



EXERCISE AND INFLAMMATORY RESPONSE: MECHANISM OF INTERLEUKIN-6 EXPRESSION CHANGES

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ABSTRACT

Exercise has a broad impact on health through various physiological mechanisms, one of which is through the regulation of interleukin-6 (IL-6). IL-6 is a pleiotropic cytokine that plays a role in immune responses, inflammation, and energy metabolism regulation, and is produced not only by immune cells but also by skeletal muscle as myokine during physical activity. This article aims to examine the physiological adaptations of exercise to IL-6 production and function and its relationship to energy metabolism, mitochondrial function, and inflammatory response. The research method employed was a literature review utilizing a descriptive approach. In acute exercise, muscle contraction triggers a rapid and temporary increase in IL-6 through mechanisms involving changes in calcium homeostasis, activation of AMP-activated protein kinase (AMPK) due to decreased energy reserves, oxidative stress, and epigenetic regulation. This study was conducted using a descriptive literature review approach. Relevant primary research articles and review papers were systematically identified through electronic databases, the selected literature was analyzed and synthesized to explore the mechanisms underlying exercise-induced changes in Interleukin-6 (IL-6) expression and signaling, with particular emphasis on acute and chronic exercise adaptations, energy metabolism, mitochondrial function, and inflammatory responses. The increase in IL-6 during this phase plays a role in maintaining energy homeostasis by increasing glucose transport, fatty acid oxidation, and modulating the immune response. Conversely, regular exercise induces long-term adaptations in the form of increased mitochondrial number and function, increased antioxidant capacity, and increased muscle sensitivity to IL-6 through the classical signaling pathway. These adaptations enhance IL-6 signaling efficiency, enabling metabolic and anti-inflammatory responses to be achieved with lower IL-6 production. Thus, regular exercise plays a crucial role in reducing systemic inflammation, improving energy metabolism, and supporting health and the prevention of chronic diseases.

Keywords: cytokine; exercise; exercise adaptation; interleukin-6

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INTRODUCTION

Exercise provides many health benefits.(Abu-Omar et al., 2023)Exercise has long-term effects on physical health and mental health. (Dimitri et al., 2020; Okely et al., 2021)Exercise adequately affects various physiological processes in the body, increases endurance, and influences the immune system. (Światowy et al., 2021). Domin (2021) states that acute exercise that is short-lived or occurs only once has a different effect on cytokines when compared to prolonged activity or repeated routine exercise.(Domin et al., 2021).Al-Mhanna (2022) in his literature review concludes that physical activity provides benefits in improving quality of life and immunity markers in cancer patients both before therapy, during therapy and after therapy in the form of a significant decrease in tumor necrosis factor- α (TNF- α), C Reactive Protein (CRP), interleukin-8 (IL-8) and interleukin-6 (IL-6) (AL-Mhanna et al., 2022).Park (2023), who reviewed literature from various sources on physical activity and immunity in the elderly, concluded that physical activity can delay the decline in immune system function that occurs with age (immunosenescence) and enhance the immune system through both innate and acquired immunity. (Park, 2023)

In recent decades, research on the effects of exercise on inflammatory responses has attracted significant attention. Interleukin 6 (IL-6), one of the cytokines that plays a key role in the inflammatory response during exercise, remains a subject of debate in terms of its dynamics during physical activity. Therefore, a deeper understanding of the relationship between exercise and IL-6 is crucial, not only for the development of effective exercise programs but also for prevention strategies and interventions in various health conditions. This article aims to analyze the mechanisms underlying changes in the expression and function of Interleukin-6 (IL-6) in response to acute and regular exercise, as well as its relationship with energy metabolism, mitochondrial function, and inflammatory responses.

METHOD

This article was written using a literature review method from several primary sources, such as national and international scientific articles and online media, namely Google and journal websites (PubMed, NCBI, Mendeley, ACS, etc.), with the aim of increasing knowledge and understanding of the topic discussed.

