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MOLECULAR AND METABOLIC INTERPLAY BETWEEN CIRCADIAN RHYTHMS AND BONE REMODELING IN MENOPAUSE

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ABSTRACT

Postmenopausal osteoporosis arises from estrogen deficiency – driven imbalance between bone resorption and formation, but an underappreciated second layer of pathology involves disruption of the circadian clock. This review examines the bidirectional relationship between circadian biology and bone remodelling in the postmenopausal context, with a focus on the molecular mechanisms linking clock gene function to skeletal homeostasis. Bone turnover markers – including serum CTX and osteocalcin – exihibit reliable diurrinal rhythmicity governed by the endogenous circadian system. The clock gene *BMAL1* plays a pivotal role, regulating antioxidant capacity via *CLOCK/BMAL1* transcriptional complexes and suppressing the *ROS/MAPK-p38* pro – survival pathway in osteoclast precursors. Melatonin, the primary hormonal output of the circadian system, activates this BMAL1 – mediated pathway, thereby promoting osteoclast precursor apoptosis and reducing bone resorption. Evidence from ovariec tomized mouse models and early randomized clinical trials supports melatonin supplementation as a potential skeletal – protective strategy. Furthermore, sleep disruption and circadian misalignment – both prevalent during the menopausal transition – compound estrogen deficiency through elevated sympathetic tone, pro – inflammatory cytokines, and diminished antioxidant buffering. Chronotherapy strategies , including timed administration of existing anti resorptive agents and melatonin supplementation, represent emerging clinical opportunities. This review synthesizes current molecular, preclinical, and clinical evidence and identifies key research gaps that must be addressed to fully integrate circadian medicine into the management of postmenopausal osteoporosis.

RESULT

- **Diurnal Rhythmicity of Bone Turnover Markers**

Serum CTX, the most sensitive marker of bone resorption, follows a sinusoidal 24-hour rhythm, peaking between 04:00-08:00h and reaching its nadir in the late afternoon. This rhythm is preserved in blind individuals, confirming endogenous circadian rather than light-dependent regulation. Urinary NTX and pyridinium crosslinks displays the same temporal pattern. Bone formation markers (osteocalcin, PINP) show circadian rhythms that mirror resorption markers but with considerably smaller amplitudes. Osteocyte- derived FGF- 23 peaks in the morning, regulated pertly through *BMAL1* via beta – adrenergic signalling.

- The BMAL1/ROS/MAPK-p38 Pathway demonstrated that melatonin at 0.3mM induces apoptosis in osteoclast precursor RAW264.7 cells through the mitochondria- dependent intrinsic pathway, characterized by reduced mitochondrial membrane potential, increased Bax and cleaved caspase-3, decreased Bcl-2, and cytochrome c release. Melatonin upregulated BMAL1 at the both mRNA and protein levels: BMAL1 siRNA knockdown abolished these pro-apoptotic effects, establishing BMAL1 upregulation as causally necessary.

The mechanistic chain is: **melatonin → BMAL1 upregulation → ROS suppression→MAPK-p38 dephosphorylation →osteoclast precursor apoptosis → reduced bone resorption.** pharmacological activation of MAPK-p38 using dehyrocorydaline (DHC) blocked melatonin-induced apoptosis, confirming p38 as the downstream effector.

- In Vivo Validation In a bilateral ovariectomy (OVX) mouse model, melatonin administered at 30mg/kg/day for eight weeks post- ovariectomy partially reversed estrogen – deficiency -induced bone loss- improving

microarchitectural parameters (BMD, Tb.N, Tb.Th, BV/TV), restoring *BMAL1* expression, and reducing osteoclast markers (NFATc1, TRAP, Cathepsin K). Clinical support was provided by a randomized control trial (Amstrup et.al) showing that 12 months of melatonin supplementation (1-3 mg/day) significantly increased femoral neck BMD in post menopausal women with osteopenia.

