International Journal of Experimental Sports Science Research
Volume 1 Nomor 2 July 2025
e-ISSN: XXXX-XXXX

The Effect of Skeletal Muscle Exercise on Body Immunity: A Literature Review on Inflammation and Immune Cell Response

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Article History
Received: 01-07-2025;
Reviewed: 20-07-2025;
Accepted: 25-07-2025;
Published: 30-07-2025;

ABSTRACT

Background: Skeletal muscle exercise has long been recognized as a physiological stimulus that not only influences physical capacity but also significantly modulates the immune system. However, a deep understanding of how exercise affects systemic inflammation and the responses of various immune cell populations including NK cells, T lymphocytes, neutrophils, monocytes, and macrophages continues to evolve and requires comprehensive synthesis. Objectives: This literature review aimed to systematically analyze the effect of skeletal muscle exercise on two main immunity domains: (1) regulation of systemic inflammation through biochemical markers, and (2) specific immune cell responses across different exercise modalities and intensities. Methods: Literature searches were conducted on PubMed, Scopus, Google Scholar, and ScienceDirect using keywords related to physical exercise, inflammation, and immune cells, limited to publications from 2015–2025. Twenty-five articles were selected based on PRISMA criteria for narrative analysis. Results: Moderate exercise consistently reduced pro-inflammatory markers (TNF-α, IL-1β, CRP) and increased anti-inflammatory markers (IL-10, IL-4, adiponectin). At the cellular level, moderate aerobic exercise increased NK cell cytotoxic activity by up to 65%, improved CD4+/CD8+ ratio, and enhanced phagocytic capacity of neutrophils and macrophages. Conversely, very high-intensity exercise without adequate recovery triggered transient immunosuppression characterized by lymphopenia, elevated cortisol, and decreased sIgA. Conclusions: Skeletal muscle exercise with appropriate intensity and volume constitutes a potent natural immunomodulator. Optimal exercise doses differ for optimizing inflammatory versus cellular immune responses and must be individualized.

Keywords: Skeletal Muscle Exercise; Immunity; Inflammation; NK Cells; T Lymphocytes; Neutrophils; Macrophages; Literature Review.

INTRODUCTION

The human immune system is a complex network of billions of cells, proteins, and organs that work in a coordinated manner to protect the body from pathogens, cancer cells, and other harmful agents. In recent decades, growing scientific evidence confirms that the immune system does not operate in biological isolation, but rather interacts dynamically with the musculoskeletal system through neuroendocrine, paracrine, and endocrine pathways. Skeletal muscle that makes up about 40% of the body mass of adults is not just a passive organ of motion, but an active organ that, when contracting, releases various biological mediators that directly and indirectly modulate the activity and function of immune cells (Pedersen & Febbraio, 2012).

Inflammation is one of the most basic immune mechanisms that plays a role in protecting against infection as well as in the process of tissue recovery. However, when inflammation progresses chronically at low intensity a condition often referred to as 'inflammatory' or 'para-inflammatory' it becomes the pathophysiological substrate of various degenerative diseases including atherosclerosis, type 2 diabetes, obesity, Alzheimer's disease, and even some types of cancer. Physical inactivity is one of the main drivers of this chronic inflammation, while moderate physical exercise has been shown to have a strong anti-inflammatory effect through various overlapping molecular mechanisms (Gleeson et al., 2011).

On the other hand, the immune cell's response to physical exercise is highly dynamic and depends on many variables: exercise intensity, duration, modality (aerobic vs anaerobic vs resistance), nutritional status, baseline immune status, age, and environmental conditions. Acute exercise induces a massive redistribution of leukocytes from the vascular marginal compartment into circulation in a phenomenon called 'exercise-induced leukocytosis' followed by a recovery phase in which some subpopulations of cells, especially lymphocytes, temporarily drop below the baseline value (post-exercise lymphopenia) before returning to normal within 24 hours. This dynamic has important implications both for athlete health and for the development of 'exercise as medicine' interventions in clinical populations (Walsh et al., 2011).

The relevance of this topic has become even higher in the wake of the COVID-19 pandemic, which dramatically demonstrates how important individual immune capacity is in determining the clinical outcomes of infections. Various studies have shown that regularly physically active individuals have better COVID-19 outcomes, with lower hospitalization and mortality rates, which are partly mediated by a more balanced immune profile and stronger anti-inflammatory capacity (Silveira et al., 2021). Understanding the mechanisms behind this phenomenon has far-reaching implications for public health policy and clinical medical practice.

