

- Comment -

The immune-modulatory effects of exercise should be favorably harnessed against COVID-19

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Abbreviations:

AMPK, 5' AMP-activated protein kinase; GLP-1, glucagon-like peptide 1; IGF, insulin-like growth factor; IL, interleukin; NK, natural killer; NF- κ B, nuclear transcription factor; TNF, tumor necrosis factor; URTI, upper respiratory tracts infections.

What COVID-19 lockdowns mean to the possibility of being physically active

This COVID-19 crisis imposes a revolution of habits and lifestyles that present-day societies appear unprepared to. Social distancing may be naturally associated with reduced levels of physical activity: home residing may augment sedentary behaviors (sitting time, watching-tv, using smart-devices). In turn, this may result in the worsening of chronic diseases such as obesity, type 2 diabetes, hypertension and the deleterious effects of aging. These syndromic features are all pooled within a dysmetabolic continuum for which regular physical activity of moderate intensity is salutary. In other words, low physical fitness, dysmetabolic conditions (*in primis*, obesity), and an altered immune system could be seriously adverse for a subject exposed to this coronavirus, SARS-CoV-2.

Moreover, consequences induced by societal changes in response to such a pandemic viral infection may aggravate psychosocial issues by weakening immunological defenses (“psychoneuroimmunity”) [1].

The harmful effects of physical inactivity

Countless studies have documented how abnormal responses from the immune system and the triggering of local inflammation, even at low-grade, in key cells and tissues, are the *primum movens* for the development of chronic metabolic diseases [2]. Obesity, strictly linked to sedentary behaviors, is an evident example of this. In addition, the involvement of cell types from both adaptive and immune immunity in the visceral adipose tissues of obese humans and mice underpins an immune-metabolic *milieu*, for which obesity-related insulin resistance and inflammation may have a proper autoimmune component [3]. The “disuse syndrome” encompasses low mechanical load, energy expenditure and metabolic rate, therefore implying metabolic derangements, ranging from insulin resistance and inflammation to impairments in insulin signaling, adipose tissue lipolysis and mitochondrial

functions [4]. Acutely, a concomitant increase of sedentary behaviour and physical inactivity impairs multi-organ insulin sensitivity and cardiorespiratory fitness – reversibly – and may be accompanied by concurrent dyslipidaemic profiles with fat accumulation at liver and central sites [5]. Even reducing the daily step count and step intensity has been associated with all-cause mortality and may lead to metabolic disorders in healthy adults [6].

However, during crisis like COVID-19, human physiology is not the sole one to be rapidly impaired by physical inactivity. Physical inactivity *per se* deteriorates mood profiles and has been associated with poor mental wellness. Although a clear psychological impact of COVID-19 is fairly unknown, either infected patients or asymptomatic individuals may experience anxiety, depression, stigma, anger, frustration [7]. These psychological variables may reduce immunity and negatively affect recovery.

The favorable immune-metabolic modulation induced by exercise

Regular exercise and/or physical activity have been proved to elicit a wide-ranging of health-promoting effects, bearing preventive, therapeutic, and sometimes even reverting actions, in a multitude of diseases.

Exercise induces a cascade of events, mostly favorable, leveraging the immune system, via an ultimately anti-inflammatory pattern within organ crosstalk (Fig. 1).

Skeletal muscle – Although IL-6 is itself a proinflammatory cytokine, it leads to an anti-inflammatory balance. In contracting muscles, marked increases of myokine IL-6 determine a downregulation of proinflammatory TNF as well as an upregulation of anti-inflammatory cytokines interleukin (IL)-10 and IL-1 receptor antagonist (IL-1ra). Moreover, IL-6, being pleiotropic, exerts systemic effects by enhancing insulin-secretion via GLP-1; insulin-stimulated glucose uptake (through AMPK activation) both in skeletal muscle and adipose tissue; lipid oxidation peripherally and whole-body. Circulating levels of IL-15 are

also increased in skeletal muscle following acute resistance training and enact protective responses by modulating cells of both the innate (NK) and adaptive immune systems (T cells).

Brain - Exercise augments endogenous β -endorphin levels in cerebrospinal fluid, increasing natural killer (NK)-cell-mediated cytotoxicity *in vivo*. Through the hypothalamic-pituitary-adrenal axis activation, adrenal cortex and medulla are stimulated to release cortisol and adrenaline, respectively. These two hormones inhibit proinflammatory TNF-cytokines by monocytes.

Heart and lungs – Adaptations to exercise training improve cardiorespiratory fitness, spanning from hemodynamic to hormonal changes. These result in improved oxygen capacity (uptake and delivery), larger breathing reserve and greater respiratory muscle efficiency. Myocardial function assessed at maximum minute volume is increased with training as well as systemic arterial compliance and stroke volume. Blood pressure reduction is brought by diminishing vasoconstriction and catecholamine levels. In fact, the sympathetic nervous and the renin-angiotensin systems are calmed by training. Muscle cytochrome C oxidase activity is also boosted by exercise leading to reduce local expression of proinflammatory cytokines and inducible nitric oxide synthase while augmenting insulin-like growth factor (IGF-1).

