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Exercise, Immunometabolism & Genetics: Implications for Health and Sports Medicine – a review

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Abstract

Exercise was shaped by the demands of hunting and escaping danger. Today, people exercise mostly voluntarily, activating molecular pathways that regulate metabolism, immunometabolism, and gene expression. This review focuses on exercise and its role in metabolism, immunity, genes and gene expression, health and prevention of diseases, as well as how exercise shapes and influences it. Pathways such as AMPK, mTOR, and PGC-1α are activated during exercise, while hormones and antioxidants are produced. Genetics can predispose to a certain athletic performance, while exercise, epigenetically, also regulates gene expression, promoting overall health. Exercise was shown to improve immune and vaccine response, while intense physical activity can have the opposite effect on the immune system. Integration of exercise immunology and biochemistry can be used in sports monitoring to improve performance. Personalized training plans based on genetic and biochemical profiles can offer the most effective way of training, as well as reduce recovery time. Furthermore, exercise prevents chronic diseases, has anti-inflammatory and anti-aging effects, and has benefits for vulnerable populations. However, gaps remain. Longitudinal and multi-omics studies, integration of AI and machine learning into exercise-related research, and its translation into medical practices are needed.

Keywords: Exercise; Immunometabolism; Genetics; Health; Sports medicine

1. Introduction

The main objective of this review is to provide a comprehensive and in-depth picture of the relationship between physical activity, immunometabolism and genetics. To this end, modern and relevant scientific data on issues such as the relationship between exercise and biochemical pathways (including immune response pathways), adaptation and risk in exercise immunology, the influence of genetic and epigenetic factors on physical activity, physical activity in the prevention of chronic diseases, sports medicine, and athlete health management, were systematized. At the end of the review, the shortcomings of current research are outlined and possible directions for future development are indicated. One of the groups of processes positively influenced by physical exercise is immunometabolism, i.e. the set of metabolic processes that regulate immune responses. Among the main mechanisms by which exercise controls immunometabolism, we can highlight the stimulation of T-cell movement through the regulation of nutrient absorption (e.g., glucose and fatty acids), the release of signaling molecules (hormones, cytokines, etc.) and the production of energy necessary for the use of macrophages through the citric acid cycle and oxidative phosphorylation [1], [2]. The production of myokines in skeletal muscles is also important, as these substances play a role, for example, in regulating insulin sensitivity and weight [3]. It should be also noted that anti-inflammatory factors are released during physical exercises [4].

Physical activity triggers a complex cascade of biochemical processes aimed at supporting the body's energy needs and long-term adaptation to physical exertion. Among the key metabolic pathways activated by exercise are the AMP-activated protein kinase (AMPK) pathway [5], which is the cell's energy sensor; the mechanistic target of rapamycin (mTOR) pathway [6], which regulates cell growth and protein biosynthesis; and the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) pathway [7], which regulates mitochondrial biogenesis, angiogenesis, and oxidative metabolism. Among the main hormones whose metabolism is affected by exercise, we can highlight cortisol [8], which is secreted and provides gluconeogenesis, protein catabolism, and lipolysis, ensuring energy availability; insulin [9], whose level decreases as its sensitivity increases for improved glucose uptake and glycogen resynthesis. It should also be noted that physical exercise increases the production of reactive oxygen species (ROS), excessive levels of which are harmful, while moderate levels trigger antioxidant reactions and mitochondrial adaptation [10]. To study the proteomics and metabolomics of physical exercise, laboratories use methods such as mass spectrometry and nuclear magnetic resonance [11]. The correlation between the effect of physical exercise on immune system function and the ability to resist infection is reflected in the J-shaped curve hypothesis. Within this model, people who exercise moderately improve their immune control. At the same time, high-intensity exercise suppresses immunity and negatively affects the body's resistance to infections [12]. It should also be noted that physical exercise has the potential to support immunity in older age, including improving people's response to vaccination [13]. The response to exercise depends on several genetic and epigenetic factors. For example, genetic polymorphisms can lead to changes in protein expression, which can affect an athlete's ability to exercise [14]. Among the epigenetic changes caused by exercise, DNA methylation, histone modification, and microRNA activity are noteworthy [15]. These changes affect gene expression regulation, leading to improved metabolic functions. It is important to understand that the same types of exercise can have different effects on different people, so in each case, the selection of exercises should be carried out individually. Genome-wide association study (GWAS) aimed at identifying genetic variants associated with individual differences in response to physical activity and serve this purpose [16]. Physical exercise plays a role in preventing chronic diseases and alleviating their symptoms. For example, physical exercise releases anti-inflammatory cytokines [17], which reduce the risk of developing various diseases, including cancer. It has also been shown that increasing muscle mass percentage increases life expectancy [18] by accelerating basal metabolism and the associated acceleration of food digestion while reducing food waste. Immunology and exercise biochemistry can be successfully integrated into sports monitoring. Using certain physiological, biochemical, and immunological markers (e.g., CD45RO+ expression on T lymphocytes), it is possible to determine overtraining, which will help to rationally plan the exercise and rest regime of athletes [19]. By regulating athletes' nutrition, their immune system can be strengthened. For example, micronutrients such as zinc and iron play an important role in antioxidant protection, limiting cell damage [20].