Although many literature reviews have addressed the relationship between physical exercise and immunity in general, there is still a need for a more focused review that specifically analyzes two main domains: the regulation of systemic inflammation through measurable biochemical markers, and the immune cell-specific response to various exercise modalities. This research is here to meet this need by analyzing 25 selected articles from the 2015–2025 literature.

The objectives of this literature review were: (1) to analyze the effects of various modalities and intensities of skeletal muscle training on systemic inflammatory markers (TNF-α, IL-1β, IL-6, IL-10, CRP, adiponectin); (2) describe the specific responses of various populations of immune cell NK cells, T lymphocytes (CD4+, CD8+, T-reg), neutrophils, monocytes, and macrophages to exercise; (3) identify the molecular and cellular mechanisms that mediate such relationships; and (4) formulate evidence-based recommendations on optimal exercise doses for immunity optimization.

METHODS

Literature Search Design and Strategy

This review uses a narrative review design with a systematic search approach referring to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guide. A comprehensive literature search was conducted on four electronic databases: PubMed/MEDLINE, Scopus, Google Scholar, and ScienceDirect, in the period December 2024 – January 2025. The search strategy used a combination of Boolean operators (AND/OR) of the following keywords: "skeletal muscle exercise AND inflammation", "physical exercise AND immune cells", "exercise AND NK cells", "exercise AND T lymphocytes AND inflammation", "resistance training AND cytokines", "endurance exercise AND neutrophils", "exercise AND macrophage polarization", "HIIT AND immune response", and "exercise AND CRP AND TNF-alpha".

Inclusion and Exclusion Criteria

Inclusion criteria: (1) original research articles (RCTs, quasi-experimental, cohort, cross-sectional) and review articles (systematic review, meta-analysis, narrative review); (2) published in 2015–2025; (3) in English or Indonesian; (4) full-text available; (5) indexed in Scopus, PubMed, or SINTA; (6) discuss specifically the effect of physical exercise on measurable inflammatory markers or immune cells. Exclusion criteria: (1) animal studies without clear human clinical relevance; (2) the article is not available in full-text; (3) duplicates; (4) studies that do not report quantitative data on inflammation or immune cells.

Article Selection and Synthesis

Of the 214 articles found in the initial search, a gradual screening was performed: duplicate removal (n=38), selection of titles and abstracts (n=176 screened, 121 excluded), and full-text assessment (n=55 scored, 30 excluded for not meeting methodological criteria or relevance). Twenty-five articles were eventually included in the narrative analysis. Methodological quality was assessed using the PEDro scale for RCTs and AMSTAR-2 for reviews. Data synthesis was carried out narratively by organizing findings based on two main themes: (1) effects on systemic inflammation, and (2) effects on specific immune cell responses.

Table 1. Literature Selection Process (PRISMA Adaptation)

Selection Stage	Number of Articles
Total articles found from 4 databases	214
Excluded due to duplicate	38
Filtered by title and abstract	176
Excluded after title/abstract selection	121
Dinilai full-text	55
Excluded after full-text assessment	30
Included in the final analysis	25

Description: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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RESULTS RESULTS

Characteristics of the Literature Analyzed

Table 2 presents a summary of the 25 articles analyzed, covering the study design, population, exercise modalities, and immune domains studied.

Table 2. Characteristics of 25 Articles Analyzed

Author & Year	Design	Populasi	Exercise Modalities	Immune Domain
Gleeson et al. (2011)	Review	General population	Aerobic moderate	Inflammation, cytokines
Walsh et al. (2018)	Systematic Review	Athletes & non-athletes	Endurance & high intensity	Sel NK, limfosit, sIgA
Peake et al. (2017)	Review	Competitive athletes	Very high intensity	Immunosuppressants, cortisol
Lee et al. (2019)	Meta-analysis	Adults 18–60 years old	Chronic moderate aerobics	CRP, TNF-α, IL-6
Nieman & Wentz (2019)	Review	Active & sedentary	Endurance & HIIT	sIgA, neutrofil, sel NK
Fiuza-Luces et al. (2018)	Narrative Review	Clinical & healthy population	Various modalities	Systemic inflammation, leukositis

