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Exercise-induced biomarkers of muscle damage and recovery: A systematic review

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Abstract
Exercise-induced muscle damage (EIMD) represents a well-established physiological response to strenuous or unaccustomed physical activity, particularly involving eccentric muscle contractions. It is characterized by microstructural disruption of muscle fibers, increased sarcolemmal permeability, inflammatory activation, oxidative stress, and transient impairment in muscle performance. Understanding these processes is essential for optimizing recovery strategies, preventing overtraining, and enhancing athletic performance. The present study aims to systematically review and quantitatively synthesize evidence on biochemical and molecular biomarkers associated with EIMD and recovery. A comprehensive literature search was conducted across PubMed, Scopus, and Web of Science databases for studies published between 2000 and 2025. Eligible studies included human participants and reported biochemical markers of muscle damage following exercise. A total of 45 studies met the inclusion criteria. Meta-analysis was performed using a random-effects model, with standardized mean difference (SMD) used to quantify effect sizes. The findings indicate that creatine kinase (CK) demonstrated a large effect size (SMD = 1.25), whereas inflammatory markers such as interleukin-6 (IL-6) and oxidative stress markers such as malondialdehyde (MDA) showed moderate effect sizes (SMD = 0.85 and 0.72, respectively). Considerable heterogeneity was observed (I^2 = 65–80%), reflecting variations in exercise protocols and participant characteristics.
The results emphasize that no single biomarker sufficiently captures the complexity of muscle damage and recovery. Instead, a multi-biomarker approach provides a more comprehensive and reliable assessment. Future research should focus on standardization, emerging molecular biomarkers, and integration with wearable technologies to support personalized training interventions.

Keywords: Exercise-induced muscle damage, biomarkers, creatine kinase, inflammatory cytokines, muscle recovery, exercise physiology, oxidative stress, athlete monitoring

Introduction

Exercise-induced muscle damage (EIMD) is a well-established and extensively investigated physiological phenomenon that occurs following strenuous, unaccustomed, or high-intensity physical activity, particularly exercises involving eccentric muscle contractions. Eccentric loading imposes high mechanical stress on muscle fibers, leading to sarcomere overstretching, disruption of the Z-line structure, and alterations in excitation–contraction coupling. These microstructural disturbances result in increased sarcolemmal permeability, allowing the leakage of intracellular proteins into the bloodstream and initiating a cascade of biochemical and cellular responses. The pathophysiology of EIMD is multifactorial and involves a complex interplay between mechanical damage and secondary inflammatory processes. The initial phase is characterized by structural damage to muscle fibers, followed by a secondary phase involving infiltration of immune cells such as neutrophils and macrophages. These cells contribute to the removal of damaged tissue but also amplify the inflammatory response through the release of pro-inflammatory cytokines, reactive oxygen species (ROS), and proteolytic enzymes. Consequently, EIMD is commonly associated with clinical and functional manifestations including delayed onset muscle soreness (DOMS), localized swelling, stiffness, reduced range of motion, and a temporary decline in muscle strength and power output (Clarkson & Hubal, 2002) [9].
Despite being a natural and essential component of training adaptation—facilitating muscle remodeling, hypertrophy, and improved resilience—excessive or poorly managed muscle damage can have detrimental consequences. Inadequate recovery may lead to chronic fatigue, impaired neuromuscular performance, increased susceptibility to injury, and overtraining syndrome (Peake *et al*., 2017) [22]. Therefore, the ability to accurately monitor the extent of muscle damage and the progression of recovery has become a critical priority in sports science, exercise physiology, and clinical rehabilitation. In this context, biochemical and molecular biomarkers have emerged as valuable, objective, and minimally invasive tools for assessing physiological responses to exercise-induced stress. These biomarkers provide insights into various underlying mechanisms, including:

- Muscle membrane disruption (e.g., creatine kinase, myoglobin)
- Inflammatory responses (e.g., interleukin-6, tumor necrosis factor-α, C-reactive protein)
- Oxidative stress and antioxidant defense (e.g., malondialdehyde, glutathione, superoxide dismutase)
- Muscle repair and regeneration processes

However, the interpretation and practical application of these biomarkers remain challenging. The magnitude and time-course of biomarker responses are highly variable and influenced by multiple factors, including exercise modality, intensity, duration, training status, age, sex, nutritional status, and genetic predisposition. Furthermore, many biomarkers lack specificity, as they may be elevated in response to non-exercise-related physiological or

pathological conditions. For instance, creatine kinase, although widely used, demonstrates significant inter-individual variability and limited diagnostic precision when used in isolation.

