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Exercise as medicine for COVID-19: On PPAR with emerging pharmacotherapy

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ABSTRACT

Coronavirus disease 2019 (COVID-19) may have a metabolic origin given strong links with risk factors such as lipids and glucose and co-morbidities such as obesity and type 2 diabetes mellitus. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein mediates viral cellular entry via the ACE2 receptor. The cytoplasmic tail of this spike protein is heavily palmitoylated. Emerging studies suggest that SARS-CoV-2 alters lipid metabolism in the lung epithelial cells by modulating peroxisome proliferator-activated receptor alpha (PPARα), possibly contributing to lipotoxicity, inflammation and untoward respiratory effects. Disruption of this process may affect palmitoylation of SARS-CoV spike protein and thus infectivity and viral assembly. COVID-19 is also increasingly being recognized as a vascular disease, with several studies noting prominent systemic endothelial dysfunction. The pathogenesis of endothelial dysfunction may also be linked to COVID-19-mediated metabolic and inflammatory effects. Herein, exercise will be compared to fenofibrate as a possible therapeutic strategy to bolster resilience against (and help manage recovery from) COVID-19. This paper will explore the hypothesis that exercise may be a useful adjuvant in a setting of COVID-19 management/rehabilitation due to its effects on PPARα and vascular endothelial function.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) currently shows no sign of disappearing on its own. Globally, Coronavirus disease 2019 (COVID-19) cases have surpassed 21 million, contributing to over 775,000 deaths. In the United States, the CDC projects that COVID-19 will be a top 10 leading cause of death for the year 2020. While we all eagerly await the development of a vaccine, scientists and clinicians have begun exploring “off-label” use of various drugs with that hope that strategic repurposing may help manage and treat COVID-19 [1]. Fenofibrate (a peroxisome proliferator-activated receptor alpha agonist) is one such medication that holds promise given its favorable effects on inflammation and endothelial function [1]. Herein, exercise will be compared to fenofibrate as a possible therapeutic strategy to bolster resilience against (and help manage recovery from) COVID-19. This paper will explore the hypothesis that exercise may be a useful adjuvant in a setting of COVID-19 management/rehabilitation due to its effects on PPARα and vascular endothelial function.

COVID-19 progression has been suggested to have a metabolic origin given that elevated glucose and lipid levels are risk factors. The SARS-CoV-2 spike protein mediates viral cellular entry via the ACE2 receptor (please see our previous paper on the possible role of exercise as a mediator of ACE2) [2]. The cytoplasmic tail of this spike protein is heavily palmitoylated (i.e. a 16 carbon fatty acid chain is added to palmitate), a common post-translational modification that increases the hydrophobic nature of a protein [3]. Emerging studies suggest that SARS-CoV-2 alters lipid metabolism in the lung epithelial cells by modulating PPARα, possibly contributing to lipotoxicity and untoward respiratory effects [4]. PPARα belongs to the nuclear receptor (NR) family and is considered a key transcriptional factor that regulates lipid metabolism. PPARα is constitutively expressed in the lung. Not surprisingly, alveolar epithelial cells have been shown to conduct fatty acid oxidation, a function that serves a critical role in maintaining optimal lung function [5]. Disruption of this process may affect palmitoylation of SARS-CoV spike protein and thus infectivity and viral assembly [3,4]. In response to pulmonary inflammation induced by lipopolysaccharide (LPS) or TNFα, PPARα mRNA in the lung can be reduced by 50–60% [6]. Subsequently, there may be substantial impairment of fatty acid oxidation in alveolar epithelial cells contributing

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to diminished bioenergetics, epithelial cell apoptosis and acute lung injury [5]. Moreover, PPARα-deficient mice have an exaggerated pulmonary inflammatory response to LPS-induced inflammation [7]. Thus reductions in PPARα from COVID-19 may be an important effector of pulmonary inflammation and mechanistically involved in the pathogenesis of acute lung injury [5].

