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Perspective

Circadian Rhythm, Clock Genes and Osteoarthritis: The Dream of a Good Night's Sleep

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ABSTRACT: Circadian rhythm is an endogenous 24-hour timing system that coordinates metabolic, inflammatory, and reparative processes required for tissue homeostasis. Disruption of this temporal organization, increasingly common because of shift work, sleep disturbance, and other modern lifestyle factors, has been implicated in chronic inflammatory and metabolic diseases, including osteoarthritis (OA). Experimental studies indicate that circadian dysregulation in joint tissues can alter chondrocyte metabolism, extracellular matrix turnover, synovial inflammatory tone, and subchondral bone remodeling. At the molecular level, perturbation of core clock components such as *BMAL1, PER,* and *CRY* is associated with oxidative stress, an imbalance between anabolism and catabolism, and increased sensitivity to inflammatory stimuli. Human evidence currently supports an association between circadian misalignment, disturbed sleep, and greater OA symptom burden, but direct causal inference remains limited. OA-related pain, reduced physical activity, and metabolic dysfunction may, in turn, aggravate sleep and circadian disruption, creating a bidirectional cycle. This review synthesizes mechanistic, animal, and human evidence on circadian regulation of joint homeostasis and discusses translational opportunities, including chronotherapy, rhythm-aligned behavioral interventions, and pharmacological modulation of clock pathways. We also highlight major limitations of the current literature and priorities for future phase-informed precision studies in OA.

Keywords: osteoarthritis, circadian rhythm, clock genes, neuroendocrine, metabolism, inflammation

1. Introduction

Circadian rhythms are endogenous 24-hour fluctuations that are crucial for regulating gene expression, hormone secretion, and metabolic pathways in living organisms [1]. These rhythms persist even under constant environmental conditions and synchronize with external cues such as light, temperature, and nutrients, thereby

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influencing a wide range of physiological processes [2]. Disruption of the circadian system, such as misalignment with environmental cycles or disturbances in core clock gene expression, leads to systemic imbalance. Clinically, this manifests as sleep disorders, endocrine and metabolic abnormalities, and chronic inflammation [3, 4]. Chronic circadian misalignment is associated with increased risks of cardiovascular disease, metabolic syndrome, depression, cognitive decline, and cancer [5]. In modern society, night shift and rotating shift work, which affect around 20% of the workforce, are major contributors to circadian disruption. Lifestyle factors like insomnia, sleep deprivation, excessive screen time, and stress further exacerbate this issue, particularly in adolescents and young adults [6, 7]. Prolonged disruption not only impairs cognitive function but also compromises immune and metabolic homeostasis.

Osteoarthritis (OA), a chronic degenerative joint disease, is a leading cause of disability, especially in older adults. By 2035, OA is projected to affect 7.7% of the global population, imposing a substantial burden on healthcare systems [8]. While traditional risk factors such as aging, inflammation, and mechanical injury have been well studied, recent work suggests that circadian rhythm disruption and sleep disturbance may also be relevant to OA susceptibility and symptom burden. Lifestyle and behavioral patterns that disturb circadian organization often cluster with broader adverse health behaviors and worse long-term outcomes [9, 10], supporting investigation of circadian dysregulation as a potentially underrecognized contributor to OA.

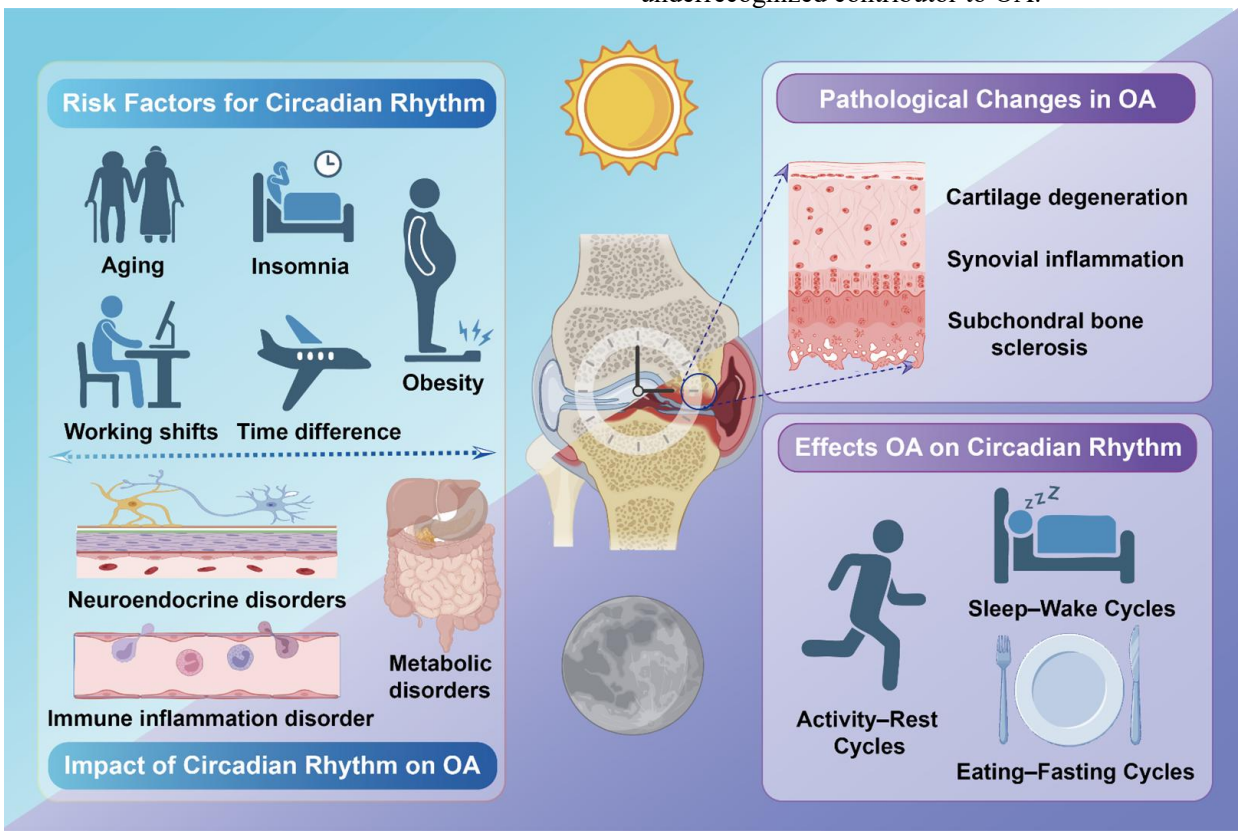


Figure 1. Circadian Rhythms: Risk Factors and Effects in OA. This figure summarizes the bidirectional OA-circadian cycle. Aging, insomnia, obesity, shift work, and other rhythm-disrupting exposures can perturb neuroendocrine, metabolic, and immune-inflammatory signaling, thereby affecting cartilage, synovium, and subchondral bone. OA-related pain, inflammation, reduced activity, and psychological stress then further destabilize sleep and daily behavioral rhythms, reinforcing disease burden.

Recent studies highlight that the circadian rhythm is functional within joint tissues. Clock genes in cartilage, synovium, and subchondral bone regulate processes like metabolism, matrix synthesis, and antioxidant defense. Disruption of these rhythms can activate inflammatory pathways, such as nuclear factor-κB (NF-κB) signaling, promoting cartilage degradation and disturbing bone remodeling [11]. As illustrated in Figure 1, circadian disruption not only accelerates OA progression through various molecular mechanisms but also creates a bidirectional cycle in which OA-related pain, inflammation, and psychological stress further disrupt sleep and circadian rhythms. Clinical observations suggest that OA patients experience changes in sleep, physical activity, and dietary patterns, indicating potential

reciprocal interactions between circadian disruption and OA pathophysiology.

With the advent of multi-omics technologies and chronotherapeutics, it is now possible to investigate this relationship at cellular and molecular levels [12]. Despite growing evidence, a comprehensive synthesis of the interplay between circadian disruption and OA remains scarce. Given the rising prevalence of both circadian misalignment and OA, this review synthesizes molecular, animal, and clinical research to explore the bidirectional relationship between circadian rhythm disruption and OA, aiming to provide new insights into non-classical OA pathogenesis and offering theoretical foundations for early intervention, precision therapies, and public health strategies.

2. Impact of Circadian Rhythm on OA

The circadian system comprises a central pacemaker and peripheral clocks that together coordinate rhythmic physiological activities and systemic homeostasis. The central clock, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, receives photic input from the retina and synchronizes peripheral rhythms through neural, endocrine, and humoral signals [13]. Through this coordination, the circadian system regulates sleep–wake cycles, glucocorticoid and melatonin secretion, metabolism, and immune activity, thereby helping maintain tissue integrity and inflammatory balance [14-16].

