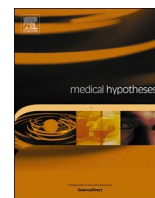




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The potential use of lactate blockers for the prevention of COVID-19 worst outcome, insights from exercise immunology

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ABSTRACT

Abbreviations: ALI, acute lung injury; AM, alveolar macrophages; Anti HSA antibody, anti-human serum albumin antibody; ARDS, acute respiratory distress syndrome; B cell, bursa-derived lymphocyte; CD, cluster of differentiation; COVID-19, coronavirus 19; CRP, C-reactive protein; DC, dendritic cells; cDCs, conventional dendritic cells; pDCs, plasmacytoid dendritic cells; ES, endostatin; FABP4, fatty acid binding protein 4; FCN-1, ficolin-1; FSC, forward scatter; HIV, human immunodeficiency virus; IL, interleukin; IT, immunotype; LPS, lipopolysacchride; M1, inflammatory macrophages; M2, wound-healing macrophages; NETs, neutrophil extracellular traps; NK cell, natural killer cell; OPN, osteopontin; PA, physical activity; PPAR γ , peroxisome proliferator-activated receptor gamma; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SPP1+, secreted phosphoprotein 1; Tcell, thymus-derived lymphocyte; Th cells, T helper cells; VO2 Max, maximum volume of oxygen.

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Following the decline in Physical Activity (PA) due to COVID-19 restrictions in the form of government mandated lockdowns and closures of public spaces, the modulatory effect of physical exercise on immunity is being heavily revisited. In an attempt to comprehend the wide discrepancy in patient response to COVID-19 and the factors that potentially modulate it, we summarize the findings relating PA to inflammation and immunity. A distinction is drawn between moderate intensity and high intensity physical exercise based on the high lactate production observed in the latter. We hypothesize that, the lactate production associated with high intensity anaerobic exercise is implicated in the modulation of several components of the innate and adaptive immunity. In this review, we also summarize these immunomodulatory effects of lactate. These include increasing serum IL-6 levels, the main mediator of cytokine storms, as well as affecting NK cells, Macrophages, Dendritic cells and cytotoxic T-lymphocytes. The implications of high lactate levels in athletic performance are highlighted where athletes should undergo endurance training to increase VO₂ max and minimize lactate production. Tumor models of hypoxia were also reported where lactate levels are elevated leading to increased invasiveness and angiogenesis. Accordingly, the novel lactate blocking strategy employed in cancer treatment is evaluated for its potential benefit in COVID-19 in addition to the readily available beta-blockers as an antagonist to lactate. Finally, we suggest the diagnostic/prognostic purpose of the elevated lactate levels that can be determined through sweat lactate testing. It is the detrimental effect of lactate on immunity and its presence in sweat that qualify it to be used as a potential non-invasive marker of poor COVID-19 outcome.

Background

The Coronavirus Disease 2019 (COVID-19) pandemic is the largest turning point of the century. To date, there are more than 37 million confirmed cases and 1 million deaths worldwide [1]. Clinical manifestations of COVID-19 are classified according to the severity of symptoms into: mild, moderate (80.9% of cases), severe (13.8% of cases), and critical (4.7% of cases). Critical cases could progress to extreme manifestations such as Acute Respiratory Distress Syndrome (ARDS), whereas 10 to 25% of hospitalized patients may require ventilation for several weeks [2,3]. Furthermore, critical cases may develop dire consequences due to clinical deterioration leading to complications such as, multiple organ affection including liver injury, cardiomyopathy, acute kidney failure, gastrointestinal, and central and peripheral nervous system affection [2,4]. The reasons behind the huge discrepancy in case presentation could be attributed to the variable immunity of different people rather than the viral load. This is reinforced by several studies highlighting the disparities in the severity of COVID amongst different factions such as race, age, obesity, and sex [5]. When it comes to disease severity, Mathew et al characterized the existence of two main immunotypes: Immunotype 1 (IT-1) related to severe disease, and Immunotype 2 (IT-2) related to the mild form. This was reinforced by our working group as they denoted a similar inflammatory state to that of immunotype 1 in severe COVID cases. This is also in agreement with Liao et al, as he successfully demonstrated pro-inflammatory macrophage subtypes, depleted dysfunctional resident T lymphocytes, and a cytokine storm in the lung milieu of severe COVID cases, as opposed to mild cases [6,7]. Switching the immune response from IT-1 to IT-2 appears to be an interesting strategy that can promise rapid improvement of cases, as well as, preventing the worst case scenario whilst building a life-long immunity against COVID-19.