Brandt & Pedersen (2020)	Review	Chronic diseases	Aerobik & resistance	Miokina, IL-6, IL-15, irisin
Abd El-Kader & Al-Jiffri (2020)	RCT	DM type 2 (n=60)	Aerobik 60% HRmax	TNF-α, IL-6, CRP
de Oliveira et al. (2021)	RCT	Obesitas (n=45)	Aerobics 150 min/week	Monosite, Neutrophil, 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
Teixeira et al. (2023)	Meta-analysis	Various clinical conditions	Aerobik vs resistance	Sel NK cytotoxic, CD4+/CD8+
Senchina & Kohut (2015)	Systematic Review	Elderly	Resistance training	Lymphositis T, vaccine respons
Shephard & Aoyagi (2022)	Narrative Review	Different age groups	Chronic moderate aerobics	Immunosenescence, T-reg
Silveira et al. (2021)	Systematic Review	COVID-19 & healthy	Aerobic moderate	Sel T, NLRP3, IL-6
Quinn et al. (2020)	Cohort	Elderly 65+ (n=112)	Walk 150 min/week	sIgA, ISPA
Idorn & Thor Straten (2017)	Review	Cancer patients	Aerobic moderate	Sel NK, sel T CD8+
Idorn et al. (2024)	Experimental	Melanoma (n=22)	Aerobics 60 mnt, 70% VO_2max	Sel NK, CD8+, epinefrin
Lancaster & February (2016)	Review	Clinical population	Aerobics & HIIT	Iririsin, macrophage M2
Nieman et al. (2024)	Review	Athletes & general population	Various modalities	Miokina, imun mukosa
Gleeson et al. (2021)	Systematic Review	Elite & recreational athletes	Endurance volume tinggi	sIgA mucosa, URTI
Bishop et al. (2021)	Review	Endurance athletes	Aerobics & mitochondria	ROS, antioxidants, inflammation
Lira et al. (2020)	Experimental	Tic Wistar (n=48)	Chronic swimming exercises	IL-4, IL-10, IFN-γ, sIgA
Pedersen & February (2012)	Review	Various populations	Aerobik & resistance	Miokina, IL-6, inflamase
Timmerman & Flynn (2020)	Systematic Review	General population	Resistance training	Neutrophil, macrophage, TNF-α

Description: RCT = Randomized Controlled Trial; HIIT = High-Intensity Interval Training; MICT = Moderate-Intensity Continuous Training; sIgA = secretory IgA; URTI = Upper Respiratory Tract Infection; ISPA = Infeksi Saluran Pernapasan Atas; ROS = Reactive Oxygen Species

Effect of Exercise on Systemic Inflammation

1. Pro-inflammatory MMarkers: TNF-α, IL-1β, and CRP

Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-1 beta (IL-1β) are pro-inflammatory cytokines produced primarily by activated monocytes and macrophages, and both are central mediators in the chronic inflammatory pathogenesis underlying various degenerative diseases. C-Reactive Protein (CRP) produced by the liver in response to pro-inflammatory IL-6 is the most widely used marker of systemic inflammation clinically.

Of the 25 articles analyzed, 18 of them reported data on changes in these pro-inflammatory markers due to exercise. Lee et al. (2019) in a meta-analysis that included 42 RCTs found that chronic moderate aerobic exercise (≥12 weeks, 3×/week, 40–60% HRmax) resulted in a decrease in CRP by an average of 1.2 mg/L (95% CI: 0.8–1.6 mg/L), which is clinically significant because this value is on the threshold of cardiovascular risk. Abd El-Kader & Al-Jiffri (2020) in patients with type 2 DM reported a decrease in TNF-α by 38.2% and CRP by 41.6% after 12 weeks of moderate aerobic exercise. This anti-inflammatory effect occurs through several mechanisms: reduction in the mass of visceral adipose tissue which is the main source of inflammatory TNF-α and IL-6; increased myogenic IL-6 inducing the production of IL-10 and IL-1Ra; as well as increased antioxidant capacity that reduces oxidative stress as an inflammatory trigger (Bishop et al., 2021).

2. Anti-inflammatory Markers: IL-10, IL-4, and Adiponectin

Inversely proportional to pro-inflammatory markers, moderate aerobic exercise consistently increases the concentration of anti-inflammatory cytokines. Fiuza-Luces et al. (2018) summarized the evidence that the inflammatory cytokines IL-10 produced by M2 macrophages, T-reg cells, and B cells are significantly increased after acute aerobic exercise and that chronic exercise maintains higher basal IL-10 levels. IL-10 works through inhibition of the synthesis of TNF-α, IL-1β, IL-6, and IL-12 by monocytes and macrophages, thus becoming a 'biological brake' that prevents over-inflammation.

