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# Sleep Disruptions and Bone Health: What Do We Know So Far?

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## Abstract

**Purpose of review:** This review briefly summarizes the growing body of literature addressing the skeletal consequences of sleep and circadian disruption.

**Recent findings:** The most recent data in the field suggest that 1) the diurnal variation in bone turnover markers are due to endogenous circadian rhythmicity linked to clock genes in all bone cells; 2) in a small human intervention study, cumulative sleep restriction with concurrent circadian disruption negatively alter bone turnover markers in a way that could explain the lower BMD and increased fracture risk identified in some prior night shift work studies; 3) abnormal sleep duration and obstructive sleep apnea are associated with low BMD and increased fracture risk in some, but not all studies.

**Summary:** Normal physiology and some animal and human intervention studies suggest that sleep and circadian disruptions such as night shift work, abnormal sleep durations and obstructive sleep apnea are detrimental to skeletal health. However, additional research in this area is needed to determine which sleep/circadian disturbances are most detrimental to skeletal health, the reversibility of such impairments, and underlying mechanisms.

### Keywords

sleep; bone metabolism; night shift work; sleep disruption; sleep restriction

## Introduction

Disruptions in sleep, including abnormal sleep duration, sleep-disordered breathing such as obstructive sleep apnea (OSA) and altered sleep timing as occurs in night shift work, are associated with an increased risk of obesity, diabetes mellitus, and cardiovascular disease (1–6). A growing body of literature suggest abnormal sleep duration and circadian disruption (e.g., night shift work) may impact bone health including the risk of osteoporosis and fracture (7). The effects of disrupted sleep on bone health may be particularly relevant for those with medical conditions that predispose individuals to both sleep disturbances and skeletal fragility (e.g., patients with diabetes mellitus). This review focuses on the most recent publications describing the biological basis for a connection between sleep/circadian

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systems and bone health and how sleep and circadian disruptions such as night shift work, abnormal sleep duration and OSA may negatively affect bone metabolism. Additional literature exists on how other aspects of sleep and circadian disruption (e.g., sleep quality, chronotherapy, melatonin, and medications used to treat sleep and circadian disorders) affect bone health. However, these topics are outside the scope of this review. Readers are referred to other more extensive reviews for a discussion of these topics (7–11).

## Methods

Relevant articles on sleep and bone health were obtained from the author's electronic reference database which is derived from ongoing literature searches on this topic and a targeted PubMed search performed on February 4, 2021. On February 4, 2021, PubMed was searched for pertinent articles based on the author's review of the title and, if seemingly relevant, the abstract, using the following search terms: "sleep bone", "sleep duration bone", "circadian bone", "shift work bone", "clock gene bone", "sleep apnea bone".

### Biological Link Between the Circadian System and Bone Metabolism

Bone turnover markers (BTMs) are components or products of the bone remodeling process that can be measured in blood and urine to assess the number or activity of bone cells and subsequent bone resorption and formation (12). BTMs should be checked in the morning after an overnight fast because they display diurnal variation, the amplitude of which is influenced by food intake (12, 13). The amplitude of this rhythm is greater for markers of bone resorption than formation, but levels of all BTMs peak overnight with a nadir in the afternoon (13–15). Prior work has demonstrated that the rhythmicity of bone resorption markers such as C-telopeptide of type I collagen (CTX) is independent of age, sex, menopausal status, cortisol, posture, light/dark cycles and parathyroid hormone (PTH) (13, 16). Rhythmicity observed in *ex vivo* murine bone culture suggest that BTM rhythmicity is due to endogenous circadian rhythmicity (17), which was confirmed in a recent human study (18). St. Hilaire et al used a "constant routine" protocol in which environmental and behavioral cues such as food intake and light exposure are distributed evenly throughout the day to separate endogenous rhythmicity from exogenous inputs (18). This study demonstrated a persistent 24-hour rhythm of the bone resorption marker, N-telopeptide of type I collagen (NTX), in healthy premenopausal women, thereby confirming that BTM rhythmicity is due to endogenous circadian control with amplitude modification due to environmental inputs (18). Clock genes, which are important for regulating endogenous circadian rhythms, have been identified in osteoclasts (19), osteoblasts (20) and osteocytes (21), which provides further evidence of endogenous circadian rhythms in bone turnover. Further strengthening the link between the circadian system and bone metabolism, skeletal phenotype is altered in clock gene knockout studies in animals (20–26). The endogenous circadian system in humans has a significant role in the ability to get an adequate amount of restful sleep during the biological night.

### Night Shift Work and Bone Health

Night shift work causes circadian misalignment, or a mismatch between an individual's internal biological clock and the external environment. As a result of this circadian

disruption, individuals who work the night shift report less sleep and sleepiness and are at increased risk for accidents and falls that may increase one's risk of fracture (27–31). In fact, postmenopausal women in the Nurses' Health Study with 20+ years of rotating night shift work had a 37% (95% confidence interval (CI) 4%-80%) increased risk of hip and wrist fractures compared to women who never worked the night shift (32). The risk was higher (RR = 2.36; 95% CI 1.33-4.20) in women with a normal BMI and in those without a history of using hormone replacement therapy (32). It is not clear what underlies this increased risk, however, this association persisted even after adjusting for differences in lifestyle factors such as smoking, diet, and physical activity (32).

