therefore an OSA population may be predisposed to fracture, unrelated to BMD.

OSA and poor sleep quality/duration have also been linked to mild cognitive impairment (64, 122, 125), frailty (126), depression (127, 128), falls (129) and medications that predispose to falls (64). Benzodiazepines, sometimes used for insomnia, are associated with an increased risk of hip fracture in epidemiological studies (130). Some data suggest that it is sleep loss itself, independent of medication use, that is associated with balance impairment and falls (131, 132). Sleep restriction, napping and nocturnal hypoxemia were also associated with falls in community-dwelling older men (17) and women (64). OSA predisposes to daytime sleepiness and falls which may lead to progressive immobility and subsequent bone loss.

Overall, those with OSA and other sleep disturbances have more co-morbidities including multiple metabolic and hormonal disorders. Therefore, it is a challenging population to study and to isolate the specific pathophysiological mechanisms responsible for the reported associations of OSA with skeletal outcomes.

Chronotherapeutics (133) and Bone

The expression of clock genes in bone cells, the presence of rhythms in relevant endocrine/metabolic systems, and the diurnal variation of bone turnover markers may indicate that there is an optimal therapeutic window for bone-related medications. Zhang et al recently studied gene expression across 12 tissues in mice and found that the rhythm of circadian gene transcription and the expression of its receptors were often organ-specific (133). These patterns were substantially conserved in humans (133, 134). This suggests that the regulation of biological rhythms is specific to each organ. They also noted that the majority of the best-selling medications on the market today target genes with rhythmic expression, including skeletally relevant medications such as testosterone, estradiol, ergo/cholecalciferol, hydrochlorothiazide and dexamethasone (133). Although Zhang et al did not specifically examine bone, the concept of “chronotherapeutics” implies that a drug’s half-life and the timing of gene and receptor expression in a target organ could have important implications for the treatment of skeletal disorders (133, 134).

Effects of osteoporosis on sleep

The relationship between sleep and bone is probably bidirectional. In a 2003 survey by the National Sleep Foundation, those with osteoporosis were 67% more likely to report decreased sleep time (122) but were not at increased risk of other sleep disturbances (daytime sleepiness, breathing pauses, restless leg syndrome). Although causality cannot be established from this epidemiological analysis, this association could mean that those with osteoporosis suffer from poorer sleep quality and that their fractures or fracture-related pain/kyphosis could lead to sleep restriction. Indeed vertebral fractures have been associated with the development of poor sleep (135, 136). This may create a self-perpetuating cycle of worsening bone health and sleep disruption.

Skeletal implications of OSA for children and adolescents

Although OSA is common in older men, it also affects younger populations, especially those with enlarged tonsils/adenoids. OSA is increasingly common in younger individuals because of the growing prevalence of childhood obesity. Up to 45% of adolescents with moderate to severe obesity have polysomnographic evidence of OSA (137). These adolescent populations may be especially susceptible to OSA-mediated insults to bone, which could result in a large population at risk for low bone mass due to failure to reach their peak skeletal mass, suboptimal bone modeling and subsequent accelerated loss if OSA is superimposed on estrogen deficient states.

The skeletal effects of hypoxia on bone may differ according to the remodeling vs. modeling state of bone and could have significant implications for adolescents affected by OSA. The available data seem to suggest that in remodeling bone, exposure to hypoxia and HIF-1α leads to bone loss by stimulating osteoclasts and suppressing osteoblasts at many levels. The long-term implications of skeletal exposure to OSA and intermittent nocturnal hypoxia during early life and adolescence have not yet been studied. However, rats exposed to hypoxia during the first 7 days of life were found to have lower BMD that recovered after a period of normoxia (138). The exact site of BMD analysis was not specified. Hypoxia was associated with an increase in corticosterone levels and a decrease in food intake, which may have affected BMD. Sleep restriction, metabolic disturbance, hypogonadism and other sequelae of OSA may also be present in children/adolescents and could have effects on the growing skeleton. If these effects are present during growth, it would be important to diagnose and treat OSA early so normal bone modeling can resume and correct any deficits in bone mass and/or microarchitecture/strength. If left untreated, the peak bone mass in OSA-affected individuals may be reduced, thereby predisposing them to low bone mass later in life. The issue of OSA during adolescence is likely to be of increasing importance with the growing prevalence of obesity in younger age groups.

