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Protective Roles of Exercise and Nutritional Factors for Immune System During Delta Variant-COVID-19 Outbreaks: Evidence Review and Practical Recommendations

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ABSTRACT

The coronavirus disease 2019 (COVID-19) is a deadly viral infection causing death due to impaired immunity. Therefore, an investigation of factors affecting the immune system should be considered. It is well documented that regular sessions of moderate-intensity exercise training with up to 1-hour duration boost the immune functions through anti-inflammatory and antioxidant effects. Besides, a diet containing functional and nutritious foods is also needed to aid the immune system. Herein, we have summarized available data on how exercise and nutritional factors help promote immunity against various infections. More importantly, this review provides practical and valuable guidance for sedentary adult people and non-professional athletes on how to do aerobic and resistance training and stretching exercises at home with no special types of equipment required during the outbreaks of delta variant-COVID-19. Some significant exercise-related nutritional considerations regarding carbohydrates, fibers, vitamins, zinc, and omega-3 fatty acids were also supplied that help to create better adaptations and improve immune responses.

Keywords: COVID-19 quarantine, Home-based exercise training, Non-functional foods, Pandemic, Professional athletes, Sedentary people

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1 Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory disease that has created a deadly pandemic that rapidly spreads worldwide. To date, the virus has infected 191,000,000 people, including more than 4,100,000 deaths, according to the World Health Organization (WHO) **(1, 2)**. Information on the COVID-19 can be found on various websites. The WHO website shows daily reports in all parts of the world. Reports indicate that some countries have reduced the number of people infected with the virus, but many other countries create new cases at alarming rates. Recently, the emergence of different variants with mutations in COVID-19, especially the delta variant, is the issue that has multiplied concerns. The delta variant has affected many countries due to its rapid transition. It is reportedly increasing in Iraq,

South Korea, Iran, Pakistan, Kazakhstan, Bangladesh, Japan, Myanmar, Vietnam, Thailand, and Malaysia **(3)**. Research has shown that most people who gave up their lives fighting against COVID-19 had underlying diseases and low immune functions. The findings of various studies have also confirmed that many people with sufficient immune functions can be infected with viruses without any symptoms **(4)**. Therefore, it has been suggested that one of the ways to deal with COVID-19 is to build up the immune system function and strengthen the body because the immune system inability causes the defeat of suffering people against the terrible virus **(5-7)**. Thus, the generalization of all recommendations by the WHO and various researchers in the field of COVID-19 can be helpful for new variants of the virus. However, self-isolation and staying at home during the pandemic may induce various negative characteristics of sedentary behaveiors, such as decreased physical fitness and immune functions **(6, 8)**. The present article focuses on practical exercise training approaches and nutritional items for sedentary people across the delta variant of COVID-19 outbreaks.

2. Distinction of Delta Variant of COVID-19

During the SARS-CoV-2 pandemic, mutations of the virus led to the development of different variants, including alpha (B.1.1.7), beta (B.1.351), gamma (B.1.1.28.1), and delta (B.1.617.2), which constitute a significant threat to public health because of their potential escape from the immune system and greater transmissibility **(9)**. The delta variant of COVID-19 was first identified in India, more prevalent than the alpha variant. The delta variant is more frightening because of the increased risk of hospitalization and higher transfer rates (e.g., 60% faster than the alpha type) and requires more oxygen. It is important to note that among patients with delta variant, the number of people hospitalized who have not yet been vaccinated is higher than those who have not been vaccinated **(10-12)**. Patients with this variant have moderate to severe cold manifestations. Recently, loss of taste and smell and shortness of breath cannot be obvious symptoms because patients' vaccination status and age complicate their diagnosis based on the delta variant. Hence, the symptoms of the delta variant are milder than those of the SARS-CoV-2 virus, so patients may think they have hay fever or a cold and that these patients are indistinguishable from others **(11)**.