It is possible that the increased risk of fracture identified in the night shift workers in the Nurses' Health Study could be due to unfavorable alterations in bone metabolism resulting in lower bone mineral density (BMD), thereby increasing fracture risk. A study of ten healthy men identified clinically and statistically significantly lower levels of the bone formation marker N-terminal propeptide of type I procollagen (P1NP) after 3 weeks of sleep restriction (~5.6h per 24h day) and concurrent circadian disruption (33). This acute decline in P1NP was greater in young men (−21.43 ± 1.05 mcg/L, $p < 0.001$) compared to older men (−9.80 ± 1.32 mcg/L, $p < 0.001$), occurred despite no change in a marker of bone resorption (CTX), and did not recover with ongoing exposure (33, 34). More recently, an analysis of BTM change in women from the same study revealed similar results (35). Women had significant declines in the bone formation markers P1NP (−9.5 ± 2.8 mcg/L, $p = 0.01$) and osteocalcin (−2.3 ± 0.9 ng/mL, $p = 0.04$) (35). Similar to previous findings in men, declines were greater in young women compared to older women (35). Importantly, young women also had an increase in CTX (0.182 ± 0.069 ng/mL, $p = 0.04$), indicating a particularly detrimental "double hit" with less bone formation but more bone resorption (35). Over time, the decline in bone formation with no change or an increase in bone resorption observed in this study in response to a protocol designed to simulate the stresses endured during rotating shift work, would be predicted to cause bone loss and potentially low BMD and osteoporosis. However, results from epidemiological human studies on the association between night shift work and BMD have been mixed. Two studies identified lower bone mineral density (BMD) in night shift workers (36, 37) while two others found no difference in BMD according to shift worked (38, 39). Although human studies on the association between night shift work and BMD are mixed and human intervention studies have not been long enough to evaluate changes in BMD or bone microarchitecture, insight was gained from a study by Lucassen et al in mice (40). Mice exposed to 24 weeks of constant light to induce circadian disruption, had significant deterioration in trabecular bone (40). Interestingly, these changes reversed over the subsequent 24 weeks when normal light dark cycles were restored (40).

## Bone Health is Associated with Abnormal Sleep Duration

The National Institutes of Health (NIH) recommends adults get 7-8 hours of sleep per night (41). However, over one-third of adults report getting less than this (42), which could negatively influence their bone health. Most studies have evaluated the association between sleep duration and BMD with the idea that abnormal sleep duration may negatively impact bone. However, the sleep-bone relationship may be bidirectional as osteoporosis and

osteoporotic fractures can also influence sleep duration and quality. The 2003 National Sleep Foundation Survey found that individuals with osteoporosis were 67% more likely to report short (<6 h/night) sleep duration (43). Pain after fracture negatively impacts sleep duration including ability to fall asleep and early awakenings (44). If altered sleep impacts bone health and bone healing, then this bidirectional relationship may set up a vicious cycle of fracture and sleep impairment.

The association between self-reported sleep duration and BMD in adults has been examined in 18 publications, including two meta-analyses (45–62). Results from these studies have been inconsistent, in part due to differences in population studied, method of BMD assessment, and definitions of “short”, “normal” and “long” sleep duration with or without naps. No association was found between self-reported nighttime sleep duration and areal BMD (aBMD) measured by dual energy x-ray absorptiometry (DXA) in women in two studies (60, 62) or between self-reported 24-hour sleep duration and volumetric BMD (vBMD) measured by computed tomography (CT) in men or women (59). However, in one of these studies, men with shorter sleep duration did have lower BMD at the lumbar spine (60). The most recent meta-analysis, published in 2018, identified a U-shaped relationship indicating that both short (defined as ≤7h/night) and long (defined as ≥9 h/night) sleep durations were associated with low BMD in middle-aged and elderly adults (49). The lowest risk of osteoporosis in that meta-analysis was with 8 hours of sleep per day (49).

More recently, data from the Women’s Health Initiative identified self-reported short sleep (defined as ≤5 hours/night) was associated with lower BMD, higher risk of osteoporosis, and higher risk of fracture (61, 63). The increased risk of fracture with short sleep duration identified in the WHI study is similar to results from two studies that used self-reported data from the China National Fracture Study (64, 65). In the most recent publication, Zhu et al identified an increased risk of fracture in Chinese men and women 50 years of age or older sleeping less than 7 h/day, but did not adjust for falls (65). Conversely, long sleep duration (≥10 h/day including naps) was associated with an increased risk of non-spine fractures compared to 8 to <9 h of sleep per day in older postmenopausal women in the SOF study in age adjusted but not multivariate analyses (66).