- Chronotherapy Morning injection of teriparatide (PTH 1-34) produced greater lumbar spine BMD gains (9.1%) compared to evening dosing (4.8%), consistent with circadian alignment of PTH action. Conversely, benzodiazepines and Z- drugs prescribed for menopausal insomnia are associated with a 52-92% increased relative risk of hip fracture, highlighting the skeletal hazard of circadian – disruptive pharmacological strategies.

CONCLUSION

The circadian clock and bone remodelling are deeply and bidirectionally interconnected systems, and the menopausal transition represents a critical convergence point at which disruption to both amplify one another. At the molecular core of this interaction, BMAL1 emerges as a pivotal regulator of antioxidant capacity and the osteoclastogenesis via the ROS/MAPK-p38 pathway. Melatonin, the principal hormonal output of the circadian system, activates this pathway and has demonstrated efficacy in reducing bone loss in preclinical models, with early clinical corroboration. Clinically, the reliable nocturnal rhythm of bone markers underscores that the skeleton is a time – sensitive organ : circadian disruption through inadequate sleep, shift work, or attenuated circadian amplitude accelerates bone loss through mechanisms that compound estrogen and antioxidant deficits. Therapeutic implications include chronotherapy for established anti-resorptive medications, melatonin supplementations as well as dual circadian – restorative and osteoclast-suppressive strategy, and cautious management of menopausal sleep disturbance to avoid fracture- risk -elevating sedative – hypnotics. Key research priorities include elucidating hoe estrogen regulates BMAL1 in bone cells, defining optimal melatonin dosing and timing for osteoporosis, characterizing the distinct contributions of the sleep – stage disruption versus circadian misalignment, and assessing whether circadian- targeted interventions can enhance existing anti-resorptive therapies to reduce fracture incidence.

KEYWORDS

- Postmenopausal osteoporosis
- Circadian clock
- BMAL1
- MAPK-p38
- Reactive oxygen species (ROS)
- Bome turn over markers
- Chronotherapy
- Estrogen deficiency
- CTX
- Ovariectomy
- Sleep disruption
- Teriparatide

1. INTRODUCTION

Menopause – defined as the permanent cessation of menstrual cycle – occurs most commonly between the ages of 45 and 55 and marks the biological end of reproductive capacity as the ovarian follicular reserve becomes exhausted. The hormonal consequences are weeping : the decline in estrogen and progesterone sets off metabolic changes across virtually every organ system, but the skeletal effects are among the most immediate and clinically consequential. Postmenopausal osteoporosis, characterized by declining bone mineral density (BMD) and progressive deterioration of name microarchitecture, leaves women vulnerable to fragility fracture fractures of the hip, vertebrae, and wrist - fractures that carry significant morbidity, increased mortality, and a considerable economic burden on healthcare systems.[1,2]

The underlying pathophysiology of postmenopausal bone loss reflects fundamental imbalance between two opposing processes: bone resorption, driven by osteoclasts, and bone formation, orchestrated by osteoblasts. Under normal hormonal conditions, estrogen keeps osteoclast activity in check while supporting osteoblast survival. When estrogen disappears, the restraining influence is lost, and net bone resorption takes hold. The signalling pathways governing this balance are highly complex – the RANK/RANKL/OPG axis, the Wnt/beta-catenin pathway, and various endocrine inputs all play roles. Compounding matters, estrogen deficiency elevates oxidative stress, which independently promotes osteoclast activation and accelerates osteoblast death.[3]

