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Review Paper
A Brief Review of the Role of Ghrelin in Osteoarthritis

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ABSTRACT

Ghrelin, often referred to as the hunger hormone, is a peptide produced primarily in the stomach that plays an essential role in managing energy balance, appetite, and the release of growth hormone. It exhibits effects similar to growth hormone-releasing hormone and can effectively stimulate the secretion of growth hormone (GH) from pituitary GH cells. As a result, ghrelin is thought to contribute to the promotion of bone growth and development. Recent evidence indicates that ghrelin may also be involved in the regulation of inflammatory and degenerative processes within joint tissues. Osteoarthritis (OA) is a common chronic degenerative disease characterized by degeneration in the joints and subsequent destruction of cartilage and bone, yet much remains to be elucidated regarding its molecular mechanism. In this article, the roles of ghrelin in osteoarthritis were summarized to reveal the potential effects of ghrelin as a key target in the treatment of osteoarthritis.

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Introduction

Osteoarthritis (OA) is a progressive joint disorder characterized by chronic pain and gradual degeneration that affects the whole joint. As a significant cause of disability worldwide, OA poses a major public health and economic issue, impacting around 303 million adults globally [1]. Despite its high prevalence, there are currently no medications available that alter the progression of OA. Existing treatments mainly concentrate on symptom relief and often include non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids. Although these medications can effectively alleviate symptoms in the short term, long-term use carries significant risks of adverse effects and toxicity [2]. The inflammatory nature of OA, especially synovitis, has led to studies investigating anti-inflammatory agents that are effective in reducing inflammatory conditions in the joints. Among the studies that have received attention recently is the study of the effects of anti-inflammatory adipokines [3]. One of these is ghrelin. Ghrelin is a hormone, often classified as an adipokine, which plays a key role in regulating appetite and energy balance. While ghrelin is primarily produced in the stomach, it is considered an adipokine because it is also found in adipose tissue and influences fat storage and metabolism [4]. Ghrelin is also expressed in chondrocytes and plays an important role in chondrocyte differentiation [5]. Recent studies suggest that ghrelin may also play a role in managing inflammatory and degenerative processes within joint tissues [6]. This article aimed to comprehensively review the roles and molecular mechanisms of ghrelin in OA.

Ghrelin structure, function and mechanism of action

Ghrelin or lenomorelin, is often called a "hunger hormone" because it increases the drive to eat. Ghrelin was initially identified and designated by Kojima et al. Its discovery followed the identification of the ghrelin receptor, known as the growth hormone secretagogue type 1A receptor (GHS-R), in 1999. The hormone's name reflects its function as a peptide that stimulates the release of GH, derived from the Proto-Indo-European root $g^{h}re$-, which translates to "to grow."

The *GHRL* gene encodes a preproghrelin protein consisting of 117 amino acids, which is subsequently cleaved to yield proghrelin, leading to the formation of a unacylated 28-amino acid ghrelin and an acylated C-ghrelin [7]. Ghrelin is biologically active only after caprylic (octanoic) acid is enzymatically attached to the serine residue at the 3-position by the enzyme known as ghrelin O-acyltransferase (GOAT), creating a proteolipid [8]. Activated ghrelin binds to the ghrelin receptor, GHS-R, whereas desacyl ghrelin, the form that lacks octanoylation, cannot bind to this receptor [9]. GHS-R is linked to the G (q) and G (s) signaling pathways, resulting in an increase in intracellular calcium concentration upon the binding of ghrelin or synthetic peptidyl and nonpeptidyl ghrelin mimetics [10].

Ghrelin plays a role in the intricate process of energy homeostasis, which regulates both energy intake through hunger signals and energy expenditure by determining how much energy is allocated to ATP production, fat storage, glycogen storage, and short-term heat loss. The collective outcomes of these activities are reflected in body weight and are consistently monitored and adjusted according to metabolic indicators and requirements [11]. Besides its role in energy balance, various central and peripheral effects of ghrelin have been observed, such as enhancing gut motility and gastric acid secretion [12], managing glucose metabolism [13], influencing sleep patterns [14], preventing muscle wasting [15], inhibiting brown fat thermogenesis [16], supporting bone growth and development [17], and providing chondroprotective and anti-inflammatory benefits to joints [18].

