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Review

Protective Effects of Exercise Become Especially Important for the Aging Immune System in The Covid-19 Era

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ABSTRACT: Aging is a complex, multietiological process and a major risk factor for most non-genetic, chronic diseases including geriatric syndromes that negatively affect healthspan and longevity. In the scenario of "healthy or good aging", especially during the COVID-19 era, the proper implementation of exercise as "adjuvant" or "polypill" to improve disease-related symptoms and comorbidities in the general population is a top priority. However, there is still a gap concerning studies analyzing influence of exercise training to immune system in older people. Therefore, the aim of this review is to provide a brief summary of well-established findings in exercise immunology and immunogerontology, but with a focus on the main exercise-induced mechanisms associated with aging of the immune system (immunosenescence). The scientific data strongly supports the notion that regular exercise as a low-cost and non-pharmacological treatment approach, when adjusted on an individual basis in elderly, induce multiple rejuvenating mechanisms: (1) affects the telomere-length dynamics (a "telo-protective" effect), (2) promote short- and long-term anti-inflammatory effects (via e.g., triggering the anti-inflammatory phenotype), 3) stimulates the adaptive immune system (e.g., helps to offset diminished adaptive responses) and in parallel inhibits the accelerated immunosenescence process, (4) increases post-vaccination immune responses, and (5) possibly extends both healthspan and lifespan.

Key words: aging process, exercise, immune system, immunosenescence, COVID-19

Aging is a complex, multietiological process and a major risk factor for most non-genetic, chronic and non-communicable diseases (NCDs) including geriatric syndromes that negatively affect healthspan and longevity [1, 2, 3]. Age-related disorders account for ~25% of the global burden of disease and continue to increase [4]. From a biological perspective, aging is associated with cellular senescence. This specific irreversible processwas first identified by Hayflick and Moorhead [5] who discovered that diploid cells (fibroblasts) invariably undergo a finite and predictable number of cell divisions due to telomere shortening. This process was termed as "replicative senescence". In subsequent years, the telomere length-independent senescence was described in detail by Roy Walford [6], known as the immunologic theory of aging. According to his classical book, age-

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related pathological phenomenon defined as "immunosenescence" leads the immune system to a progressive reduction in the ability to trigger effective cellular and antibody responses against the virulence of infectious diseases and vaccinations. It also affects both ancestral/innate and acquired/adaptive immunity, although T lymphocytes are dramatically affected [6]. However, age-related immunosenescence is more extensively influenced by acquired immunity than innate immunity [7].

In general, human immunosenescence may be influenced by several factors inlcuding genetics, exercise, nutrition, previous exposure to microorganisms, biological sex, persistent human cytomegalovirus (HCMV) and Epstein-Barr virus (EBV) infectionsand other environmental factors such as air pollution [8-12]. Additionally, some processes seem particularly important for aging in the context of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. First, older adults with immunosuppressed or weak immune defense are susceptible to coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2. Recently there have been more concerns directed toward this group since the latest studies confirm a dramatic decrease in their engagement in physical activity (PA) in outdoor green settings [13, 14]. It is important to note that physical inactivity is the 4th most important risk factor for global mortality [15] and sedentary time results in limited non-exercise physical activity (NEPA) of daily life [16]. Unfortunately, ~1/3 of adults worldwide are currently physically inactive [17], which got further exacerbated by COVID-19 and resulted in pandemic sedentariness/ physical inactivity. This trend, as an effect of various restrictions aimed at reducing social and physical contact, is especially dangerous for patients who had been prescribed therapeutic exercise programs. Second, the public health service has been ineffective in many countries since the surge of the COVID-19 pandemic and older adults have died due to the inability to be admitted to hospitals and many suffered from an acute or chronic condition that can normally be treated, such as strokes and heart attacks. Moreover, according to recent data, COVID-19 should be referred to as a "gerolavic" (from Greek, géros "old man" and epilavís, "harmful") disease, because the global statistics show that substantially more severe symptoms and lethality occurs in the population aged >60 years old [18].

Additionally, the immunopathological mechanisms of COVID-19 and associated death rates are still unclear. It is predicted that by 2050 there will be 40% of people over the age of 60 in Poland [19], and globally, the coming "tsunami" of aging of societies are also expected. Thus, the percentage of older people in the structure of society turns the age pyramid.

These circumstances force health and exercise specialists in PA to realize that regular physical exercise (even in a form of home-based exercise) have not only affect positive body image, sexual desirability, well-being and "endorphins", but it becomes a matter of survival for the older population in the COVID-19 era.

Therefore, the aim of this review is to provide a brief summary of well-established findings in exercise immunology and immunogerontology, but with a focus on the main exercise-induced mechanisms associated with aging of the immune system (immunosenescence).