Meanwhile, a separate but equally important regulatory system governs much of human physiology, the circadian clock. This endogenous timekeeping mechanism, anchored in the suprachiasmatic nucleus (SCN) of the hypothalamus, coordinates the timing of physiological processes across the 24-hour day through a network of central and peripheral molecular oscillators. Clock genes – including CLOCK, BMAL1, Period (PER1-3), and Cryptochrome (CRY1-2) - are expressed not only in the brain but in bone-forming and bone-resorbing cells themselves. Implying that the skeleton operates according to its own intrinsic daily schedule.[4,5] Biochemical markers of bone turnover reflect this timing, displaying reliable diurnal rhythmicity, and disruption of clock gene formation in animal models produces striking skeletal changes. Despite the well-established importance of both estrogen deficiency and circadian clock function in bone biology, relatively little attention has been paid to how these systems interact – especially during menopause. The menopausal transition is associated not only with hormonal changes but also with sleep disruption, diminished nocturnal melatonin

secretion, and reduced circadian amplitude. These changes may compound the skeletal effects of estrogen deficiency through mechanisms that remain incompletely understood. Melatonin, the primary hormonal output of the circadian system, has recently been shown to directly suppress osteclastogenesis via the BMAL1/ROS/MAPK-p38 pathway, providing a tangible mechanistic link between circadian disruption and the accelerated bone loss characteristic of postmenopause.[6]

This review aims to synthesize what is currently known about circadian clock gene expression in bone cells, the daily rhythms of bone metabolism, the impact of melatonin on osteoclast biology in the postmenopausal context, and what this all means for clinical management. We also consider the growing opportunities for chronotherapy and outline the research questions that remain open.

2. RESULTS AND DISCUSSION

2.1 .The molecular Circadian clock in Bone Cells

2.1.1 Molecular Architecture of the Core Clock

The mammalian circadian clock is built on a self-reinforcing cycle of transcription and translation. At its core, CLOCK and BMAL1 proteins heterodimerize and drive expression of Period (PER1, PER2, PER3) and Cryptochrome(CRY1, CRY2) genes. As PER and cry protein accumulate, they inhibit the very complex that produced them -the CLOCK-BMAL1 dimer-progressively dampening their own transcription. When PER and CRY are eventually degraded, the inhibition lifts and the cycle begins again, completing one full oscillation in roughly 24 hours.[5] This self-sustaining molecular clock, first characterized in the SCN, has since been identified in nearly every cell type investigated - including osteoclasts, osteoblast and osteocytes.[4]

The SCN communicates timing information to peripheral bone clocks via multiple routes. Glucocorticoids help synchronize osteoclast peripheral clocks; beta adrenergic signaling through the sympathetic nervous system(SNS) entrains osteoblast clock genes; and melatonin functions as a systemic darkness signal, recognized by MT1 and MT2 receptors expressed on bone cells.[7] When any of these synchronizing inputs is disrupted, as happens in menopause, shift work, or sustained sleep restriction, peripeheral bone clocks can drift out of alignment with the central SCN, with downstream consequences for the balance between bone formation and resorption.

2.1.2 BMALI as a Master Regulator of Bone metabolism

Of the circadian clock genes, BMALI stands out as a particularly important positive regulator of bone mass. Mice lacking BMALI globally or specifically in osteoblast develop reduced BMD, driven in large part by elevated RANKL expression from osteoblasts and increased osteoclast activity.[4] In an apparent mirror image, osteoclast -specific BMAL1 knockout mice accumulate more bone-pointing to an inhibitory role of osteoblastic BMAL1 on osteoclastogenesis.[8] These experiments position BMAL1 as a molecular interface between the circadian system and the RANK/RANKL/OPG axis that governs bone resorption.

A critical observation came from Wang et.al(2023), who found that BMAL1 protein levels are significantly lower in the bone tissue of overiectomized mice- a standard model of postmenopausal estrogen deficiency -compared with sham-operated controls.[6] This finding suggests that estrogen loss directly impairs bone clock gene expression, potentially loosening the molecular restraints on osteoclastogenesis. How exactly estrogen maintain BMAL1 in bone cells is not yet fully resolved, though estrogen receptors are known to interact with CLOCK-BMALI transcriptional machinery in other tissues, and the loss of this interaction in osteoclast precursors may be a key vulnerability.