Ghrelin levels are influenced by age, and alterations in body composition linked to aging, like reductions in body fat and muscle mass, can lead to lower concentrations of this hormone. This decline in plasma ghrelin levels might be related to changes in GH activity and the occurrence of anorexia nervosa among older adults [19]. In addition, research indicates that as individual's age, ghrelin's impact on bone composition shifts from a central/systemic stimulating effect to a localized inhibitory one [20]. Studies involving aged mice lacking the ghrelin receptor reveal an increase in osteoclast formation and a reduction in bone mass, suggesting that the systemic stimulation pathway is weakened with ageing, thereby allowing the local inhibitory effect of ghrelin to predominate. It is worth mentioning that this age-dependent relationship between ghrelin and bones is reversed during ageing. In a study of adolescent boys, ghrelin showed no correlation with markers of bone resorption, and it also did not relate to bone mass in young men [21]. However, in a large sample study of older men, there was a negative correlation with bone resorption and a positive correlation with bone mass [22].

Ghrelin and OA

OA is the most prevalent debilitating condition, representing a significant source of disability, and is marked by persistent pain and various joint issues, including damage to the articular cartilage, inflammation of the synovial membrane, alterations in the subchondral bone, and the formation of osteophytes [23, 24]. OA impacts various joints, including the knee, hip, lumbar facet joint, and temporomandibular joint (TMJ) [25]. The risk factors associated with OA in the knee and hip comprise genetics, aging, being female, ethnicity, certain occupations (especially those involving physical labor), obesity, hypertension, abnormal joint alignment, inadequate muscle strength, high-intensity physical activity, and a history of joint injuries [26, 27]. These overarching vulnerability factors and localized elements can result in disruptions in signaling pathways and the associated regulatory networks of critical molecules that convey pain signals and manage chondrocyte balance, survival, and apoptosis, ultimately contributing to joint discomfort and pathological alterations in the cartilage of the synovial joint in OA. The exact pathological mechanisms behind OA remain unclear.

Many studies have been conducted in this field, and the roles of several proteins in promoting or preventing osteoarthritis have been identified. Ghrelin is one of the proteins that has been proposed to prevent and alleviate OA symptoms and may thus play a protective role in OA. Ghrelin expression is significantly reduced in serum and synovial fluid and is linked to disease severity in osteoarthritis patients [28, 29]. Research suggests that ghrelin may influence the progression of OA through several mechanisms, such as suppression of inflammatory responses, reduction of chondrocyte apoptosis and autophagy, and maintenance of cartilage matrix components.

Suppression of inflammatory responses:

Various studies indicate that ghrelin may influence inflammatory reactions. Zou et al. [28] first reported that GH secretagogue receptor (GHS-R) and ghrelin are expressed in human T lymphocytes and monocytes, and ghrelin, by binding to GHS-R, specifically inhibits the expression of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α. Studies have shown that the effects of ghrelin on inflammatory responses are evident in some cases, such as ankle osteoarthritis after trauma or acute cartilage damage, where serum and synovial ghrelin concentrations correlate with disease severity and there is an inverse relationship between ghrelin and TNF-α and IL-6 levels [28, 29]. In addition, Granado et al. examined the effect of administration of the ghrelin agonist GH-releasing peptide-2 (GHRP-2) to arthritic rats. They found that GHRP-2 administration has an anti-inflammatory effect in arthritic rats that seems to be mediated by ghrelin receptors directly on immune cells [30]. Waseem et al. illustrated the presence of ghrelin and GHS-Rs in macrophages from mice. They demonstrated that exogenous ghrelin inhibited the production of proinflammatory cytokines (IL-1β and TNF-α) while enhancing the release of the anti-inflammatory cytokine IL-10 in macrophages stimulated by lipopolysaccharide (LPS). Possible mechanisms of ghrelin action on the production of these inflammatory mediators have been reported, the most important of which are reduced NF-κB activation and increased mitogen-activated protein kinase (MAPK) activation [31]. A summary of studies on ghrelin and inflammation is provided in Table 1.