1. Exercise and immunity

In general, exercise (a part of PA) is defined as a planned and structured behaviour, which aims to improve specific health and physical performance outcomes, such as functional ability or cardiorespiratory fitness [20]. Exercise can be classified into four subclasses: resistance, endurance, cognicise (*cogni*tive and exer*cise*) [21,22] and patterned movements [23]. Resistance, endurance and cognicise exercise are recognized as stimualtion of the body that has a significant influence on skeletal muscle tissue, nervous system and a more youthful immune phenotype [12]. In turn, patterned movement exercises concern mainly a motor program in the central nervous system and result in relatively non-signifficant changes in muscles physiology [23]. Thus, the following questions arise:

1. Can regular PA ameliorate immunosenescence and thereby reduce age-related multi-morbidity?

2. What kind of PA and which mode best fits for elderly in the context of immunosenescence?

Regular PA is recommended by World Health Organization [15] due to well-established association with increased longevity as a consequence of a reduced risk of developing cardiovascular diseases (CVDs), neuro-degenerative diseases, type 2 diabetes mellitus (T2D), metabolic syndrome, hypertension, infectious diseases and cancer [24-27]. Studies focused on analysing the effects of exercise training interventions on immunity in older people usually adopt a longitudinal randomized controlled trials (RCTs) to document immune changes in response to an intervention ora cross-sectional model to discriminate between active and inactive subjects [28]. The most frequent exercise training intervention protocols analyze aerobic or resistance exercise (or a combination of both, *i.e.*, concurrent strength and endurance training) ranging from 8-weeks to 12-months. However, there is still a gap concerning studies analyzing influence of cognicise training to immune system in older people.

The most common outcome data concerned: 1) T-cells: subset numbers, mitogen-induced T-cell proliferation, phenotype characteristics, 2) serum

antibody titres following vaccination, 3) cytotoxic activity of NK-cells, and 4) neutrophil/monocyte phagocytic function [29]. For instance, the amount of PA required to maintain neutrophil/monocyte phagocytic function equates to ~10,000 steps/day [30].

However, more often than not, the comparative analysis of the results among the longitudinal studies is complicated since different exercise protocols have been applied including different modes, volume, intensity, and frequency of a single bout. Additionally, age of participants varies between experiments and in some studies, it is not clear what exclusion criteria were adopted. Although in this review we have focused literally on the relationship between exercise and the immunosenescence, we must not forget about the broader consequences well beyond the effects on the immune system of exercise in the elderly. This means that in order for the analysis not to be purely theoretical, we must not overlook the other needs of the aging organism, such as plasticity of nervous system, general cardiorespiratory fitness and other important variables during healthy aging.

2. Exercise and aging of the cell

Telomeres

Telomeres are stretches of repetitive DNA (5′-$TTAGGG_n$-3′) sequences that cap eukaryotic chromosomal ends guarding genomic DNA from enzymatic degradation and are shortened progressively with each cycle of mitosis. Currently, leukocyte telomere length (LTL) is one of the most accepted markers of biological aging since Njajou et al. [31] observed strong possitive association between LTLwith the number of years of healthy living. Thus, a shorter LTL is recognized to be older than longer ones [32]. It has been proven that average telomere length diminishes from 11 kilobases after birth [33] to less than 4 kilobases at an older age [34]. Senescence is triggered when the telomeric terminal restriction fragment (TRF) reaches length of 4–7 kilobaseson average [35].

Moreover, LTL is influenced not only by numbers of succesive mitosis but also by other factors such as gender, BMI, smoking history, leisure time and PA, even after adjusting for age [36]. The study on 2401 white twins (2152 women and 249 men) also reported that LTL was even 200 nucleotides longer in physically active individuals compared to age-matched sedentary subjects [36]. This value corresponds to ~10 years of estimated biological aging. Several subsequent studies confirmed such relationships [37, 38]. More detailed information concerning PA and telomeres was shown by Ludlow et al. [39], who reported that individuals expending less than 990 kcal per week had shorter leukocyte telomeres than subjects expending between 991 and 2340 kcal per week, however no differences were observed for telomerase activity, which synthesizes telomeric DNA repeats. Recently, Simões et al. [40] presented data suggesting that longer LTL and higher physical fitness protect master athletes from severe consequences of SARS-CoV-2 infection.

While numerous studies indicate association between LTL, aging and PA, such positive associations have been refuted by several observational and interventional studies [see review, 41]. Nevertheless, the proposed associations of LTL with aging and exercise are biologically plausible. However, the mechanism explaining how training and PA affect LTL has still not yet been discovered [42, 43]. Overall, the presented data indicate a potential "telo-protective" effect of exercise on leukocytes, although it also applies to other cells (e.g., cardiac and liver cells) [44].

Oxidative stress

Reactive oxygen species (ROS), including superoxide anion (O2−), hydrogen peroxide (H2O2), and hydroxyl radical (HO•), consist of radical and non-radical oxygen species formed by the partial reduction of oxygen. The generation of cellular ROS are produced by immune cells – neutrophils and macrophages – as a result of increased aerobic metabolism during vigorous immune responses (the process of respiratory burst) and are considered as an important defense mechanism against pathogens [45]. Free radicals are unstable atoms that are considered as the "prime suspect" of aging processes and an actual source that contribute to cellular senescence, at least partially [46]. This approach was first outlined by Denham Harman in 1956 [47].