Future Research Considerations

The relationship between disrupted sleep and bone is difficult to study for many reasons. First, melatonin levels, total sleep time and SWS decrease with age (139) and sleep patterns and circadian rhythms change throughout life, so the potential for internal circadian desynchrony and the magnitude of sleep-induced alterations in bone may vary over a lifetime. In addition, changes in bone are often measured over years during which sleep patterns may change, which makes it challenging to relate a specific sleep phenotype directly to skeletal outcomes (64). Secondly, the effects of sleep disturbance are difficult to study in isolation due to the multiple biological, metabolic and hormonal disruptions implicit in the clinical syndrome of OSA. Finally, it has been difficult to draw overall conclusions because the severity of sleep disturbance often differed between studies and sleep disturbance may affect bone differently depending on the site (cortical vs. trabecular), stage of life, and/or the presence of other disturbances in remodeling/modeling. These inter-related factors will need to be considered in future research on bone and sleep to answer a number of important questions, including:

1. Does the osteocyte have a circadian rhythm or function?

2. How does circadian rhythm disturbance affect bone metabolism?
3. Is the timing of osteoporosis medication administration important with regards to rhythmic receptor expression?
4. Do the bone-related effects of OSA differ according to the severity, duration and/or chronicity of OSA, cortical vs. trabecular bone or by the presence of other skeletal disturbances?
5. How does sleep disruption during growth affect bone? For example, does OSA during adolescence predispose to lower than expected peak bone mass and an increased incidence of osteoporosis and/or fracture?
6. Does OSA treatment improve bone health and skeletal outcomes?
7. What are the skeletal implications of other sleep problems (e.g. shift work, jet lag)?

Conclusions

OSA may be an unrecognized cause of secondary osteoporosis. The diurnal rhythm of bone turnover is likely important for normal remodeling. OSA (via sleep restriction, decreased sleep quality, nocturnal hypoxia, inflammation, etc.) may disrupt this rhythm and/or affect bone metabolism via other mechanisms and predispose individuals to low bone mass and fracture. As the U.S. population ages and the prevalence of obesity rises we are likely to see more patients at risk for both osteoporosis and OSA. It is therefore important to determine the relationship between these two increasingly common diseases, understand the biological processes that drive the relationship and establish appropriate screening and interventions to decrease the morbidity, mortality and costs associated with OSA/osteoporosis so that we may ultimately benefit patients.

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Abbreviations

BMI	body mass index
BMD	bone mineral density

OSA	obstructive sleep apnea
AHI	apnea-hypopnea index
SCN	suprachiasmatic nucleus
Per1 and Per2	Period 1 and 2
Cry1 and Cry2	Cryptochrome 1 and 2
TMN	tuberomammillary nucleus
VLPO	ventrolateral preoptic nucleus
NREM	non-REM
SWS	slow wave sleep
SNS	sympathetic nervous system
BTMs	bone turnover markers
PTH	parathyroid hormone
GH	growth hormone
OPG	osteoprotegerin
HIF	Hypoxia-Inducible Factor
VEGF	vascular endothelial growth factor
MSC	mesenchymal stem cells
L-spine	lumbar spine
pQCT	peripheral quantitative computed tomography
vBMD	volumetric BMD
aBMD	areal BMD
pSSI	polar stress strain index
CI	confidence interval
NPY	neuropeptide-Y
CRH	corticotropin-releasing hormone

