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The Role of Myokines in Obesity-Related Osteoarthritis: Linking Physical Activity to Joint Health

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Abstract:

Background:

Osteoarthritis is a chronic, degenerative joint disease, which manifests mainly with joint pain, but with disease progression may also lead to much lower quality of life and disability. Its progression is associated with obesity and a sedentary lifestyle, while physical activity seems to be a protective factor. Studies in murine models suggest a potential role for myokines – molecules secreted by skeletal muscle during contraction. They appear to have anti-inflammatory effects and may improve joint health.

Aim:

The aim of this review was to evaluate the role of myokines as potential mediators linking obesity, physical activity and osteoarthritis progression. Additionally, we aimed to summarise current evidence on the impact of obesity and weight loss on osteoarthritis and to assess the immunomodulatory functions of selected myokines, particularly irisin and IL-6.

Materials and methods:

This paper is a narrative review. A literature search was conducted in the PubMed database up to February 2026. For part 2., the following terms were used: “osteoarthritis” combined with “obesity” with a preference for meta-analyses and large cohort studies. For part 3., the following terms were used: “myokines”, “irisin”, “IL-6” alone or combined with “obesity” or “knee osteoarthritis”. Due to the narrative nature of this review, selection bias cannot be excluded.

Conclusions:

Obesity is associated with osteoarthritis progression, as it increases joint pain and radiographic progression. Weight loss and physical exercise are effective treatment strategies in patients with osteoarthritis both treated surgically and non-surgically. Irisin shows anti-inflammatory effects in in vitro and in vivo studies, but in human it is rather a modulator or marker of exercise efficacy. IL-6 is a highly context-dependent cytokine that is generally considered pro-inflammatory but may also exert anti-inflammatory effects when acting as a myokine.

Keywords: obesity, osteoarthritis, myokines, irisin, IL-6

1. Introduction

Osteoarthritis (OA) is a chronic, degenerative joint disease, and with over 0.5 billion cases in 2019, it is the most common joint disease worldwide. It is characterised by female predominance and shows geographical variation, being more prevalent in high-income countries, especially in North America. It affects mainly older people, and its incidence is increasing after the age of 50 [1]. OA primarily affects weight-bearing joints such as the knees, hips, as well as the hands. In its early stages, it manifests primarily with activity-related joint pain, while disease progression results in functional impairment and disability. It is among the leading causes of disability worldwide, especially in older adults. OA is now recognised as a disease of the whole joint, involving complex biomechanical and immunological processes. Its pathogenesis includes not only cartilage degradation but also low-grade synovial inflammation, driven by pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6, alongside increased activity of matrix-degrading enzymes, including MMP-1, MMP-13, and ADAMTS-4/5, which collectively contribute to progressive joint destruction [2]. Obesity is considered one of the most significant modifiable risk factors for OA and exacerbates disease progression. Increased body mass leads to joint overload, while adipose tissue acts as an active endocrine organ, releasing adipokines that promote chronic low-grade inflammation. Associations between obesity and OA appear to be even more complex. Overweight and obese people are generally less physically active. A study by B. Hansen et al., involving 3,867 Norwegian adults with objectively measured physical activity using accelerometers, demonstrated that obese participants exhibited 19% and 25% lower total physical activity compared to normal-weight people on weekdays and weekends, respectively, with a particularly marked reduction in vigorous-intensity activity [3]. This reduction in physical activity is especially pronounced in the context of muscle-strengthening exercise (MSE), which plays a critical role in musculoskeletal and metabolic health. According to a study by J. Bennie et al., conducted on over 280,000 European adults, only 17.3% engaged in a sufficient amount of MSE (≥2 times per week): 19.8% of males, 15.0% of females, 20.9% of people with normal BMI, 15.7% of overweight, and only 11.5% of obese people [4]. This is clinically relevant, as insufficient muscle loading contributes to sarcopenia, impaired joint stabilisation, and reduced production of lubricating and protective factors within the joint. Skeletal muscles also function as an endocrine organ, releasing myokines during contraction. Myokines, including irisin, fibroblast growth factors (FGF)2 and FGF21, IL-6, IL-10, and IL-15 exert anti-inflammatory and metabolic effects that may counterbalance the pro-inflammatory activity of adipokines derived

