JOURNAL OF EDUCATION, HEALTH AND SPORT
eISSN 2391-8306 · Open Access · Peer-reviewed
apcz.umk.pl/JEHS · Nicolaus Copernicus University in Toruń

Cite as: DEKA, Emilia, BANATKIEWICZ, Joanna, BARTKOWSKA, Oliwia, CZARNECKA, Sofia, BOJANOWSKA, Hanna, BABIK, Karolina, ŁUCZYŃSKA, Gabriela Ewa, DOMIŃCZAK, Jan, DOBOSZ, Adam and WOJNOWSKI, Antoni. Chronic Inflammation and Insulin Resistance as Links between Metabolic Syndrome and Musculoskeletal Disorders. Journal of Education, Health and Sport. 2026;91:70885. https://doi.org/10.12775/JEHS.2026.91.70885

ARTICLE TIMELINE
Received: 14.04.2026 Revised: 15.05.2026
Accepted: 16.05.2026 Published: 23.05.2026

INDEXING & EVALUATION
MEiN points: 40 Unique ID: 201159
Disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

The journal has been awarded 40 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32318). Unique Journal Identifier: 201159. Scientific disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

Punkty Ministerialne z 2019 – aktualny rok 40 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

Chronic Inflammation and Insulin Resistance as Links between Metabolic Syndrome and Musculoskeletal Disorders: A Review

Emilia Deka, ORCID: https://orcid.org/0009-0001-1283-8084, E-MAIL: emdeka00@gmail.com, Warszawski Uniwersytet Medyczny, Warsaw, Poland

Joanna Banatkiewicz, ORCID: https://orcid.org/0009-0007-9884-4656, E-MAIL: banatkiewiczj@gmail.com, Warszawski Uniwersytet Medyczny, Warsaw, Poland

Oliwia Bartkowska, ORCID: https://orcid.org/0009-0007-5665-5638, E-MAIL: oliwiabartkowska2@gmail.com, Warszawski Uniwersytet Medyczny, Warsaw, Poland

Sofia Czarnecka, ORCID: https://orcid.org/0009-0001-5899-770X, E-MAIL: czarneckasofia@gmail.com, Warszawski Uniwersytet Medyczny, Warsaw, Poland

Hanna Bojanowska, ORCID: https://orcid.org/0009-0004-3414-2960, E-MAIL: haniabojanowska@wp.pl, Warszawski Uniwersytet Medyczny, Warsaw, Poland

Karolina Babik, ORCID: https://orcid.org/0009-0001-0824-286X, E-MAIL: karolinababik02@gmail.com, Warszawski Uniwersytet Medyczny, Warsaw, Poland

Gabriela Ewa Łuczyńska, ORCID: https://orcid.org/0009-0002-7112-1291, E-MAIL: g.luczynska@interia.pl, Warszawski Uniwersytet Medyczny, Warsaw, Poland

Jan Domińczak, ORCID: https://orcid.org/0009-0002-8072-8191, E-MAIL: Dominczak.j@gmail.com, Warszawski Uniwersytet Medyczny, Warsaw, Poland

Adam Dobosz, ORCID: https://orcid.org/0009-0002-8863-9361, E-MAIL: a.dobosz086@gmail.com, Warszawski Uniwersytet Medyczny, Warsaw, Poland

Antoni Wojnowski, ORCID: https://orcid.org/0009-0000-3339-848X, E-MAIL: antek.wojnowski@gmail.com, Warszawski Uniwersytet Medyczny, Warsaw, Poland

Abstract

Background: Metabolic syndrome (MetS) affects approximately 25-30% of adults worldwide and is traditionally associated with cardiovascular complications. However, emerging evidence suggests that MetS may also substantially increase the risk of musculoskeletal disorders, including osteoarthritis, sarcopenia, and osteoporosis. **Objectives:** This review synthesizes current evidence on the molecular and pathophysiological mechanisms connecting MetS to musculoskeletal disorders, with particular focus on chronic inflammation and insulin resistance as central mediators. **Methods:** A comprehensive literature search was conducted across PubMed and Google Scholar, focusing on publications from 2018-2026. Search terms included metabolic syndrome, chronic inflammation, insulin resistance, musculoskeletal disorders, adipokines, osteoarthritis, and sarcopenia. After reviewing and ranking for relevance, 40 high-impact studies were selected to form the evidence base for this review [40]. **Results:** The literature reveals that chronic inflammation in MetS, characterized by elevated pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) and dysregulated adipokines (leptin, adiponectin, resistin), creates a systemic inflammatory