2. Exercise and Immunometabolism

2.1. Definition and emerging relevance of immunometabolism in exercise science

Immunometabolism is a term that pertains to metabolic processes, both molecular and cellular, associated with regulation of immune responses [21]. It studies the way metabolic factors such as the availability of nutrients affect the immune system cell behavior and function [22]. The link between immune system and metabolism has been set upon discovery that inflammatory cytokines are found in obese adipose tissues and contribute to metabolic diseases [23].

Moreover, it has been found that certain immune cells are activated by different metabolic pathways like how glycolysis and fatty acid synthesis influence lipopolysaccharide-activated macrophages, effector T cells are more linked to glycolysis while memory T cells are more oriented towards an oxidative metabolism [24]. Due to the complexity of metabolism and metabolic processes, the influences of immune system have been investigated through numerous ways including extracellular flux analysis like mitochondrial stress test, or single cell approaches like flow cytometry [25].

When it comes to exercise science, upon muscular regeneration and recovery, the activation of immune cells along with increased levels in metabolic pathways, is crucial [26]. It has been hypothesized that lifelong exercise can delay the decrease in immune system functionality that comes naturally with age by changing metabolism of immune cells, which ultimately causes their improved viral responses [27]. The previous claim pertains specifically to natural killer cells (NK) and aerobic exercise.

2.2. Mechanisms by which exercise regulates immune cell metabolism

It is also known that metabolic processes influence immune system regulation through utilization of the citric acid cycle, oxidative phosphorylation, glycolysis and the amino acid metabolism since activation of the immune system requires increased energy production [28]. Exercise positively influences the immune response by reducing low-level inflammation. The immune system cell mobilization heavily depends on the uptake of certain nutrients like glucose and fatty acids as mentioned previously [29] which in turn, stimulates T cell movement. Furthermore, due to exercise, other than $CD8^+$ T cells, $CD16^+$ monocytes are activated as well [30]. Due to an upregulation of many different types of immune cells, it is crucial to manage appropriate nutritional uptake accordingly. Other than increasing production of immune cells overall, a reduction of several factors including programmed cell death protein 1 (PD-1) and tumor necrosis factors (TNF), was observed after high intensity exercise [31].

Exercise releases signaling molecules also termed “exerkines” including hormones, cytokines, RNA and metabolites that influence the immune system cell environment [21]. As a result, the molecular movement triggers the release of anti-inflammatory agents therefore it is advised to incorporate both moderate aerobic and high intensity exercises [29].

Macrophage utilization also requires large amounts of energy predominantly stemming from the citric acid cycle and oxidative phosphorylation [29]. On the other hand, regulatory T cells acquire energy predominantly from oxidation of higher fatty acids [32]. Metabolic recovery after intense exercise can be restored with intake of fruit high in sugar or phytochemicals [33]. Overall, incorporating exercise during lifetime, stimulates T cell movement and production by cell overturn where senescent T cells are replaced by novel T cells in the vacant space [34].

2.3. Role of skeletal muscle as an endocrine organ – myokines and cytokines

During exercise, the role of skeletal muscles is incredibly important. Not only because of locomotion, but also due to the production of myokines that influence organs through either endocrine, paracrine or autocrine mechanisms [35], [36]. Currently, the known roles of myokines are preservation of functionality and enhancement of skeletal muscles by regulation of insulin sensitivity, energy oxidation, weight, tumor growth, and cognitive function improvement [36]. Furthermore, exercise is highly advised since the lack of myokine production through muscle contractions can lead to chronic diseases due to inactive muscle tissue [37]. Cytokines can act on the body in different ways. In terms of post exercise, they are mostly associated with propagation or mitigation of inflammation in muscular and skeletal health [38]. The elevation of cytokines, as one of the most prevalent inflammatory molecular signals, indicates that there has been strenuous exercise involving skeletal muscles; but they have not been associated with muscle damage [39]. Interleukin 6 (IL-6) has been identified as a factor whose elevation indicates both the intensity and duration of exercise depending on the level. It has also been associated with potential roles in mediation of metabolic changes upon exercise [40]. Other pro- and anti-inflammatory cytokines have been identified including TNF, various IL receptors and antagonists, and macrophage inflammatory proteins [41].

