

Exercise as a Moderator of Persistent Neuroendocrine Symptoms of COVID-19

Candida J. Rebello¹, Christopher L. Axelrod¹, Charles F. Reynolds, III², Frank L. Greenway¹, and John P. Kirwan¹

¹Pennington Biomedical Research Center, Baton Rouge, LA; and ²University of Pittsburgh School of Medicine, Pittsburgh, PA

REBELLO, C.J., C.L. AXELROD, C.F. REYNOLDS, F.L. GREENWAY, and J.P. KIRWAN. Exercise as a moderator of persistent neuroendocrine symptoms of covid-19. *Exerc. Sport Sci. Rev.*, Vol. 50, No. 2, pp. 65–72, 2022. *Precipitated by chronic psychological stress, immune system dysregulation, and a hyperinflammatory state, the sequelae of postacute COVID-19 (long COVID) include depression and new-onset diabetes. We hypothesize that exercise counters the neuropsychiatric and endocrine sequelae of long COVID by inducing the release of circulating factors that mediate the anti-inflammatory response, support brain homeostasis, and increase insulin sensitivity.* **Key Words:** exercise, COVID-19, psychological stress, immune dysregulation, hyperinflammation

KEY POINTS

- Postacute COVID-19 hyperglycemia likely results from lingering inflammation or chronic psychological stress that is compounded by β -cell dysfunction.
- Chronic psychological stress produces a dysregulated and overactive hypothalamic-pituitary-adrenal axis that drives sympathetic nervous system activation and an exaggerated immune response, which promotes insulin resistance and β -cell dysfunction.
- High local concentrations of interleukin-1 β (IL-1 β) in the β -cell microenvironment inhibit insulin secretion, trigger β -cell dysfunction and apoptosis, increase levels of glucose, and prompt IL-1 β autostimulation.
- Regular exercise plays a key role in protecting against psychologic and metabolic aspects of stress to alleviate insulin resistance and symptoms of depression.
- We hypothesize that exercise will attenuate β -cell dysfunction and the long-term neuroendocrine effects of COVID-19 by moderating the inflammatory response, supporting brain homeostasis, and promoting insulin sensitivity.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the pathogen that causes coronavirus disease 2019 (COVID-19) and has contributed to millions of deaths globally. In some

cases, persistent symptoms and development of sequelae occur 4 to 12 wk after onset of acute COVID-19 symptoms (long COVID) (1). The antibody response is consistent with durable immunity against secondary COVID-19 disease (2). Nevertheless, SARS-CoV-2 mRNA and protein are active in the small intestinal epithelium of some individuals nearly 6 months after a COVID-19 diagnosis (3).

The underlying pathophysiology of COVID-19 is multifaceted, and the components seem inextricably linked. The variability of the clinical disease trajectories in patients with COVID-19 is marked by disparities that outweigh commonalities (1). Therefore, understanding the cellular mechanisms and critically evaluating convergence among observations become necessary to arrive at an informed strategy for managing the risk of long COVID and preventing its escalation.

SARS-CoV-2 bind to the ACE2 receptor expressed on pancreatic β cells and induce cell damage that can worsen pre-existing diabetes or precipitate the onset of diabetes (4,5). Diabetic ketoacidosis typically observed in type 1 diabetes, which is an autoimmune condition, occurs in patients without a preexisting diabetes diagnosis weeks to months after resolution of COVID-19. Cytokines such as interleukin-6 (IL-6) and tumor necrosis factor α (TNF- α) are elevated in patients with severe COVID-19 (1).

Physical inactivity is associated with an increased risk for development of type 2 diabetes and more severe outcomes from COVID-19. The odds that a physically inactive person will encounter severe COVID-19 outcomes exceed that of most chronic diseases (6). We hypothesize that exercise promotes the release of circulating mediators that are central to attenuation of the long-term neuroendocrine symptoms of COVID-19 (Fig. 1). In this review, we present biological insights into maladaptive stress patterns that predispose individuals to clinical depression and glucose dysregulation characteristic of type 2 diabetes. We evaluate the evidence to support our testable

Address for correspondence: John P. Kirwan, Ph.D., Integrative Physiology and Molecular Medicine Laboratory, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808 (E-mail: John.Kirwan@pbrc.edu).

