Perspective

Immunometabolism and Covid-19: Could Lifelong Exercise Training Have a Protective Effect?

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ABSTRACT

The world is experiencing a severe new pandemic, in which the elderly afflicted with chronic diseases are the most affected. The aging of the immune system (immunosenescence) reduces its efficacy against viral infections and increases its susceptibility to repeated acute infections, such as the flu. The improvement of the immune system functioning leading to a reduced incidence of infections can be achieved with regular physical exercise, besides its countless other benefits. The immunosenescence delay in master athletes, protecting them from possible viral infections, has been recently shown. Here the role of aerobic exercise training as an immune system fine-tuning regulator was discussed, focusing on lifelong athletes and specifically on the age-impaired antibody production in immunized elderly and the effects of lifelong physical exercise on the anti-inflammatory and vaccine response optimization. Moreover, the aerobic training effects on the natural killer (NK) cell activity and the underlying mechanisms responsible for a better antiviral response in active elderly and/or master athletes were addressed. It was hypothesized that lifelong exercise training delays age-related decrements in immunity by remodeling the metabolism of different cells (e.g., NK cells), creating a metabolic scenario that in turn improves the immune system's viral response. Lifelong exercisers present a preserved immune response to exercise, indicating that they are better prepared to respond to new immune challenges. Thus, master athletes and lifelong exercisers are possibly protected against or could mitigate the COVID-19 disease.

Received: 13 August 2020
Accepted: 30 October 2020
Published: 27 November 2020

KEYWORDS: exercise training; master athletes; viral infections; NK cells; COVID-19

INTRODUCTION

Viral infections are very common. Indeed, all individuals have already experienced symptoms, such as sore throat, fever, and headaches, among others. Typically, it takes up to 7 days for the immune system to resolve viral infections. Since birth, humans are exposed to different types of viruses, leading the human body to quickly trigger an immune response to eliminate the virus, incorporating a recognition pattern (innate immunity), and producing memory cells (acquired immunity). Thus, the immune system will act more efficiently if the virus is again found in the circulation.

Regular physical exercise is closely related to the immune response's response to viral infections. Studies have shown the enhanced role of the immune system and the enhanced anti-inflammatory response to chronic and acute exercise sessions of different intensities in subjects who regularly exercise and/or lifelong athletes compared to sedentary subjects [1–7].

The intensity and duration of physical exercise are crucial factors to determine the different alterations in the immune system. Acute physical exercise, when performed, can generate several transient changes in the body. Besides, physiological adaptations are also developed in response to stress to reestablish homeostasis, greatly influencing the immune response [8–10]. Throughout the athlete's life, immune cells undoubtedly suffer from metabolism transformation when adapting to periods of energy overload and physiological stress, thus creating a metabolic landscape that, in turn, improves immunosurveillance and viral response. This metabolic reprogramming of immune cells may be particularly important for natural killer (NK) cells. NK cells are the immune cells most responsive to exercise, acutely mobilized into the circulation, during exercise performance [11,12]. Over time, these transient exercise-induced alterations promote an increase in selective lymphocyte subsets, enhanced immunosurveillance, and lower inflammation [13], which may be of particular clinical value for infected individuals. Furthermore, physical exercise up-regulates NK cell proliferation while stimulating their maturation and activation [14]. The exercise-dependent metabolic reprogramming of NK cells remains still unexplored. However, it is widely recognized that chronic training-induced alterations include improved metabolic health. Herein, it is hypothesized that lifelong exercise training induces metabolism remodeling of different cells, particularly NK cells, creating a metabolic landscape that improves viral response.