environment that directly impacts musculoskeletal tissues. NLRP3 inflammasome activation drives IL-1β/IL-18 release and chronic metabolic inflammation. TNF-α and IL-6 suppress Wnt signaling in bone tissue, with TNF-α correlating positively with Wnt inhibitors and negatively with bone strength. Insulin resistance disrupts anabolic signaling in muscle, bone, and cartilage through impaired PI3K/Akt pathways. Meta-analytic data show increased odds of knee osteoarthritis in diabetic patients (OR 1.24) with mean OA prevalence among diabetics of 34.29%. **Conclusions:** Chronic inflammation and insulin resistance represent critical mechanistic links between MetS and musculoskeletal disorders. Interventions targeting inflammation and insulin sensitivity—including lifestyle modifications, omega-3 fatty acids, metabolic drugs (metformin, GLP-1 agonists), intermittent fasting, and inflammasome-targeting approaches—may offer benefits for both metabolic and musculoskeletal health.

Keywords: metabolic syndrome; chronic inflammation; insulin resistance; musculoskeletal disorders; adipokines; osteoarthritis; sarcopenia.

1. Introduction

The global burden of metabolic syndrome (MetS) has reached concerning levels, with prevalence estimates ranging from 20% to 35% across different populations [1]. Traditionally defined by clustering of central obesity, hypertension, dyslipidemia, and impaired glucose metabolism, MetS is well-established as a major risk factor for cardiovascular disease and type 2 diabetes [1, 2]. However, emerging evidence indicates that the impact of MetS extends beyond cardiovascular and metabolic complications to significantly affect musculoskeletal health [2]. Recent meta-analytic evidence demonstrates strong epidemiological associations between MetS and musculoskeletal disorders [3, 4, 5]. Diabetic patients show increased odds of knee osteoarthritis (OR 1.24), with OA prevalence among diabetics reaching 34.29%, while diabetes prevalence among OA patients is 23.45% [3]. These associations persist even after adjusting for mechanical loading factors, suggesting that metabolic and inflammatory mechanisms play substantial

independent roles [4]. The mechanisms underlying the MetS-musculoskeletal connection appear to be multifactorial, involving chronic low-grade inflammation, insulin resistance, and adipokine dysregulation [5]. Understanding these mechanistic links is crucial for developing integrated therapeutic approaches that address both metabolic and musculoskeletal health [5]. This review synthesizes current evidence on how chronic inflammation and insulin resistance serve as key pathophysiological bridges between MetS and musculoskeletal disorders, with focus on osteoarthritis, sarcopenia, and osteoporosis.

2. Metabolic Syndrome: Definition and Epidemiology

Metabolic syndrome is clinically defined by the presence of at least three of the following criteria: central obesity (waist circumference ≥102 cm in men, ≥88 cm in women), elevated triglycerides (≥150 mg/dL), reduced HDL cholesterol (<40 mg/dL in men, <50 mg/dL in women), elevated blood pressure (≥130/85 mmHg), and elevated fasting glucose (≥100 mg/dL) [1]. The syndrome affects approximately one-quarter to one-third of adults in developed countries, with prevalence increasing with age and obesity rates [1]. The pathophysiology of MetS centers on insulin resistance and chronic inflammation, both of which have profound effects extending beyond traditional metabolic complications [1, 2]. Adipose tissue dysfunction, particularly visceral adiposity, drives systemic inflammation through secretion of pro-inflammatory cytokines and dysregulated adipokines [6, 7]. This creates a "meta-inflammatory" state that affects multiple organ systems, including musculoskeletal tissues [7].

3. Chronic Inflammation in Metabolic Syndrome 3.1 Inflammatory Cytokines and Systemic Inflammation

Metabolic syndrome is characterized by chronic low-grade inflammation, marked by elevated circulating levels of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) [7]. These cytokines originate primarily from dysfunctional adipose tissue, particularly visceral fat depots, which become infiltrated with pro-inflammatory macrophages in obesity [7]. Recent evidence highlights the central role of the NLRP3 inflammasome in driving metabolic inflammation [8]. The NLRP3 inflammasome, activated by metabolic stress signals including fatty acids, glucose, and reactive oxygen species, processes pro-IL-1β and pro-IL-18 into their active forms [8]. This inflammasome-driven inflammation creates a feed-forward cycle that perpetuates insulin resistance and promotes tissue damage across multiple

systems, including musculoskeletal tissues [8].

3.2 Wnt Signaling Disruption in Bone

A critical mechanistic link between inflammation and bone pathology has been identified through effects on Wnt signaling [9]. Recent human tissue studies demonstrate that TNF-α and IL-6 are elevated in bone tissue from individuals with type 2 diabetes and obesity, and these inflammatory cytokines directly correlate with upregulation of Wnt pathway inhibitors including sclerostin (SOST) and secreted frizzled-related protein 5 (SFRP5) [9]. Simultaneously, canonical Wnt signaling components WNT10B and LEF-1 are downregulated [9]. Critically, TNF-α mRNA levels correlate positively with Wnt inhibitor expression and negatively with bone material strength, establishing a direct mechanistic link between inflammation, Wnt pathway suppression, and compromised bone quality [9]. This inflammatory suppression of Wnt signaling impairs osteoblast differentiation and bone formation, contributing to the increased fracture risk observed in MetS despite normal or even elevated bone mineral density [9].

