

Melatonin and Osteoarthritis: An Overlooked Mediator?

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Abstract

Introduction: Osteoarthritis, a prevalent chronic disabling disease, is also an independent risk factor for COVID-19 infections among the elderly.

Aim: To examine what is known about the endocrine hormone melatonin and its possible utility for intervening in the osteoarthritis disability cycle, potentially heightened in the context of COVID-19 and its persistence and restrictions.

Methods: The PUBMED electronic data base was searched in its entirety, from 1992 - 2021 using the key terms: melatonin and osteoarthritis.

Results: Very few clinical studies on this topic prevail, even though almost all preclinical studies imply a favorable role for melatonin in enhancing osteoarthritis pathology, as well as COVID-19 immunity. Conversely, a deficit in melatonin appears associated with many features of osteoarthritis pathology, as well as its extra-articular symptoms, such as impaired sleep.

Conclusion: Melatonin has potent antioxidant, analgesic, regenerative, and anti-inflammatory properties that should be studied further in the context of efforts to improve the outlook for many older osteoarthritis sufferers, especially those residing in the community, and affected by the COVID-19 pandemic lockdown restrictions.

Keywords: Articular Cartilage; Bone; COVID-19; Inflammation; Melatonin; Osteoarthritis; Pain; Prevention

Introduction

Osteoarthritis, a chronic disabling joint disease predominantly affecting older adults is strongly associated with inflammation, various degrees of bone pathology, as well as articular cartilage attrition. In addition, pathological as well as physiological changes of the surrounding muscles and soft tissues of one or more commonly affected freely moving joints such as the knee joint are common [1,2], as are significant accompanying symptoms of depression, oftentimes intractable pain, sleep problems, anxiety, and multiple functional limitations, that are not only highly limiting, but may predispose to the risk of COVID-19 due to associated factors of fatigue, weakness and oftentimes accompanying chronic health conditions and obesity that appear to be significantly heightened in the face of COVID-19 pandemic restrictions [3,4].

Although not well studied, in this context, the neuro endocrine hormone melatonin produced in the pineal gland and certain peripheral cells, including those of the immune system [5] and that can be released into the bloodstream and thereby to internal neural and other structures especially during sleep may have therapeutic implications for multiple diseases, including osteoarthritis as well as COVID-19 [6]. A compound that is not only produced endogenously, but can be administered orally, as capsules, tablets or liquids, sublingually, or as transdermal patches [7], as well as in the form of a dietary nutrient, injection, as a topical cream, or via intravenously, intrathecal or intraperitoneal approaches, melatonin has been shown to have multiple physiological benefits in cases where its deficiency is apparent [8].

In particular, among its many physiological roles, melatonin has been shown to be a potent antioxidant with significant analgesic and antinociceptive and inflammatory properties [9-12] that is of high relevance in the context of aging, where inflammation may be rife. In addition, melatonin may favorably impact aging muscle and strength capacity [13], as well metabolic health, depression, blood pressure, sleep, COVID-19 and multiple rheumatological disease processes [11-13]. As well, melatonin reportedly stimulates cartilage matrix synthesis, thus may prove extremely helpful in mitigating osteoarthritis disease progression and disability, at a time when osteoarthritis surgery is on hold in many instances, but where more pain has been identified [3]. It can also influence immune and bone health [5,8,12] and have a protective effect on the synovial membrane [14].

As such, melatonin may thus prove of high value not only in explaining some manifestations of osteoarthritis pathology, but as an effective adjunctive intervention for purposes of averting both excess osteoarthritis disability, as well as fostering cartilage reparative processes. As well, melatonin has a strong influence on those chronic diseases that are strongly associated with osteoarthritis, such as diabetes and obesity [15].

The risk of COVID-19 may be lower as well, if osteoarthritis cases are not excessively weakened by lockdowns and their ramifications, given that a deficit in melatonin alone that often occurs in aging adults, may also heighten the risk of weakness among older adults, as well as COVID-19 risk, especially among older community dwelling elderly adults during this ongoing pandemic period.