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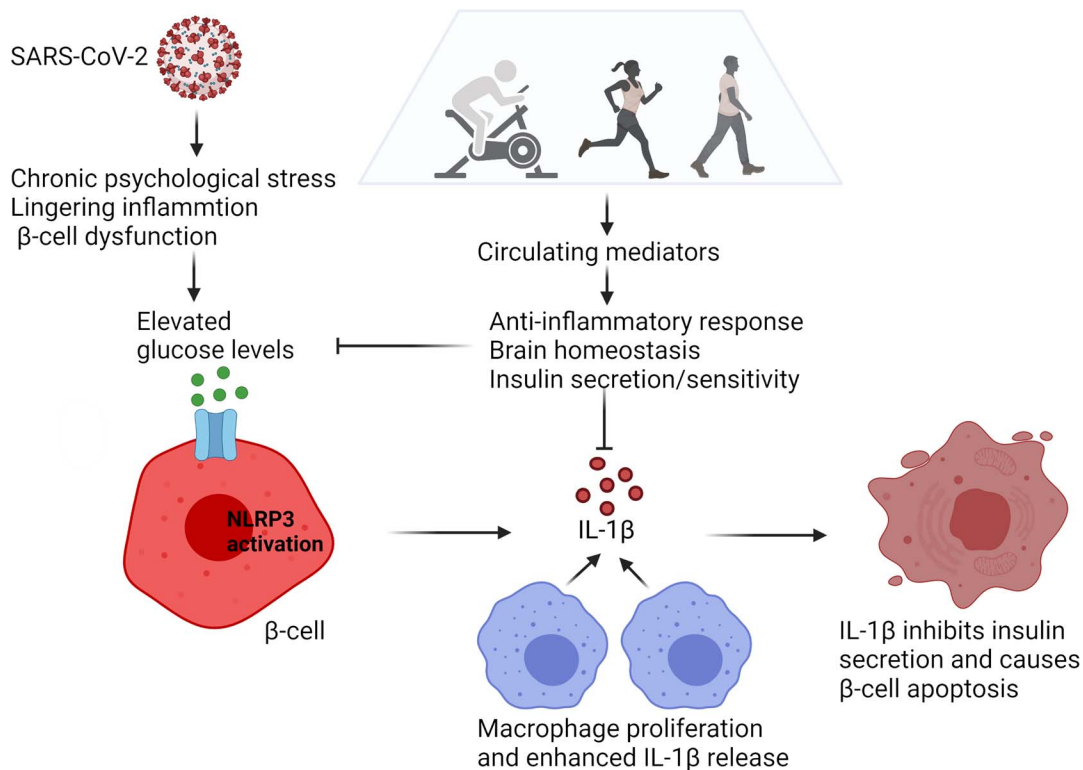


Figure 1. The development of hyperglycemia arising from disruption of immune metabolic homeostasis in COVID-19. High glucose levels induced by psychological stress, lingering inflammation, and β-cell dysfunction can lead to activation of the NLRP3 inflammasome in pancreatic β cells. As a result, pro-IL-1β is processed to the biologically active IL-1β. IL-1β released from β cells causes the recruitment and activation of macrophages, which prompts the release of more IL-1β. High local concentrations of IL-1β in the β-cell microenvironment may inhibit insulin secretion and trigger β-cell dysfunction and apoptosis. This leads to further increases in levels of glucose, thereby causing IL-1β autostimulation and establishing a vicious cycle. Exercise induces the release of circulating factors that mediate the anti-inflammatory response, support brain homeostasis, and increase insulin sensitivity. The net effect is the lowering of glucose levels and could be envisioned as a remission-induction therapy to counter the sequelae of COVID-19 (graphics program: Biorender). IL-1β, Interleukin-1β; NLRP3, NOD-, LRR-, and pyrin domain-containing protein 3.

hypothesis that exercise can prevent or mitigate the long-term sequelae of COVID-19.

