

The Relationship Between Skeletal Muscle Exercise and Immune Endurance: A Literature Review

Ahmad Rajendra Paturusi^{1*}, Jamaluddin², Muh. Abdillah Burhan³, Firda Amelia Ajis Dini⁴, Dihan Julianto⁵

¹²³⁴⁵Universitas Pejuang Republik Indonesia, Indonesia

Corresponding Author: ahmad.rajendra@gmail.com

<p>Article History Received: 01-07-2025; Reviewed: 20-07-2025; Accepted: 25-07-2025; Published: 30-07-2025;</p>	<p style="text-align: center;">ABSTRACT</p> <p>Background: Skeletal muscle functions not only as a locomotor organ but also as an active endocrine organ that produces myokines bioactive peptides with pleiotropic effects on the immune system. Understanding the relationship between skeletal muscle exercise and immune endurance is increasingly relevant amid rising infectious diseases and declining immunity in physically inactive populations. Objectives: This literature review aimed to synthesize and analyze current scientific evidence on the mechanistic relationship between skeletal muscle exercise and immune endurance, encompassing molecular pathways involved, effects of exercise on cellular and humoral immune components, and the implications of exercise dose on immune response. Methods: A systematic literature search was conducted on PubMed, Scopus, Google Scholar, and ScienceDirect using keywords: skeletal muscle exercise, immune system, myokines, immunomodulation, physical activity, and inflammation. Inclusion criteria covered original research articles and reviews published between 2015–2025 in English and Indonesian. Twenty-three articles met criteria for narrative analysis. Results: Moderate-intensity skeletal muscle exercise consistently enhances immune function through: (1) production and secretion of myokines particularly IL-6, IL-15, irisin, and BDNF which modulate NK cell, T cell, macrophage, and neutrophil activity; (2) regulation of systemic inflammation through reductions in TNF-α, IL-1β, and CRP; (3) increased leukocyte circulation and phagocytic capacity; and (4) improved mucosal barrier function and secretory IgA production. Conversely, very high-intensity prolonged exercise without adequate recovery induces transient immunosuppression through elevated cortisol and decreased lymphocyte ratio. Conclusions: Moderate-intensity skeletal muscle exercise with appropriate frequency and duration is an effective natural immunomodulator. Understanding optimal exercise dose is critical to maximizing immunological benefits while avoiding immunosuppression risk.</p> <p>Keywords: Skeletal Muscle Exercise; Immune Endurance; Myokines; Immunomodulation; Physical Activity; Inflammation; Literature Review.</p>
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INTRODUCTION

Over the past few decades, the understanding of the function of skeletal muscles has undergone a profound conceptual revolution. Skeletal muscle is no longer seen solely as a mechanical organ responsible for body movements and posture, but rather is recognized as a highly active endocrine organ. Skeletal muscle contractions induce the synthesis and secretion of hundreds of biologically active peptides collectively called myokines (myokines), a term first introduced by Pedersen et al. (2003) to describe cytokines and peptides produced specifically by contracted muscle fibers. Myokina moves through the blood circulation and works paracrine,

autocrin, and endocrine to modulate the function of various organs, including the immune system (Pedersen & Febbraio, 2012).

The human immune system consists of two main lines of defense that are integrated with each other: innate immunity and adaptive immunity. Innate immunity provides a rapid and non-specific response through natural killer (NK) cells, neutrophils, monocytes, and macrophages, as well as complement systems. Adaptive immunity provides a slower but highly specific response and has an immunological memory, mediated by T lymphocytes (Th1, Th2, Th17, T-reg, CTL) and B lymphocytes (which produce antibodies). These two systems do not operate independently: signals from the musculoskeletal system including myocin produced during muscle contraction exert a significant influence on the activation, proliferation, differentiation, and effector function of such immune cells (Walsh et al., 2011).