Review Aims

In recognition of the role that might be played by melatonin in both the underlying pathology of osteoarthritis and its resolution, this mini review aimed to examine the degree of support for considering a role for melatonin in the context of efforts to minimize osteoarthritis disability as well as COVID-19 risk among older home bound community dwelling adults in the context of the coronavirus epidemic that began in December 2019.

Methods

A comprehensive examination of the present topic of interest was undertaken using the PUBMED electronic data base. This data base was selected due to its high volume of sound peer reviewed works and was hence searched for relevant peer reviewed full-length articles documented over the entire publication period of January 1, 1992 - April 30 2021. In addition, reference lists were reviewed, and materials were downloaded, as indicated. The key words applied independently or simultaneously were articular cartilage, osteoarthritis, melatonin, pain, inflammation and COVID-19. All types of research as well as reviews were deemed acceptable. Excluded were largely those studies that focused solely on rheumatoid arthritis, were incomplete studies, or preprints.

After examining potential articles, those that were salient were selected and reviewed in detail. The diverse nature of the data and its very limited focus on any one issue precluded anything but a very limited descriptive report of some key observations.

The facts as presented are also possibly limited by the nature of the experimental models employed to study melatonin effects in the laboratory, but the detailed molecular pathways are not included. Readers can refer to Lu., *et al.* [16] for an apt summary here.

Results

After a dedicated electronic search, only 27 general articles on melatonin and osteoarthritis were found to be listed on PUBMED as of April 30, 2021, while 60 articles encompassing melatonin and cartilage were available. There were 605 articles linked to melatonin and pain, but almost none were directly relevant to osteoarthritis and melatonin in any obvious way. A dearth of clinical studies was clear, however as discussed by Lu., *et al* [16]. As well, Posadski., *et al.* [7] for example who studied 195 eligible publications on melatonin health effects and related topics, did not present any data specifically on osteoarthritis.

General observations: As outlined above, despite many past as well as present articles that report on melatonin and health in general, especially sleep health in several contexts, including rheumatoid arthritis where there are 74 listings, very few published studies mentioning any linkage to osteoarthritis, the most widespread chronic disease disabler among older adults are cited on the PUBMED data base, even when including all years available, or at least 30 years of publication time. However, in one of the earliest publications referring to the current topic of osteoarthritis, West and Oosthuizen [17] reported that melatonin, a hormone, and product of the pineal gland, and one that is structurally related to indomethacin, a derivative of methylated indole used successfully in patients suffering from certain chronic inflammatory conditions, such as rheumatoid might also be helpful in osteoarthritis. This led the authors to examine if melatonin also possesses anti-inflammatory properties, and even though osteoarthritis was not specifically studied, it appeared cases of rheumatoid arthritis, which can lead to osteoarthritis, tended to exhibit lower than normal melatonin levels. Of related significance was the report by Oskoi, *et al.* [18] who did find melatonin to also be reduced in a clinical sample of osteoarthritis cases. Hence, in both osteoarthritis and rheumatoid arthritis, it has been proposed that melatonin, linked to circadian rhythms, and clock gene mechanisms that mediate joint function may have a significant bearing on these diseases both directly or indirectly if levels are subnormal [19]. As well, melatonin, which may act as a free radical scavenger, with associated anti-inflammatory properties, as well as circadian timekeeping properties, may be expected to be implicated in both diseases. Melatonin is also shown to stimulate cartilage destruction/regeneration through direct/indirect modulation of the expression of the main circadian clock genes, such as BMAL, CRY and/or DEC2 [19] and may be helpful in attenuating sleep deficits and chronic pain [20-22]. According to Xie, *et al.* [23] melatonin can be produced by chondrocytes and many other tissues and organs in response to circulating exogenous melatonin and can upregulate melatonin receptor expression. Melatonin also regulates cartilage growth and maturation through melatonin receptor 1 (MTNR1A) and melatonin receptor 2 (MTNR1B), but may decline in effectiveness with aging [24]. It may thus render joints and body systems more susceptible to destruction if deficient, plus inflammation, as well as potentially impacting degenerative cartilage destruction, matrix synthesis and the expression of chondrogenic marker genes [10].