from excess adipose tissue [5]. Notably, some molecules, such as IL-6, may act as both a myokine and an adipokines. This suggests that physical activity, particularly resistance exercise, may potentially modulate OA progression not only through biomechanical improvements but also via systemic immunometabolic pathways. Despite growing evidence linking obesity, inflammation, and OA, the extent to which exercise-induced myokines can mitigate the deleterious effects of adiposity on joint health remains insufficiently characterised. This study aims to evaluate the current state of knowledge on impact of obesity on OA progression and to explore the potential of physical exercise as a therapeutic strategy, with particular emphasis on the interplay between adipokines and myokines.

2. Clinical impact of obesity on OA

Both general and central obesity are associated with an increased risk of OA development. BMI is most strongly correlated with KOA, but also with hand and hip OA, which also proves the dual influence of obesity on disease development by increasing low-grade inflammation, and mechanical loading and friction [6-8]. Moreover, low muscle mass index (MMI) and sarcopenic obesity, but not low muscle mass and sarcopenia, increase the risk of knee osteoarthritis (KOA), which reflects the role of adipokine and myokine imbalance and loss of joint stability as factors contributing to OA [9]. Obesity also influences physical fitness, especially in OA patients, lowering gait speed, increasing comorbidity and the number of drugs taken, and aggravating pain. Overweight and obese people report lower quality of life, lower physical activity, and increased risk of disability, which worsens their disease, creating a self-perpetuating cycle of disease progression [10-12]. Weight loss remains the only non-surgical intervention with disease-modifying potential in OA; a combination of psychological support, low-calorie diet, physical exercises, and bariatric surgeries gives the best results for pain relief and physical condition improvement in obese OA patients [13-15]. Encouragingly, weight loss is associated with a reduced risk of knee and hip replacement; however, this effect seems to be clinically important with a loss of more than 7.5% of initial body mass [16,17]. BMI alone should not be considered a contraindication for unicompartmental knee arthroplasty (UKA), as obese patients achieve outcomes comparable to, or in some cases exceeding, those of normal-weight patients with surgical treatment, and early as well as late complications of UKA, such as infection or venous thromboembolism, do not significantly differ between obese and normal-weight patients, nor does the frequency of revision [18,19]. Furthermore, in obese patients, pre-operative 5% weight loss does not appear to affect postoperative complication and outcomes in knee and hip arthroplasty [20]. However, this does not negate the importance of recommending

weight loss in these patients. Summary of key studies is included in Table 1, while mechanisms on how obesity impacts OA progression are illustrated in Figure 1.

Table 1. Clinical impact of obesity on osteoarthritis

Study	Key findings
retrospective cohort study by D. Park et al., 2023, 1139463 people [6]	in people aged 50+ with general obesity without central obesity (HR = 1.281, 95% CI 1.270–1.292), central obesity without general obesity (HR = 1.167, 95% CI 1.150–1.184) and both general with central obesity (HR = 1.418, 95% CI 1.406–1.429) were associated with increased KOA in comparison to normal weight; these effects were stronger in women and younger people; weight loss and remission of general or central obesity over two years was associated with decreased KOA risk (HR = 0.884, 95% CI 0.867–0.902; HR = 0.900, 95% CI 0.884–0.916, respectively)
meta-analysis by H. Zheng et al., 2015, 896818 people [7]	overweight with RR = 2.45 (95% CI 1.88–3.20) and obesity with RR = 4.55 (95% CI 2.90–7.13) were significantly associated with higher KOA risk each 5 kg/m^2 increase in BMI was positively correlated with increase of KOA risk with RR = 1.35 (95% CI 1.18–1.53)
prospective cohort study by C. Reyes et al., 2016, 1764061 people [8]	people were observed for 4-5 years overweight was associated with increased risk of KOA (HR = 2.00, 99% CI 1.94–2.06), hip OA (HR = 1.46, 99% CI 1.39–1.52), hand OA (HR = 1.22, 99% CI 1.17–1.27); obesity with BMI > 35 was associated with increased risk of KOA (HR = 4.72, 99% CI 4.56–4.89), hip OA (HR = 1.93, 99% CI 1.82–2.05), hand OA (HR = 1.31, 99% CI 1.24–1.38); results are adjusted by age and gender
meta-analysis by Q. Wu et al., 2024, 32013 people [9]	low MMI with OR = 1.36 (95% CI 1.13–1.64) and sarcopenic obesity (coexistence of obesity and sarcopenia) with OR = 1.78 (95% CI 1.35–2.34) increase the odds of KOA; however there was no association between general sarcopenia or low muscle mass with KOA

