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Implications of engaging in regular exercise and reducing sedentary behavior during a global pandemic: An immunometabolic perspective in patients with obesity and type 2 diabetes

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Abstract: Many reports showed a dramatic decrease in the levels of physical activity during the current pandemic of SARS-COV-2. This has substantial immunometabolic implications, especially in those at risk or with metabolic diseases including individuals with obesity and Type 2 diabetes. Here we discuss the route from physical inactivity to immnometabolic aberrancies; focusing on how insulin resistance could represent an adaptive mechanism to the low physical activity levels and/or high energy intake and on how such an adaptive mechanism could derail to be a pathognomonic feature of metabolic diseases creating a vicious circle of immune and metabolic aberrancies. We provide a theoretical framework to the severe immunopathology of COVID-19 in patients with metabolic diseases. We finally discuss the idea of exercise as a potential adjuvant against COVID-19 and emphasize how even interrupting prolonged periods of sitting with short time breaks of very light activity could be a feasible strategy to limit the deleterious effects of sedentary behavior.

Keywords: sedentarism, exercise, immunometabolism, SARS-COV-2, Cytokines, immunity

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1. Introduction

The world is going through tough time due to the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) pandemic. Since declared a pandemic by the World Health Organization (WHO) on March 11, 2020, home lockdown and social distancing have become the new standards of our daily life to limit the virus spread. These measures while important for containing the virus, they may have exacerbated an old pandemic – physical inactivity [1]. Moreover, even though many countries start to reopen progressively, individuals who are vulnerable to the severe forms of novel Corona virus disease (COVID-19) may prefer to not risk themselves and may avoid crowded places including physical activity facilities in the absence of viable vaccines.

Physical inactivity is considered the fourth leading cause of death by the WHO, and is fuelling the risks of metabolic diseases, including obesity and type 2 diabetes (T2D) [2]. Besides being a root cause of metabolic diseases, physical inactivity may have more profound deleterious effects on those with pre-existing chronic metabolic conditions [3]. Therefore obesity and T2D patients may pay high prices by not being active during this global pandemic. Here we highlight the deleterious effects of physical inactivity on glucose metabolism, and how this may lead to metabolic and immune aberrancies. We discuss a hypothetical scenario of the immunopathology of COVID-19 in patients with obesity and T2D and how the immuno-metabolic dysregulations, characterizing these diseases, may perturbate immune defenses, leading therefore to poor COVID-19 prognosis. We finally provide a theoretical framework on how exercise by its anti-inflammatory effects may prevent the severe complications of COVID-19 and how even reducing sedentary time by very light physical activity may help by reducing metabolic derangements.

2. On the ruins of two pandemics: the road from couch to metabolic and immune aberrancies

Data from activity trackers showed a dramatic decrease in step counts ranging from 7-38% in European countries during the early weeks of the pandemic [4, 5]. Similarly, an Italian study showed a significant decrease in weekly energy expenditure and that overweight individuals had the lowest levels of physical activity during quarantine [6]. This may have serious health implications since time spent sitting is now considered an independent risk factor for all cause mortality even after adjusting for physical activity levels [7]. As such time spent sitting seems to have deleterious effects even in those meeting the current physical activity guidelines.

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However in physically active individuals, health concerns seem to be less pronounced compared to the non-active counterparts [8-10]. In line with this, Gennuso, Gangnon [11] found that total sedentary time as measured by accelerometers was linearly associated to an increase in the odds of metabolic syndrome components, and that moderate to vigorous physical activity modified the magnitude of these associations. Conversely, more recent reports demonstrated that 4 days of prolonged sitting (13,5 h of sitting with ~3,500-4,000 steps/day) mitigated the beneficial effects of 1-hour bout of exercise on postprandial blood lipid, Insulin and glucose in healthy individuals [12]. van der Berg, Stehouwer [13] reported that an extra hour increase in sedentary time increases the odds for contracting type 2 diabetes and metabolic syndrome by 22% and 39% respectively. Mechanistically, several interventional studies demonstrated that a decrease in insulin sensitivity and metabolic flexibility; defined as the ability to adapt fuel oxidation to fuel availability, may underpin these associations [14, 15]. However, acute or short term fluctuations in insulin resistance could reflect a physiological adaptive mechanism rather than a pathological situation, to handle excess nutrients availability and/or low energy expenditure [16].

