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Literature Review: Intermittent fasting in osteoarthritis: Mechanistic perspectives and therapeutic potential

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Abstract

Osteoarthritis (OA) is a chronic degenerative joint disorder characterized by progressive cartilage degradation, synovial inflammation, subchondral bone remodeling, and disturbances in metabolic regulation. Current therapeutic approaches primarily aim to alleviate symptoms, while their ability to modify disease progression remains limited. In recent years, intermittent fasting (IF) has gained attention as a potential non-pharmacological strategy due to its regulatory effects on metabolic processes, inflammatory responses, oxidative stress, autophagy, and gut microbiota composition. This literature review examines current evidence regarding the potential role of IF in OA management, focusing on its underlying molecular mechanisms, findings from preclinical studies, and emerging clinical evidence. Existing research indicates that IF may influence OA progression through several interconnected pathways, including enhanced insulin sensitivity, attenuation of inflammatory signaling, stimulation of autophagic activity, reduction of oxidative stress, and regulation of the gut–joint axis. Although findings from animal models and preliminary clinical investigations suggest potential therapeutic benefits, further large-scale randomized controlled trials are required to establish the efficacy, optimal implementation, and long-term safety of IF as an intervention for OA management.

Keyword: Osteoarthritis; Intermittent fasting; Diet; Caloric restriction; Metabolic regulation; Synovial inflammation

1. Introduction

Osteoarthritis (OA) is among the most common musculoskeletal conditions globally and remains a major contributor to chronic pain and disability, particularly in the elderly population [1–3]. The pathological changes associated with OA extend beyond articular cartilage deterioration, involving multiple joint structures, including the synovium, subchondral bone, ligaments, and periarticular muscles [4]. Current evidence indicates that OA is a complex, multifactorial disease rather than a simple result of mechanical degeneration. Its progression is influenced by persistent low-grade inflammation, metabolic disturbances, oxidative stress, mitochondrial impairment, and alterations in immune regulation [5–7]. Several metabolic factors, including obesity, insulin resistance, and metabolic syndrome, have been identified as significant contributors to increased OA risk and disease progression [8,9].

Intermittent fasting (IF) describes dietary patterns characterized by alternating periods of fasting and food intake [10]. Various IF approaches have been studied, including alternate-day fasting, the 5:2 diet, and time-restricted feeding [11]. In contrast to conventional continuous caloric restriction, IF induces a metabolic transition from glucose utilization toward increased fatty acid oxidation and ketone body generation [12]. This adaptive metabolic response activates several cellular mechanisms associated with metabolic regulation and stress resistance, including AMP-activated protein kinase (AMPK), sirtuin-1 (SIRT1), and autophagy-related pathways [13]. Given that these mechanisms are

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closely involved in OA pathophysiology, IF has emerged as a potential intervention for maintaining joint homeostasis and modulating disease progression [14].

2. Pathophysiology of Osteoarthritis

Current evidence suggests that chronic low-grade inflammation is a key mechanism underlying OA pathogenesis and progression [15]. In response to inflammatory stimuli, synovial cells and chondrocytes release various pro-inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). These cytokines promote the activation of matrix metalloproteinases, leading to progressive extracellular matrix degradation and cartilage destruction [16]. Continuous stimulation of inflammatory pathways, particularly NF-κB and NLRP3 inflammasome signaling, further exacerbates joint tissue damage and contributes to pain development [17].

Metabolic disturbances represent another major factor involved in OA progression. Obesity promotes systemic inflammation through increased adipokine production, especially leptin, which enhances cartilage breakdown and stimulates inflammatory responses within the synovium [18]. Furthermore, insulin resistance and hyperglycemia contribute to oxidative stress and the formation of advanced glycation end products, disrupting cartilage integrity and impairing normal tissue maintenance [19]. Alterations in lipid metabolism may also influence OA progression by promoting subchondral bone remodeling abnormalities and inflammatory activation [20].

Mitochondrial impairment and oxidative stress have increasingly been recognized as important pathological mechanisms in OA development [21]. Excessive reactive oxygen species (ROS) accumulation causes mitochondrial DNA damage, compromises ATP production, and promotes chondrocyte apoptosis [22]. At the same time, impaired autophagic activity limits the ability of chondrocytes to eliminate dysfunctional organelles, thereby accelerating cellular senescence and extracellular matrix degradation [23]. Recent findings have also emphasized the contribution of gut microbiota dysbiosis to OA progression, particularly through disruption of intestinal barrier function, increased intestinal permeability, and subsequent systemic inflammatory responses [24].

