The Influence of Circadian Rhythms on Joint Health

Saim Mahmood Khan, MBBS; Maryam Zehra, MBBS; Shaikh Saadi, MBBS; Surraiya Riaz Mahmood Khan, PharmD; Jawairya Muhammad Hussain, MBBS

Joint health is a critical component of physical well-being and mobility. Key factors that influence joint health include sufficient formation of synovial fluid, regulated cartilage metabolism, and control of inflammatory agents. Recent studies reveal that circadian rhythms—biological clocks within the body—play a significant role in regulating clock genes, hormone synthesis, cell repair, and inflammation—all of which support joint health.[1] These determinants share a synergistic relationship with hormones such as cortisol and melatonin, which act as antiinflammatory agents and facilitate optimal joint function in patients with joint pathologies.[2-3] Furthermore, these hormones are also strongly influenced by circadian rhythms, as their concentrations vary throughout the day and night in response to the biological clock.[2-4] Here we explore the coordination between circadian rhythms and joint health to inform targeted, innovative approaches for treating joint diseases. Although existing literature indicates that circadian rhythms affect joint stability and lubrication, circadian-based interventions are lacking.

Circadian rhythm, governed by clock genes such as brain and muscle ARNT-like protein 1 (*BMAL1*), period 1 and 2 (PER1/2), and cryptochrome circadian regulator 1 and 2 (CRY1/2), modulates key pathways for cartilage homeostasis, including extracellular matrix (ECM) remodeling. Several recent investigations indicate that ECM composition and distribution are regulated by circadian rhythms.[5] This includes the activity of enzymes such as a disintegrin and metalloproteinase with thrombospondin motifs 4 and 5 (ADAMTS4/5), which degrade aggrecan, a cartilage matrix component, and matrix metalloproteinases (MMPs), which primarily degrade type II collagen. These enzymes maintain ECM turnover and cartilage integrity, ultimately influencing joint lubricant production.6 Mechanical loading and osmotic changes also follow circadian patterns, further supporting the hypothesis that circadian rhythms influence joint health. Research also has shown that lubrication peaks during increased exercise, emphasizing the importance of proper joint care at optimal times of day. Sustained or intermittent loading can cause degenerative changes, including joint degradation and inflammation.[7]

> Circadian rhythms...play a significant role in regulating clock genes, hormone synthesis, cell repair, and inflammation—all of which support joint health.

Circadian rhythms regulate numerous biological functions over a 24-hour cycle, including hormonal secretion. Cortisol, released in response to stress, peaks in the morning and decreases throughout the day. Melatonin, secreted at night, improves cartilage and reduces oxidative stress in tissues. Both of these hormones positively influence synovial fluid production.[8,9] A cohort study of diurnal cortisol production found that patients with rheumatoid arthritis (RA) exhibit different cortisol release patterns compared to healthy controls; reduced morning cortisol correlates with higher disease activity, highlighting its clinical impact.[8] Adequate cortisol levels maintain synovial fluid viscosity and lubrication, while melatonin supports synovial membrane integrity.[9] Clock genes regulate circadian rhythms and have been shown to affect health by influencing synovial fluid production and cartilage repair.

Recent findings highlight the importance of *BMAL1*, which plays a key role in regulating interstitial cells—particularly fibroblast-like synovial cells (FLS) and chondrocyte development.[4] Other studies have shown that normal expression of PER 1 supports cartilage homeostasis and reduces risk of inflammation.[10] *CRY1* and *CRY2* also maintain cartilage integrity; their inhibition has been shown to improve osteoarthritis (OA).[11] Other circadian clock-regulated enzymes, such as ADAMTS4/5 and MMP14, influence ECM remodeling by balancing carti-

Author Affiliations: Karachi Medical and Dental College, Karachi, Pakistan (SM Khan, Hussain); Jinnah Sindh Medical University, Karachi, Pakistan (Zehra); Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan (Saadi); Sohail University, Karachi, Pakistan (SRM Khan).