prospective cohort study by J. Bastis et al., 2015, 2378 people at baseline, in 6 years follow-up 1727 people mean age 68 [10]	at baseline, obese patients compared to overweight and normal were on a greater number of medications (4.28 vs. 3.63 vs. 3.32), had lower gait speeds (1.22 vs. 1.32 vs. 1.36 m/s), higher Charlson scores (0.59 vs. 0.37 vs. 0.30), and higher WOMAC scores (right: 14.8 vs. 10.3 vs. 7.5; left: 14.4 vs. 9.9 vs. 7.5) at 6 year, obese patients compared to overweight and normal had lower scores of SF-12 (99.5 vs. 101.1 vs. 102.8), PASE (115.1 vs. 126.2 vs. 131.4) and LLDI (78.6 vs. 81.2 vs. 82.5)
meta-analysis by M. Hall et al., 2019, 2140 OA patients [13]	in overweight and obese patients diet-only treatment did not significantly reduce pain (SMD = -0.13, 95% CI -0.37 to 0.10), but combination of diet and physical exercises moderately reduced pain (SMD = -0.37, 95% CI -0.69 to -0.04) diet-only treatments improved moderately physical function (SMD = -0.30, 95% CI -0.52 to -0.08), however combined with physical exercises gives a stronger effect (SMD = -0.32, 95%CI -0.56 to -0.08) dietary treatment also reduced IL-6 level, but not CRP
meta-analysis by Z. Salis et al., 2022, 8145 patients [15]	in people with or at risk of clinically significant KOA, every 1% weight loss was associated with a 2% reduced risk of knee replacement and - in those people who also had one or more persistently painful hips - a 3% reduced risk of hip replacement, regardless of baseline BMI
meta-analysis by J. Lua et al., 2023, 42434 patients [18]	obesity may decrease risk of revision after UKA surgeries, for BMI > 30 kg/m^2 OR = 0.91 (95% CI 0.79–1.05), for BMI > 35 OR = 0.70 (95% CI 0.48–1.01), and for BMI > 40 OR = 0.66 (95% CI 0.41–1.07) as these results are close to be statistically significant obese patients had significant improvement after UKA in Oxford Knee Scores with OR = 2.68 (95% CI 1.79–3.57) compared to normal weight patients, but there was no differences in VAS or KNS scores
meta-analysis by N. Agarwal et al.,	30 studies with a mean follow-up of 5.42 years, allowing assessment of both early and late complications, found no significant differences

2021, 80798 patients [19]	between obese and normal-weight patients in minor or major complications, infections, VTE risk, or revision surgeries (especially due to infection or aseptic loosening) after UKA

Abbreviations: OA – osteoarthritis, KOA – knee OA, MMI – muscle mass index [skeletal muscle mass (kg) / (height (m))^2], ROA – radiographic OA, KL – Kellgren and Lawrence scale, JSN – joint space narrowing, WOMAC – Western Ontario and McMaster University OA index, SF-12 – short form 12 questionnaire, PASE – physical activity scale for the elderly, LLDI – late-life disability index, UKA – unicompartmental knee arthroplasty, VAS – visual analogue score, KNS – Knee Society score, VTE – venous thromboembolism