Mutations in L452R and P681R (splice binding domain of the SARS-CoV-2 spike protein receptor from the delta variant) have been shown to cause high transmission as well as rapid propagation in heavy waves in India. In addition, concerns were raised about the effectiveness of the species and the ability to escape the vaccine **(13, 14)**. All parameters that play a key role in COVID-19 transmission rate such as production time (interval between primary and secondary infection), the incubation period (period from infection to disease onset), and serial interval (interval between onset of symptoms in primary and secondary cases) were shorter in the delta variant than previous variants **(15)**. The high number of newly infected individuals per day leads the Indian healthcare system to failure as hospitals run out of beds, lack oxygen, and cannot serve critically ill patients **(13)**. For that reason, the delta variant is an "improved" virus of the alpha variant, which increases transmission and anxiety due to some mutations, especially mutations in the spike protein. A major mutation has occurred at the furin cleavage site, resulting in greater airway compatibility than the Wuhan COVID-19. The adaptation of airway cells increases the virus in infected patients; therefore, the probability of transmitting the virus from patients to air is more than its transfer to other people. With this explanation, the probability of infecting people after exposure to less viral infection is also high because this variant has a higher efficiency in infecting human airway cells **(16)**. The important thing is that the delta variant in families and indoor exercises is transmitted **(13)**. In these circumstances, compliance with the protocols proposed by the WHO, including a distance of one meter from others, the use of masks, and handwashing, should be a priority.

Plus, researchers recommend that the proposed exercises to strengthen the immune system be done outdoors. Several abnormalities in coagulation and activation of the complement system also occurred in severe COVID-19 with symptoms containing elevation on fibrin degradation products, dimero-D, and C-reactive protein (CRP). Also cytokine storm was characterized by the increase of circulating cytokines such as interleukin (IL)-6, IL-1β, IL-10, IL-2, IL-8, IL-17, monocyte chemoattractant protein 1 (MCP-1), tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), macrophage inflammatory protein 1 alpha (MIP-1α), gamma-induced protein 10 (IP10), granulocyte-colony stimulating factor (G-CSF), and other molecules. In this situation, although in contrast to increase of inflammation markers such as IL-1β, IP10, MCP-1, and IFN-γ by T helper lymphocytes 1 response, increase of IL-4, IL-5, and IL-10 for suppressing the inflammation via T helper lymphocytes 2 to minimize inflammatory tissue damage, causes an imbalance in immune regulation. In COVID-19 patients, cytokine storm develops an immunological system attack to different body organs such as lungs, kidneys, heart, liver, brain, spleen, and lymph nodes, leading to significant lesions **(17, 18)**. Therefore, regular physical exercise, on the one hand, leads to a decrease of inflammatory responses and stress hormones; It increases immature B cells, natural killer (NK) cells, lymphocytes, and monocytes. Consequen-tly, the

improvement of the immune system and the reduction of the systemic inflammatory process occurring in the body, which confirms the contribution of the immune system by regular physical activity **(17)**, resulting in helping to prevent respiratory diseases and protecting against infections such as the delta variant of COVID-19.

3. Exercise Training Approaches

Regimented exercise is considered an important and effective tool in preventing and managing chronic non-communicable diseases risk **(8, 18-21)**. Global recommendations on physical activity for health suggest 60 min/day of moderate-to-vigorous physical activity for children and youth (5 to 17 years), and 75 min/week of vigorous or 150 min/week of moderate physical activity for adults and elderly (≥ 18 years) **(22)**.

Nowadays, we know that regular exercise training combined with proper nutritional strategies would enhance immune function **(23-25)**. In general, each session of moderate-intensity exercise training with the appropriate duration is an immune system adjuvant, and when repeated regularly, induces anti-inflammatory and antioxidant effects that can protect against mortality and incidence rates for chronic diseases, influenza, and the risk of upper respiratory tract infection (URTI) **(8, 23, 25)**. There are several mechanisms related to beneficial effects of regular exercise training, including recirculation of anti-inflammatory cytokines, immature B cells, cytotoxic T cells, NK cells, immunoglobulins such as immunoglobulin A (IgA), and immune cells such as neutrophils, together with improving the functional activity of tissue macrophages against pathogens **(8, 23, 26)**. In this regard, Klentrou et al. reported that 12 weeks of moderate exercise increased salivary IgA in a group of healthy men and women, compared with sedentary controls **(27)**. In another study with the same training period, moderate-intensity exercise modulated inflammatory cytokines, including TNF-α, IL-2, IL-4, and IL-6, more than low-intensity exercise training in obese type 2 diabetic patients **(28)**. In addition, comparative data from a human study showed that long-term moderate exercise in sedentary older adults and women resulted in a significant increase in the number of T helper cells. In contrast, non-exercise control subjects did not show significant changes **(29)**. Hence, regular moderate exercise seems to be associated with better immune functions and be helpful for a decrease in the risk of infections.