Meng, *et al.* [25] noted that melatonin can also possibly impact osteoarthritis severity and possibly its progression due to its additional apparent immunity boosting, and cardiovascular protection, plus anti-diabetic, anti-obesity, neuroprotective and anti-aging effects. One theory is that this process may be triggered by improper secretion of circadian clock-regulated hormones, such as melatonin, thyroid-stimulating hormone (TSH), or cortisol. The imbalance of these hormones alters the expression of pro-inflammatory cytokines and cartilage degenerative enzymes in articular cartilage, resulting in cartilage erosion, synovial inflammation, and osteophyte formation, the major hallmarks of osteoarthritis [26] according to Xie, *et al.* [23]. However, melatonin may be especially helpful in this regard, and appears to be a suitable adjunct in cartilage engineering efforts [27]. Although most authors call for more research, the research already conducted may be revealing, as outlined below in table 1.

General Attributes of Osteoarthritis	Sources Supporting a Melatonin Linkage
Altered circadian clock mechanisms	Rong, <i>et al.</i> [28]
Pain	Jahanban-Esfalhan, <i>et al.</i> [19]
Inflammation	Lim, <i>et al.</i> [9]
Anxiety	Hajmirzaeyian, <i>et al.</i> [29]
Depression	Zhou, <i>et al.</i> [30]
Sleep problems	Jahanban-Esfalhan, <i>et al.</i> [19]
Fatigue/energy deficits	Cipolla-Neto, <i>et al.</i> [31]
Muscle pathology	Stachiotti, <i>et al.</i> [32]
Bone attrition/microfractures	Halici, <i>et al.</i> [33]; Lu, <i>et al.</i> [16]
Cartilage loss	Gao, <i>et al.</i> [34]; Pei, <i>et al.</i> [35]
Obesity	Cipolla-Neto, <i>et al.</i> [31]
Metabolic diseases	Bazyar, <i>et al.</i> [36]
Nerve pathology	Yazar, <i>et al.</i> [37]
COVID-19 risk	Chitimus, <i>et al.</i> [11]

Table 1: Table outlining common attributes of osteoarthritis and peer reviewed evidence of a linkage to melatonin production or supplementation.

Research observations

Given the great need to find efficacious remedies to counter osteoarthritis pathology, as depicted below, several groups have conducted a variety of basic research studies over the years that tend to support a favorable role for melatonin in efforts to protect articular cartilage and bone status or improve its quality (See table 2).