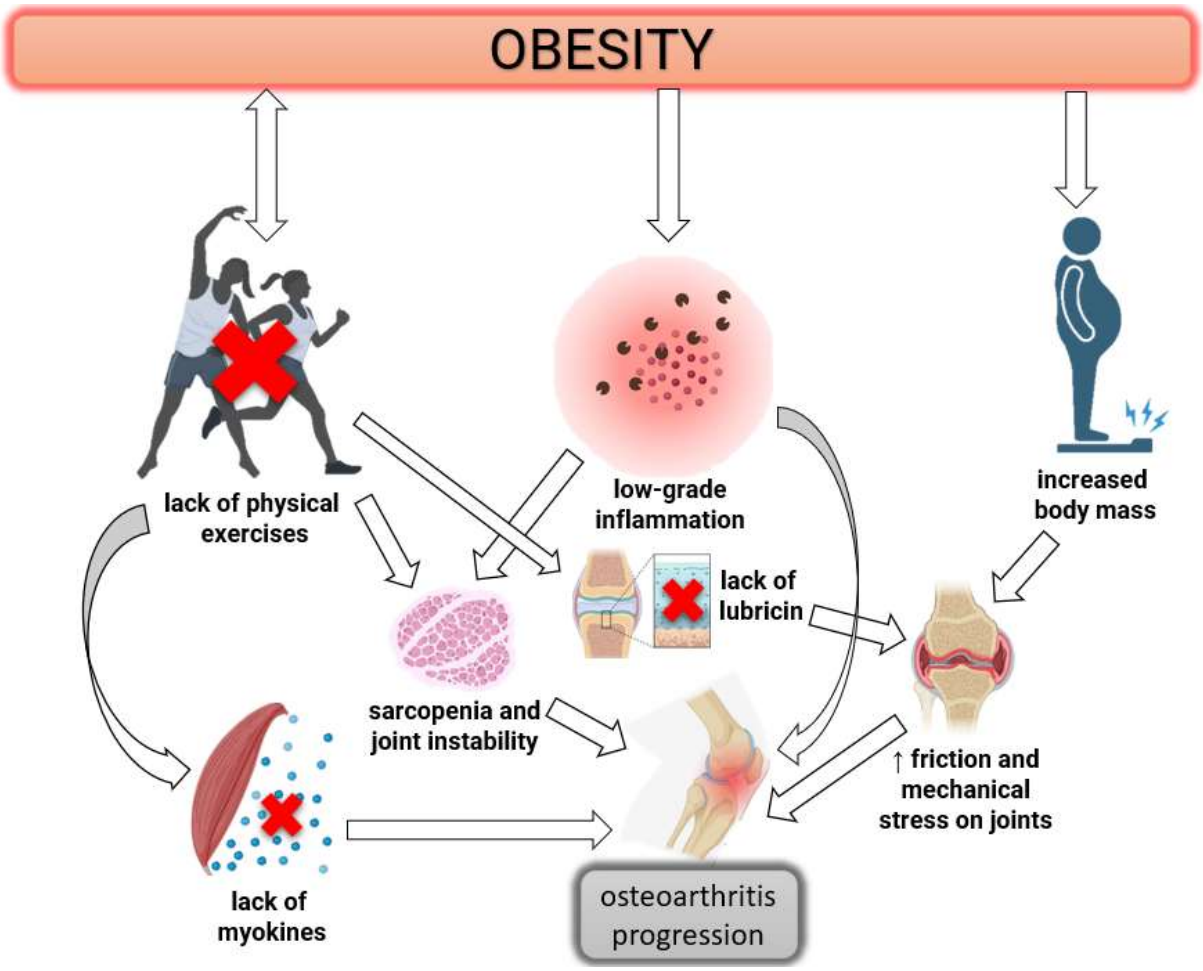

Figure 1. Role of obesity and myokines in OA progression
The role of obesity in OA progression is complex. Excess body mass increases mechanical load on joints and friction during physical activity. Obesity-related chronic low-grade inflammation contributes to sarcopenia and joint instability, while also increasing the levels of pro-inflammatory cytokines and metalloproteinases within the joint. Obesity is often associated with reduced physical activity, which leads to decreased secretion of myokines. This reduction may exacerbate the negative effects of adipokines, promote sarcopenia and joint instability, and impair lubricin production, thereby increasing joint friction. Created in BioRender [65]

3. Myokines as modulators of inflammation

Based on current evidence, the negative impact of obesity on OA progression is rather well documented. Moreover, weight loss is considered as a key part of treatment of this disease. However, some of the studies mentioned above also suggest that physical exercise and the

associated increase in skeletal muscle mass may be important factors in OA [9,10,13]. A potential link between exercise and improvement in OA may involve myokines, including irisin and IL-6.