In OA, circadian disruption is increasingly linked to altered neuroendocrine signaling, immune activation, and metabolic imbalance across cartilage, synovium, and subchondral bone. Because several mechanisms recur across compartments, the following sections summarize shared pathways once and then emphasize tissue-distinctive features. Importantly, the evidence base spans in vitro studies, animal models, and more limited human data, so confidence differs across mechanisms. In this Perspective, the key issue is not that every circadian-associated pathway has been proven in OA, but that convergent evidence supports a bidirectional framework in which rhythm disruption may amplify joint vulnerability across multiple tissues and biological levels.

2.1 Neuroendocrine Rhythms and Joint Homeostasis

Neuroendocrine rhythms help align tissue repair, inflammatory restraint, and metabolic demand over the day-night cycle. Table 1 highlights representative hormones whose circadian variation may influence joint homeostasis. The main pathogenic themes are shared, but their dominant manifestations differ across cartilage, synovium, and subchondral bone.

Table 1. Overview of Neuroendocrine Rhythms and Joint Homeostasis.

Circadian Hormone	Tissue	Key Factors	Circadian Rhythm Mechanisms
Cortisol	Cartilage	MMPs, COL2A1, oxidative stress pathway	**Normal:** The peak in the morning regulates glucocorticoid receptors, maintains cartilage matrix homeostasis, and inhibits excessive inflammation [19]. **Disrupted:** Long-term high cortisol or low-level rhythm loss during, leading to accelerated matrix degradation, disordered sugar metabolism, and enhanced inflammation [20, 181].
	Synovium	GR pathway, IL-1β, IL-6, TNF-α, TGF-β1, 11β-HSD1/2	**Normal:** Inhibit excessive synovial inflammation and reduce MMPs and ILs levels [23]. **Disrupted:** The inflammation inhibition effect is weakened, and the pro-inflammatory state is enhanced [26].
	Subchondral Bone	Osteogenesis/osteoclast balance pathway, VEGF, angiogenesis, 11β-HSD enzyme system	**Normal:** Remodeling balance and regulates VEGF and angiogenesis [29]. **Disrupted:** Rhythm disturbances or long-term high levels of cortisol lead to osteoblast apoptosis↑, osteoclast activity↑, osteopenia, and impaired angiogenesis [31].
Melatonin	Cartilage	NF-κB, iNOS, COX-2, IL-1β, TNF-α, MTNR1A/B, COL2A1, TGF-β/Smad2, SIRT1, ROS/antioxidative enzymes	**Normal:** The peak of nocturnal secretion activates MT1/MT2 receptors, inhibits NF-κB, iNOS/COX-2, and reduces the release of inflammatory factors; activates TGF-β/Smad2 and SIRT1 to promote COL2A1 synthesis and antioxidant [34, 35, 37, 38].

			Disrupted: ROS accumulation and matrix synthesis decrease at disorder or low levels, resulting in cartilage degeneration [41, 42].
	Synovium	MT1/MT2 MMP-9, PI3K/AKT, ERK, NF-PIE, MIR-3150A-3P, IL-1β, IL-6, IL-8, TNF-α, VEGF	**Normal:** MT1/MT2 inhibits MMP-9, PI3K/AKT, ERK, NF-κB, reduces IL-1β, IL-8, VEGF, and reduces inflammation and angiogenesis [44, 45]. **Disrupted:** Immune regulation is weakened when disordered or low levels occur, and ROS accumulation occurs; some dose-dependent studies suggest that inflammation may be aggravated [182].
	Subchondral Bone	PI3K/AKT, BMP/Smad, MAPK, NF-κB, Nrf2/HO-1, Wnt, SIRT1, VEGF, Ang-2/4	**Normal:** Promote osteogenesis and differentiation of MSCs and inhibit osteoclastogenesis; activate PI3K/AKT, BMP/Smad, MAPK, NF-κB, Nrf2/HO-1, Wnt, SIRT1, and other pathways; promote angiogenesis (VEGF, Ang-2/4) [48]. **Disrupted:** Bone mass decrease, metabolic imbalance, and angiogenesis abnormality during disorders[50, 51].
GH	**Cartilage**	GH/IGF-1 axis, COL2A1, ACAN, TGF-β/Smad	**Normal:** The pulse secretion peak during the deep sleep period at night directly promotes the synthesis of COL2A1 and proteoglycans and stimulates the differentiation of precursor cells; promotes proliferation and matrix synthesis through IGF-1 [54, 183]. **Disrupted:** GH/IGF-1 decreases, and synthesis ability is weakened; overexpression or decreased sensitivity can also lead to degeneration [57].
PTH	**Subchondral Bone**	AK2/STAT3, WNT5A/ROR2, BMP/Smad, Wnt	**Normal:** In the evening/night secretion peak, early morning trough; activate osteoblasts under normal rhythm, promote matrix synthesis and bone remodeling [68, 69]. **Disrupted:** Long-term high level of PTH → bone resorption ↑, subchondral bone abnormality; too low → insufficient bone remodeling, risk of joint degeneration ↑ [70].

11β-HSD1/2: 11B-hydroxysteroid dehydrogenase 1 and 2; ACAN: Aggrecan; BMP: Bone Morphogenetic Protein; COL2A1: Type II Collagen Alpha 1 Chain; COX-2: Cyclooxygenase-2; ERK: Extracellular Signal-Regulated Kinase; GH: Growth Hormone; GR: Glucocorticoid Receptor; IGF-1: Insulin-Like Growth Factor-1; ILs: Interleukins; iNOS: Inducible Nitric Oxide Synthase; MAPK: Mitogen-Activated Protein Kinase; MMPs: Matrix Metalloproteinases; MSCs: Mesenchymal Stem Cells; MT1: Melatonin Receptor 1A; MT2: Melatonin Receptor 1B; NF-κB: nuclear factor-κB; PTH: Parathyroid Hormone; PI3K/AKT: Phosphatidylinositol-3-Kinase/Protein Kinase B; ROS: Reactive Oxygen Species; SIRT1: Sirtuin 1; Smad2: Smad family member 2 ; TGF-β: Transforming Growth Factor-β; TNF-α: tumor necrosis factor-α; VEGF: Vascular Endothelial Growth Factor.

2.1.1 Effects of Cortisol Circadian Rhythm in Joint Tissue

The hypothalamic-pituitary-adrenal (HPA) axis, with cortisol as its principal effector, peaks in the early morning and declines at night, thereby coordinating stress responses, metabolism, and inflammatory restraint [17, 18]. In joint tissues, the key issue is not cortisol exposure alone but loss of rhythmic glucocorticoid signaling. Cartilage: physiologic glucocorticoid tone appears necessary for homeostasis, whereas sustained elevation or flattened oscillation favors catabolism. Biomarker studies link abnormal cortisol rhythmicity to higher cartilage-related inflammatory signaling [19, 20], meta-analytic data support dose-dependent cortisol toxicity to cartilage morphology and viability [21], and experimental disruption of glucocorticoid signaling can attenuate OA-like cartilage degeneration [22]. Taken together, these findings support a role for rhythmic glucocorticoid control in cartilage maintenance, although the causal chain in human OA remains incompletely defined. Synovium: rhythmic cortisol signaling normally restrains inflammatory mediators through glucocorticoid receptor-dependent pathways. Mouse synoviocyte data and clinical observations support reduced matrix remodeling and a less inflammatory synovial profile under appropriate glucocorticoid control [23-25], whereas rhythm disruption associated with aging or obesity correlates with elevated interleukin-6 (IL-6)/tumor necrosis factor-α (TNF-α) and persistent synovitis [26, 27]. These data support an anti-inflammatory role for cortisol rhythmicity in synovium, but they still do not establish that altered cortisol timing is an independent driver of OA synovitis. Subchondral bone: direct OA-specific evidence remains limited. Broader skeletal studies show that excess glucocorticoid exposure suppresses osteoblast activity,

prolongs osteoclast survival, and impairs angiogenesis [28-31]. These observations raise the possibility that disrupted glucocorticoid rhythmicity could destabilize subchondral remodeling and vascular coupling in OA, but this remains inferential rather than directly established [32].

