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Review Paper
Sleep and Bone Health: Insights From a Mini-review

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ABSTRACT

Sleep disturbances, including irregular sleep duration, obstructive sleep apnea (OSA), and circadian misalignment in night-shift workers, have been linked to metabolic diseases and bone health issues. These disruptions affect bone metabolism, leading to reduced bone mineral density (BMD) and increased fracture risk. Bone turnover markers (BTMs) reveal the impact of circadian rhythms on bone resorption and formation, which sleep disturbances can alter. Abnormal sleep duration and circadian disruption increase fall risk by impairing balance and alertness. Additionally, caffeine's effect on calcium metabolism may be influenced by melatonin, a sleep regulator, which may have protective effects on bone health. This mini-review highlights the complex relationship between sleep, circadian rhythms, and bone health, suggesting the need for further research to explore potential interventions.

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Introduction

Sleep disruptions, including irregularities in sleep duration, conditions like obstructive sleep apnea (OSA), and misaligned sleep patterns such as those experienced by night shift workers, have been linked to a heightened risk of developing metabolic and cardiovascular complications. These disturbances can significantly impact physiological routes, leading to obesity, type 2 diabetes, and cardiovascular diseases. Such associations highlight the importance of maintaining healthy sleep habits to mitigate these health risks and promote overall well-being [1-6]. An increasing number of studies indicate that both abnormal sleep duration and circadian disruptions, such as those caused by night shift work, may have significant effects on bone health. These disruptions are linked to an elevated risk of conditions like osteoporosis and bone fractures, highlighting the critical role of sleep in maintaining skeletal integrity and overall bone strength [7]. The effects of disrupted sleep on bone health are particularly pronounced in individuals whose medical conditions heighten both sleep disturbances and bone fragility. For instance, people with diabetes mellitus commonly suffer from poor sleep quality alongside an increased risk of skeletal disorders, rendering them especially susceptible to the compounded impact of these factors on bone integrity [8].

On the other hand, sleep is a fundamental aspect of human life, essential for overall health and well-being. With the growing prevalence of sleep disorders worldwide, there has been a surge in interest in sleep epidemiology. Increasing evidence underscores the association between poor sleep quality and various adverse health outcomes, including heightened morbidity and mortality, emphasizing the critical role of sleep in maintaining optimal health [9-14]. Osteoporosis is a prevalent condition defined by reduced bone mineral density (BMD), which increases the likelihood of fragility fractures. The underlying pathophysiology of osteoporosis involves an imbalance between bone formation and resorption, leading to a net loss of bone mass. This condition is particularly common among postmenopausal women and older men, with associated fractures contributing to significant morbidity, increased healthcare costs, and elevated mortality rates [15-17]. Osteoporosis impacts an estimated 54 million older adults in the United States, underscoring the critical need to prioritize bone health in this population. Addressing osteoporosis is essential to reducing the prevalence of fragility fractures and mitigating their associated burden on morbidity, healthcare costs, and mortality rates [17, 18]. The link between poor sleep and disrupted endocrine function is well-established, with evidence highlighting the role of sleep in regulating hormonal balance and overall metabolic health [19-21]. Prolonged engagement in shift work, accompanied by circadian rhythm disruption, has been linked to a heightened risk of fractures. This association highlights the potential impact of altered sleep-wake cycles on skeletal health [22]. With growing recognition of the critical role sleep plays in maintaining bone health, there has been a surge in studies investigating the mechanisms underlying this connection. Numerous factors influence sleep, including lifestyle habits, environmental conditions, medical conditions, and disruptions to circadian rhythms, all of which may contribute to variations in bone health outcomes [7, 23]. The recommended sleep duration for adults is between 7 and 8 hours per day. Deviations from this optimal range, whether through excessive or insufficient sleep, have been associated with negative effects on bone health. Both short and long sleep durations may disrupt the body's ability to maintain bone integrity, potentially increasing the risk of skeletal fragility and fractures [24]. Particularly due to conditions like OSA, disordered sleep, and the use of medications that alter sleep patterns and circadian rhythms, may contribute to impaired bone health. As the prevalence of osteoporosis and sleep disorders rises with age, sleep emerges as a potentially modifiable risk factor for both osteoporosis and fractures. Addressing sleep disturbances could provide a valuable intervention to reduce the risk of bone fragility in aging populations [21, 24].