2.1 Acute or short term sedentary behavior-induced insulin resistance: a pivotal role?

Short term bed rest studies, as a model of sedentary behavior, conclusively showed deteriorations of glucose metabolism and insulin sensitivity, with a duration ranging from 5-10 days of bed rest [17-19]. However, bed rest is an extreme and an unrealistic model of sedentary behavior in the global population; therefore many studies echoed a more realistic model of reduced physical activity and prolonged sedentary time by reducing daily steps. Olsen, Krogh-Madsen [20] reported that a decrease in daily steps, from 6200 to 1400, increases insulin resistance in healthy individuals. Similarly, Two weeks reduction in daily steps from ≈ 10.000 to 1.500 increases peripheral insulin resistance without any effect on endogenous glucose production, implying that peripheral insulin resistance precedes hepatic insulin resistance [21]. Another study reported that two weeks reductions in daily steps from ≈ 10.000 to 1.500 combined with overfeeding decreases insulin stimulated glucose uptake without affecting inflammatory markers [22]. Importantly, because insulin sensitivity levels are very sensitive to energy balance, this increase in insulin resistance could result from a positive energy balance if energy intake was not matched to energy expenditure [23, 24], which was the case in the two latter studies. In this regard Stephens, Granados [25] showed that one day of prolonged sedentary time significantly reduced insulin sensitivity even when

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energy intake was matched to energy expenditure. However, short term decrease in insulin sensitivity is more and more considered as a physiological defense to divert excess nutrients from tissues with limited storage capacity (i.e. skeletal muscle and liver) to adipose tissue with almost unlimited storage capacity – a physiological response to prevent glucolipotoxicity [26, 27]. In line with this, Dirks, Wall [28] showed that 7 days of bed rest does not result in ectopic fat deposition – a hallmark of pathologic insulin resistance – while in the same time cause insulin resistance. Animal model studies of physical inactivity confirm also these findings [29]. This is, perhaps, best reflected by the fact that healthy individuals may to some extent tolerate the effects of physical inactivity and restore their insulin sensitivity levels once returned to habitual physical activity [22]. On the long run, though, it is believed that the chronic storage of excess nutrients in adipose tissue, resulting from low levels of physical activity and/or excess food intake, leads to adipocytes enlargement (hypertrophy) and multiplication (hyperplasia) and therefore to increased fat mass [30, 31]. This is believed to be the critical point that initiates adipose and systemic immune and metabolic aberrancies (See Figure 1) lipid engorged adipocytes express a stress phenotype characterized by activation of inflammatory signaling pathways that regulate stress-induced cell death. Cell death promotes macrophages and T cells recruitment [32, 33], polarization of macrophages and T cells towards an inflammatory phenotype [34], blunted B cell antigen production, and expression of a more pro-inflammatory cytokines repertoire [35, 36]. Among the pro-inflammatory cytokines, tumor necrosis factor (TNF-α) was the first to be reported to interact with metabolism, and to blunt insulin action through insulin receptor substrate phosphorylation at serine residues leading thereafter to adipose and systemic insulin resistance [37, 38].