Exercise leads to increased oxidative stress (Ox stress). However, exercise-related oxidative damagealso seems necessary to trigger the adaptive up-regulation of molecular and cellular pathways (including endogenous antioxidant defense mechanisms) according to the hormesis theory [48, 49].

The hormesis concept, proposed for the first time by Southam and Ehrlich [50], assumes that in contrast to the obvious toxic effect of high doses of certain harmfull environmental factors (materials, irradiation, Ox stress, etc.), low doses of them tend to be beneficial and, moreover, help to eliminate (or prevent) the deleterious effect of high doses exposed after it [51]. Some authors emphasise that hormesis is an important factor of (human) evolution protecting human from harmful impacts, similar to the role of immunity [52, 53]. Specifically, hormesis hypothesis suggests that the organism's response to amplified increases in ROS production via exercise bouts triggers adaptive mechanisms [54].

Adaptive mechanism enhances an antioxidant upregulation including catalase (CAT), glutathione peroxidase (GPx), superoxide dismutase (SOD), glutathione reductase, glutathione-S-transferase, as well as nonenzymatic antioxidants (vitamins A, E, C) that protects the body against excessive oxidative stress related to aging. A number of studies proved the hypothesis that ROS are required for the health-promoting effects of exercise, causing an increase in endogenous antioxidant defense mechanisms (via up-regulated expression of antioxidant genes) and consequently, prolong healthspan and mean lifespan [55, 56]. However, as the relationship between oxidative stress and PA is still poorly explained, particularly in advanced age, at least two questions arise here concerning two main exogenous adaptive factors: antioxidants and exercise. First, is it really a common supplementation of antioxidants a better approach than well-balanced diet rich in fruits, vegetables and fiber, which may act in synergy to optimize the antioxidant effect [54]? Second, how can we detect or estimate which volume, intensity, frequency, and exercise loads are beneficial in the release of antioxidant mechanisms, and determine which PA load has a negative and devastating effect on the body?

3. The effects of exercise on the adaptive immune system

Acquired immunity of the organism is related to the response of the T and B lymphocytes to an antigen and it generally lasts for 2 up to 5 days, while repeated exposure of the organism to a pathogen produces immune memory [57]. According to Littman [58], the T lymphocytes may be further divided into subclasses depending on the expression of the CD4 and CD8 molecules on the cell surface. The T CD4+ lymphocytes recognise antigens as presented by major histocompatibility complexes (MHC) class II; these are typically the T helper (Th) lymphocytes. The other subclass comprises the T CD8+ lymphocytes. They recognise the MHC class I and are mainly the Tc lymphocytes, which are responsible jointly with cytotoxic cells for the destruction of cancer cells as well as cells infected by microorganisms [58]. They coordinate acquired immune response through the PAMP complex and dendritic cells secreting cytokines (CCL3, CXCL9, CXCL10) e.g., in the respiratory tract [59]. The molecular response pattern to pathogen infection, described by Müller et al., are involved in the inhibition of virion replication or destruction of the infected structure. Thus, the joint response of T CD4+ and CD8+ lymphocytes protects against respiratory diseases caused e.g. by influenza A or parainfluenza viruses. In healthy individuals during resting state, the CD4:CD8 ratio does not drop below 1.0 [60]. Physical activity of excessive intensity in relation to the organism's capacity, regardless of endurance or resistance exercise, leads to a reduction of the CD4:CD8 lymphocyte subpopulation to below 1 [61]. In older people a decreased blood level of T lymphocytes including its subpopulations has been noticed [62]. Linton and Thoman and Phillips et al. explained this phenomenon among other things by the age-related thymus atrophy, as well as an increased concentration of antigen-committed memory T cells and a decrease in the level of naïve T cells capable of responding to new antigens [62,63]. Compared to younger individuals, the frequency of T lymphocytes type KLRG1+, CD57+ and CD28− is also greater in older people [64-66]. Moreover, a reduced proliferation, secretion and signalling capacity, as well as an increased apoptotic lymphocyte capacity were shown in older people [67, 68, 69]. For this reason, the overall immune performance of the organism is decreased with age. High mortality caused by infectious diseases, influenza or pneumonia has been observed in the population of older people. A study in 2020 concerning immune changes in the acute phase of the SARS-CoV-2 infection showed that in 80% of all cases, a decrease of CD4+ and CD8+ T lymphocyte subpopulation is observed along with an increase in blood proinflammatory cytokines [70]. Thus, methods that reduce inflammatory response, modulate oxidative stress, and increase the synthesis of nitric oxide (NO), can all enhance the immune system and may be helpful in the control of many diseases, including the SARS-CoV-2 infection [71-72].