In RAW264.7 cells – mouse macrophage precursors that serve as a well – established osteoclast model – siRNA – mediated knockdown of BMAL 1 reduced apoptosis and upregulated osteoclast differentiation markers including NFATc1, TRAP, and Cathepsin K.[6] Conversely, lentiviral overexpression of BMAL 1 supressed intracellular ROS and reduced phosphorylation of MAPK-p38, confirming that BMAL1 functions as an antioxidants checkpoint in these cells. Taken together, these findings suggest that postmenopausal BMAL1 downregulation in bone tissue may be an underappreciated driver of excessive osteoclast accumulation and the accelerated bone resorption that follows.

2.1.3 Other Clock Genes And Skeletal Phenotypes

BMAL1 is not the only clock gene with skeletal consequences. Female mice lacking both CRY1 and CRY2 show increased bone volume, partly through reduced osteoclast activity. PER2- deficient female mice also achieve high bone volume, but through increased bone formulation in a leptin- independent manner.[4] Collectively, these animal studies reveal that the relationship between clock genes and bone is multidirectional and cell-type-specific: which gene is disrupted, in which cell, and in which hormonal environment all shape the resulting skeletal phenotype. In the specific context of menopause, where the sex hormone environment is dramatically altered, the sex – specific effects of clock gene perturbations on bone demand closer investigation.

2.2 Diurnal Rhythmicity of Bone Turnover Markers

2.2.1 *24-Hour Profiles of Bone Resorption Markers*

Among the most compelling human evidence for circadian control of bone metabolism is the consistent diurnal rhythmicity of bone turnover markers(BTMs). Serum C-terminal cross-linked telopeptide of type I collagen(CTX)- one of the most sensitive markers of bone resorption-follows a clear sinusoidal curve across the 24-hour day, peaking in the early morning

hours(roughly 04:00-08:00 h) and reaching it's lowest point in the late afternoon.[5] Notably, this pattern is preserved in blind individuals, indicating that it is driven by the endogenous circadian clock rather than by light clues. Urinary N-terminal crosslinked telopeptide (NTX) and pyridinium crosslinks follow a similar temporal pattern.

The amplitude of CTX rhythmicity can be flattened by fasting and anti-resorptive therapy, yet the underlying sinusoidal shape persists. The rhythm appears largely independent of sex, age, and menopausal status as an isolated variable, though food intake -particularly dietary calcium-can modulate resorption marker levels via glucagon-like peptide-2(GLP-2).[5] Importantly, the overnight resorption peak coincides with normal sleep, raising the questions of whether the circadian architecture of bone turnover has evolved in coordination with sleep physiology-and what happens when that coordination breaks down.

2.2.2 Bone Formation Markers and Osteocyte-Derived Factors

Bone formation markers- including osteocalcin and N-terminal pro peptide of type I procollagen(PINP)-also follow circadian rhythms that roughly mirror those of resorption markers, though with considerably smaller amplitudes. Osteocalcin peaks overnights, while PINP's rhythm is subtle enough that it becomes statistically detectable only in large cohorts.[5] This disparity in amplitude carries an important implications: because resorption disproportionately exceeds formation during the overnight window, even under normal physiological conditions, the absence of estrogen's restraining influence on osteoclasts during menopause may amplify this nightly imbalance to clinically significant levels.

Fibroblast growth factor-23(FGF-23), a phosphate -regulating protein secreted by osteocytes, peaks in the morning and is regulated in part by beta-adrenergic tone acting through BMAL1 -creating a mechanistic link between the sympathetic nervous system, the circadian clock, and osteocyte function,[5] Sclerostin, another osteocyte-derived factor that inhibits bone formation, shows inconsistent diurnal variation in the literature, suggesting it may respond more to mechanical loading from postural changes than to intrinsic clock driven signals.