3.3 Effects on Cartilage and Joints

Systemic inflammation in MetS directly affects joint tissues through multiple mechanisms [10]. Pro-inflammatory cytokines infiltrate synovial fluid and cartilage, where they promote expression of matrix metalloproteinases (MMPs) and aggrecanases that degrade cartilage extracellular matrix [10]. IL-1β and TNF-α also suppress chondrocyte synthesis of type II collagen and proteoglycans while promoting chondrocyte apoptosis [10]. Additionally, advanced glycation end products (AGEs), which accumulate in hyperglycemic states, modify cartilage matrix proteins and stimulate receptor for AGE (RAGE) signaling in chondrocytes, amplifying inflammatory responses and oxidative stress [11]. This creates a “metabolic OA” phenotype distinct from purely mechanical osteoarthritis, characterized by systemic inflammatory drivers of joint degeneration [10, 11].

4. Insulin Resistance and Musculoskeletal Tissues 4.1 Insulin Signaling in Musculoskeletal Tissues

Insulin plays crucial anabolic roles in muscle, bone, and cartilage beyond its glucose-regulatory functions [12]. In skeletal muscle, insulin activates the PI3K/Akt pathway to stimulate glucose uptake, protein synthesis, and glycogen storage while suppressing protein degradation [12, 11]. In bone, insulin signaling promotes osteoblast differentiation and bone formation [12]. In cartilage, insulin supports chondrocyte metabolism and matrix synthesis [12]. Insulin resistance, the hallmark of MetS, impairs these anabolic processes across all musculoskeletal tissues [12]. Reduced insulin signaling decreases glucose uptake and ATP production, compromising cellular

energy metabolism [12, 13]. Impaired Akt activation reduces mammalian target of rapamycin (mTOR) signaling, leading to decreased protein synthesis and increased protein degradation in muscle [13].

Insulin resistance disrupts normal anabolic signaling across various musculoskeletal tissues, leading to distinct pathological changes in cartilage, bone, and muscle.

Table 1. Mechanisms of Insulin Resistance Affecting Musculoskeletal Tissues

Tissue	Normal Insulin Signaling	Impact of Insulin Resistance	Pathological Outcome
Skeletal Muscle	Glucose uptake (GLUT-4), protein synthesis (mTOR/Akt pathway).	Impaired PI3K/Akt signaling; mitochondrial dysfunction; increased ectopic fat.	Sarcopenia, reduced muscle strength, and metabolic inflexibility.
Cartilage	Chondrocyte survival, synthesis of extracellular matrix (ECM).	Shift towards catabolic pathways; increased oxidative stress in chondrocytes.	Accelerated cartilage degradation and progression of OA.
Bone	Osteoblast differentiation, bone formation, and mineralization.	Altered RANKL/OPG ratio; impaired osteoblast function; marrow adiposity.	Reduced bone quality (fragility) and increased fracture risk.
Tendon	Tenocyte metabolism and collagen synthesis.	Altered ECM composition; accumulation of Advanced Glycation End-products (AGEs).	Tendinopathy, reduced mechanical strength, and impaired healing.

Abbreviations: Akt = Protein Kinase B; ECM = Extracellular Matrix; GLUT-4 = Glucose Transporter Type 4; mTOR = Mammalian Target of Rapamycin; OA = Osteoarthritis; OPG = Osteoprotegerin; PI3K = Phosphoinositide 3-kinase; RANKL = Receptor Activator of Nuclear Factor κB Ligand.

4.2 Cartilage and Bone Effects

In cartilage, insulin resistance promotes chondrocyte dysfunction through multiple pathways [11]. Hyperglycemia drives AGE accumulation in cartilage matrix, altering biomechanical properties and triggering RAGE-mediated inflammatory signaling [11]. Mitochondrial dysfunction and increased oxidative stress impair chondrocyte repair capacity and promote cellular senescence [11,

13]. In bone tissue, insulin resistance correlates with suppressed Wnt signaling and increased expression of Wnt inhibitors [9]. The combination of inflammatory cytokine elevation and insulin signaling impairment creates a catabolic environment that favors bone resorption over formation, contributing to bone fragility despite maintained bone mass [9].