Researchers	Key findings
Guo., <i>et al.</i> [38]	Melatonin repressed the expression of relevant genes in a rat model of osteoarthritis. Overall, it appeared that that melatonin effectively reduced IL-1 β -induced MMP production by inhibiting Sirt1-dependent NAMPT and NFAT5 signaling in chondrocytes, suggesting it may prove useful as a therapeutic alternative for fostering chondroprotection among osteoarthritis cases
Fu., <i>et al.</i> [39]	Melatonin has a direct effect on mouse chondrocyte genes and caused enhanced cell growth and increased expression of cartilage matrix compounds Exogenous and endogenous melatonin work in synergy in chondrocytes to adjust rhythmic expression to the central suprachiasmatic nucleus clock
Gao., <i>et al.</i> [40]	Melatonin has the potential to reverse inflammation and foster chondrogenesis in a cellular model of bone marrow mesenchymal stem cells exposed to inflammation
Ge., <i>et al.</i> [41]	Melatonin applications may be helpful in averting or reducing spinal intervertebral disc degeneration processes associated often with spinal osteoarthritis
Huang., <i>et al.</i> [42]	Delivery of a 0.2 m solution of melatonin by intra-articular injection and followed for 4 weeks was found to inhibit the progress of cartilage defects in a rat model via mechanisms known to be associated with osteoarthritic cartilage repair processes
Hong., <i>et al.</i> [1]	Melatonin with treadmill exercise tended to produce both a preventive as well as a synergistic effect on decreasing cartilage degeneration processes
Han., <i>et al.</i> [14]	Melatonin treatment attenuated cell senescence and decreased the expression of harmful proteins in an experimental model, and may impact hyaluronic acid production and aging synovial membrane cells favorably
Lim., <i>et al.</i> [9]	Intra-articular injection of melatonin significantly reduced cartilage degradation, indicating that melatonin can exert cytoprotective and anti-inflammatory effects in an oxidative stress-stimulated chondrocyte and rabbit osteoarthritis model
Liu., <i>et al.</i> [43]	Melatonin tended to help maintain mesenchymal stem cells survival and promoted osteogenic differentiation in an inflammatory environment induced by interleukin [IL-1 β], suggesting melatonin treatment could be a promising method for bone regenerative engineering in future studies
Pei., <i>et al.</i> [35]	In a porcine model, it was shown that melatonin enhanced cartilage matrix synthesis of articular chondrocytes in a serum-containing pellet culture system, likely through the transforming growth factor {TGF-beta} signal pathway Melatonin may prove to be a highly valuable addition to current therapeutic models for degenerative cartilage repair
Song., <i>et al.</i> [44]	Fabricated sustained release melatonin-loaded aligned polycaprolactone electrospun fibrous membranes promoted chondrogenic differentiation of human bone marrow-derived mesenchymal stem cells in a long-term chondroid pellet model After implanting this in a rat acute rotator cuff tear model, the melatonin-loaded membranes inhibited inflammation an increased chondroid zone formation, and collagen maturation, while decreasing fibrovascular tissue formation, thereby improving the biomechanical strength of the regenerated bone-tendon interface
Turgot., <i>et al.</i> [45]	There was a regression in histopathological changes after melatonin treatment of intevertebral pathology, with disk appearances similar to those of the control group in a rat model
Zhang., <i>et al.</i> [46]	<i>In vivo</i> experiments demonstrated that intra-articular injection of melatonin prevented disruptions of cartilage matrix homeostasis and successfully alleviated the progression of surgery-induced osteoarthritis in mice
Wu., <i>et al.</i> [47]	Collectively, it appeared that modification of bone marrow mesenchymal stem cells using melatonin or micro [mi] RNA transduction could prove to be an effective therapy for repairing cartilage damage and degeneration

Table 2: Table showing possible benefits of melatonin for ameliorating selected aspects of osteoarthritis tissue damage as reported in animal models, cell based studies, and in vitro approaches.

Discussion

Joint diseases such as osteoarthritis, the most common joint disease, are commonly accompanied by intermittent periods of severe pain, along with variable inflammatory processes, in which pro-inflammatory cytokines mediate the generation of intracellular reactive oxygen species that can compromise the survival of subchondral osteoblasts, as well as cartilage chondrocytes [46]. Other research shows that in the first instant, melatonin, a hormone with multiple health promoting properties [12] is capable of manipulating bone formation and osteogenic differentiation potentially favorably [43]. As well, Zhang, *et al.* [46] showed melatonin applications to favorably impact on artificially created lesions in a mouse articular cartilage model. Furthermore, as discussed by Reynolds, *et al.* [48], as well as Lu, *et al.* [16] melatonin also exerts other physiological effects, including antiinflammatory and oxidative functioning effects, the resetting of circadian rhythms and the promotion of wound healing and tissue regeneration, plus the fostering of immune, bone and cartilage health. Combined with strontium, melatonin was found to produce significant chondroprotective effects in an animal model [49], and its application also portrayed the ability to enhance cartilage proteoglycan component synthesis when employed in a hydrogel mode [27].

As outlined almost 30 years ago and examined in this mini review, melatonin, an endocrine hormone believed to convey photoperiodic messages, and functions chiefly related to chronobiology and modulation of the body hormonal milieu [50] may yet prove helpful for secondary or tertiary prevention purposes in the case of osteoarthritis, where sleep problems and others associated with age associated melatonin declines arguably prevail (See table 1). Thus, even though no actual studies to this effect in humans appear to have been published over time, promising cartilage repair and regenerative interactions can be demonstrated in various models as per table 2, and hence, as such, we concur with MacDonald, *et al.* [51] as well as Lu, *et al.* [16] who suggest melatonin does appear to serve as a link between circadian rhythms and joint diseases, including multiple pathways involved in osteoarthritis.