The world has been greatly affected by the COVID-19 pandemic. The pathogenic mechanism of SARS-CoV-2 infection is complex and still poorly understood. SARS-CoV-2 can cross mucous membranes, especially the

nasal and laryngeal mucosa, entering the lungs through the respiratory tract. As a result, SARS-CoV-2 can migrate, attacking target organs expressing the angiotensin-converting enzyme 2, such as the lungs, heart, kidney system, gastrointestinal tract, and endothelial cells [15–18]. After a few days of regression of signs and symptoms, more precisely between the 7th and 14th days after the onset of infection, SARS-CoV-2 starts a second attack. The worsening of clinical conditions in this second phase may be due to the acquired immunity's inability to respond to the challenges imposed by SARS-CoV-2. During the second phase, a reduction in B lymphocytes can occur, affecting the antibody production in patients [19]. The total number of lymphocytes and $CD4^+$ T, $CD8^+$ T, B, and NK cells are decreased in COVID-19 patients, with a lymphopenia of about 70% [20].

In contrast, lifelong trained older adults (presenting an improved physical fitness condition) show preserved $CD4^+$ naive T-cell population and decreased senescent T-cell percentages [1]. It is possible that maintaining high levels of aerobic fitness during the natural course of aging may help to increase immunosurveillance by preserving the number of $CD4^+$ naive T cells [1], which in turn could be critical for detecting SARS-CoV-2-infected cells.

Therefore, in this perspective article, the role of aerobic exercise training as a fine-tuning regulator of the immune system was addressed, focusing on lifelong athletes. The effects of lifelong physical exercise on improving the anti-inflammatory and vaccine responses and the impaired antibody production in immunized elderly were discussed. To a more detailed level, the possible effects of aerobic training on NK cell activity and the molecular mechanisms that could explain a better antiviral response in active older persons and master athletes were explored.

COULD LIFELONG PHYSICAL EXERCISE CREATE AN ANTI-INFLAMMATORY SCENARIO THAT ALLEVIATES THE "CYTOKINE STORM" PHENOMENON?

Clinical studies have identified a cytokine storm (sustained responses of cytokines and chemokines) in critical patients with COVID-19 [21], pointing that patients in this condition present a higher incidence of immune disorders, acute respiratory distress syndrome, and/or extrapulmonary multiple-organ failure, which are the critical factors for COVID-19 exacerbation or even death [22]. In particular, increased levels of cytokines, including interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-10, IL-17, interferon-γ (IFN-γ), tumor necrosis factor (TNF), granulocyte colony-stimulating factor, γ-induced protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein (MIP)-1α (MIP1-α), and other molecules, characterize the cytokine storm [23–25].

Whereas the cytokine storm seems to be a key pathophysiological mechanism in elderly COVID-19 patients [23], regular endurance training may play a role in lowering some markers of systemic inflammation and regulating important metabolic and physiological muscle parameters with

aging [3,26]. In general, a single bout of exercise induces an inflammatory response similar to that caused by infection or trauma. The classical proinflammatory cytokines TNF and IL-1β are not normally increased after exercise [27,28], indicating that the cytokine cascade induced by exercise clearly differs from the cytokine cascade caused by infection. The augmentation in IL-6 concentrations during exercise seems to be responsible for the further increase in the concentrations of anti-inflammatory cytokines, such as IL-10 and IL-1 receptor antagonist (IL-1RA), by stimulating cortisol release and reducing TNF concentrations [29]. Besides, elevated concentrations of IL-6 from skeletal muscle trigger an anti-inflammatory signaling cascade that inhibits the secretion of proinflammatory cytokines, such as TNF or IL-1β, downturn the secretion of C-reactive protein from the liver [8], down-regulate the monocyte Toll-like receptor expression at both mRNA and cell surface protein levels, and lastly inhibit the IκB kinase/nuclear factor-κB (NF-κB) pathway [30,31]. A decreased plasma IL-6 level in response to regular exercise is illustrated as a normal training adaptation [32]. Studies have shown that acute and regular exercise can reduce the activation of this inflammatory signaling pathway (for review, see [31]) in master athletes [33].

