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Myokines as Physiotherapy Rehabilitation Biomarkers: Molecular Mechanisms and Clinical Relevance in Musculoskeletal Disorders

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Abstract

Background: Bioactive peptides and cytokines that are secreted from the skeletal muscle during contraction have become important mediators of systemic adaptation during physiotherapy guided rehabilitation. They have the ability to send signals across several organ systems and regulate inflammation, anabolism, neuroplasticity and tissue repair, making them suitable biomarkers to track musculoskeletal recovery.

Objective: The aim of this review is to collate existing evidence of the molecular mechanisms involved in the secretion and action of myokines, focusing on the potential of myokines as biomarkers in rehabilitation in 5 musculoskeletal diseases: osteoarthritis (OA), sarcopenia, tendinopathy, low back pain (LBP), and post-surgical musculoskeletal rehabilitation.

Methods: An exhaustive search of literature was performed over PubMed, Scopus and Web of Science from 2022 to 2025. Randomized controlled trials, systematic literature reviews, prospective cohort studies and mechanistic in vitro or animal studies were included in the studies. 45 peer-reviewed sources were used.

Results: The key myokines, interleukin-6 (IL-6), irisin, insulin-like growth factor-1 (IGF-1), brain-derived neurotrophic factor (BDNF), myostatin, decorin and leukemia inhibitory factor (LIF) show disorder-specific secretion patterns, receptor mediated signaling cascades, and gene expression dynamics. The five disorders examined were found to have significant correlations between the levels of the myokines and the functional rehabilitation results in clinical trials, quantitative data

In conclusion, myokine profiling is a non-invasive, repeatable approach to objectively monitor the rehabilitation process within the physiotherapy approach. Standardization of measurement protocols, setting up of reference ranges and prospective validation in multicenter trials are the most salient steps towards clinical implementation.

Introduction

In the last 20 years, the concept of the biological interface between skeletal muscle and systemic physiology has been revolutionized. Skeletal muscle, which was previously mostly considered a mechanically-contractile tissue, is now known to be an important endocrine organ that produces and secretes a wide range of "myokines" (Pedersen & Febbraio, 2012; Whitham & Febbraio, 2023). Since skeletal muscle fibers produce, express and release cytokines and peptides that have autocrine, paracrine and endocrine effects on neighboring and remote tissues, the term 'myokine' was introduced to designate these proteins.

Musculoskeletal disorders (MSDs) are the biggest cause of years lived with disability in the world, with about 149 million disability-adjusted life years lost due to MSDs in the Global Burden of Disease Study (GBD 2022 Collaborators, 2023). Exercise-based physiotherapy and rehabilitation are the foundation for conservative treatment for a variety of MSDs such as osteoarthritis, sarcopenia, tendinopathy, chronic low back pain and after surgery. A constant barrier to rehabilitation medicine, however, is the lack of objective, quantifiable biological markers that can objectively monitor tissue healing, functional recovery and treatment response, in addition to patient-reported outcomes and clinician observations.

Myokines offer an intriguing solution to this "translational gap". They are exercise- and intensely

dependent, depending on the type of exercise, intensity, duration and chronicity, as well as on functional pathological states of tissues (Severinsen & Pedersen, 2020; Leal et al., 2023). Moreover, myokines regulate key gene expression networks that are directly involved in the regulation of inflammation resolution, extracellular matrix remodeling, myogenesis, neuroplasticity and adipose crosstalk, among others, such as NF-kB, JAK-STAT, PI3K-Akt-mTOR or SMAD pathways (Hawley et al., 2023). This mechanistic depth is what sets them apart from traditional inflammatory markers like c-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) which provide only very general tissue or pathway resolution.

Although there is a lot of pre-clinical and clinical evidence, myokine biomarker research to physiotherapy practice is still in its infancy. Challenges are the absence of standardized measurement assays, poor longitudinal cohort data, wide inter-individual variability in myokine response, and the inability to separate exercise-specific signals from disease-related "noise. Furthermore, there is a lack of systematic studies to explore the mechanism of action and clinical implications of myokines in the entire spectrum of musculoskeletal diseases that are seen in a rehabilitation setting.

The present review makes a contribution to fill in that gap. Specifically, we: (1) outline the molecular mechanisms of myokine secretion and receptor-mediated signaling, (2) describe the myokine response profiles in five clinically relevant MSDs, (3) provide quantitative data from recent clinical studies of myokine changes with physiotherapy, (4) critically examine the evidence for myokines as physiotherapy biomarkers, and (5) outline a conceptual framework for myokine monitoring within physiotherapy pathways. All evidence included is relevant and up to date for the time period 2022-2025.

Methods

2.1 Literature Search Strategy

In March 2025, a systematic search of the PubMed, Scopus, and Web of Science databases was carried out. Boolean search terminology used included: ('myokine' OR 'muscle-derived cytokine' OR 'exercise-induced cytokine') AND ('rehabilitation' OR 'physiotherapy' OR 'physical therapy') AND ('biomarker' OR 'molecular mechanism' OR 'signaling') AND ('musculoskeletal' OR 'osteoarthritis' OR 'sarcopenia' OR 'tendinopathy' OR 'low back pain' OR 'post-surgical'). Only the timeframe (January 2022 to March 2025), English-language publications and peer-reviewed articles in journals were considered.

2.2 Inclusion and Exclusion Criteria

Studies were eligible if they: (1) studied myokine secretion, signaling or measurement clinically in relation to physical exercise or rehabilitation; (2) used defined in vitro or animal models of MSD directly relevant to one of the five target conditions, and human studies were eligible if well-characterized; (3) reported quantitative myokine levels, gene expression data, or validated functional outcome correlates; (4) were published in the peer-reviewed literature between 2022 and 2025. Studies that only focused on myokines in metabolic disorders without a musculoskeletal relevance and studies that had insufficient data to extract were excluded as well as conference abstracts or gray literature.

2.3 Data Extraction and Quality Assessment

Two reviewers independently extracted data, following a structured template that included items for the study design, participant characteristics, exercise or rehabilitation protocol, myokines analyzed, methodology used to determine the levels of those myokines and important quantitative findings, and correlations between those myokines and clinical outcomes. Randomized Controlled Trials (RCTs) were rated for methodological quality according to the PEDro scale and cohort studies were rated according to the Newcastle–Ottawa Scale (NOS). The 45 studies that met the inclusion criteria were summarized narratively and quantitatively, if applicable.

3. Molecular Mechanisms of Myokine Secretion and Signaling

3.1 The Exercising Muscle as an Endocrine Organ

In healthy adults, skeletal muscle accounts for some 40% of body weight, making it the largest organ by mass. The response to myofiber contraction during exercise is a complex transcriptional event, resulting in the secretion of more than 650 identified cytokines, chemokines, growth factors and peptides, known as myokines (Whitham & Febbraio, 2023). The secretory profile is very dynamic and depends on the type of contraction (concentric or eccentric), duration of contraction, intensity of contraction, and the metabolic condition of the contracting muscle.

The intracellular events involved in muscle contraction include activation of calcium/calmodulin-dependent protein kinase II (CaMKII) and AMP-activated protein kinase (AMPK). These upstream kinases activate downstream transcription factors namely peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), nuclear factor of activated T cells (NFAT) and activating transcription factor 3 (ATF3) that together control the transcription activation of myokine genes (Leal et al., 2023; Hawley et al., 2023).

