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Exercise as part of anxiety coping management in the Covid-19 pandemic era

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ABSTRACT

Containment effort in the COVID-19 pandemic could disrupt circadian rhythms which play an essential role in the development of mood and anxiety disorders. Exercise is one of several recommendations for anxiety coping during the COVID-19 pandemic. However, not every person has a similar response to an exercise stimulus and gets the same optimal benefits. For the best exercise results, we must consider individual needs and capacities, including circadian rhythm, in determining the exercise dose. This review briefly summarizes the exercise' mechanism as an anxiolytic through skeletal muscle-brain crosstalk and designing exercise program with the individual optimal dose as part of anxiety coping management in the COVID-19 pandemic situation, considering exercise as good stress and circadian rhythm.

ABSTRAK

Upaya pencegahan penyebarluasan infeksi di masa pandemi COVID-19 dapat mengganggu irama sirkadian yang berperan penting pada perubahan mood dan gangguan kecemasan. Olah raga dan aktivitas fisik adalah salah satu rekomendasi untuk mengatasi kecemasan selama pandemi COVID-19. Namun, tidak setiap orang memiliki respon yang sama terhadap stimulus olah raga dan mendapatkan manfaat yang sama. Agar olah raga bermanfaat secara optimal, kita harus mempertimbangkan kebutuhan dan kapasitas individu, termasuk irama sirkadian, khususnya dalam menentukan dosis olahraga. Kajian pustaka ini merangkum secara singkat mekanisme latihan sebagai ansiolitik melalui komunikasi antara otot rangka dengan otak. Selain itu dibahas bagaimana merancang program latihan dengan dosis optimal untuk individu sebagai bagian dari manajemen kecemasan dalam situasi pandemi dengan mempertimbangkan olah raga sebagai stres yang baik dan irama sirkadian.

Keywords:
anxiety ;
COVID-19 pandemic;
circadian rhythm;
skeletal muscle;
brain crosstalk;
exercise;

INTRODUCTION

World Health Organization (WHO) declared a new coronavirus disease called COVID-19 as a pandemic on Mar 11th, 2020.[1] The outbreak of COVID-19 may be stressful not only for the public but also for the medical personnel. Fear and anxiety due to the worldwide pandemic can be overwhelming and cause strong emotions of all ages. During this pandemic, people facing many stressors included self-quarantine, infection fears, frustration, depression, boredom, inadequate supplies, inadequate information, financial loss, and stigma.[2] For many people, the uncertainty surrounding corona virus is the hardest thing to handle. We do not know how exactly it will impact or how bad things might get. Then, this makes people anxious and depressed.

Prevention efforts such as social distancing and instruction to working or learning from home may impact circadian rhythms. Disrupted circadian

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rhythms play an important role in mood and anxiety disorders. Circadian rhythms regulate by a master clock located in the suprachiasmatic nucleus (SCN). Animal models of mood and anxiety disorders often exhibit blunted rhythms in locomotor activity and clock gene expression.[3] Since anxiety and depression can become risk factors for lower health-related quality of life, increased risk of all-cause mortality, and various physical health problems, particularly cardiovascular disease (CVD).[4]

Exercise is one of many recommendations for coping with anxiety and depression due to the COVID-19 pandemic.[5,6] Exercise may act through a range of different physiological and psychological mechanisms. One of the effects of exercise in homeostasis is regulating the autonomic nervous system, which maintenance balance sympathetic-parasympathetic.[7] Other physiological mechanisms are the hypothalamic-pituitary-adrenal (HPA) axis[7] and brain mitochondria's biogenesis.[8-10] Biogenesis of brain mitochondria modulate neurotransmitter activity (e.g., serotonin, norepinephrine, gamma-aminobutyric acid [GABA]) and increasing brain-derived neurotrophic factor (BDNF).[11] The psychological mechanisms suggested by the distraction and the self-efficacy hypothesis.