RESULT

Exercise and The Acute Response of Interleukin-6

Interleukin-6 (IL-6) is a cytokine produced by skeletal muscle in response to physical activity.(Fischer, 2006; Nash et al., 2023) This cytokine is produced not only by immune cells (T and B lymphocytes, NK cells, and monocytes) but also by non-immune cells (glial cells, smooth muscle cells, chondrocytes, and astrocytes). IL-6 is a potent mediator of the acute phase, which is a series of responses triggered by stressors such as inflammation, tissue damage, or strenuous physical activity. The mechanism aims to prevent further damage and initiate the repair process.(Małkowska & Sawczuk, 2023) During exercise, muscle contraction triggers increased IL-6 production in response to several factors that affect cellular metabolism.(Fischer, 2006) IL-6 produced by skeletal muscle during exercise is also triggered by several factors such as duration, intensity, and glycogen availability.(Nash et al., 2023)

Muscle contraction during exercise causes changes in calcium homeostasis. When muscles contract, depolarization of the muscle cell (myocyte) membrane occurs. This process begins with the activation of sodium channels that allow sodium (Na^+) to enter the cell, which then causes depolarization. Depolarization of the cell membrane triggers the release of calcium from the sarcoplasmic reticulum into the cytosol. This mechanism can occur through ryanodine channels in the sarcoplasmic reticulum, which rapidly transport calcium into the cytosol, and also through purinergic (P2Y) receptor mechanisms. Activation of these receptors stimulates the release of calcium from the sarcoplasmic reticulum, resulting in a slow increase in calcium in the cytosol.(Nash et al., 2023) Increased intracellular calcium levels play an important role in activating signaling pathways that trigger IL-6 gene expression. Calcium acts as a signal that activates several transcription factors, including Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and nuclear factor interleukin-6 (NFIL6).(Fischer, 2006) When calcium accumulates, these factors trigger the transcription of IL-6 mRNA, which is then translated into IL-6 protein.(Nash et al., 2023)

Poor energy conditions stimulate IL-6 production.(Kistner et al., 2026; Nash et al., 2023) When glucose is low, the body responds by increasing glucose production using reserve energy sources derived from glycogen and lipids.(Fischer, 2006; Nash et al., 2023) Calcium interacts with the AMPK (AMP-activated protein kinase) enzyme, which functions as a cellular energy sensor. When energy reserves decrease, AMPK is activated.(Domin et al., 2021; Nash et al., 2023) AMPK activation will increase IL-6 levels, which then trigger fatty acid oxidation and lipolysis in adipose tissue, as well as increase glucose transport into muscles through GLUT4 transporter translocation.

In addition, low glycogen reserves also increase IL-6 mRNA expression in myocytes.(Domin et al., 2021; Kistner et al., 2026; Nash et al., 2023)

Exercise can increase IL-6 expression through epigenetic modification. (Hunter et al., 2023; Li et al., 2022) Exercise causes a decrease in DNMT (DNA methyltransferase) concentration, particularly DNMT3b. DNMT functions in the DNA methylation process, which involves the addition of methyl groups to cytosine in DNA. Methylation inhibits gene expression by altering chromatin structure, thereby affecting gene transcription. When DNMT is active, methylation increases in the IL-6 gene promoter, changing the chromatin structure to become more compact, which inhibits IL-6 gene transcription. Methylation in the IL-6 promoter region prevents the transcription factors needed to express the gene from binding to DNA properly, thereby reducing IL-6 mRNA production, which results in decreased IL-6 protein production. During exercise, the expression of DNMT, particularly DNMT3b, decreases, causing epigenetic changes, a reduction in methylation of the IL-6 gene, which in turn increases IL-6 production. (Hunter et al., 2023; Li et al., 2022)

Exercise also triggers the formation of reactive oxygen species (ROS). ROS can induce the activation of the NF- κ B pathway. NF- κ B activation will increase IL-6 mRNA expression. IL-6 will be produced in response to oxidative stress and released into the circulation as a pro-inflammatory cytokine, resulting in increased IL-6 levels. (Fischer, 2006; Nash et al., 2023) In addition, ROS also acts as a signal that induces epigenetic changes. ROS can modify DNA methylation patterns and post-translational histone modifications, which are key components in genetic regulation. ROS can decrease DNA methylation through mechanisms involving enzymes such as DNMTs. ROS levels stimulate the activity of TET (Ten-eleven translocation enzymes), which function to stimulate the conversion of 5-methylcytosine to 5-hydroxymethylcytosine. This process promotes DNA demethylation, which is associated with increased IL-6 expression.(Li et al., 2022) ROS also causes histone modifications, such as acetylation, which can affect IL-6 gene expression, so that any changes in histone acetylation can impact IL-6 production.(Li et al., 2022)