2.1.2 Effects of Melatonin Circadian Rhythm in Joint Tissue

Melatonin, secreted nocturnally under SCN control, acts through melatonin receptor 1 (MT1)/MT2 signaling and receptor-independent antioxidant pathways [33]. Across joint tissues, it has been linked to inflammatory restraint, redox control, and matrix or bone metabolism, but its effects are dose-, tissue-, and context-dependent. Cartilage: evidence is comparatively consistent in supporting chondroprotection. Melatonin suppresses NF-κB, inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), IL-1β, and TNF-α, while promoting chondrogenic differentiation, type II collagen synthesis, and antioxidant defense through MT1/MT2-related, transforming growth factor-β1 (TGF-β1)/Smad2, sirtuin 1 (SIRT1), and phosphatidylinositol-3-kinase/protein kinase B pathway (PI3K/Akt)-extracellular signal-regulated kinase (ERK) pathways [34-40]. Impaired melatonin signaling may therefore contribute to oxidative stress, senescence, and matrix loss, although most mechanistic support comes from cell and animal studies [41, 42]. Synovium: the evidence is thinner and less uniform. Some OA and arthritis models suggest reduced PI3K/Akt, ERK, NF-κB, cytokine, and vascular endothelial growth factor (VEGF) signaling with melatonin exposure [43-45], whereas disrupted melatonin rhythms may permit oxidative stress and persistent synovitis [46]. However, data from rheumatoid arthritis (RA) and other inflammatory arthritis models also show that low-dose melatonin can aggravate inflammation under some conditions [182]. For OA synovium, melatonin should therefore be discussed as biologically relevant but context-dependent, rather than uniformly anti-inflammatory. Subchondral bone: current evidence is drawn mainly from osteoporosis and general bone biology rather than OA. Timed melatonin supplementation supports osteogenesis, mineralization, and angiogenesis-related coupling via PI3K/Akt, Bone morphogenetic protein (BMP)/Smad, mitogen-activated protein kinase (MAPK), Wnt, and antioxidant pathways [47-49]. These mechanisms are relevant to subchondral remodeling, but the direct link between endogenous melatonin rhythm disruption and OA bone lesions remains inferential [50-52].

2.1.3 Effects of Other Circadian Hormones in Joint Tissue

Beyond cortisol and melatonin, other rhythmic hormones may influence the joint microenvironment, although OA-specific data are more fragmentary. Cartilage: growth hormone (GH) peaks during deep sleep and supports type II collagen (COL2A1), proteoglycan synthesis, and insulin-like growth factor-1 (IGF-1)-dependent chondrocyte anabolism [53, 54]. Aging, circadian disruption, and OA are associated with reduced GH/IGF-1 signaling, IGF-1 resistance, and weaker extracellular matrix (ECM) renewal, whereas GH excess can also be detrimental, underscoring that both loss and dysregulation of rhythmic GH signaling may impair cartilage homeostasis [55-58]. Subchondral bone: parathyroid hormone (PTH) follows a biphasic circadian rhythm and helps coordinate calcium handling and bone remodeling [59, 60]. OA-specific evidence is limited, but broader skeletal data suggest that chronically elevated PTH shifts remodeling toward resorption and structural imbalance, whereas insufficient PTH suppresses turnover and may weaken bone quality [61-64]. These observations are consistent with endocrine involvement in OA, but they remain less directly validated than the literature on cortisol and melatonin.

2.2 Circadian Control of Inflammation and Immunity in Joint Tissues

The immune system exhibits robust circadian fluctuations in leukocyte trafficking, activation, and cytokine production [65]. As summarized in Table 2, macrophages and lymphocytes use time-of-day variation to constrain inflammation and coordinate repair [66]. In OA, the main implication is not that every immune pathway becomes circadian-driven, but that loss of rhythmic control repeatedly converges on a limited set of inflammatory hubs, including NF-κB, janus kinase/signal transducer and activator of transcription (JAK-STAT), MAPK, and PI3K/Akt. The dominant pathological output then differs by tissue, appearing mainly as matrix catabolism in cartilage, persistent synovitis in synovium, and remodeling imbalance in subchondral bone.

2.2.1 Circadian Regulation of Macrophage Activity

Macrophage polarization between M1 and M2 states follows circadian oscillation, with repair-oriented M2 activity enriched during the rest phase and inflammatory M1 activity more prominent during the active phase [67]. OA-related circadian disruption shifts this balance toward sustained M1 dominance [68]. Cartilage: the key consequence is prolonged exposure to TNF-α, IL-1β,

matrix metalloproteinases (MMPs), and A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), which accelerates collagen II and aggrecan loss [69-72]. This supports that disturbed macrophage rhythmicity indirectly amplifies cartilage catabolism. Synovium: macrophage rhythmicity is especially important because this compartment is shaped by intensive macrophage-fibroblast-like synoviocyte (FLS) crosstalk. Circadian misalignment has been linked to increased M1 accumulation, Notch-associated inflammatory loops, and impaired resolution, thereby sustaining synovitis and pain [73-78]. Compared with other immune mechanisms, this macrophage-centered axis currently offers one of the more coherent explanations for how circadian disruption may reinforce OA synovitis. Subchondral bone: direct rhythmic evidence is less extensive, but macrophage-derived cytokines can promote receptor activator of nuclear factor-κB ligand (RANKL)-mediated osteoclastogenesis and abnormal angiogenesis, suggesting that clock disruption may influence bone remodeling indirectly through osteoimmune signaling rather than through a cartilage-like catabolic program [79-81].

Table 2. Overview of Circadian Control of Inflammation and Immunity in Joint Tissues.

Cell	Tissue	Key Factors	Circadian Rhythm Mechanisms
Macrophages	**Cartilage**	NF-κB, JAK-STAT; IL-10, TGF-β, IL-1β, TNF-α, IL-6; MMP-3, MMP-13, ADAMTS	**Normal:** M2 macrophages predominate at night, secreting IL-10 and TGF-β to promote matrix synthesis and chondroprotection. Transient M1 activation after injury facilitates immune clearance and subsequent M2-driven repair [69]. **Disrupted:** Persistent M1 polarization with excessive TNF-α, IL-1β, and IL-6 production activates inflammatory cascades and matrix-degrading enzymes, leading to collagen loss and impaired nocturnal regeneration [72].
	Synovium	Notch, JAK-STAT, NF-κB, MAPK; IL-10, IGF-1, TGF-β, TNF-α, IL-1β, IL-6	**Normal:** M2 macrophages maintain immune homeostasis and tissue repair via IL-10, TGF-β, and IGF-1; their proportion increases at night under melatonin regulation, supporting clearance of daytime stress and microdamage [73]. **Disrupted:** Enhanced M1 activity and fibroblast–macrophage crosstalk amplify inflammation, with overactivation of Notch, NF-κB, and JAK-STAT pathways causing chronic synovitis and reduced regenerative capacity [76, 77].
	Subchondral Bone	RANKL, TGF-β, BMP-2, VEGF, HIF-1α; pro-/anti-inflammatory cytokines	**Normal:** Circadian macrophage fluctuation balances bone resorption and formation; M1 macrophages support osteoclast differentiation, whereas M2 promote osteogenesis and angiogenesis through TGF-β and BMP-2 signaling [79, 80]. **Disrupted:** Dominant M1 phenotype enhances osteoclast activity and aberrant angiogenesis, accompanied by VEGF elevation and HIF-1α activation, contributing to subchondral sclerosis and cartilage erosion [81].
Lymphocytes	**Cartilage**	IL-10, TGF-β, IL-17, IFN-γ, IL-6, IL-1β, TNF-α; MMP-13	**Normal:** Treg cells and B cells maintain immune tolerance and secrete IL-10 and TGF-β to suppress inflammation and support cartilage homeostasis. Th17 activity shows diurnal variation, balancing repair and defense [184]. **Disrupted:** Circadian disruption breaks the Treg/Th17 equilibrium, enhancing IL-17, IL-6, and TNF-α release, promoting MMP-13-mediated ECM degradation and chondrocyte apoptosis [86].
	Synovium	IgA, IgM, IL-10, IL-6, TNF-α; MHC II, CD80, CD86	**Normal:** Synovial T and B cells coordinate with macrophages and FLS to preserve tissue tolerance and joint barrier integrity. B cells produce IgA, IgM, and IL-10, contributing to immune homeostasis [185, 186]. **Disrupted:** Aberrant activation of $CD4^+$ T cells and B cells leads to excessive IL-6 and TNF-α production, antigen presentation through MHC II and costimulatory signals, driving chronic synovitis [87, 88].
	Subchondral Bone	IL-10, RANKL, IL-17, IL-6, TNF-	**Normal:** Enhanced Treg-mediated IL-10 production inhibits RANKL-induced osteoclastogenesis and maintains bone remodeling balance

α, IL-1β; ACPA	**Disrupted:** Disruption reduces Treg activity and enhances Th17-derived IL-17 and RANKL expression, accelerating osteoclast activation and bone resorption. B cell-derived IL-6, TNF-α, and autoantibodies further exacerbate subchondral bone damage [89, 90].

ACPA: Anti-Citrullinated Protein Antibody; ADAMTS: A Disintegrin and Metalloproteinase with Thrombospondin Motifs; BMP-2: Bone Morphogenetic Protein-2; ECM: Extracellular Matrix; FLS: Fibroblast-Like Synoviocyte; HIF-1α: Hypoxia-Inducible Factor-1α; IFN-γ：Interferon-γ; IGF-1: Insulin-Like Growth Factor-1; ILs: Interleukins; JAK-STAT: Janus Kinase–Signal Transducer and Activator of Transcription; MAPK: Mitogen-Activated Protein Kinase; MHC II: Major Histocompatibility Complex Class II; MMP: Matrix Metalloproteinase; NF-κB: nuclear factor-κB; RANKL: Receptor Activator of Nuclear Factor-κB Ligand; TGF-β: Transforming Growth Factor-β; TNF-α: tumor necrosis factor-α; VEGF: Vascular Endothelial Growth Factor.