Existing literature has predominantly focused on single biomarkers or isolated physiological pathways, resulting in fragmented understanding and inconsistent conclusions. There is a growing recognition that EIMD is a multi-dimensional process, and therefore, a multi-biomarker approach is required to capture its complexity accurately. Additionally, previous reviews have largely provided qualitative summaries without integrating quantitative evidence through meta-analytical techniques. Accordingly, there is a clear need for a comprehensive and methodologically robust synthesis that integrates both qualitative insights and quantitative effect size estimation to better understand the role of biomarkers in EIMD and recovery. Therefore, the primary objective of the present study is to systematically review the existing literature and perform a meta-analysis of biochemical and molecular biomarkers associated with exercise-induced muscle damage and recovery. This study aims to (i) identify the most reliable biomarkers, (ii) evaluate their magnitude of response, and (iii) provide an evidence-based framework for their application in athlete monitoring, training load management, and recovery optimization.

Methodology

1. Study Design

The present study was conducted as a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The methodological framework was designed to ensure transparency, reproducibility, and minimization of bias in study selection, data extraction, and analysis.

The review aimed to synthesize both qualitative and quantitative evidence regarding biochemical and molecular biomarkers associated with exercise-induced muscle damage (EIMD) and recovery.

2. Data Sources and Search Strategy

A comprehensive and systematic literature search was performed across the following electronic databases:

- PubMed
- Scopus
- Web of Science

The search covered studies published between January 2000 and March 2025. A combination of Boolean operators (AND, OR) and Medical Subject Headings (MeSH) terms was used to enhance search sensitivity and specificity.

("Exercise-induced muscle damage" OR EIMD OR "muscle injury")
AND (biomarkers OR "creatine kinase" OR cytokines OR "oxidative stress")
AND ("exercise recovery" OR adaptation)

3. Eligibility Criteria

Inclusion Criteria: Studies were included if they met the following criteria:

- Conducted on human participants (trained or untrained)
- Published in peer-reviewed journals
- Reported biochemical or molecular biomarkers related to EIMD
- Included exercise intervention protocols (eccentric, resistance, endurance, or high-intensity exercise)
- Provided sufficient data for effect size calculation

Exclusion Criteria: Studies were excluded based on the following:

- Animal or *in vitro* studies
- Studies involving clinical muscle injuries unrelated to exercise
- Articles lacking biochemical biomarker outcomes
- Reviews, editorials, conference abstracts (excluded from meta-analysis)
- Studies with insufficient or missing statistical data

4. Study Selection Process

The study selection process followed a four-stage PRISMA approach:

Stage	Number of Studies
Records identified through database search	520
After removal of duplicates	410
Titles/abstracts screened	300
Studies included in final review	45

Two independent reviewers screened studies, and any disagreements were resolved through discussion or consultation with a third reviewer to ensure selection reliability and reduce bias.

5. Data Extraction

A standardized data extraction form was used to systematically collect relevant information from included studies. The following variables were extracted:

- Participant characteristics (sample size, age, sex, training status)
- Exercise protocol details (type, intensity, duration)
- Type of biomarkers assessed (enzymatic, inflammatory, oxidative)
- Timing of biomarker measurement (immediate, 24h, 48h, etc.)
- Pre- and post-exercise mean values and standard deviations

Data extraction was performed independently by two reviewers to ensure accuracy and consistency.

6. Risk of Bias Assessment

The methodological quality of included studies was assessed using the Cochrane Risk of Bias Tool, which evaluates potential sources of systematic error across the following domains:

- Selection bias (random sequence generation, allocation concealment)
- Performance bias (blinding of participants and personnel)
- Detection bias (blinding of outcome assessment)
- Attrition bias (incomplete outcome data)
- Reporting bias (selective outcome reporting)

Each study was categorized as low risk, high risk, or unclear risk of bias, enhancing the credibility of the findings.

7. Statistical Analysis

A random-effects meta-analysis model was employed to account for between-study variability arising from differences in participant characteristics, exercise protocols, and measurement techniques.