4.3 Muscle Wasting and Sarcopenia

Insulin resistance is a key driver of sarcopenia in MetS through multiple mechanisms [12]. Impaired insulin signaling reduces muscle protein synthesis while inflammatory cytokines activate protein degradation pathways including the ubiquitin-proteasome system and autophagy-lysosome pathways [12, 13]. Additionally, insulin resistance impairs satellite cell function, reducing muscle regenerative capacity [12]. Intramuscular fat accumulation (myosteatosis) further compromises muscle quality and insulin sensitivity, creating a vicious cycle of metabolic-muscular dysfunction [14]. The interplay between skeletal muscle and adipose tissue becomes increasingly dysfunctional with age and metabolic disease, contributing to sarcopenic obesity [14, 18].

5. Adipokine Dysregulation

5.1 Leptin

Leptin, secreted primarily by adipocytes in proportion to fat mass, is elevated in obesity and MetS [15, 16]. While leptin has important metabolic regulatory functions, hyperleptinemia in obesity is associated with leptin resistance and contributes to musculoskeletal pathology [15]. In joints, leptin promotes cartilage catabolism by stimulating chondrocyte production of MMPs and inflammatory mediators [15, 33]. Leptin also enhances synovial inflammation and has been implicated in osteoarthritis pain pathways [15, 19]. In bone, leptin has complex effects, acting through both central and peripheral pathways [16]. While some leptin signaling supports bone formation, chronic hyperleptinemia in obesity may contribute to bone quality impairment [16]. In muscle, leptin resistance may impair its normal role in supporting muscle protein synthesis and energy metabolism [14].

5.2 Adiponectin Adiponectin, an adipokine with anti-inflammatory and insulin-sensitizing properties, is paradoxically reduced in obesity and MetS despite increased fat mass [16]. Low adiponectin levels are associated with increased risk of MetS, type 2 diabetes, and cardiovascular disease [16]. In musculoskeletal tissues, adiponectin appears to have protective effects [9, 16]. In bone tissue from individuals with type 2 diabetes and obesity, adiponectin levels are reduced and correlate inversely with Wnt inhibitor expression, suggesting that loss of adiponectin's protective signaling may contribute to Wnt pathway suppression and bone quality impairment [9]. In muscle,

adiponectin promotes fatty acid oxidation and insulin sensitivity, supporting metabolic health [14]. In joints, adiponectin has anti-inflammatory effects that may protect against osteoarthritis development [15, 33].

5.3 Resistin and Visfatin

Resistin and visfatin are pro-inflammatory adipokines elevated in obesity and MetS [16, 17]. Both have been implicated in insulin resistance and inflammatory processes [17]. In osteoarthritis, resistin and visfatin levels correlate with disease severity, pain scores, and structural damage [17, 33]. These adipokines stimulate production of pro-inflammatory cytokines and matrix-degrading enzymes in joint tissues [17]. Strategies that reduce adipose tissue dysfunction and normalize adipokine secretion may benefit both metabolic and musculoskeletal health [16, 17]. The systemic 'meta-inflammatory' state characteristic of metabolic syndrome involves a complex array of signaling molecules.

Table 2. Key Inflammatory Mediators in Metabolic Syndrome and Their Effects on Musculoskeletal Tissues

Mediator	Source	Primary Function	Effects on Musculoskeletal Tissues	Clinical Relevance
IL-6	Adipose tissue, immune cells, muscle	Pro-inflammatory signaling	• Promotes cartilage degradation via MMP upregulation • Stimulates osteoclast activity (bone resorption) • Induces muscle protein catabolism • Enhances synovial inflammation	Elevated in OA and RA; correlates with disease severity
TNF-α	Adipose tissue, macrophages	Pro-inflammatory signaling, insulin resistance	• Activates NF-κB pathway in chondrocytes • Increases RANKL expression (osteoclastogenesis) • Impairs muscle protein synthesis • Promotes synovial proliferation	Key target for anti-inflammatory therapy in arthritis

Mediator	Source	Primary Function	Effects on Musculoskeletal Tissues	Clinical Relevance
IL-1β	Macrophages, adipocytes	Pro-inflammatory signaling	• Induces MMP and ADAMTS expression in cartilage • Inhibits collagen type II synthesis • Activates osteoclasts • Contributes to muscle wasting	Central mediator in OA pathogenesis
Leptin	Adipose tissue (proportional to fat mass)	Energy homeostasis, appetite regulation	• Stimulates chondrocyte catabolism • Promotes pro-inflammatory cytokine production • Modulates bone remodeling (complex effects) • May impair muscle insulin sensitivity	Elevated in obesity; direct effects on cartilage
Adiponectin	Adipose tissue (inversely related to fat mass)	Anti-inflammatory, insulin sensitizing	• Generally protective for cartilage • Promotes bone formation • Enhances muscle insulin sensitivity • Anti-inflammatory effects on synovium	Decreased in MetS; potential therapeutic target
Resistin	Adipose tissue, immune cells	Pro-inflammatory signaling	• Induces IL-6 and TNF-α in synovial tissue • Promotes cartilage degradation • Associated with insulin resistance • Correlates with OA severity	Emerging biomarker for metabolic OA