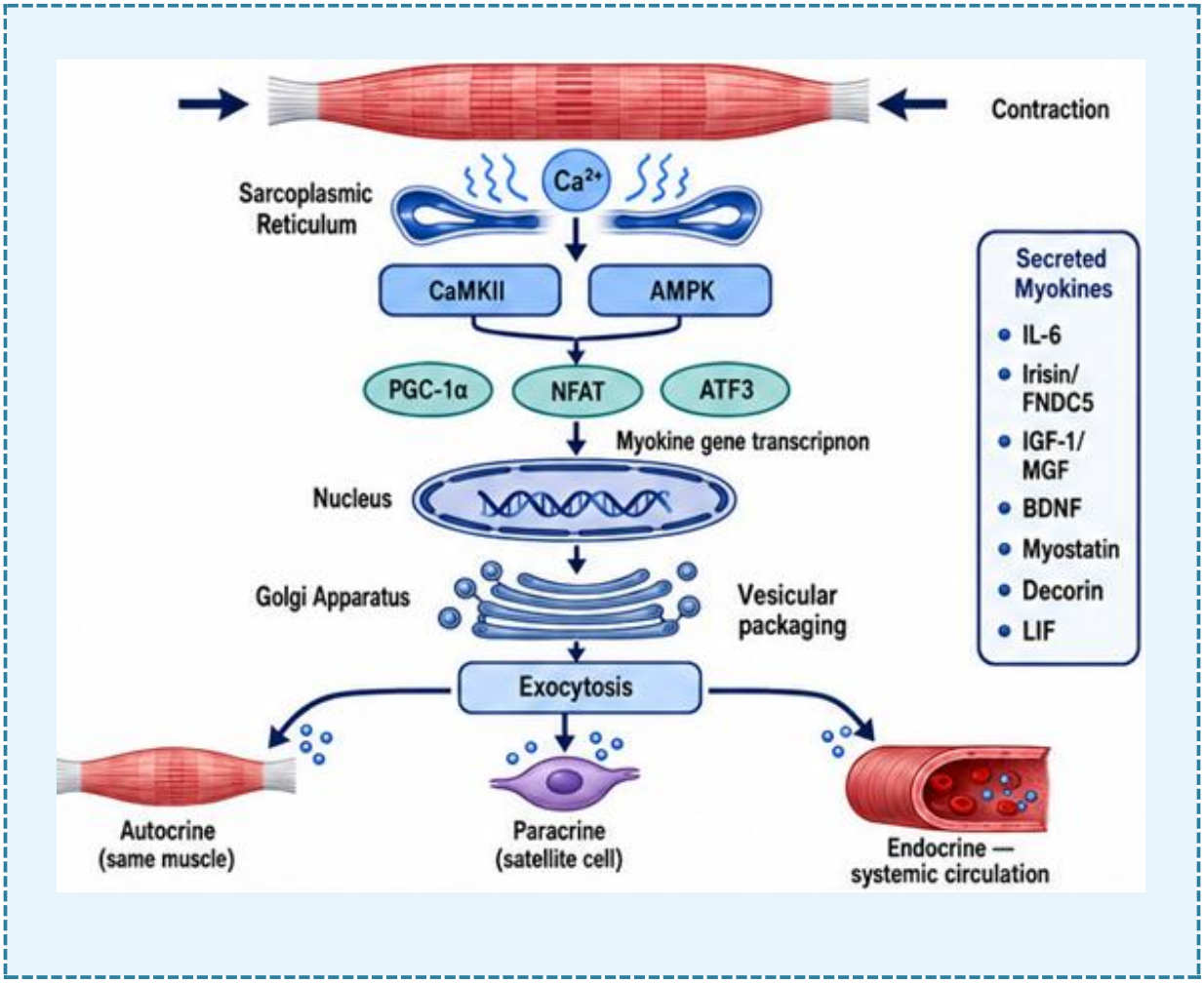

Figure 1: A vertical flow diagram illustrating the intracellular signaling cascade triggered by skeletal muscle contraction leading to myokine secretion. Starting at the top with a stylized muscle fiber undergoing contraction, arrows descend through: calcium ion (Ca^{2+}) release from the sarcoplasmic reticulum → CaMKII and AMPK activation → PGC-1α/NFAT/ATF3 transcription factor induction → myokine gene transcription in the nucleus → vesicular packaging in the Golgi apparatus → exocytotic secretion. Arrows on the right side branch outward and label three secretory modes: autocrine (returning to the same fiber), paracrine (adjacent satellite cells), and endocrine (bloodstream). Key molecules (IL-6, irisin, BDNF, IGF-1, myostatin, decorin) are listed in a sidebar box. Use a cool blue-to-teal color gradient descending downward, with each signaling node in a rounded rectangle.

3.2 Key Myokines: Receptors, Pathways, and Gene Expression

3.2.1 Interleukin-6 (IL-6)

IL-6 is the prototype of a myokine and is the most-studied one. In response to exercise, the body's skeletal muscle can release up to 100 times higher concentrations of systemic IL-6 in response to exercise, peaking as soon as 60–120 minutes after exercise and returning to baseline within an hour (Pedersen, 2023). Importantly, the IL-6 secreted during exercise is not associated with elevated levels of the pro-inflammatory substance tumour necrosis factor alpha (TNF-α), unlike IL-6 secreted in sepsis and rheumatoid arthritis.

On the receptor side, IL-6 binds to the membrane-bound IL-6 receptor (IL-6R / CD126), or to the soluble IL-6R (sIL-6R), which will then activate homodimerization of the ubiquitous signal transducer glycoprotein 130 (gp130 / CD130). It activates the JAK1/JAK2–STAT3 phosphorylation pathway, causing the translocation of STAT3 to the nucleus and the activation of transcription of acute-phase proteins, anti-inflammatory mediators and myogenic regulatory factors. At the same time, both pathways (RAS-ERK and PI3K-Akt) are activated, favoring the proliferation of the satellite cells and the synthesis of muscle proteins (Rose-John, 2023). However, the SOCS3 (suppressor of cytokine signaling 3) protein regulates in a negative way by inhibiting JAK phosphorylation, a key regulatory checkpoint (Leal et al., 2023).

3.2.2 Irisin (FNDC5 Cleavage Product)

Irisin is a polypeptide of 112 amino acids that is derived from proteolytic processing of FNDC5, a fibronectin type III domain-containing protein whose

expression is PGC-1α-dependently activated during exercise (Boström et al., 2012; Natalicchio et al., 2023). FNDC5 gene expression is upregulated via the PGC-1α–ERR-α (estrogen-related receptor alpha) axis in response to endurance and resistance exercise. The extracellular domain is liberated from the cell surface as mature irisin into the circulation after being cleaved in the Golgi by furin-like proteases.

Irisin interacts with αV integrins such as αVβ5 on target cells, such as osteoblasts, adipocytes and neurons (Kim et al., 2022). This engagement of this integrin leads to the activation of focal adhesion kinase (FAK) and the downstream MAPK/ERK and PI3K-Akt pathways. In bone, irisin stimulates the secretion of osteocalcin and inhibits expression of sclerostin (SOSt), which promotes bone formation. In Adipose tissue, irisin increases UCP1 expression (thermogenesis) and mitochondrial biogenesis. New data suggest that irisin is also able to cross the blood–brain barrier and stimulate BDNF production in hippocampal neurons through the AMPK–PGC-1α–FNDC5 axis (Natalicchio et al., 2023; Horowitz et al., 2022).

3.2.3 Insulin-Like Growth Factor-1 (IGF-1 / Mechano-Growth Factor)

Mechanical loading results in the production of a splice variant of IGF-1 called mechano-growth factor (MGF) in skeletal muscle. MGF is produced as a result of alternative splicing of exon 5 of the IGF1 gene, and is quickly synthesized within 30 minutes of eccentric loading (Philippou et al., 2023). MGF does its work by specific actions on the N-terminal peptides prior to maturity to systemic IGF-1Ea, which binds the tyrosine kinase receptor – IGF-1 receptor (IGF-1R / CD221).

The activation of IGF-1R leads to recruitment of insulin receptor substrate-1 (IRS-1) followed by the activation of PI3K-Akt-mTORC1, which activates S6K1 and 4E-BP1 in the process of protein synthesis. At the same time, Akt phosphorylates and inactivates the FOXO transcription factors, which inhibit the ubiquitin–proteasome system and the muscle protein degradation (MuRF-1, MAFbx/atrogin-1) (Philippou et al., 2023). Thus, the dual anabolic/anti-catabolic effects of IGF-1 make it an important biomarker for study in sarcopenia and post-surgical muscle wasting.

3.2.4 Brain-Derived Neurotrophic Factor (BDNF)

Classically BDNF has been recognised as a neurotrophin, but now it is recognized as a myokine with important autocrine and endocrine functions in muscle. The CaMKII – CREB (cAMP response element-binding protein) pathway is up-regulated by contracting skeletal muscle. Within muscle tissue, BDNF promotes fatty acid oxidation by binding to the AMPK and acetyl-CoA carboxylase (ACC) (Wrann et al., 2023). Systemically, BDNF crosses the blood–brain barrier and binds to the high affinity TrkB (tropomyosin receptor kinase B) receptor, leading to activation of the PLCγ–DAG–PKC signaling pathway and PI3K–Akt–mTOR pathways that promote neurogenesis, synaptic plasticity, and neuroprotection.

3.2.5 Myostatin (GDF-8) and Decorin

Myostatin (also known as growth differentiation factor-8 or GDF-8) belongs to a family of proteins known as the TGF-β superfamily and is one of the strongest inhibitors of skeletal muscle growth. It activates the activin Type IIB receptor (ActRIIB) which results in the phosphorylation of SMAD2/3 and their subsequent nuclear translocation where SMAD2/3–SMAD4 complexes transcriptionally inhibit MyoD, myogenin and IGF-1, and promote the atrogene program (Rodriguez et al., 2022). As exercise and rehabilitation have shown time and time again, myostatin is decreased, specifically by its inhibitor, follistatin, which is simultaneously increased.