2.4. Effects of acute vs. chronic exercise on systemic inflammation and metabolic health

Due to emerging studies focusing on the benefits of exercise on immunometabolism, it has been proposed as a therapeutic strategy in autoimmune diseases namely multiple sclerosis [42]. Additionally, physical activity is beneficial for all organ systems, specifically the cardiovascular system. The benefits are focused on the improvement of cardiac health, increase in both maximum output of the heart and increase in blood flow capacity [43]. It is also important to denote that regular physical exercise can prevent and regulate many metabolic diseases including type 2 diabetes by increasing the blood glucose uptake into the cells and thus releasing anti-inflammatory factors that regulate signaling pathways interfering with blood glucose uptake [44]. In the said metabolic diseases, due to unhealthy lifestyle and emergence of cancer, exercise could potentially aid as a therapeutic approach due to maintaining homeostasis, and preventing tumorigenesis [45]. On the other hand, acute high intensity exercise without proper rest or insufficient recovery can influence the body and immune system in a negative way inducing upper respiratory tract infections and even depression [46]. The main reason behind the frequent upper respiratory tract infections is the reduction in saliva production thus reducing levels of lysozyme, and immunoglobulin A (IgA) [46]. Furthermore, in chronic exercise, cortisol levels are continuously increased thus has led to a conclusion that hypercortisolism then causes reduced sensitivity in order to protect the muscles [47]. On a more positive note, chronic exercise leads to a better and more balanced energy levels in longer term, as well as improved sensitivity for appetite control [48].

3. Biochemical Pathways in Exercise Response

Physical activity triggers a complex cascade of biochemical responses that support immediate energy needs and long-term physiological adaptations. These responses involve the activation of various signaling pathways, hormonal changes, and redox regulation, as well as comprehensive shifts in the metabolome and proteome. Understanding these molecular processes is essential in both clinical health and sports science contexts.

3.1. Key metabolic pathways activated during exercise

AMPK serves as a cellular energy sensor. It becomes activated when the AMP:ATP ratio increases, typically during high energy-demand states. AMPK stimulates glucose uptake by promoting GLUT4 translocation to the cell membrane and enhances fatty acid oxidation by inhibiting acetyl-CoA carboxylase (ACC). Furthermore, AMPK activation promotes mitochondrial biogenesis through upregulation of PGC-1α, facilitating oxidative capacity in skeletal muscle [49]. mTOR is a key regulator of cell growth and protein synthesis, particularly during resistance exercise. Activated by mechanical stress, insulin, and amino acids, mTOR promotes anabolic processes including ribosomal protein synthesis. This leads to muscle hypertrophy and recovery post-exercise [50]. PGC-1α is a transcriptional coactivator that regulates mitochondrial biogenesis, angiogenesis, and oxidative metabolism. Its expression is induced by both AMPK and p38 mitogen-activated protein kinases (MAPK) during endurance training, facilitating fiber-type transitions and enhanced oxidative metabolism [51].

3.2. Hormonal responses to exercise

As a glucocorticoid hormone, cortisol is released during prolonged or intense physical stress. It facilitates gluconeogenesis, protein catabolism, and lipolysis, ensuring energy availability. Chronic elevation, however, may impair immune function and recovery [52].

Exercise decreases circulating insulin levels, but enhances insulin sensitivity, particularly in skeletal muscle. This leads to improved glucose uptake and glycogen resynthesis during recovery phases [53].

The catecholamines - epinephrine and norepinephrine released from the adrenal medulla, activate glycogenolysis and lipolysis, increase cardiac output, and redirect blood flow toward active muscles. These effects are essential for meeting the energy demands of exercise [54].

3.3. Redox balance and oxidative stress in exercise

Exercise increases mitochondrial respiration and ROS production. While excessive ROS can damage proteins, lipids, and DNA, moderate levels act as signaling molecules triggering antioxidant responses and mitochondrial adaptations. Enzymes such as superoxide dismutase, catalase, and glutathione peroxidase are upregulated post-exercise, enhancing redox homeostasis [55]. ROS activate transcription factors like NF-κB and Nrf2, which regulate genes involved in inflammation and antioxidant defense, respectively.