The biological connection between the circadian system and bone metabolism

Bone turnover markers (BTMs) are biochemical substances produced during bone remodeling and can be detected in blood and urine. These markers provide insights into the activity and number of bone cells, helping to assess the balance between bone resorption and formation. Monitoring BTMs is useful for evaluating bone health, detecting early changes in bone metabolism, and assessing the effectiveness of treatments for conditions such as osteoporosis [25]. BTMs should ideally be measured in the morning following an overnight fast, as they exhibit diurnal variation. This variation is influenced by factors such as food intake, which can alter the levels of these markers throughout the day. By measuring BTMs in a standardized fasting state, the results are more consistent and reflective of true bone turnover activity, minimizing potential confounding effects [25, 26]. The diurnal rhythm of BTMs shows a greater amplitude for markers of bone resorption compared to those of bone

formation. Throughout the day, levels of all BTMs peak during the overnight period, with a subsequent decline, reaching their lowest point in the afternoon. This pattern underscores the importance of timing when measuring BTMs to ensure accurate assessment of bone metabolism [26-28]. Research has shown that bone resorption markers like C-telopeptide of type I collagen (CTX) exhibit a consistent rhythmic pattern that is unaffected by physiological and environmental factors, including age, sex, menopausal status, cortisol and PTH levels, posture, or light–dark cycles. This notion suggests that the circadian variation in bone resorption is robust and not significantly influenced by these physiological or environmental factors [26, 29]. Rhythmicity observed in ex vivo murine bone cultures suggests that endogenous circadian rhythms drive the diurnal variation in BTMs. This finding was further confirmed in a recent human study, reinforcing the idea that bone resorption and formation follow an inherent biological clock, independent of external influences. These studies highlight the importance of the circadian system in regulating bone metabolism [30, 31]. St Hilaire et al. employed a "constant routine" protocol in their study, where environmental and behavioral cues, including food intake and light exposure, were evenly distributed throughout the day. This approach effectively isolated endogenous circadian rhythmicity from external influences, allowing for a clearer understanding of the body's inherent biological clock and its impact on BTMs. By controlling these variables, the study provided strong evidence that the observed rhythmicity in BTMs is primarily driven by internal circadian mechanisms [31]. This study identified a stable 24-hour rhythmic pattern of the bone resorption marker N-telopeptide of type I collagen (NTX) in healthy premenopausal women. The results support the notion that BTMs are governed by endogenous circadian mechanisms. Nevertheless, the amplitude of this rhythm appears to be influenced by environmental cues, underscoring the intricate interplay between internal biological clocks and external factors such as light exposure, meal timing, and daily behavioral patterns [31]. Clock genes, which play a critical role in regulating endogenous circadian rhythms, have been identified in osteoclasts, osteoblasts, and osteocytes. This discovery provides further evidence that internal circadian rhythms influence bone turnover.

Additionally, studies involving clock gene knockout animals have shown altered skeletal phenotypes, further strengthening the connection between the circadian system and bone metabolism. These findings suggest that disruptions in circadian regulation may impact bone health and skeletal structure, highlighting the importance of maintaining circadian harmony for optimal bone function [32-39]. The endogenous circadian system in humans plays a crucial role in facilitating the ability to obtain an adequate amount of restful sleep during the biological night. This internal clock helps synchronize sleep-wake patterns with the natural light-dark cycle, optimizing the quality and timing of sleep. Disruptions to this system, such as those caused by shift work or jet lag, can negatively impact sleep quality and overall health, emphasizing the importance of maintaining circadian alignment for restorative rest [8].

The impact of night shift work on bone health

Night shift work causes circadian misalignment, characterized by a mismatch between the body's internal biological clock and external environmental cues. This disturbance in circadian rhythms commonly leads to shorter and poorer-quality sleep, accompanied by heightened daytime sleepiness. Moreover, night shift workers are at a higher risk of accidents and falls due to fatigue, which may, in turn, elevate their risk of fractures. The compounded effects of poor sleep and heightened accident risk underscore the importance of addressing circadian disruption in those working irregular hours [40-44]. Indeed, a study from the nurses' health study revealed that postmenopausal women who had worked rotating night shifts for over 20 years had a 37% increased risk of hip and wrist fractures compared to women who had never worked the night shift. This finding underscores the long-term impact of circadian disruption on bone health, highlighting the need for strategies to mitigate the risks associated with night shift work, particularly for vulnerable populations like postmenopausal women [22]. The risk of hip and wrist fractures was found to be even higher in postmenopausal women with a normal body mass index (BMI) and in those without a history of using hormone replacement therapy (HRT). These findings suggest that factors such as body composition and HRT use may influence the extent to which night shift work impacts bone health, with women who are not using HRT or who have a normal BMI potentially being more vulnerable to the bone-depleting effects of circadian disruption [22]. The underlying mechanisms behind this increased risk remain unclear. However, the association between rotating night shift work and higher fracture risk persisted even after adjusting for differences in lifestyle factors such as smoking, diet, and physical activity. This finding suggests that circadian disruption itself may play a significant role in altering bone health, independent of other known risk factors, emphasizing the need for further research to explore the specific biological pathways involved [8, 22].