3. Potential Mechanisms of Intermittent Fasting in Osteoarthritis

Intermittent fasting (IF) may influence OA progression through several interconnected biological mechanisms. First, IF contributes to metabolic regulation by enhancing insulin sensitivity and reducing circulating concentrations of insulin, triglycerides, and low-density lipoprotein levels [25]. Decreased adipose tissue accumulation may further reduce leptin-associated inflammatory signaling, potentially limiting cartilage degradation and synovial inflammation [26]. In addition, activation of the AMPK/SIRT1 pathway during fasting conditions may promote mitochondrial function and support cartilage homeostasis [27].

Second, IF demonstrates significant anti-inflammatory effects. During fasting periods, increased production of ketone bodies, particularly β-hydroxybutyrate, can inhibit NLRP3 inflammasome activation and reduce the expression of pro-inflammatory cytokines [28]. Clinical investigations have reported decreased levels of inflammatory markers, including C-reactive protein, TNF-α, and IL-6, following IF interventions [29]. Through these mechanisms, IF may attenuate the persistent inflammatory processes that contribute to cartilage damage and OA progression.

Third, IF promotes autophagy and mitophagy through cellular energy regulation. Energy restriction activates AMPK signaling while inhibiting mTOR activity, resulting in enhanced removal of damaged proteins and dysfunctional mitochondria through autophagic processes [30]. Experimental studies have shown that IF-induced mitophagy can protect chondrocytes against apoptosis and reduce the progression of cartilage degeneration [31]. This pathway may have particular relevance in age-related OA, in which impaired autophagic activity contributes to cellular dysfunction and disease progression.

Fourth, IF may contribute to joint health by modulating gut microbiota composition. Repeated fasting cycles have been associated with increased microbial diversity and enrichment of beneficial bacteria capable of producing short-chain fatty acids [32]. These microbial metabolites support intestinal barrier function, reduce systemic exposure to endotoxins, and may consequently attenuate inflammatory responses involved in OA progression [33].

4. Preclinical and Clinical Evidence

Intermittent fasting (IF) has been consistently associated with reductions in body weight and improvements in various cardiometabolic parameters. However, findings from numerous randomized trials suggest that the metabolic benefits

of IF are generally comparable to those achieved through continuous energy restriction [34]. A separate study reported that IF interventions reduced body mass index, body weight, waist circumference, and insulin resistance among individuals with metabolic syndrome. These metabolic improvements may have clinical relevance in OA, as several of these factors are closely associated with disease development and progression [35].

Clinical evidence regarding the application of IF in musculoskeletal disorders remains limited, with current findings showing variability across studies. Nevertheless, preliminary evidence suggests that IF may provide potential benefits when incorporated into a broader pain management strategy [36]. In the context of OA, supplementation with omega-3 polyunsaturated fatty acids has demonstrated potential effects in reducing pain severity and improving joint function. A meta-analysis of randomized controlled trials (RCTs) reported significant improvements compared with placebo, without an increased risk of serious adverse events [37]. The proposed mechanisms underlying the effects of omega-3 involve suppression of pro-inflammatory cytokine activity, reduction of cartilage degradation, and modulation of inflammatory pathways, including HMGB1-RAGE/TLR4 signaling. However, much of the available evidence remains derived from preclinical investigations and mechanistic studies [38]. Despite these promising findings, current research evaluating IF in OA remains constrained by methodological limitations, including relatively small sample sizes and short follow-up periods.

5. Future Perspectives and Conclusion

Despite the growing interest in intermittent fasting (IF) as a potential therapeutic approach for OA, several challenges remain unresolved. The majority of current evidence is derived from preclinical models or studies with limited sample sizes, while large-scale randomized controlled trials are still needed to establish the most effective fasting protocols, evaluate long-term safety, and assess patient adherence [39]. Additional considerations are required when applying IF in specific populations, particularly older adults and individuals with diabetes or existing nutritional deficiencies.

Nevertheless, IF represents a potential complementary strategy in OA management due to its ability to influence multiple pathological mechanisms involved in disease progression, including metabolic dysregulation, chronic inflammation, oxidative stress, mitochondrial dysfunction, and gut microbiota alterations. Future research investigating the combination of IF with exercise interventions, optimized nutritional approaches, and pharmacological therapies may provide further insights into improving clinical outcomes among patients with OA. Collectively, current evidence suggests that IF may have a potential role as part of a comprehensive and multidimensional approach to osteoarthritis management.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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