3.1 Irisin

Irisin is primarily produced by skeletal muscle in response to contraction, but it is also secreted by visceral adipose tissue, classifying it as both a myokine and an adipokine [21]. It exerts its biological activity via binding to a receptor complex composed of heat shock protein Hsp90α and integrin αVβ5, although the detailed mechanisms remain incompletely elucidated [22]. Physical activity stimulates the expression of PPARγ coactivator-1α (PGC1α), possibly mediated by an increase in polyunsaturated fatty acids such as arachidonic acid and docosahexaenoic acid [23]. PGC1α induces the expression of fibronectin type III domain-containing protein 5 (FNDC5), a membrane protein cleaved and released as the soluble hormone irisin; however, referring to irisin as FNDC5 is imprecise [24]. In murine models, irisin stimulates uncoupling protein 1 (UCP1) expression and browning of white adipose tissue, though in humans this effect remains weak and has not been definitively confirmed [25,26]. A. Shoukry et al. demonstrated that irisin levels are positively correlated with BMI in patients with type 2 diabetes [27], while R. Werida et al. confirmed a similar correlation in non-diabetic individuals [28]. A meta-analysis by J. Jia et al. supported this association only in children and African populations [29], whereas some smaller studies reported an inverse relationship [30,31]. These discrepancies highlight the need for further investigation. These divergent findings may stem from the fact that irisin is secreted by both muscle and adipose tissue, and some studies suggest the possible presence of irisin resistance in metabolic syndrome, analogous to leptin resistance, although the concept remains poorly understood [32,33]. Irisin exhibits immunomodulatory and predominantly anti-inflammatory effects, particularly through its influence on macrophages. Via interaction with integrin αVβ5, irisin promotes phosphorylation of JAK2/STAT6, leading to activation of PPARγ and nuclear factor erythroid 2-related factor (Nrf2). PPARγ promotes M2 macrophage polarization through the upregulation of Arg1, mannose receptor C-type 1 (Mrc1/CD206), and IL10 [34]. This mechanism appears to be independent of the canonical STAT6 activation by IL-4 via JAK1/3 or by IL-13 via JAK2 and TYK2 [35]. Irisin also activates AMPK, which inhibits IκB kinase (IKK), preventing degradation of IκB and thereby suppressing NF-κB activation [36]. It also inhibits LPS-induced phosphorylation of ERK, JNK, and Akt, reduces expression of TLR4 and MyD88, suppresses M1 macrophage polarization, and promotes M2 repolarization. This results in downregulation

of pro-inflammatory cytokines such as IL-1β, IL-6, IL-12, IL-23, TNF-α, MCP-1, and HMGB1 [37,38]. Irisin also activates the Nrf2 pathway, which induces expression of the anti-inflammatory and antioxidant enzyme heme oxygenase-1 (HO-1), further contributing to the suppression of HMGB1 release. The activation of the Nrf2/HO-1/HMGB1 axis additionally reduces M1 macrophage polarization and further inhibits NF-κB signaling [39,40]. Irisin also attenuates activation of the NLRP3 inflammasome and reduces production of caspase-1, IL-1β, and IL-18 [41]. Beyond its immunomodulatory properties, irisin plays an important role in bone and cartilage metabolism. It promotes the differentiation of mesenchymal stem cells into osteoblasts and chondrocytes, inhibits their adipogenic differentiation, and stimulates autophagy. In osteoblasts, irisin enhances proliferation, osteogenic differentiation, and bone formation, while promoting cell survival by inhibiting apoptosis and ferroptosis. It has also been reported to suppress osteoclastogenesis and may reduce bone resorption. In osteocytes, irisin promotes proliferation, inhibits apoptosis, and supports dendrite formation, thereby enhancing intercellular communication. In chondrocytes, irisin improves mitochondrial function, inhibits inflammation and pyroptosis, and promotes extracellular matrix synthesis [42]. In vitro studies by G. Vadalà et al. showed that irisin increased human osteoarthritic chondrocyte (hOAC) cell number and type II collagen gene expression and protein levels, while simultaneously decreasing type X collagen gene expression and protein levels. Furthermore, irisin decreased IL-1, IL-6, MMP-1, MMP-13, and iNOS gene expression and increased TIMP-1 and TIMP-3 levels. These effects appeared to be mediated by inhibition of the p38, Akt, JNK, and NF-κB signaling pathways. This suggests that irisin may stimulate hOAC proliferation and promote anabolism, while inhibiting catabolism through inactivation of p38, Akt, JNK, and NF-κB in vitro, demonstrating crosstalk between muscle and cartilage [43]. The in vitro and in vivo studies presented above suggest that exercise-induced irisin has the potential to reduce systemic low-grade inflammation in obesity and also exerts local effects in joint tissues. Therefore, it should be considered a potential molecular link that requires further evaluation in clinical studies on OA patients. However, human data on irisin in OA are very limited. Study by Y. Mao et al. showed that in KOA patients, serum irisin concentrations appear to be lower (118 vs 146 ng/mL in whole group, 114 vs 141 ng/mL in overweight subgroup) compared to healthy controls, synovial fluid (SF) irisin concentrations were also decreased (37 ng/mL). Serum and SF irisin levels were negatively correlated with radiographic progression assessed by Kellgren and Lawrence (KL) grading criteria [44]. C. Orellana et al. showed that in symptomatic (VAS > 4) KOA patients plasma and synovial irisin levels were strongly related ($r = 0.7$). Plasma and synovial irisin levels showed a significant inverse association with physical activity levels in