-Strict public health measures implemented by various governments, whilst being a great preventive procedure, has unfortunately altered how people live their day-to-day lives and made maintaining physical activity (PA) rather challenging. In a study conducted by Meyer et al, it was found that the COVID-19-related restrictions such as social distancing, quarantine, work from home, etc. have led to a decline in the level of PA amongst previously active adults by 32.3%. Similar results were echoed in Shanghai adolescents [8,9]. Moreover, Italian undergraduates have shown a steep decline in their weekly walking time during the lockdown in Italy [10].

In this context, several studies have highlighted the role of moderate regular exercise in functional changes to the response of the immune system by enhancing the T cell response, increasing CD4+ T cell proliferation capacity, and augmenting T cell memory. Da Silveira review is one of best reports that have hypothesized the possible immunomodulatory role of exercise in COVID-19 cases [11]. It was published in July

2020 before the release of the mentioned series of Mathew et al series, which led to better characterization of the best immune response in the lung microenvironment of COVID19 patients, needed to improve COVID-19 outcome.

The classic cliché suggested by most of the reviews is a beneficial effect of regular moderate intensity exercise on various aspects of the immune system, whereas high intensity exercise seems to largely suppress the immune system. Hence, this classic model is an oversimplification of the actual cross-talk between muscles and inflammation [12] as the actual difference between regular moderate intensity exercise.

It is well established that the actual in-depth discrepancy between moderate intensity and high intensity exercise is the anaerobic contribution to each of them. While moderate intensity regular exercise relies mainly on aerobic energy production mediated by oxidative muscle fibers, high intensity uninterrupted exercise is mainly accounted for by glycolytic fibers operating under anaerobic conditions. This anaerobic energy production leads to an exponential increase in lactate levels; however, little is known about the relationship between lactate relationship to inflammation and immunity [13].

Lactate threshold is defined as the point of exercise at which the level of lactate produced by muscles rises exponentially and exceeds the capacity of the body to clear it. Hence, it becomes the defining threshold between useful and harmful inflammation. Evidence suggests that lactate release by muscles during exercise stimulates IL-6 release by lactate dependent proteases. Hojman and associates identified a linear relationship between lactate and IL-6 levels during exercise. Immunohistochemical analyses showed that intramuscular lactate and hyaluronidase injections led to release of IL-6-containing intra-myocellular vesicles. They identified a pool of IL-6 located within vesicles of skeletal muscle fibers, which could be readily secreted upon protease activity. This protease-dependent release of IL-6 was initiated by lactate production [14]. Additional evidence about the relationship between lactate and baseline levels of IL-6, are shown in the study of FitzGerald and colleagues as they demonstrated the direct relationship between physical activity levels and systemic levels of Lactate and IL-6. Regular physical activity has been shown to decrease muscle stores of IL-6, probably due to predominance of oxidative fibers, which have lower levels of IL-6 transcription compared to glycolytic fibers [15].

The current evidence that suggests a mechanistic and pathogenic connection between lactate levels and their influence on immunity and COVID19 disease is as follows:

- **NK cells:** A recent study revealed that in COVID19 patients with moderate or severe disease, NK levels were severely reduced but strongly activated when compared with controls [16]. Additionally, there was a predominance of the NKdim phenotype compared to the

NKbright phenotype. NK dim cells have a pro-inflammatory and cytotoxic role that is counterbalanced by the NK bright cells. Evidence suggests a differential mobilization of NK cell subsets in response to **aerobic** exercise (associated with low lactate levels); however, during the post-exercise recovery period (up to 1 h), the ratio of CD56 (bright): CD56 (dim) cells favors the CD56 (bright) subset [17]. Tumor models also showed that lactic acidosis suppressed the production of IFN γ by NK cells, and upon reversal of tumor bed acidosis there was improved NK cell activity and regression of tumor cells [18,19].