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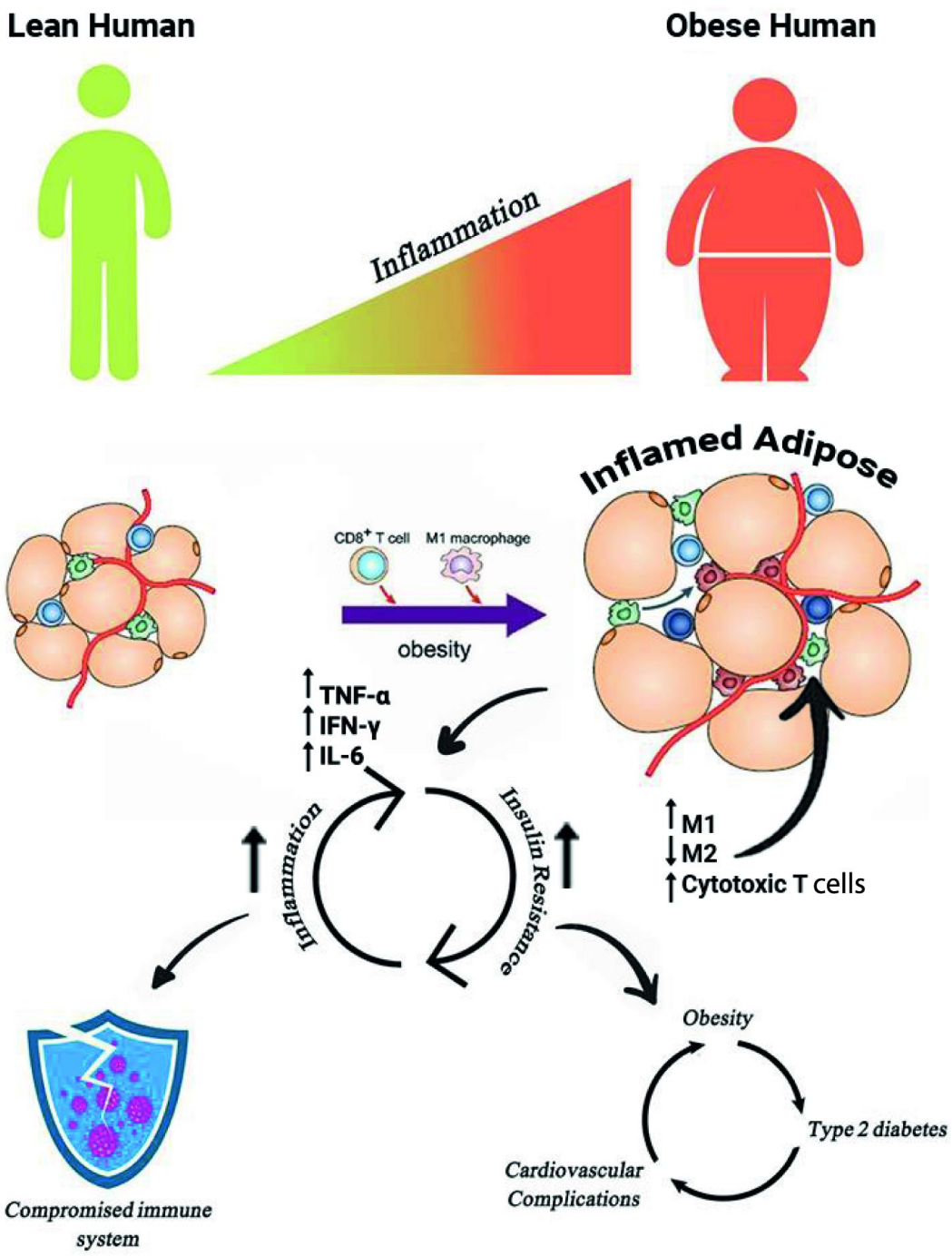

Figure 1. Obesity and its associated metabolic and immune abnormalities. Adipose tissue expansion in obesity is accompanied by an increase in size and number of adipocytes. This drives a shift of local immune cells homeostasis towards a more pro-inflammatory phenotype, which communicates insulin resistance at a systemic level through pro-inflammatory mediators. Importantly this immuno-metabolic complications create a feed forward loop that compromises the cardiometabolic health; leading to cardio-metabolic diseases, and compromises the immune system; leading to increased infection risks.

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The discovery of TNF-α; as a mediator of insulin resistance, was one of the earliest clues of metabolic and immune connection that paved the way for the birth of the Immunometabolism field [39]. The birth of this field led to the recognition that besides the metabolic component, obesity has an inflammatory component; featured by the subclinical elevations of many pro-inflammatory cytokines and the polarization of many of the immune cells towards an inflammatory phenotype [39]. Also of importance, studies in this field revealed that the elevated nutrients characterizing obesity and its associated complications are recognized by innate immune sensors, specifically pattern recognition receptors, and are a well documented trigger of inflammation [40, 41]. For example Toll like receptor (TLR); a pattern recognition receptor, is known to be activated by saturated fatty acids (SFA) [40] and glucose [42], which leads to the activation of inflammatory signaling pathways and expression of pro-inflammatory cytokines. Moreover, Palmitate, a SFA, activates NLPR3 inflammasome, leading to IL-18 and IL-1β production in hematopoietic cells, and this blunts insulin signaling, impairs glucose tolerance and insulin sensitivity in multiple other tissues [43]. Finally, the mounting of an effective immune response to defend the host, requires glucose to be directed towards immune cells, and this involves peripheral insulin resistance [44, 45].