3.4. Metabolomics and proteomics in exercise science

This field involves comprehensive analysis of metabolites in biological samples. Exercise induces changes in metabolites such as lactate, acylcarnitine, and ketone bodies. These shifts reflect substrate utilization and metabolic flexibility. Technologies like mass spectrometry and nuclear magnetic resonance are widely used [56]. Proteomics enables the study of exercise-induced changes in protein expression, structure, and post-translational modifications. Proteomic profiling identifies biomarkers of muscle adaptation, fatigue, inflammation, and recovery, such as heat shock proteins and myokines [57].

4. Exercise Immunology: Adaptation and Risk

4.1. Exercise and induced immune changes: J curve hypothesis

The association between the impact of physical activity on the immune function has been studied in the field of exercise immunology. The J-curve hypothesis reflects on the relationship between the effects of exercise on the immune system's function and susceptibility to resist infection [58].

4.2. Moderate-intensity exercise on the J-curve

The J-curve model illustrates different levels where people engage in exercises and the impact on the immune system. People who engage in moderate-intensity exercise tend to have an improvement in their immune surveillance, meaning their immune system is functioning and is ready to fight any infection. Thus, this can reduce the chance for those people to get infected, compared to the people who don't include any exercise in their daily lives [58]. The immune system during these practices is being activated, but in a regulated and healthy manner. Upon exercising regularly, the body starts producing more cells that support the immune system, primarily NK cells. These cells are responsible for disruption of both viral and cancerous cells. Neutrophils are needed for the first response to any infection, and additionally, the cytotoxic T cells that destroy the infected cells. Moderate intensity exercises increase the chance of having a quick response from the immune system [59]. Interestingly, the practice of moderate exercise can support the release of cytokines. One of the strongest examples is IL-6, its level increases with the application of exercise, which in turn enhances the quality of communication between the immune cells [60].

4.3. High-intensity exercise on the J-curve

On the other hand, people who engage in highly intense exercise can have an opposite response in their body, due to insufficient time given for recovery. The immune system during this period enters a state where it becomes weak, a state known as transient immunosuppression. Which is also described as the open window, meaning the body is prone to any infection, specifically the respiratory infections [58].

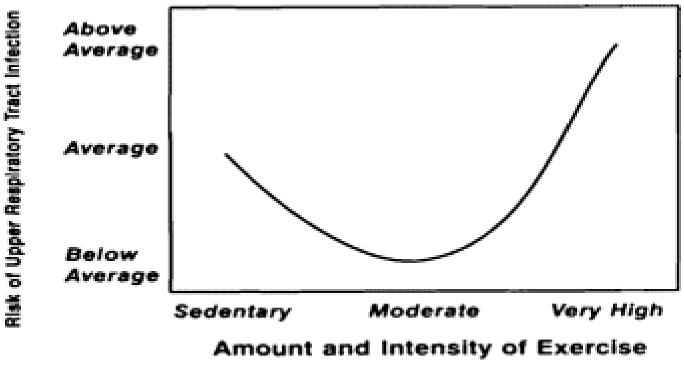

Figure 1: J-curve illustrates the relation between exercise intensity and immune function

4.4. Impact of different types of training on immune competence

It is well-known that the different types of physical training are considered an alternative strategy, which is a non-pharmacological way to improve health and modulate the immune system. This can be beneficial in regions where chronic diseases are prevalent.

Cystic fibrosis is a genetic disorder that can have a huge impact on many organs, namely the lungs, weakening the immune system severely making people more prone to infections overall. This chronic disease is a well-established example to study the association between the effects of exercise on the immune system [61]. A study conducted by Ashkan Sohrabi illustrates that exercising can improve the function of the lungs and support physical strength and endurance. The study examined the effect of three different training types on lung function, endurance, resistance, and concurrent. They have been evaluating the pulmonary function, and the health-related quality of life, reflecting how the disease might affect the individual's daily life. This study was conducted on 60 children between the ages of 8 to 15; these children were diagnosed with mild to moderate cystic fibrosis. Each group was engaged in the moderate-intensity exercise program [61]. As a result of the 10-week training, all three programs gave highly positive results in terms of lung function. However, the concurrent training had the highest impact on pulmonary function.

4.5. The impact of acute exercise on vaccine response

Having an exercise session before taking a vaccine can result in an improved immune response due to short-term stress triggering that can boost the activity of white blood cells which allow for better detection of the antigen [62].

However, a distinction must be made whether the vaccine is taken at full or half dose. A study showed the impact difference on two groups: a group that did an exercise for 15 minutes, and the other group that had rested. When the rested group took half a dose, the same level of antibody production was not observed opposed to the group that had exercised. Nevertheless, when both groups took the full dose, both of them had similar results, and the equal production of antibodies [63].