IL-1β and TNF are two cytokines related to the inflammatory cascade. High levels of IL-1β are expected after muscle damage, whereas exercise can or cannot increase IL-1β levels [34]. Conversely, IL1-RA is an anti-inflammatory cytokine secreted primarily by monocytes and macrophages, and inhibits the proinflammatory actions of IL-1β. In particular, IL-1RA prevents inflammatory processes by blocking proinflammatory cytokine IL-1-induced signal transduction, creating an anti-inflammatory balance to the proinflammatory stimulus induced by IL-1β [8]. The equilibrium between IL-1 and IL-1RA in local tissues influences the potential development of inflammatory disease and its structural damage. Increased levels of IL-1RA have been observed in master athletes compared to age-matched sedentary subjects and young individuals [33].

Still, in an IL context, IL-10 has a crucial role in preventing inflammatory and autoimmune pathologies [35]. It appears to contribute to adaptive immune response down-regulation and reduction of inflammatory-induced tissue damage. The latter IL-10 contribution is mediated by decreased major histocompatibility complex molecule expression and the intercellular adhesion molecule-1 and costimulatory CD80 and CD86 molecules in antigen-presenting cells [8]. Likewise, IL-10 interferes with or completely inhibits the expression of various proinflammatory cytokines and other soluble mediators. Thus, IL-10 is a potent promoter of an anti-inflammatory state [36–38]. Exercise-induced IL-10 secretion may be associated with increased circulating regulatory T (Treg) cells, the primary source of IL-10 within the body [8]. Handzlik et al. showed that high training loads are related to higher resting Treg cell count and superior IL-10 production, resulting in antigen stimulation [39].

The authors' laboratory corroborated these findings, demonstrating adaptive responses to exercise in master athletes, which are translated to the sustained number and function of Treg cells and elevated *IL-10* gene expression [2].

Physical fitness status also promotes a positive impact in the monocyte/macrophage phenotype outcome and consequently in the anti-inflammatory response. IL-6 released during exercise drives differentiation to an anti-inflammatory state while stimulating IL-10 and IL-1RA release mediated by peroxisome proliferator-activated receptor-γ in these cells [40]. Intracellular mechanisms in monocytes/macrophages mediating the transcriptional changes in response to anti-inflammatory cytokines may be related to energetic sensor activation, such as Adenosine monophosphate-activated protein kinase (AMPK) [41]. Acute exercise-induced immunometabolic alterations in these cells are driven by lower glucose levels, leading to AMP accumulation, which in turn stimulates AMPK activity, potentially inhibiting NF-κB transcription factor, and resulting in a sustained anti-inflammatory scenario [42]. This immunometabolic profile supports the known anti-inflammatory effects of physical exercise [43].

This exercise-induced cytokine response is one of several other mechanisms by which exercise exerts anti-inflammatory effects [8]. The overall anti-inflammatory profile exhibited by master athletes could likely alleviate the cytokine storm induced by COVID-19 infection, preventing health deterioration in general.

VACCINE, AGING, AND EXERCISE TRAINING: WHAT COULD WE EXPECT DURING COVID-19 INFECTION?

Vaccination is the primary pharmacological strategy to reduce the incidence and severity of viral diseases. Here, how aging-associated immunosenescence could reduce vaccination efficacy on those more vulnerable to the severe form of COVID-19, the elderly population, is discussed [44]. Additionally, how physical activity could improve the vaccination response in the elderly is addressed.

Antibody production after vaccination in the elderly can be decreased. For instance, antibody titers produced after the current influenza vaccine are 70% to 90% effective in young adults but only 17% to 53% in the elderly, revealing a huge impairment in vaccination efficiency [45,46]. This immune system's impaired ability to respond to vaccines can be explained by several modifications on the antigen presentation system and the reduced immune cells' effector function. Besides a defective antigen presentation system, dendritic cells showing reduced distribution and migratory capacity have also been described during the aging process [47]. Furthermore, reduced antigen-induced phagocytosis and IFN-γ and IL-12 secretion were observed, causing decreased lymphocyte proliferation and activation.