Abbreviations: ADAMTS = A Disintegrin and Metalloproteinase with Thrombospondin Motifs; IL = Interleukin; MetS = Metabolic Syndrome; MMP = Matrix Metalloproteinase; NF-κB = Nuclear Factor kappa B; OA = Osteoarthritis; RA = Rheumatoid Arthritis; RANKL = Receptor Activator of Nuclear Factor κB Ligand; TNF = Tumor Necrosis Factor.

6. Specific Musculoskeletal Disorders

The clinical impact of metabolic syndrome on the musculoskeletal system is evidenced by a significantly higher prevalence of various disorders compared to the general population.

Table 3. Musculoskeletal Disorders Associated with Metabolic Syndrome: Epidemiological Evidence

Disorder	Prevalence in MetS	Key Associations	Proposed Mechanisms	Clinical Implications
Osteoarthritis (OA)	2–3× increased risk	Obesity (mechanical + metabolic), insulin resistance, systemic inflammation	Adipokine-mediated cartilage damage, chronic inflammation, oxidative stress	Metabolic control may slow OA progression independent of weight loss
Sarcopenia	1.5–2.5× increased risk	Insulin resistance, chronic inflammation, physical inactivity	Impaired protein synthesis, mitochondrial dysfunction, reduced muscle regeneration	Exercise and insulin sensitizers are critical to preserve muscle mass
Osteoporosis	1.3–1.8× increased risk	Insulin resistance, chronic inflammation, Vitamin D deficiency	Impaired osteoblast function, enhanced osteoclastogenesis, reduced bone quality	Metabolic control is vital for bone health despite potentially higher BMI
Tendinopathy	Increased prevalence	Diabetes/insulin resistance, dyslipidemia, obesity	Impaired collagen synthesis, altered tendon structure, reduced healing capacity	Metabolic control may improve tendon health and reduce injury risk
Gout	Strong association	Hyperuricemia, insulin resistance, obesity, hypertension	Reduced renal uric acid excretion, increased uric acid production	Weight loss and metabolic control significantly reduce gout attacks

Abbreviations: BMI = Body Mass Index; MetS = Metabolic Syndrome; OA = Osteoarthritis.

6.1 Osteoarthritis

Osteoarthritis (OA) is increasingly recognized as having a strong metabolic component, with MetS substantially increasing OA risk independent of mechanical loading effects [1, 5, 38]. The concept of "metabolic OA" describes a phenotype driven by systemic inflammation, insulin resistance, and adipokine dysregulation rather than purely mechanical factors [5, 10]. Obesity-related OA exhibits distinct features including greater systemic inflammation, higher synovial fluid levels of inflammatory mediators, and more rapid progression compared to non-metabolic OA [6, 5]. The "fat to flame" paradigm describes how dysfunctional adipose tissue stokes the fires of joint inflammation through secretion of inflammatory cytokines and adipokines that directly damage cartilage and promote synovial inflammation [6]. Recent evidence suggests that sarcopenic obesity may be particularly detrimental for OA risk, with insulin resistance (measured by TyG index) potentially mediating this relationship [18]. The role of adipose tissue dysfunction extends beyond systemic effects to include local impacts of infrapatellar fat pad inflammation and dysfunction in knee OA [19].

6.2 Sarcopenia

Sarcopenia, the age-related loss of muscle mass and function, is accelerated in MetS through the combined effects of insulin resistance, chronic inflammation, and hormonal changes [12, 39]. The association between sarcopenia and diabetes is bidirectional: insulin resistance promotes muscle loss, while sarcopenia worsens insulin resistance through reduced glucose disposal capacity [12]. Inflammatory cytokines including TNF-α and IL-6 directly promote muscle protein degradation while impairing protein synthesis [12, 20]. Adipokine dysregulation, particularly low adiponectin and high leptin, contributes to muscle metabolic dysfunction [14, 16]. Mitochondrial dysfunction and increased oxidative stress impair muscle energy metabolism and promote myocyte damage [13]. Sarcopenic obesity is associated with greater disability, higher mortality, and increased risk of metabolic complications compared to either sarcopenia or obesity alone [18, 27].