Recent publications on the relationship between sleep duration and BMD were the first to use wrist actigraphy instead of self-report on questionnaire to establish sleep duration. The association between BMD and objectively measured sleep duration was evaluated using the Osteoporotic Fractures in Men (MrOS) Study and the Study of Osteoporotic Fractures (SOF) cohorts (67, 68). Although no significant association was identified between objectively-determined nighttime sleep duration and BMD in either cohort, these papers did raise two potential considerations for future research (67, 68). In SOF, longer 24-hour sleep duration, including daytime naps, was associated with lower BMD at the total hip in older, postmenopausal women ($\beta = -0.005$, $p = 0.04$) (67). In older men with 25-hydroxyvitamin D levels less than 20 ng/mL, longer nighttime sleep duration was associated with higher BMD at the total hip ($\beta = 0.016$, $p = 0.04$) (68). These data indicate that vitamin D status may modify the relationship between sleep duration and BMD and that naps may be important to include in future analyses that examine the association between sleep duration and BMD in older women (67, 68). The latter point is potentially reinforced by Saetung et

al's recent paper in which higher frequency of self-reported napping and longer napping duration were associated with lower BMD at the total hip in elderly Thai women (62).

One recent intervention study examined the effect of significant sleep restriction (2 hours per night for three nights) on bone turnover markers in ten healthy male soldiers (69). Bone formation (as represented by bone specific alkaline phosphatase (BSAP)) declined after just one night whereas bone resorption (as represented by CTX and tartrate-resistant acid phosphatase (TRAP)) were increased after two nights (69). This uncoupling of bone turnover, where resorption exceeds formation, would be expected to decrease BMD if sustained over time. However, the ability to recover with ongoing exposure or recovery sleep is unknown.

The data above indicate that both short and long sleep durations are associated with low BMD and increased fracture risk in adults. The associations between sleep duration and bone health in children has only been explored in a few studies (70–74). Most recently, Dumuid et al evaluated several lifestyle factors, including physical activity and sleep duration, to determine the composition of a given day that was associated with the most optimal bone health parameters (termed a "Goldilocks Day") (74). Based on 8 days of accelerometry data, 10.9 (10.5-11.5) hours of sleep per day was associated with optimal bone structure and function in 11-12 year olds, as assessed by peripheral quantitative computed tomography (pQCT) at the tibia (74). The authors also identified that at that age, the optimal sleep duration associated with the best composition for overall bone health may be longer for boys than for girls (74). The impact of sleep disturbance and abnormal sleep duration in childhood and adolescence on attainment of optimal peak bone mass may be particularly important for determining fracture risk later in life (75).

## OSA and Bone Health

In 2008, Tomiyama et al demonstrated that urinary CTX was higher in men with severe OSA compared to those with no or only mild OSA, and that levels improved after 3 months of continuous positive airway pressure (CPAP) therapy (76). Data on the association between OSA and BMD in humans are mixed (77–84). Most of these studies, including two meta-analyses done on this topic (85, 86), found that sleep apnea was associated with lower BMD (77–81). Despite the somewhat mixed literature on the association with BMD, OSA and its associated nocturnal hypoxia and snoring have been associated with an increased risk of falls and fractures (87–90). This includes the most recent study by Huang et al that demonstrated an increased risk of clinical vertebral fracture, but not hip fracture, in women with OSA in the Nurses' Health Study (87). Notably, the association with vertebral fractures was strongest in those with associated daytime sleepiness, potentially suggesting that severity of OSA may contribute to the increased fracture risk (87). Although not statistically significant, the risk of vertebral fracture in women with OSA was increased in those without traditional risk factors for fracture including women with no history of osteoporosis and those with a BMI > 30 (87). Readers are referred to other papers for a more comprehensive review of the literature on the relationship between OSA and bone health (8, 9).

## Conclusion

Endogenous BTM rhythmicity, clock genes in bone cells, and altered skeletal phenotype in clock gene knockout animal models suggest that the circadian system is important for optimal skeletal health and that sleep or circadian disruptions may be detrimental to bone. An increased risk of fracture in nurses with 20+ years of night shift work reinforces this hypothesis. Although somewhat mixed, epidemiological studies suggest that other sleep disruptions such as abnormal sleep duration and OSA are associated with lower BMD and increased fracture risk. Additional research is needed to determine mechanisms by which sleep and circadian disturbance affect bone health.

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**Key Points:**

- The endogenous rhythm in BTMs, the presence of clock genes in bone cells, and altered skeletal phenotype in clock gene knockout animal models suggest that the circadian system is important for optimal skeletal health and that sleep or circadian disruptions may be detrimental to bone.
- Human intervention studies show adverse changes in bone turnover markers in response to cumulative sleep restriction and concurrent circadian disruption that may underlie the increased risk of fracture identified in the night shift workers in the Nurses' Health Study.
- Although somewhat mixed, epidemiological studies suggest that other sleep disruptions such as abnormal sleep duration and obstructive sleep apnea are associated with lower BMD and increased fracture risk.