Alveolar epithelial cells are not the only cell line important for gas exchange and pulmonary inflammatory status. Pulmonary microvascular endothelial cells also play a role in maintaining homeostasis. In its quiescent state, the endothelium is anti-inflammatory and antithrombotic. Emerging studies suggest that COVID-19 may be a vascular disease, causing systemic endothelial activation and dysfunction [8]. Patients presenting with COVID-19 demonstrate elevated levels of von Willebrand Factor and P-selectin with levels of thrombomodulin correlating with mortality [8]. Endothelial cells express ACE2 receptors. SARS-CoV-2 may cause endothelial cell infection, endotheliallitis (i.e. inflammation of the endothelium), apoptosis/pyroptosis and ultimately microvascular dysfunction [9]. Unlike influenza, patients who die from COVID-19 associated respiratory failure present with a distinct vascular phenotype. Histologic analysis of pulmonary microvessels reveal diffuse endothelial injury and disrupted endothelial cell membranes [10]. Thus, endotheliopathy may be a consequence of and contributor to the pathogenesis of COVID-19 [8,11]. Like alveolar epithelial cells, pulmonary endothelial cells express PPARα [12] and conduct fatty acid oxidation which parenthetically is required for endothelial cell proliferation [13]. Indeed, PPARα is considered an endogenous regulator of endothelial colony-forming cells and circulating endothelial progenitor cell fate [14]. Disruption of this process in the endothelial cell (as described above) likely leads to inflammation and cytokine production (i.e. cytokine storm syndrome), reduction of nitric oxide and impaired vascular reactivity. Alterations in pulmonary vascular reactivity may affect gas exchange (i.e. alveolar-capillary barrier disruption) and be partially responsible for ventilation-perfusion mismatches and hypoxemia seen with COVID-19 [11].

As alluded to previously, PPARα-activation has anti-inflammatory effects mainly achieved via transrepression, a process whereby pro-inflammatory genes are downregulated. As such, use of the PPARα agonists may serve a useful therapeutic role by helping to reverse the inflammatory and metabolic changes induces by SARS-CoV-2. A recent study by Ehrlich et al found that the PPARα agonist fenofibrate prevented phospholipid accumulation within SARS-CoV-2 infected cells, blocking viral replication [4] Authors concluded that disrupting the SARS-CoV-2 lifecycle with fenofibrate could prove an effective therapeutic target in the ongoing battle against COVID-19. Fenofibrate has been shown to suppress the downregulation of PPARα activation caused by inflammation, attenuate cytokine production triggered by LPS or TNFα [6,7], and improve fatty acid oxidation, preventing acute lung injury [5]. Indeed, Fenofibrate itself has anti-inflammatory properties [15]. Fenofibrate may also have a favorable effect on vascular endothelial function. Fibrates inhibit endothelin-1 production and increase nitric oxide production [16]. Specifically, fenofibrate has been shown to suppress microvascular inflammation and apoptosis through inhibition of nuclear factor-κB and activation of adenosine monophosphate (AMP)-activated protein kinase leading to endothelial nitric oxide synthase phosphorylation and NO production [17–21]. It is interesting to note that although AMPK is not a canonical NR co-regulator, it interacts with NRs and is highly involved in their regulation of energy metabolism. Fenofibrate may also increase tetrahydrobiopterin levels (BH_4), an essential cofactor for eNOS and ultimately NO production [22,23]. With increases in NO bioavailability, comes improved vascular reactivity in vivo [24,25]. Although studies examining changes in endothelial function with fenofibrate in humans have been relegated to the brachial artery, changes in brachial endothelial-dependent flow-mediated dilation correlate with changes in coronary [26] and pulmonary vascular endothelial reactivity [27], suggesting the fenofibrate may have favorable systemic endothelial effects, particularly in vascular beds impacted by COVID-19 [28–31].

As can be seen, Fenofibrate holds promise as a therapeutic agent to mitigate the detrimental cardio-pulmonary damage associated with COVID-19. And with this revelation comes an important hypothesis generating question. What else can be done to possibly disrupt SARS-CoV-2 mediated lipid metabolism derangement and inflammation? In one word – *exercise*.