At this point, it is important to distinguish between physical inactivity-induced insulin resistance and the insulin resistance featuring chronic diseases: physical inactivity-induced insulin resistance, is an adaptive mechanism, and is not accompanied by inflammation [46, 47], however; metabolic diseases-induced insulin resistance is a combination of both inflammatory and metabolic aberrations. Therefore patients with metabolic diseases, with an already abrogated immunometabolic profile may be particularly vulnerable to physical inactivity. In support of this notion, a study demonstrated in overweight aged pre-diabetic individuals that two weeks of step reductions impaired glucose control, insulin sensitivity and inflammatory markers (TNF-α, IL-6, CRP) [3]. Importantly these effects did not resolve two weeks after returning to the pre-step reduction phase, which is in contrast with the findings in healthy adults and aged individuals [22, 47]

In conclusion, this overlap between immune and metabolic pathways determines in metabolic diseases a feed forward loop of complications between inflammation and insulin resistance (see figure 1), which alters metabolic health and drives obesity-associated cardio-metabolic complications. It is noteworthy that the contribution of defective immunometabolic profile in metabolic diseases is less well characterized in the context of infections, and could

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play an important role in the increased susceptibility and the bad prognosis in infectious diseases [48-50].

3. Why patients with obesity and type 2 diabetes are more susceptible to the severe COVID-19: A nutrient perspective

The presence of chronic diseases, including obesity and T2D, has been associated with the development of the severe form of COVID-19 [51-54]. Severe COVID-19 include acute respiratory distress syndrome (ARDS), septic choc, multiple organ failure and death [55]. The severity of the disease is usually accompanied by elevated inflammatory cytokines: IL-2R, IL-10, IL-6, IL-8 and TNF-α, reminiscent of the cytokines releasing syndrome [53, 56, 57]. This is also seen in SARS-COV-1, which shares 80% homology with SARS-COV-2 [58]. Importantly, ARDS, during SARS-COV outbreak was shown to occur despite reductions in viral load, suggesting altered host response rather than viral virulence.

In a retrospective multicentred cohort of 7,336 confirmed COVID-19 cases with or without diabetes in Hubei Province, China, diabetics had significantly higher mortality rate and higher multi-organ injury [59]. In this cohort, controlled blood glucose levels correlated with improved outcomes and were associated with markedly lower mortality rate compared to uncontrolled glucose status. In the whole cohort, as well as in the diabetic group, lymphocytopenia, neutrocytosis, and increased circulating IL-6 correlated with blood glucose. The group with controlled blood glucose showed lower lymphocytopenia, lower neutrocytosis, and lower IL-6 levels, all of which correlated with the controlled glucose status [59], suggesting an interaction between glucose and immune cells.

Pathogen associated molecular pattern (PAMPs) are recognized by the innate microbial sensors, called pathogen recognition receptors (PRRs). In the case of SARS-COV-2, the genomic viral RNA could be recognized by Toll like receptors, NOD-like receptors or RIG-I-like receptors [60, 61]. This recognition activates downstream signaling and promotes pro-inflammatory cytokines production in a nuclear factor kappa B (NF- B) and in an interferon regulatory factor (IRF) 3/7 dependent manner [61, 62]. Importantly, IRF 3/7 are known to upregulate Type I interferon (IFN-I) production leading to the activation of interferon stimulated genes and to the secretion of many pro-inflammatory which constitutes an early first line of innate immune defense that interferes with viral replication [63]. In an elegant study, Hu, Xia [64] investigated the effect of acute and short term effects of hyperglycemia on IFN-I production and signaling by peripheral blood mononuclear cells