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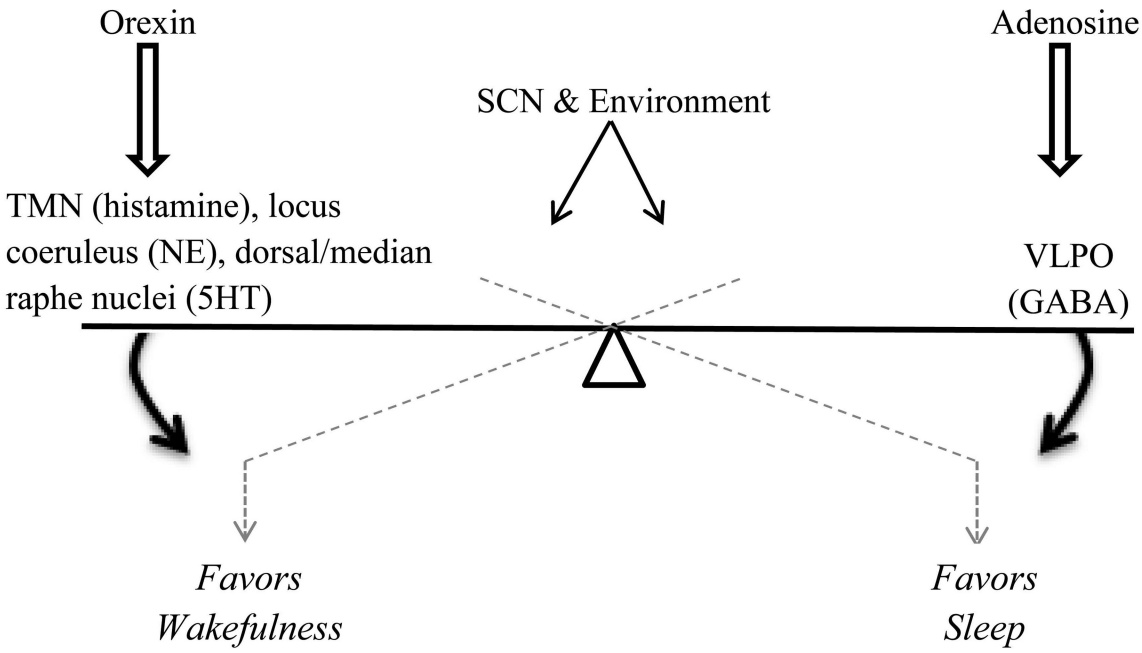

Figure adapted (with permission) from Saper CB, Cano G and Scammell TE. Homeostatic, Circadian and Emotional Regulation of Sleep. The Journal of Comparative Neurology. 2005 493:92-98.

Figure 1. Neuronal balance of normal sleep vs. wake

The relative firing rates of different groups of neurons help govern the sleep/wake balance. Neurons are represented in the figure as "Anatomical region (neurotransmitter)". When the firing rates of the ventrolateral preoptic nucleus (VLPO) dominates, this tips the balance towards sleep. When the firing rates of the tuberomammillary nucleus (TMN) and noradrenergic (NE)/serotoninergic (5HT) neurons in the locus coeruleus and dorsal/median raphe nuclei dominate, they tip the balance towards wakefulness. The hypothalamic wake-promoting neurotransmitter orexin can stabilize this balance and prevent rapid transitions from wakefulness to sleep. On the other hand, the neurotransmitter adenosine accumulates in the basal forebrain during wakefulness, promotes drowsiness and is thought to play a role in the homeostatic drive for sleep through actions on VLPO neurons. This system is also influenced by the circadian drive for sleep, represented by the suprachiasmatic nucleus (SCN), and environmental inputs such as stress and food intake. Adapted (with permission) from Saper et al 2005.