Of note, sirtuin-1 (SIRT-1) is essential for dendritic cells' correct mediation of immune responses. It was recently demonstrated that the specific deletion of SIRT-1 was sufficient to induce an excess of reactive oxygen species and impaired cytokine production in bone marrow dendritic cells infected with respiratory syncytial virus [48]. Disrupted dendritic cell response in SIRT-1 knockouts was restored by inhibiting acetyl-CoA carboxylase [48]. Thus, it is possible that aging-associated mitochondrial dysfunction in dendritic cells could be sufficient to disturb an immune response.

At the same time, aging also reduces naive circulating lymphocytes and $CD4^+/CD8^+$ ratio [49], although, within $CD8^+$ and $CD4^+$ T memory lymphocytes, the late differentiated effector-memory subset will increase, showing higher CD45RA, $CCR7^+$, and $CD62L^-$ expression [50]. Also, effector-memory lymphocytes show a reduction in IL-2 expression and consequently in clonal expansion and cytolytic activity [46].

Overall, besides reduced antigen presentation and $CD8^+$ T-cell cytotoxicity, diminished NK cell and B lymphocyte activity has been reported for elderly populations [49]. Aging reduces memory B-cell function and long-lived plasma cells, leading to reduced antibody production after vaccination [51].

Lifelong athletes show many adaptations at the molecular level that slow down immunosenescence. This population has presented better responses to vaccination with increased antibody production than age-matched controls [52]. Recently, Wong et al. have also observed that elderly women with increased fitness levels exhibited higher antibody titers 18 months after influenza immunization [53].

An array of immunological parameters is affected by exercise training in the elderly, explaining this improvement in vaccine response. For instance, in master athletes, the reduction of $CD8^+$ and $CD4^+$ T senescent central memory cells have been reported [1], besides exercise training inducing the chronic turnover of lymphocytes and causing increased apoptosis of senescent lymphocytes while increasing naive T-cell mobilization [54]. Furthermore, regular exercise stimulated memory B lymphocytes and antibody-producing cells function, as athletes showed high levels of circulating antibodies [55]. Wong et al. showed that high fitness older women had increased gene expression involved with phagocytic function in monocytes/macrophages accompanied by increased antibody production by B lymphocytes [53].

Regarding NK cells, the most important subsets in fine-tuning the antiviral response are the (i) $CD56^{bright}CD16^-$ cells that produce high levels of cytokines and rapid proliferation and (ii) $CD56^{dim}CD16^+$ cells that are a mature subset with high cytotoxic capacity [56]. In the elderly, this subset of lymphoid immune innate cells showed increased surface markers of exhausted NK cells ($CD56^-CD16^+$) that present dysfunctional cytokine production, impaired cytotoxic activity, and reduced proliferation [57]. NK cells' correct functioning is essential for the immune system to fight viral

infections. The antiviral response of NK cells is mediated by the expression of cytotoxic molecules (i.e., granzymes and perforin) or the direct interaction with death receptors [58]. Also, NK cells produce many types of cytokines and chemokines that recruit other immune cells [59]. NK-mediated immunity can be achieved in the presence or absence of antibodies [58].

As mentioned above, NK cells have a central role in antiviral response. Next, the effects of exercise on NK cells' immunometabolism regulation are described in detail. It is hypothesized that NK metabolic adaptation has a major responsibility for improving the antiviral response in master athletes.

It is noteworthy that the vulnerable population developing the severe form of COVID-19 is the same population that shows reduced vaccine efficiency. Thus, lifelong exercise training could be an efficient approach to improve not only the immune response against viral pathogens but also vaccine efficiency in the older population.

EFFECTS OF LIFELONG AEROBIC TRAINING ON NK CELL ACTIVITY: DO MASTER ATHLETES HAVE A BETTER ANTIVIRAL RESPONSE?