- **Dendritic cells (DC):** There are two major human DC subsets described: conventional DCs (cDCs), generally considered immunogenic, and plasmacytoid DCs (pDCs), which can exhibit regulatory functions. Immune profiling of the lung milieu in severe vs. mild COVID-19 patients succeeded to demonstrate that CD1c+ conventional dendritic cells preferentially migrate from blood to lungs in patients with severe COVID-19, whereas CD123hi plasmacytoid dendritic cells were depleted from blood, and almost absent in the lungs in patients with severe infection [20]. Brown and colleagues, showed that **aerobic** exercise induces opposite changes in the differential distribution of DCs to that observed in severe COVID-19, where aerobic exercise induced peripheral mobilization of pDC's into the blood stream and relative reduction of cDC's [21]. The decreased mobility of DC's into the blood stream is due to the accumulation of lactate [22].
- **Macrophage phenotype switching:** Different stimuli can trigger phenotypic changes in macrophages through a process termed Polarization into either inflammatory macrophages (M1) or wound-healing macrophages (M2). M1 macrophages are characterized by the expression of high levels of pro-inflammatory cytokines, strong microbicidal and tumoricidal action, high production of reactive nitrogen and oxygen species, and promotion of the Th1 response. On the other hand, M2 macrophages are involved in parasite clearance, tissue remodeling, and inflammatory resolution, but they facilitate tumor development and suppress effector T cells [21]. In the lung milieu in severe COVID-19 patients showed macrophages that shared predominant features of M1 macrophages with high Forward Scatter (FSC) [5]. Mild to moderate aerobic exercises are found to be effective in macrophage phenotypic switching from M1 state to M2 state, which causes an improvement in the inflammatory status due to a decrease in lipopolysaccharide caused by exercise [23]. Strength exercises increase M2 and decrease M1 expression, whilst aerobic exercises up-regulate M2 and down-regulate M1 markers [24].
- **Cytotoxic T cell responses**
 - a) **Resident T cell proliferation:** severe COVID-19 cases showed a proliferation of resident T cells in the lung environment, constituting the major proportion of the T cell population as opposed to CD8+ effector cells in mild cases. This is the result of an interplay between pulmonary alveolar macrophages and Resident CD-8 cells [25]. Neutrophil extracellular traps (NETs) play an important role in Lipopolysaccharide (LPS)-induced Acute Lung Injury (ALI), and a positive correlation exists between NET formation and proinflammatory macrophage polarization [26]. Beiter et al demonstrated that aerobic exercise succeeded in reduction of NET mediated ALI. This suggests a possible role of exercise in preventing deleterious resident T cell proliferation observed in severe COVID-19 patients [27,28].
 - b) **T cell effector function and mobility inhibited by Lactate accumulation**

Increase of lactate levels during glycolysis is found to play a significant role in modulating T- cell effector function in inflammatory states, where it was found to promote a stop- migration signal. Moreover, sodium-lactate stimulates CD4+ T-cells to produce higher amounts of pro inflammatory cytokine IL-7, but not IFN- γ , and to help down-regulate glycolytic enzymes such. On

the other hand, lactic acid inhibits CD8+ T-cell mediated killing. According to Pucino et al, lactic acid should be considered as a pro-inflammatory mediator secreted by tumor cells and it can activate the IL-23/IL-17 pro-inflammatory pathway; which is regarded as an important deleterious pathway in the context of COVID-19 infection [27].

Hypothesis

Lactate levels are closely intertwined with serum Interleukin (IL)-6 levels. Furthermore, lactate levels during different types of exercises affect the immune response differentially, whereby high lactate is associated with adverse effects of COVID-19. Therefore, we hypothesize the following:

- a. The need to tailor exercise intensity prescription according to readiness of athletes to protect them from worst outcomes of COVID-19
- b. Sweat Lactate testing can be used to assess the severity in COVID-19 patients.
- c. Lactate blockers can be used to treat COVID-19 patients

Evaluation of the suggested hypotheses and their implications

Hypothesis 1: tailoring athletes' training according to lactate threshold in amidst COVID-19