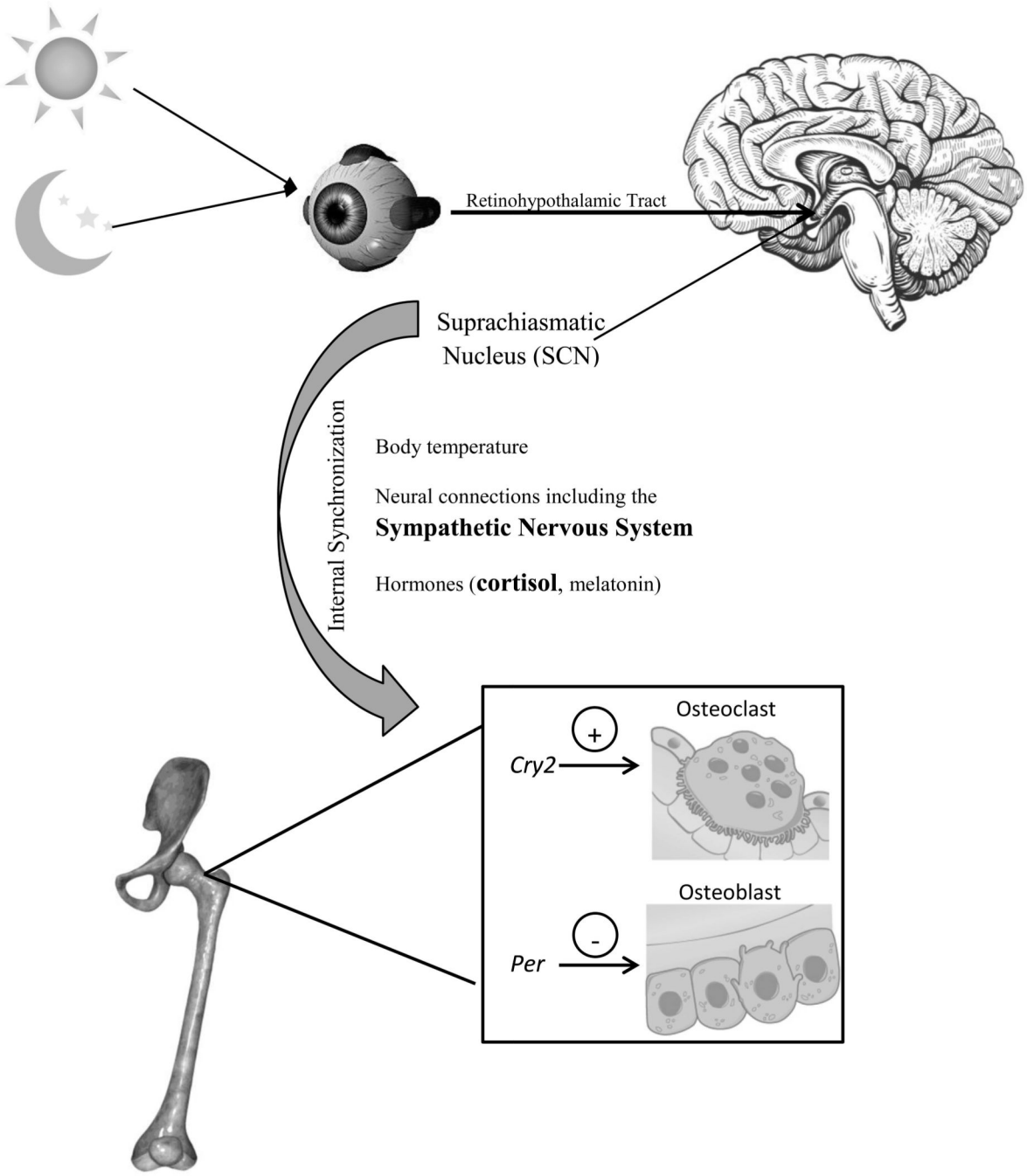

Figure 2. Internal synchronization of central (SCN) and peripheral (*Cry, Per*) clocks in osteoblasts and osteoclasts

Light is perceived by the retina and transmitted to the SCN by the retinohypothalamic tract. The SCN synchronizes with clocks in the periphery through a variety of mechanisms. The SCN communicates with the osteoblast and osteoclast mostly via glucocorticoids and the sympathetic nervous system.

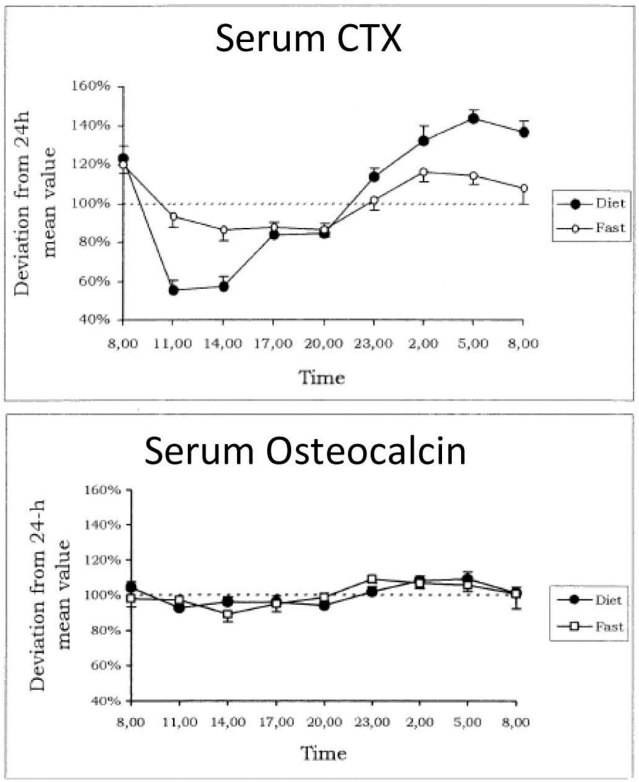

Figure adapted with permission from Qvist P, Christgau S, Pedersen BJ, Schlemmer A, Christiansen C. Circadian variation in the serum concentration of C-terminal telopeptide of type I collagen (serum CTx): effects of gender, age, menopausal status, posture, daylight, serum cortisol, and fasting. Bone. 2002 Jul;31(1):57-61. PubMed PMID: 12110413

Figure 3. Normal day/night rhythm of serum CTX and osteocalcin

The amplitude of the rhythm is blunted by fasting, compared to the fed state for serum CTX. Levels of serum CTX and osteocalcin increase overnight and decline with food intake. Adapted (with permission) from Qvist et al Bone 2002.