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(PBMC). The study consisted in incubation of PBMC with different glucose concentrations and Polyinosinic:polycytidylic acid (polyI:C) stimulation, with polyI:C being a double stranded RNA (dsRNA) that stimulate IFN-I via Toll like receptor (TLR) 3. The authors demonstrated that blood glucose levels differentially affect IFN-I production and signaling in both acute and short term conditions: moderately elevated glucose (8 mmol) promoted IFN-I production, however, highly elevated glucose levels (24 mmol) impaired it. These acute and short term results have important implications; as outlined earlier, the inflammatory response is glucose dependent, therefore acute moderate elevations in blood glucose may boost the immune response against pathogens, in part by increased IFN-I production. Further confirming this notion is that acute incubation with moderately elevated glucose and polyI:C increased CD169, a sensitive IFN-I signaling marker, expression on PBMC, while acute incubation with highly elevated glucose and polyI:C decreased CD169 expression [64]. Therefore by suppressing IFN-I, high glucose levels may promote viral replication and persistence. Furthermore, high glucose levels, from the latter study, also increased many cytokines, including; IFN-γ, TNF-α, IL-1β, IL-6, IL-8, IL-10 [64]. Importantly most of these cytokines were reported to be elevated in severe COVID-19 patients, suggesting that hyperglycemia could contribute to the immunopathology of COVI-19. [53, 57].

Many mechanisms by which hyperglycemia reprogram leucocytes to an inflammatory profile: for example advanced glycation end products (AGEs) mediate the M1 program of macrophages by the activation of NF- B pathway, which promote IL-6 and TNF-α expression [65]. Similarly, upregulation of glucose metabolism promotes an inflammatory phenotype of macrophages characterized by an oxidative stress-mediated increase in pro-inflammatory mediators [66].

Besides hyperglycemia, dyslipidemia is also a common feature of obesity and T2D. Both diseases are characterized by increased concentrations of circulating non-esterified fatty acids of which saturated fatty acids (SFAs) constitute the major type governing the plasma [67]. SFAs are integral components in active microbial patterns, and the biosynthetic replacement of SFAs by monounsaturated fatty acids in those patterns blunts the pro-inflammatory activity [68]. Importantly SFAs can act as PAMPSs and are capable of activating Toll like receptors (TLRs) [69], a family of transmembrane proteins known to play an important role in innate antigen recognition [70]. For example, TLRs activation increases the expression of many pro-inflammatory cytokines including, but not restricted to; TNF-α, IL-1 and IL-6 in a NF- B dependent manner [71]. Patients with Obesity and overweight show

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also increased levels of TLR4 and TLR2 [72]. Moreover, high glucose levels exacerbate SFAs-mediated TLR expression and activity on monocytes, and increase pro-inflammatory cytokines production in a reactive oxygen species-dependent manner [73].

Obesity and T2D display increased NLRP3 inflammasome components levels which correlate with the severity of T2D [74]. NLRP3 is a family member of NOD like receptors that play an important role in the recruitment and activation of Caspases which in its turn initiates the production of IL-1β and IL-18 [75]. Importantly, SARS-COV was shown to drive inflammation in an NLRP3 dependent manner [76-78], therefore the pre-existing metabolic derangements resulting in high levels of NLPR3 components in obesity and T2D could lead to uncontrolled NLRP3-mediated inflammation contributing to the immunopathology of COVID-19. In this regard, there is evidence suggesting that TLR activation by palmitate could induce inflammasome activation which results in IL-1β expression and therefore increased inflammation [79].

Therefore, integrative strategies that aim to improve the inflammatory and the metabolic profile characterizing these diseases are of paramount importance at the preventive level. One of these strategies includes physical exercise.

4. Exercise as an adjuvant: A COVID-19-centred perspective

Robert N. Butler once said: “if exercise could be packed into a pill, it would be the single most widely prescribed, and beneficial, medicine in the nation.” [80]. Exercise is the only intervention that has the potential to confer wide spread preventive advantages, ranging from immuno-metabolic to mental health, against the deleterious effects of SARS-COV-2 outbreak. Since we cannot predict when the vaccine is going to be ready, when this outbreak will end, and if there will be new waves before discovering the vaccine, we need a strong shield – stronger than ever. Therefore we focus this section to discuss how exercise boosts our immune shield (see Figure2.), and how even if this shield is troubled, like in chronic diseases, exercise could restore functionality and confer some protection against COVID-19.