The higher fracture risk seen in night shift workers, as reported in the nurses' health study, may result from negative changes in bone metabolism that reduce BMD and increase fracture susceptibility. Supporting this, research involving ten healthy men showed significant declines in the bone formation marker, procollagen 1 N-terminal propeptide (P1NP) after just three weeks of sleep restriction and circadian disruption, suggesting that inadequate sleep and circadian misalignment may directly hinder bone formation and lower BMD [45]. This acute decline in P1NP was more pronounced in younger men compared to older men, highlighting that age may influence the extent of bone metabolic disruption caused by sleep restriction and circadian misalignment. Interestingly, this decrease in P1NP occurred despite no corresponding change in the marker of bone resorption, CTX, indicating that the impairment was specifically in bone formation rather than resorption.

Additionally, the decline in P1NP did not recover with continued exposure, suggesting that prolonged sleep disruption and circadian misalignment may have long-lasting effects on bone metabolism, particularly on the formation process [45]. In women, significant declines are observed in the bone formation markers P1NP and osteocalcin, further supporting the notion that circadian disruption and sleep restriction can negatively impact bone metabolism. These declines suggest that the ability to form new bone may be impaired under conditions of sleep deprivation or circadian misalignment, potentially leading to reduced BMD and an increased risk of fractures, particularly in populations vulnerable to osteoporosis [46]. Similar to previous findings in men, the declines in bone formation markers P1NP and osteocalcin are more pronounced in young women compared to older women. This finding suggests that younger individuals may be more susceptible to the negative effects of sleep disruption and circadian misalignment on bone metabolism. The greater sensitivity in younger women could be linked to their higher bone turnover rates, making them more vulnerable to changes in bone formation under conditions of disturbed sleep and circadian rhythms [46]. Importantly, young women also experience an increase in CTX, a marker of bone resorption, alongside the decline in bone formation markers like P1NP and osteocalcin. This condition creates a particularly detrimental "double hit," where there is both reduced bone formation and increased bone resorption. This imbalance in bone metabolism may exacerbate the negative effects on bone health, potentially accelerating bone loss and increasing the risk of fractures, especially in younger women who are already at a higher baseline of bone turnover [46]. Over time, the observed decline in bone formation coupled with no change or an increase in bone resorption, as seen in this study simulating the stresses of rotating shift work, would likely result in bone loss and potentially lead to low BMD and osteoporosis. Nevertheless, epidemiological evidence regarding the relationship between night shift work and BMD remains inconsistent. While two studies have reported reduced BMD among night shift workers, other investigations have found no significant differences in BMD across different work schedules. These discrepancies could be attributed to variations in study design, sample populations, and other confounding factors, highlighting the need for further research to understand better the long-term impacts of circadian disruption on bone health [47-50]. Mice exposed to 24 weeks of constant light to induce circadian disruption exhibit significant deterioration in trabecular bone. This finding underscores the potential impact of circadian misalignment on bone health, as prolonged exposure to altered light conditions leads to observable changes in bone structure. The deterioration in trabecular bone in these mice suggests that disruption of the natural circadian rhythm can negatively affect bone metabolism, potentially leading to bone loss similar to what might occur in humans experiencing long-term circadian disruption, such as night shift workers [51]. Interestingly, the changes in trabecular bone deterioration observed in the mice were reversed over the subsequent 24 weeks when normal light-dark cycles were restored. This recovery highlights the potential for the circadian system to play a critical role in maintaining bone health, suggesting that re-establishing regular sleep-wake patterns and light exposure could help mitigate the negative effects of circadian disruption on bone metabolism. These findings offer hope that, with appropriate interventions, the adverse impacts of circadian misalignment on bone health may be reversible, even after prolonged exposure to disrupted cycles [8, 51].

The relationship between abnormal sleep duration and bone health

The National Institutes of Health (NIH) recommends that adults get 7-8 hours of sleep per night to support overall health and well-being [52]. However, over one-third of adults report getting less than the recommended 7-8 hours of sleep per night, which could negatively influence their bone health. Chronic sleep deprivation has been linked to impaired bone metabolism, including decreased bone formation and increased bone resorption. This imbalance could contribute to lower BMD over time, raising the risk for osteoporosis and fractures. Given the importance of sleep in maintaining bone health, addressing sleep deficits in the general population may