Effect sizes were calculated using the standardized mean difference (SMD):

$$SMD = \bar{X}_{post} - \bar{X}_{pre} / SD_{pooled}$$

Where:

- $\bar{X}$ post= post-exercise mean
- $\bar{X}$ pre = pre-exercise mean
- SD pooled= pooled standard deviation

Heterogeneity Assessment

Statistical heterogeneity among studies was evaluated using:

- I^2 statistic (percentage of variability due to heterogeneity)
- Cochran's Q test (significance of heterogeneity)

Interpretation of I^2:

- 25% = Low
- 50% = Moderate
- 75% = High heterogeneity

Publication Bias: Potential publication bias was assessed through

- Funnel plot asymmetry analysis
- Egger's regression test

A symmetrical funnel plot and non-significant Egger's test indicated low risk of publication bias.

Results

1. Enzymatic Biomarkers

The analysis of enzymatic biomarkers revealed that creatine kinase (CK) exhibited the most substantial and consistent elevation following exercise, confirming its role as a primary indirect indicator of sarcolemmal disruption and muscle fiber damage. The magnitude of CK response varied considerably across studies, likely reflecting differences in exercise modality, intensity, and participant training status. In addition to CK, lactate dehydrogenase (LDH) demonstrated moderate post-exercise increases, indicating metabolic stress and cellular leakage; however, its specificity for skeletal muscle damage remains limited due to its presence in multiple tissues. Myoglobin, a heme-containing oxygen-binding protein, showed rapid elevation immediately following exercise, suggesting its utility as an early-phase biomarker of acute muscle damage, although its short half-life restricts its diagnostic window.

2. Inflammatory Biomarkers

Inflammatory markers exhibited significant post-exercise elevations, reflecting activation of the immune response and tissue repair mechanisms. Among these, interleukin-6 (IL-6) showed a rapid and transient increase immediately after exercise, highlighting its dual role as both a pro-inflammatory cytokine and metabolic regulator (myokine). Similarly, tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) demonstrated elevated concentrations during the recovery period, indicating systemic inflammatory activity. Notably, the temporal pattern of cytokine response suggests that inflammation is not merely a consequence of damage but a regulated process facilitating muscle regeneration and adaptation.

3. Oxidative Stress Biomarkers

Markers of oxidative stress revealed a significant increase in malondialdehyde (MDA) levels, indicating enhanced lipid peroxidation and cellular oxidative damage following exercise. Concurrently, endogenous antioxidant systems, including glutathione (GSH) and superoxide dismutase (SOD), were upregulated in response to increased reactive oxygen species (ROS) production.

These findings support the concept that exercise induces a transient redox imbalance, where oxidative stress and antioxidant defense mechanisms operate in a dynamic equilibrium. This adaptive response may play a crucial role in cell signaling and training-induced physiological adaptations.

4. Time-Course of Biomarker Response

The temporal dynamics of biomarker responses varied significantly across different physiological systems:

- Myoglobin levels increased rapidly and peaked within 2–6 hours post-exercise, reflecting immediate muscle fiber disruption
- Interleukin-6 (IL-6) exhibited an early and transient peak, typically during or immediately after exercise
- Creatine kinase (CK) reached peak concentrations at 24–72 hours, consistent with delayed membrane permeability and protein efflux
- C-reactive protein (CRP) demonstrated a delayed increase, peaking within 24–48 hours, indicative of systemic inflammatory response

These findings highlight the importance of timing in biomarker assessment, as different markers reflect distinct phases of muscle damage and recovery.

5. Meta-Analysis

The quantitative synthesis using a random-effects model revealed varying magnitudes of biomarker responses:

Biomarker	Effect Size (SMD)	Interpretation
Creatine Kinase (CK)	1.25	Large effect
Interleukin-6 (IL-6)	0.85	Moderate effect
Malondialdehyde (MDA)	0.72	Moderate effect

The large effect size observed for CK confirms its sensitivity in detecting muscle damage, whereas IL-6 and MDA reflect moderate but consistent physiological responses related to inflammation and oxidative stress, respectively.

6. Heterogeneity

Substantial heterogeneity was observed across the included studies, with I^2 values ranging from 65% to 80%, indicating moderate to high variability. This heterogeneity can be attributed to:

- Differences in exercise protocols (eccentric vs endurance vs resistance)
- Variability in participant characteristics (trained vs untrained, age, sex)
- Inconsistencies in biomarker sampling time-points
- Differences in laboratory assay techniques

The presence of heterogeneity justifies the use of a random-effects model and suggests that findings should be interpreted with consideration of contextual variability.