There is a lack of empirical evidence that exercise can act as an anxiolytic depending on increasing physical fitness. However, exercise could reduce inflammation via several different processes (inflammation, cytokines, toll-like receptors, adipose tissue, and via the vagal tone), contributing to better health outcomes in people with anxiety. In addition to the above mentioned, the positive effects of exercise on health, partially mediated by an exercise-induced change in tissue molecular clocks. The skeletal muscle with myokines has a robust circadian profile affect by exercise. The effect of exercise as an anxiolytic is partially due to crosstalk between skeletal muscle and brain.[12] For the best results of exercise for anxiety during the COVID-19 pandemic, we must consider the effect of circadian rhythm in determining the exercise dose. This review aimed to briefly summarize exercise as an anxiolytic through skeletal muscle-brain crosstalk. The optimal dose of exercise as part of anxiety coping management in the COVID-19 pandemic situation considering circadian rhythm was also discussed.

DISCUSSION

Circadian rhythm disruption in the COVID-19 pandemic and anxiety disorders

The COVID-19 pandemic can disrupt circadian rhythms, mainly due to daily routine changes and reduced direct exposure to the outside environment. In addition, a physical distancing policy as a significant containment effort to prevent transmission of COVID-19 can also harm circadian rhythms.[3] Some policies to encourage working from home to support physical distancing have been implemented by the Government. Although the working from home offers a more flexible schedule, it can disrupt the daily routine that has been a time keeper for the body's circadian rhythm and also increasing the blue light exposure of the digital device because of alonger screen time.[13] The working from home also means reducing social interactions.[2] Disrupted daily routines, increased exposure to blue light, and reduced social interactions are responsible for disrupting circadian rhythms.[3]

From the perspective of the HPA axis hypothesis, the impact of circadian rhythm disruption on anxiety development is postulate through disruption on hippocampal neurogenesis

and mitochondrial biogenesis[8-10,14-16] (FIGURE 1). A study in animal models suggested that dentate gyrus granule cell activities were responsible for suppressing anxiety since inhibition of hippocampal neurogenesis exhibited avoidance behavior in coping with threatening conditions.[17,18] Hippocampal neurogenesis will mediate negative feedback on the HPA axis and stop the stress system.[19,20] If circadian rhythm disrupts, there will be a decrease in hippocampal neurogenesis and responsible for dampened negative feedback on the HPA axis, leading to a vicious cycle of a maladaptive stress response. Growing evidence also hypothesized that disruption of mitochondrial biogenesis act as a moderator between disrupted circadian rhythm and anxiety disorder. Usually, circadian rhythmicity in mitochondrial network morphology changes from fragmented mitochondria in the active phase into elongated mitochondria in a passive phase. Disruptions in a daily rhythmic disturbed the mitochondrial biogenesis; thus, mitochondrial networks remain fragmented.[21,22] The disrupted mitochondrial morphology could not provide sufficient energy to maintain appropriate neuronal plasticity responding to stress. Insufficient energy can interfere physiological function of the HPA axis.[23,24]