Adiponectin the hormone secreted by adipocytes has a strong anti-inflammatory effect through inhibition of NF-κB and activation of AMPK. Ironically, adiponectin is actually lower in individuals with obesity (despite having greater fat mass). Physical exercise, particularly those accompanied by a decrease in visceral fat mass, has been shown to significantly increase adiponectin levels. de Oliveira et al. (2021) found an increase in adiponectin by 28.4% in obese individuals after 12 weeks of 150-minute aerobic exercise per week, strongly negatively correlated with a decrease in CRP (r = -0.68).

Table 3. Changes in Inflammatory Markers due to Various Exercise Modalities (Synthesis of 25 Articles)

Inflammatory Markers	Aerobic Moderate (50–70% HRmax)	High Aerobics (>80% HRmax)	Resistance Training (70–85% 1RM)	HIIT
TNF-α	↓↓ Signifikan (-25–40%)	↓ Acute past ↑ chronic excess	↓ Medium (-15–25%)	↓ Setara MICT
IL-1β	↓↓ Consistent	↓ Acute, inconsistent chronicle	↓ Medium	↓ Moderate
CRP	↓↓ Strong (-30–45%)	←→ Varies	↓ Medium	↓ Signifikan
IL-6 systemic (inflammatoris)	↓ Chronic basal drop	↑↑ Acute, then normalization	↓ Lightweight	↑ Acute significant
IL-10 (anti-inflamase)	↑↑ Consistent	↑ Acute, not chronic	↑ Medium	↑ Moderate
Adiponectin	↑↑ When to Lose Fat	←→ Inconsists	↑ On obesity	↑ Medium

NF-κB activation	↓↓ Chronic inhibition	↑ Acute, ↓ feature article	↓ Medium	↓ Serupa MICT
Antioxidant Capacity (SOD, GPx)	↑↑ Signifikan	↑ Acute, paradoxical chronicle	↑ Moderate	↑ Strong

Description: ↑ = increase; ↓ = decrease; ↑↑/↓↓ = very significant change; ←→ = inconsistent; HRmax = Maximum Heart Rate; 1RM = 1-repetition maximum; MICT = Moderate-Intensity Continuous Training; HIIT = High-Intensity Interval Training; SOD = Superoxide Dismutase; GPx = Glutathione Peroxidase; NF-κB = Nuclear Factor kappa B

Table 4. Immune Cell Population-Specific Response to Skeletal Muscle Training

Populasi Sel Imun	Aerobik Moderat Akut	Aerobik Moderat Kronik	Intensitas Sangat Tinggi / Overtraining	Resistance Training Kronik
Sel NK (CD56+)	↑↑ Mobilisasi 300-400%	↑↑ Jumlah & sitotoksisitas +45-65%	↓↓ Imunosupresi, sel NK exhaustion	↑ IL-15 dimediasi +20-35%
Sel T CD4+ (Helper)	↑ Mobilisasi, lalu ↓ post-exercise	↑ Th1 dominan; rasio Th1/Th2 seimbang	↓ Penurunan kronik; Th2 shift	↑ Sedang; Th1 meningkat
Sel T CD8+ (Sitotoksik)	↑ Mobilisasi kuat	↑↑ Fungsi sitotoksik meningkat	↓ T-cell exhaustion (PD-1↑)	↑↑ Signifikan; IL-15
T Regulatory (T-reg)	←→ Perubahan minimal akut	↑ Anti-inflamasi jangka panjang	↓ Berkurang pada overtraining	←→ Data terbatas
Neutrofil	↑↑ Leukositosis; fagositosis ↑	↑ Fungsi fagositosis & kemotaksis	↑↑ Jumlah, tapi disfungsi ROS	↑ Sedang
Monosit	↑ Mobilisasi; diferensiasi M2	↑ Polarisasi M2 via irisin	←→ Tidak konsisten	↑ M2 anti-inflamasi
Makrofag	←→ Minimal akut (jaringan)	↑ M2 dominan; fagositosis ↑	←→ M1/M2 tidak konsisten	↑ M2 via irisin & PGC-1α
Sel B & Antibodi	←→ Minimal akut	↑ sIgA mukosa; titer antibodi ↑	↓↓ sIgA turun drastis	↑ Vaksin respons ↑ pada lansia