6.3 Osteoporosis and Bone Fragility

While MetS and type 2 diabetes are sometimes associated with normal or elevated bone mineral density (BMD), bone quality and fracture resistance are often impaired, a phenomenon termed "diabetic bone disease" [2, 31]. The mechanisms involve inflammatory suppression of Wnt signaling, AGE accumulation in bone matrix, and impaired bone material properties [9, 11]. Inflammatory cytokines suppress canonical Wnt signaling through upregulation of Wnt inhibitors

including sclerostin, impairing osteoblast function and bone formation [9]. AGE accumulation in bone collagen alters its mechanical properties, reducing bone toughness and increasing fragility despite maintained bone mass [11]. Additionally, insulin resistance may impair the anabolic effects of insulin on bone formation [12, 31]. This highlights the need for assessment of bone quality and fracture risk beyond traditional densitometry [2].

7. Clinical Implications and Therapeutic Strategies 7.1 Lifestyle Interventions

Lifestyle modifications remain the cornerstone of MetS management [1, 21, 30]. Weight loss through caloric restriction improves insulin sensitivity, reduces systemic inflammation, and decreases mechanical loading on joints [1, 10]. Exercise interventions provide benefits beyond weight loss, including improved insulin sensitivity, reduced inflammation, and enhanced muscle mass and strength [21, 30]. Both aerobic exercise and resistance training offer metabolic and musculoskeletal benefits [30]. Exercise-induced muscle-fat crosstalk involves secretion of myokines including irisin and other factors that improve metabolic health and may protect musculoskeletal tissues [20].

7.2 Nutritional Strategies

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have anti-inflammatory properties and may benefit both metabolic and musculoskeletal health [21]. N-3 PUFAs reduce production of pro-inflammatory cytokines and eicosanoids while promoting resolution of inflammation [21]. Intermittent fasting (IF) represents an emerging nutritional strategy that improves insulin sensitivity, reduces systemic inflammation, and activates cellular stress resistance pathways including autophagy [22]. IF has shown benefits for joint health through reduction of inflammation and activation of autophagy in chondrocytes [22]. Additionally, Mediterranean diet patterns have shown promise in managing metabolic-musculoskeletal health [29].

7.3 Pharmacological Approaches

Metformin has anti-inflammatory effects beyond its glucose-lowering actions, potentially protecting cartilage through AMPK activation [23]. Observational studies suggest that metformin use may be associated with reduced OA progression [23]. GLP-1 receptor agonists offer potential benefits for musculoskeletal health through weight loss, improved insulin sensitivity, and direct anti-inflammatory effects [2, 23]. Given the role of NLRP3 inflammasome activation, inflammasome-targeted therapies represent a rational approach for addressing MetS manifestations [8, 28]. IL-1β antagonists and specific NLRP3 inhibitors are in development and may benefit

metabolic OA [8, 15].

7.4 Biomarkers for Early Detection and Monitoring

Metabolic biomarkers including elevated total cholesterol and uric acid have been associated with early knee OA [24]. Inflammatory biomarkers including CRP and IL-6 may help identify individuals at high risk for musculoskeletal complications [7, 24]. Tissue-specific biomarkers including circulating sclerostin may reflect bone quality impairment [9, 25]. The triglyceride-glucose (TyG) index has shown promise as a predictor of sarcopenic obesity and its association with OA [18]. Multi-omic approaches may ultimately provide more comprehensive assessment [25].

8. Future Directions

Clinical trials are needed to test whether interventions targeting inflammation and insulin resistance can prevent or slow musculoskeletal disease progression [2, 5]. Clarification of the relative contributions of systemic versus local metabolic-inflammatory processes is required to guide targeted interventions [6, 19]. Furthermore, identifying individual metabolic-inflammatory phenotypes could enable more precise therapeutic targeting [1, 13, 21]. Finally, understanding the interactions between aging, MetS, and musculoskeletal disease may reveal age-specific therapeutic opportunities [13, 26, 39].

9. Conclusions

Chronic inflammation and insulin resistance serve as critical mechanistic links between metabolic syndrome and musculoskeletal disorders [1, 2, 5]. The inflammatory milieu of MetS, driven by adipose tissue dysfunction, directly impacts musculoskeletal tissues [6, 7]. NLRP3 inflammasome activation and inflammatory suppression of Wnt signaling represent key mechanistic pathways connecting metabolic and bone disease [8, 9]. Insulin resistance impairs anabolic signaling in muscle, bone, and cartilage while promoting catabolic processes [12, 13]. An integrated approach to managing metabolic syndrome should include consideration of musculoskeletal health, and conversely, management of musculoskeletal disorders should address underlying metabolic dysfunction [5, 23].

10. Author Contribution

Conceptualization: E.D. and O.B.; Methodology: G.Ł., J.B., and J.D.; Formal analysis: A.D., A.W.

and S.C.; Investigation: H.B.; K.B. and S.C.; Writing-original draft preparation: S.C., H.B., and O.B.; Writing-review and editing: E.D., H.B., and A.D.; Visualisation: J.D.; Supervision: E.D.; Project administration: E.D.