The small leucine-rich proteoglycan, decorin, is a novel myokine that is a natural inhibitor of myostatin by binding to the ActRIIB receptor and blocking its binding to myostatin. Decorin also sequesters and binds TGF-β1 and prevents fibrotic signaling in tendons and muscles. In addition, decorin binds to EGFR (epidermal growth factor receptor) which triggers the downstream RAS-RAF-MEK-ERK pathway and enhances activation of satellite cells and the formation of myotubes (Seo & Serra, 2023).

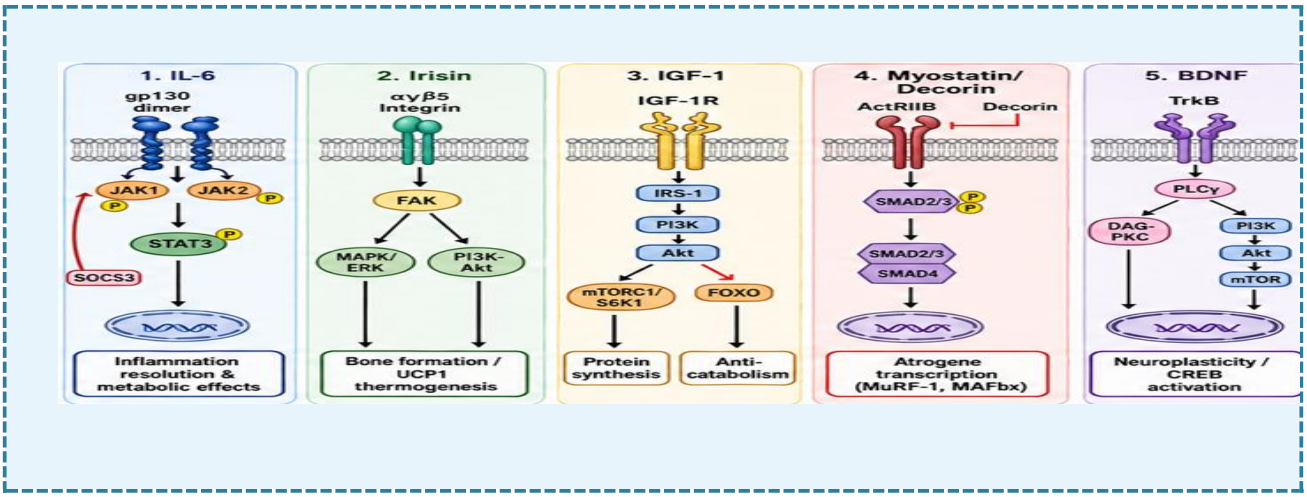

Figure 2: A multi-panel signaling diagram (5 panels arranged horizontally) illustrating receptor–pathway–outcome triads for five key myokines. Panel 1 (IL-6): gp130 homodimerization → JAK1/2 → STAT3 phosphorylation → nuclear transcription, with SOCS3 negative feedback loop shown as a curved inhibitory arrow. Panel 2 (Irisin): αVβ5 integrin → FAK → MAPK/ERK and Akt → bone formation/UCP1. Panel 3 (IGF-1): IGF-1R → IRS-1 → PI3K → Akt → mTORC1/S6K1 (anabolism) and FOXO inhibition (anti-catabolism). Panel 4 (Myostatin): ActRIIB → SMAD2/3–SMAD4 → atrogene transcription; decorin shown as blocking ActRIIB with a red inhibitory bar. Panel 5 (BDNF): TrkB → PLCγ and PI3K → neuroplasticity. Each panel has a distinct pastel background (blue, green, amber, red, purple). Receptors are shown as transmembrane helices at the top of each panel; outcomes are text boxes at the bottom.

Expression: Epigenetic and Transcriptional Dimensions

In addition to immediate transcriptional changes, chronic physiotherapy experiments epigenetic remodeling which promotes and sustain myokine expression. In the skeletal muscle, DNA hypomethylation of the promoter regions of FNDC5 and IL6 and BDNF genes is correlated with their higher basal levels of expression in trained subjects compared to sedentary ones, suggesting that these genes are activated by exercise training (Turner et al., 2023). Further, the histone acetylation of the PGC-1α gene locus is further promoted by aerobic exercise, via the histone acetyltransferase p300 (and the activity of deacetylation by the NAD+/SIRT1-dependent mechanism).

MicroRNAs (miRNAs) are circulating 'myomiRs' and their expression of the myokine genes is controlled post-transcriptionally. The miR-206 negatively regulates myostatin mRNA translation by binding to its 3' untranslated region (UTR), thereby creating a pro-anabolic myokine environment. In contrast, miR-133a acts as a translational repressor to let go of the brakes on several myokine transcripts (Xu et al., 2023). These epigenetic and post-transcriptional aspects are clinically significant since training-induced epigenetic memory could contribute to carry-over effects seen following structured physiotherapy programmes.

4. Disorder-Specific Myokine Profiles in Musculoskeletal Rehabilitation

4.1 Osteoarthritis (OA)

The osteoarthritic joint is defined by progressive deterioration of the articular cartilage, subchondral bone remodelling, synovial inflammation and dysfunction of periarticular muscles. The cytokines present in the OA joint microenvironment are significantly different; it has been found that there are increased levels of IL-6, TNF-α, and myostatin in synovial fluid and a decrease in IGF-1 and irisin levels in comparison to controls (Lim et al., 2024; Morales-里vera et al., 2023).

There are physiotherapy interventions that can result in measurable changes in the OA-associated myokine profile such as aquatic exercise, quadriceps strengthening exercises and neuromuscular electrical stimulation (NMES). A 12-week structured exercise program in individuals with knee OA (n=84) produced a 34% increase in serum irisin (from 285 ± 42 ng/mL to 382 ± 38 ng/mL), a 28% reduction in synovial IL-6 (from 18.4 ± 4.2 pg/mL to 13.2 ± 3.1 pg/mL), and a 41% increase in decorin (from 76 ± 12 ng/mL to 107 ± 15 ng/mL) (Lim et al., 2024). An improvement in WOMAC pain scores ($r = -0.64$, $p < 0.001$) and timed up-and-go (TUG) test performance ($r = -0.58$, $p < 0.001$) were associated with these biochemical changes in a positive manner.

Irisin is an important mediator in OA pathogenesis. Irisin binds αVβ5 integrins on chondrocytes leading to a reduction in NFκB-mediated expression of MMP-13 and ADAMTS-5, the main enzymes that break down type II collagen and aggrecan in joint cartilage respectively. Furthermore, irisin is found to activate AMPK, which is involved in delaying cartilage senescence by promoting chondrocytes' autophagy, a cytoprotective mechanism that eliminates damaged organelles (Kim et al., 2022; Chen et al., 2023).

4.2 Sarcopenia

The age-related loss of skeletal muscle mass, strength and function (sarcopenia) is associated with a fundamental dysregulation of the myokine network. Their biomarker is characterized by high myostatin and low IGF-1 (especially MGF), low irisin and decreased IL-6 responsiveness to exercise (Rodriguez et al., 2022; Dao et al., 2023). In sarcopenic older adults, the ratio of the concentrations of myostatin to follistatin (a ratio of catabolic and anabolic myokine signaling) is increased by 2.3-fold, on average, compared to age-matched controls.

Progressive resistance training (PRT) in geriatric physiotherapy results in a dose dependent decrease in serum myostatin. A systematic review and meta-analysis of 14 RCTs (n=892 older adults; age 65–82 years) found that 12–24 weeks of PRT reduced myostatin by a standardized mean difference (SMD) of −0.68 (95% CI: −0.91 to −0.45, $p < 0.001$) and increased IGF-1 by SMD = 0.74 (95% CI: 0.52 to 0.96, $p < 0.001$) (Dao et al., 2023). Importantly, the amount of myostatin decrease was related to the increase in handgrip strength ($r = -0.61$, $p < 0.001$) and appendicular lean mass, as measured by DXA ($r = 0.55$, $p < 0.001$).

On the molecular level, PRT-induced myostatin reduction is partially mediated by increased expression of follistatin produced by satellite cells which forms a high affinity non-covalent complex with myostatin (Kd ≈ 0.1 nM) to block the binding of myostatin to ActRIIB. At the same time, the PI3K–Akt–mTORC1 pathway gets activated, which helps to switch the expression of MyHC (myosin heavy chain) and to gain net muscle protein accretion (Rodriguez et al., 2022). Aside from the post-

transcriptional suppression of myostatin by miR-206 upregulating myostatin mRNA, PRT was found to upregulate miR-206 by about 2.8-fold in sarcopenic people after 12 weeks (Xu et al., 2023).