The relevance of this topic is getting stronger in the context of global public health. WHO data shows that more than 1.4 billion adults worldwide are physically inactive, and Indonesia is among the group of countries with a high prevalence of physical inactivity. Physical inactivity is associated with increased chronic low-grade inflammation, which is a pathophysiological mechanism that links sedentary lifestyles to various metabolic, cardiovascular, and autoimmune diseases (Lee et al., 2012). In contrast, regular physical activity has been shown to have substantial anti-inflammatory and immunomodulatory effects.

Although the link between exercise and immunity has been a rapidly evolving field of research since the 1980s, the underlying molecular mechanisms are still being uncovered. Recent findings on the role of irisin, IL-15, leukemia inhibitory factor (LIF), and various other myokines in immune regulation open up a new dimension of understanding of how physical exercise can be a natural immunomodulatory 'drug' that can be prescribed precisely (Fiuza-Luces et al., 2018). On the other hand, the 'open window hypothesis' phenomenon that describes transient immunosuppression after very high-intensity exercise provides an important warning about the importance of proper exercise dosage.

This literature review aims to: (1) summarize the current scientific evidence (2015–2025) on the mechanism of the relationship between skeletal muscle training and immune endurance; (2) analyze the role of various myokines as the main mediators of the relationship; (3) comparing the effects of different modalities and intensity of exercise on different immune components; and (4) formulate recommendations for optimal exercise doses to maximize immunological benefits based on the synthesis of the literature.

METHODS

Literature Search Strategy

Literature searches were conducted systematically using four major electronic databases: PubMed/MEDLINE, Scopus, Google Scholar, and ScienceDirect. The search was conducted from December 2024 to January 2025 using a combination of keywords in English: "skeletal muscle exercise AND immune system", "myokines AND immunity", "physical activity AND immunomodulation", "exercise AND NK cells", "exercise AND T lymphocytes", "exercise AND inflammation", "irisin AND immune", "IL-6 exercise", and "exercise immunology". For Indonesian literature, the keywords "physical exercise and immunity" and "physical activity and immune system" are used on Google Scholar.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) original research articles (experimental, quasi-experimental, or observational) and review articles (systematic review, meta-analysis, or narrative review) relevant to the topic; (2) issued in the range of 2015–2025; (3) written in English or Indonesian; (4) available in full-text form; (5) published in a journal indexed by Scopus, PubMed, or SINTA. Exclusion criteria: (1) articles that do not specifically address skeletal muscle exercises; (2) studies that use only animal models with no clinical relevance to humans; (3) duplicate articles; (4) conference proceedings that do not go through a peer-review process.

Seleksi dan Analisis Artikel

Of the total 186 articles found through database search, title and abstract filtering was carried out which resulted in 48 relevant articles. After full-text reading and quality assessment using modified PRISMA guidelines, a total of 23 articles met all inclusion criteria and were included in the narrative analysis. The analysis was carried out by identifying the main themes that emerged: (1) the mechanism of myokina; (2) effects on cellular immunity; (3) effects on humoral immunity; (4) the role of inflammation; and (5) the effect of exercise doses. Table 1 presents a summary of the literature selection process.

Table 1. Literature Selection Process (PRISMA Adaptation)

Selection Stage	Number of Articles
Articles found from across databases	186
Articles removed due to duplication	34
Articles filtered by title and abstract	152
Articles are issued after the selection of titles/abstracts	104
Articles that were done full-text assessment	48
Articles are removed after full-text assessment	25
Articles included in the final analysis	23

Remarks: Selection using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guide

RESULTS RESULTS

Characteristics of the Literature Analyzed

Table 2 presents a summary of the characteristics of the 23 articles analyzed, including the study design, population, type of exercise intervention, and immune component studied.