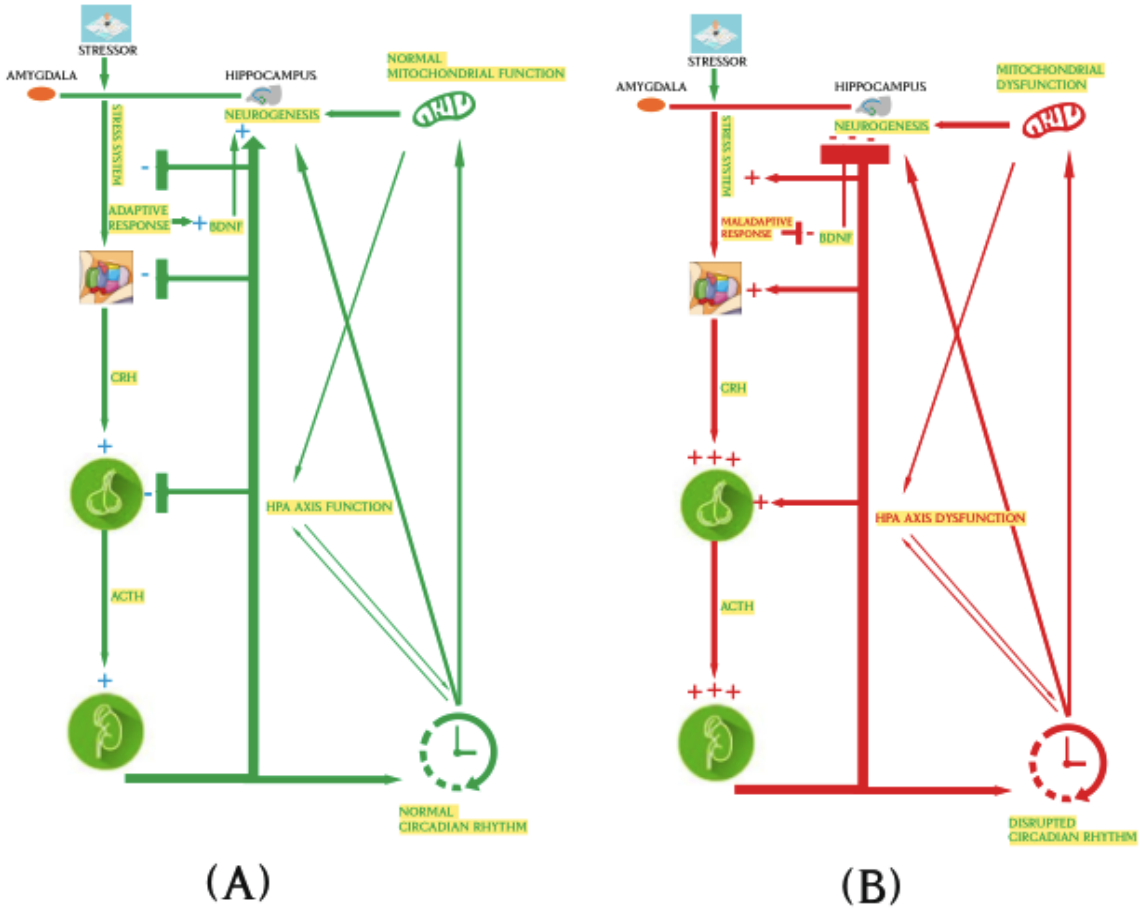

FIGURE 1. HPA Axis hypothesis in stress response. (A) Normal HPA axis function in an adaptive response to a stressor. (B) Disrupted HPA Axis function in a maladaptive response to a stressor

Potential mechanism exercise act as anxiolytic trough skeletal muscle-brain cross talk

The term anxiety refers to several mental and physiological phenomena, including individual awareness about undesirable events in the future, fear of actual situations, unreasonable or excessive reactions to current or future threats.[25] The exact mechanism of anxiety is not entirely known. Hypothetically, anxiety symptoms due to disrupted modulation within the central nervous system. However, anxiety is not always pathological or maladaptive to the situation, but common emotions such as fear, anger, sadness, and happiness. Besides, anxiety has an essential function concerning survival and self-protection. which is part of the fight or flight mechanism.[13,26] Growing evidence showed that exercise could improve anxiety symptoms in animals[17,27,28] and humans, in people with an anxiety disorder[14-16] and without established anxiety disorders or non-clinical population[18,29-31] and those with chronic disease.[32-35] There are several debates on the mechanism of exercise in reducing anxiety symptoms. The dysregulation of neurogenesis[24,35,36] and mitochondrial biogenesis[8-10,22] in the brain hippocampus are the potential targets for an exercise intervention in anxiety disorders. Thus, this article's discussion is limited to skeletal muscle-brain cross talk related to those two pathways.

The hippocampus plays an essential role in responding to stress by neurogenesis and mitochondrial biogenesis.[22,23,37,38] Evidence from animal models suggested that induction of neurogenesis of granule cells in the dentate gyrus, a part of the hippocampus, could reduce anxiety. While inhibiting neurogenesis in that area produced anxiety-related behavior.[39] Several animal studies also found that exercise could increase mitochondrial biogenesis, which led to the improved mitochondrial ability to produce energy, supporting neuronal plasticity to respond to stress. Since the hippocampus is the most affected area of the brain by exercise, it clearly understood that exercise has a vital role in improving anxiety by improving hippocampal neurogenesis and mitochondrial biogenesis.[12,39-41]

As an acute response to exercise, skeletal muscles communicate with other organs by producing and releasing myokines. Myokines can exert autocrine, paracrine, or endocrine effects and mediate signaling within the muscle. Myokines also mediate muscle cross talk to the liver, gut, pancreas, adipose tissue, bone, vascular bed, skin, and brain.[12,42-45] Irisin and BDNF are two myokines that have essential roles in reducing anxiety.[12,41,43,45] Besides myokine secretion, endocannabinoids are also secrets at the end of the session as an acute response to exercise.[46,47] Chronic regular exercise also poses benefits on improving anxiety symptoms through its regulation on several proteins, including peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α), fibronectin type III domain-containing protein 5 (FNDC5), and uncoupling protein (UCP) (FIGURE 2).