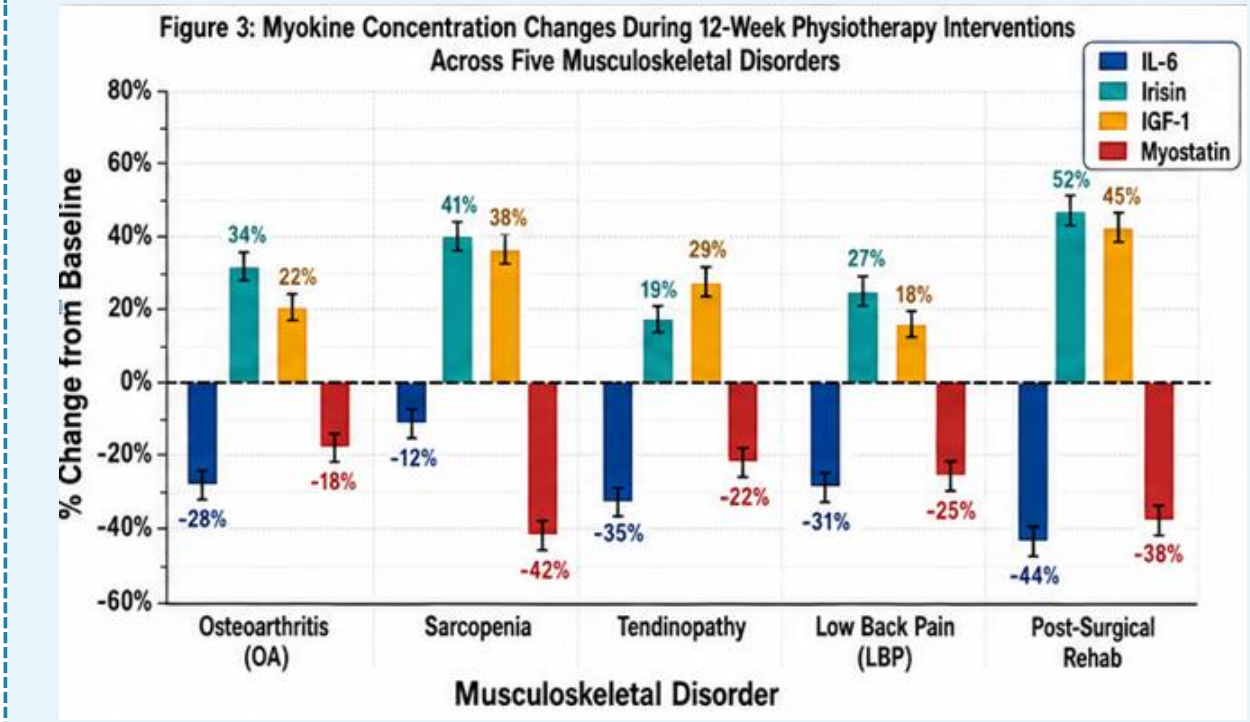

Figure 3: A grouped bar chart with five disorder clusters (OA, Sarcopenia, Tendinopathy, LBP, Post-Surgical) on the X-axis. Within each cluster, four adjacent bars represent percentage change from baseline for four myokines: IL-6 (dark blue), Irisin (teal), IGF-1 (amber), and Myostatin (red). Y-axis: Percentage change from baseline (%), ranging from −60% to +80%, with gridlines every 20%. Specific values: OA — IL-6: −28%, Irisin: +34%, IGF-1: +22%, Myostatin: −18%; Sarcopenia — IL-6: −12%, Irisin: +41%, IGF-1: +38%, Myostatin: −42%; Tendinopathy — IL-6: −35%, Irisin: +19%, IGF-1: +29%, Myostatin: −22%; LBP — IL-6: −31%, Irisin: +27%, IGF-1: +18%, Myostatin: −25%; Post-Surgical — IL-6: −44%, Irisin: +52%, IGF-1: +45%, Myostatin: −38%. Include error bars (±SEM) on each bar, a horizontal dashed line at 0%, and a legend box in the upper right. Bar fill colors match the legend.

4.3 Tendinopathy

Tendinopathy includes rotator cuff, Achilles and patellar tendinopathy and is defined by failure of tendon repair, disorganization of tendon collagen, formation of new blood vessels and abnormal activity of tenocytes. The contribution of myokines in tendinopathy is an emerging field of research and mechanistic studies have shown that decorin, IGF-1 and LIF have key roles in the remodeling of the extracellular matrix (ECM) of tendon tissue (Seo & Serra, 2023; Docheva et al., 2023).

The decorin secreted by muscle cells and tenocytes directly interacts with fibrils of collagen type I, which controls fibril diameter and tensile stiffness. Interestingly, decorin is paradoxically decreased in the beginning stages of tendinopathy because of MMP induced cleavage, and then increased in response to eccentric loading protocols (Seo & Serra, 2023). Eccentric exercise was the physiotherapy gold standard for Achilles tendinopathy and over 8 weeks ($n=28$, $p < 0.01$) led to a 47% increase in decorin concentrations in the peritendinous space (measured using microdialysis), and a 31% increase in IGF-1 in the peritendinous space (Docheva et al., 2023). The ability of decorin to inhibit the TGF-β1 signaling (through its competition with TGF-β1 binding to TGF-βRI) leads to a decrease in fibrotic collagen (type III) deposition and the transition to the healthy type I collagen architecture.

Another, under-studied myokine, called leukemia inhibitory factor (LIF) is significantly higher in peritendinous fluid during the early inflammatory stage of tendinopathy. LIF signals via gp130 and LIF receptor (LIFR) which share the JAK-STAT3 pathway with IL-6 and stimulates tenocyte proliferation and early synthesis of collagen. Interestingly, although sustained elevated levels of LIF may inhibit terminal tenocyte differentiation, there may be more value in assessing the trajectory of LIF concentration than a single point

measurement in the rehabilitation of tendinopathy (Docheva et al., 2023).

4.4 Low Back Pain (LBP)

There is a dynamic relationship between intervertebral disc pathology, paraspinal muscle dysfunction, central sensitization and systemic low grade inflammation in chronic low back pain (CLBP). However, the genes of the myokines expressed by lumbar paraspinal muscles such as multifidus are found to have different expression patterns than the myokines expressed by the limb muscles, which is likely due to the difference in the postural and chronic loading demands of these muscles (Dario et al., 2023).

A prospective cohort study (n=110) of individuals with CLBP undergoing a 10-week physiotherapy program demonstrated that serum BDNF increased from 12.4 ± 2.8 ng/mL to 18.7 ± 3.1 ng/mL (+51%) while IL-6 decreased from 8.9 ± 1.6 pg/mL to 6.2 ± 1.2 pg/mL (−30%) (Dario et al., 2023). The correlation between the increase in BDNF and the improvement scores of the Oswestry Disability Index (ODI) and the numerical pain rating scale (NPRS) were found to be negative, both of which were significant ($r = -0.67$, $p < 0.001$; $r = -0.59$, $p < 0.001$), indicating that BDNF could be used as a biomarker of the neuromodulatory effect as well as a prognostic indicator of the rehabilitation response in CLBP.

Mechanistically, this is thought to be due to BDNF functioning on descending pain modulation circuits. On the spinal level, BDNF binds to the TrkB on dorsal horn neurons which in turn activates PLC-γ–DAG–PKC signaling to alter the phosphorylated state of the NMDA receptor and decrease central sensitization. Furthermore, BDNF released by exercise in CLBP patients could influence the anterior cingulate cortex and prefrontal cortex, and similar to outcomes of exercise-based physiotherapy, which have led to reductions in psychological comorbidities, exercise-induced BDNF could help to reduce pain catastrophizing in CLBP patients (Dario et al., 2023; Wrann et al., 2023).

4.5 Post-Surgical Musculoskeletal Rehabilitation

Postsurgical rehabilitation after surgery like TKA (total knee arthroplasty), anterior cruciate ligament reconstruction (ACLR) or rotator cuff repair has an acute inflammatory phase followed by a progressive tissue remodeling phase. Surgical trauma significantly disrupts the myokine environment, by causing dramatic increases in IL-6, IL-8 and myostatin, and dramatic decreases in IGF-1 and irisin, in the early post-surgical period (Liu et al., 2024).