Numerous factors affect the performance of the immune system. To date, research has shown the effect of physiological factors, nutrition, psychological factors and environmental conditions on the rate of which immune performance deteriorates with age. Regular, moderate exercise will help boost the immune system at any age, thus reducing the risk of incidence or severe course of many diseases [73]. Just 10 consecutive days of endurance exercise contributes to significant protection against respiratory dysfunctions [74]. Exercise promotes apoptosis of aging T lymphocytes and stimulates synthesis of new, fully functional immune cells. Although the total number of lymphocytes and the subpopulation of the T lymphocytes released to blood during exercise probably is not age-dependent, the phenotypes of mobilised cells vary among individuals in different age groups [75]. Some of the positive effects of regular exercise are related to an increased proliferation capacity of the T lymphocytes, the activity of neutrophils and cytotoxic activity of the NK cells. This change is dependent on the level of physical fitness, duration of exercise, its intensity and particularly acidification of the organism. The leukocyte count increases with an increase in the intensity of exercise and blood lactate levels. In

accordance with the generally known phenomenon of hormesis, which as an adaptive response explains both the advantageous and disadvantageous effects of exercise. In particular the lymphocyte subtypes of high cytotoxic potential (i.e., the NK cells, the T CD8+ cells) are more sensitive to stress induced by exercise compared to the T CD4+ lymphocytes or the B lymphocytes, which exhibit limited cytotoxic capacity and are mobilised in a relatively lower number [76]. In a situation when effort is made, considerably exceeding the physical fitness capacity of the organism, it leads to leukopenia, deregulation of inflammatory processes and reduced capacity to maintain homeostasis and particularly the reduction of systemic immunity. Also, in the period of post-exercise regeneration of the organism, a transitional lymphocyteopenia lasting for 6–24 h is observed [77]. This is probably caused by increased apoptosis or migration of cells outside the vascular area. Both these mechanisms may overlap. Thus, this condition is called by many authors "the open window" [78]. The mechanisms underlying exercise-induced changes in the immune system include among other things changes in the concentration of neurohormonal factors depending on the intensity of exercise (e.g., cortisol, catecholamines, the growth hormone, endorphins, sex steroids), specific immune parameters (e.g., mucosal lactoferrin, immunoglobulin A) and cytokines (e.g., TNF, IL-1, IL-6) [79]. Additionally, changes in blood concentrations of glutamine, glucose, lipids or thermal shock proteins contribute to the incidence and development of leukocytosis. In the initial phase of exercise, the increase in the number of leukocytes is caused by the action of catecholamines, whereas a successive, already slower increase results from the effect of cortisol on the bone marrow. It is known that cortisol has an immunosuppressive effect. It may thus inhibit the function of cytokines and the NK cells, as well as reduce the production of the T lymphocytes during high intensity exercise.

4. Exercise and viral infections

The intensity of exercise plays an important role in the clinical resistance to infections. Short-term exercise of low intensity, as recommended by American College of Sports Medicine [80] for individuals of a low physical fitness level, has a slight effect on changes in blood antibody concentrations. Martin *et al.* [81] put forward a hypothesis that it is regular exercise in moderate intensity and duration that leads to an increase in stress hormone concentrations at any age, at the same time reducing inflammation in the airways, thus promoting activation of innate antiviral resistance. From this perspective, such exercise is associated with a reduced incidence, duration and severity of upper respiratory tract infections (URTIs), especially respiratory viruses as influenza and rhinovirus [82]. The cellular and molecular mechanisms underlying this phenomenon are related with changes in the intensity of the immune response reflected in the T helper 1/T helper 2 (Th1/Th2) ratio. The primary role of the Th1 lymphocytes includes their participation in the cellular response reactions, as they exhibit a proinflammatory action in viral and protozoan infections as well as cancer. Active substances released by this type of lymphocytes include interleukin 2 (IL-2), interferon gamma (IFN-γ) and tumour necrosis factor α (TNF-alfa). The Th2 lymphocytes play a key role in humoral immune responses. Characteristic compounds produced by the Th2 lymphocytes include anti-inflammatory interleukins 4 (IL-4), IL-5, IL-9, or interleukin 13 (IL-13). The interdependence between these types of lymphocytes have been described. Cytokines produced by Th1 have an adverse effect on the development of the Th2 cells and vice versa. The described phenomena underlie the immune polarization, and they serve a crucial role in the regulation of immune response. Physical activity of moderate-intensity causes a slight increase in blood concentrations of glucocorticosteroids, catecholamines or IL-6 leading to a slight deviation in the Th1/Th2 ratio towards Th2. Thus, they determine an appropriate development of adaptive immune response. Very high-intensity exercise results in a considerable increase in blood concentrations of glucocorticosteroids and catecholamines, causing a marked shift in the Th1/Th2 ratio towards Th2. This leads to a reduction of proinflammatory response by a decrease in the function of effector cells (Mϕ, NK) and an inappropriate development of adaptive immune response [81, 83]. Existing studies mostly concern the efficacy of regular PA in controlling the course of respiratory viral diseases in an animal model and in humans [84, 85]. At the same time, experimental studies on animals have shown the efficacy of PA of varying intensity as a protective mechanism against infection or infection symptoms, as well as mortality due to respiratory system viruses [86, 87]. Unfortunately, application of excessively intensive exercise resulted in increased morbidity and mortality rates caused by viral respiratory infections [88]. A similar mechanism is likely found in humans. In view of the high annual incidence of influenza given the current healthcare system overload, it is highly advisable to maintain health-promoting PA in combination with vaccinations provided by the public healthcare system. Chubak et al. [89] in their study assessed the effect of moderate-intensity exercise on the development of common cold symptoms in obese, physically inactive postmenopausal women. Based on 12-month observations those researchers stated that exercising individuals