Evaluation of hypothesis 1

Exercise prescription commonly refers to the specific plan of fitness-related activities that are designed for a specified purpose. Exercise prescription has gained over the previous years, special interest in the context of cancer patients and cancer survivors. This interest has been attributed to the effects of aerobic exercise (with minimal elevation of lactate) in improving the overall immune response thus improving immune surveillance to different types of tumors. In general exercise prescription in cancer patients involved 150 min of moderate or 75 min of intermitted high intensity exercise or an equivalent combination. The reason behind this prescription is to minimize the lactate peak and to raise lactate threshold in such patients. The need for individualized exercise prescription is highlighted by studies that specifically identify individuals that do not systematically improve exercise capacity, even though the training intervention was well structured. It is increasingly recognized; currently that measuring lactate threshold is mandatory to tailor such exercise prescriptions.

Understanding the unwanted systemic effects of anaerobic exercise has urged scientists to develop the concept of endurance training to protect athletes performing high intensity exercise from its subsequent anaerobic nature. Endurance/resistance training is the act of exercising to increase endurance. The term endurance training generally refers to training the aerobic system as opposed to the anaerobic system. It has been observed that highly trained athletes perform high intensity exercise at a high percentage of their VO₂max with minimum lactate accumulation. Salamat and colleagues have concluded that 10 weeks of endurance training with moderate to high intensity has led to: (1) reduced systemic inflammatory environment and (2) prevented excessive increase in IL-6 levels. It has also been shown that high intensity interval training can delay this anaerobic transition, minimizing the exponential increase of lactate and pro-inflammatory cytokines such as IL-6 [29].

Implications of hypothesis 1

We can therefore conclude from cancer patients' model the following implications in athletes amidst COVID-19:

- It is important to assess the readiness of athletes, in COVID-19 era, to high intensity exercise by screening their lactate threshold. This can

be achieved by the classic serum sampling during exercise testing, or alternatively by wearable systems measuring lactate through sweat.

- Taking short breaks (intervals) during high intensity exercise (especially in athletes who did not go through endurance training) will minimize the deleterious inflammatory effects of anaerobic metabolism that usually happens during exercise.

Hypothesis 2: Sweat lactate a mirror of serum Lactate, and a good predictor of COVID-19 severity

Evaluation: sweat lactate a non-invasive reflection of serum lactate

Lactate is also retrievable from sweat and can be tested through special devices. This might allow minimal contact and minimal mobility of infected patients if such devices are made readily available, giving them a superiority over serum markers [30].

Several serum markers have been proposed to stratify cases infected with COVID-19, starting from inexpensive CRP, Ferritin, and D-Dimer to the very expensive serum IL-6 [31–33]. Risk stratification is of utmost importance to reduce the pressure on healthcare facilities and to classify patients at highest need for hospital admission.

Implications of sweat lactate use in COVID-19

Given the previous data, and the important relationship between Lactate threshold and IL-6 threshold, we can suggest that the higher the lactate threshold the less is the risk of infected COVID-19 patients to develop the so-called Cytokine Storm [29,34].

Serum lactate levels have been proposed as prognostic indices in acute respiratory distress in Influenza. Miller and colleagues succeeded in demonstrating that baseline serum lactate can predict the in-hospital mortality rate for influenza [35].

Hypothesis 3: decreased lactated levels can improve COVID-19

Through lactate blockers

1. *Evaluation of effect of lactate blockade on improving inflammation in tumor model*

The acidic tumor microenvironment due to an induced hypoxic state will trigger the tumor cells to release an abundant amount of lactic acid. The oversupply of lactic acid will further decrease the pH, and this will endorse the adverse cancer properties ranging from defective angiogenesis to metastasis [36].

The aggravation of cancer destructive effects has strongly provoked researchers to work on lactate blockade as a curative agent to impede tumor progression. Various small molecules have showed assuring anticancer activity in-vitro and in-vivo, whether as a solo agent or combined with other therapeutic approaches [37].