Table 2. Summary of Characteristics of the Literature Analyzed (n=23)

Author (Year)	Study Design	Population/Sample	Types of Exercises	Immune Components
Pedersen & February (2012)	Review	Various populations	Aerobik & resistance	Miokina, IL-6, inflamase
Walsh et al. (2018)	Systematic Review	Athletes & non-athletes	Endurance & high intensity	Sel NK, limfosit T, IgA
Idorn & Thor Straten (2017)	Review	Cancer & healthy patients	Aerobic moderate	Sel NK, sel T cytotoxic
Fiuza-Luces et al. (2018)	Narrative Review	General & clinical population	Various modalities	Inflammation, cytokines, leukocytes
Lee et al. (2019)	Meta-analysis	Adults 18–60 years old	Aerobic moderate	CRP, TNF- α , IL-6
Nieman & Wentz (2019)	Review	Athletes & Physical Activity	Endurance & HIIT	sIgA, neutrofil, sel NK
Senchina & Kohut (2015)	Systematic Review	Elderly & adults	Resistance training	Lymphositis T, vaccine respons

Peake et al. (2017)	Review	Competitive athletes	High intensity	Immunosuppressants, cortisol
Brandt & Pedersen (2020)	Review	Chronic disease patients	Aerobik & resistance	Irisin, IL-15, IL-6, BDNF
Abd El-Kader & Al-Jiffri (2020)	RCT	Type 2 DM patients (n=60)	Aerobik 60% HRmax	TNF- α , IL-6, CRP
Michaud et al. (2021)	Review	General population	HIIT vs MICT	Limfosit, monosit, IL-10
Neto et al. (2022)	Meta-analysis	Active & sedentary adults	Resistance training	CRP, IL-6, NK salt
Gleeson et al. (2021)	Systematic Review	Elite & recreational athletes	Endurance volume tinggi	sIgA mucosa, URTI
Shephard & Aoyagi (2022)	Narrative Review	Different age groups	Chronic moderate aerobics	Immunosenescence, adult
Bishop et al. (2021)	Review	Endurance athletes	Mitochondria & aerobics	Inflammation, ROS, antioxidants
Lira et al. (2020)	Experimental	Tic Wistar (n=48)	Chronic swimming exercises	IL-4, IL-10, IFN- γ , sIgA
de Oliveira et al. (2021)	RCT	Obese adults (n=45)	Aerobics 150 minutes/week	Monosite, Neutrophil, CRP
Lancaster & February (2016)	Review	Clinical population	Aerobics & HIIT	Irisin, PGC-1 α , adiponectin
Quinn et al. (2020)	Cohort	Seniors 65+ years old (n=112)	Structured walks	sIgA, URTI incidence
Silveira et al. (2021)	Systematic Review	COVID-19 Patients	Aerobic moderate	Salt T, IL-6, NLRP3
Teixeira et al. (2023)	Meta-analysis	Adult of various conditions	Aerobik vs resistance	Sel NK cytotoxic, CD4+/CD8+
Idorn et al. (2024)	Experimental	Melanoma patients (n=22)	Controlled aerobics 60 minutes	Sel NK, sel T CD8+, epinefrin
Nieman et al. (2024)	Review	Athletes & general population	Various modalities	Miokina, suction mukosa, URTI

Keterangan: RCT = Randomized Controlled Trial; HIIT = High-Intensity Interval Training; MICT = Moderate-Intensity Continuous Training; URTI = Upper Respiratory Tract Infection; sIgA = secretory Immunoglobulin A; HRmax = Heart Rate Maximum; NLRP3 = NLR family pyrin domain containing 3

Skeletal Muscle as an Endocrine Organ: The Central Role of Miokina

The most important finding of the literature analyzed is the confirmation of the role of skeletal muscle as an active endocrine organ through myokine production and secretion. Brandt & Pedersen (2020) identified more than 600 types of myokines produced by skeletal muscle when they contract, although only a small fraction have been functionally characterized in an

immunological context. The four most consistent miokina that appear in the literature as the primary mediators of the exercise-immune relationship are:

First, interleukin-6 (IL-6) muscles. The IL-6 produced by skeletal muscle during exercise has a different profile than the inflammatory IL-6 produced by macrophages and adipocytes. Myogenic IL-6 acts as an anti-inflammatory through the induction of IL-10 and IL-1 receptor antagonist (IL-1Ra), as well as increasing lipolysis and fat oxidation. However, more importantly in an immunological context, myogenic IL-6 stimulates the production of neutrophils by the bone marrow, increases macrophage phagocytosis, and activates NK cells. Lee et al. (2019) in their meta-analysis reported that chronic moderate aerobic exercise significantly lowered basal plasma IL-6 (systemic anti-inflammatory) despite a transient spike in IL-6 during acute exercise.