Two important factors, low body fat mass and healthy nutritional habits, can help explain the possible low susceptibility to viral infections in master athletes. Chiappetta et al. (2020) have reported that obese people with hyperinflammation are more susceptive to the moderate or severe form of COVID-19 infection [60]. Continuous overnutrition leads to excessive availability of nutrients in the circulation, mainly glucose and fatty acids [41]. These nutrients exert a sufficient regulation on metabolic pathways, mostly regulated by two cellular energy sensors: AMPK and mammalian target of rapamycin (mTOR) [61]. Clinical findings showed that hyperglycemia leads to poor prognosis in COVID-19 patients. In contrast, diabetic patients treated with metformin (a pharmacological activator of AMPK) showed a reduction in mortality [62]. The activation and inhibition of these pathways can change cell function, especially immune cells, such as NK cells.

The main functions of activated NK cells are (i) killing virus-infected or malignantly transformed cells and (ii) triggering the adaptive immune response through the release of cytokines (e.g., IFN-γ and TNF) and chemokines (e.g., MIP-1β). When encountering target cells, NK cells release the content of their cytotoxic granules (e.g., perforin and granzymes) into the immune synapse to kill their targets. In the last years, the scientific literature has highlighted the importance of NK cell metabolism in facilitating robust NK cell effector functions [63].

Resting human NK cells have low basal metabolic rates of glycolysis and oxidative phosphorylation to meet their homeostatic needs. When NK cells become activated, they change their metabolism. After overnight stimulation with IL-2 or IL-12 plus IL-15, activated NK cells undergo dramatic metabolic reprogramming, up-regulating rates of glucose uptake

and glycolysis [64], the mTORC1 activity being essential for attaining this elevated glycolytic state [65]. When NK cells are stimulated over longer periods, IL-2 drives mTORC1-dependent glycolytic reprogramming of NK cells, sustaining NK cell effector functions and allowing them to work in parallel with the adaptive immune response [66]. mTORC1 inhibition by rapamycin specifically diminished IL-2 and IL-12 stimulation-dependent increase of glycolysis, leading to impaired cell growth and limited IFN-γ production and granzyme B expression [65]. Interestingly, in a lipid-rich environment, such as in obesity, the inhibition of mTORC1 activation in human NK cells inhibits their effector function [67]. Thus, the mTORC1 pathway is crucial for NK cell function [67].

Notably, strategies that reduce metabolic rates in mouse NK cells inhibit cytokine-induced proliferation and impair NK cell cytotoxicity. Murine cytomegalovirus-infected mice treated with the glycolytic inhibitor 2-deoxy-D-glucose presented impaired clearance of NK-specific target cells and increased viral burden [68]. Under conditions of glucose limitation, a plasticity of the immune cell metabolic pathways occurs; however, it is still poorly understood how NK cell metabolic pathways adapt to metabolically restrictive environments.

Altogether, a metabolic reprograming of NK cells during an exercise session and more robustly with lifelong exercise training is proposed. During a physical exercise session, NK cells experience low-energy conditions. This could acutely favor the activation of energetic sensors (here, the AMPK is suggested), mainly stimulating GLUT1 translocation to the cell membrane for glucose uptake purposes. This momentarily active, insufficient condition during exercise drives NK cells to function in an "economical mode." However, after the end of the exercise training session, with adequate rest and nutrition, the stimulation of the mTOR pathway begins, in turn promoting metabolic reprogramming in an attempt to create a more efficient cellular and functional profile. Thus, exercise-induced activation of mTORC1 via muscle-derived IL-6 and adrenaline secretion promotes an efficient NK cell pathogen elimination. This repeated stimulus, given the high volume and intensity of exercise training sessions, enhances NK cell adaptations over time. Therefore, lifelong exercise would induce a metabolic remodeling in NK cells: increasing glycogen (glucose) availability, facilitating GLUT1 translocation, and enhancing the expression of glycolytic pathway metabolic enzymes. This hypothesis is illustrated in Figure 1.