Role of transcription factor peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1**α**)

The transcription factor peroxisome PGC-1α in skeletal muscle is increased and activated by many types of exercise like endurance,[48,49] resistance,[49-51] acute,[49] and chronic regular exercise,[42] force and voluntary exercise.[52] The PGC1α is expressed in high levels in mitochondrial-rich cells with high energy demands such as skeletal and heart muscle cells also neurons. *In vitro* studies showed an increase in PGC1-alpha expression mediated by reactive oxygen species (ROS) production from lactate metabolism. Both continuous and intermittent exposure to L-lactate can cause the up-regulation of PGC1-alpha.[44] In skeletal muscle, PGC-1α activation drives a genetic program that promotes structural and functional adaptation to exercise by control the expression and release of several myokines such as irisin, β-aminoisobutyric acid (BAIBA), meteorin like, neurturin, and IL-6.[35]

PGC1α has a central role in mediating many of the metabolic effects of exercise locally within the muscle. It is a transcriptional co-activator of mitochondrial biogenesis and oxidative metabolism in muscle and brown adipose tissue. Agudelo *et al.*[45] reported that high expression of PGC1α in skeletal muscle induces a change in kynurenine metabolism by stimulating kynurenine aminotransferase (KAT). High KAT expression led to increased conversion of kynurenine (KYN) into kynurenic acid (KYNA). The KYN can cross the blood-brain barrier (BBB), cause nerve inflammation, and inhibit neurogenesis, and responsible for leading anxiety symptoms. If KYN can convert into KYNA, which can not cross the BBB, it could have a neuroprotective effect and inhibitanxiety.[46,47] Exercise has proved to increase plasma kynurenic acid levels in rodents and humans.[35,45,48,52]

Role of fibronectin type III domain-containing protein 5 (FNDC5)

The PGC-1α also interacts with estrogen-related receptor alpha (ERRα) to regulate the expression of FNDC5. Increased expression and activation of the PGC1α during exercise will promote the cleavage of FNDC5 to irisin. Irisin, in turn, led to the expression of hippocampal BDNF. Some studies reported that endurance and resistance exercise led to increased FNDC5 expression or circulating irisin concentrations in healthy men.[44] Another study reported that regular endurance exercise with high-intensity interval training led to acute increased FNDC5 expression in healthy men skeletal muscle.[53]