Corresponding Author: Saim Mahmood Khan, MBBS, Karachi Medical and Dental College, M block of North Nazimabad Karachi, 74600, Pakistan, email saimmahmoodkhanrajput@gmail.com; ORCID ID 0009-0001-6023-5835

lage breakdown and repair, respectively, resulting in rhythmic variation in joint lubrication.[12] These insights underscore the broader implications of circadian regulation in joint diseases, supported by evidence from animal studies.

Several recent studies have explored the complex interplay between circadian rhythms and joint-related diseases, particularly OA. One study identified two genes—*PFKFB4* and *DDIT4*—with expression patterns linked to circadian regulation and knee osteoarthritis (KOA) development. These genes govern a variety of cellular processes, immune modulation, and tissue repair, enhancing our understanding of KOA pathophysiology—especially in aging populations more prone to joint diseases due to aging and altered circadian rhythms. They also serve as potential biomarkers for early diagnosis and targeted, timed interventions. Additional research into circadian rhythm therapies should focus on treatment options for joint conditions that affect older patients.[13]

Animal studies and clinical trials support the association between circadian clocks and joint health. *BMAL1* knockout models in mice demonstrated joint destruction and increased inflammation.[4] Similarly, the deletion of CRY 1/2 in models promoted OA development.[11] These findings suggest that clock genes may be therapeutic targets in joint disease. Furthermore, synovial fluid viscosity and lubrication peak in the morning, consistent with clinical manifestations of morning stiffness in individuals with OA. Circadian rhythms also influence inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which peak from midnight to early morning and are associated with morning stiffness in RA.[14] This disruption affects joint lubrication and increases wear and tear, emphasizing the importance of treatment timing due to hormonal and cytokine fluctuations throughout the day.

Other studies on circadian rhythm therapies for joint diseases have primarily used animal models, showing promising outcomes. Research on moxibustion treatment at various times of day demonstrated regulation of Clock and *BMAL1* gene expression in synovial tissue, reducing inflammation and pyroptosis (programmed cell death with inflammation).[15] While animal experiments suggest circadian therapies may be effective, human studies are limited. Clinical trials on chrono-moxibustion, a therapy timed with the body's circadian rhythm, are underway to evaluate its impact on RA outcomes.[16] However, insufficient human data on circadian-based RA treatments presents challenges for clinical application. Additional research is needed to bridge finding from animal models to human trials.

Chronotherapy, which aligns treatment with the body's circadian clock, offers an effective strategy for improving outcomes in joint diseases.[17,18] For example, two randomized controlled trials found that administering prednisone at midnight was more effective in reducing joint stiffness than morning administration.[17] This timing reduces IL-6 and other pro-inflammatory cytokines that accumulate overnight and contribute to morning stiffness in RA.[17] Similarly, teriparatide, a recombinant parathyroid hormone used in postmenopausal osteoporosis, is more effective when administered in the morning, as it reduces C-terminal telopeptide (CTX) levels, promoting bone formation and enhancing bone mineral density.[18] Circadian rhythms also affect the oral bioavailability of bisphosphonates, standard osteoporosis treatments, due to diurnal variation in intestinal activity.[18]

Circadian rhythms influence joint health primarily through clock genes that regulate synovial fluid production and cartilage integrity, enhancing joint lubrication and mobility. Inhibition of CRY 1/2 promotes OA, further highlighting their role in joint disease.[11] The connection between circadian rhythms and joint health presents opportunities for chronotherapeutic interventions and targeted treatments.[17,18] However, existing literature on this topic lacks longitudinal studies on circadian rhythm-based treatments in joint disorders. Thus, randomized controlled trials to clarify the direct role of circadian rhythms in the progression and prognosis of joint diseases such as RA and OA are needed.

Funding/Support: None declared.

Financial Disclosures: None declared.