NEUROPATHOLOGY OF COVID-19

Approximately 30%–40% of patients present with clinically significant anxiety and depression after a COVID-19 infection consistent with previous severe coronavirus infections (1). The probability of a new psychiatric illness such as anxiety and mood disorders within 90 d of a COVID-19 diagnosis was a striking 5.8% in an analysis of 62,354 patients (7). Autopsy results show that COVID-19 produces several types of pathological lesions that may contribute to neurological manifestations in patients with COVID-19. Para-infectious conditions, such as postviral autoimmune disorders, have been described in association with a variety of viruses, including coronaviruses. Para-infectious neuropathological processes typically present after a latent period following an infectious disease (8). A rapidly evolving area with converging evidence suggests that COVID-19 may induce autoimmunity in predisposed individuals (9). Whether the autoantibodies affect pancreatic β cells likely will be answered by ongoing research on viruses and autoimmunity. Importantly, depression amplifies the disability occasioned by comorbidities such as diabetes by exacerbating physical inactivity and poor treatment adherence to coprescribed regimens (10). This interplay exemplifies what occurs with other medical comorbidities of depression. Physical activity may serve to reverse

the downward spiral by reducing inflammation and ameliorating symptoms of distress and insulin resistance.

ALLOSTATIC LOAD MODULATION

The concept of allostasis describes the capacity of an organism to maintain homeostatic systems that are essential to life in the face of environmental changes and stressful challenges by actively adjusting to predictable and unpredictable events. Allostatic load represents the cumulative impact of physiologic wear and tear that arises out of chronic exposure to stress and predisposes individuals to disease. The biological systems involved in the physiologic adaptation to change and stressful events include the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system, and the immune system.

Activation of the HPA Axis

The HPA axis is activated in response to physiologic or psychological stressors, which induces the release of the glucocorticoid hormone cortisol from the adrenal gland. Stimulation of the sympathetic nervous system accompanies activation of the HPA axis, resulting in a cytokine surge that includes catecholamines and IL-6. Cortisol release exceeds typical levels in an effort to coordinate a temporary fight-or-flight response and compensate for a potential exaggeration of the immune response (7). Resolution of the stressful event terminates the response through a negative feedback loop. Cortisol secretion follows a diurnal pattern that helps regulate glucose metabolism and

the immune response. Chronic stress may impair the return of these hormonal systems to normal, resulting in elevation in cortisol, catecholamines, and inflammatory markers (7).

Psychological Stress, Depression, and Type 2 Diabetes

Chronic psychological stress occurs when responses to environmental demands are perceived as exceeding an individual's adaptive capacity. Depression represents a state of greater mental wear and tear than chronic psychological stress, which is a risk factor for and a component of clinical depression. The risk of type 2 diabetes increases as the psychological load progressively rises. Although the evidence to support an association between general chronic psychological stress and diabetes risk suggests a positive association, the results are not entirely consistent because of variation in study design and approach (8). However, depression predisposes individuals to onset and progression of type 2 diabetes. It is estimated that at least 10% to 15% of individuals with type 2 diabetes experience depression. Furthermore, depression is twice as likely to be present in individuals with type 2 diabetes compared with those without type 2 diabetes, and individuals with depression have a 1.5 times increased risk of type 2 diabetes (9).

Chronic exposure to elevated cortisol affects the structure and function of glucocorticoid receptors and regions of the brain required for processing emotional and cognitive functions (10). The biological association between depression and type 2 diabetes seems to be related to dysregulated hypercortisolemia consistent with an overactive HPA axis that drives visceral adiposity and creates deficits in insulin sensitivity and secretion. Glycemic control and related health outcomes such as weight gain, compliance with therapeutic regimens, and vascular complications worsen when type 2 diabetes is accompanied by depression. Type 2 diabetes and depressive symptoms predispose to each other, suggesting a bidirectional link (8).

Pharmacotherapy to treat depression has been shown to improve glycemic control in some but not all studies (11,12). Similarly, in a cohort of patients with depression, intranasal insulin to address alterations in insulin availability did not improve depressive scores (13). However, when patients with comorbid depression and type 2 diabetes are treated with metformin, the first-line drug for treating type 2 diabetes, depressive behavior improves (14). In contrast, in patients with impaired glucose tolerance, metformin did not improve depressive scores compared with placebo (15). Interventions directed at the HPA axis ideally would improve outcomes in both depression and type 2 diabetes; however, pharmacotherapy has not been particularly successful.