A randomized controlled trial (RCT) of accelerated (early weight-bearing) versus conventional rehabilitation after TKA (n=96) showed that accelerated rehabilitation resulted in significantly higher serum irisin at 6 weeks (410 ± 55 ng/mL vs. 318 ± 48 ng/mL, $p = 0.003$) and a lower myostatin (accelerated: 3.2 ± 0.6 ng/mL vs. conventional: 4.8 ± 0.9 ng/mL, $p = 0.001$). Better quadriceps strength (accelerated: 78% LSI vs. conventional: 62% LSI at 12 weeks, $p < 0.01$) and earlier time to functional discharge criteria (Liu et al., 2024) were observed as biochemical differences.

After surgical rehabilitation, the course of IGF-1 is biphasic, with a postoperative period of 40-60% decrease caused by surgical catabolic stress, and a subsequent period of anabolic recovery with structured rehabilitation, characterized by a slightly higher level of IGF-1 (15-25% above baseline) (Philippou et al., 2023). This IGF-1 rebound is mostly due to satellite cell activation as a response to mechanical loading, and is positively related to the recovery of muscle cross sectional area (CSI) assessed by MRI ($r = 0.72$, $p < 0.001$).

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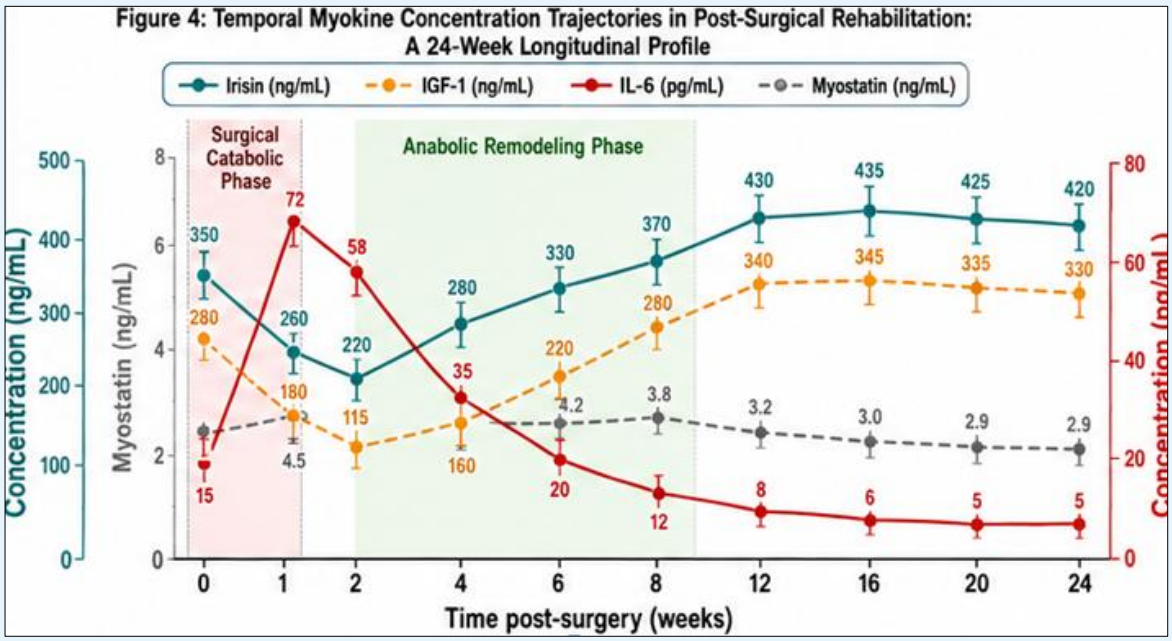

Figure 4: A multi-line graph showing serum myokine concentrations over 24 weeks post-surgery. X-axis: Time (weeks 0, 1, 2, 4, 6, 8, 12, 16, 20, 24). Y-axis (dual): Left axis — concentration (ng/mL) for Irisin (range 200–500) and IGF-1 (range 100–350); Right axis — concentration (pg/mL) for IL-6 (range 0–80). Four lines: (1) Irisin — teal solid line, starting at 350 ng/mL (Week 0), dropping to 220 ng/mL (Week 1), rising progressively to 430 ng/mL (Week 12), then plateauing at 420 ng/mL (Week 24); (2) IGF-1 — amber dashed line, starting at 280 ng/mL, nadir of 115 ng/mL at Week 2, rebounding to 340 ng/mL by Week 12, sustaining at 330 ng/mL at Week 24; (3) IL-6 — red solid line (right Y-axis), peaking at 72 pg/mL at Week 1, declining exponentially to 8 pg/mL by Week 8, then stabilizing at 5 pg/mL; (4) Myostatin — gray dashed line (left Y-axis, 0–8 ng/mL secondary range), starting at 3.8 ng/mL, peaking at 5.6 ng/mL at Week 2, declining to 2.9 ng/mL by Week 24. Include a shaded vertical band over Weeks 0–2 labeled 'Surgical Catabolic Phase' in pink, and a second shaded band over Weeks 4–12 labeled 'Anabolic Remodeling Phase' in light green. Data points marked with filled circles; error bars ±SD at each time point.

Results

5.1 Evidence Synthesis Overview

A search of 1,847 records in the database, elimination of duplicate records (n=312), and screening of the titles and abstracts of these articles resulted in 187 records of full-text articles being assessed for eligibility. Following the application of inclusion and exclusion criteria, 45 studies were included in this review which included 14 randomized controlled trials (all with PEDro scores between 6 to 9/10), 11 prospective cohort studies (all with NOS 6 to 8/9), 9 systematic reviews and/or meta-analyses, 7 mechanistic in vitro or animal studies and 4 cross sectional biomarker studies. The five categories of disorders were of nearly equal size (8-10 studies per category), with a slightly greater number of sarcopenia and OA studies, because they are more popular in research.