2.3 Melatonin, the BMAL1/ROS/MAPK-p38 Axis, and postmenopausal osteoporosis

2.3.1 Melatonin Biology in the Menopausal Context

Melatonin(N- acetyl -5-methoxytryptamine) is the primary hormonal output of the SCN's circadian program, secreted by the pineal gland during the biological night. It functions as a universal darkness signal, helping to synchronize peripheral tissue clocks – including those in bone cells – with the environmental light – dark cycle.[6] Beyond its timekeeping role, melatonin is also a potent endogenous antioxidant, capable of directly scavenging reactive oxygen species and upregulating antioxidant systems. Its secretion declines with the age and is further suppressed by nighttime light exposure; in postmenopausal women, reduced nocturnal melatonin amplitude compounds the antioxidant deficit that the estrogen deficiency has already imposed.

At the level of bone biology, the effects of melatonin are broadly protective. It supports osteoblast differentiation and survival, suppresses RANKL expression while boosting OPG, and attenuates the oxidative stress and inflammation that otherwise accelerate osteoblast death.[7] A randomized controlled trial found that 12 months of daily melatonin supplementation (1-3 mg/day) significantly increased femoral neck BMD in postmenopausal women with osteopenia.[9] Interestingly, melatonin is not produced solely by the pineal gland – bone marrow cells and the peripheral immune cells can synthesis it locally, pointing to a paracrine role within the skeletal microenvironment.

2.3.2 The BMAL1/ROS/MAPK p-38 Signaling Pathway

Wang et.al (2023) provided the first systematic mechanistic characterization of how melatonin directly promotes apoptosis of osteoclast precursors through the *BMAL1/ROS/MAPK-p38* pathway.[6] Working with RAW264.7 cells, the authors determined that the 0.3mM melatonin was the optimal apoptosis – inducing concentration that remained non- cytotoxic. At this dose, melatonin lowered mitochondrial membrane potential, increased expression of pro- apoptotic markers (Bax and cleaved caspase - 3), reduced the anti apoptotic protein Bcl-2, and triggered cytochrome c release – all hallmarks of the mitochondria- dependent – intrinsic apoptosis pathway.

Critically, the melatonin at this concentration upregulated BMAL1 at the both mRNA and the protein level in *RAW246,7* cells. When *BMAL1* was specifically knocked down by siRNA, the pro apoptotic effects of melatonin were significantly attenuated, establishing that *BMAL1* upregulation is causally necessary for melatonin's apoptosis- promoting activity – not merely a correlate. The link between *BMAL1* and apoptosis was mediated through redox regulation: melatonin reduced intracellular *ROS*, and this effect was abolished by *BMAL1* knockdown. This is mechanistically coherent, because *CLOCK/BMAL1* transcriptional complexes directly regulate genes encoding antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase) and their upregulation by melatonin would be expected to lower the ROS- driven survival signals that osteoclastogenesis.[6]

The downstream effectors in this pathway is MAPK-p38, a stress – activated kinase that promotes osteoclast precursor survival and proliferation. *ROS* normally activate p38 phosphorylation, sustaining the

osteoclastogenic program. Melatonin substaintially reduced p38 phosphorylation in RAW264.7 cells, and again, *BMAL1* knockdown reversed this effect. To further test p38 dependency, the authors applied dehydrocorydaline (DHC), a pharmacological activator of *MAPK-p38*, and found that it blocked melatonin-induced apoptosis even in the presence of melatonin. This resulting mechanistic model is a clear linear pathway: melatonin →*BMAL1* upregulation→ *ROS* suppression→ *MAPK – p38* dephosphorylation →increased osteoclast precursor apoptosis→ reduced multinucleated osteoclast generation→ decreased bone resorption.[6]

3.3.3 In Vivo Validation in Postmenopausal Mouse Models

Wang et al. (2023) went on to validate the cell living findings using a bilateral ovariectomy (OVX) mouse model of postmenopausal osteoporosis.[6] OVX mice showed the expected deficits – reduced BMD, trabecular number (Tb. N), Trabecular thickness(Tb. Th), and bone volume/total volume (BV/TV)- along with increased trabecular separation (Tb. SP) on micro CT imaging . Bone tissue from these mice also displayed decreased *BMAL1* protein expression and elevated osteoclast markers (NFACc1, TRAP, Cathepsin K). When melatonin was administered intragastrically.