Effects of Exercise on Depression in Type 2 Diabetes

Regular exercise plays a key role in protecting against psychologic and metabolic aspects of stress to alleviate symptoms of depression (16). Repeated bouts of contractile muscle activity during exercise improves glucose tolerance and insulin sensitivity in individuals with insulin resistance and in patients with type 2 diabetes (17). Exercise training may lead to adaptation of the responses to stressful stimuli. Reduced cortisol and catecholamine levels in response to stressful stimuli among individuals who exercise suggests that exercise regulates the HPA axis and the sympathetic nervous system (18).

Among older adults, exercise has been shown to be as effective as selective serotonin reuptake inhibitors for the treatment of depression, with participants in the exercise group showing a

lower rate of relapse compared with those receiving the pharmacologic treatment (19). There are relatively few studies that have investigated the effect of exercise on depressive symptoms in patients with type 2 diabetes. A meta-analysis composed of 12 studies examining the relation between exercise and depression in type 2 diabetes found that individuals with depression were 1.2 to 1.9 times more likely to be physically inactive. Furthermore, inactive adults with type 2 diabetes were 1.72 to 1.75 times more likely to be depressed than their more active counterparts (20).

In a 10-week randomized controlled trial to assess the effect of resistance training on depressive symptoms in adults at high risk (two or more risk factors) or low risk (none or one risk factor) for type 2 diabetes, improvements in depressive symptoms were observed only in the high-risk group. This study did not assess measures of glycemic control (21). In a cohort of 291 veterans with type 2 diabetes and depressive symptoms, after a 12-week intervention combining physical activity with cognitive behavioral therapy (CBT), participants reported improvements in depressive symptoms (58% reduced symptoms vs 39% reduction in the control group). However, there were no changes in HbA_{1C} (22).

Program ACTIVE (Adults Coming Together to Increase Vital Exercise) was a pilot and feasibility study to assess the effect of an intervention that combined community-based aerobic exercise and CBT in patients with type 2 diabetes and depression. The program demonstrated feasibility of the intervention, and participants experienced improvements in depressive symptoms and glycemic control, which were sustained 3 months after the intervention. Participants also reported a host of improvements in psychosocial outcomes assessed in the study (23). Program ACTIVE II was a multicenter study that used a community-engaged research approach to parse out the effects of exercise and CBT (24). Program ACTIVE II demonstrated that exercise alone, CBT alone, and the combination were comparable in improving depressive symptoms. There was no effect of the interventions on HbA_{1C} compared with usual care. However, in an exploratory analysis that included patients with baseline elevated HbA_{1C} (>7%), combination therapy showed a clinically significant reduction of 0.74%. Importantly, the improvements in psychosocial outcomes were consistent with Program ACTIVE (24).

Depression is known to reduce the level of self-care and adherence to medication regimens in individuals with type 2 diabetes and is associated with low levels of physical activity and less engagement with exercise interventions. A pooled analysis of two studies specifically designed to evaluate the effectiveness of physical activity interventions in real-world settings was conducted using an objective measure of physical activity (pedometer). In this study, depressive symptoms were shown to reduce the effectiveness of the intervention (25). The beneficial effects of physical activity on symptoms of depression and cardiometabolic outcomes when assessed separately are well established (26,27). Heterogeneity in the pathophysiology perhaps explains the conflicting evidence that exercise improves both depressive symptoms and glycemic control in patients with these comorbidities.

IMMUNE MEDIATORS IN TYPE 2 DIABETES

The onset and progression of type 2 diabetes typically follow a path where insulin resistance creates a burden on pancreatic β

cells, ultimately leading to loss of function. The ensuing fall in insulin secretion manifests in hyperglycemia and glycosuria. Innate immune signaling, and IL-1 (IL-1 α and IL-1 β) in particular, plays an important physiologic role in priming insulin secretion under conditions of stress and increased demand for insulin (28). A transient low-grade inflammatory response to meals that has been shown to occur in healthy adults is perhaps necessary for metabolic homeostasis. In the short term, the inflammatory response promotes β -cell proliferation and insulin production, which can compensate for insulin resistance (28).