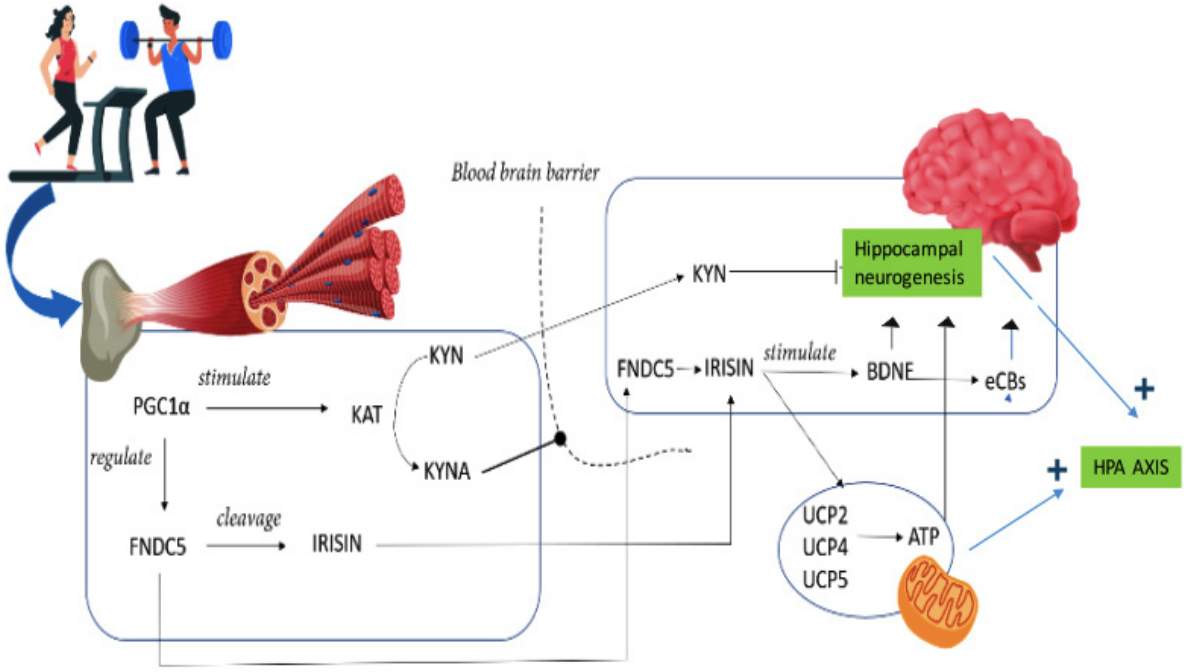

FIGURE 2. Endurance and resistance exercise act as anxiolytic through the activity of skeletal muscle-brain cross talk. The transcription factor peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α) released by skeletal muscle during endurance and resistance exercise and inhibit anxiety through activation of Irisin/BDNF and blocked kynurenine cross the blood-brain barrier. PGC1α expression in muscle stimulates an increase in the expression ofFNDC5, a membrane protein that is cleaved and secreted into the circulation as the myokine irisin during exercise will pass through the blood-brain barrier and stimulate BDNF. A high level of kynurenine (KYN) inhibits hippocampal neurogenesis, which is associated with anxiety. Exercise enhances the PGC1α-dependent muscular expression of the kynurenine aminotransferase (KAT),which converts neurotoxic KYN into neuroprotective kynurenic acid (KYNA), thereby reducing anxiety. In contrast to KYN, KYNA is not able to cross the blood-brain barrier. The imbalance between the neuroprotective KYNAand the neurotoxic KYN metabolites propose to be an essential factor in developing anxiety. In the brain, irisinincrease the uncoupling protein two, four, and five (UCP2, UCP4, and UCP5) that led to improve mitochondrial biogenesis and increase ATP production. Adequate ATP production needs for maintaining the HPA-axis function required for adaptive response to a stressor. (pictures downloaded from http://freepick.com) PGC1α: peroxisome proliferator-activated receptor gamma co-activator 1-alpha; FNDC5: fibronectin type III domain-containing protein 5; KYN: kynurenine; KAT: kynurenine aminotransferase; KYNA: kynurenic acid; BDNF: brain-derived neurotrophic factor; UCP: uncoupling protein; eCBs: endocannabinoids.

FNDC5, a glycosylated type I membrane protein mainly expressed in skeletal muscle, cleaved proteolytically and released into the circulation as irisin. Irisin acts preferentially on the subcutaneous fat and acts in a thermogenic mechanism. Clinical studies in humans have confirmed a positive effect of exercise on FNDC5 expression and circulating irisin. The increased expression of FNDC5 induces neuronal development and differentiation in certain parts of the brain. Several studies demonstrated that there is a homeostatic FNDC5/BDNF feedback loop.[54,55]

Role of irisin

Irisin is a newly defined myokine and mainly synthesized in the muscle tissue. Irisin also exists in cerebrospinal fluid, Purkinje cells, intercellular nerve endings, and neuron andneuroglia.[56] Irisin regulates hippocampal neurogenesis by increasing the size and blood flow, changes the morphology of dendrites, increases the synapses, and finally increases neural proliferation. Animal studies found that irisin's primary effect is the induction of BDNF in the hippocampus and forced expression in hippocampal neurons' cell culture.[54] Mice subjected to three weeks of freewheel running showed enhanced muscle mRNA expression and 65% elevated irisin plasma concentrations. In another study, ten weeks of supervised endurance exercise training revealed a twofold increase in circulating irisin levels. *In vitro*, irisin regulates central mechanisms that mediate adaptive responses by (a) improving neuronal mitochondrial de-coupling and (b) increasing neurotrophin expression and the other neuroprotective proteins.[12,44,57]

Role of brain-derived neurotrophic factor (BDNF)