Much of the research to date on PPARs and exercise has focused on modulation of other isoforms (namely PPARγ but also PPARδ/β) or key co-regulator/co-activators (e.g. peroxisome proliferator-activated receptor γ 1α, PGC-1α) in skeletal muscle. PPARα is expressed in cardiac myocytes, hepatocytes, enterocytes, lymphocytes, monocytes, adipocytes, smooth muscle cells, and as alluded to previously endothelial cells and epithelial cells. As such, PPARα plays an important role for systemic metabolic processes (heart, kidney, central nervous system, bone, intestines, pancreas, liver, lung). While PPARγ is responsible for synthesis and storage (adipogenesis and lipid synthesis), PPARα is involved with catabolism and oxidation. Along these lines, Iemitsu et al. demonstrated that exercise training was able to improve the age-associated decrease in PPARα mRNA and protein expression in the heart while also enhancing PPARα DNA binding to PPRE (response element). In turn, there were commensurate and favorable changes in PPARα target genes related to fatty acid metabolism (β-oxidation) such as carnitine palmitoyl transferase-I (CAT) and acyl-CoA synthase, 3-hydroxyacyl CoA dehydrogenase (HAD). Similarly, Zhang et al. reported that exercise training increased PPARα mRNA expression in liver with subsequent favorable changes in target genes related to fatty acid metabolism including carnitine palmitoyl transferase 1 (CPT-1), catalase (CAT) and ATP binding cassette transporter A1 (ABCA1). Horowitz et al. studied the effect of 12 weeks of endurance exercise training on PPARα skeletal muscle protein content in the vastus lateralis of young women [32]. Results revealed that exercise training doubled levels of muscle PPARα as well as PPARα target proteins (medium-chain and very long chain acyl-CoA dehydrogenase). Schmitt et al. examined PPARα mRNA expression in the tibialis anterior of habitually endurance exercise trained and untrained young men [33]. There was a trend ($p = 0.1$) for PPARα mRNA concentration to be higher in exercise trained compared to sedentary muscle. There were strong correlations noted between PPARα mRNA concentration and the expression of other genes involved in oxidative metabolism (hormone sensitive lipase, fatty acid binding protein and cytochrome *c* oxidase I). Taken together there is a limited but provocative literature supporting a role for exercise as a modulator of PPARα in various organs/tissues.

Exercise is also well established to have ubiquitous effects on systemic endothelial function [34,35] and inflammation [36]. For an excellent review on the anti-inflammatory effects of exercise as they relate to immunovigilance against COVID-19, please see da Silveira et al. [37]. Regular/habitual exercise increases eNOS expression/activation and BH_4 bioactivity while reducing expression and/or activity of ET-1, nuclear factor-κB, and NADHP oxidase resulting in increased NO bioavailability and increased vascular reactivity [38,39]. Exercise also increases the number of circulating endothelial progenitor cells, suggesting a milieu that favors regeneration and re-endothelialization of injured endothelium [40]. Such an environment would prove valuable in a setting of COVID-19 mediated endothelial apoptosis and endothelial cell membrane disruption. Interestingly, PPARs may be required for exercise to attenuate endothelial dysfunction [41]. Research will be needed to explicitly explore PPARα as a mediator of exercise-induced improvements in endothelial function in specific vascular beds including the pulmonary circuit.

Although studies have yet to explore the effect of exercise on PPARα in the lung, it is reasonable to speculate that mechanisms responsible for transcriptional changes in the heart and skeletal muscle would be similar in the lung. That is, the lung as a target organ is essential for mounting an optimal exercise response and delivering oxygen rich blood to the working skeletal muscle (i.e. cardio-respiratory fitness).