The IL-1 response stimulates the synthesis of other inflammatory molecules including IL-6, IL-8, IL-33, TNF- α , and CC-chemokine ligand 2 (CCL-2). Macrophages and other immune cells are enlisted to augment the β -cell immune response. A rise in glucose can lead to induction of the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3), an intracellular sensor that detects a broad spectrum of microbial motifs, endogenous cytokines, and environmental irritants. The resulting formation and activation of the NLRP3 inflammasome in β cells facilitate the processing of pro-IL-1 β to biologically active IL-1 β . Over long-term exposure, the interaction between β -cell amyloid polypeptides and immune cells may lead to a vicious cycle of IL-1 β autostimulation and a mounting of the proinflammatory cytokine network followed by β -cell dysfunction and apoptosis (28).

Mediated by cytokine-stimulated protein kinase cascades, acute and chronic stress also cause insulin resistance. Activated by TNF- α , IL-6, and IL-1 β , protein kinases such as I κ B kinase (IKK), c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (MAPK) in muscle and fat cells have been shown to contribute to insulin resistance by phosphorylating inhibitory serine residues on the insulin receptor substrate 1 downstream of the insulin receptor, which blocks signal transduction (29–31).

Pharmacotherapies for type 2 diabetes are designed to lower blood glucose by direct or indirect mechanisms. The most recently developed classes of drugs include glucagon like peptide-1 (GLP-1) analogs that potentiate glucose-stimulated insulin secretion, and the glucose-eliminating sodium-glucose cotransporter 2 (SGLT2) inhibitors. GLP-1-based therapies target the metabolic, oxidative, and inflammatory pathways that underlie the pathology of type 2 diabetes, but improvements in β -cell functional mass have not been demonstrated in human trials (28).

The pathological processes that cause β -cell failure lie at the crux of the challenge to find a cure for diabetes. Anakinra is an IL-1 receptor antagonist (IL-1Ra) that has been shown to increase insulin secretion and reduce HbA_{1C} in patients with type 2 diabetes (32). The short half-life of anakinra necessitates daily injections, which led to the development of antibodies to IL-1 β (canakinumab), allowing monthly to quarterly dosing. Although the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) was not focused on diabetes outcomes, the reduction in HbA_{1C} lends support for targeting immune mediators to address β -cell preservation (33).

Anti-Inflammatory Effects of Exercise

Based on the observation that insulin reinforces the inflammatory state of macrophages, protracted exposure to IL-1 β activation and concomitant hyperinsulinemia during the onset of type 2 diabetes may be a determining factor in the progression of the disease. Although preliminary studies support the efficacy

of anti-IL-1 β drug therapy, the cost and likelihood of immunosuppression are potential limitations (28). On the other hand, lifestyle interventions provide a safe alternative that targets the pathogenic inflammatory processes that drive β -cell failure. The effect of exercise on the immune system largely has been ascribed to its anti-inflammatory effects via reductions in visceral fat mass or the induction of anti-inflammatory cytokines including IL-1Ra, IL-6, and IL-10.

Several cytokines are released by the exercising skeletal muscle, but the prototypical myokine released from contracting muscle is IL-6. Generally viewed as a proinflammatory cytokine, IL-6 released during exercise stimulates an anti-inflammatory systemic environment. Thus, IL-6 increases the production of IL-1Ra and IL-10. IL-1Ra inhibits IL-1 β signal transduction, and IL-10 inhibits synthesis of TNF- α . In humans, infusion of recombinant human IL-6 at levels observed during exercise increases IL-1Ra levels (34). The difference between the response to endotoxemia and exercise-induced production of cytokines is that the release of IL-6 by skeletal muscle is not preceded by increases in TNF- α and IL-1 β . Chronic elevation of IL-1 β accentuates β -cell damage, but it is TNF- α that plays a key role in peripheral insulin resistance (30,35). In healthy subjects randomized to either rest or exercise before administration of low dose *Escherichia coli* endotoxin, circulating levels of TNF- α increased in resting subjects by two- to threefold. Exercise blunted the TNF- α response, and the effects could be recapitulated by an infusion of IL-6 (36).