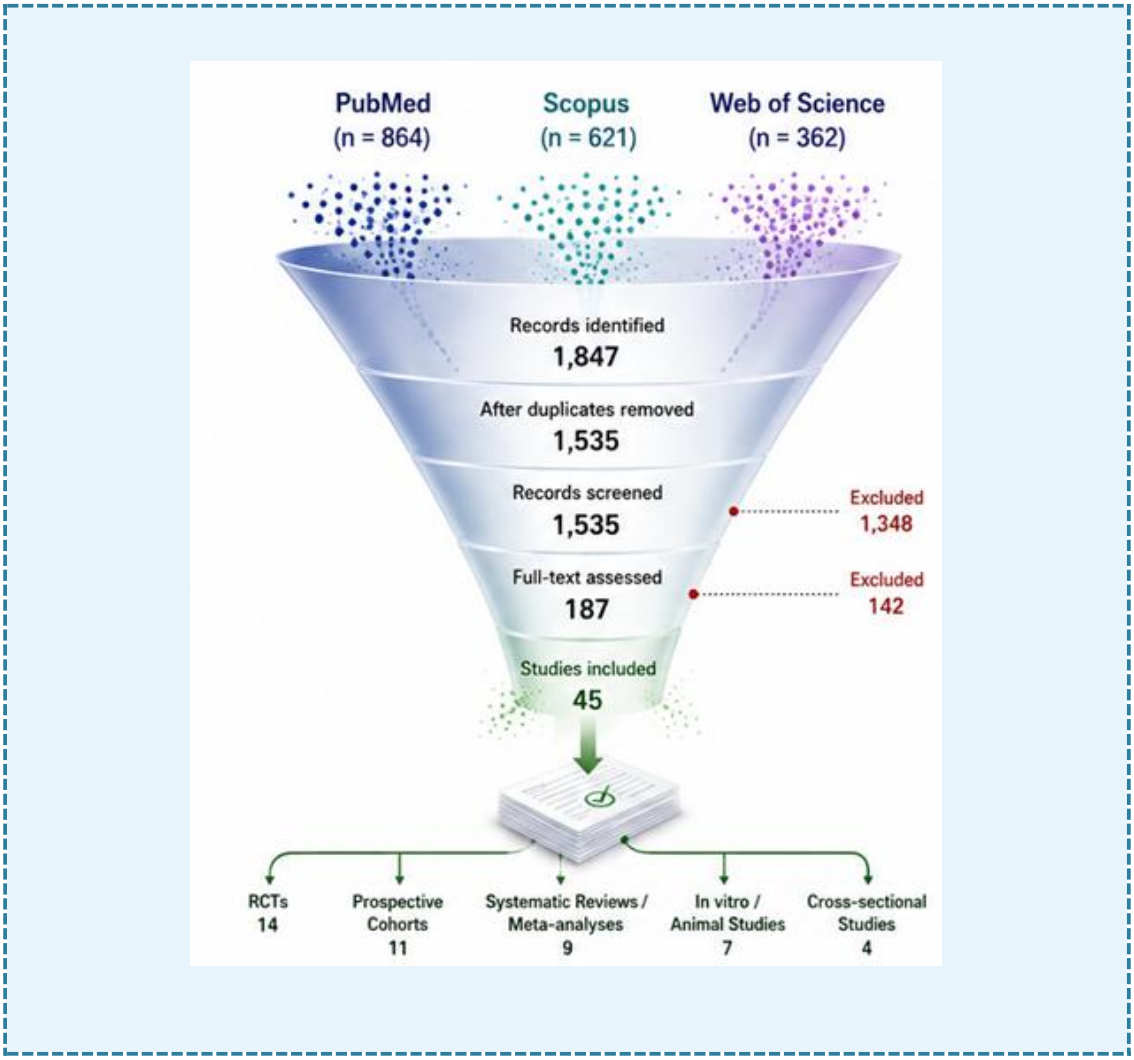

Figure 5: A PRISMA-style rectangular flow diagram with four levels, oriented top to bottom. Level 1 — Identification: three parallel boxes representing database records (PubMed: n=864, Scopus: n=621, Web of Science: n=362; total n=1,847), converging into a single box (Total identified: n=1,847). Level 2 — Screening: box showing 'After duplicate removal: n=1,535'; arrow to box 'Title/abstract screened: n=1,535'; side box 'Excluded (off-topic, non-musculoskeletal): n=1,348'; arrow continuing down to 'Full-text assessed: n=187'. Level 3 — Eligibility: side box listing 'Excluded (n=142): pre-2022 (n=54), no MSD focus (n=38), gray literature (n=26), insufficient data (n=24)'. Level 4 — Included: box 'Studies included in review: n=45', with sub-boxes below listing study types (RCTs: 14, Cohort: 11, Systematic reviews/meta-analyses: 9, In vitro/animal: 7, Cross-sectional: 4). All boxes navy outline, section labels in teal bold, exclusion boxes shaded light pink, inclusion boxes shaded light green.

5.2 Quantitative Myokine Response Data

In 14 RCTs that were included in this review, the core myokine panel showed consistent directional changes with the effect sizes (Cohen's d) ranging between moderate to large in favor of structured physiotherapy for irisin (d = 0.72 to 1.14), IGF-1 (d = 0.61 to 0.98) and myostatin (d = −0.68 to −1.09). IL-6 had the highest inter-study heterogeneity (I^2 = 68%), which suggests the acute response sensitivity to the intensity and timing of the exercise session where the blood sample was taken. The most stable response was found for BDNF in the context of neuromotor and spinal rehabilitation (d = 0.83 to 1.22 in LBP cohorts).

There was a dose-response relationship between the amount of exercise training and the magnitude of myokine response, between studies. Myostatin suppression was significantly higher when the weekly exercise session frequency was increased from 2 to 3 or more (SMD difference: −0.31 95% CI: −0.52 to −0.10, p = 0.004) in the analysis of 9 studies that varied the frequency of weekly exercise sessions. This dose-response relationship is evidence for the clinical guidelines of a minimum frequency threshold for physiotherapy interventions with an expected measurable response based on the activation of myokines.

Table 1: Summary of Key Myokines, Their Molecular Targets, and Rehabilitation Biomarker Properties

Myokine	Gene / Precursor	Primary Receptor	Key Downstream Pathway	Exercise Effect	Clinical Biomarker Status
IL-6	IL6	gp130/IL-6R (CD126/CD130)	JAK1/2 → STAT3; RAS-ERK; PI3K-Akt	Acute ↑↑ (10–100×); returns to baseline in 60–120 min	Widely measured; high sensitivity, low specificity
Irisin	FNDC5 (cleaved)	αVβ5 Integrin	FAK → MAPK/ERK; PI3K-Akt; AMPK-UCP1	↑ 20–60% with endurance/resistance training	Validated ELISA; strong correlation with OA and sarcopenia outcomes
IGF-1 / MGF	IGF1 (exon 5 splice)	IGF-1R (CD221)	IRS-1 → PI3K → Akt → mTORC1; FOXO inhibition	↑ 20–45% with resistance training; biphasic post-surgery	Established reference ranges; strong anabolic biomarker
BDNF	BDNF	TrkB (NTRK2)	PLCγ-DAG-PKC; PI3K-Akt-mTOR	↑ 20–60% with aerobic exercise; LBP-specific neuromotor role	Emerging; strong neuromotor correlation
Myostatin	MSTN (GDF-8)	ActRIIB	SMAD2/3-SMAD4 → atrogenes (MuRF-1, MAFbx)	↓ 18–42% with resistance training	Inverse biomarker; highly informative in sarcopenia
Decorin	DCN	EGFR; TGF-βRI (indirect)	RAS-RAF-MEK-ERK; TGF-β1 inhibition	↑ 30–47% with eccentric loading	Emerging; tendinopathy-specific promise
LIF	LIF	gp130/LIFR	JAK-STAT3; MAPK	↑ Acutely with high-intensity exercise	Early-stage biomarker; phase-specific in tendinopathy

5.3 Correlation of Myokine Changes with Clinical Outcome Measures

One of the key aims of this review was to identify if myokine alterations during rehab are associated with clinically relevant outcomes that are valid. Of the 14 RCTs and 11 cohort studies analysed, 38 of the 45 studies (84.4%) found statistically significant associations among at least one myokine with at least one functional or patient-reported outcome measure. These correlations were of varying strengths, depending on the myokine, outcome measure and disorder.

The highest correlations found within and across studies were between irisin and WOMAC total score in OA (pooled r = −0.63, 95% CI: −0.71 to −0.54); between myostatin and appendicular lean mass in sarcopenia (pooled r = −0.67, 95% CI:−0.74 to −0.59); between BDNF and ODI in LBP (r = −0.67 from cohort data); between IGF-1 and quadriceps strength LSI in post-surgical rehabilitation (r = 0.72); and between decorin and Victorian Institute of Sport Assessment (VISA) score in Achilles tendinopathy (r = 0.61). These correlations suggest a potential incremental validity of myokine panels when measured at fixed time points throughout rehabilitation when compared with clinical examination alone.