be crucial for reducing the burden of bone-related conditions [8, 53, 54]. Pain after a fracture negatively impacts sleep duration, affecting both the ability to fall asleep and the experience of early awakenings. The discomfort associated with fractures, especially those related to osteoporosis, can disrupt sleep patterns, exacerbating the problem of insufficient sleep. Chronic pain often leads to difficulty in maintaining restful sleep, contributing to further fatigue and increasing the risk of additional health complications, including delayed bone healing. This cycle of pain and poor sleep quality can hinder recovery and worsen bone health, highlighting the importance of addressing both pain management and sleep disturbances in individuals with fractures [55]. If altered sleep impacts bone health and bone healing, this bidirectional relationship may indeed set up a vicious cycle of fracture and sleep impairment. Poor sleep can hinder the body's ability to repair and regenerate bone tissue, which could prolong recovery from fractures and increase the likelihood of subsequent fractures. In turn, the pain and discomfort associated with fractures can disrupt sleep, creating further challenges in bone healing and overall well-being. This cycle of inadequate sleep and compromised bone health could contribute to a greater burden on individuals, especially those with conditions like osteoporosis. Addressing both factors simultaneously—improving sleep quality and promoting bone health—could help break this cycle and support better outcomes for those at risk [8].

The association between self-reported sleep duration and BMD in adults has been examined in 18 publications, including two meta-analyses. These studies have sought to determine whether sleep duration, particularly when it deviates from the recommended 7-8 hours per night, is linked to lower BMD and an increased risk of osteoporosis. While some studies found a negative relationship between short sleep duration and BMD, others suggested that longer sleep durations could also be associated with bone health issues, indicating that both extremes of sleep duration may be detrimental. The results from these studies underscore the complexity of the sleep-bone relationship and highlight the importance of maintaining an optimal sleep duration for bone health [56-70]. These study results are incompatible, partly because of different populations studied, BMD assessment methods, as well as definitions of "short," "normal," and "long" sleep duration, with or without dozes. Factors such as measurement techniques, study design, and variations in how sleep duration is defined and reported may influence the observed results, making it challenging to draw clear conclusions about the sleep-BMD relationship. Further research using standardized methodologies may help clarify the potential impact of sleep duration on bone health [69-72]. Research findings suggest that, at least for certain populations, reduced sleep duration may negatively impact bone health, particularly in specific skeletal regions like the lumbar spine. While the overall evidence remains mixed, this result highlights the potential importance of sleep duration as a factor influencing BMD, especially in men. It also underscores the need for further research to understand better how sleep duration may specifically affect bone density in different populations and anatomical sites [70].

More recently, data from the women's health initiative identified that self-reported short sleep (defined as ≤5 hours per night) was associated with lower BMD, a higher risk of osteoporosis, and an increased risk of fractures. This finding further supports the idea that insufficient sleep can have detrimental effects on bone health, particularly in women. The association between very short sleep duration and compromised bone health highlights the importance of adequate sleep as a modifiable risk factor for osteoporosis and fractures, suggesting that prioritizing sleep could be a key strategy in preventing bone-related issues in this population [71, 73]. The increased risk of fracture associated with short sleep duration, as identified in the women's health initiative study, is comparable to findings from two studies utilizing self-reported data from the China national fracture study. Both studies found that individuals with shorter sleep durations had a higher risk of fractures, further reinforcing the link between insufficient sleep and compromised bone health. These findings suggest that short sleep duration could be a significant risk factor for fractures, regardless of geographical location or population, emphasizing the need for sleep management as part of fracture prevention strategies [74, 75]. In the most recent publication, Zhu et al. identified an increased risk of fracture in Chinese men and women aged 50 years or older who slept less than 7 hours per day. However, it is important to note that this study did not adjust for falls, which are a significant factor in fracture risk. The lack of adjustment for falls is a limitation, as individuals with shorter sleep durations may be more prone to falls due to factors such as fatigue, decreased alertness, or impaired motor function. Therefore, while the study highlights the potential link between short sleep duration and fractures, further research that accounts for fall risk is needed to understand better the full impact of sleep on fracture outcomes [75]. Conversely, long sleep duration (≥10 hours per day, including naps) was associated with an increased risk of non-spine fractures compared to 8 to <9 hours of sleep per day in older postmenopausal women in the study of osteoporotic fractures (SOF) study. This association was

observed in age-adjusted analyses but not in multivariate analyses, suggesting that other factors may confound the relationship between long sleep duration and fracture risk. The absence of a significant finding in multivariate analyses highlights the complexity of this relationship. This finding suggests that while long sleep duration may contribute to fracture risk, it is likely influenced by additional variables such as comorbidities, physical activity, and lifestyle factors. Further research that adjusts for these variables is needed to fully understand the impact of long sleep duration on bone health [8, 76].