2.2.2 Circadian Regulation of Lymphocyte Function

Adaptive immune cells also display circadian variation in distribution and effector function [65]. Regulatory T cells (Treg) activity tends to dominate during the rest phase, whereas T helper 17 cells (Th17) responses and B-cell effector programs become more pro-inflammatory when rhythmic organization is disrupted [82-84]. Cartilage: altered Treg/Th17 balance increases IL-17-driven MMP-13 expression and amplifies catabolic signaling at the synovial-cartilage interface [85, 86]. Synovium: circadian disruption appears to favor CD4+ T-cell and pathogenic B-cell activation, which can intensify macrophage-FLS inflammatory circuits, although direct OA-specific circadian studies remain limited [87, 88]. Subchondral bone: reduced bone marrow Treg/IL-10 restraint and enhanced Th17- or B-cell-derived osteoclastogenic signals may promote bone resorption and remodeling imbalance [89-91]. Overall, lymphocyte data support immune involvement in OA circadian biology, but the mechanistic specificity remains less developed than for macrophages. Accordingly, these findings are better interpreted as supporting a broader immune-timing framework than as defining established OA-specific causal pathways.

2.3 Metabolic Rhythms and Energy Regulation in Joint Tissues

Joint energy metabolism is coordinated by both the SCN and local peripheral clocks. In metabolic OA, this coordination may be blunted, linking rhythm disruption to insulin resistance, altered substrate use, and catabolic stress [92-96]. Here again, the central Perspective point is not that each tissue has a wholly distinct metabolic clock program, but that circadian-metabolic misalignment may be expressed in tissue-specific ways across cartilage, synovium, and subchondral bone. *(Brain and Muscle ARNT-Like 1) BMAL1* is an important integrator within this framework, although the downstream consequences vary by compartment (Table 3).

Table 3. Overview of Metabolic Rhythms and Energy Regulation in Joint Tissues.

Energy Metabolism	Tissue	Key Factors	Circadian Rhythm Mechanisms
Glucose Metabolism	**Cartilage**	Insulin, glucocorticoids; GLUT1, *BMAL1*	**Normal:** Glucose diffuses from synovial fluid and supports chondrocyte viability and ECM synthesis. Central and peripheral clocks coordinate glucose uptake and utilization through rhythmic secretion of glucocorticoids and insulin [95]. **Disrupted:** Circadian disruption impairs insulin sensitivity and GLUT1 expression, leading to chondrocyte hypertrophy, matrix degradation, and enhanced OA susceptibility. *BMAL1* downregulation further aggravates glucose utilization defects and cartilage damage [96, 101].
	Synovium	HIF-1α, JAK-STAT, PI3K-AKT; HK2, PFKFB3, PKM2; IL-6, TNF-α	**Normal:** Glucose metabolism maintains synovial cell activity and supports tissue homeostasis. **Disrupted:** Disruption induces a persistent glycolytic phenotype resembling the Warburg effect, driven by HIF-1α, JAK-STAT, and PI3K-AKT pathways, enhancing lactate accumulation, angiogenesis, and chronic inflammation. Altered rhythmic cytokine secretion and glycolytic enzyme expression contribute to sustained synovial activation [102, 103].

	Subchondral Bone	Osteocalcin, CTX, GLP-1, GLP-2, GIP; *BMAL1*, SIRT1, GSK3β	**Normal:** Bone remodeling exhibits clear circadian patterns, with bone formation and resorption markers showing nocturnal elevation and daytime suppression. Gut-derived hormones such as GLP-1, GLP-2, and GIP synchronize bone metabolism with feeding–fasting cycles, maintaining skeletal stability [105, 106]. **Disrupted:** Circadian disruption attenuates these protective signals, resulting in excessive bone resorption and microstructural fragility. Downregulation of *BMAL1* under hyperglycemic or oxidative stress conditions impairs osteoblast differentiation and promotes bone loss [107].
	Cartilage	TLR4, CD36, ROS, NF-κB; IL-1β, TNF-α, MMPs, ADAMTS; nuclear receptors	**Normal:** Lipid metabolism maintains balanced fatty acid oxidation and cholesterol turnover, providing energy for chondrocyte survival and ECM synthesis. **Disrupted:** Lipid accumulation, mitochondrial dysfunction, oxidative stress, and activation of inflammatory cascades. Excess fatty acids and oxidized lipids stimulate TLR4/CD36–NF-κB signaling, increasing IL-1β, TNF-α, and matrix-degrading enzymes (MMPs, ADAMTS), resulting in ECM degradation and chondrocyte hypertrophy [112, 113].
Lipid Metabolism	**Synovium**	TLR4, CD36, NF-κB, MAPK; IL-6, IL-8, MMPs; LTB4, PGE2, LXA4, RvE1	**Normal:** Lipid metabolism supports FLS and macrophage activity, with circadian rhythm regulating inflammatory thresholds and lipid mediator synthesis. **Disrupted:** Disrupted lipid rhythmicity promotes pro-inflammatory activation of FLS and macrophages, with increased IL-6, IL-8, and MMPs expression. Disturbed timing of arachidonic acid metabolites (e.g., LTB4, PGE2) and impaired production of specialized pro-resolving mediators (LXA4, RvE1) result in persistent inflammation and angiogenesis [114].
	Subchondral Bone	LXR, ABCA1, ABCG1, PPAR; RANKL; BMAT	**Normal:** Normal lipid metabolism supports bone remodeling through balanced osteogenesis and osteoclastogenesis, regulated by cholesterol efflux (LXR–ABCA1/ABCG1) and PPAR signaling [115]. **Disrupted:** Cholesterol efflux defects amplify RANKL signalling, osteoclast activity↑. Excess BMAT suppresses osteogenesis, with worsened glucose tolerance → impaired bone remodelling, and joint load buffering [116].

ABCA1: ATP-Binding Cassette Transporter A1; ABCG1: ATP-Binding Cassette Transporter G1; ADAMTS: A Disintegrin and Metalloproteinase with Thrombospondin Motifs; BMAL1:Brain and Muscle ARNT-Like 1; BMAT: Bone Marrow Adipose Tissue; CTX: C-Terminal Telopeptide of Type I Collagen; ECM: Extracellular Matrix; GIP: Glucose-Dependent Insulinotropic Polypeptide; GLP-1: Glucagon-Like Peptide-1; GLP-2: Glucagon-Like Peptide-2; GLUT1: Glucose Transporter 1; GSK3β: Glycogen Synthase Kinase 3β; HIF-1α: Hypoxia-Inducible Factor-1α; HK2: Hexokinase 2; JAK-STAT: Janus Kinase–Signal Transducer and Activator of Transcription; LTA4: Leukotriene B4; LXA4: Lipoxin A4; LXR: Liver X Receptor; MAPK: Mitogen-Activated Protein Kinase; MMPs: Matrix Metalloproteinases; NF-κB: nuclear factor-κB; OA: Osteoarthritis; PFKFB3: 6-Phosphofructo-2-Kinase/Fructose-2,6-Bisphosphatase 3; PGE2: Prostaglandin E2; PI3K-AKT: Phosphatidylinositol-3-Kinase/Protein Kinase B; PKM2: Pyruvate Kinase M2; PPAR: Peroxisome Proliferator-Activated Receptor; RANKL: Receptor Activator of Nuclear Factor-κB Ligand; ROS: Reactive Oxygen Species; RvE1: Resolvin E1; SIRT1: Sirtuin 1; TLR4: Toll-Like Receptor 4; TNF-α: Tumor Necrosis Factor-α.

2.3.1 Circadian Rhythm of Glucose Metabolism Regulates Joint Tissue

Glucose metabolism shows strong circadian variation, aligning glucose tolerance, insulin secretion, and tissue uptake with behavioral demand [97, 98]. In joints, the central theme is that rhythm disruption uncouples substrate supply from tissue-specific repair or remodeling. Cartilage: the *BMAL1-glucose transporter 1 (GLUT1)* axis helps coordinate chondrocyte glucose handling. Experimental diabetes and OA models show that impaired GLUT1 expression and glycolytic activity accelerate cartilage damage, and clinical observations suggest that systemic insulin dysfunction may worsen chondrocyte vulnerability [99-101]. These data support a direct link between circadian-metabolic disruption and cartilage stress. Synovium: direct OA data are sparse, but RA and arthritic models support a rhythm-sensitive glycolytic shift in FLSs involving HK2, PFKFB3, hypoxia-inducible factor-1α (HIF-1α), and JAK-STAT signaling [102-104]. Whether the same mechanism drives lower-grade OA synovitis remains unresolved. These findings are biologically informative, but whether the same mechanism operates in the lower-grade inflammatory setting of OA synovitis remains unresolved. Subchondral bone: bone turnover is tightly coupled to feeding-related endocrine signals such as glucose-dependent insulinotropic polypeptide (GIP) and

glucagon-like peptide (GLP) [105, 106]. High-glucose oxidative stress can suppress *BMAL1* in osteoblasts [107], suggesting a plausible route by which circadian-metabolic misalignment impairs subchondral support, although OA-specific evidence remains limited.