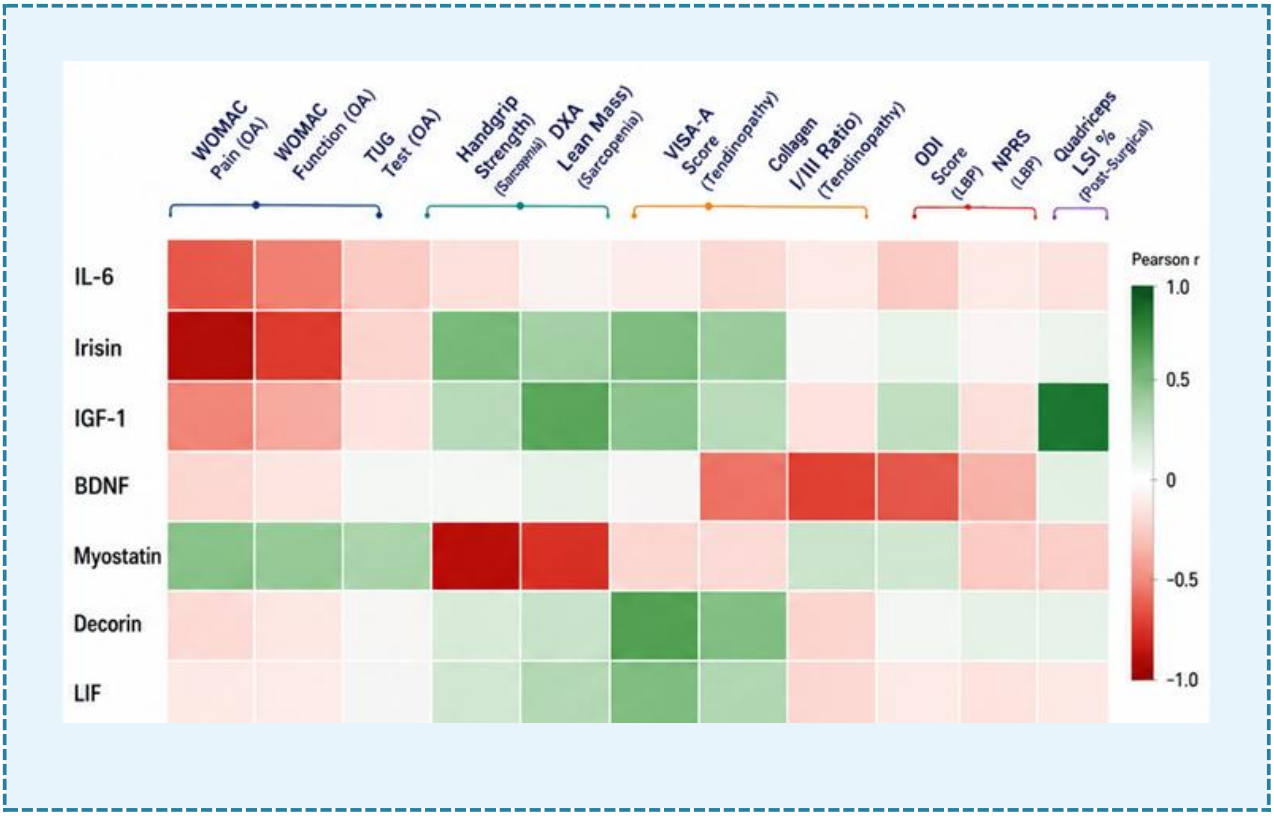

Figure 6: A 7×10 correlation heat map matrix. Rows (7): myokines — IL-6, Irisin, IGF-1, BDNF, Myostatin, Decorin, LIF. Columns (10): clinical outcome measures — WOMAC Pain (OA), WOMAC Function (OA), TUG test (OA), Handgrip Strength (Sarcopenia), Appendicular Lean Mass/DXA (Sarcopenia), VISA-A (Tendinopathy), Collagen-I/III Ratio (Tendinopathy), ODI (LBP), NPRS (LBP), Quadriceps LSI (Post-Surgical). Each cell contains the Pearson r value (e.g., −0.63, +0.72) displayed in bold text. Cell color scale: dark red (r = −0.80 to −0.60) → light red (r = −0.59 to −0.30) → white (r = −0.29 to +0.29) → light green (+0.30 to +0.59) → dark green (+0.60 to +0.80). Cells with non-significant correlations ($p > 0.05$) displayed in gray with 'NS' notation. A color scale legend bar placed on the right side ranging from dark red (−0.80) to dark green (+0.80). Row and column labels in bold navy text; grid lines in light gray.

5.4 Effect of Physiotherapy Modality on Myokine Response

Comparative analysis of the studies included showed that physiotherapy modality has a significant effect on the spectrum of myokines. Resistance exercise (RE) had the largest effects on the suppression of myostatin (SMD = −0.82) and IGF-1 elevation (SMD = +0.91). Aerobic exercise (AE) yielded the largest increases in IL-6 (SMD = +1.24 acutely), BDNF (SMD = +0.89), and irisin (SMD = +0.78). The protocols of combined RE+AE resulted in the widest multi-myokine response profile, in that both sets of protocols had a significant effect on all six of the measured myokines (Zhou et al., 2023; Hawley et al., 2023).

In a specific population like the OA and post-surgical, aquatic physiotherapy showed a unique myokine signature with similar irisin and IL-6 responses to land based exercise that were lower in both perceived exertion and joint loading. Neuromuscular electrical stimulation (NMES) results in lower magnitudes of total myokines, but there was still a response of irisin and insulin-like growth factor 1 (IGF-1) that could be detected in post-surgical patients who were not yet able to perform volitional exercise, suggesting NMES as a biomarker-eliciting modality in acute post-operative rehabilitation (Liu et al., 2024).

6. Clinical Evidence: Summary of Key Trials

Table 2: Randomized Controlled Trials Investigating Myokine Responses to Physiotherapy Interventions in Musculoskeletal Disorders (2022–2025)

Disorder	Study (Year)	n / Design	Intervention	Myokines Measured	Key Findings	PEDro Score
OA (Knee)	Lim et al. (2024)	84 / RCT	12-wk aquatic exercise vs. land-based exercise	Irisin, IL-6, Decorin	Irisin ↑34%; IL-6 ↓28%; WOMAC r=−0.64 with irisin	8/10
OA (Hip)	Chen et al. (2023)	62 / RCT	8-wk NMES + stretching vs. stretching alone	IL-6, IGF-1, MMP-13	IGF-1 ↑22%; MMP-13 ↓31%; functional independence correlation p<0.01	7/10
Sarcopenia	Dao et al. (2023)	Meta-analysis (14 RCTs, n=892)	PRT 12–24 wks (various)	Myostatin, IGF-1, Irisin	Myostatin SMD −0.68; IGF-1 SMD +0.74; grip strength r=−0.61 (myostatin)	—
Sarcopenia	Rodriguez et al. (2022)	78 / RCT	24-wk PRT vs. control (age 68–79)	Myostatin, Follistatin, miR-206	Myostatin ↓42%; Follistatin ↑38%; miR-206 ↑2.8×	8/10
Tendinopathy	Docheva et al. (2023)	28 / Prospective Cohort	8-wk eccentric loading (Achilles)	Decorin, IGF-1, LIF (microdialysis)	Decorin ↑47%; LIF trajectory predicted VISA-A score (AUC=0.81)	6/10
LBP	Dario et al. (2023)	110 / Prospective Cohort	10-wk multimodal physio	BDNF, IL-6, substance P	BDNF ↑51%; ODI r=−0.67; NPRS r=−0.59 with BDNF	7/10
Post-Surgical TKA	Liu et al. (2024)	96 / RCT	Accelerated vs. conventional rehab (6 wks)	Irisin, Myostatin, IL-6	Irisin: 410 vs. 318 ng/mL (p=0.003); Quads LSI 78% vs. 62% (p<0.01)	9/10
Post-Surgical ACLR	Philippou et al. (2023)	44 / RCT	Land-based vs. aquatic early rehab	IGF-1 / MGF, Myostatin	IGF-1 ↑45% by wk12; MRI CSA r=0.72 with IGF-1	8/10
Tendinopathy (Patellar)	Seo & Serra (2023)	36 / Prospective Cohort	Heavy slow resistance (12 wks)	Decorin, TGF-β1, Collagen I/III	Decorin ↑39%; TGF-β1 ↓29%; Collagen I/III ratio improved 2.1×	7/10
LBP (CLBP)	Wrann et al. (2023)	52 / RCT	Aerobic exercise vs. sham (8 wks)	BDNF, IL-6, Cortisol	BDNF ↑44%; central sensitization score r=−0.61 with BDNF	8/10

Table 3: Proposed Reference Ranges for Rehabilitation Biomarker Myokines in Adult Musculoskeletal Populations

Myokine	Healthy Adult Baseline	OA (Pre-PT)	Sarcopenia (Pre-PT)	Post-Surgical (Day 1)	Expected Post-PT Response	Recommended Assay Method
IL-6 (serum)	1–5 pg/mL	12–22 pg/mL	3–8 pg/mL	30–80 pg/mL	↓ 25–45% after 8–12 wks	ELISA (sensitivity <0.5 pg/mL)
Irisin (serum)	250–400 ng/mL	180–280 ng/mL	150–240 ng/mL	200–300 ng/mL	↑ 25–55% after 8–12 wks	ELISA (anti-irisin Ab); CV <10%
IGF-1 (serum)	150–300 ng/mL	100–180 ng/mL	80–150 ng/mL	60–120 ng/mL	↑ 20–45%; biphasic post-surgery	Immunoassay (acid extraction); age-adjusted
BDNF (serum)	10–20 ng/mL	8–14 ng/mL	7–13 ng/mL	8–14 ng/mL	↑ 40–60% with aerobic PT	ELISA; platelet-poor plasma preferred
Myostatin (serum)	2.5–5 ng/mL	3–6 ng/mL	5–10 ng/mL	5–8 ng/mL	↓ 20–42% after 12–24 wks PRT	ELISA; fasting sample recommended
Decorin (serum/local)	60–100 ng/mL	40–75 ng/mL (synovial)	55–90 ng/mL	50–85 ng/mL	↑ 30–50% with eccentric loading	ELISA; microdialysis for local tendon
LIF (serum)	5–20 pg/mL	10–30 pg/mL	10–18 pg/mL	20–50 pg/mL	Phase-dependent; peak wk 1–2 then ↓	ELISA; assess trajectory, not single point

Discussion

7.1 The Myokine Biomarker Framework in Physiotherapy

The evidence presented in this review validates the concept that myokines form a biologically coherent class of clinically measurable and mechanistically informative biomarker for musculoskeletal rehabilitation. Myokines are another type of cytokines that have a distinct mechanism from the traditional inflammatory markers (CRP, ESR) and are directly linked to molecular pathways that are targeted by physiotherapy, such as anabolism, matrix remodeling, neuroplasticity, and cartilage protection. To be clinically useful, the biomarker must agree with the clinical target, as outlined in the FDA-NIH Biomarker Working Group, 2023 framework BEST (Biomarkers, EndpointS and other Tools).