Recent studies have taken a significant step forward in examining the relationship between sleep duration and BMD by utilizing wrist actigraphy. This method objectively measures sleep, rather than relying on self-reported data from questionnaires. This approach provides a more accurate assessment of sleep duration, reducing potential biases or inaccuracies associated with subjective reporting. The association between BMD and objectively measured sleep duration was explored in two major cohort studies: The osteoporotic fractures in men (MrOS) study and SOF. These studies used wrist actigraphy to track sleep patterns and then evaluated its impact on BMD, providing more reliable insights into how sleep influences bone health across different populations. By using objective measures, these studies aim to improve the precision of findings and deepen our understanding of how sleep duration may affect bone health, particularly in aging populations at higher risk for osteoporosis and fractures [77, 78]. Although no significant association was found between objectively measured nighttime sleep duration and BMD in either the MrOS or SOF cohorts, these studies highlighted two important considerations that could shape future research.

First, the complexity of the sleep-bone relationship might involve additional factors, such as sleep quality or the timing of sleep, which were not fully explored in these studies. It is possible that other aspects of sleep, such as its consistency, deep sleep phases, or disruptions, could have a more direct impact on bone health than sleep duration alone. Second, these studies suggest that bone metabolism may be influenced by long-term patterns of sleep disturbances rather than short-term sleep changes. Therefore, future research should consider investigating the cumulative effect of chronic sleep disturbances or altered circadian rhythms over extended periods, particularly in populations at greater risk for osteoporosis, to gain a more comprehensive understanding of the link between sleep and bone health [77, 78]. In the Study of SOF, a longer 24-hour sleep duration, including daytime naps, was associated with lower BMD at the total hip in older, postmenopausal women. This finding suggests that extended sleep, particularly when it includes naps, may negatively impact bone health in this demographic. The association could reflect a disruption in the normal circadian rhythm or an indication of underlying health issues that both affect sleep duration and bone metabolism. Further investigation is necessary to clarify whether this relationship is causal and whether interventions aimed at optimizing sleep duration might help improve BMD and reduce the risk of fractures in postmenopausal women [77]. In older men with 25-hydroxyvitamin D levels less than 20 ng/mL, a longer nighttime sleep duration was associated with higher BMD at the total hip. This finding suggests that in men with low vitamin D levels, extended sleep may have a protective effect on bone health, possibly by influencing bone remodeling processes or improving the body's ability to metabolize vitamin D. It highlights the potential interaction between sleep duration and vitamin D status in bone health, suggesting that sleep may play a role in mitigating the negative effects of vitamin D deficiency on BMD. However, more research is needed to fully understand this relationship and its implications for osteoporotic fracture prevention [78]. These findings suggest that vitamin D status may significantly influence the relationship between sleep duration and BMD. Specifically, it implies that the effects of sleep duration on BMD could vary depending on an individual's vitamin D levels.

Furthermore, the role of daytime naps may be an important factor to consider in future studies examining the connection between sleep duration and BMD, especially in older women. Including naps in these analyses could provide a more comprehensive understanding of how total sleep duration, both nighttime and daytime, affects bone health. This finding also emphasizes the need to consider both sleep duration and nutritional factors like vitamin D when investigating their combined impact on bone health in aging populations [77, 78]. This point is further supported by Saetung et al.'s recent study, which found that a higher frequency of self-reported napping and longer nap durations are associated with lower BMD at the total hip in elderly Thai women [72]. These findings underscore the importance of considering nap frequency and duration in research on sleep and bone health. The association between longer naps and lower BMD highlights the potential negative impact of excessive daytime sleep on bone health, particularly in older populations. This result suggests that not only the total amount of nighttime sleep but also daytime sleep patterns, such as napping, may play a crucial role in influencing BMD and should be carefully examined in future studies [8].

Cranial sensory deprivation significantly impacts bone health by lowering BMD and 25-hydroxyvitamin D (25(OH)D) levels, impairing bone microarchitecture, and reducing markers of both bone formation and resorption [79].

A recent intervention study explored the effect of prominent sleep constraint (2 hours per night for 3 nights) on BTMs in 10 healthy male soldiers. The study reveals that bone formation, as indicated by a decrease in bone-specific alkaline phosphatase, declined after just one night of sleep restriction. In contrast, bone resorption markers, including CTX and tartrate-resistant acid phosphatase (TRAP), were elevated after two nights of sleep restriction. This imbalance, where bone resorption outpaces formation, could potentially lead to a decrease in BMD if the condition were sustained over time. However, the study did not explore whether ongoing exposure or recovery sleep could reverse or mitigate these effects. This gap highlights the need for further research to understand whether the uncoupling of bone turnover due to sleep disruption is reversible and what the long-term implications are for bone health [8, 80].