reported a much lower number of cold symptoms compared to the physically inactive controls [89]. In contrast to numerous studies showing efficacy of exercise in the prevention of viral infections, a study by Weidner et al. [90] indicated a lack of efficacy of moderate exercise in reducing the incidence of rhinovirus-caused upper respiratory illness (URI) among vaccinated and non-vaccinated individuals. A possible limitation in this case may be related to the relatively high baseline level of physical fitness in the participants prior to the experiment. For ethical reasons, no data are available in literature on the efficacy of PA in a similar experimental model, where participants have more serious viral infections caused by the influenza virus, adenoviruses or enteroviruses.

Thus, according to Momesso dos Santos et al. [91], it is moderate-intensity exercise that may have an anti-inflammatory and immunomodulatory effect. In view of the above-mentioned phenomena, exercise may be the safest form of immunotherapy both in children and adults [91]. Moreover, it was also shown that extended exercise enhances the immune response against bacteria and viruses. Considering the currently high morbidity and mortality, particularly among older people due to SARS-CoV-2, a regular individualised training programme in the period before the development of pathological changes may protect against serious consequences of the infection. To date, there has not been studies on the effect of PA on immune performance of the organism infected by SARS-CoV-2.

It may be assumed that inactivity influences not only the course, but also the severity of many comorbidities, which significantly increases mortality rates caused by infection [92]. Physically active muscles release cytokines, which are capable of counter the proinflammatory mediators, *i.e.*, IL-1β and IL-18, at the same time increasing the concentration of interleukins, TGFβ, IL-1rα and IL-10, which enhance the anti-inflammatory effect of the immune response [93, 94]. During PA the secretion of hormonal inhibitors of cytokines (cortisol, prostaglandins, soluble receptors against TNF and IL-2) is also modified or the expression of TLR4 is inhibited, thus facilitating control of inflammatory conditions in patients suffering from chronic diseases [95]. In the course of a severe form of the COVID-19 disease, an overproduction of cytokines and immune cells takes place ("cytokine storm"), causing dangerous arterial hypertension, damage to the lungs or other internal organs. For this reason, the role of PA to reduce the inflammation and increase synthesis of anti-inflammatory cytokines, postulated in many publications, may play an important role in the course and prognosis in SARS-CoV-2 infections.

5. Exercise and vaccine efficacy

Upon neutralisation of the antigen by the immune system, most cells undergo apoptosis. The other cells remain alive and become the so-called antigen-specific memory cells. As a result, in the future when exposed to the same antigen they are capable of a prompt response. The described mechanism of generating immune memory cells constitutes the basis for vaccine efficacy. Multicentre randomised studies within the last 15 years have shown that exercise taken both before and after vaccination induce a higher antibody titre to the administered antigen. Those studies concerned the efficacy of vaccinations against influenza, tetanus, meningitis, diphtheria, meningococci or pneumococci [96-98]. Most presented studies were conducted on young individuals with a relatively strong antibody response to vaccination. In this group an additional intervention provided by PA did not contribute to an increased antibody titre, while efficacy of vaccination in prevention of hospitalisation amounted to approx. 75%; unfortunately, it dropped to 45% and 30% in individuals aged 65 and 75 years, respectively. This suggests that the older population exhibiting a decreased antibody response to vacciations may experience greater benefits from the exercise intervention than populations with greater immunity [99]. In another study the immunoglobulin M (IgM) and immunoglobulin G (IgG) antibody titres and immune response to a flu vaccine were assessed in the period of 2 weeks after immunisation. It was shown that a higher titre of antibodies was recorded in physically active older adults [100]. In line with this finding, it was showed that a 3-month cardiovascular exercise training extends influenza (H3N2 variants) vaccine seroprotection in sedentary older adults [101]. Unfortunately, prophylactic vaccination is less effective in older population, especially in those who are frail [102]. Therefore, it seems highly promising to apply regular PA to older people, who will be vaccinated against SARS-CoV-2 in the nearest future.

6. Exercise and age-associated inflammation

Inflammaging, influenced by immunosenescence, is a term proposed by Franceschi et al. [103] and is the combination of "inflammation + aging" to indicate the chronic, low-grade inflammation status is interconnected with the aging process. Inflammaging is believed to be a consequence of a cumulative lifetime exposure to antigenic load and stress, associated with continous inflammatory stimuli representing a biological background which leads to age-related diseases [104, 105].