Hindrance of glycolytic activity showed a powerful effect against cancer cells with mitochondrial deformities or under a hypoxic state, the latter cells are known to be associated with cellular resistance to traditional anti-cancer medications and radiation therapy. These glycolytic inhibitors exhibit a promising therapeutic approach. A recent study has demonstrated the anti-glycolytic action of 3-bromopyruvate on rat mammary tumor cells or dichloroacetate as inhibitors of cancer-cell-specific aerobic glycolysis. The cautious adjustment of the therapeutic doses of these anti-cancer inhibitors is crucial as normal cells also rely on aerobic glycolysis while obtaining their energy from it [38].

Alternative proposals on interrupting the generation of lactic acid production are also under experimentation. Three main versions of pH regulators have been established: 1) bicarbonate transporter family, 2) the sodium-proton exchanger family, and the 3) monocarboxylate transporter family (MCT). Histone acetylation has been recognized as a method in adjusting intercellular pH. The more acidic the condition gets, the more histones are deacetylated by histone deacetylases, and the released acetone anions are co-exported with protons out of the cell by

MCTs, restraining additional pH reduction [39].

2. *Evaluation of effect of lactate blockade on improving inflammation and progression of infarction*

In case of brain ischemia, the process of anaerobic glycolysis results in lactic acid production and accumulation promoting an acidic environment, which allows an increase in the size of the infarct. This is achieved by the lactic acidosis stimulating severe oxidative injury and apoptosis causing neurons dysfunction or astrocytes loss due to hypoxia. Furthermore, neuronal damage is exacerbated by the release of TNF-alpha, IL-6 and IL-1 beta, stimulated by lactate [40].

As lactic acid executes these mechanisms through G protein-coupled receptor 81 (GPR81), several clinical trials were conducted to develop GPR81 inhibitors. To illustrate, Shen et al demonstrated that neuronal cell death in ischemic stroke can be diminished by inhibiting putative GPR81. In this context, similar therapeutic strategy can be used to attenuate the devastating effect of lactate in severe COVID19 infection [41].

3. *Implications of lactate blockers in COVID-19*

To conclude, all of the previously mentioned approaches are considered promising therapeutic targets in preventing acute lung injury and in combating the fatal deteriorations of COVID-19 manifestations [39].

Beta blockers: a potential therapeutic target through lactate reduction

To date, there is no single study exploring the effect of beta-blockers on the rate of complications and mortality from COVID-19. But several articles have suggested that beta-blockers can exert several effects that can decrease the likelihood of complications. One of the theories suggested is that beta-blockers can cause a knockout of ACE2 receptors, thus blocking the cellular entry of SARS-CoV-2. Another hypothesis is the effect of beta-blockers on cytokines' release [42]. The role of beta blockers' use in patients with severe systemic inflammatory syndrome has been explored in large systematic reviews, Chacko and associates have shown a beneficial effect of beta blockers' use in septic shock, chronic beta blockers' use has also been shown to reduce baseline lactate levels. Given the body of evidences presented above, this might signify that an additional benefit of beta blockers in the setting of COVID-19 might be exerted by its interplay with lactate metabolism [42].

Conclusions and summary of implications

It has been increasingly recognized that the key to understanding the severity of COVID manifestations underlies in the body's immune mechanism, rather than direct viral load. Numerous studies have therefore strived to outline the possible patient characteristics that can modulate the immune response to a more favorable one, of which exercise has proven to be a strong contender. In particular, lactate levels have proven to be intertwined not only with serum IL-6 levels, implicated in the cytokine storm responsible for severe multisystem COVID-19 manifestations but also with various other aspects of the innate and specific immunity.

Lactic acid should be considered as pro-inflammatory, where its exponential increase seen in uninterrupted high-intensity exercise stimulates the protease-dependent release of IL-6 and activates the IL-23/IL-17 pro-inflammatory pathway. Lactic acidosis further inhibits CD8+ T-cell-mediated killing. Regular physical activity, on the other hand, has been shown to have an antithetical anti-inflammatory impact through decreasing muscle stores of IL-6, mediating macrophage phenotypic switching from an inflammatory M1 to a wound-healing M2 state, reducing neutrophils extraction trap mediated acute lung injury and favoring CD56 (bright) natural killer cells for up to 1 h following