2.3.2 Circadian Rhythm of Lipid Metabolism Regulates Joint Tissue

Lipid metabolism also follows circadian timing, and rhythm disruption can shift lipid handling toward inflammation rather than resolution [108-111]. Across joint tissues, the shared mechanism involves excess saturated fatty acids or oxidized lipids engaging toll-like receptor 4 (TLR4)/CD36 and amplifying NF-κB-dependent catabolic programs. Cartilage: dysregulated fatty-acid oxidation and cholesterol turnover promote oxidative stress, mitochondrial dysfunction, and matrix-degrading enzyme expression [112, 113]. Synovium: altered timing of free-fatty-acid signaling and arachidonic-acid mediators may prolong fibroblast/macrophage activation and delay resolution [114]. Subchondral bone: disturbed cholesterol efflux, peroxisome proliferator-activated receptor (PPAR)-related signaling, and marrow adiposity can bias remodeling toward bone loss or structural weakness [115, 116]. Thus, the value of circadian lipid biology in OA is less that each tissue uses a unique pathway, and more that shared metabolic stress is expressed through tissue-specific pathology.

3. Clock Genes in OA Progression

Circadian clock genes form a transcription-translation feedback network that maintains temporal homeostasis across tissues. As illustrated in Figure 2, the BMAL1-CLOCK positive arm drives *Period* (*PER*) and *Cryptochrome* (*CRY*) transcription through E-box binding, whereas accumulated PER/CRY complexes feed back to repress this activity [117]. Auxiliary loops involving nuclear receptor subfamily 1 group d member1/2 (REV-ERBα/β) and retinoic acid-related orphan receptor (ROR) stabilize phase and amplitude, while metabolic and stress-responsive inputs such as AMPK, SIRT1, mechanistic target of rapamycin (mTOR), oxidative stress, and epigenetic regulation further shape clock output [118, 119]. Although *BMAL1*-associated findings dominate the OA literature, *CLOCK* is not merely passive; it also contributes transcriptional activation and histone-acetyltransferase activity that shape circadian amplitude and downstream gene accessibility. The challenge is that direct *CLOCK*-specific OA evidence remains comparatively sparse.

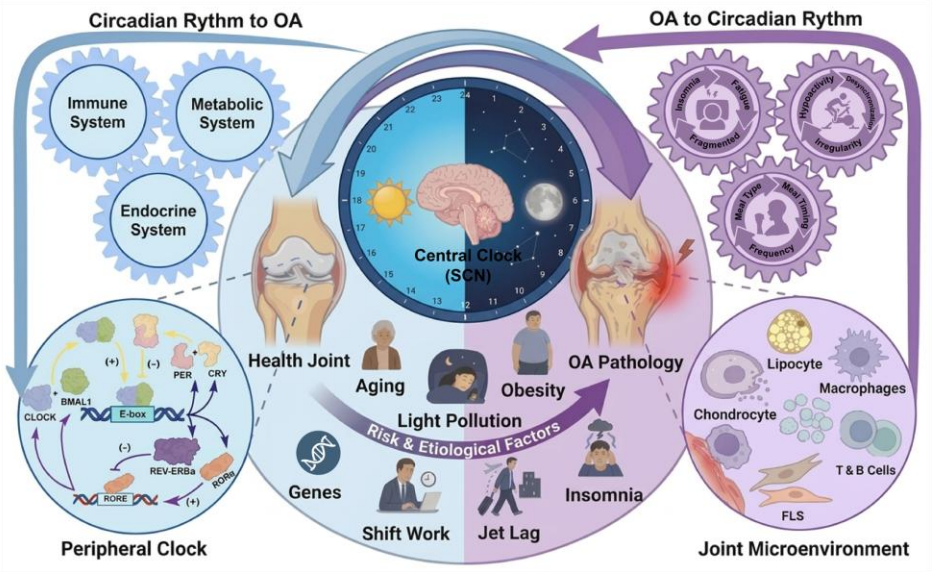


Figure 2. Integrative Model of Bidirectional Circadian-OA Interactions. This figure is intended as a conceptual integration rather than a catalogue of mechanisms. The left side summarizes how systemic circadian cues and local joint clocks coordinate inflammatory tone, metabolism, and tissue remodeling across cartilage, synovium, and subchondral bone. The right side shows the feedback loop by which OA-related pain, inflammation, sleep disruption, reduced activity, and altered feeding behavior can further destabilize circadian organization. The model highlights shared pathways at a high level, while the text focuses on tissue-specific distinctions and current evidence limits. CRY: Cryptochrome; E-BOX: Enhancer Box; FLS: Fibroblast-like synoviocytes; Nr1dα: Nuclear Receptor Subfamily 1 Group D Member 1; PER: Period; RER: Respiratory Exchange Ratio; RORα: Retinoid-Related Orphan Receptor α; RORE: ROR Response Element; SCN: Suprachiasmatic Nucleus.

Functionally, circadian genes regulate transcription, proliferation, DNA repair, apoptosis, metabolism, and immune tone across peripheral tissues [120, 121]. In joints, these rhythmic programs help coordinate ECM turnover, synovial inflammatory thresholds, and subchondral remodeling**.** Table 4 and Table 5 therefore group clock genes according to their shared modules, but the evidence within each module is uneven: *BMAL1* has stronger direct OA support than *CLOCK*, and *CRY* has been studied more extensively than *PER*. The following sections retain the grouped structure while making those evidence limits explicit.

3.1 Positive Regulators *BMAL1* and *CLOCK* in Joint Tissue Homeostasis

BMAL1 and *CLOCK* together form the positive arm of the core clock, but OA evidence for the two genes is not symmetrical. *BMAL1* has the clearest direct mechanistic support, whereas *CLOCK*-specific conclusions are often inferred from its role as BMAL1's heterodimeric partner rather than from isolated OA loss-of-function or gain-of-function models. However, *CLOCK* should not be viewed as merely passive, because its transcriptional co-activating and histone-acetyltransferase functions are relevant to circadian amplitude and downstream gene accessibility. The current literature therefore supports the importance of the *BMAL1-CLOCK* axis in OA, while also indicating that the strongest causal data remain *BMAL1*-centered [108, 122]. Cartilage: *BMAL1* helps preserve chondrocyte phenotype and extracellular matrix support, in part through Hedgehog-related regulation [109]. Reduced *BMAL1* expression in OA has been associated with apoptosis, collagen disorganization, and induction of catabolic enzymes [72, 123], and chondrocyte-specific *BMAL1* knockout models provide some of the strongest available evidence that intrinsic clock disruption can drive OA-like degeneration [124].

Table 4. Overview of Core Clock Proteins and Evidence Boundaries.

Clock Protein / Module	Cellular Location	Upstream Regulators	Downstream Targets	Representative Function / Evidence Note
BMAL1 and CLOCK	Cell nucleus	REV-ERBα/β, RORα/γ, CK1, SIRT1, TNF-α, IL-1β, AMPK/NAD^+	PER1/2, CRY1/2, REV-ERBα/β, NF-κB signaling, metabolic, and tissue-specific remodeling genes	Positive-arm transcriptional regulators. In OA, direct evidence is stronger for BMAL1, whereas CLOCK-specific effects are usually inferred from its heterodimeric and histone-acetyltransferase roles within the complex.
PER and CRY	Cytoplasm↔nucleus shuttle	BMAL1/CLOCK, CK1δ/ε, FBXL3/FBXL21, inflammatory cytokines	SOX9-related matrix gene rhythms, DBP/TEF output genes, NF-κB–mediated catabolic signaling	Negative-arm repressors. In OA, CRY has clearer functional support, whereas PER-specific effects are narrower and more context-dependent, especially when distinguishing PER1 from PER2.

AMPK/NAD^+: AMP-Activated Protein Kinase / Nicotinamide Adenine Dinucleotide (oxidized form); BMAL1:Brain and Muscle ARNT-Like 1; CLOCK: Circadian locomoter output cycles protein kaput; CK1: Casein Kinase 1; CK1δ/ε: Casein Kinase 1 delta/epsilon; CRY: Cryptochrome; DBP/TEF: D-Box Binding Protein / Thyrotroph Embryonic Factor; FBXL3/FBXL21: F-Box and Leucine-Rich Repeat Protein 3 / 21; IL-1β: Interleukin-1β; NF-κB: nuclear factor-κB; OA: Osteoarthritis; PER: Period; REV-ERBα/β: Reverse ErbA α/β (Nuclear Receptor Subfamily 1 Group D Member 1/2, NR1D1/NR1D2); RORα/γ: Retinoid-Related Orphan Receptor α/γ; SIRT1: Sirtuin 1; SOX9: SRY-Box Transcription Factor 9; TNF-α: Tumor Necrosis Factor-α.