It has been concluded that acute exercise stimulates the continuous exchange of distinct and key immune cells, such as leukocytes, between the circulation and tissues associated with improved immune functions **(23)**. Increased cardiac output, vascular vasodilation, and blood flow with acute exercise lead to greater mechanical forces on the endothelium, causing leukocytes to demarginate and enter the blood-stream. This is accompanied by more shear stress levels within the capillary structures that contain marginated leukocytes, which can drive more leukocytes into the peripheral circulation **(30)**. Additionally, lymph is emptied into the blood via the thoracic duct during exercise, increasing lymphatic flow **(31)**. In contrast, long-lasting, intense exercise training may be immunosuppressive. Exposure to this stressor increases susceptibility to infection and illness through increased intestinal permeability, oxidative stress, and induction of muscle damage or fatigue that leads to acute inflammation **(8, 25, 26, 32)**. Therefore, choosing the correct training variables, especially for sedentary people and amateur athletes, is principal to prevent such adverse effects and maintain or improve the principal health-related physical fitness components **(26, 33)**.

In that regard, outdoor activities are typically more available, and many types of physical exercises can be performed, but there are still many possibilities for home-based exercises during quarantine. Indeed, it should be emphasized that "doing at least some exercise is better than nothing" **(33, 34)**. According to the reasons listed above, we have provided practical recommendations for specific home-based exercise training across the situation of the COVID-19 pandemic (Table 1).

4. Nutritional Recommendations

Sufficient intake of carbohydrates, polyphenols, and vitamins could be helpful **(8, 23, 51-53)**. To improve viral protection and reduce exercise-induced inflammation, a well-balanced diet containing a variety of carbohydrate and protein sources, grains, fruits, and vegetables is needed to provide sufficient energy and antioxidants **(8, 23, 51, 52, 54)**. Here, we have summarized some applicable nutritional items which may be more important and usable during the COVID-19 outbreaks (Table 2).

Table 1. Home-based exercise recommendations for sedentary adult people and amateur athletes to do during delta variant-COVID-19 outbreaks.

Frequency At least 3 and preferably 5 days per week	
Type **Combined training (60 min) including aerobic (30 min) and resistance (30 min) training regimens**	
Evidence-based reasons	
Aerobic training **1) Continuous or interval training:** Exercises: treadmill running or brisk walking, cycling on a stationary bike (if available), different types of dancing Duration: 30-min continuously or three 10-min intervals with 1-2 min rest between them Intensity: 60%-90% of HR_{max} (5-10% increases per week) **2) Interval training with shorter duration:** Exercises: jogging in place, jumping jacks, jumping rope (visible or invisible, depending on the individual proficiency), squat thrusts (Burpees), high knees, skaters, and other full-body exercises like these. Duration: 30 min including 3-4 intervals of each exercise with 10-20 reps (depend on the type of exercise), and 30-45 s and 1-2 min rest between the intervals and exercises, respectively. Intensity: 60%-90% of HR_{max} (5-10% increases per week)	↓ TNF-α (28, 35-38) ↓ CRP (36, 38, 39) ↓ HbA1c (28) ↓ IL-2, IL-4 (28) ↓ IL-18 (35, 40) ↓ IL-6 (28, 36-39) ↑ IL-10 (37) ↑ $CD3^+$ (37) ↑ $CD4^+$ (29, 37) ↑ $CD8^+$ (37) ↓ $CD4^+/CD8^+$ ratio (37) ↑ $CD28^+CD4^+$ (29) ↑ salivary IgA (27) ↓ MIP-1γ (35)
Resistance training **1) resistance band training:** Exercises: seated row, pull apart, push-ups, decline push-ups, lateral raise, shoulder press, forward raise, biceps curls, squats, decline triceps extensions, etc. **2) dumbbells (or bottles of water or sand), free weights, or other types of** available resistance equipment: Exercises: reverse fly, bent over row, chest press, shoulder press, forward raise, biceps curls, overhead triceps extensions, squats, stationary lunges, toe raise, etc. **3) Bodyweight training:** Exercises: sit-ups, push-ups, pull-ups, dips, plank, glute bridge, squats, Bulgarian split squats, overhead lunges, bicycle crunches, etc. Duration: 30 min including 3-4 sets of selected exercises with 10-20 reps (depend on the type of exercise), and 60-90 sec and 2-3 min rest between the sets and exercises, respectively. **Intensity:** level 11-16 according to Borg's scale (i.e., scores 11 and 12 as light, 13 and 14 as somewhat hard, and 15 and 16 as hard exercise).	↓ CRP (41-44) ↓ IL-6, TNF-α (43, 45) ↑ IL-10 (42, 44) ↓ IL-18 (35) ↓ NKTNF-α, NKTTNF-α (46) ↓ HbA1c (47) ↓ LDL-c (47) ↓ TLR2 and TLR4 (44) ↓ MIP-1γ (35)
Cool-down **1) static stretching:** Exercises: chest stretch, upper back stretch, shoulder and triceps stretch, wrist stretch, side stretch, calf stretch against a wall, hip flexor stretch, quadriceps stretch, seated glute stretch, seated hamstring stretch, low-back stretch on the ground, abdominal stretch, etc. Duration: 6-10 sec per limb/muscle. Intensity: until the onset of pain in the muscle.	↑ salivary IgA (48) ↑ testosterone (48) ↓ cortisol (48) ↓ neutrophil count (49) ↓ inflammatory lesion thickness (49) ↑ $IL\text{-}2^+CD8^+$ (50)