BDNF is one of the neurotrophic factors that influence cell growth, cell differentiation, synaptic modification, and neuroplasticity. It can signal via both TrkBand p75NTR receptors, highly expressed in the hippocampus, and increased in exercised rats and humans.[40,58] Low expression of BDNF in the hippocampus is a risk factor for anxiety.[9,41] Decreased secretion of BDNF exhibited by a mutation in the BDNF gene showed a decreased hippocampal volume linked to anxiety disorder.[55] In addition to hippocampal neurogenesis, another critical role of BDNF is to facilitate mitochondrial biogenesis. Regarding Markham *et al.*,[59] BDNF increases the respiratory control index (RCI), a measure of respiratory coupling efficiency, ATP synthesis, and organelle integrity of rat brain mitochondria, resulting in a 64% increase in the efficiency of respiratory coupling.

BDNF also acts as a modulator of endocannabinoids (eCBs)-mediated synaptic plasticity synthesis. eCBs release resulting in improvement of the anxiety-coping mechanism. Several studies suggest that the balance between eCBs and glucocorticoids will control emotional, physiological, and adaptive responses to stress. The exercise is known to activate the HPA axis and increase cortisol levels and corticosteroids, known to stimulate eCBs biosynthesis.[60,61] The role of eCBs in anxiety could also be mediated by 5-hydroxytryptamine (5-HT) modulation, which has an essential role in regulating behavior, mood, and memory.[60,62] Several studies reported that eCBs and BDNF concentrations in humans and animals were positively correlated with each other at the end of the exercise, regardless of the intensity level.[46,47,60,61] Since eCBs concentration is associated with a euphoric feeling, the increased eCBS concentration at the end of the exercise session at any intensity level could be caused by the positive effect after self-selected intensity exercise proposed by the Dual Mode Theory.[63]

Role of uncoupling proteins (UCPs)

The uncoupling proteins (UCPs), which are protein families, are in the mitochondria's inner membrane and facilitate proton flux through the internal mitochondrial membrane, thereby dissociating the oxidative phosphorylation of ATP synthesis. Improved proton flux processes can reduce the potential of mitochondrial membranes, improve respiration function in mitochondria, lower the ATP/ADP ratio, and dissipate energy in the form of heat. Acute mitochondrial de-coupling reduces mitochondrial ATP production; however, chronic mitochondrial de-coupling promotes mitochondrial biogenesis and an increased ATP production level. There are five different UCP homologs distributed in different tissues, of which UCP4 and UCP5 are highly expressed in the hypothalamus, hippocampus, and cortex.[10,56]

Optimal dose of exercise to reduce anxiety symptoms

Some literatures and many meta-analyses have discussed the effect of exercise on anxiety. Several randomized controlled trials involving subjects with a standard or increased level of anxiety who do not meet the criteria for psychiatric diagnosis have shown that physical activity can reduce anxiety symptoms.[7,64] An exercise training program must be individualized and supervised to be beneficial. Like prescribing drugs, patients are prescribed a specific amount in a specific time or duration of the exercise. According to ACSM guideline,[65] general principles of exercise prescription should employ the frequency (how often), intensity (how hard), time (how long), type (what kind), total volume (amount), and progression (advancement) or FITT-VP principle (TABLE 1). To design an exercise program, we must consider the purpose of the exercise and should be evidence-based. It is also worth noting that not all individuals will have the same response and results. Several components play a pivotal role in the exercise mechanism as anxiolytic, PGC1α, FNDC5, Irisin, BDNF, eCBs, and UCP have their characteristics that need to be considered in designing exercise programs.

Referring to ACSM guidelines for exercise prescription, determining the type of exercise is the most important for anxiety.[65] In this pandemic situation, we have to pay attention to security, safety, and physical distance and anxiety as special considerations. The type of exercise selected must be fun and doable because exercise could be "bad stress" that triggers or worsens anxiety symptoms. Several studies have shown that restricting freedom of choice or control increase stress in both human and animals. Forced running exercise in rodents can lead to anxiety and increase corticosterone serum levels, evoking an inflammation response in the brain and inhibits hippocampal neurogenesis. While rewarding exercise increases the corticosterone, BDNF, and 5-HT, which promotes neurogenesis and improves anxiety symptoms.[66,67] An exercise program should include a variety of exercises beyond activities performed as part of daily living. The optimal exercise program should address 1) endurance training for cardiorespiratory fitness and improves body composition, 2) resistance training for muscular strength and endurance, 3)stretching activity to improves flexibility such as range of motion, 4) neuromuscular activity to increase agility, balance and proprioception and 5) mind fulness exercise which involves breathing methods, guided imagery, and other practices to relax the body and mind and help reduce stress.[65,68,69]