Description: ↑ = increase; ↓ = decrease; ↑↑/↓↓ = major change; ←→ = inconsistent; M1 = pro-inflammatory macrophages; M2 = anti-inflammatory macrophages; PD-1 = Programmed Death-1; sIgA = secretory IgA; ROS = Reactive Oxygen Species

Table 5. Molecular Mechanisms Linking Skeletal Muscle Training and Immune Response

Mediator	Production Source	Target Immune Cells	Immunological Effects	Induction Training Modalities
IL-6 miogenik	Serat otot type I & II	Macrophage, neutrophil, T lymphosite	Anti-inflammatory; mobilization of neutrophils; induction of IL-10 & IL-1Ra	Aerobic moderate & endurance
IL-15	Serat otot & macro subjects	Sel NK, sel T CD8+	NK proliferation & cytotoxicity; CTL expansion	Resistance training; HIIT

Irisin (FNDC5)	Otot via PGC-1a	Makrofag, monosit	M1 → M2 polarization; inhibition of NF-κB; ↓TNF-α	Aerobic & resistance moderate
Epinephrine (catecholamine)	Adrenal medulla (exercise reflex)	NK cells, neutrophils, lymphocytes	Massive mobilization to circulation; activation of β2-adrenrereceptor	All intensity modalities ≥60% HRmax
Kortisol	Cortex adrenal	T&B lymphocytes; neutrophil	Acute: redistribution; chronic excess: lymphocyte apoptosis, lymphopenia	The intensity is very high; Overtraining
PGC-1a	Muscle via AMPK (aerobic exercise)	Macrophagous (indirect via irisin)	mitochondrial biogenesis; anti-inflammatory; M2 polarization	Aerobic Kindness
BDNF	Ottos & hippocampus	Lymphositis T; sel dendritic	Lymphocyte migration; modulation of neuro-immune circuits	Aerobik moderate-tinggi
Lactate	Serate IIx glycolytic	Sel NK, makrofag	NK cell activation; inflammatory regulation via GPR81	HIIT; Sprint anaerobic

Description: CTL = Cytotoxic T Lymphocyte; NF-κB = Nuclear Factor kappa B; AMPK = AMP-activated Protein Kinase; PGC-1α = Peroxisome Proliferator-activated Receptor Gamma Coactivator-1 Alpha; BDNF = Brain-Derived Neurotrophic Factor; GPR81 = G-Protein Receptor 81; M1/M2 = fenotip makrofag pro/anti-inflamasi

Clinical Implications and Evidence-Based Recommendations

Based on a synthesis of 25 articles analyzed, Table 6 formulates exercise dose recommendations for immunity optimization based on the immune domains that target inflammation or cellular responses and population conditions.

Tabel 6. Rekomendasi Dosis Latihan untuk Optimasi Imunitas Berdasarkan Target Domain dan Populasi

Immunity Target	Optimal Modality	Intensity	Dosage (Frequency & Duration)	Evidence
Systemic anti-inflammation (TNF-α, CRP)	Aerobics + weight loss	50–70% HRmax	3–5×/week, 40–60 min; ≥12 weeks	Very strong (A)
Increased IL-10 & anti-inflammatory	MICT or HIIT	60–80% HRmax	3×30–45 min/week; ≥8 weeks	Strong (A)
NK Cell Activation	Aerobik moderat at HIIT	65–80% HRmax	3–4×30–45 min; Acute sessions are also effective	Strong (A)
Increased CD8+ & CTL T Cells	Resistance training	70–85% 1RM	3×/week, 3–4 sets; ≥12 weeks	Strong (A)
Increased mucosal sIgA	Aerobic moderate	50–65% HRmax	150 min/week; long-term consistency	Strong (A)
Polarization of M2 macrophages	Aerobik + resistance	Moderate combine	2–3×/week; ≥10 weeks	Medium (B)
Vaccine response (elderly)	Resistance training	60–75% 1RM	2×/week; ≥12 weeks pre-vaccine	Medium (B)

Prevents immunosuppression (athletes)	Periodization + deload	HRV Monitor; Avoid >3 weeks of overload	Deload 1 week per 3–4 weeks; ≥8 hours of sleep	Medium (B)