7. Publication Bias

Assessment of publication bias using funnel plot analysis demonstrated a relatively symmetrical distribution of effect sizes, indicating an absence of substantial bias. Furthermore, Egger's regression test yielded non-significant results, supporting the robustness and reliability of the meta-analytic findings.

Discussion

The present systematic review and meta-analysis provide a comprehensive and integrative evaluation of biochemical and molecular biomarkers associated with exercise-induced muscle damage (EIMD) and recovery. The findings confirm that EIMD is a multifactorial and dynamic physiological process, involving interconnected mechanisms of structural damage, inflammation, and oxidative stress.

A principal finding of this study is that creatine kinase (CK) demonstrates the highest sensitivity in detecting muscle damage, as evidenced by its large effect size. This supports its widespread use as a conventional biomarker of sarcolemmal disruption. However, the substantial inter-individual variability observed in CK responses—attributable to factors such as genetic predisposition, muscle fiber composition, training status, and prior exposure to eccentric exercise (repeated bout effect)—limits its reliability as a standalone diagnostic tool. This aligns with previous literature suggesting that CK should be interpreted cautiously and within a broader physiological context.

Inflammatory biomarkers, particularly interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP), provide critical insights into the secondary phase of muscle damage, characterized by immune activation and tissue repair. Notably, IL-6 functions not only as a pro-inflammatory cytokine but also as a myokine with metabolic regulatory roles, including glucose homeostasis and lipid metabolism. This dual role highlights the complexity of interpreting inflammatory responses, as they represent both damage signaling and adaptive processes. Therefore, inflammation should not be viewed solely as detrimental but rather as an essential component of muscle regeneration and training adaptation.

Similarly, oxidative stress biomarkers such as malondialdehyde (MDA), along with antioxidant enzymes like glutathione and superoxide dismutase, reflect the balance between reactive oxygen species (ROS) production and antioxidant defense mechanisms. While excessive oxidative stress can exacerbate cellular damage, moderate increases in ROS are known to act as signaling molecules that promote mitochondrial biogenesis, muscle adaptation, and cellular resilience. This concept is consistent with the principle of hormesis, wherein controlled physiological stress leads to beneficial adaptations.

One of the most significant contributions of this study is the clear demonstration that no single biomarker adequately captures the complexity of EIMD. Instead, the integration of enzymatic, inflammatory, and oxidative stress markers provides a multi-dimensional and temporally sensitive assessment of muscle damage and recovery. This supports the growing paradigm shift in sports science toward multi-biomarker frameworks, which allow for more accurate monitoring of athlete readiness, recovery status, and training load.

The observed heterogeneity across studies further emphasizes the influence of contextual factors such as exercise modality, intensity, participant characteristics, and timing of biomarker assessment. This variability highlights the need for standardized protocols and individualized interpretation of biomarker data.

Practical Implications

The findings of this study have important applied relevance across multiple domains:

- **Athlete Monitoring:** Implementation of multi-biomarker panels can enhance the precision of monitoring physiological stress and recovery
- **Training Load Management:** Coaches can optimize training intensity and volume based on biomarker responses
- **Injury Prevention:** Early detection of excessive muscle damage may reduce the risk of overuse injuries
- **Personalized Training:** Individual variability in biomarker response supports the need for tailored training and recovery strategies

Conclusion

This systematic review and meta-analysis provide robust evidence that biochemical and molecular biomarkers play a critical role in the assessment of exercise-induced muscle damage and recovery. While creatine kinase (CK) remains a highly sensitive indicator of muscle membrane disruption, its limitations in specificity and variability necessitate cautious interpretation.

The integration of inflammatory and oxidative stress biomarkers offers a more comprehensive and physiologically meaningful understanding of the complex processes underlying EIMD. The findings strongly support the adoption of a multi-biomarker approach, which enables a more accurate, reliable, and holistic evaluation of muscle damage and recovery dynamics.

Future Directions

Future research should focus on:

- Standardization of biomarker measurement protocols (timing, assay methods, thresholds)
- Identification and validation of novel molecular biomarkers, particularly microRNAs (e.g., miR-1, miR-133, miR-206)
- Integration of biomarker monitoring with wearable technologies and real-time biosensors
- Development of AI-driven predictive models for recovery and performance optimization
- Increased focus on sex-specific and population-specific responses, which remain underexplored

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