4.6. Immunosuppression risk in elite athletes and overtrained individuals

As mentioned previously, moderate exercise led to the improvement of immune function. However, excessive exercising can lead to serious risks like impaired immune function due to the clash and interference of the required performance, mental pressure, and the environment [60].

Recent studies show that the effect of highly intense training depends on gradual progression, meaning the body’s response to training can be based on how much stress is being experienced, and how much time there is to recover. A condition known as non-functional overreaching, which is reflected in the athletes who overload themselves with training, can end up in disruption of their performance. Thus, they will experience deregulation in the immune system function and hormonal imbalance. Repeatedly, this can cause overtraining syndrome resulting in chronic fatigue and ultimately leading to immune suppression. This illustrates the importance of having balance in the training progression and proper recovery [64].

5. Genetic and epigenetic influences on exercise responses

Physical exercise plays a crucial role in a healthy lifestyle, significantly enhancing overall well-being when complemented by a balanced diet. Regular physical activity has been shown to provide numerous benefits to every organ system in the body [65]. As an environmental stimulus, physical activity also induces epigenetic modifications. Beyond well-known mechanisms such as DNA methylation and histone acetylation, recent research has identified novel epigenetic modifications including lactylation, a histone modification induced by lactate [66],[67].

5.1. Genetic polymorphisms influencing training adaptations

In addition to natural talent, determination, and hard work, genetic predisposition plays a significant role in overall performance. Research has demonstrated that genetic polymorphisms can lead to variations in protein expression, which can influence an athlete's ability to exercise. Notably, the ACE I/D and ACTN3 R577X polymorphisms are frequently discussed in the literature for their impact on physical performance and athletic success [68]. Understanding these genetic factors can provide valuable insights into how our biology contributes to our capabilities in various fields.

5.2. Inter-individual variability in exercise outcomes: implications for personalized medicine

Inter-individual variability refers to the diverse behavioral patterns exhibited within a population [69]. This variability extends to how individuals respond to external stimuli, such as changes in diet or levels of physical activity. Consequently, the same type of exercise may produce varying outcomes for different people [70]. Recognizing this diversity is essential, as it underscores the importance of personalized approaches to fitness and nutrition, allowing for more effective strategies that cater to individual needs and responses.

When it comes to exercise, inter-individual variability is frequently underestimated because a single exercise model does not accommodate the diverse needs of every individual. This is particularly evident in patients undergoing rehabilitation, where tailored approaches can significantly impact recovery outcomes [71]. To maximize the effectiveness of exercise interventions, it is crucial to personalize exercise models to align with each person's unique circumstances and capabilities. By recognizing and addressing these differences, we can enhance the overall efficacy of rehabilitation programs and support individuals on their path to recovery.

5.3. Genome Wide Association Study in exercise genomics

GWAS is dealing with detection and identification of genetic variants related to individual differences in exercise responses. The focus is on detecting and identifying genetic variants that contribute to individual differences in exercise responses [72]. By uncovering the specific genetic factors that influence how individuals react to various exercise regimens, studies aim to refine and enhance existing exercise models. This knowledge allows for a deeper understanding of the biological underpinnings of fitness and performance, paving the way for personalized exercise prescriptions that can optimize training outcomes. Ultimately, GWAS plays a crucial role in bridging the gap between genetics and exercise science, facilitating more effective and tailored fitness strategies for diverse populations [73].

6. Exercise, health, and disease prevention

Nowadays, with the rapid rise of sedentary jobs, the risk of chronic diseases such as type 2 diabetes mellitus, cardiovascular disease and metabolic syndromes has increased [74]. Introduction of the highly processed food filled with sugars, additives, and harmful chemicals has definitely contributed to the rising cause [75]. On the other hand, following strict diets can also be very harmful in terms of losing weight and maintaining a healthy body and mind. Incorporating strict diets can be beneficial short – term but can lead to obesity in the long run [76]. Strict dieting can also put the body into a highly stressful environment [77]. Therefore, it is necessary to follow a healthy, balanced diet and include moderate exercise.

6.1. Cardiovascular exercises vs weightlifting

Cardiovascular activity (cardio) elevates the heart, lungs and blood vessels into a high-performance state. In a study done by Parker, et al., the effects of cardio opposed to strength training had been investigated. It was found that combining both types of exercise can be optimal for blood pressure regulation and muscle strength overall, however, cardio alone has a higher impact on the body in terms of lowering body fat percentage and body weight in general [78]. When it comes to the advantages of weight-lifting, it heavily affects the increase in lean body mass, endurance, and strength improvement [79]. Therefore, it is advised to balance cardiovascular exercise with weight-lifting for optimal results.