However, do we really have a problem with inflammaging per se or maybe this pathological aging mechanism should be rather explained by "inflamm-inactivity"? The latter term constitutes a new paradigm

introduced by Flynn et al. [106] to highlight exercise as a major component in the inflammaging model. In this context, can we assume that inflammaging is escapable? If the answer is positive, it would mean that the key solution is in our hands. In other words, to control and moderate the effects of immunosenescence and inflammaging, we need to focus on the manipulation of certain lifestyle factors, like increasing PA levels [107]. It remains unclear whether exercise can prevent or transiently reverse these hallmarks of aging process, but in this area, we have a large evidence-based data of positive impact of vary and chronic exercise training interventions [12, 108, 109, 110]. Indeed, one of the highly effective non-pharmacological strategies that reduce age-related inflammation and the associated diseases within the "diseasome of physical inactivity" [111], and at the same time improve the quality of life (QoL) in older adults is regular, planned exercise [112]. In the scenario of "healthy or good aging", especially during the COVID-19 era, the proper implementation of exercise as "adjuvant" or "polypill" to improve disease-related symptoms and comorbidities in the general population is a top priority [17].

Regular, long-term exercise training is a major geroprotective intervention as it ameliorates immune function, whereas a prolonged period of sedentary lifestyle accumulated over weeks, months or years (activities that require low energy expenditure, e.g., sitting: <1.5 METs – metabolic equivalents; 1 MET = 3.5 mL O2·kg^{-1}·BM·min^{-1}) leads to immune supression [113] and hyper-inflammation state [106, 114]. The study on exceptional longevity in men provided information that vigorous exercise was associated with approx. 20–30% decreased mortality risk before age 90 years in a cohort of 2357 men (mean age was 72 years, range 66–84 years) [115]. A number of previous scientific reports have demonstrated an inverse dose–response relationship between systemic inflammation (e.g., circulating C-reactive protein, CRP) and exercise training and fitness status [116, 94, 117]. This dose-dependent effect is a multi-factor product of underlying mediators: the mode, duration, intensity, and frequency of exercise, that accumulate in a lifetime exposure [12]. This is due to different types of exercise evoke significant short-term (the minutes and hours after a single bout of exercise), medium-term (e.g., 1–3 weeks) and long-term (e.g., months or years of regular structured exercise) anti-inflammatory effects both in women and men, irrespective of age [93, 118, 111]. For example, among people 70–79 years old enrolled in the Health, Aging and Body Composition (ABC) study, trends for decreased cytokine concentrations (IL-6, TNF-α and CRP) were linear with increasing amounts of reported exercise [94]. The exercise-induced anti-inflammatory mechanisms control and resolve the inflammatory processess and inhibit age-related pathologies in many ways [119]. In healthy aging, the specific variants of regular exercise (particularly aerobic exercise training, AET, or cardiovascular exercise, e.g., walking, running, cycling): acute bouts of moderate-intensity (3–6 METs or 50–69% of maximal oxygen consumption; $\dot{V}O_{2max}$) and vigorous-intensity exercise (>6 METs or ≥70 % $\dot{V}O_{2max}$) when achieving moderate-to-high peak cardiorespiratory fitness, reduce the risk of CVD and all-cause mortality [27]. These types of exercise also appear to positively affect the immune system, enhancing adaptive responses and reducing chronic inflammation [29, 118]. Practically, the recent recommendations for immunoprotective exercise are as follows: intensity of exercise should be 60–75% of HR_{max} or 50–60% of $\dot{V}O_{2max}$ with rating of perceived exertion (RPE) of 10–14/20, frequency of exercise being 3–5 days/week and sessions ranging from 20 to 60 min [108]. Moreover, 75 minutes per week of specific high-intensity interval training (HIIT, with single session up to 10 min) is considered to be an effective strategy to achieve optimal functionality of the immune system in the elderly [120]. In the framework of HIIT also resistance training (e.g., bodyweight exercises) with sets of short exercise (< 1 min) or low number of repetitions (< 12 reps per set) and higher speeds of movement would be beneficial in older individuals [121]. However, a relatively high individual variability of the immune response to exercise-induced stress was observed [122]. The recommended strategy to reduce exercise-induced physiological stress in the elderly is to use longer recovery intervals in relation to the stimuli (work-to-rest ratios e.g., 1:2; 1:3; 1:4) [123]. Given the subjective RPE, exercising at an RPE of 11–13 is suggested for sedentary individuals, whereas an RPE of 13–15 may be recommended for those who have been previously exercising [124]. Aerobic exercise training is considered a single, hormetic stress stimulus that initiate mitochondrial biogenesis, antioxidant defense, cellular repair and recycling, and immunity [125, 49]. Recently, running was even termed the "key lifestyle medicine for longevity" [126]. Hence, according to a few large population-based cohort studies and meta-analyses, it is not surprising that the risk of CVD-related and cancer-related mortality in runners compared with non-runners (after adjusting for potential confounders) is reduced by 45–70% and 30–50%, respectively [127-130]. Additionally, running exerts protective effects on neurological health, reducing the systemic inflammation and consequently the risk of e.g., Alzheimer's and Parkinson's disease [127]. The problematic issue concerns running participation as it continues to decline 5–10% per decade, and less than 2% of people continue to run over 65 years of age [131].