Gut – A growing body of evidence suggests that moderate increments of physical fitness ensure integrity of the intestinal barrier permeability by short chain fatty acids activation, and an overall anti-inflammatory profile even in chronic and immune-based diseases.

Multiple organs are implicated in a crosstalk fashion during exercise, initiating diverse anti-inflammatory responses.

Physical activity at the crossroad between prevention and vulnerability

An inverse relationship does exist between volume of physical activity and all-cause mortality rates in men, women, younger- and older adults. However, highest volumes of strenuous exercise may become concerning from an immunological standpoint.

It has been suggested that the cytokine response to strenuous exercise can be viewed as a model of the cytokine response to a traumatic event like sepsis or an extraordinarily intense “fight-or-flight” situation. Early report on COVID-19 described an associated upsurge of proinflammatory cytokines, including IL-1 β and IL-6 [8]. In addition to IL-6, other inflammatory biomarkers, like C-reactive protein, serum ferritin and coagulation index, and D-dimer were found elevated in patients with COVID-19 and diabetes compared with those without diabetes, indicating that patients with comorbidities are more prone to an inflammatory storm with a possible degeneration of COVID-19 [9]. Alike, absolute counts of lymphocytes, erythrocytes, and hemoglobin were all diminished among patients with COVID-19 and diabetes compared to those without diabetes [9]. These stressors resemble a post-traumatic status, so does the cytokine response of an extreme or ultra-prolonged exercise (e.g. marathon running or Ironman triathlon) that could be associated with muscle damage and even systemic endotoxemia.

Beyond the “open-window” period, in which the URTI risk is greater, hyperventilation of a typical running of strenuous intensity may exacerbate the pattern of breathing, with a potential inhalation of several agents, including the SARS-Cov-2 to deepest areas of the lungs. If infection occurs, the exercise-increased air flow could hypothetically expedite the virus diffusion to the lower airways and alveoli during the incubation period [10].

The line of demarcation between immunoprotection and immunodepression is thin, thus an exercise-strategy must be cautiously orchestrated, considering the adjunct risk represented by immunosenescence.

One lesson that can be learnt by this pandemic is that not only responses to diseases are heterogenous but also responses to exercise may vary across populations depending on a multitude of factors. Either the physical fitness status, the characteristics of the training, or the individual immunological integrity and responsiveness may be harshly predicted, controlled and finally managed. For these reasons, now more than ever, a targeted combination of competences and expertise are highly warranted, encompassing a teamwork of physicians, psychologists and exercise scientists.

Therefore, an anamnestic triage for a personalized exercise prescription during a SARS-CoV-2 outbreak is envisaged (Fig. 2).

Healthcare policies to harness the pleiotropic actions of exercise during pandemics

Certainly, government health directives have become more unified in their response to this coronavirus. Countries enabled coordinated actions, in terms of capacities regarding both health and social support.

Whilst many excellent digital resources, online exercise recommendations, have been readily available, more in-depth exercise prescriptions should be progressively developed as far as they now are being largely applied to diversified societal, sports and clinical contexts.

According to our representative sample of 2,400 web-surveyed people, aged 18-67, the prevalence of physical inactivity in Italy has moved from 8%, before the outbreak, to 23% after this virus surge (interviews administered through 17-22 March 2020). In the quarantine period, modalities of training and workouts were radically changed, performed with no

equipment (44%), tutored by social-network (13%) and video-calling (9%), or followed by on-purpose apps (11%).

During lockdowns, people are home confined. Although home-based exercise are safe and may vary extensively, performing physical activity outdoor has been shown to amplify the beneficial effects of exercise [11]. Besides, lack of commuting time should be virtuously replaced because, at present, like in quarantine periods, it is worryingly converted in physical inactivity. An ultimate set of factors pertains the mandatory graduality of the exercise schedules, which should be substantially diminished as to intensities and volumes (Fig. 2), according to the individual sports background: long-lasting periods of detraining, comparable to periods of reduced responsiveness (e.g. aging, spaceflight, injuries) may result in impaired performance and/or augmented injury risk.

It is important to understand the underlying mechanisms behind the exploitable effects of exercise, whether is moderate or intense, tailored on individualized immunological responses (which are upstream mediated by preexisting physiological and psychological conditions). The fascinating challenge will be whether we can capture the intimate mechanisms by which exercise comes to the forefront in the battle against pandemics like COVID-19.

Competing Interests

The authors declare that they have no competing interests.

Authors' contributions

All authors were responsible for drafting the manuscript and revising it critically for valuable intellectual content. All authors approved the version to be published.

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Figure Captions

Figure 1. Exercise-induced organ crosstalk. Beneficial effects are maximized at doses corresponding to moderate intensity, regular frequency.

Figure 2. Diagram of the anamnestic triage for a personalized exercise prescription during pandemics, such as COVID-19 outbreak.