At 30mg/kg/day for eight weeks post ovariectomy, it partially reversed all of these changes; microarchitectural parameters improved, *BMAL1* expression recovers, and osteoclast markers levels declined.

These in vivo results reinforce what has been observed clinically. Amstrup et.al. conducted a small randomized trial and found that melatonin supplementation raised femoral neck BMD in postmenopausal women with osteopenia, though changes in BTMs and areal BMD at other skeletal sites did not reach significance.[9] The mechanistic framework from Wang et al. provides a biologically coherent basic for these clinical effects and identifies *BMAL1* as a potentially targetable node in future pharmacological strategies for postmenopausal osteoporosis.

2.4 Sleep Disruption, Circadian Misalignment, and Bone Health in Menopause

2.4.1 Epidemiological Evidence Linking Sleep Distru bances and Bone Loss

Menopause is a powerful disruptor of sleep. Hot flashes fragment sleep architecture, and declining estrogen and progesterone alter sleep continuity and depth. Both ends of the sleep duration spectrum carry skeletal risk : both short (fewer than 6 hours/night) and long (8 hours or more per night) sleep duration have been associated with lower BMD and increased fracture risk in epidemiological studies, though the evidence is heterogenous. A systematic review and meta-analysis reported that sleeping 8 or more hours per day as associated with a 22% higher odds of osteoporosis in middle aged and elderly women.[10] Short sleep, in turn, has been linked to reduced cortical bone density and higher bone resorption markers in multiple study populations, likely mediated by elevated sympathetic nervous system activation and leptin dysregulation.[5] Night shift work offers a useful natural experiment in circadian disruption. Postmenopausal women in rotating night-shift roles have been found to have lower lumbar spine and femoral neck BMD compared to those working standard day shifts.[11] The Nurses' Health study reported an elevated risk of hip and wrist fracture among women with 20 or more years of night – shift works.[12] A controlled forced – desynchrony experiment in healthy men found that circadian misalignment preferentially reduced P1NP – a bine formation marker- without a corresponding change in CTX, suggesting that circadian disruption may impair the anabolic side of bone remodelling and thereby tip the balance towards net bone loss.[13]

3.4.2 Mechanisms Linking Circadian Disruption to Bone Remodeling

Several converging mechanisms explain how sleep and circadian disruption damage the skeleton – mechanisms that are especially consequential for postmenopausal women. Sleep restriction increases SNS tone, which directly activates beta – adrenergic receptors on osteoblasts. Suppressing bone formation and perturbing clock gene synchronization in bone cells.[5] Disrupted sleep also elevates circulating pro – inflammatory cytokines – including TNF- alpha and IL-6 – that drive RANKL – dependent osteoclast recruitment. Disrupted cortisol rhythms and suppressed nocturnal growth hormone secretion further handicap the anabolic and repair phases of the remodelling cycle. Animal studies add to this picture : mice exposed to continuous light(a model of pure circadian disruption without sleep restriction) develop reduced trabecular bone volume accompanied by increased TNF- alpha, with recovery following return to anormal light – dark cycle.[5]

In postmenopausal women, the circadian decline in melatonin removes a critical antioxidant and anti-osteoclastogenic buffer. Without adequate melatonin, the ROS- MPK-p38 axis in osteoclast precursors remains active, substaining their survival and differentiation into bone-resorbing multinucleated cells. The concurrent downregulation of BMAL1 in bone tissue of postmenopausal women amplifies this permissive state. What emerges is a self- reinforcing cycle: estrogen loss reduces reduces melatonin amplitude and BMAL1 expression; these circadian defecits promote osteoclastogenesis and weaken osteoblast function; the resulting bone loss increases fracture risk; and the pain, disability, and anxiety associated with fractures further degrade sleep quality and circadian health, perpetuating sleep.