patients with symptomatic knee OA: no exercise 763 ng/mL, occasional exercise 632 ng/mL and regular exercise 523 ng/mL. Patients with severe pain and disability (Lequesne algofunctional score >11) had higher plasma (792 vs 680 ng/mL) and synovial (711 vs 469 ng/mL) irisin levels compared to patients with less disability and pain. However, no relationship was found between irisin concentration in plasma or synovial fluid and radiographic severity [45]. In humans, irisin is predominantly released in response to acute, high-intensity exercise, whereas the effects of long-term training on baseline irisin levels are inconsistent [46]. A study on a small sample of men (n = 6) with sedentary lifestyle showed that 40 min of high-intensity exercise (80% of VO2max) significantly increases irisin blood concentrations at 6 h (18% increase) and 19 h (23% increase) after exercise, but shorter 20 min low-intensity exercise may even reduce its levels [47]. Moreover, study on patients after hip or knee replacement surgery showed that irisin levels increased after a 21-day individualized rehabilitation exercise program by about 60 ± 160 ng/mL (95% CI 10-120) [48]. Results are generally very heterogeneous. Serum irisin levels between studies seem to differ between studies by several times. The role of irisin remains uncertain, it may be a contributor to inflammation and joint degeneration or only a marker of effectiveness of physical exercises. Moreover, its relevance in humans remains unclear. To sum up, as far as the effectiveness of physical exercises in OA treatment and rehabilitation is well established, available data do not allow for clear identification of irisin as a mediator of this improvement.

3.2 IL-6

IL-6 is a cytokine that functions both as an adipokine and a myokine. It is produced in WAT by adipocytes and macrophages, and in skeletal muscle in response to contraction [49], as well as by endothelial cells and fibroblasts [50]. IL-6 binds to its specific receptors: membrane mIL-6R (classic signaling pathway with anti-inflammatory responses and regulatory functions, mainly in hepatocytes and leukocytes) and soluble sIL-6R (trans-signaling pathway with pro-inflammatory responses) [51]. In both cases, this dimer associates with membrane glycoprotein gp130, forming a hexameric complex [52]. IL-6 concentration rises in obesity; there is a positive correlation with BMI, waist circumference, and waist-to-height ratio [53]. Its level also increases in association with obesity-related obstructive sleep apnoea, especially if it causes hypoventilation [54]. Its impact on glucose homeostasis is dual: when secreted acutely during fasting or exercise, it improves insulin sensitivity, but long-term elevated levels, as in obesity, cause insulin resistance and type 2 diabetes mellitus (T2DM) [55]. IL-6 production is upregulated by NF-κB (activated by various stimuli including leptin, resistin, and visfatin),