Interleukin-6 Adaptation in Regular Exercise

Interleukin-6 is a cytokine that has dual action, acting as both a proinflammatory cytokine and an anti-inflammatory cytokine, depending on cell signaling. (Małkowska & Sawczuk, 2023) During exercise, IL-6 levels increase dramatically, with the aim of preventing further damage and initiating the repair process. Soluble IL-6 receptors are involved in pro-inflammatory effects, while glycoprotein 130 (gp130) receptors are involved in anti-inflammatory effects.(Małkowska & Sawczuk, 2023) A temporary increase in IL-6 stimulates the production of anti-inflammatory cytokines. IL-6 binds to the glycoprotein 130 (gp130) receptor on target cells, activating a complex signaling pathway. Activation of this pathway increases the expression of SOCS (Suppressor of Cytokine Signaling), which inhibits further pro-inflammatory signals. (Małkowska & Sawczuk, 2023; Nash et al., 2023; Villar-Fincheira et al., 2021)

Regular exercise triggers an increase in the number and activity of mitochondrial enzymes.(Nash et al., 2023) Mitochondria function as the center of cellular energy production. Regular physical exercise increases the number and function of mitochondria, which has an impact on increasing cellular oxidative capacity and energy use efficiency. With an increase in the number of mitochondria, cells will produce ATP more efficiently in high-performance situations. In addition, cells will be better able to utilize various substrates, such as glucose and fatty acids, for energy production.(Berg, 2025; Małkowska & Sawczuk, 2023) Regular exercise also increases insulin sensitivity and improves lipid metabolism, so that with increased mitochondrial number and activity, muscle cells become more efficient at producing energy through the aerobic oxidation of fat and glucose. The use of reserve energy sourced from glycogen and lipids will become more efficient, which will indirectly affect the production of IL-6. (Berg, 2025; Nash et al., 2023)

Exercise also increases the body's antioxidant capacity, which helps reduce oxidative stress.(Nash et al., 2023) Regular exercise increases the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT). SOD converts superoxide radicals into hydrogen peroxide, while CAT converts hydrogen peroxide into water and oxygen, helping to reduce oxidative stress. Regular exercise also stimulates mitochondrial biogenesis, which triggers an increase in cellular energy production. More active mitochondria have a higher capacity to neutralize ROS and reduce oxidative stress. As is well known, oxidative stress often contributes to inflammation, so this reduction in oxidative stress has an impact on IL-6 levels.(Liu et al., 2024)

Regular exercise can also increase the expression of IL-6 receptors on the surface of muscle cells, which can increase muscle sensitivity to IL-6. Regular exercise increases IL-6R gene expression in myocytes, which can increase sensitivity to classical signaling. Signal efficiency occurs, and metabolic response remains optimal even with minimal IL-6 levels. This is due to adaptive downstream signaling (AMPK, GLUT-4, fat oxidation) () that causes muscles to become more sensitive, reducing IL-6 mRNA and IL-6 release despite increased work capacity. (Nash et al., 2023).

DISCUSSION

Exercise And Inflammatory Response

Exercise Has Beneficial Physiological Effects On Health And Is Widely Promoted As A Non-Pharmacological Intervention To Support Health. The Various Benefits Are Inseparable From The Modulation Of Cytokines Released By Various Tissues In Response To Muscle Contraction During Exercise And The Physiological Adaptations That Occur. (Poorhabibi Et Al., 2025)

Cytokines Are Bioactive Proteins Produced By Various Cells In The Form Of Proteins Secreted By Leukocytes And Various Other Types Of Cells (Endothelial Cells, Fibroblasts, Keratinocytes, Osteoblasts, Chondrocytes, Etc.) That Play A Role In Regulating Immunological Responses, Hematopoietic Development, And Intercellular Communication As Well As Host Responses To Infectious Agents And Inflammatory Stimuli.(Stenken & Poschenrieder, 2015)Based On Their Biological And Functional Effects, Cytokines Are Classified Into Proinflammatory Cytokines, Anti-Inflammatory Cytokines, And Dual-Function Cytokines That Respond To Both Proinflammatory And Anti-Inflammatory Conditions. (Abbas, Abdul K., Lichtman, Andrew H., 2022)Proinflammatory Cytokines Are Produced In Response To The Entry Of Pathogens Or Cell Damage. Proinflammatory Cytokines Include Interleukin-1 (Il-1), Interleukin-6 (Il-6), And Tumor Necrosis Factor-Alpha (Tnf-A). Conversely, Anti-Inflammatory Cytokines Are Important Regulators That Suppress The Production Of Various Proinflammatory Cytokines. Cytokines That Have Anti-Inflammatory Effects Include Interleukin-10 (Il-10) And Transforming Growth Factor-Beta (Tgf-B), Which Are Multifunctional Cytokines That Have Various Biological Effects, Including Anti-Inflammatory, Immunosuppressive, And Profibrotic Activities, And Contribute To The Resolution Of The Inflammatory Process By Inhibiting The Production Of Proinflammatory Cytokines. Dual-Function Cytokines Are Cytokines That Play A Role In Both Pro-Inflammatory And Anti-Inflammatory Responses Depending On The Biological Context And Receptor Pathways Involved. The Existence Of Cytokines With Dual Functions, Such As Il-6 And Il-8, Confirms That Immune And Inflammatory Responses Are Dynamic And Highly Dependent On The Physiological Context And Microenvironment In Which The Cytokines Work. (Reddy Et Al., 2024)