6.2. Correlation of autophagy with exercise and longevity

Combination of regular physical activity and fasting can promote longevity and prevent chronic diseases. Autophagy as a cleaning mechanism, guides misfolded proteins and dysfunctional organelles towards lysosomes to be degraded [80]. Autophagy combined with exercise prevents tissue damage, enhances tissue integrity, and lowers autoinflammatory reactions [81].

7. Sports medicine and athlete health management

Sports medicine practice requires a team of professionals in various health- related fields, that could answer the challenges in doping control, athlete's nutrition and environmental factors. Studies on training techniques have led to improved recommendations for elite athletes and the general population alike [82].

7.1. Integration of exercise immunology and biochemistry in sports performance monitoring

Well-balanced exercise dosages are necessary to maximize health gains and minimize negative impact on homeostasis. Acute exercise improves defense activity and metabolic health; while the immune response depends on many factors including the intensity, duration, and mode of exercise, change in body temperature, concentrations of hormones and cytokines, and so on [83]. Habitual exercise improves immune regulation and delays the onset of immune dysregulation that leads to immunosenescence. Evidence from epidemiological studies show that regular physical activity and long-term exercise reduce the incidence of communicable (e.g., bacterial and viral infections) and non-communicable diseases (e.g., cancer), implying that immune competency is enhanced by regular exercise [84].

Blood biomarkers can objectively reflect training load, fatigue, and recovery needs; therefore, to ensure a correct state of health, athletes regularly undergo health checks that rely on biochemical parameters [85]. However, other biomarkers are used to assess different aspects of health, sport performance, and recovery. Which is why a comprehensive performance set of biomarkers should include: nutrition and metabolic health, hydration status, muscle status, endurance performance, injury status and risk, and inflammation as seen in Figure 2 [86].