CLOCK is likely involved in the same program because E-box-dependent cartilage rhythms require the heterodimer, but direct CLOCK-specific evidence in OA cartilage remains limited. The interpretation, therefore, is stronger for disruption of the positive arm as a whole than for isolated *CLOCK* causality. Synovium: *BMAL1* interacts bidirectionally with inflammation. TNF-α can transiently increase BMAL1 in FLSs, and this response may promote MMP-3, C-C motif chemokine ligand 2 (CCL2), and IL-6 expression under chronically inflamed conditions [125]. However, much of the detailed *BMAL1/CLOCK* inflammatory evidence in synovium comes from RA or related models rather than OA, and whether a similar compensatory-to-failure transition occurs in OA synovium remains unresolved [126]. Subchondral bone: *BMAL1* coordinates osteoblast-osteoclast balance through TGF-β/BMP and NF-κB-related pathways, and *BMAL1* deficiency disrupts bone mass and microarchitecture [124, 127-130]. *CLOCK* is likely relevant to the same transcriptional program, but OA-specific *CLOCK* data in subchondral bone are still sparse. Taken together, the positive arm is mechanistically important in OA, but current evidence is *BMAL1*-dominant rather than evenly shared between *BMAL1* and *CLOCK*.

3.2 Negative Regulators *PER* and *CRY* in Joint Tissue Homeostasis

The negative arm of the core clock, composed of PER1/2 and CRY1/2, represses BMAL1-CLOCK-driven transcription. As with the positive arm, the OA evidence is uneven. *CRY* has clearer functional support across several models, whereas *PER*-related findings are fewer, sometimes divergent between PER1 and PER2, and often derived from in vitro systems or from non-OA inflammatory settings [108]. The most defensible interpretation is therefore that negative-arm disruption matters in joint biology, while *PER*-specific causal conclusions in OA remain comparatively underdeveloped. Cartilage: *CRY2* deficiency accelerates cartilage attrition and disrupts circadian output genes such as Nuclear Receptor Subfamily 1 Group D Members 1 (*Nr1d1)*, *Nr1d2*, *Dbp*, and *Tef*, supporting a protective role for *CRY* in chondrocyte homeostasis [131]. *PER* should not be treated only as an afterthought, however. PER2 has been linked to rhythmic COL2 and ACAN synthesis via mTOR signaling [123], whereas PER1 may facilitate catabolic responses under IL-1β exposure and NF-κB/p65 activation [11]. These findings suggest that *PER* genes influence both anabolic timing and inflammatory susceptibility, but direct causal evidence in human OA remains lacking. Synovium: *PER2* appears relevant to inflammatory restraint, because lipopolysaccharide (LPS) or TNF-α can suppress *PER2*-centered circadian transcriptional programs in arthritic synoviocytes [132, 133]. CRY proteins also limit cytokine escalation: *CRY* deficiency enhances inflammatory mediator expression, and *CRY1* overexpression suppresses TNF-α transcription in arthritis models [134, 135]. Here again, the limitation is that much of the evidence comes from RA or antibody-induced arthritis rather than OA synovitis. Subchondral bone: *PER2* mutant mice show increased bone formation, implying that *PER2* participates in timing osteoblast activity [136]. *CRY1* and *CRY2* influence osteoblast differentiation and osteoclast-related remodeling through Wnt/β-catenin, PI3K-AKT, and MAPK-ERK-linked pathways [137-139]. Overall, both *PER* and *CRY* are relevant to the negative arm in joint biology, but current OA inference is stronger for *CRY* and for general clock disruption than for *PER*-specific causal effects.

Table 5. Overview of Clock Gene Modules in OA Progression.

Clock Gene Module	**Tissue**	**Physiological Role**	**Molecular Linkage with OA**
BMAL1/CLOCK (BMAL1-dominant evidence)	Cartilage	*BMAL1* has the clearest evidence for maintaining chondrocyte rhythmicity, matrix synthesis, and metabolic balance; *CLOCK* is expected to support this program through the shared E-box transcriptional complex [109, 122].	*BMAL1* loss or downregulation in OA is linked to apoptosis, matrix disorganization, and catabolic signaling [72, 187]. Direct *CLOCK*-specific OA cartilage evidence remains limited.
	Synovium	Rhythmic *BMAL1/CLOCK* activity is reported in FLSs and is thought to shape inflammatory thresholds, although detailed OA evidence remains limited.	TNF-α-induced *BMAL1* changes may promote MMP-3, CCL2, and IL-6 expression, but much mechanistic detail derives from inflammatory arthritis models rather than OA [125, 126].
	Subchondral Bone	*BMAL1*-centered clock activity coordinates osteoblast-osteoclast balance; *CLOCK* is presumed to participate in the same transcriptional program [127].	Loss of *BMAL1* impairs bone mass and microarchitecture, whereas direct *CLOCK*-specific subchondral OA data remain sparse [124, 130].
PER/CRY (CRY-stronger evidence)	Cartilage	*CRY2* has the clearest evidence for maintaining cartilage clock output and ECM homeostasis, while *PER2* appears to support rhythmic matrix synthesis and *PER1* may modulate inflammatory responsiveness [11, 123, 131].	*CRY2* downregulation and inflammation-associated *PER* dysregulation are linked to enhanced catabolic signaling, but *PER*-specific causal evidence in human OA is limited [11, 123, 188].
	Synovium	*PER2*- and *CRY*-linked circadian programs appear to restrain synovial inflammatory tone, although most data come from RA or other inflammatory models [132, 133].	TNF-α/LPS-mediated *PER2* suppression and *CRY* deficiency enhance inflammatory signaling, but OA-specific validation remains incomplete [133-135].
	Subchondral Bone	*PER2* helps time osteoblast activity, whereas *CRY1/CRY2* regulate osteogenesis and resorption-related signaling [136-138].	Disruption of *PER/CRY* expression alters bone turnover rhythms; however, subchondral bone-specific OA models remain limited, and the relative

contributions of *PER* versus *CRY* are not fully resolved [136-139].

BMAL1:Brain and Muscle ARNT-Like 1; CCL2: C-C Motif Chemokine Ligand 2; CLOCK: Circadian locomoter output cycles protein kaput; CRY: Cryptochrome; ECM: Extracellular Matrix; FLS: Fibroblast-Like Synoviocyte; IL-6: Interleukin-6; LPS: Lipopolysaccharide; MMP: Matrix Metalloproteinase; OA: Osteoarthritis; PER: Period; RA: Rheumatoid Arthritis; TNF-α: Tumor Necrosis Factor-α.

4. Combined Effects and Risk Factors of OA on Circadian Rhythms

With increasing insight into circadian regulation across organs and tissues, clinical and epidemiological studies suggest that OA not only is influenced by circadian biology but also perturbs it [140]. Figure 2 summarizes this bidirectional framework: joint tissue inflammation and remodeling feed back into sleep, activity, and metabolic rhythms, which in turn shape OA symptom burden and possibly progression. The following sections focus on these behavioral manifestations rather than repeating tissue-level mechanisms.

4.1 Risk Factors Linking OA to Circadian Disorder

OA is a multifactorial chronic joint disease influenced by several systemic risk factors. These factors not only impair joint homeostasis but may also disrupt circadian regulation, thereby indirectly contributing to OA progression. Aging is one of the strongest risk factors for OA. Age-related cellular senescence, reduced cartilage repair capacity, mitochondrial dysfunction, and chronic low-grade inflammation all contribute to increased OA susceptibility [141]. At the same time, circadian rhythmicity gradually deteriorates with aging. Older adults often exhibit advanced sleep–wake timing, reduced adaptability to environmental light changes, and fragmented sleep patterns [142]. Thus, aging may create a background in which both joint resilience and circadian stability are reduced.

Obesity is another major risk factor for OA. The lifetime risk of knee OA is approximately 60% higher in obese individuals than in those with a body mass index (BMI) below 25 [143]. In addition to increased mechanical loading, obesity is associated with chronic inflammation and metabolic dysfunction that disturb cartilage homeostasis. Emerging evidence also links obesity with circadian disruption. High-fat diets can alter circadian rhythms in animal models, and obesity-related changes in gut microbiota composition may influence host circadian regulation through microbial metabolites [144, 145]. Together, these findings indicate a bidirectional relationship between obesity and circadian disruption, suggesting that optimizing circadian timing of diet and lifestyle may offer new approaches for OA prevention and management. Ultimately, the intersection of aging and obesity creates a permissive environment for both joint degeneration and clock impairment, leading to the diverse behavioral and physiological rhythm disturbances frequently observed in clinical OA populations. This perspective is important because it reframes behavioral rhythm disruption in OA as more than a secondary quality-of-life issue. Rather, OA often develops in individuals who are already vulnerable to clock instability, and the disease may then amplify that vulnerability over time.