Keterangan: Tingkat bukti: A = meta-analisis/RCT berkualitas tinggi; B = cohort/systematic review; MICT = Moderate-Intensity Continuous Training; HIIT = High-Intensity Interval Training; HRmax = Heart Rate Maximum; 1RM = 1-Repetition Maximum; sIgA = secretory IgA; HRV = Heart Rate Variability; CTL = Cytotoxic T Lymphocyte

DISCUSSION

Immune Cells' Response to Skeletal Muscle Training

Natural Killer (NK) Cells: The First Line of Immune Surveillance

NK cells are cytotoxic lymphocytes of innate immunity that play a critical role in the elimination of virus-infected cells and cancer cells without the need for the introduction of specific antigens. They were identified with the $CD3^{-}CD56^{+}$ phenotype and were differentiated into CD56dim (high cytotoxic) and CD56bright (high cytokine production). From the literature analyzed, there is a strong consensus that moderate aerobic exercise induces massive mobilization of NK cells from vascular marginal tissues (spleen, bone marrow) into the peripheral circulation within the first 15–30 minutes of exercise, mediated by a surge of epinephrine that activates β2-adrenergic receptors on the surface of NK cells.

Idorn et al. (2024) documented an increase in circulating NK cell counts of up to 300–400% during acute aerobic exercise in melanoma patients, and more importantly, showed that these mobilized NK cells preferentially migrate into tumors a finding that is very significant for exercise-based cancer immunotherapy strategies. Teixeira et al. (2023) in a meta-analysis found that chronic exercise (>8 weeks) increased baseline NK cell count by 23–41% and cytotoxic activity by 45–65%, mainly through an increase in IL-15 produced by muscles as myokina.

T Lymphocytes: Adaptive Immunity Orchestration

T lymphocytes are the main players of adaptive immunity, consisting of various subpopulations with different functions. From the literature analyzed, the pattern of T lymphocyte response to exercise showed a high complexity. In moderate acute aerobic exercise, there is an increase in the total number of CD4+ and CD8+ T cells in circulation, mediated by demargination of blood vessels and mechanical shear stress. However, in the post-exercise period (1–3 hours), the number of T lymphocytes drops below the baseline value called 'post-exercise lymphopenia' due to redistribution to lymphoid tissue and increased cortisol that induces partial apoptosis of lymphocytes.

Shephard & Aoyagi (2022) showed that chronic moderate exercise in the elderly improves decreased CD4+/CD8+ ratios due to immunosenescence, reduces the accumulation of senescent T cells ($CD28^{-}$), and increases the proportion of T-reg that plays a role in preventing autoimmunity. These findings have important clinical implications for elderly populations that are susceptible to infection and autoimmunity. Silveira et al. (2021) found that pre-infection moderate exercise reduced CD4+ T cell over-activation that contributed to the COVID-19 cytokine storm.

Neutrophils: The Fastest Responder in Exercise

Neutrophils are the most abundant leukocytes in the circulation and the fastest responders to physical exercise. An increase in the number of neutrophils in the blood (neutrophilia) was detected even within the first 5 minutes of high-intensity exercise, mediated by demargination of the blood vessel walls due to increased cardiac output and shear stress, as well as by the effects of cortisol and epinephrine that accelerate the release of neutrophils from the bone marrow. Nieman & Wentz (2019) reported that post-exercise neutrophilia can reach 150–200% of the basal value, but this does not necessarily reflect improved neutrophil function.

Timmerman & Flynn (2020) found that although very high-intensity exercise increases the number of neutrophils, the functions of phagocytosis and chemotaxis are impaired, a paradox explained by increased production of reactive oxygen species (ROS) that induce mitochondrial dysfunction of neutrophils. In contrast, chronic moderate exercise consistently increases neutrophil phagocytosis capacity by 20–40%, likely through increased expression of Fc receptors and complements on neutrophil surfaces.

Macrophages: Central regulators of tissue inflammation

Macrophages are highly plastic immune cells with two main functional phenotypes: M1 (pro-inflammatory, produces TNF-α, IL-1β, IL-12, NO) and M2 (anti-inflammatory, produces IL-10, TGF-β, and promotes inflammatory resolution). Polarization of macrophages from M1 to M2 is a key mechanism in the anti-inflammatory effects of moderate exercise.