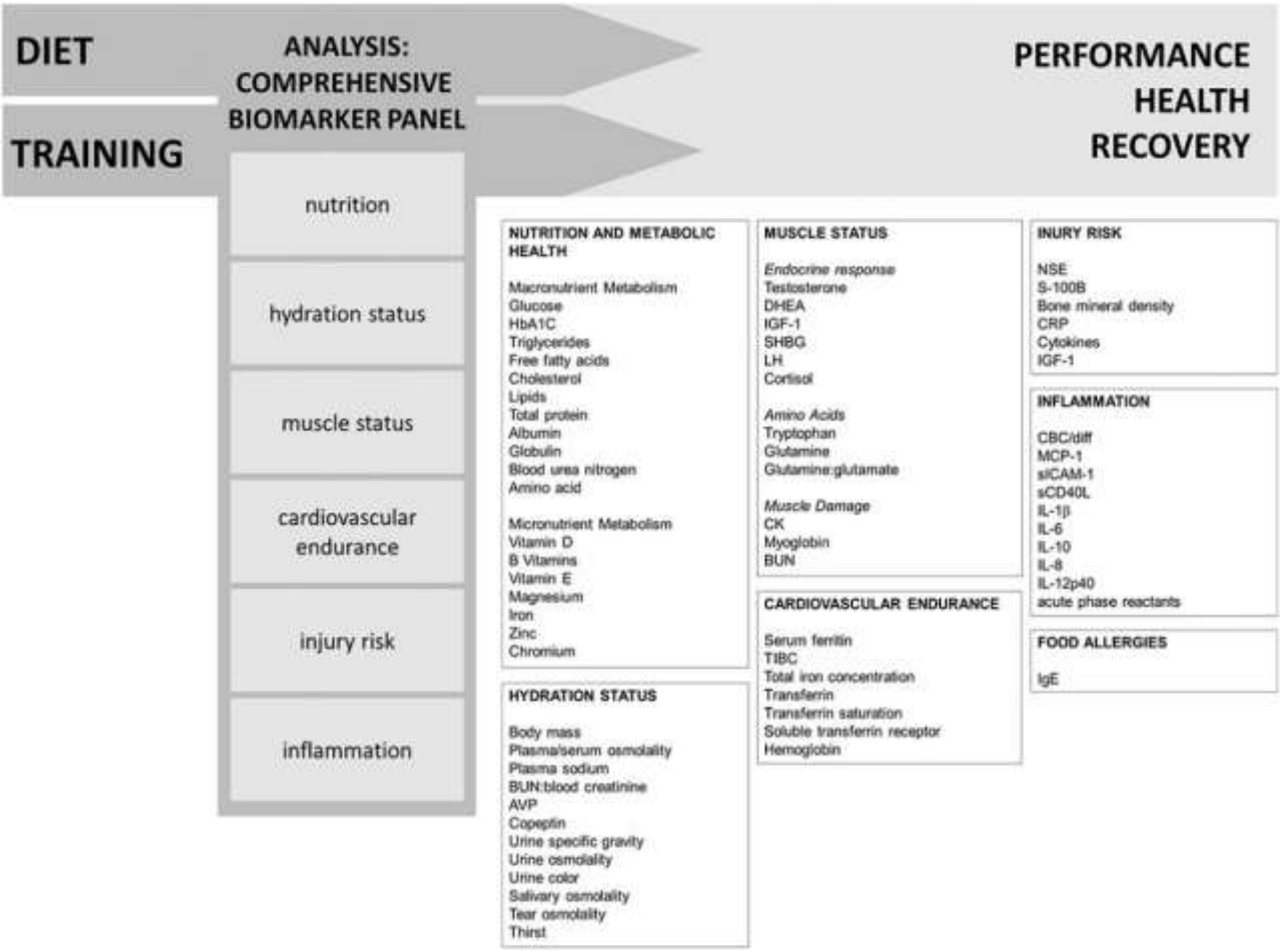

Figure 2. Comprehensive approach to biomarker analysis

Some markers are regulated depending on the level of muscle damage, while others have dependencies on neuroimmunological processes, energy deficit, or heat production. Creatinine and sodium are key urine biomarkers which indicate an athlete's hydration status and metabolic response. Salivary biomarkers have valuable advantages like convenience, frequency of sampling, and the ability to monitor an athlete's well-being closely throughout training and competition. They include alpha-amylase, IgA and nitric oxide [87]. Researchers' goal is to identify biomarkers that represent appropriate and reliable responses to training load, reflect recovery cycles and regeneration processes.

7.2. Overtraining syndrome: immunological and biochemical markers

Overtraining is an accumulation of training stress resulting in long-term decrement in performance capacity [88]. The primary hormone products serve to redistribute metabolic fuels, maintain blood glucose, and enhance the responsiveness of the cardiovascular system, therefore, repeated exposure to stress may lead to 'stress-disturbance', causing the disruption of endocrine system.

Given that recovery should be easier, faster, and less likely to compromise a training program, the identification of overtraining syndrome (OTS) at earlier stages is highly desirable. Some experts consider the existence of OTS impossible without a decline in performance because fatigue and underperformance would be likely to appear in milder forms including functional and nonfunctional overreaching, while a complete recovery would avoid the development of OTS [89].

However, no single biomarker has been able to reliably distinguish OTS-affected athletes from healthy individuals, due to the high variability in how OTS presents across individuals. In prolonged training, glycogen stores get close to full depletion, glycogenolysis and glucose transport are downregulated in muscle and liver, as well as the liver production of insulin-like growth-factor I, and catabolism is induced. Most of the blood parameters, when measured under standardized conditions at rest, may provide information concerning an elevated muscular and/or metabolic strain [90]. Although, creatine kinase remains a valuable biomarker for assessing muscle injury. Myoglobin, released into the bloodstream shortly after damage, serves as a short-term indicator of muscle injury.

The measurement of cortisol and testosterone during a training season may provide a relative indication of anabolic-catabolic balance, especially in male athletes. Low testosterone to cortisol ratio, that has dropped by more than 30, is considered to be the threshold of overtraining [86].

T-lymphocyte CD4/CD8 ratios, lymphocyte antibody synthesis and NK cell cytotoxic activity have been shown to be lower following increases in the training load in already well-trained athletes. The expression of CD45RO on Th CD4 cells (but not the circulating numbers of CD45RO T-cells) was significantly higher in athletes suffering from OTS compared with healthy well-trained controls, thus, higher expression of CD45RO on T cells may merely be indicative of the presence of acute infection, which is, of course, a possible cause of the underperformance [88].

Evidence shows IL-6 as a potential biomarker of overtraining. Data on multiple inflammatory cytokines, endocrine markers of long-term dysregulation and overtraining like testosterone and cortisol, and muscle damage markers like creatine kinase can be integrated to provide precise and accurate information about an athlete's health and overtraining status [91].

7.3. Nutritional and recovery strategies to modulate immune response

Immunonutrition refers to using specific nutrients to support and improve how the immune system works, especially during times of stress, illness, or recovery from injury. This support can come in different forms, like supplements, drinks, or meals, and can be given in various ways depending on the situation.