During exercise, skeletal muscle-derived IL-6 promotes the production of GLP-1 in intestinal L cells and pancreatic α cells and acts on β cells to stimulate insulin secretion in a glucose-dependent manner (37). In healthy individuals, IL-6 plays a beneficial regulatory role in glucose disposal, but β -cell dysfunction and insulin resistance are enhanced when the prevailing milieu is inflammatory (38). Nevertheless, marked systemic increases in plasma IL-6 only occur if the exercise is prolonged and involves recruitment of a sizeable muscle mass. Moderate-intensity exercise for approximately 1 h induces peak plasma IL-6 concentrations up to 10 pg·mL⁻¹ for only a short period. In contrast, the response to severe systemic infections can reach 10,000 pg·mL⁻¹ (39). Evidence from a case-control study showed that elevated concentrations of IL-1 β and IL-6 together increased the risk of developing type 2 diabetes, but IL-6 alone had no effect (40). These observations suggest that a transient increase in IL-6 after exercise may act on nonmuscle tissues in a hormone-like manner to promote beneficial effects, whereas a chronic increase may be detrimental. The exercise-induced increase in IL-6 secreted by muscle and the subsequent return to basal levels seem to be tightly regulated.

Toll-like receptors (TLRs) together with IL-1R form the innate immune receptor superfamily that is highly conserved across plant and animal species, pointing to their central role in host survival. However, the activation of TLRs, and TLR-4 in particular, may play an important part in mediating whole-body inflammation and the development of obesity-induced insulin resistance. The canonical ligands for TLR-4 are lipopolysaccharides derived from the outer cell wall of gram-negative bacteria, but several host molecules that are elevated in metabolic disease such as saturated fatty acids and oxidized low-density lipoprotein cholesterol also bind to TLRs (41). As a result, an inflammatory response is triggered.

Acute aerobic and chronic resistance exercise in elderly women decreased monocyte cell surface expression of TLRs (42). A subsequent study showed that chronic exercise (combined aerobic and resistance) over 12 wk decreased both inflammatory cytokines and cell-surface expression of TLR-4 (43). In the skeletal muscle of patients with type 2 diabetes, the inhibitor of kappa B ($I\kappa B\beta$) was 60% lower compared with controls. A reduction is considered an indicator of excessive activity of the inflammatory nuclear factor (NF)- κB pathway in skeletal muscle. In response to 8 wk of moderate-intensity (70% of VO_{2max}) endurance training, $I\kappa B\alpha$ and $I\kappa B\beta$ increased to levels comparable with that of control subjects (44). These data suggest that the exercise-induced regulation of TLR-4 expression and cytokine release may provide important mechanisms for the anti-inflammatory effects of exercise.

Proinflammatory macrophages promote the development of insulin resistance and progression to diabetes. Exercise training typically enhances insulin sensitivity, but it can paradoxically promote insulin resistance if it causes muscle damage. The effect seems to be related to TNF- α , which inhibits downstream signaling to the glucose transporter (GLUT4) and impairs glucose uptake. However, these effects last for less than 72 h and can be avoided by an exercise regimen that is gradually increased in intensity and is limited in eccentric contractions (45).

Exercise Dose, Immune Linkages, and Type 2 Diabetes

Prolonged periods of intensive exercise training marked by extreme exercise stress can depress immunity. Intensive training activates the p38 MAPK and NF- κB and are a necessary response to chronic and intermittent stress, respectively. Therefore, MAPK and NF- κB are perhaps necessary for exercise-induced muscle plasticity (46). Exercise causes brief but robust perturbations in cellular stress, increases in reactive oxygen species (ROS), and metabolism, which reach a stable state shortly after the onset of exercise. Type 2 diabetes is marked by a chronic state of continual ROS production, inflammation, and hypermetabolism. In these conditions, unrestrained signaling through the MAPK and NF- κB pathways exacerbates the inflammatory and insulin-resistant condition (46).

During moderate-intensity exercise of less than 60-min duration, the antipathogen activity of tissue macrophages occurs in parallel with the interchange of innate immune cells between lymphoid tissues and the blood compartment. Natural killer cells and CD8+ T lymphocytes that exhibit high toxicity are preferentially mobilized. Nevertheless, stress hormones, which can depress immune cell function, and proinflammatory cytokine release commensurate with intense metabolic activity do not reach high levels during moderate-intensity exercise of short duration. Over time, these transient exercise-induced increases in particular subsets of lymphocytes contribute to enhanced immunosurveillance and reduced inflammation. Thus, moderate exercise training stimulates the exchange of leukocytes between the circulation and tissues and serves to positively modulate the plasticity of the immune system (47).