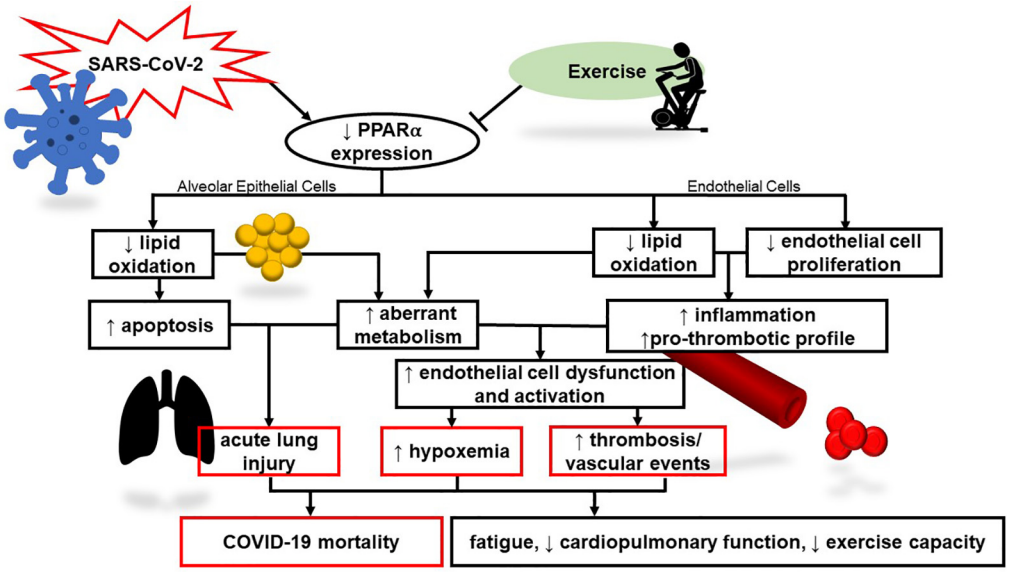

Fig. 1. Theoretical model linking SARS-CoV-2 to COVID-19-mediated morbidity and mortality via PPARα. Viral infection may alter lipid metabolism and endothelial function contributing to inflammation and untoward systemic consequences. Exercise may have a favorable effect PPARα and is known to be anti-inflammatory and improve endothelial function.

The classic Karlman Wasserman "gear wheel model" describes the integrated exercise response as linking mitochondria, skeletal muscle, heart-blood (circulatory system) and lungs as inter-connected cogs. Increases in mechanical and metabolic factors that govern changes in PPARα in the heart and skeletal muscle may spill over to the respiratory system to ensure a concerted effort to match metabolic demand with cardio-respiratory supply. That habitual exercise training can modulate PPARα in the lung remains, at this time, a hypothesis. Conversely, there may be some redundancy between PPARα and PPARδ/β such that PPARδ/β can compensate for reductions PPARα and this may be target organ specific and differentially affected by exercise [42]. Empirical data will be needed to support (or refute) our hypothesis. Given the known effect of COVID-19 on the heart as an incendiary for cardiac damage [43,44], aforementioned findings of changes in cardiac PPARα with exercise training may still have important implications for overall cardiovascular function and cardiovascular disease risk [45].

As alluded to previously, the cytokine storm associated with COVID-19 may lead to reductions in PPARα. These reductions may have important implications for exercise capacity. Emerging studies suggest a role for PPARα in glucose and amino acid metabolism [46]. Genes involved in gluconeogenesis have been identified as targets of PPARα and these include phosphoenolpyruvate carboxykinase (Pck1), pyruvate carboxylase (Pcx), and lactate dehydrogenase A [42]. PPARα-knock out mice exhibit hypoglycemia and lower serum lactate levels, suggesting increased reliance on anaerobic metabolic pathways to generate gluconeogenic precursors [42]. Synthesis of glycogen is also affected in PPARα-knock out mice. Not surprisingly, these PPARα knock out mice demonstrate very low aerobic exercise tolerance compared to wild-type mice [42]. It is interesting to note that survivors of SARS and MERS present with reduced exercise capacity [47]. PPARα-knock out mice also gain more weight and adipose mass compared to wild-type animals, thus reductions in PPARα α- also have implications for obesity [48]. In PPARα-knock out mice chronically fed a high-fat diet, expression of inflammatory genes in adipose tissue is more pronounced compared to wild-type mice [49]. Parenthetically, an anti-obesity role for PPARα is supported by studies in which obese rodents were administered synthetic PPARα agonists such as fenofibrate and demonstrated marked weight loss [50]. Overall, reductions in PPARα from COVID-19 may cause a downward spiral whereby altered metabolism and inflammation contributes to diminished exercise capacity, which further begets unfavorable changes in metabolism and inflammation [51]. Changes in PPARα from COVID-19 may prime the body for fatigue, inactivity and obesity. Exercise and increases in cardiorespiratory fitness may thus be needed for secondary prevention to mitigate the possibility of further disuse, chronic disease and disability [52].

Studies are beginning to emerge suggesting that COVID-19 survivors may have reduced cardiopulmonary function, with even non-hospitalized patients presenting with notable dysfunction [53,54]. Cardiopulmonary rehabilitation may be needed to help individuals regain functional quality of life [55]. Thus, exercise may be a useful adjuvant for the management and treatment of COVID-19 survivors. Compared to emerging drugs that are being repurposed for the possible treatment of COVID-19 and its related cardiopulmonary and metabolic sequela, exercise may be on PPAR.

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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Appendix A. Supplementary data

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