↑ increase, ↓ decrease, HR_{max}: maximal heart rate, TNF-α: tumor necrosis factor-alpha, IL: interleukin, IgA: immunoglobulin A, NK: natural killer cell, NKT: natural killer T-cell, CRP: C-reactive protein, HbA1c: glycated hemoglobin, TLR: Toll-like receptor, MIP-1γ: macrophage inflammatory protein 1 gamma.

It should be noted that the recommendations regarding vitamin D depend on the dietary habits of the country considered. For instance, Iran, emphasizing plant-based diets, has lower 25-hydroxycho-

lecalciferol concentrations than Japan, with high ocean fish consumption. It has been suggested that daily 3000–5000 IU of vitamin D supplementation (i.e., cholecalciferol) is needed to maintain serum 25-hydroxycholecalciferol concentration during the winter months when substantial cutaneous production of vitamin D is inadequate **(55)**.

On the other hand, recent clinical trials have also recommended higher doses of vitamin C (e.g., 0.000015-0.000024 kg/day) for patients with COVID-19 **(56)**. However, research in this field is ongoing, and a more certain conclusion cannot be drawn until further investigations confirm the results.

Table 2. Exercise-related nutritional recommendations to do across delta variant-COVID-19 outbreaks.

	Description
Carbohydrates (57)	• 0.3-0.4 kg of carbohydrates such as pasta, rice and bread, 3-4 hours prior to training • 0.001-0.0012 kg/kg body weight/hour of carbohydrates such as potatoes and pasta after training
NOTE: RDA for carbohydrates is 0.13 kg/day for adults and children aged ≥ 1 year (58). This is the amount of glucose needed for optimum brain and nervous system functions. However, carbohydrates can make up 45-65% of a healthy person's daily diet (59). For instance, this equates to 0.225-0.325 kg/day for a 2,000 kcal diet.	
Fruits (23)	• Small portions of fruits such as bananas, dates, and raisins during training • Bigger portions after training
NOTE: Fiber can make up 0.14-0.34 kg/1,000 kcal of a daily diet of everyone aged ≥ 2 years, depending on age-sex groups (59). For instance, this equates to 2 cups of fruit and 2.5 cups of vegetables per day for a 2,000 kcal diet.	
Vitamins (51)	• Vitamin C: 0.0002 kg per day • Vitamin D: 2000 IU per day
NOTE: RDA for vitamin C is 0.000015-0.00009 kg/day, and for vitamin D is 600-800 IU/day, for everyone aged ≥ 2 years, depending on age-sex groups (59).	
Others (51)	• Zinc: 0.000008-0.000011 kg per day • Omega-3 fatty acids: 0.00025 kg per day
NOTE: RDA for zinc is 0.000003-0.000011 kg/day, and for omega-3 fatty acids is 0.007-0.017 kg/day, for everyone aged ≥ 2 years, depending on age-sex groups (59).	

RDA: Recommended Dietary Allowance.

5. Conclusion

Although staying at home will affect peoples' immune functions and physical fitness due to significant decreases in daily physical activity, regular moderate-intensity home-based exercise programs provide an opportunity for people to promote their immune system and fitness. However, exercise training without a proper diet, especially sufficient carbohydrates, vitamins, and polyphenols, will not be effective and efficient. As a result **(60)**, exercise and proper diet can be key factors in boosting immune responses and fighting against COVID-19.

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Competing Interests

None declared.

Patient Consent

Not required.

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Conflict of Interest

Not required.

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