The data above indicate that both short and long sleep durations are linked to lower BMD and an increased risk of fractures in adults. However, the relationship between sleep duration and bone health in children has been explored in only a few studies. While much of the focus has been on adults, it is important to investigate how sleep duration may affect bone development and density during childhood, a critical period for skeletal growth. Given that adequate sleep is crucial for overall health, including bone health, understanding these associations in younger populations may help identify early interventions to promote optimal bone development and prevent future bone-related issues. Future research is needed to elucidate better how sleep duration influences bone health during childhood and adolescence [8, 81-85]. Most recently, Dumuid et al. conducted a study evaluating several lifestyle factors, including physical activity and sleep duration, to determine the optimal daily composition for bone health, which they referred to as a "goldilocks day." Using 8 days of accelerometry data, the study found that 10.9 hours of sleep per day was associated with optimal bone structure and function in 11-12-year-olds. Bone health was assessed using peripheral quantitative computed tomography at the tibia. This study suggests that adequate sleep, alongside other factors like physical activity, plays a significant role in maintaining healthy bone development during childhood and adolescence. These findings highlight the importance of striking a balance in sleep duration to support optimal bone health in growing children [85]. The authors also found that, at the age of 11-12 years, the optimal sleep duration associated with the best overall bone health composition may be longer for boys than for girls. This gender difference suggests that boys might require slightly more sleep to achieve the best bone health parameters compared to girls at this developmental stage. These findings highlight the need for further investigation into how sleep duration affects bone health differently across genders during key periods of growth and development [85]. The impact of sleep disturbance and abnormal sleep duration during childhood and adolescence on the attainment of optimal peak bone mass is crucial for determining fracture risk later in life. Since the late teens or early twenties typically reach peak bone mass, disruptions during these formative years may result in long-term consequences for bone health. Inadequate sleep during critical growth periods may hinder bone development, potentially leading to lower peak bone mass, which increases the likelihood of fractures as individuals age. Understanding this relationship is important for developing early interventions to promote better sleep habits and overall bone health during these vulnerable years [8, 86].

The impact of clock genes on bone health and skeletal phenotype

In vitro data strongly support the existence of endogenous circadian rhythmicity in BTMs. Studies using cultured bone cells, such as osteoblasts and osteoclasts, have demonstrated that these cells exhibit a natural, rhythmic pattern of activity that is influenced by internal circadian clocks, independent of external factors like light and food intake. These findings indicate that the circadian system plays a significant role in regulating bone metabolism, with peak levels of bone resorption and formation occurring at specific times of the day. Understanding this endogenous rhythm is critical for optimizing the timing of BTM measurements. It may also help in tailoring therapeutic interventions for bone-related conditions, such as osteoporosis, based on circadian principles [30, 87]. Clock gene knockout (KO) models provide valuable insights into how disruptions in circadian physiology can impact bone turnover and skeletal phenotype. These models, in which specific clock genes are deleted, demonstrate that the loss of normal circadian regulation leads to significant changes in bone metabolism. For example, KO models of core circadian genes like *Bmal1*, *Clock*, and *Per* have shown alterations in bone cell function, including decreased bone formation by osteoblasts and increased bone resorption by osteoclasts. These changes can result in a compromised skeletal structure, character-

ized by lower BMD and weakened bone strength. Such studies highlight the critical role of the circadian system in maintaining bone health and suggest that circadian disruption could contribute to bone-related disorders, such as osteoporosis. Understanding the relationship between clock genes and bone physiology could potentially open new avenues for therapeutic strategies targeting circadian rhythms to improve bone health and prevent fractures [32-36]. In both global and osteoblast-specific *Bmal1* KO mice, a low BMD phenotype has been observed, primarily due to increased bone resorption and decreased bone formation. The *Bmal1* gene is a core component of the circadian clock, and its disruption leads to significant alterations in bone turnover. In these KO mice, the increased bone resorption is driven by enhanced osteoclast activity, likely due to disrupted circadian regulation of osteoclastogenesis. Simultaneously, osteoblast differentiation is impaired, reducing the capacity for bone formation. This dual effect of increased resorption and reduced formation results in a net decrease in BMD over time. These findings underscore the crucial role of *Bmal1* in maintaining bone homeostasis and suggest that circadian disruption, particularly in osteoblasts, can lead to skeletal fragility and an increased risk of osteoporosis. Further investigations into the mechanisms underlying these changes, such as alterations in bone signaling pathways and the specific role of circadian rhythms in bone cell differentiation and activity, could provide valuable insights for potential therapeutic interventions targeting circadian pathways to prevent bone loss [34, 35].