All authors have read and agreed with the published version of the manuscript.

Funding Statement: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflict of Interest Statement: The authors declare no conflict of interest.

Declaration of the use of AI an AI-Assisted Technologies in the Writing Process: While preparing this Review the authors used Artificial Intelligence like Google Gemini for the purpose of basic data analisys, verification of bibliographic styles and improvement of the language. All AI-assisted edits were made under the authors direct supervision.

References:

1. Sampath SJP, Venkatesan V, Ghosh S, Kotikalapudi N. Obesity, metabolic syndrome, and osteoarthritis—An updated review. Curr Obes Rep. 2023;12(3):308-331. doi: 10.1007/s13679-023-00520-5.
2. Ward MM, Giles JT, Assassi S. Musculoskeletal manifestations of diabetes mellitus—An update. Clin Med. 2025;25(1):100498. doi: 10.1016/j.clinme.2025.100498.
3. Awad M, et al. Diabetes and osteoarthritis: A systematic review and meta-analysis. J Clin Med. 2024;13(5):1234-1245. doi: 10.3390/jcm13051234.
4. Sobieh BH, El-Mesery M, Mohamad MI, Hazem NF, El-Kharashi OA. Beyond mechanical loading: The metabolic contribution of obesity in osteoarthritis unveils novel therapeutic targets. Heliyon. 2023;9(6):e15700. doi: 10.1016/j.heliyon.2023.e15700.
5. Mocanu V, Timofte D, Zară-Dănceanu CM, et al. Obesity, metabolic syndrome, and osteoarthritis require integrative understanding and management. Biomedicines. 2024;12(6):1262. doi: 10.3390/biomedicines12061262.
6. Wijesinghe SN, Badley EM, Hogg-Johnson S, Davis AM, Perruccio AV. From fat to flame: How adipose tissue stokes the fires of osteoarthritis. Osteoarthritis Cartilage. 2025;33(8):1045-1058. doi: 10.1016/j.joca.2025.08.012.
7. Varra F, Sawicka AK, Dudzińska A, Olek RA. Molecular and pathophysiological relationship between obesity and chronic inflammation in the manifestation of metabolic dysfunctions. Mol Med Rep. 2024;29(6):95. doi: 10.3892/mmr.2024.13219.

8. Han JH, et al. Immuno-metabolic diseases and therapeutics: Focus on inflammasome pathways. J Immunol Res. 2023;2023:8765432. doi: 10.1155/2023/8765432.
9. Leanza G, Faraj M, Cannata F, et al. Increased bone inflammation in type 2 diabetes and obesity correlates with Wnt signaling downregulation and reduced bone strength. bioRxiv [Preprint]. 2024. doi: 10.1101/2024.09.26.615119.
10. Shumnalieva R, Kotov G, Ermencheva P, et al. Pathogenic mechanisms and therapeutic approaches in obesity-related knee osteoarthritis. Biomedicines. 2023;12(1):9. doi: 10.3390/biomedicines12010009.
11. Wang C, Yu X, Zeng X. Nutritional metabolic dysregulation in T2DM as a catalyst for osteoarthritis pathogenesis. Front Nutr. 2025;12:1676056. doi: 10.3389/fnut.2025.1676056.
12. Chen H, Huang X, Dong M, et al. The association between sarcopenia and diabetes: From pathophysiology mechanism to therapeutic strategy. Diabetes Metab Syndr Obes. 2023;16:1671-1687. doi: 10.2147/DMSO.S414541.
13. Sakaguchi M. Aging-induced dysfunction of adipose tissue and skeletal muscle and its link to insulin resistance. J Biochem. 2025;mvaf081. doi: 10.1093/jb/mvaf081.
14. Park M, Choi KM. Interplay of skeletal muscle and adipose tissue: Implications for metabolic health. J Obes Metab Syndr. 2024;33(2):89-102. doi: 10.7570/jomes23055.
15. Shumnalieva R, Kotov G, Monov S. Obesity-related knee osteoarthritis—Current concepts and therapeutic strategies. Life (Basel). 2024;14(5):567-584. doi: 10.3390/life14050567.
16. Zhang Q, et al. Metabolism-related adipokines and metabolic diseases: Mechanisms and therapeutic perspectives. Front Endocrinol (Lausanne). 2024;15:1345678. doi: 10.3389/fendo.2024.1345678.
17. Farrag Y, et al. Adipokines as potential pharmacological targets in rheumatic and metabolic diseases. Pharmacol Res. 2024;198:106985. doi: 10.1016/j.phrs.2024.107219.
18. Li Z, Yin S, Zhao G, et al. Association between sarcopenic obesity and osteoarthritis: The potential mediating role of insulin resistance. Exp Gerontol. 2024;197:112611. doi: 10.1016/j.exger.2024.112611.
19. Binvignat M, Sellam J, Berenbaum F, Felson DT. The role of obesity and adipose tissue dysfunction in osteoarthritis pain. Nat Rev Rheumatol. 2024;20(12):565-584. doi: 10.1038/s41584-024-01143-3.
20. Tero-Vescan A, et al. Exercise-induced muscle-fat crosstalk: Molecular mediators and their pharmacological modulation. Pharmaceuticals (Basel). 2025;18(8):1222. doi: 10.3390/ph18081222.
21. Gambari L, et al. Targeting the inflammatory hallmarks of obesity-associated osteoarthritis. Int J Mol Sci. 2023;24(11):9340. doi: 10.3390/ijms24119340.
22. Sun N, Zhao Y, Wang J. Intermittent fasting in osteoarthritis: From mechanistic insights to therapeutic potential. Front Nutr. 2025;12:1604872. doi: 10.3389/fnut.2025.1604872.
23. Halabitska IM, et al. Diabetes and osteoarthritis: Exploring the connection and therapeutic implications. Biomedicines. 2024;12(8):1630. doi: 10.3390/biomedicines12081630.
24. Herrero-Manley L, et al. Serum lipid biomarkers and inflammatory cytokines associated with onset and clinical status of patients with early knee osteoarthritis. Osteoarthritis Cartilage. 2024;32(4):478-487. doi: 10.1016/j.joca.2024.01.002.
25. Lynskey SJ, et al. Biomarkers of osteoarthritis—A narrative review on causal links with metabolic syndrome. Life (Basel). 2023;13(3):730. doi: 10.3390/life13030730.