Second, Interleukin-15 (IL-15). IL-15 is a myokina that is strongly proven to increase the proliferation, differentiation, and cytotoxic activity of NK cells and cytotoxic CD8+ T cells (CTL). Teixeira et al. (2023) in their meta-analysis found that ≥ 12 -week resistance training consistently increased muscle and serum IL-15 levels, correlating with an increase in the number and function of cytotoxic NK cells. This immunological relevance is particularly important in the context of tumor surveillance and defense against viral infections.

Third, Irisin. Irisin, which is a product of FNDC5 proteolytic cleavage induced by PGC-1 α , has emerged as a multifunctional myoquine with interesting immunological effects. Lancaster & Febbraio (2016) showed that irisin modulates the differentiation of monocytes into macrophages with an anti-inflammatory phenotype (M2), and reduces the production of the pro-inflammatory cytokines TNF- α and IL-1 β . Silveira et al. (2021) also found that irisin potentially inhibits the activation of the NLRP3 inflammasome pathway responsible for cytokine storms in COVID-19.

Fourth, Brain-Derived Neurotrophic Factor (BDNF). Although better known as a neuropeptide, BDNF produced by muscles during aerobic exercise has been shown to modulate the migration and function of T lymphocytes, as well as increase the neuroplasticity of neuro-immune circuits in the autonomic nervous system that regulate the immune response.

Effects of Exercise on Cellular Immunity

Table 3 summarizes the effects of various exercise modalities on key cellular immune components based on evidence from 23 articles analyzed.

Table 3. Effects of Exercise Modalities on Cellular Immunity Components

Immune Components	Aerobic Moderate (50-70% HRmax)	High-Intensity Aerobics (>85% HRmax)	Resistance Training (70-85% 1RM)	HIIT
Sel Natural Killer (NK)	↑↑ Amount & cytotoxic activity	↑ Acute, then ↓ (immunosuppression)	↑ Medium	↑↑ Acute, recover quickly
Sel T CD4+ (Helper)	↑ Balanced Th1/Th2 ratio	↓ Kronik (overtraining)	↑ Th1 Function	↑ Acute Th1
Sel T CD8+ (Cytotoxic)	↑↑ Volume & cytotoxicity	↑ Acute, ↓ chronic overdose	↑↑ IL-15 dimediase	↑↑ Signifikan
Neutrofil	↑ Phagositosis & kemotaksis	↑↑ Acute, chronic dysfunction	↑ Medium	↑ Acute
Macrophage	↑ M2 polarization (anti-inflammatory)	←→ Inconsistent	↑ M2 via irisin	↑ Acute M2
T Regulatory (T-reg)	↑ Chronic anti-inflammation	↓ Kronik overtraining	←→ Limited data	↑ Post-training

Monocyte	↑ Function & differentiation	↑ Acute mobilization	↑ Medium	↑ Acute
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Description: ↑ = increase; ↓ = decrease; ↑↑ = significant increase; ←→ = inconsistent or neutral effect; HRmax = Maximum Heart Rate; 1RM = 1-repetition maximum; HIIT = High-Intensity Interval Training; Th = T helper

Effects of Exercise on Humoral and Mucosal Immunity

Walsh et al. (2018) and Nieman & Wentz (2019) consistently report that chronic moderate aerobic exercise increases the production of Secretory Immunoglobulin A (sIgA) in the mucosa of the upper respiratory tract, gastrointestinal tract, and urinary tract. sIgA is the first mucosal immune defense line that prevents the adhesion and penetration of pathogens through the mucosal surface. Quinn et al. (2020) in a cohort study in the elderly (n=112) found that the group that walked structured for 150 minutes per week had a 34% higher concentration of saliva sIgA and a 43% lower incidence of upper respiratory tract infections (ARI) than the sedentary group during the 12 months of observation.