REFERENCES

1. Kulkarni A, Demory-Beckler M, Kesselman MM. The role of clock genes in maintaining circadian rhythm and rheumatoid arthritis pathophysiology. *Cureus*. 2023;15(5):e39104. doi:10.7759/cureus.39104

2. Macfarlane E, Seibel MJ, Zhou H. Arthritis and the role of endogenous glucocorticoids. *Bone Res*. 2020;8:33. doi:10.1038/s41413-020-00112-2

3. Lu KH, Lu PW, Lu EW, et al. The potential remedy of melatonin on osteoarthritis. *J Pineal Res*. 2021;71(3):e12762. doi:10.1111/jpi.12762

4. Chen G, Zhao H, Ma S, et al. Circadian rhythm protein Bmal1 modulates cartilage gene expression in temporomandibular joint osteoarthritis via the MAPK/ERK pathway. *Front Pharmacol*. 2020;11:527744. doi:10.3389/fphar.2020.527744

5. Dudek M, Swift J, Meng QJ. The circadian clock and extracellular matrix homeostasis in aging and age-related diseases. *Am J Physiol Cell Physiol*. 2023;325(1):C52-C59. doi:10.1152/ajpcell.00122.2023

6. Li Y, Yuan Z, Yang H, Zhong H, Peng W, Xie R. Recent advances in understanding the role of cartilage lubrication in osteoarthritis. *Molecules*. 2021;26(20):6122. doi:10.3390/molecules26206122

7. Roggio F, Petrigna L, Trovato B, Di Rosa M, Musumeci G. The role of lubricin, irisin and exercise in the prevention and treatment of osteoarthritis. *Int J Mol Sci*. 2023;24(6):5126. doi:10.3390/ijms24065126

8. Yavropoulou MP, Filippa MG, Vlachogiannis NI, et al. Diurnal production of cortisol and prediction of treatment response in rheumatoid arthritis: a 6-month, real-life prospective cohort study. *RMD Open*. 2024;10(1):e003575. doi:10.1136/rmdopen-2023-003575

9. Lu X, Yu S, Chen G, et al. Insight into the roles of melatonin in bone tissue and bone related diseases (Review). *Int J Mol Med*. 2021;47(5):82. doi:10.3892/ijmm.2021.4915

10. Wei JM, Tu SQ, Wang YX, et al. Clock gene Per1 regulates rat temporomandibular osteoarthritis through NF-κB pathway: an in vitro and in vivo study. *J Orthop Surg Res*. 2023;18(1):817. doi:10.1186/s13018-023-04301-7

11. Bekki H, Duffy T, Okubo N, et al. Suppression of circadian clock protein cryptochrome 2 promotes osteoarthritis. *Osteoarthritis Cartilage*. 2020;28(7):966-976. doi:10.1016/j.joca.2020.04.004

12. Pérez-García S, Carrión M, Gutiérrez-Cañas I, et al. Profile of matrix-remodeling proteinases in osteoarthritis: impact of fibronectin. *Cells*. 2019;9(1):40. doi:10.3390/cells9010040

13. Li H, Yang Y, Li B, et al. Comprehensive analysis reveals the potential diagnostic value of biomarkers associated with aging and circadian rhythm in knee osteoarthritis. *Orthop Surg*. 2025;17(3):922-938. doi:10.1111/os.14370

14. Lee Y. Circadian rhythms and the treatment of rheumatoid arthritis. *Arch Rheumatol Arthritis Res*. 2021;1(3). doi:10.33552/arar.2021.01.000515 15. Mingfang Y, Bailu C, Xinling H, Aiyang W, Xiao W. Effects of chrono-moxibustion on core clock genes Clock, Bmal1 and pyroptosis in rats with rheumatoid arthritis. *Chin J Tissue Eng Res*. 2022;26(35):5700-5706. doi:10.12307/2022.939

16. Yu M, Yang S, Chen B, et al. Effect of chrono-moxibustion and its influence on circadian rhythm for rheumatoid arthritis: a study protocol for a randomized controlled trial. *Medicine (Baltimore)*. 2022;101(38):e30701. doi:10.1097/MD.0000000000030701

17. Kikyo N. Circadian regulation of macrophages and osteoclasts in rheumatoid arthritis. *Int J Mol Sci*. 2023;24(15):12307. doi:10.3390/ijms241512307

18. Winter EM, Kooijman S, Appelman-Dijkstra NM, Meijer OC, Rensen PC, Schilperoort M. Chronobiology and chronotherapy of osteoporosis. *JBMR Plus*. 2021;5(10):e10504. doi:10.1002/jbm4.10504

advancing the art & science of medicine in the midwest

WMJ

WMJ (ISSN 2379-3961) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

Visit www.wmjonline.org to learn more.