EXERCISE AND POSTACUTE COVID-19

Exercise targets the neuropsychiatric and endocrine sequelae of long COVID precipitated by increased allostatic load that arises from chronic psychological stress, immune system dysregulation, and stimulation of a hyperinflammatory state. Disruption

of allostasis if left untreated causes glucose dysregulation and development of diabetes, which may tip the balance toward clinical depression because of their bidirectional relation. Lenze *et al.* (48) demonstrated that the antidepressant fluvoxamine, which has high affinity at the sigma-1 receptor, prevents progression to severe illness after a SARS-CoV-2 infection. Sigma-1 receptors play a key role in the replication of the virus, and the resulting endoplasmic reticulum (ER) stress may promote the inflammatory cascade through its interaction with the ER stress-sensing protein, inositol-requiring enzyme 1 (IRE1) α (49). Sigma-1 receptor ligands attenuate the inflammatory response. Therefore, fluvoxamine, which is a strong sigma-1 receptor agonist, was selected for its effects on regulation of inflammatory cytokine production, and its beneficial effects were demonstrated in a randomized placebo-controlled trial of adults in an outpatient setting.

ER stress is critical to the initiation and integration of pathways of inflammation and insulin action as seen in obesity and diabetes. The two principal inflammatory pathways that disrupt insulin action, JNK activator protein 1 and inhibitor of NF- κB kinase B, are linked to IRE1 (50). Therefore, the ER is a site for sensing of metabolic stress and the production of inflammatory signals in response to stress. The ER is very sensitive to glucose or energy availability as well as pathogens and may be considered a site for integration of the nutrient and pathogen responses (50). Moreover, inflammatory mediators can trigger ER stress that leads to a propagation of a systemic stress response.

All the pathways that act at the intersection of metabolic and inflammatory pathways, particularly those relating to ER stress, have effects on β cells (51). β cells may be a direct target of SARS-CoV-2, but it is highly plausible that the ER stress-induced inflammatory response arising from a viral infection precipitates β -cell dysfunction, leading to insulin resistance and defects in insulin secretion. Experimental evidence clearly demonstrates that the inflammatory mediators induced by severe infections can trigger insulin resistance in humans. Thus, inflammation is a critical process during events, leading to metabolic deterioration that results from COVID-19. The results of the fluvoxamine trial suggest that therapeutic approaches targeting stress-induced inflammation are effective in mitigating the long-term effects of COVID-19.

Like fluvoxamine, exercise has antidepressant and immunomodulatory effects that make it imminently suitable for selective prevention in slowing the cascade of events that arise from chronic psychological stress and lead to depression and type 2 diabetes. Importantly, exercise increases peripheral insulin sensitivity in impaired glucose tolerance and type 2 diabetes, measured using the gold standard hyperinsulinemic-euglycemic clamp test (52). In patients with preexisting type 2 diabetes, a blood glucose concentration of $6.4 \text{ mmol}\cdot\text{L}^{-1}$ was associated with reduced risk of all-cause mortality and adverse outcomes from COVID-19 compared with a blood glucose of $10.9 \text{ mmol}\cdot\text{L}^{-1}$ (53). Thus, maintenance of glycemic control seems to be a judicious recommendation to reduce the severity of the SARS-CoV-2 infection and its postacute outcomes. By modulating psychological stress, protracted inflammation, and insulin sensitivity, exercise constitutes a plausible intervention to prevent or mitigate the long-term endocrine effects of COVID-19 (Fig. 2).

High-intensity aerobic exercise for more than 6 wk in subjects with type 2 diabetes improves glycated hemoglobin (HbA_{1C}),