The positive effects of exercise on anxiety may be depending on when

exercise performed. The timing of exercise is involved in the regulation of circadian clocks. Some studies have shown that exercise could shift the circadian rhythm phase and entrains the molecular clock in the SCN and peripheral tissues.[70,71] The central circadian clock located in the suprachiasmatic nucleus is sensitive to light as the essential cue (Zeitgeber) regulating circadian rhythm. Interestingly, peripheral tissues have their own clocks, which are synchronized by the central clock, but they can also be influenced by behavior, such as feeding or exercise.[71] This review discusses the possible exercise mechanism as anxiolytic through an increase of PGC1α, a clock-controlled genes in skeletal muscle. The physiological role of PGC-1α is influenced by the daily variation of skeletal muscle activity, body temperature, and metabolic rate.[71]

Several studies conducted in human showed that skeletal muscle torque, strength, and power are higher in the late afternoon, between 4:00 and 6:00 PM, compared to the morning.[72,73] In the exercise for anxiety management, morning exercise is proposed to improve the master clock and sleep-wake phase so that the circadian rhythm becomes well organized. Because one of the triggers of anxiety is the disruption of the circadian rhythm and sleep-wake cycle.[54,72] Considering the body's response curve to exercise, the best time to exercise for anxiety management is around 7:00 AM or between 1:00 and 4:00 PM.[74]

Numerous meta-analyses and systematic review studies have concluded that exercise can significantly act as an anxiolytic in dose-response dependent.[75-77] Components of exercise dosage are frequency, duration, and intensity. Frequency is calculated as sessions, episodes, or physical activity per day or per week. Duration is the length of time for each physical activity. Intensity is the energy expenditure rate necessary to perform the activity to accomplish the desired function or the magnitude of the force exerted. How hard a person does the exercise can be defined on either an absolute or a relative scale. Absolute intensity refers to the amount of energy expended per min of activity.[65,78]

In contrast, relative intensity considers the level of exercise capacity or cardiorespiratory fitness to assess the level of effort. Either use a scale to monitor the intensity of aerobic exercises. Recommendation based on the general concept of training starts with low-intensity and graded to moderate intensity, with a gradual increase in duration.[79] The dose-response relationship between exercise and anxiety symptoms is a U-shape curve. This U-shape curve means the optimal exercise intensity for reducing anxiety symptoms is moderate intensity. The low intensity is less effective, and high intensity will worsen the symptom due to muscle soreness or fatigue.[75]

The most efficacious endurance exercise levelis moderate-intensity or 1,800–3,000 METs-min/week, equal to brisk walking at 5-6 km/h. Low intensity is less significant, and high intensity provides no significant reduction of anxiety symptoms.[75,80] The cytokines, hypothalamic, and glycogen hypotheses are most strongly supported the effect of excessive exercise on anxiety symptoms.[75]

The recommendation in this COVID-19 pandemic situation is to do exercise at home. Monitoring exercise intensity is more practical using a Borg scale, which does not require special equipment or expertise. To monitor the exercise intensity until it gradually reaches a Borg Scale of 15–16. The training should be on the Borg Scale 12–13 for 10–20 min by a gradual increase to 15–16 for 30 min. As a rule of thumb from the Borg Scale, intensity aerobic exercise is being assessed by being able to speak with whole sentences but not being able to sing. If it ca not

say more than a few words without panting, then it includes high intensity. Studies by Broman-Fulks *et al*.[42] found a negative relationship between exercise frequency and anxiety symptoms. The American College of Sports Medicine and the Centers for Disease Control and Prevention recommended moderate-intensity endurance exercise done on most days of the week but at least three to five days.[65,78]

TABLE 1. Exercise recommendation for anxiety coping management in the COVID-19 pandemic situation