CREB (part of CAP1-PKA/CREB pathway activated by resistin), IRF-1 (part of TLR4/MyD88/IRF-1, also activated by resistin), and AP-1 (activated by MAPKs: ERK1/2, JNK, p38, thus by leptin, resistin, and visfatin) and downregulated by RNA-binding protein regnase-1 and various microRNAs [56]. Interestingly, IL-6 together with Th17-type cytokines (IL-17A, IL-17F, IL-21, IL-22) and TNF-α synergistically activates STAT3 (through JAK1, JAK2, and TYK2 [57]) and NF-κB, creating a positive feedback loop [58]. Via JAK2 kinase, IL-6 also activates the RAS/RAF/MEK/ERK pathway [59], PI3K/AKT/NF-κB pathway, and disturbs the Th17/Treg balance in favour of Th17 [60]. All these actions of IL-6 are pro-inflammatory, but it is important to note that IL-6 may also exert anti-inflammatory functions in some specific contexts: it can reduce TNF-α and IL-1β levels, increase IL-10 levels, and promote macrophage polarization toward the M2 phenotype. IL-6 is a pleiotropic cytokine: when secreted acutely and locally, it has protective and regenerative effects (e.g., after exercise), but when secreted chronically and systemically in obesity, it promotes inflammation. The biological effect of IL-6 is highly context-dependent, and interactions with other stimuli, especially TNF-α, as well as duration and the local versus systemic nature of its signaling, are crucial [61,62]. The role of IL-6 as a myokine is hard to evaluate in the context of OA, because it is usually a marker of inflammation. Its impact is estimated indirectly: there is some evidence that IL-6 acts as a myokine and has anti-inflammatory functions, resistance training increases IL-6 levels acutely, but decreases them in the long term, physical activity improves OA symptoms, so IL-6 may be a potential molecular bridge [63]. However, until it is directly measured in studies, it remains a hypothesis partially supported by evidence.

There is generally a lack of human studies on myokines, other than irisin and IL-6, in context of OA. The one which was found concerned IL-15. It showed that serum IL-15 levels were significantly higher in OA patients compared with controls. Serum IL-15 levels were independently and positively correlated with WOMAC-pain scores but not KL grades in OA patients [64]. It is consistent with main role of IL-15 as a pro-inflammatory cytokine, but does not reflect its role as myokine.

4. Conclusions and future directions

The role of obesity in OA is well documented. It increases the risk of disease development, aggravates pain and correlates positively with radiographic progression. Weight loss and physical exercise are established components of OA management. However, the mechanisms by which physical exercise leads to improvement in OA are not fully understood. It contributes to weight loss and increases muscle mass. Additionally, it enhances lubricin

production, which stabilises joints and reduces friction. Studies in murine models and in vitro human cells suggest a potential role of myokines – molecules secreted by skeletal muscles in response to contraction. Irisin exerts anti-inflammatory effects and protects mice from diet-induced obesity; however, these effects appear much weaker in humans. It may play immunomodulatory roles, but may also be only a marker of exercise efficacy. The data from human studies are very heterogeneous and it is hard to make a clear conclusion. IL-6, which was first described as a myokine, also shows anti-inflammatory functions in a specific context, however due to its main pro-inflammatory role it is hard to evaluate if it is significant in the context of OA. There are very limited human data on other myokines, making this an interesting area for future research. Current evidence suggests that myokines are likely to act as modulators rather than primary drivers of OA progression in humans.

Disclosure

Author contributions

Conceptualisation: Mateusz Pysiewicz, Paweł Budzik; Literature Search: Mateusz Pysiewicz, Paweł Budzik, Julia Elżbieta Wolnik, Martyna Grzywacz; Data analysis and interpretation: Mateusz Pysiewicz, Szymon Mokrzecki, Elizabeth Malaya, Olga Stadnicka; Writing – Original Draft Preparation: Mateusz Pysiewicz, Paweł Budzik, Julia Elżbieta Wolnik, Martyna Grzywacz; Writing – review and editing: Elizabeth Malaya, Szymon Mokrzecki, Olga Stadnicka; Supervision: Elizabeth Malaya

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Conflicts of Interest

The authors declare no conflict of interest.

Declaration of AI use

While preparing this manuscript, the authors used ChatGPT to perform linguistic editing, including correction of grammar, syntax, and spelling and to provide better readability. After using this tool, the authors thoroughly reviewed and edited the content as needed and accept

full responsibility for the substantive content of the publication.

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