Lifelong exercise training could delay age-related decrements in immunity. Lifelong exercisers would display a preserved immune response to exercise, indicating that they are better prepared to adapt (or respond) to new immune challenges, such as a viral infection. Metabolic programming in immune cells could be a determinant for better antiviral response, such as that needed to fight SARS-CoV-2. Studies on this topic could shed light on the understanding of how lifelong exercise could lead to immunoprotection.

In summary, repetitive episodes of exercise throughout life may induce metabolic changes (systemic and intracellular), forcing the immune cells to work in different metabolic scenarios (catabolic and anabolic conditions) and promoting important intracellular adaptations for a better response against viral infections. This new metabolic and anti-inflammatory profile could help block/prevent the cytokine storms observed during COVID-19 infection. The fundamental message is that people should expose immune cells to energy deprivation situations during the day, for instance, by adopting regular physical exercise during their lifetime. This “simple” habit can promote greater immune system efficiency.

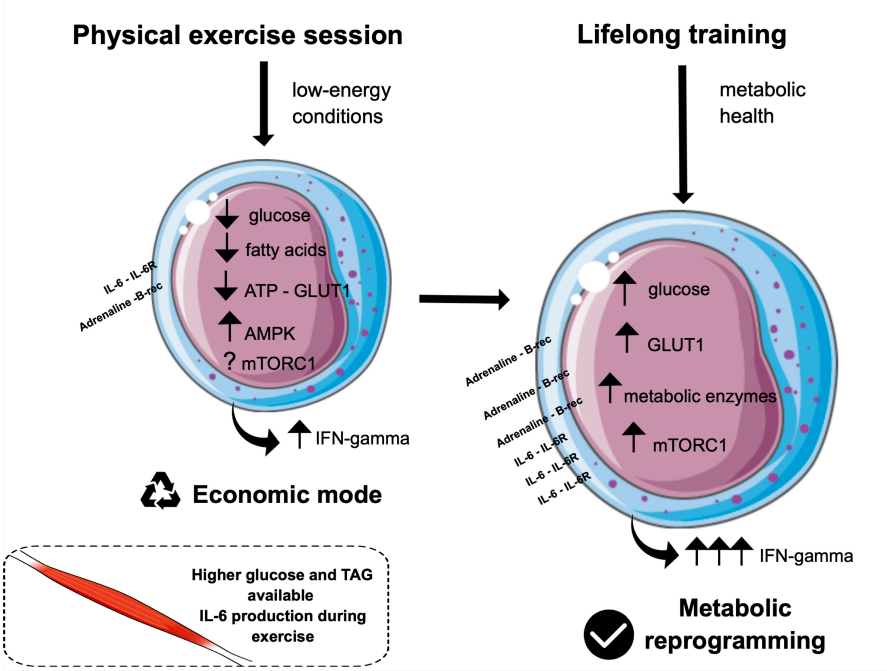

Figure 1. Immunometabolism of NK cells during an exercise session and with lifelong exercise training.

AUTHOR CONTRIBUTIONS

FSL and JCR conceived the present idea. LGM, FSL and JCL wrote the paper with input from all authors. AMT and RVTS did a critical revision of the article. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

The present manuscript was accomplished with support from CAPES, Coordination for the Improvement of Higher Education Personnel, Brazil (Capes-print Unesp, Capes 001) and São Paulo Research Foundation (Fapesp 2019/10187-7).

ACKNOWLEDGMENTS

The present study was conducted in honor of the 15-year anniversary of the death of Professor Luis Fernando Pereira Bicudo Costa Rosa, an eminent exercise immunology researcher in Brazil, whose ideas, erudition, critical sense and honesty continue to inspire us.

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How to cite this article:
Minuzzi LG, Teixeira AM, Thomatieli-Santos RV, Rosa-Neto JC, Lira FS. Immunometabolism and Covid-19: Could Lifelong Exercise Training Have a Protective Effect? Immunometabolism. 2021;3(1):e210001. https://doi.org/10.20900/immunometab20210001