Changes In Cytokine Concentration Are Specific And Depend On Various Characteristics Of Exercise. Important Features That Influence This Are The Type Of Exercise, Such As Endurance, Resistance, Dynamic Strength, Or High Intensity Interval Training (Hiit). In Addition, It Is Related To The Mode Of Metabolism, Such As Aerobic, Anaerobic, Or Mixed. The Amount And

Duration Of Exercise Also Influence Cytokine Release. Short-Duration Exercise Or A Single Acute Training Session Has A Different Effect On Cytokines Compared To Regular, Repeated Exercise. Furthermore, An Individual's Baseline Fitness Level Also Influences The Type And Degree Of Cytokine Response To Exercise.(Domin Et Al., 2021) Islam (2024) Demonstrated That There Are Differences In Cytokine Response During The Acute Phase After Exercise And The Recovery Phase. High-Intensity Exercise Produces A More Significant Decrease In Anti-Inflammatory Cytokines Compared To Light Exercise.(Islam Et Al., 2024)

Interleukin-6

Interleukin-6 (Il-6) Is A Major Member Of The Il-6 Cytokine Superfamily, A Protein Consisting Of 212 Amino Acids And Having A Mass Of 21–26 Kda.(Villar-Fincheira Et Al., 2021) Il-6 Plays A Role In Immune Regulation By Activating A Cell Surface Signaling Complex Consisting Of Il-6, The Il-6 Alpha Receptor (Il-6 α), And The Gp130 Co-Receptor. The Structure Of The Extracellular Signaling Complex, With A Resolution Of 3.65 Angstroms, Shows An Interlinked Hexameric Arrangement Mediated By A Total Of 10 Symmetrically And Thermodynamically Interconnected Interfaces. (Boulanger Et Al., 2003)

The Il-6 Response To Exercise Has Been Extensively Studied And Is Widely Recognized As A Key Cytokine In Exercise Physiology.(Docherty Et Al., 2022) Interleukin-6 (Il-6) Is A Cytokine That Is Rapidly And Transiently Produced In Response To Infection And Tissue Injury, Contributing To The Body's Defense Through Stimulation Of The Acute Phase Response, Hematopoiesis, And Immune Reactions. Il-6 Is Associated With The Acute Phase Of Inflammatory Responses Such As Sepsis And Viral Infections, , As Well As Conditions With Chronic Inflammatory Components Such As Rheumatoid Arthritis, Type 2 Diabetes, And Obesity.(Nash Et Al., 2023) Il-6 Strongly Induces Acute Phase Proteins, C-Reactive Protein (Crp), Several Complement System Proteins, And The Coagulation Cascade. Il-6 Also Regulates Body Thermogenesis As An Endogenous Pyrogen, Stimulates Hematopoietic Precursor Growth, And Promotes T And B Lymphocyte Differentiation And Maturation.(Villar-Fincheira Et Al., 2021) Il-6 Also Plays A Role In Regulating Serum Iron And Zinc Levels By Stimulating Hepcidin Production, Which Inhibits Iron Transporters, And Increasing Zinc Transporter Expression In Hepatocytes. Il-6 Triggers Megakaryocyte Maturation In The Bone Marrow, Contributing To Platelet Release. Additionally, Il-6 Plays A Role In T Cell Differentiation And The Development Of Adaptive Immune Responses, And Can Trigger B Cell Differentiation Into Antibody-Producing Plasma Cells. Excessive Il-6 Production Can Cause Hypergammaglobulinemia And Autoantibody Production, Associated With The Development Of Various Autoimmune And Chronic Inflammatory Diseases. (Docherty Et Al., 2022; Tanaka Et Al., 2014)