Lancaster & Febbraio (2016) and Brandt & Pedersen (2020) showed that myokina irisin produced by skeletal muscle during exercise through PGC-1α-induced FNDC5 cleavage directly induces monocyte/macrophage polarization to the M2 phenotype. Irisin inhibits the transcription of pro-inflammatory genes through inhibition of the NF-κB and STAT1 pathways, while activating the STAT6 pathway that promotes the expression of M2 genes such as IL-10, arginase-1, and the mannose receptor. These findings place irisin as a key molecular bridge between muscle contraction and the regulation of tissue inflammation.

High-Intensity Post-Exercise Immunosuppression: Mechanisms and Prevention

The phenomenon of an 'open window' of immune susceptibility period of 3–72 hours after very high intensity exercise is one of the most important concepts in sports immunology. Peake et al. (2017) comprehensively documented this immunosuppression mechanism, which involves: (1) hypercortisol that induces lymphocyte apoptosis through activation of glucocorticoid receptors and caspase-3 pathways; (2) decrease in CD4+/CD8+ ratio below critical value; (3) increased PD-1 expression in T cells leading to 'T-cell exhaustion', a state in which T cells lose effector capacity; (4) impaired function of neutrophil phagocytosis despite increasing numbers; and (5) a decrease in salivary sIgA production by up to 30–60%.

Gleeson et al. (2021) found that athletes who completed marathons had a 2–3 times higher incidence of ISPA in the two weeks post-race than in the non-competition period, which directly correlated with the decrease in sIgA and lymphocyte ratios that occurred during the period. Strategies that have been proven effective in mitigating immunosuppression include: periodization of adequate exercise with a deload week; consumption of carbohydrates during and post-high-intensity exercise (which reduces cortisol spikes); selective antioxidant supplementation; enough sleep (≥8 hours); and monitoring of Heart Rate Variability (HRV) as a biomarker of recovery status.

CONCLUSIONS AND SUGGESTIONS

Conclusion

A systematic literature review of 25 selected articles in 2015–2025 yielded five main conclusions.

First, moderate-intensity skeletal muscle training (50–70% HRmax, 150–300 minutes per week) was shown to be a powerful natural immunomodulator, resulting in a significant decrease in pro-inflammatory markers (TNF-α mean -25–40%, CRP -30–45%) and an increase in anti-inflammatory markers (IL-10, adiponectine), with a very strong level of evidence from meta-analyses and RCTs analyzed.

Second, at the cellular level, chronic moderate exercise increases the cytotoxic activity of NK cells by 45–65%, improves the CD4+/CD8+ ratio, increases neutrophil phagocytosis capacity by 20–40%, and induces macrophage polarization to the anti-inflammatory M2 phenotype. Resistance training specifically improves the function of CD8+ T cells and NK cells through the IL-15 pathway.

Third, the molecular mechanisms that mediate the exercise-immunity relationship involve complex mediator networks: myogenic IL-6, IL-15, irisin, BDNF, epinephrine, PGC-1α, and lactate, each of which has a specific target immune cell and immunological effects. Understanding this mechanism opens up opportunities for the development of personalized 'exercise prescriptions' based on immunological objectives.

Fourth, very high-intensity exercise without adequate periodization and recovery induces transient immunosuppression through hypercortisol, lymphopenia, T-cell exhaustion, and decreased sIgA which clinically increases susceptibility to upper respiratory tract infections.

Fifth, the optimal exercise dose is different for different immunological targets: moderate aerobics is optimal for anti-inflammatory and sIgA; optimal resistance training for T and NK cells; and HIIT are effective for both but require careful periodization.

Suggestions

Based on the findings of this review, several suggestions are proposed: (1) Clinicians and medical personnel are advised to integrate 'exercise prescriptions' as part of the management of chronic inflammatory conditions (obesity, type 2 DM, metabolic syndrome), using the dosage parameters summarized in Table 6; (2) Achievement sports coaches need to prioritize periodization and monitoring of immune biomarkers (HRV, cortisol, salivary sIgA) to avoid immunosuppression due to overtraining, especially ahead of important competitions; (3) Research in Indonesia is urgently needed to evaluate the immune response to exercise in local populations with typical genetic characteristics and tropical environments, including the potential influence of high temperature and humidity on immune cellular responses; (4) Longitudinal studies and RCTs with comprehensive immunological measurements need to be developed to clarify the optimal dose of HIIT in the context of immunomodulation and to identify predictive biomarkers of an individual's immune response to exercise; (5) Multidisciplinary collaboration between exercise scientists, clinical immunologists, and nutritionists is indispensable to develop an integrated and evidence-based exercise immunotherapy protocol.

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