Reduction of chondrocyte apoptosis and autophagy:

Elevated chondrocyte apoptosis is often observed with cartilage deterioration. The NF-kB signaling pathway plays a crucial role in the degeneration of cartilage as it relates to aging. Research indicates that the activation of NF-kB signaling speeds up the progression of cartilage-related diseases linked to aging, while its suppression helps to reduce these issues [32]. QU et al. observed that the levels of p-IkBa significantly increase in chondrocytes treated with inflammatory cytokines and in degenerative cartilage; however, this increase is predominantly counteracted by the addition of exogenous ghrelin. Additionally, they discovered that the nuclear translocation of p65, which is recognized as a hallmark of NF-kB signaling pathway activation, was inhibited by ghrelin. These findings imply that ghrelin suppresses excessive activation of the NF-κB signaling pathway in chondrocytes and potentially reduces cartilage degeneration [33]. Ghrelin has been shown to counteract the suppression of the chondrocyte AKT signaling pathway and the activation of NF-κB signaling during the development of OA, helping to restore normal anabolic processes, inhibit inflammatory cytokines, or prevent the excessive activation of NF-κB signaling in chondrocytes, while also downregulating IL-1β–mediated catabolic processes. Furthermore, ghrelin levels in degenerating cartilage, in chondrocytes stimulated by inflammatory cytokines, and in cartilage from a surgically induced arthritis model were notably decreased, indicating that ghrelin may play a role in OA progression [33]. In two models of surgically induced OA, ghrelin delivered systemically or topically markedly diminished disease severity, suggesting a protective role in articular cartilage degeneration. Re-

Table 1. Summary of studies on ghrelin and inflammation

Mode/Subjects	Findings	Mechanism/Notes
Human T lymphocytes & monocytes	Ghrelin and GHS-R are expressed; ghrelin inhibits proinflammatory cytokines (IL-1β, IL-6, TNF-α).	Ghrelin binds to GHS-R on immune cells.
Patients with ankle osteoarthritis / cartilage damage	Ghrelin levels in serum and synovial fluid correlate with disease severity; ghrelin levels have an inverse relationship with TNF-α and IL-6.	Ghrelin has a protective/anti-inflammatory role in joint disease.
Arthritic rats, GHRP-2 (ghrelin agonist)	GHRP-2 has anti-inflammatory effects.	Mediated by ghrelin receptors on immune cells.
Mouse macrophages	Exogenous ghrelin decreases IL-1β and TNF-α, and increases IL-10 (anti-inflammatory).	Via reduced NF-κB activation and increased MAPK activation.

Table 2. Summary of studies on reduction of chondrocyte apoptosis and autophagy

Model/Subjects	Findings	Mechanism/Notes
Cartilage & aging models	NF-κB activation accelerates cartilage degeneration; suppression reduces damage.	NF-κB plays a central role in aging-related cartilage disease.
Chondrocytes treated with cytokines; degenerative cartilage	p-IκBα levels increase with cytokines and degeneration; ghrelin counteracts this. Ghrelin inhibits the nuclear translocation of p65.	Ghrelin suppresses NF-κB signaling and reduces degeneration.
Chondrocytes, surgically induced arthritis model	Ghrelin prevents the suppression of AKT signaling, inhibits NF-κB activation, and downregulates IL-1β–mediated catabolism.	Restoring anabolic processes; ghrelin levels are reduced in OA models.
Two surgically induced OA models	Systemic and topical ghrelin reduced OA severity.	Protective role of ghrelin in cartilage degeneration.
OA patients; synovial cells	Ghrelin levels are significantly decreased in the serum OA patients. Ghrelin promotes synovial cell proliferation and inhibits apoptosis and autophagy.	Ghrelin effect is mediated via the ADORA2B/PI3K/Akt/mTOR signaling pathway, with reduced LC3-I, BECLIN-1, and BAX levels and increased Bcl-2 levels

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cently, Ye et al. found that the expression of ghrelin significantly decreases in the serum of patients with OA. In addition, they discovered that ghrelin promotes the proliferation of synovial cells while concurrently inhibiting both apoptosis and autophagy, as indicated by reduced levels of LC3/I, BECLIN-1, and BAX (proteins that regulate apoptosis and autophagy), along with an increase in Bcl-2 expression. This modulation was mediated via the ADORA2B signaling pathway, regulating the PI3K/Akt/mTOR axis. These results demonstrate that ghrelin inhibits apoptosis and autophagy in the synovial cells of OA by influencing the ADORA2B/PI3K/Akt/mTOR signaling pathway [29]. A summary of studies on the reduction of chondrocyte apoptosis and autophagy is provided in Table 2.