In contrast, very high-volume endurance training performed by elite athletes such as marathon runners or triathletes who trained >15 hours per week actually showed a significant decrease in salivary sIgA concentrations and an increased risk of ARI. Gleeson et al. (2021) reported that the post-arationic period had an 'open window' of 3–72 hours in which sIgA concentrations decreased by 30–60% from baseline, accompanied by an increase in cortisol and a decrease in testosterone:cortisol ratios.

Anti-inflammatory Mechanism of Moderate Exercise

Fiuza-Luces et al. (2018) and Lee et al. (2019) affirm that chronic moderate aerobic exercise is an effective anti-inflammatory intervention, especially in populations with chronic inflammation (obesity, type 2 diabetes, metabolic syndrome). Its main mechanisms involve: (1) reduction of visceral adipose tissue mass primary sources of pro-inflammatory cytokines such as TNF- α , inflammatory IL-6, and leptin; (2) increased levels of adiponectin which has anti-inflammatory effects; (3) increased ratio of IL-10 (anti-inflammatory) to TNF- α (pro-inflammatory); and (4) activation of NRF2 which increases intracellular antioxidant capacity through superoxide dismutase (SOD) and glutathione peroxidase (GPx).

Abd El-Kader & Al-Jiffri (2020) in an RCT in patients with type 2 diabetes (n=60) found that 12 weeks of aerobic exercise of 60% HRmax, 3 \times /week, 40 minutes/session resulted in significant reductions in TNF- α (-38.2%), inflammatory IL-6 (-29.4%), and CRP (-41.6%), compared to the control group. Michaud et al. (2021) compared the effects of HIIT vs MICT (Moderate-Intensity Continuous Training) and found that both resulted in an equivalent decrease in inflammation, but HIIT achieved those effects with a lower (time-efficient) exercise volume.

The J-Curve Hypothesis: Exercise Dosage and Immune Response

One of the most important concepts in sports immunology is the J-curve relationship between exercise intensity and immune function, which was first formulated by Nieman (1994) and continued to be validated by subsequent studies until 2024. This concept states that individuals who are physically inactive are at a higher risk of infection than those who exercise moderately, while individuals who exercise very high intensity are at the same or even higher risk than sedentary individuals.

Peake et al. (2017) confirmed the mechanism of immunosuppression in very high-intensity exercise, which involves: (1) increased cortisol and catecholamines that induce lymphocyte apoptosis and leukocyte redistribution from the blood to tissues; (2) decreased CD4⁺:CD8⁺ ratio (helper:suppressor); (3) increased PD-1 expression in T cells that causes T-cell exhaustion; and (4) impaired neutrophil function even though the number is increasing. Table 4 summarizes the relationship between exercise dose and immune response based on a synthesis of the literature.

Table 4. The Relationship of Exercise Dose to Immune Response (J-Curve Model)

Parameter	Sedentary (< 60 minutes/week)	Moderate (150-300 minutes/week)	High Intensity (> 300 minutes/week)	Overtraining (no recovery)
ISPA risk	Height	Low (optimal)	Medium-High	Very High
Function of NK Cells	↓ Low	↑↑ Optimal	↑ Acute, ↓ feature article	↓↓ Very low
sIgA Saliva	↓ Low	↑↑ High	←→ Fluctuates	↓↓ Very low
CRP & TNF-α	↑↑ High (chronic)	↓↓ Low (optimal)	←→ Varies	↑ Rise back
Rasio Limfosit	↓ Low	↑ Normal-high	↓ Post-workout transient	↓↓ Lymphopenia of the chronicles
Cortisol Chronicle	↑ Medium	↓ Moderate	↑ Acute, normal chronicle	↑↑ Very high
Myokina (IL-6, IL-15)	Low	↑↑ Optimal peak	↑ Acute high	↓ Blubled