Our immune system relies on a steady supply of nutrients to work properly, not just for energy but also to help immune cells multiply, move toward infections, and destroy harmful invaders. Nutrients like zinc, iron, copper, selenium, magnesium, and vitamins A, B6, C, D, and E are especially important for these processes [92].

For athletes, long and intense workouts put the body under a lot of physical stress. Research has shown that consuming carbohydrates during these workouts can help by reducing some of the immune and inflammatory responses. This led scientists to explore how different nutrients affect the immune system in athletes [93]. Exercise immunology proposes that after intense exercise, some immune variables transiently decrease below pre-exercise levels. Microbial agents, especially viruses, may invade the host or reactivate from a latent state, leading to infection as a result of this immunodepression. Repeated exercise could lead to a greater degree of immunodepression while the immune system is still depressed. After intense exercise, in the recovery phase, there is an increased blood concentration of neutrophils and inflammatory cytokines, while lymphocytes are suppressed, and concentration of secretory IgA in mucosa decreases [94].

While vitamin D is known for supporting bone growth and balancing calcium levels, it also supports the immune system, especially the innate immune response including regular monocyte and macrophage function. Vitamin E is a powerful antioxidant found in the outer membranes of all cells. Because immune cells are continually active, they produce more free radicals, and vitamin E prevents cell damage. Vitamin E is thought to help T cells by strengthening their cell membranes and supporting the chemical signals they need to activate [95].

Zinc is a mineral that plays a crucial role in keeping the immune system balanced. A lack of zinc weakens both the innate and adaptive immune systems. It can shrink the thymus, Th1 cells, and impair responses like antibody production, inflammation, and the activity of NK cells. Zinc also helps regulate different T cell types. It supports T regulatory (Treg) cells, which calm inflammation, and suppresses Th17 and Th9 cells. Because of this, zinc may help reduce the risk of autoimmune conditions where the immune system attacks the body by mistake [95].

8. Future directions and research Gaps

While a considerable amount of progress has been made in explaining the molecular pathways linking exercise, immunometabolism, and genetics, numerous research gaps remain. Connecting these gaps is essential for advancing personalized health strategies and optimizing athletic performance.

8.1. The need for longitudinal and multi-omics studies

Many existing studies focus on short-term responses to exercise, which limits the insight into long-term molecular adaptations. Longitudinal studies that follow individuals over months or years are essential to understand the increasing effects of physical activity on immune and metabolic gene regulation [96].

Multi-omics approaches, combining genomics, transcriptomics, proteomics, metabolomics, and epigenomics, can provide a systems-level perspective on how exercise affects immune and metabolic function. For example, transcriptomic changes in T cells after prolonged lasting training have revealed immune modulation pathways relevant for aging and chronic inflammation [97].

Approaches like these can also help explain person-to-person variability in exercise response. For example, some individuals show minimal gains in endurance or strength despite having similar training, a phenomenon referred to as “non-responders” [98]. Multi-omics profiling could help categorize responders and tailor interventions accordingly.

8.2. Integration of AI and big data in exercise-genetics research

The fast growth of omics datasets and wearable health devices has opened the door for many AI-driven models that can identify patterns that are too complex for traditional statistics. Machine learning and deep learning are increasingly applied to predicting different exercises, injury risk, and immune recovery based on genetic and physiological inputs [99], [100]. Combining data from GWAS, continuous glucose monitoring, and immune panels allows for highly personalized exercise prescriptions. However, the regulation of data sources, the capability of understanding AI models, and protection of genetic data remain key challenges [101].

8.3. Translating molecular exercise science into clinical and performance settings

Although significant discoveries have been made at the molecular level, translating these findings into clinical and sports medicine settings remains limited. Few clinical trials include molecular endpoints, such as cytokine profiling, to guide rehabilitation or treatment decisions [102], [103]. More research is needed to verify molecular biomarkers in diverse populations and settings.

In an athletic context, genetic screening and personalized training are gaining attention. Ethical concerns surrounding data misuse, informed consent, and potential discrimination need to be addressed before widespread adoption [104]. Good and effective translation will require a broad-ranging team across molecular biology, AI, clinical medicine, and exercise physiology.

9. Conclusion

Despite the scientific discoveries and achievements listed above, there is still ample room for further research into the relationship between exercise, immunometabolism and genetics. For example, to understand the impact of physical activity on the body in dynamics, more long-term studies using a combined (multi-omics) approach are needed; the processing of large data sets obtained in these studies can be accelerated with the help of AI and machine learning models. Finally, there is a need for greater implementation of scientific findings into clinical practice in order to improve the healthcare system.

Declaration of Competing Interest

The authors declare that they have no known financial or non-financial competing interests in any material discussed in this paper.

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