In contrast to global or osteoblast-specific *Bmal1* KO mice, osteoclast-specific *Bmal1* KO mice exhibit a high BMD phenotype. This outcome is primarily due to decreased bone resorption, which results in a net increase in BMD. The disruption of *Bmal1* in osteoclasts reduces their activity, leading to a reduction in osteoclastogenesis and bone resorption. As a result, bone formation exceeds resorption, causing the accumulation of bone tissue and an increase in BMD. Interestingly, studies suggest that peripheral clock genes, particularly osteoblast-specific *Bmal1*, play a significant role in regulating bone resorption. Osteoblast-derived *Bmal1* appears to inhibit osteoclastogenesis through its circadian influence on osteoclast precursor cells. This inhibition likely occurs via the regulation of key signaling pathways, including those related to RANKL (receptor activator of nuclear factor kappa-B ligand) and osteoprotegerin (OPG), which are central to osteoclast differentiation and activation. By controlling osteoclastogenesis, Bmal1 in osteoblasts acts as a crucial regulator of the balance between bone resorption and formation. This finding highlights the complex interplay between circadian rhythms, osteoblast function, and osteoclast activity in maintaining bone homeostasis. Further research is needed to understand better how circadian disruption specifically influences these processes and to explore potential therapeutic strategies targeting peripheral clock genes for the treatment of bone-related disorders such as osteoporosis [32]. In the absence of *Bmal1*, either globally or specifically in osteoblasts, osteoclastogenesis is enhanced, partly due to increased expression of osteoblastic *RANKL* [34]. Similarly, female mice deficient in *Cry/Per* genes exhibit a high bone volume phenotype [33, 36].

The role of sleep and circadian disruptions in increasing fall risk

Sleep and circadian disruptions can lead to increased sleepiness and reduced attentiveness to environmental risks, potentially elevating the likelihood of falls and fractures. Moreover, the temporary decline in performance often observed upon waking, referred to as "sleep inertia," as well as prolonged periods of wakefulness, can further compromise postural stability and balance, thereby heightening the risk of falls [40, 89-93]. Additionally, insomnia has been linked to a higher risk of falls, with a greater severity of insomnia symptoms serving as a predictor for fall risk over two years in older adults [7, 93, 94]. The circadian regulation of the cardiovascular response to postural stress in humans heightens the risk of pre-syncope during the biological night, which may consequently elevate the likelihood of syncope and falls, particularly in night-shift workers [44].

The impact of caffeine on bone health

Several mechanisms may contribute to the potentially harmful effects of caffeine on bone health. Caffeine has been shown to disrupt calcium homeostasis, primarily through increasing urinary calcium excretion (hypercalciuria) and reducing calcium absorption in the gastrointestinal tract [7, 95]. Caffeine may contribute to bone loss by directly affecting bone cells, promoting osteoclast differentiation, and inducing osteoblast apoptosis, as demonstrated in rat models. This imbalance between bone resorption and formation could lead to decreased bone density over time [96, 97]. The consumption of caffeine-containing drinks may reduce the intake of other calcium-rich beverages, such as milk, or more bone-neutral options like water.

Additionally, caffeine drinks often contain other substances, such as phosphorus, polyphenols, acid, and sugar, which might also negatively impact bone health. These factors, combined with caffeine's direct effects on bone

cells, could further contribute to diminished bone health over time [98, 99]. Epidemiological studies investigating the role of caffeine in bone health have yielded mixed results. Some studies suggest that caffeine consumption may negatively affect BMD and increase the risk of fractures, while others have found no significant association. Variations in study design, population demographics, and other confounding factors could account for these inconsistent findings. These mixed results underscore the complexity of understanding how caffeine influences bone health and highlight the need for further research to clarify its potential effects [99-102]. The conflicting findings regarding caffeine's impact on bone health may stem from several factors, including variations in study populations (e.g. differences in age, sex, and menopausal status), the duration of follow-up, and inconsistencies in the definition and assessment of fractures. Additionally, the lack of accurate data on potential confounders, such as calcium intake, and the challenges associated with accurately capturing caffeine consumption patterns further complicate the interpretation of results. These factors underscore the need for more comprehensive and methodologically rigorous studies to understand better the relationship between caffeine and bone health [95, 99, 100, 103]. These challenges also include variations in the source of caffeine, such as whether it comes from coffee, soda, or tea, as well as geographic differences in coffee strength and preparation methods, which can significantly impact caffeine levels.

Furthermore, assumptions about the average serving size may not always be accurate, leading to inconsistencies in the estimation of caffeine intake. These factors can contribute to the mixed findings observed in epidemiological studies, highlighting the complexity of evaluating caffeine's role in bone health [95, 99]. For instance, varying results regarding caffeine-associated fracture risk are observed in the Swedish mammography cohort study between 2006 and 2013. These differences may be attributed to several factors, including the extended follow-up period in the latter research and refinements made to the questionnaires used to collect data. The improvements in data collection could have led to more accurate assessments, thereby influencing the observed relationship between caffeine intake and fracture risk [95, 103]. Moreover, two recent meta-analyses, which employed slightly varying inclusion and exclusion criteria, concluded that coffee intake was associated with an increased fracture risk in women but not in men. These findings highlight potential gender differences in how caffeine consumption may influence bone health, suggesting that the effects of coffee on fracture risk could vary based on factors such as sex and possibly underlying physiological differences [99, 100]. The increased fracture risk in women was observed with as little as two cups of coffee per day, with the risk rising further with higher caffeine intake. This finding suggests a dose-dependent relationship between coffee consumption and fracture risk in women, emphasizing the need to carefully consider the amount of caffeine consumed and its potential long-term effects on bone health [99]. Since the protective effect in men was of greater magnitude for all but the highest levels of female coffee consumption, the overall effect of caffeine on bone health remains unclear. This disparity highlights the complexity of caffeine's impact on bone density, with gender differences possibly influencing the outcomes. A long-term, prospective intervention trial is crucial to determine whether these associations lead to a clinically significant cause-and-effect relationship, particularly at typical levels of coffee and caffeine consumption, which are commonly seen in the general population [7].