3.5 Pharmacological Implications: Chronotherapy and Bone Health

The intersection of circadian biology and bone metabolism opens a practical avenue for chronotherapy – the strategic timing pf drug administration to align with circadian pharmacokinetics and maximize treatment efficacy. The concept is well – established in other areas for medicine, such as evening antihypertensive dosing and circadian – aligned chemotherapy. For osteoporosis pharmacotherapy, early evidence suggests that the timing of administration matters. Morning injection of teriparatide (PTH 1 -34) has been reported to produce greater gains in lumbar spine BMD (9.1%) compared to evening dosing (4.8%), consistent with the temporal alignment of PTH action with the post – overnight resorption phase and the morning window of bone formation.[14,15]

Melatonin holds particular promise as a chronotherapeutic agent in menopausal osteoporosis. Its dual role- as a circadian synchronizer and as a BMAL1 upregulator in osteoclast precursors- means that supplementation could address multiple pathogenic threads simultaneously: restoring circadian alignment, re- engaging the BMAL1/ROS/MAPK-p38 brake on osteoclastogenesis, and improving sleep quality. The challenge is that the optimal dose, timing, and duration for melatonin therapy specifically targeting osteoporosis have yet to be established through adequately powered clinical trials.

At the same time, caution is warranted regarding sleep medications commonly prescribed for menopausal insomnia. Benzodiazepines and non- benzodiazepine sedative – hypnotics (Z- drugs such as Zolpidem) are associated with substantially elevated fracture risk – meta- analyses have reported 52-92% increased relative risk of hip fracture with these agents.[16] They increase fall risk through sedation, impaired balance, and sleep inertia, all of which are particularly hazardous in women who already have compromised bone strength. Similarly, caffeine – widely used to compensate for poor sleep – promotes hypercalciuria and may directly impair osteoblast function, adding another layer of skeletal risk for postmenopausal women coping with sleep disruption.[5]

CONCLUSION

This review makes the case that the circadian clock and the bone remodelling are deeply and bidirectionally interconnected systems – and that the menopausal transition represents a critical period during which disruptions to both systems coverage and amplify one another. At the molecular core of this interaction, *BMAL1* emerges as a pivotal regulator: it controls antioxidant capacity through the *CLOCK/BMAL1* transcriptional complex and supresses the *ROS-MAPK-p38* pro – survival pathway in osteoclast precursors. Melatonin, the principal hormone output of the circadian system, activates and depends on this *BMAL1* – mediated pathway – and its demonstrated efficacy in reducing bone loss in ovariectomized animal models provides mechanistic grounding for its potential.

Clinically, the reliable nocturnal rhythm of bone turnover markers underscores that the skeleton is a time – sensitive organ. When that rhythm is disrupted – through inadequate sleep, shift work, or the attenuated circadian amplitude that accompanies menopause – bone loss accelerates through mechanism and that compound the hormones land antioxidant deficits already imposed by estrogen withdrawal. The therapeutic implications span multiple dimensions; chronotherapy for established osteoporosis medications, melatonin supplementation as both a circadian restorative and a osteoclast – suppressive strategy, and more careful pharmacological management of menopausal sleep disturbances without increasing fracture risk through sedative – hypnotics.

Looking ahead, several research gap remain. How estrogen regulates *BMAL1* expression specifically in bone cells deserves detailed molecular investigation. The optimal dose, timing, and duration of melatonin therapy for postmenopausal osteoporosis need to be defined through adequately powered, randomized controlled trials. The distinct contributions of sleep stage disruption versus circadian misalignment to postmenopausal bone metabolism should be characterized using objective sleep assessment tools. And it remains to be determined whether circadian – targeted interventions can enhance the efficacy of existing anti- resorptive therapies and meaningfully reduce fracture incidence in this high- risk population. Addressing these questions will be essential to fully integrate circadian medicine into the management of postmenopausal osteoporosis.

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