Maintenance of cartilage matrix components

Ghrelin helps maintain cartilage matrix components in OA by reducing the expression of matrix-degrading enzymes, like matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTSs), which degrade collagen and aggrecan, key components of the cartilage matrix [34]. MMPs, ADAMTSs, IL-8, and complement factors are activated by IL-1, which drives the breakdown of car-

Table 3. Summary of studies on ghrelin's role in the maintenance of cartilage matrix components

Model/Subjects	Findings	Mechanism/Notes
Cartilage matrix biology	IL-1 activates MMPs, ADAMTS, IL-8, and complement factors, leading to cartilage matrix breakdown.	Matrix degradation mainly via ADAMTS-4/5 and MMP-3/13.
Chondrocytes stimulated by IL-1β	Ghrelin reduces the degradation of type II collagen and aggrecan. It suppresses ADAMTS-4/5 and MMP-3/13 expression induced by IL-1β (gene and protein level).	Ghrelin acts in a concentration-dependent manner and prevents collagen II and aggrecan loss.
Chondrocytes from OA patients	IL-1β elevates IRF-1 mRNA expression; ghrelin mitigates this effect.	Ghrelin inhibits the JAK2/STAT3 pathway, lowering IRF-1 expression.
Human chondrocyte aggregates	Ghrelin decreases the levels of MMP-3, MMP-13, ADAMTS-4, ADAMTS-5, and blocks the JAK2/STAT3 pathway (not p38).	Ghrelin restores the balance between matrix synthesis & degradation; it protects cartilage.

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tilage matrices [35]. Ghrelin can reduce IL-1β-induced degradation of type II collagen (Col II) and aggrecan, with aggrecan degradation being a significant pathological process in OA primarily controlled by ADAMTS-4 and ADAMTS-5. Ghrelin suppresses the expression of ADAMTS-4 and ADAMTS-5 induced by IL-1β at both the gene and protein levels. Additionally, MMP-3 and MMP-13 are linked to the degradation of Col II. Ghrelin inhibits the levels of MMP-3, MMP-13, ADAMTS-4, and ADAMTS-5 induced by IL-1β in a concentration-dependent fashion, thereby mitigating the degradation of Col II and aggrecan [36]. The expression levels of interferon regulatory factor 1 (IRF-1) are elevated in chondrocytes from individuals with OA in response to IL-1β, while ghrelin mitigates IL-1β-induced upregulation of IRF-1 mRNA. Ghrelin can decrease IRF-1 expression by inhibiting the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) pathway [34]. It has been found that ghrelin also decreases the levels of MMP-3, MMP-13, ADAMTS-4, and ADAMTS-5 while blocking activation of the JAK2/STAT3 pathway, but it does not affect the p38 MAPK pathway. Overall, ghrelin ghrelin reduces IL-1β-induced degradation of human chondrocyte aggregates and collagen type II, while inhibiting the expression of MMPs and ADAMTS molecules by interrupting the JAK2/STAT3/IRF-1 signaling axis [34, 6]. In general, ghrelin promotes restoration of the balance between matrix production and degradation in degenerated cartilage by inhibiting pro-inflammatory pathways, such as JAK2/STAT3 and preventing chondrocyte breakdown. A summary of studies on ghrelin's role in maintenance of cartilage matrix components is provided in Table 3.

Conclusion

Understanding the early changes in the progression of OA is crucial, as these alterations might still be able to be reversed, allowing for the possible initiation of preventive measures to slow or reverse further disease progression. Ghrelin has anti-inflammatory and regulatory effects on bone metabolism and can help prevent destruction of the musculoskeletal system. Ghrelin appears to have a protective role in OA due to its anti-inflammatory and cartilage-preserving effects. It is mainly produced in the gastrointestinal tract, and with increasing age, ghrelin production and the proportion of active ghrelin decrease. This age-dependent nature of ghrelin may be a critical factor in OA. As the elderly population grows and musculoskeletal disorders, particularly OA, increase, it is crucial to explore ghrelin as a potential target for treating or preventing OA. This necessitates additional research in this field.

Ethical Considerations

Compliance with ethical guidelines

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

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Authors' contributions

Data collection, analysis, and writing the original draft: Masoumeh Mohammadi; Supervision and final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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