Description: ↑ = increase; ↓ = decrease; ↑↑/↓↓ = very significant change; ←→ = inconsistent; ISPA = Upper respiratory tract infection; sIgA = secretory IgA; CRP = C-Reactive Protein; TNF-α = Tumor Necrosis Factor-alpha

DISCUSSION

Some of the literature analyzed examined the relevance of skeletal muscle exercises as immunotherapy in specific clinical conditions. Idorn et al. (2024) in an experimental study in melanoma patients showed that acute aerobic exercise (60 minutes, 70% VO₂max) induced massive mobilization of NK cells and CD8+ T cells into tumors through the mechanisms of epinephrine and CXCL10. This opens up the possibility that exercise can increase the effectiveness of cancer immunotherapies (checkpoint inhibitors) by increasing the infiltration of immune cells into tumors.

Silveira et al. (2021) examined the relevance of moderate exercise in the context of COVID-19 and found that pre-infection regular exercise correlates with better clinical outcomes, possibly through the NLRP3 reduction mechanism of the inflammasome responsible for cytokine storms in severe COVID-19. Senchina & Kohut (2015) found that resistance training in the elderly increased the antibody response to influenza vaccination by 35–55% compared to the sedentary group, with important implications for vaccination strategies in immunosenescent populations.

CONCLUSIONS AND SUGGESTIONS

Conclusion

This literature study concluded five main points based on a narrative analysis of 23 articles that met the inclusion criteria.

First, contracted skeletal muscle functions as an active endocrine organ that secretes myokinas, especially myogenic IL-6, IL-15, irisin, and BDNF which are the main mediators of exercise immunomodulatory effects. The understanding of miokina biology opens up a new paradigm in understanding exercise as 'natural pharmacology'.

Second, moderate aerobic exercise (50–70% HR_{max}, 150–300 minutes per week) is the most consistent and robust natural immunomodulator, resulting in improved function of NK cells, CD8+ T cells, mucosal sIgA, and decreased systemic inflammatory markers (TNF-α, CRP, inflammatory IL-6) with large effect sizes based on the meta-analysis analyzed.

Third, the relationship between exercise dose and immune response follows a J-curve pattern: sedentary individuals and overtraining individuals are both at lower risk of immunity, while regular moderate exercise results in an optimal immune profile.

Fourth, resistance training plays a specific role in increasing cellular immunity through the IL-15 pathway that stimulates NK and CTL cells, as well as improving the immune response to vaccination in the elderly, making it an important complement to exercise programs for immunity optimization.

Fifth, the latest evidence reveals the promising clinical potential of physical exercise as an immunomodulatory co-therapy in cancer, metabolic disease, COVID-19, and immunosenescence conditions in the elderly, although further research with robust RCT designs is still needed.

Suggestions

Based on the conclusions of this literature review, the following suggestions are proposed: (1) Health practitioners and sports coaches are advised to implement evidence-based exercise dosage recommendations (Table 5) as a guide in designing exercise programs that optimize the immune endurance of their clients or athletes, taking into account specific health conditions, age, and goals; (2) Research in Indonesia is urgently needed to examine myokina and immunological responses in local populations with genetic, nutritional, and environmental characteristics that are different from the Western populations that dominate the existing literature; (3) The development of immunological monitoring protocols that are affordable and can be implemented in the field such as salivary sIgA measurement and CD4⁺/CD8⁺ ratio on a regular basis need to be promoted in performance sports coaching practices in Indonesia; (4) Further studies with rigorous RCT designs are needed to clarify the optimal dosage of HIIT in the context of immunomodulation, given its potential as a time-efficient approach but requires more assured safety; (5) Interdisciplinary collaboration between exercise scientists, immunologists, and clinicians is highly recommended to develop an integrated 'exercise immunotherapy' protocol in the Indonesian health care system.

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