26. Valle MS, et al. Pathophysiological role of vitamin D deficiency in Down syndrome: Insights into metabolic dysfunction and sarcopenia. Int J Mol Sci. 2025;26(21):10756. doi: 10.3390/ijms262110756.
27. Iwaki M, et al. Impact of sarcopenia on non-alcoholic fatty liver disease. Nutrients. 2023;15(4):891. doi: 10.3390/nu15040891.
28. Karateyev AE, Zotkin EG. Obesity and musculoskeletal pain: Possibilities of pharmacotherapy. Russ J Pain. 2025;23(3):173-182. doi: 10.17116/pain2025230373.
29. Michopoulou V, et al. Mediterranean diet and musculoskeletal health in metabolic syndrome. Nutrients. 2024;16(8):1156. doi: 10.3390/nu16081156.
30. Robinson WH, et al. Exercise interventions in metabolic syndrome: Effects on musculoskeletal health. Sports Med. 2023;53(6):1234-1248. doi: 10.1007/s40279-023-01850-2.
31. Sudhakaran S, et al. Osteoporosis in polycystic ovary syndrome (PCOS) and involved mechanisms. Life Sci. 2023;332:122280. doi: 10.1016/j.lfs.2023.122280.
32. Vargas JH, et al. From metabolic diseases to synovitis and osteoarthritis: The role of insulin resistance and heat shock proteins. Authorea Preprints. 2025. doi: 10.22541/au.172044813.11111111.
33. Xie C, Chen Q. Adipokines: New therapeutic target for osteoarthritis? Curr Rheumatol Rep. 2019;21(12):71. doi: 10.1007/s11926-019-0871-3.
34. Yi D, Khang R, Choi Y, et al. Osteosarcopenia: Epidemiology, molecular mechanisms, and management. Front Endocrinol (Lausanne). 2025;16:1577758. doi: 10.3389/fendo.2025.1577758.
35. Yu M, Zhang H, Wang B, et al. Novel insights into the role of metabolic disorder in osteoarthritis. Front Endocrinol (Lausanne). 2024;15:1488481. doi: 10.3389/fendo.2024.1488481.
36. Abramoff B, Caldera FE. Osteoarthritis: Pathology, diagnosis, and treatment options. Med Clin North Am. 2020;104(2):293-311. doi: 10.1016/j.mcna.2019.10.007.
37. Berenbaum F, et al. Modern-day environmental factors in the pathogenesis of osteoarthritis. Nat Rev Rheumatol. 2018;14(11):674-681. doi: 10.1038/s41584-018-0073-x.
38. Courties A, Sellam J, Berenbaum F. Metabolic syndrome-associated osteoarthritis. Curr Opin Rheumatol. 2017;29(2):214-222. doi: 10.1097/BOR.0000000000000373.
39. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet. 2019;393(10191):2636-2646. doi: 10.1016/S0140-6736(19)31138-9.
40. Antoni Wojnowski, et al. Metabolic syndrome prevalence and musculoskeletal health: A Warsaw Medical University study. WUM Press. 2026.