4.2 Epidemiological Evidence Linking Osteoarthritis with Disrupted Behavioral Circadian Rhythms

Epidemiological studies indicate that OA is frequently accompanied by disturbances in behavioral circadian rhythms, particularly in sleep–wake and activity–rest cycles. Sleep disorders are highly prevalent among OA patients, with 60–80% of middle-aged and older adults reporting difficulties such as sleep initiation problems, frequent awakenings, early morning awakening, and reduced sleep quality [146]. Data from the Johnston County OA Study further showed high rates of difficulty maintaining sleep (81%), early awakening (51%), and sleep initiation problems (31%), which were significantly associated with fatigue, daytime impairment, increased use of sleep medication, and fragmented sleep architecture [147, 148]. OA is also linked to altered daily activity rhythms. Cross-national analyses found that older adults with knee OA had significantly lower total daily activity than non-OA controls (62.9 vs 81.5 min/day, $p = 0.015$), mainly due to reduced daytime baseline activity [149]. Wearable monitoring studies suggest that early OA is characterized by slower walking speed and increased gait variability later in the day, while meta-analytic evidence indicates that pain flares occurring 1–2 hours after peak activity often lead to declining afternoon and evening activity, forming a pattern of relatively active mornings followed by reduced activity later in the day [150]. These observations suggest not only reduced activity volume, but also altered temporal distribution of activity across the day. Although direct epidemiological evidence on eating–fasting rhythms in OA remains limited, circadian nutrition research indicates that meal timing, frequency, and intermittent fasting influence metabolic regulation and inflammation, factors closely linked to OA development and progression [151]. Collectively, these findings suggest that OA is associated with multidimensional disruptions of daily behavioral

rhythms that may contribute to functional decline and disease progression.

4.3 The Interplay between OA and Sleep–Wake Cycles

The sleep–wake rhythm undergoes substantial changes across the lifespan and is closely linked to biological aging. Mechanisms underlying sleep disruption in OA are multifactorial, involving circadian regulatory pathways, neuroimmune interactions, and psychosocial factors. Nocturnal pain is a key driver of insomnia: inflammatory responses and tissue stress intensify after daytime loading and are amplified at night due to posture and hemodynamic changes, resulting in prolonged sleep latency and frequent awakenings. Up to 75% of individuals with hip or knee OA experience nocturnal pain, with severity correlating with sleep impairment [152]. OA progression features increased IL-6 and TNF-α expression, sensitizing afferent neurons, enhancing N-Methyl-D-aspartate receptor activity, and activating central glia, thereby amplifying nociception and destabilizing sleep regulation [153]. Chronic nociceptive input induces central sensitization, heightening pain responses and reinforcing the cycle of pain and insomnia. In this sense, sleep disturbance in OA should not be viewed only as a parallel symptom; it may also become part of the mechanism by which symptom burden is maintained. Recent cohort studies further indicate a significantly elevated risk of obstructive sleep apnea (OSA) in OA patients, with a reported 45% higher incidence after adjusting for age, sex, and BMI. Potential contributors include shared risk factors (e.g., obesity, metabolic syndrome), chronic low-grade inflammation promoting upper airway edema, opioid-induced respiratory suppression, and pain-related decreases in nocturnal postural shifts, which increase airway collapsibility. These findings suggest that circadian disruption in OA results from the combined effects of pain, inflammation, medications, comorbidities, and psychosocial determinants [154], with severe disturbances predisposing patients to OSA. The available evidence remains largely observational, so caution is still needed when inferring directionality or mechanism.

4.4 The Interplay between OA and Eating–Fasting Cycles

The feeding–fasting cycle reflects the daily rhythm of food intake. In clinical settings, chronic pain, limited mobility, and reduced quality of life in OA often lead to depression or anxiety, which disrupts appetite regulation and contributes to irregular feeding behaviours. Patients may exhibit reduced food intake or emotional overeating, commonly accompanied by late-night eating, skipped breakfast, and sleep deficiency factors highly prevalent in OA [155]. Disturbed sleep–wake rhythms may alter ghrelin and leptin secretion, potentially promoting nocturnal eating or delayed meals, a hypothesis requiring targeted validation in OA cohorts. Obesity and metabolic syndrome, prevalent comorbidities of OA, are intrinsically tied to meal timing disturbances. Individuals with these conditions often display evening-dominant eating patterns and nighttime snacking. Reduced insulin sensitivity, leptin resistance, and abnormal ghrelin secretion impair satiety and enhance nocturnal hunger, encouraging intake of high-calorie foods [156]. In OA patients with these comorbidities, pain, inactivity, inflammation, and metabolic dysfunction may synergistically worsen feeding rhythm disturbances, promoting weight gain, glycaemic variability, and dyslipidaemia. Excess caloric intake drives fat accumulation, increasing mechanical joint loading and enhancing systemic and local inflammation through adipokines such as IL-6 and TNF-α, thereby accelerating cartilage degeneration and synovitis [157]. It states that OA likely interacts with eating-fasting dysregulation through shared behavioral and metabolic pathways, suggesting that optimizing meal timing may complement OA management. Within the current evidence hierarchy, feeding rhythm disturbance should be regarded as an important but still emerging component of the bidirectional OA-circadian framework.

4.5 The Interplay between OA and Activity–Rest Cycles

Daily physical activity follows a circadian rhythm characterized by higher daytime activity and nighttime rest. As a major cause of disability in older adults, OA disrupts physical function and rest-activity rhythms. Core OA symptoms, including pain and morning stiffness, not only reduce motivation for activity but also reshape its temporal distribution. Pain frequently worsens at night, fragmenting sleep and increasing awakenings, resulting in daytime sleepiness and cognitive fatigue that further destabilize rest patterns [158]. Impaired nocturnal recovery reduces muscle responsiveness and exercise tolerance, thereby lowering daytime activity amplitude. Joint dysfunction further contributes to rhythm disruption; reduced range of motion, antalgic gait, and lower limb weakness elevate mechanical and metabolic effort, prompting shorter, more frequent, low-intensity activity bouts. This fragmentation undermines rhythm stability [159]. From a circadian perspective, this means that OA may flatten and destabilize the rest-activity rhythm, not merely reduce step count or total activity volume. This framing is clinically useful because it links functional impairment to temporal organization. It suggests that OA

may progressively erode the regularity, amplitude, and timing of activity-rest cycles, which may in turn worsen fatigue, deconditioning, and symptom perception. However, more longitudinal and wearable-based studies are needed to determine whether they independently contribute to disease burden and treatment response

In summary, OA extends beyond localized joint degeneration and contributes to systemic circadian disruption. Such disturbances aggravate pain, fatigue, and mood symptoms, while dysregulated endocrine, immune, and metabolic rhythms may accelerate disease progression. Incorporating a circadian perspective and developing rhythm-targeted interventions may open new pathways to improve outcomes and guide comprehensive OA management. Current human evidence is most compelling at the level of symptom burden and behavioral rhythm disturbance, whereas future progress will depend on determining which aspects of this loop are measurable, modifiable, and therapeutically actionable.

5. Clinical Evidence and Translational Implications

5.1 Human and Clinical Evidence

Human evidence in this field currently centers on sleep disturbance, altered activity-rest patterns, obesity-related circadian disruption, and comorbid obstructive sleep apnea in OA cohorts [146-154]. The overall signal is clinically relevant but methodologically uneven: most studies are cross-sectional or observational, rely on self-reported sleep or actigraphy, and remain vulnerable to confounding by age, obesity, analgesic use, depression, and reduced mobility. Accordingly, the strongest conclusion at present is that circadian and sleep disruption are associated with OA symptoms and functional burden; whether they independently initiate OA, accelerate structural progression, or mainly reflect symptomatic disease remains unresolved.

5.2 Therapeutic Implications

Current therapeutic implications should be interpreted with appropriate caution. In OA, the most immediate clinical relevance of circadian biology is not yet proven disease modification, but the possibility that rhythm-informed management may help reduce symptoms, improve daily functioning, and optimize behavioral interventions. At present, the strongest human rationale is therefore pragmatic rather than definitive: interventions that improve sleep, regularize daily behaviors, or reduce pain may indirectly lessen the burden of circadian disruption, even when their precise circadian mechanisms remain incompletely understood.

Among these approaches, sleep-focused management is supported by the clearest clinical logic. Improving sleep quality and alleviating pain exert mutually reinforcing effects in the management of OA. Studies have demonstrated that a night of restorative sleep can reduce pain intensity and fatigue on the following day. Cognitive behavioral therapy for insomnia (CBT-I) has shown significant efficacy in patients with OA and comorbid insomnia, not only improving sleep quality but also reducing pain catastrophizing and enhancing functional outcomes [160]. These benefits are clinically meaningful, although they should be interpreted primarily as symptom-oriented gains rather than as evidence that CBT-I directly modifies OA structure or progression. Therefore, incorporating sleep-focused interventions such as CBT-I into multimodal OA management, together with exercise therapy, weight control, and appropriate pharmacological or intra-articular treatments, may effectively reduce pain, improve daily functioning and quality of life, and decrease long-term reliance on systemic analgesics [161].