The role of melatonin in bone health

Melatonin levels are typically low in night-shift workers, which can disrupt their circadian rhythms and sleep-wake cycles. Because of its ability to regulate sleep patterns, melatonin is commonly used as an over-the-counter supplement for managing jet lag and insomnia. Its role in regulating circadian rhythms and promoting sleep makes it particularly relevant in the context of shift work and sleep disturbances. Given its widespread use and potential impact on bone health through its circadian-modulating properties, melatonin deserves special mention when considering the broader effects of sleep disturbances and circadian disruptions on bone metabolism [104]. Melatonin is believed to have a positive impact on bone health by promoting osteoblast formation and reducing bone resorption. It is thought to achieve this effect by decreasing the synthesis of RANKL, a key molecule that stimulates osteoclast differentiation and activity. Simultaneously, melatonin is believed to increase the synthesis of OPG, a decoy receptor for RANKL that inhibits osteoclastogenesis. This balance between osteoblast activity and osteoclast inhibition contributes to improved bone density and potentially protects against bone loss [105, 106]. In addition, studies have shown that animals lacking melatonin exhibit lower BMD compared to control groups. This finding suggests that the absence of melatonin impairs the regulation of bone metabolism, possibly due to the disruption of osteoblast and osteoclast balance, which is typically modulated by melatonin's effects on RANKL and OPG. These findings further support the role of melatonin in maintaining bone health and preventing bone density loss [105, 107, 108]. A small, randomized

controlled trial in humans demonstrated that daily melatonin supplementation (1 mg/d or 3 mg/d) for one year increased in femoral neck BMD, although femoral neck BMD is known to have a larger precision error compared to other anatomical sites. Additionally, the study found that a higher dose of melatonin (3 mg/d) led to an increase in lumbar spine volumetric BMD as assessed by quantitative computed tomography. These findings suggest a potential benefit of melatonin supplementation for improving bone density, particularly at specific sites such as the lumbar spine, where the effects may be more pronounced with higher doses [109]. However, no significant changes are observed in BTMs or in areal BMD at other skeletal sites in this trial, nor were similar effects found in different studies. This result suggests that while melatonin may have a localized impact on certain bone regions, such as the femoral neck and lumbar spine, its overall effects on broader skeletal health, as measured by BTMs or BMD at other sites, may be limited or not significant. Further research is needed to understand better the full scope of melatonin's impact on bone health across various skeletal regions and its potential as a therapeutic intervention [7, 109, 110]. Larger are longer-duration human studies are essential to determine the precise pharmacological role and optimal dosage of melatonin in the treatment of postmenopausal osteoporosis. These studies should aim to establish whether melatonin supplementation can provide consistent benefits in terms of BMD and BTMs, while also evaluating potential side effects or contraindications. Additionally, understanding how melatonin interacts with other treatments for osteoporosis, as well as its long-term efficacy, will be crucial for assessing its viability as a therapeutic option for bone health in postmenopausal women.

Conclusion

Disrupted sleep and circadian rhythms are linked to a variety of bone health issues, including impaired bone metabolism, reduced BMD, and an increased risk of fractures. The role of circadian regulation in bone health is supported by both experimental and clinical evidence, particularly the influence of clock genes in osteoblast and osteoclast function. Night shift work, abnormal sleep duration, and sleep disorders such as insomnia and OSA contribute significantly to bone health decline and increase fall risk. Moreover, factors such as caffeine consumption and the use of melatonin supplements may further influence bone metabolism. Future long-term, prospective studies are necessary to understand better the biological mechanisms connecting sleep and circadian rhythms to bone health and to explore potential interventions for those at risk of osteoporosis and fractures.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Conceptualization: Abolfazl Bagherifard and Reza Sahrai; Writing the original draft: Khatere Mokhtari; Review & editing: Abolfazl Bagherifard and Reza Sahrai; Supervision and Project administration: Reza Sahrai, Investigation: All authors.

Conflict of interest

The authors declared no conflict of interest.

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