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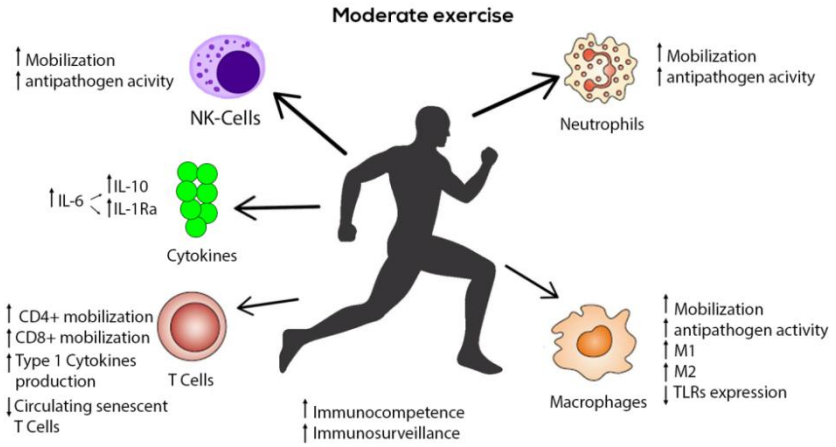

Figure 2. Exercise effects on immune system. Moderate intensity exercise increase the mobilization and the anti-pathogen activity of Natural killer (NK) cells, Neutrophils , Macrophages and T cells. In macrophages, along with increased mobilization of classically activated (M1) inflammatory Macrophages and decreased Toll like receptors (TLRs) expression, exercise training also increases the alternatively (M2) anti-inflammatory macrophages. In T cells, acute exercise increases CD4+ and CD8+ T cells subset mobilization, increase type 1 cytokines production. Chronic exercise mitigates age related decrease in T cells. Acute exercise bouts are accompanied by a transient increase in the myokine interleukine (IL)-6, which subsequently increases IL-10 and IL-1Ra levels, all of which have anti-inflammatory properties.

As highlighted earlier, obesity and diabetes status are major risk factors for contracting the severe form of COVID-19. Common to these conditions is a state of low grade inflammation and immune depression [31, 33, 34, 81-84], which is believed to contribute to the amplified immune response characterized by an overproduction of pro-inflammatory cytokines, namely the cytokine storm, typical of severe COVID-19 [85]. Interestingly exercise by its anti-inflammatory effects may confer some protection by restoring the balance between pro and anti-inflammatory immune mediators.

A single bout of exercise is accompanied by a transient increase in IL-6 [86]. The rise of IL-6 is known to stimulate lipolysis which promotes fatty acid utilization as a fuel source

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by muscles [87]. On the long run, physical exercise promotes the reduction of visceral adipose tissue, which indirectly reduces the inflammatory profile accompanying these diseases. In line with this, a study investigated the effect of tocilizumab, an Il-6 receptor antibody, on exercise-mediated reductions in visceral adipose tissue in individuals with obesity [88].The authors showed that IL-6 receptor blockade blunted these reductions. IL-6 anti-inflammatory effects are not limited to the long term reductions of visceral adipose tissue; its transient elevation in response to acute exercise is known to stimulate other anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist (IL-1ra) [89]. IL-10 is known to modulate the activity of Th1 cells, Natural killer cells (NK) and macrophages by moderating pro-inflammatory cytokines expression including IL-1α and β, IL-18, IL-12, and TNF-α and chemokines expression, including monocyte chemoattractant protein (MCP1, MCP5) [90, 91]. During infections these effects prevent excessive immune activation and tissue damage [90]. IL-1ra is known to interfere with the inflammatory action of the cytokine IL-1 by competitively binding IL-1 receptor [92]. The balance between IL-1/IL1ra is very important in health, and the disruption of this balance may lead to a broad range of diseases including insulin resistance [92-94]. This seems also to be valid in individuals with obesity, since acute moderate and high intensity interval exercises (HIIE) were shown to transiently increase IL-6 concentrations [95]. However, Dorneles, Haddad [96] showed that IL-6, IL-10 were only increased after HIIE. The relatively short duration (10 min) of the moderate intensity and the intermittent character of the exercise in this study could explain these discrepancies. The rise in catecholamines and cortisol, and their interference with acute exercise intensity could paly a role in theses anti-inflammatory effects [97, 98]. Besides cytokines, exercise is also a potent inhibitor of TLRs, in health and T2D [99, 100]