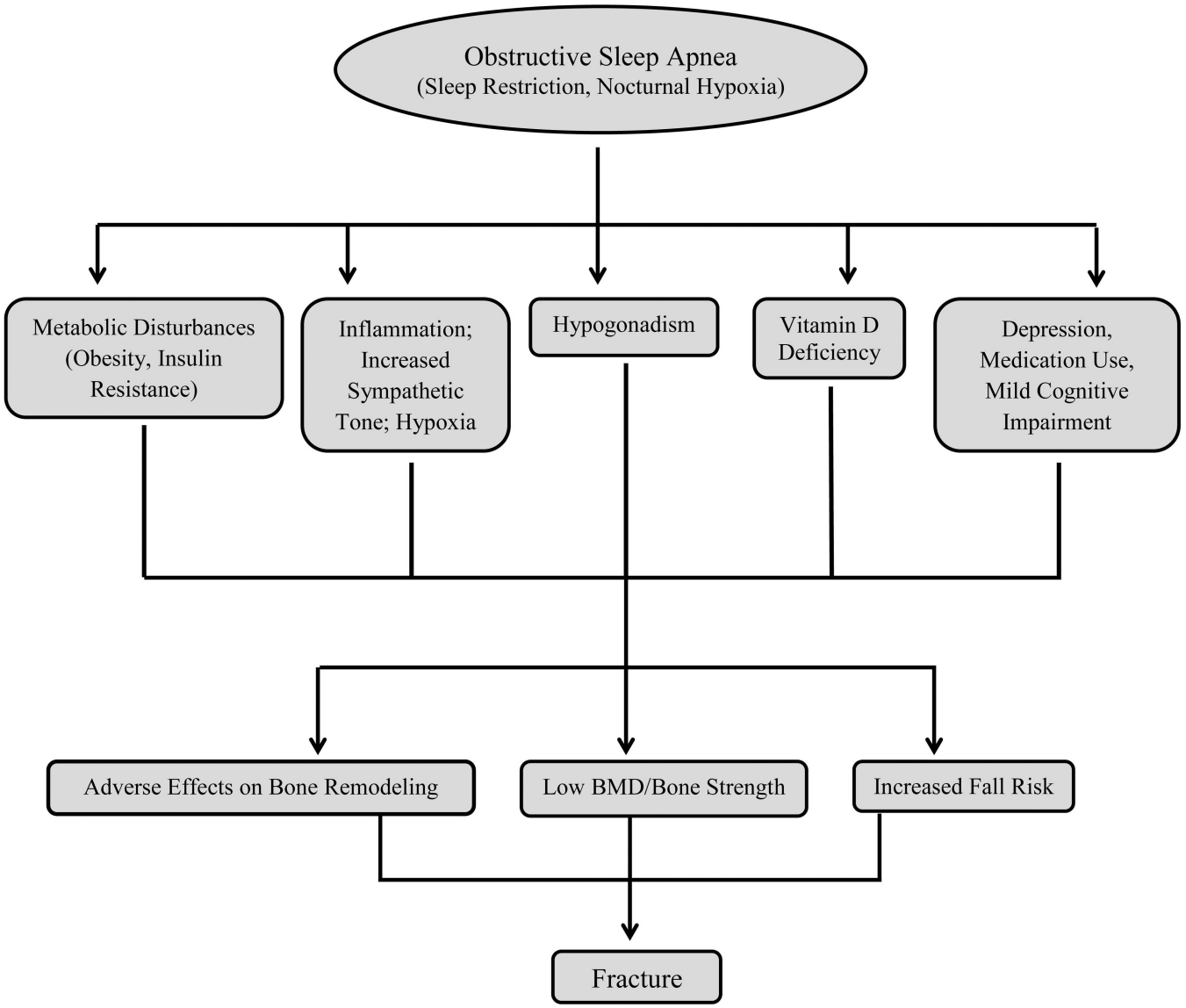

Figure 4. Schematic representation of major pathways by which obstructive sleep apnea can affect bone mass/strength and fracture risk