Moreover, Husseinzadeh, *et al.* [10] suggest that in patients with osteoarthritis, where the expression of endoplasmic reticulum stress-associated molecules is positively correlated with cartilage degeneration, this group may benefit from melatonin administration, known to regulate a variety of molecular pathways such as inflammation, proliferation, apoptosis, and cell replication processes in different pathophysiological situations, even if not explicitly discussed by Grassel, *et al.* [52]. To depict a possible linkage for future testing, figure 1 indicates hypothetical osteoarthritis-melatonin linkages, mindful that data that are available are only possible approximations of the actual clinical situation and very complex pathways involved.

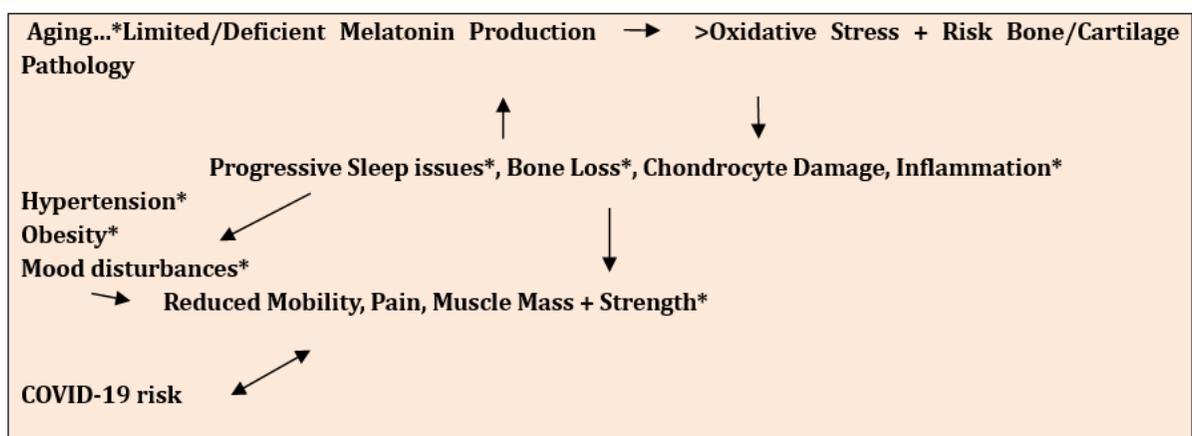


Figure 1: Points* at which melatonin or its deficiency may influence the osteoarthritis pain risk cycle
 [Adapted from references; 7, 10, 11, 15, 20, 22, 23, 31]

Of added importance in our view is the prevailing strong evidence showing older adults, especially those suffering from one or more pre existing chronic health condition, such as osteoarthritis, are not only more likely than not to be at increased risk for being infected by the novel coronavirus known as COVID-19 that can prove fatal [54,55], but those adults now under lockdown may possibly be experiencing increasing symptoms of this widespread painful joint disease disabler, even if they are not infected by COVID-19. They are also likely to be at risk for melatonin deficits, and may currently be weaker than usual, as well as overwhelmed by the demands of their condition if supportive health services have been considerably reduced or eliminated, even if they were previously functional and active. In addition, surgery as a tertiary remedy for those with severe osteoarthritis pain, while somewhat successful, now poses further added risks of intrinsic as well as acquired infections, and further debility, as well as delays, due to its oftentimes elective nature. Returning home from the hospital is also likely to be more challenging than in pre pandemic times [53].

To the contrary, efforts to promote optimal melatonin levels may yield multiple benefits in this regard and surely warrant exploration and careful examination in light of the immense burden placed currently on older adults with osteoarthritis that may be readily mitigated or improved at low cost by insightful understandings of the multiple favorable impacts melatonin may have.

Conclusion

There is a fairly robust rationale in favor of exploiting multifaceted melatonin and its effects on circadian rhythms, a multitude of tissues, plus oxidative stresses, and accompanying osteoarthritis correlates, including inflammation, bone and chondrocyte destruction.

However, to avoid overlooking a viable intervention option for many current home bound osteoarthritis sufferers, the tentative findings reported to date in preclinical studies, should be replicated in the clinical realm without delay.

Indeed, given the immense burden of osteoarthritis, and the negative impact of COVID-19 on many aspects of osteoarthritis care and disability, this line of research clearly warrants attention and should receive high priority.

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