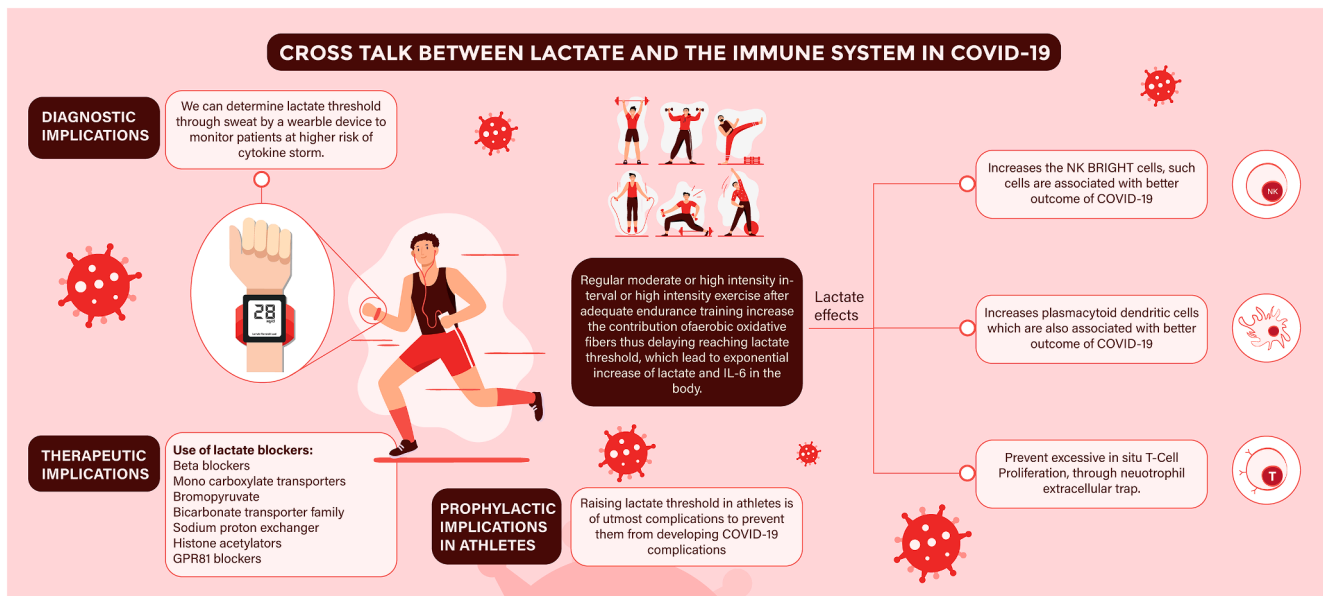


Fig. 1. Cross talk between Lactate and immune system in COVID-19. Abbreviations: COVID: Coronavirus disease, NK: Natural killer cells,

exercise. This veers away from the detrimental components of the immune system seen in COVID patients.

– Implication of hypothesis 1

In light of the previous data, and the vital relationship surmised from it between the lactate threshold and IL-6 threshold, we cannot warrant the significance of exercise alone in the efficacy of our immune system, but that regular endurance training and high-intensity interval training, in particular, are sure propellers of a reduced systemic inflammatory environment as a whole. This is achieved by delaying anaerobic transition thus minimizing the exponential increase of lactate and preventing an excessive increase in pro-inflammatory cytokines such as IL-6.

– Implication of hypothesis 2

Given the above, it is therefore vital to screen the lactate threshold, either by the classic serum sampling or through their sweat by using wearable systems, and could further lend itself as a non-invasive predictor of the likelihood of complications in COVID-19 patients in lieu of the more expensive IL-6.

– Implication of hypothesis 3:

This knowledge opens the door for new potential treatment modalities in COVID-19 management strategies by targeting lactic acid production as demonstrated in recent anti-cancer drugs on trial such as glycolytic inhibitors, pH regulators, histone acetylation, as well as the potential application of GPR18 inhibitors currently under clinical trials for the management of ischemic stroke. Finally yet importantly, beta blockers are readily available antagonists of lactate metabolism that may serve as potential prophylactic tools for complications of COVID-19.

Fig. 1 summarizes the previously discussed mechanisms and their implications.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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