Nowadays, the paradox of both inflammaging and immunosuppression is observed with increasing age worldwide [132]. However, the "anti-inflammaging" effects may also have some negative implications. For instance, there exists the theory that heavy exercise, termed as "dangerous exercise", elicits an immunological "danger" type of stress which, at some timepoints, becomes dysregulated and detrimental to health status, e.g., anaphylaxis, exercise-induced asthma, overuse syndromes, and exacerbation of intercurrent illnesses [133]. This refers to the long-duration one-off bouts of exercise (e.g., marathon running or cycling), extreme forms of exercise such as ultra-endurance races (e.g., Ironman triathlon), and long-duration (i.e., weeks or months) of very high-intensity athletic training [134]. It was recognized that acute, particularly high-volume intensive exercise sessions can cause transient immunosuppression (i.e., 1–3 h post-exercise) [135]. On this theoretical background and from the available cross-sectional data, it appears that moderate intensity exercise provides anti-immunosenescence effects (expressed by i.a., a less differentiated T-cell profile), whereas high-volume intensive exercise (typical in highly competitive athletes) drives mostly pro-immunosenescence effects (expressed by i.a., a more differentiated T-cell profile, increased expression of glycoprotein and myosin levels, and reduced thymic output) [107].

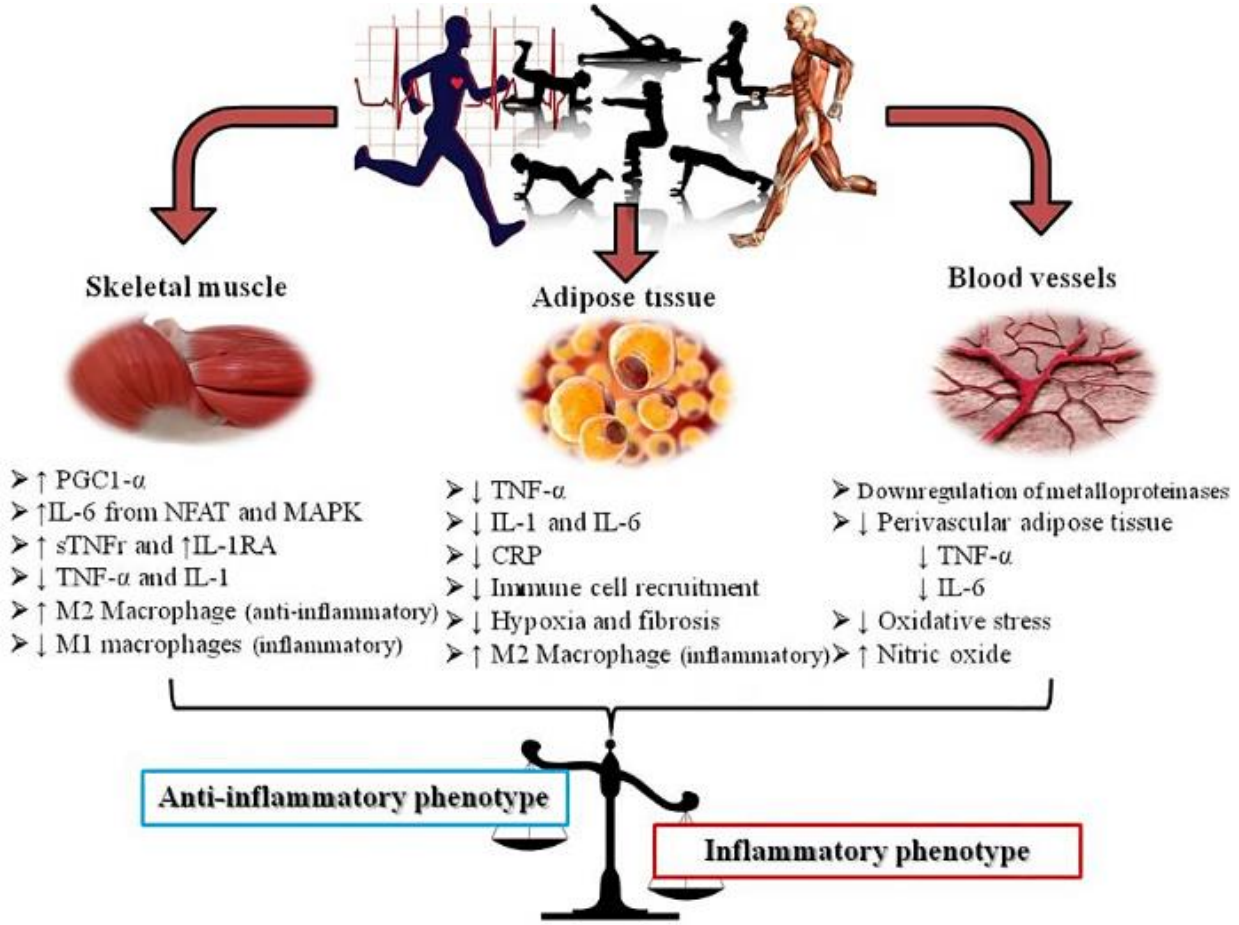

Figure 1. Mechanism of exercise in activation of anti-inflammatory phenotype in different tissues. PGC1α: peroxisome proliferator-activated receptor γ co-activator 1α, IL-6: interleukin 6, NFAT: nuclear factor of activated T-cells, MAPK: mitogen-activated protein kinase, sTNFr: soluble tumour necrosis factor receptors, IL-1RA: interleukin 1 receptor antagonist, TNF-α: tumour necrosis factor alpha, IL-1: interleukin 1, CRP: C-reactive protein. Figure adapted from Metsios et al. [20]