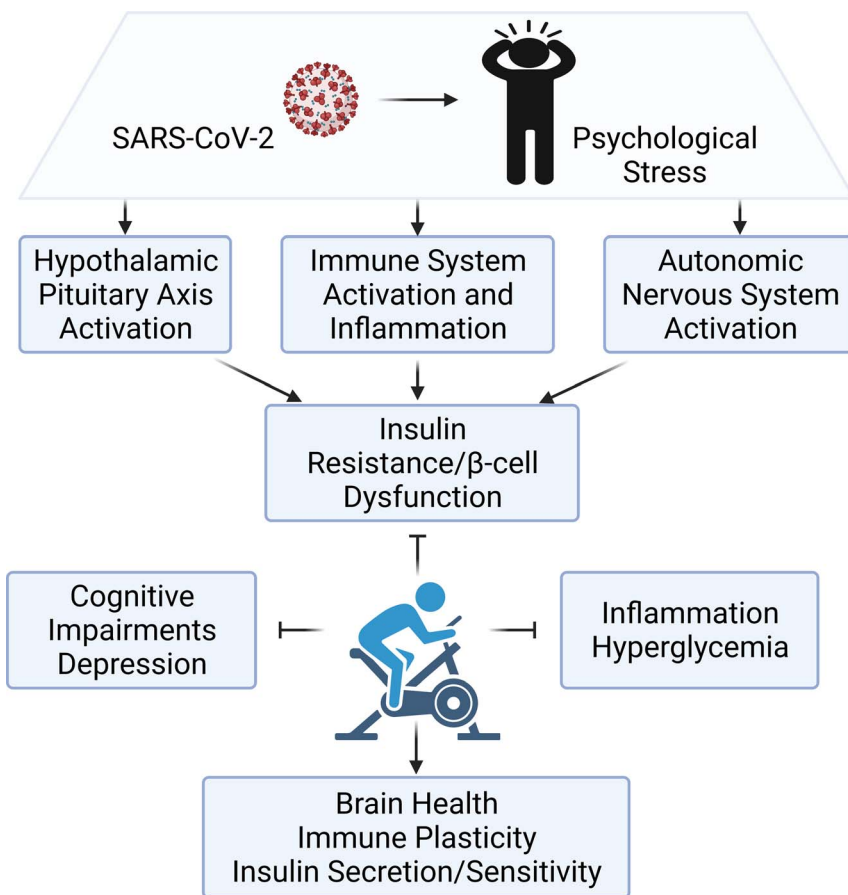


Figure 2. Dysregulation of the physiological adaptation to changes and the modulatory effects of exercise. Psychological stress as may occur with COVID-19 activates the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system, and the immune system. A dysregulated and overactive HPA axis drives sympathetic nervous system activation and an exaggerated immune response that promotes insulin resistance and β -cell dysfunction. Exercise contributes toward enhanced immunosurveillance and reduced inflammation to improve mental health outcomes and glycemic control (graphics program: Biorender).

and resistance exercise enhances the effect (54,55). An exercise regimen combining both modalities and increasing in intensity from moderate to vigorous could be prescribed post-COVID-19, particularly after persistent symptoms. The American College of Sports Medicine guidelines for adults may provide the basis for prescribing exercise intensity, frequency, and timing (56). Lowering the glycemic response likely would break the vicious cycle of IL-1 β autostimulation and β -cell dysfunction (Fig. 1).

The Best Available Treatment for COVID-19 study (ISRCTN69546370) in patients infected by SARS-CoV-2, assessing the efficacy of anti-inflammatory and immunomodulatory drugs, is underway. A large randomized, placebo-controlled trial of fluvoxamine (NCT04668950) is in progress. Questions relating to new-onset diabetes and severe metabolic complications of preexisting diabetes including diabetic ketoacidosis and hyperosmolarity will likely be answered by the global registry of patients with COVID-19-related diabetes (covid diab.e-dendrite.com). Exercise addresses each of these components of long COVID including inflammation, psychological stress, and glycemic control. Therefore, our testable hypothesis assumes tremendous importance.

CONCLUSIONS

The risk for severe SARS-CoV-2 infection and mortality is among the highest in patients with preexisting type 2 diabetes.

Modulation of the allostatic load resulting from COVID-19 as evidenced by the neuropsychiatric sequelae is implicated in the pathogenesis of type 2 diabetes, whereas diabetic ketoacidosis is an outcome of uncontrolled blood glucose. Exercise modulates the key lingering features of a SARS-CoV-2 infection that promote elevations in blood glucose concentrations including inflammation and stress. By modulating blood glucose concentrations, exercise can be used to break the vicious cycle of β -cell inflammation that leads to hyperglycemia and thus prevent the development or progression of type 2 diabetes.

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