Paradoxically, these anti-inflammatory effects, depending on exercise intensity and duration, may promote immunocompetence or immunodepression [101, 102]. Acute moderate to vigorous intensity exercise of less than 60 min enhances immunocompetence and immunosurveillance because the rise in anti-inflammatory mediators is paralleled by an increased mobilization and activation of cytotoxic T cells, NK cells and neutrophils [103, 104]. However, prolonged intense exercise – via the over-expression of anti-inflammatory cytokines – promotes a state of immunodepression [102, 105]. These observations reflect that optimal immune function requires a balance in immune cells homeostasis, and/or in pro- and anti-inflammatory immune mediators. For instance, IL-10 is a potent modulator of Th1 and Tc1 T-cells, NK cells and macrophages activity, in part by moderating pro-inflammatory

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cytokines expression, which prevents excessive inflammation and tissue damage [90, 106]. Conversely, over-abundant IL-10 impairs the inflammatory response and leads to pathogen persistence [107, 108].

In trained athletes, Handzlik, Shaw [109] showed that high load endurance training induces heightened IL-10 expression upon ex-vivo antigen stimulation compared to sprint trained and sedentary counterparts. However, high training loads concern more elite athletes, and does not concern the general and the diseased populations, for which guidelines recommend 150 min/wk of moderate-intensity activity or 75 min/wk of vigorous-intensity activity [110, 111], and even with such a small volume the majority of the population still not engage in regular exercise [112]. Moreover some researchers posited that the idea of intense exercise-mediated immunodepression is flawed, and that all the manifestations of immune depression accompanying intense exercise in athletes may in fact reflect an enhanced immune surveillance [113].

The balance between pro-inflammatory and anti-inflammatory immune cells sub-populations, and pro-inflammatory and anti-inflammatory immune mediators is critical for the immuno-metabolic health [114]. Any disruption in this balance increases susceptibility to diseases [115, 116] . In the context of COVID-19, the severity of this disease is accompanied by comorbid states in which this balance is disrupted towards an inflammatory state. Exercise presents the most effective strategy that restores the anti-inflammatory component of this balance without compromising – if not optimally enhancing – the inflammatory response [101]. The anti-inflammatory component plays an important role during infection as it controls the inflammatory process through anti-inflammatory cytokines [90, 102]. This prevents excess inflammation, and in the context of COVID-19 may prevent the cytokines storm. Of course these effects are intensity and duration dependent, but as highlighted above, unlike elite athletes, the general population does not regularly engage in intense prolonged exercise. Many reviews conclusively agreed that moderate to vigorous exercise of less than 60 min increases anti-pathogen activity and the mobilization of macrophages, NK cells, cytotoxic T cells, while in the same time, increases anti-inflammatory cytokines production, an environment that promotes metabolic health as well as optimal immune readiness [96, 101, 102].

Many reports showed that severe COVID-19 patients display reduced lymphocyte counts, particularly CD4+ and CD8+ T cells and increased cytokine levels IL-6, IL-10, and

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TNF-α [59, 117, 118]. CD4+ CD8+ T cells are very responsive to exercise in part because they carry more β2-adrenergic receptors [119, 120], and display a dose dependent mobilization with exercise intensity [121, 122]. Upon pathogen infection, the innate component of the immune system drives CD4+ and CD8+ T-cell polarization into two main subsets depending on their cytokines profiles: Type 1 T-cells (Th1,Tc1); exhibiting a pro-inflammatory cytokines profile (IFN-γ, IL-2), and are important in promoting intracellular pathogen defense and type 2 T-cells (Th2, Tc2), exhibiting an anti-inflammatory cytokine profile (IL-4, IL-10), and are important in mediating humoral immune response [123, 124]. Th1 and Th2 for type 1and type 2 helper T cells are CD4+ polarized T-cells that play a more indirect role by recruiting more immune cells to the site of infection. Tc1 and Tc2, for type 1 and type 2 cytoxic T cells are CD8+ polarized T-cells that play a direct role in clearing intracellular pathogens [124, 125]. Interestingly, Exercise is also known to enhance the functional capacity of these mature T cells in an intensity dependent manner [126]. That is, exercise influences the cytokines production by these cells; moderate intensity exercise increases type I cytokines production, which enhances the inflammatory response [127], while high intensity prolonged exercise decreases type 1 cytokines production, without affecting type 2 cytokines, which create an imbalance that may impair cellular defense [127, 128]. Along with these acute exercise effects, chronic exercise training was reported to counteract T1 and T2 age-mediated cytokines reductions and lower the number of senescent T cells [101, 129, 130]. These changes in immune cells mobilization and function in response to exercise, both acute and chronic, have led many researchers to use exercise as a strategy to improve vaccine responsiveness [131]. Briefly, both acute and chronic moderate exercise were showed to improve vaccine responsiveness and to extend vaccine seroprotection, particularly in individuals vulnerable to immune dysfunction [131, 132]. Moreover, in animal models studies of influenza infection, chronic exercise reduced symptoms, viral load and levels of inflammatory cytokines and chemokines [133]. Similarly another study showed that moderate exercise, early after influenza infection, reduced total cellular infiltration and IFN-γ gene expression in lungs, and shifted pro-inflammatory Th1 towards anti-inflammatory Th2 cells[134]. In line with these preclinical studies, epidemiological studies linked low to moderate exercise with reduced influenza mortality [135]. However this needs to be confirmed in clinical settings.