It was observed that sentinel and effector cells known as monocytes/macrophages (an important mediator of disease progression) can alter their phenotype in response to changes in the local cytokine environment [136]. In general, macrophages can be distinctly activated to either pro-inflammatory phenotype (also referred to as "M1"-like) or to anti-inflammatory phenotype (also referred to as "M2"-like) [137, 138]. Specifically, subtype 1 (M1) macrophage polarization is associated with inflammation and tissue destruction (induced by interferon-γ and/or lipopolysaccharide, LPS), whereas the subtype 2 (M2) macrophage is associated with wound repair and

angiogenesis (induced by IL-4 and IL-13) [139]. An increasing body of evidence suggests that engagement in exercise induces an anti-inflammatory phenotype in the general population, both acutely as well as in the long term (Figure 1). This is true at local and systemic level, because the short-term effects of exercise on inflammation have been mainly investigated in the skeletal muscle tissue by assessing muscle fiber-derived cytokines and peptides termed "myokines", such as IL-15, LIF, brain-derived neurotrophic factor (BDNF), irisin and fibroblast growth factor 21 (FGF-21), which increase and remain elevated during and post-exercise [111, 140, 141]. Of note, the most studied myokine IL-6 increases up to 100-fold in the circulation during physical exercise [111] or even up to 128-fold immediately after exercise compared to the pre-race value [142]. The substantial increase of IL-6 also stimulatesthe production of the classical anti-inflammatory cytokines like IL-1RA and IL-10 [143]. Importantly, older people with high levels of anti-inflammatory cytokines (especially IL-10) seem to have a healthy aging status compared to others [144]. On the other hand, the long-term effects of exercise on inflammation are mainly observed in adipose tissue with adipose tissue-derived cytokines collectively termed "adipokines" [20] or „adipocytokines" [145] (Fig. 1).

Exercise training leads to decreased white adipose tissue (WAT) inflammation, thereby ameliorating metabolic dysfunctions (*e.g.*, insulin resistance and hepatic steatosis), even in the absence of fat loss [146]. Hence, exercise-mediated reductions in WAT inflammation in humans are often weight loss-independent [147]. Nevertheless, weight loss is crucial to obtain optimal metabolic status, because it results in a substantial reduction in systemic levels of both circulating markers of inflammation (including CRP, IL-1, IL-6, IL-18, TNF-α and TNF-α receptors) and adipose-tissue cytokine production in individuals [148]. Obesity and other inflammatory degenerative diseases cause chronic inflammation silent that is without symptoms; wheras the increase in the expression of three pro-inflammatory cytokines: IL-1, IL-6 and TNF-α constitute an "inflammatory triad" – a specific hallmark of inflammaging [149]. For example, Dorneles et al. [150] found that changes in inflammatory cytokines after high-intensity interval exercise depends on a person's body mass; the increase in cytokines (IL-6 and IL-10) is higher in obese compared to lean people. Kern et al. [151] reported that pro-inflammatory cytokine TNF-α release from abdominal subcutaneous adipose tissue was 7.5-fold higher in tissue from obese (BMI 30–40 kg/m^2) compared to lean (BMI > 25 kg/m^2) individuals. The authors presented also a significant relationship between TNF-α and total body fat in kilograms (r = 0.41, p < 0.05). Conversely, it is well-established that acutely promoted anti-inflammatory effects of exercise include the significant increase of soluble TNF receptors which are naturally produced inhibitors of TNF-α [150]. In this context, the results of the Sellami et al. [144] study suggest that TNF-α could be used as an early biomarker of pro-inflammatory aging in elite athletes. Interestingly, while different classes of biomolecules are responsible for the cross-talk between distant organs and cells [152], for IL-15, it is supposed to have a role in the muscle-fat cross-talk via modulation of the visceral fat mass [153]. When combining all the information provided inflammation represents a pro-longevity factor at old age and exercise is a powerful agent that keeps inflammation in check.

In conclusion, there is growing evidence on the importance of certain forms of exercise as effective geroprotective interventions. Single exercise session and longitudinal exercise promote short- and long-term anti-inflammatory effects (via e.g., triggering the anti-inflammatory phenotype), respectively, and therefore suggesting a promising neurodegenerative and infectious diseases interventional target (including SARS-CoV-2 infection and COVID-19). This low-cost and non-pharmacological treatment approach, when adjusted on an individual basis in elderly, induce multiple rejuvenating mechanisms: (1) affects the telomere-length dynamics (a "telo-protective" effect), (2) stimulates the adaptive immune system (e.g., helps to offset diminished adaptive responses) and in parallel inhibits the accelerated immunosenescence process, (3) increases post-vaccination immune responses, and (4) possibly extends both healthspan and lifespan. From the current perspective of geroscience, the healthy-functional immunity and aging is strongly influenced by lifelong training routines and should be promoted broadly.

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