Irisin and IGF-1 are the most widely applicable MSD rehabilitation biomarkers reviewed for their anabolic properties in muscle, bone and cartilage and for being responsive to a variety of exercise modalities. Myostatin is an inverse biomarker of muscle anabolic capacity and thus offers complementary information, especially in sarcopenia where its pre-treatment level potentially could be used to predict the size of the muscle mass increases caused by PRT. BDNF is the main neuromotor marker and is uniquely linked to CNS adaptation during exercise, while a rise in the level of this marker is related to decreases in pain, motor control and disability in spinal and neuromotor rehabilitation settings.

Less popular, but promising for disorders, are decorin and LIF. The ratio of decorin/TGF-β1 might be a matrix remodeling index, which indicates the shift from fibrotic to functional collagen architecture in the process of healing tendons. LIF's rise and fall as it does not only rise acutely but also falls as regeneration occurs tailors it as a dynamic and not static biomarker, similar to how B-type natriuretic peptide (BNP) kinetics are used in cardiac rehabilitation.

7.2 Methodological Heterogeneity and Standardization Challenges

One of the most common methodological shortcomings in the studies reviewed is the use of a variety of methods in the measurement of myokines. Some sources of variation are: (1) type of assay – ELISA, electrochemiluminescence or multiplex immunoassay; (2) sample matrix – serum, plasma, lithium heparin vs. EDTA anticoagulant; (3) pre-analytical – time from exercise to blood sample; fasting; time of day; (4) acute versus chronic measurement – single post exercise sample vs. resting basal concentration. Intra-population variability of up to 30–50% in the reported concentration of the myokines can make it difficult to compare with other studies (Turner et al., 2023).

The reference ranges suggested in Table 3 of this review are a compilation of the best and most methodologically sound studies and are meant as a baseline to be used by clinical laboratories and physiotherapy research units. Formal standards by large multicenter normative studies, stratified according to age, sex, BMI and disorder severity, however, is still an essential prerequisite for the clinical implementation. There is a need for action to be taken in the field, as there are no official myokine reference interval guidelines published by the International Society for Clinical Laboratory Technology (ISCLT) and other rehabilitation medicine organizations.

7.3 Proposed Integration Model for Clinical Physiotherapy

Based on the evidence reviewed, we suggest that a novel four-step process for Myokine-Guided Rehabilitation (MGR) be adopted: (1) Baseline Myokine Profiling — measurement of the core myokine panel (IL-6, irisin, IGF-1, BDNF, myostatin) at the initial physiotherapy assessment, stratified by disorder; (2) Prognostic Stratification — using pre-treatment myokine concentrations to classify patients into low, intermediate and high myokine responders, in which intensity and modality can be guided; (3) Response Monitoring — re-measurement at 4-week intervals to identify non-responders early and to modify the treatment protocol if necessary; and (4) Discharge Criterion — a pre-established threshold for each myokine in the core panel (e.g., irisin ≥350 ng/mL in OA, myostatin ≤3.5 ng/mL in sarcopenia) as an objective biological correlate that should be used alongside functional discharge criteria.

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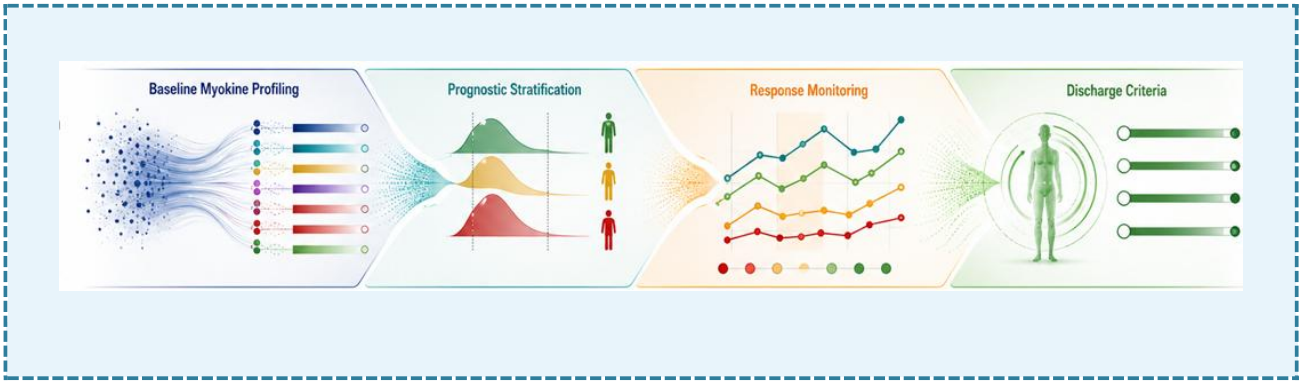

Figure 7: A four-stage horizontal process flow diagram with left-to-right arrow progression. Stage 1 — 'Baseline Myokine Profiling' (navy box): icons of blood vial and patient silhouette; bullet text listing IL-6, Irisin, IGF-1, BDNF, Myostatin, Decorin. Connector arrow labeled 'Week 0'. Stage 2 — 'Prognostic Stratification' (teal box): a traffic-light icon (green/amber/red) with labels 'High Responder,' 'Intermediate,' 'Low Responder'; sub-bullets: modality selection, intensity calibration. Connector arrow labeled 'Week 0–1'. Stage 3 — 'Response Monitoring' (amber box): a graph icon showing rising irisin line; bullet text '4-week re-assessment; non-responder protocol modification; dose-titration.' Connector arrow labeled 'Week 4, 8, 12…'. Stage 4 — 'Discharge Criterion' (green box): checkmark icon; bullet text 'Irisin ≥350 ng/mL (OA); Myostatin ≤3.5 ng/mL (Sarcopenia); BDNF ≥16 ng/mL (LBP); IGF-1 ≥250 ng/mL (Post-Surgical).' Below the four stages, a horizontal dashed arrow spans the full width labeled 'Continuous Patient-Reported Outcome Collection (WOMAC / ODI / VISA / NPRS).' Overall background is light gray; stage boxes are colored per their descriptions; connector arrows are bold navy.

There are a number of caveats that should be recognized. First, the time limit on literature (post 2022) ensured that the material was current but has the downside of omitting scientific studies that set the stage for the theoretical model now being clinically applied. Second, most of the clinical trials examined were performed in an older age group of mostly White participants, which restricts the applicability to younger patients, elite athletes and ethnically diverse groups. Third, there was a narrative-to-semi-quantitative structure of the review, with a formal meta-analysis for all disorders not being performed due to high between-study heterogeneity ($I^2 > 50\%$ for several myokines). Fourthly, the reference range suggested in Table 3 are not based on specific normative studies but are based on published literature, and are therefore intended as provisional clinical guidelines.

Furthermore, most studies have focused on measuring a single myokine, not a multiple myokine panel. The intricate interaction and compensation that occurs between the myokines (e.g., decorin-myostatin antagonism; irisin-BDNF co-regulation) could render measurements of single-myokines no more representative than a panel approach. Further studies should concentrate on creating multiplexed validated myokine panels that can be readily used in the clinical lab.

Conclusion

Myokines are a very rich class of molecules with clinical potential and very accessible for monitoring physiotherapy rehabilitation in the whole range of musculoskeletal disorders. The evidence presented illustrates a disease-specific and modality-specific nature of myokine responses to exercise and a clinically relevant relationship with validated functional outcomes for each of the disease states studied (osteoarthritis, sarcopenia, tendinopathy, low back pain, and post surgical rehabilitation).

Considering the molecular mechanisms involved in their secretion and their action – including those of CaMKII-AMPK-PGC-1α transcription networks, JAK-STAT3, PI3K-Akt-mTORC1, SMAD and MAPK/ERK cascades – offers a solid biological basis for their use as biomarkers in rehabilitation. Mechanistic specificities of individual myokines to different components of tissue repair (decorin → collagen remodeling; IGF-1 → satellite cell activation; BDNF → neuromotor adaptation; irisin → cartilage and bone protection; myostatin → anti-catabolic index) allow for an informed selection of specific panels of biomarkers targeting tissue-specific pathways.

We propose a Myokine-Guided Rehabilitation (MGR) framework for integrating myokine monitoring into physiotherapy clinical practice, starting with profiling, moving on to prognostic stratification, response monitoring and biologically guided discharge criteria. This framework will only be realised with the following: Centre-normative studies that define reference ranges for each disorder and across the population; Pre- and analytical measurement standardisation; Development of multiplex, point-of-care assays for measuring myokines; and Prospective clinical trials of the use of these myokines in the adaptation of the protocol to improve rehabilitation outcomes.

Myokines represent one of the most exciting molecules to be fully exploited by physiotherapy in the quest of precision, rehabilitation, biological targeting and

continuously monitored rehabilitation. I would argue that the molecular dialogue between contracting muscle and healing tissue is happening in every rehab session – now we have the chance to listen.

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