With respect to circadian-aligned dietary strategies, accumulating evidence suggests that energy-restricted diets provide substantial benefits for pain relief, joint function, and body weight management in patients with OA. In overweight or obese individuals with OA, combining a low-energy diet with endurance and resistance training has been shown to reduce pain, improve functional outcomes, and lower inflammatory biomarkers, while preserving lean body mass [162]. An 18-month clinical trial demonstrated that weight loss of ≥10% resulted in an approximately 50% reduction in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score and was accompanied by decreased levels of C-reactive protein (CRP) [163]. In addition, anti-inflammatory dietary patterns, such as the Mediterranean diet (MD), have demonstrated therapeutic potential. Rich in antioxidant and anti-inflammatory components, the MD may slow the progression of OA. Notably, even in the absence of explicit caloric restriction, a 12-week MD intervention has been reported to reduce pain by approximately 30% and improve physical performance in patients with OA [164]. However, these benefits are securely interpreted through weight reduction, metabolic improvement, and inflammatory modulation. Circadian-aligned nutritional strategies remain promising, but the extent to which meal timing or dietary phase interventions provide OA-specific advantages beyond established dietary care still requires direct testing.

Evidence suggests that regular aerobic exercise, such as cycling and circuit training, can significantly reduce pain while improving functional capacity and quality of life [165]. Flexibility-focused activities, including yoga

and stretching, may alleviate joint stiffness and enhance functional performance, whereas aquatic exercise is particularly beneficial for overweight individuals because it reduces mechanical loading on joints [166]. At the molecular level, regular moderate exercise may delay OA progression by inhibiting chondrocyte apoptosis, reducing pro-inflammatory cytokines such as TNF-α and IL-1β, and promoting extracellular matrix synthesis [167]. Although exercise timing is increasingly discussed in circadian medicine, direct evidence in OA remains insufficient to conclude that phase-matched exercise is superior to well-implemented untimed exercise. At present, the stronger recommendation is for consistent, sustainable physical activity, while the question of optimal timing should be regarded as a high-priority research issue rather than an established clinical rule.

Therapeutic approaches targeting circadian rhythms are emerging as a promising direction for OA management. Increasing evidence suggests that circadian rhythm disruption is an important contributor to OA pathogenesis, and circadian-based therapeutic strategies have therefore been proposed. These include optimizing the timing of pharmacological interventions, such as aligning the administration of nonsteroidal anti-inflammatory drugs (NSAIDs) or intra-articular corticosteroids with the circadian peaks of inflammation and pain, to enhance therapeutic efficacy while minimizing adverse effects [168, 169]. In addition, interventions such as controlled light exposure, time-restricted feeding, and exercise programs scheduled to individual circadian rhythms have shown potential to improve sleep quality, reduce inflammation, and disrupt the vicious cycle between pain and sleep disturbance [170, 171]. Emerging bioengineering and molecular strategies, including delivery systems for melatonin or SIRT1 agonists, gene therapy, and immunomodulatory approaches, may further enable direct targeting of circadian mechanisms involved in OA pathophysiology [172]. At present, however, these approaches remain exploratory and are far from routine clinical application. Their value lies less in immediate therapeutic readiness than in helping define whether circadian biology represents a tractable intervention axis in specific OA subgroups.

Collectively, these approaches support circadian alignment as a promising adjunct to OA care. At present, however, the strongest clinical rationale is symptom modulation and behavioral optimization rather than proven disease modification. Rhythm-informed management offers a plausible systems-level framework that now warrants more rigorous mechanistic and clinical validation.

6. Critical Appraisal and Future Directions

6.1 Evidence Hierarchy and Limitations

The literature is heterogeneous. Mechanistic causality is strongest in cell systems and genetically manipulated animal models, whereas human data mainly support association rather than direct causation. Several recurrent sources of uncertainty should be stated explicitly: confounding by age, obesity, pain severity, multimorbidity, and medication use; reverse causation, whereby OA symptoms themselves disrupt sleep and daily rhythms; extrapolation from rheumatoid arthritis, osteoporosis, or systemic circadian biology to OA-specific tissues; and limited temporal sampling, which makes true phase or amplitude changes difficult to distinguish from static group differences. These limitations do not negate the biological plausibility of circadian involvement in OA, but they substantially constrain the extent to which current therapeutic claims can be generalized.

6.2 Technological Innovations and Methodological Advances

Technological advances matter to OA circadian research mainly because they can reveal when, not just whether, joint pathways are dysregulated. One of the major historical barriers in this field has been the difficulty of capturing temporal biology in tissues that are hard to sample repeatedly and in patients whose symptoms are influenced by multiple behavioral and metabolic confounders. Temporal multi-omics, spatial profiling, and human-derived chondrocyte or organoid models can identify whether rhythm dampening or phase shift accompanies key transitions in cartilage, synovium, or subchondral bone [173, 174].

For clinical translation, the most relevant advances are those that make circadian status measurable in a feasible and patient-centered way. Wearables, simplified endocrine phase markers, digital symptom tracking, and time-aware trial designs may allow investigators to define chronotype, symptom timing, behavioral regularity, and candidate treatment windows more precisely [175-178]. Importantly, these approaches do not solve all current limitations, but they do make it increasingly realistic to test questions that were previously difficult to address, link it to joint symptoms or inflammatory activity, and test whether timed behavioral or pharmacologic interventions outperform untimed care.

6.3 Biomarker Discovery

Biomarker discovery in OA circadian medicine should prioritize three questions: can a marker capture phase,

does it relate to clinically meaningful OA states, and is it feasible in routine practice?

The most immediately usable candidates are low-burden measures such as sleep regularity, activity timing, HRV, and symptom diaries, ideally interpreted alongside simple endocrine phase markers such as melatonin or morning-evening cortisol [179]. More complex blood, synovial fluid, or imaging readouts may later refine the signal by linking circadian phase to inflammation, metabolism, cartilage hydration, or subchondral perfusion, but these approaches still require repeated sampling and careful phase anchoring rather than single time-point comparisons.

Accordingly, future cohorts should stratify participants by chronotype, sleep regularity, and irregular schedules such as shift work, then test whether a composite circadian risk score improves prediction of pain flares, progression, or treatment response beyond standard OA variables [179, 180]. Such biomarkers will matter most if they also guide action, for example by helping time NSAIDs, exercise, rehabilitation, or meal scheduling. This keeps biomarker development tied to clinical decision-making rather than to technology accumulation alone.

6.4 Testable Hypotheses and Prioritized Research Agenda

Four testable hypotheses follow from the current framework. First, persistent circadian misalignment predicts incident OA and faster structural progression, independent of obesity and physical inactivity. Second, tissue-specific clock disruption will define biologically distinct OA endotypes, particularly inflammatory-synovial versus remodeling-dominant osteochondral phenotypes. Third, phase-matched interventions such as timed exercise, sleep-targeted therapy, meal-timing optimization, or time-adjusted drug delivery will outperform equivalent untimed interventions for pain and function. Fourth, integrating wearable-derived rhythm metrics with endocrine and molecular phase markers will improve the prediction of flare risk and treatment response. On this basis, the immediate research priority is not to assume therapeutic efficacy, but to build the evidence needed to evaluate it rigorously. The field would particularly benefit from longitudinal, phase-anchored human cohorts linked to mechanistic tissue studies and randomized timing trials. Such work could help distinguish which observed clinical benefits reflect general symptom management, which are truly related to circadian alignment, and which patient subgroups are most likely to benefit from rhythm-informed care.

7. Conclusion

Overall, OA should be considered not merely as a degenerative joint disorder influenced by circadian factors, but more conceptually as a time-structured disease in which symptom fluctuation, tissue susceptibility, and metabolic-inflammatory states may be organized, at least in part, in a temporal manner. Although definitive causal inference in humans remains limited, accumulating experimental and clinical data support the biological and translational relevance of circadian disruption. The clear mechanistic support currently centered on *BMAL1 a*nd broader clock dysregulation. This perspective provides a unifying framework that links molecular mechanisms, whole-joint pathology, and clinical heterogeneity. The most important next step is to move from static descriptions to phase-informed longitudinal studies and intervention trials. If validated, circadian profiling and timing-based management could add a practical systems-level dimension to OA prevention, symptom control, and disease stratification.

Author Contributions

Conception and design: HX, XM, XF, QL; Collection and assembly of data: HX, XM, XF, YC, YW; Drafting of the article: HX, XM, XF, AS; Critical revision of the article for important intellectual content: All authors; Funding acquisition: XF, XM, QL, AS, and XW; All authors take responsibility for the integrity of the paper.

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Conflicts of Interest

The authors declare that no commercial or financial interests existed that could be interpreted as a potential conflict of interest while conducting this research.

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