Contracting Muscle Fibers Also Trigger The Production Of Il-6, Known As Myokine. Increased Il-6 Levels Occur Along With Increased Exercise Duration And Intensity, As Well As Decreased Muscle Glycogen. Il-6 Functions As A Signal To Maintain Muscle Energy Homeostasis. Il-6 Increases Glucose Transport Into Muscle Cells By Stimulating The Translocation Of The Glut4 Glucose Transporter To The Cell Surface. This Helps Increase The Availability Of Glucose As An Energy Source During Physical Activity. In Addition, Il-6 Also Increases Fatty Acid Oxidation And Inhibits The Lipogenic Effects Of Insulin. Il-6 Can Cross The Blood-Brain Barrier And Affect Activity In The Central Nervous System. This Contributes To The Perception Of Fatigue During Exercise, Which Serves As A Mechanism To Protect The Body's Homeostasis During Strenuous Physical Activity. Il-6 As A Myokine Plays An Important Role In Regulating Energy Metabolism, Controlling Inflammation, And Modifying Immune Responses During And After Exercise. This Mechanism Shows That Il-6 Not Only Plays A Role In The Inflammatory Process, But Also In The Body's Adaptation To Physical Exercise.(Nash Et Al., 2023)

There Are Two Il-6 Signaling Pathways, Namely Through The Binding Of Il-6 To The Membrane Il-6 Receptor (Il-6r), Known As The Classical Pathway, And Through The Binding Of Il-6 To The Soluble Il-6 Receptor (Sil-6r), Known As The Trans-Signaling Pathway.(Nash Et Al., 2023; Ting Et Al., 2020; Villar-Fincheira Et Al., 2021) Il-6r Is A Glycoprotein That Cannot Transmit Signals On Its Own, So It Forms A Complex With Glycoprotein 130 (Gp130). This Process Induces Gp130 Dimerization And Activation, Which Then Recruits Non-Receptor Tyrosine Kinase Jak To Phosphorylate Gp130. This Activation Creates A Recruitment Site For Other Proteins, Such As Stat1/3 And Shp-2/Erk, Which Activate Various Signaling Pathways. Il-6 Also Has A Soluble Form (Sil-6r) Produced By The Cleavage Of Il-6r By Metalloproteases. The Il-6/Sil-6r Complex Can Bind To Gp130, Which Is Expressed By Almost All Cells, Enabling Trans-Signaling Effects. This Trans-Signaling Pathway Is Regulated By Sgp130, Which Binds To The Il-6/Sil-6r Complex And Inhibits Trans-Signaling Without Affecting Classical Signaling. In General, Classical Il-6 Signaling Is Associated With Immune Responses, While Trans-Signaling Is More Associated With Systemic Processes. Although Various Studies Have Shown That Both Pathways Can Contribute To Pro-Inflammatory And Anti-Inflammatory Effects, Depending On The Context And Factors Involved. (Nash Et Al., 2023; Villar-Fincheira Et Al., 2021)

CONCLUSION

Exercise plays an important role in regulating the production and function of interleukin-6 (IL-6) as part of the body's physiological adaptation. IL-6 is a dual-action cytokine that can be proinflammatory or anti-inflammatory, depending on the signaling context, source of production, and individual physiological conditions. During acute exercise, skeletal muscle contraction triggers a rapid and temporary increase in IL-6 through mechanisms involving changes in calcium homeostasis, AMPK activation due to decreased energy reserves, oxidative stress, and epigenetic regulation. The increase in IL-6 during this phase functions as a myokine that plays a role in maintaining energy homeostasis, increasing glucose transport, fatty acid oxidation, and modulating immune and inflammatory responses.

Conversely, regular exercise induces beneficial long-term adaptations, characterized by an increase in the number and function of mitochondria, improved oxidative capacity, enhanced antioxidant systems, and increased muscle sensitivity to IL-6 through classical signaling pathways. These adaptations lead to increased IL-6 signaling efficiency, enabling metabolic and anti-inflammatory responses to be achieved even with lower IL-6 production. Thus, regular exercise does not increase chronic inflammation, but rather contributes to a reduction in systemic inflammation, improved energy metabolism, and enhanced immune function.

Overall, this article confirms that IL-6 is a key mediator linking exercise to inflammatory responses through metabolic, immunological, and mitochondrial adaptations. The different IL-6 response patterns between acute and regular exercise reflect the body's complex adaptive mechanisms, in which exercise acts as an important physiological stimulus for maintaining homeostasis, improving health, and preventing various inflammatory-related diseases and metabolic disorders

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