Based on these observations we speculate that exercise may hold substantial preventive effects against COVID-19 immunopathology. For specific physical activity

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recommendations during this period, readers are directed towards some recent articles [136, 137]

5. Breaking up sedentary behavior: Get up from the couch and enjoy some movement

As indicated above increased sedentary time constitutes a major risk factor for many chronic diseases, and could have been increased by shelter in place during this outbreak. Therefore reducing time spent sedentary could be another possible strategy, very feasible, to optimize or at least to prevent metabolic and immune health. Many studies investigated the extent of breaking up sedentary time on metabolic outcomes. Paing, McMillan [138] found a dose response relationship between the frequency of interrupting 7 hours of sitting by 3 minutes of light walking breaks on postprandial and 21-h blood glucose incremental area under the curve (iAUC) as measured by continuous glucose monitoring in T2D patients: 3 min of walking breaks every 15 min were reported to have superior effects compared to less frequent breaks (3 min walking every 30 min or 1-h). Similarly in another study they demonstrated that breaking up sitting time with 3 min light walking every 15 min improved fasting blood glucose, dawn phenomenon and night-time glucose excursions in T2 diabetics [139]. A randomized cross-over study reported that breaking up sedentary time with standing and light intensity walking improved 24-h blood glucose profiles and insulin sensitivity to a greater extent than structured exercise does [140]. In subjects with obesity, Climie, Grace [141] showed that interruption of a 3,5-h TV watching with 3-min light intensity body weight resistance activity every 20 minutes attenuate glycemic excursions during TV watching after a high energy meal. In overweight sedentary women more frequent breaks of sedentary time resulted in improved postprandial insulin profiles compared to less frequent breaks matched for time and energy expenditure [142]. Even interrupting sitting with standing breaks was reported to significantly reduce blood glucose excursions compared to uninterrupted sitting [143]. A recent systematic review with meta-analysis concluded that breaking up sitting with moderate physical activity reduced postprandial blood glucose and insulin [144], however, smaller effects on triglycerides were observed. In addition, the reduction in blood glucose was more pronounced in subjects with higher BMI. When energy expenditure was matched, more frequent breaks of sedentary time were more consistent in reducing blood glucose levels. Taken together, these studies suggest that interrupting prolonged sitting time with short bouts

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of light activity or even standing may have beneficial effects on various metabolic parameters including insulin sensitivity and blood glucose levels. The more frequent the bouts are, the more beneficial the effect is. From an immune perspective, this will indirectly have beneficial effects on immune system by minimizing accumulation of excess nutrients in adipose tissue, and therefore the typical inflammation in obesity and its associated comorbidities. A combination of reducing sedentary time or at least minimizing it and increasing participation in moderate to vigorous exercise physical activity that results in cardiorespiratory fitness enhancement is the most beneficial strategy for enhancing cardiometabolic health, as highlighted by a recent 10 years prospective population study [145].

6. Conclusion

Many reports showed a dramatic decrease in PA levels during the current pandemic. This is particularly concerning in patients with pre-existing metabolic conditions, including T2D and its associated complications. These patients may be more vulnerable to the effects of PI both immunologically and metabolically. Moderate to vigorous physical exercise may counteract the latter effects and further prevent progression to severe COVID-19, if the virus is contracted. Simpler approaches, such as breaking up sedentary time, may optimize metabolic health and analogically immune health.

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