Type	Combination of endurance (brisk walking, jogging, cycling, swimming), resistance (elastic bands, free weight), and stretching exercises.
Time	Around 7:00 AM or between 1:00 and 4:00 PM
Intensity	Gradually increase from low intensity to moderate intensity. Endurance exercise: moderate-intensity monitored with Borg Scale (can talk but not sing). Resistance exercise: low to moderate (low intensity by lift weight 8-12 times, moderate level by lifting a weight 10 to 15 times in 3 sets repetition with interval 2-3 min each). Stretching exercise: 10-30 sec each group of muscles.
Frequency	Endurance exercise: 3-5 times/week. Resistance exercise: 2-3 times/week Stretching exercise: before endurance or resistance exercise
Duration	Endurance and resistance exercise 30-45 min
Complement exercise	Tai chi: 60 min, three times/week Yoga: 90 min, 1-2 times/week

Resistance exercise include various procedures that evoke repeated muscle action against loads above those encountered in daily activities. Resistance exercise usually requires equipment (i.e., elastic bands, free weights, or resistance machines). They performed in a series of sets or a specific number of repetitions. Previous studies[69,81] suggested that resistance training at a low-to-moderate intensity produces the most reliable and robust decreases in anxiety. Like the endurance exercise, resistance exercise also begins at low intensity by lifting weight 8-12 times increase to a moderate level by lifting weights 10 to 15 times in 3 sets of repetition intervals 2-3 min each. People with anxiety should not have pain due to muscle soreness. The resistance exercise should be done with more repetitions with less weight to reduce muscle soreness and gradually work up to heavier weight in anxiety sufferers. Resistance exercise on each major muscle group for 2-3 days/week with at least 48 h separation. The major muscle groups are the chest, shoulders, upper and lower back, abdomen, hips, and legs.

Exercise for flexibility offers general health benefits. Stretching exercises can increase flexibility. Flexibility exercise should target the shoulder girdle's major muscle-tendon units, chest, neck, trunk, lower back, hips, posterior and anterior legs, and ankles. Flexibility or stretching should do before doing endurance or resistance exercise for 10 min. Each stretch should last 10 to 30 sec and be repeated 3 to 4 times.[65]

Tai chi is a form of mindfulness exercise that originated in China. Tai chi is a form of physical activity that combines Chinese martial arts and meditation to enhance the harmonization of mind and body, which involves a

series of movements performed slowly and like a beautifully flowing dance. As it comprises mental concentration, physical balance, muscle relaxation, and relaxed breathing, tai chi shows excellent potential for reducing anxiety symptoms, although there were inconsistent results in several systematic reviews.[82,83] As a complementary exercise program, the recommended dose of tai chi for anxiety is 60 min 3 times per week.[83]

Another type of mindfulness exercise is yoga, which popular for increasing strength, improving balance, and increasing body flexibility. Many people do yoga as part of a healthy lifestyle. Yoga refers to a scientific scheme of physical and mental practices that originated in India approximately 3000 years ago. The purposes of yoga practices are to facilitate the development and integration of the human body. Yoga exercise is divided into an eight-part system called Ashtanga (Sanskrit for 'eight limbs'). The system is comprised of ethical behavior (yamas), self-discipline (niyamas), postures (asanas), breath control (pranayamas), sensory withdrawal (pratyahara), expansion of awareness (dharana), meditation (dhyana), and universal consciousness (samadhi). Several studies that look at the effects of yoga on anxiety levels in non-clinical samples compared with other types of exercise, e.g., swimming, fencing, and low-intensity relaxation exercise, have a little different effect reducing anxiety symptoms. As a complementary exercise program for anxiety, yoga can be done in 90 min once or twice a week.[82,84]

CONCLUSION

There is growing evidence suggesting that exercise is associated with reduced anxiety symptoms to utilize as a part of anxiety coping management during the COVID-19 pandemic. Numerous studies found many exercise pathways as anxiolytic. The central hypothesis is skeletal muscle-brain crosstalk, which triggers neurogenesis and mitochondrial biogenesis in the hippocampus. The skeletal muscle-brain crosstalk mechanism involves the components which play an essential role in circadian rhythm nor affected by circadian rhythm to consider in prescribing an exercise program. Developing an exercise program for anxiety during the COVID-19 pandemic should be based on frequency, intensity, time, type, volume, and progress (FITT-VP). Choose the type of exercise to do at home, easily and enjoyably, does not cause muscle pain and fatigue, and does not interfere with the sleep-wake cycle.

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