Aerobic exercises recommendations and specifications for patients with COVID-19: a systematic review

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Abstract. – OBJECTIVE: This review was conducted to systematically analyze the effects of aerobic exercise on immunological biomarkers to provide safe aerobic exercise recommendations and specifications for patients with COVID-19.

MATERIALS AND METHODS: A systematic search was conducted through MEDLINE (PubMed), Science Direct, Web of Science, Scopus, Cochrane Library, and SciELO databases. The search included the following keywords “immune system”, “immune cell”, or “immune function”; “aerobic training”, “aerobic exercise”, or “physical activity”; “human” or “adult”; and “cytokine”, “killer cell”, “T cell”, “interleukin”, “lymphocyte”, “leukocyte” or “adhesion molecule”.

RESULTS: Eleven studies met the inclusion and exclusion criteria of this search. The most used exercise prescriptions included walking, cycling, or running. The duration of exercise ranged from 18 to 60 min with an intensity of 55% to 80% of VO2max or 60%-80% of maximum heart rate. The frequency range was 1 to 3 times/week. The mainly increased immunological biomarkers included leukocytes, lymphocytes, neutrophils, monocytes, eosinophils, IL-6, CD16-56, CD16, CD4, CD3, CD8, and CD19.

CONCLUSIONS: This review demonstrated that patients with COVID-19 should follow a regular program of aerobic exercise for 20-60 min. This program should be in the form of cycling or walking with an intensity of 55%-80% VO2max or 60%-80% of maximum heart rate. This program should be repeated 2-3 sessions/week. These previous parameters could safely enhance immune functions without producing any exhaustion.

Key Words: COVID-19, Aerobic exercises, Immunological markers, Exercise prescription.

Introduction

World Health Organization (WHO) has announced that COVID-19 is a public world disaster and it fastly propagates through all world countries1. On the 5th of September 2020, there were around 26,171,112 COVID-19 confirmed cases on the world2. COVID-19 is a fresh enclosed RNA beta-coronavirus. COVID-19 is recognized as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)3,4. The common COVID-19 symptoms are fever and cough5. The fever occurs in about 43.8% of the patients on hospital admission and could increase to 88.7% throughout the hospitalization. The cough occurs in approximately 67.8% of all COVID-19 patients3. Other associated symptoms include fatigue, myalgia, and dyspnea.

COVID-19 is a self-limited infection. The strength of host immunity plays a key role in countering it6. Previously, we have demonstrated that increasing the aerobic capacity produces short-term effects on immune and pulmonary functions7. We have demonstrated that the increase in the aerobic capacity improves immune functions through increasing serum immune cells and immunoglobulins, regulating serum C-reactive proteins (CRP), and reducing depression and anxiety.

Also, we have demonstrated that increasing the aerobic capacity protects and decreases the severity of COVID-19 associated disorders and symptoms through increasing lung immunity, increasing lung tissue flexibility, increasing pulmonary muscle endurance and strength, decreasing free radicals production and oxidative damage, decreasing dry cough, and clearing respiratory airflow7.
Due to the importance of increasing the aerobic capacity on immune and lung functions and the lack of studies that described safe specifications of aerobic exercise for patients with COVID-19, this review summarized aerobic exercise recommendations and specifications for patients with COVID-19. These specifications mainly included the mode, intensity, frequency, and duration of aerobic exercises.

### Materials and Methods

**Search Strategy**

This systematic review was designed according to the recommendations and guidelines of the PRISMA Systematic Review and Meta-Analysis Preferred Report Items. The search included Medline (PubMed), Science Direct, Web of Science, Scopus, Cochrane Library, and SciELO databases. The authors considered the following Boolean operators, (MESH) terms, and search strategies: "immune system", "immune cell" or "immune function"; "aerobic training", "aerobic exercises", or "physical activity"; "human" or "adult"; and "cytokine", "killer cell", "t cell", "interleukin", "lymphocyte", "leukocyte", or "adhesion molecule".

**The Mode of Aerobic Exercises**

The inclusion criteria included randomized controlled trials (RCTs) and non-randomized (Non-RCTs) published from 1990 to 2020, the performance of aerobic exercises, non-athletes of both sexes, age range is between 18 and 55 years (menopausal women excluded from this age group due to the hormonal effects), and the English language. The exclusion criteria included athletes or patients with any cardiac or immunity disorders, pregnant women, and smokers.

**Quality Assessment**

The risk of bias and quality of each included study was independently assessed by three independent persons using the PEDro scale. This scale consists of 11 items; 8 items to measure the trial’s internal validity and 3 items to measure the trial’s statistical reporting. The quality assessment of the included studies by PEDro scale is shown in Table I.

### Results

**Search Strategy**

Initially, 12411 studies were found and 5235 studies of them were excluded because of duplication. Additional 7003 studies were excluded...
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after reading their titles and abstracts. The remaining 173 studies were fully analyzed and 162 studies were excluded because they did not meet our inclusion criteria. Finally, 11 studies were included in this review. The flow and outcomes of the search strategy are shown in Figure 1.

**Study Features**

All the included studies investigated the effect of aerobic exercises on the immune system profile in non-athletes. Eight studies were RCTs and three studies were non-RCTs. Six studies performed aerobic exercise for a short period and five studies performed aerobic exercise for a long period. The physical characteristics of the included studies are shown in Supplemental Table I.

**Intervention**

The performed interventions in short-term studies were cycling and walking. The performed interventions in long-term studies were cycling, walking/running, and cycling/running. We found that exercise approaches in the included researches had some heterogeneity. To determine the exercise intensity in the short-term studies, four short-term studies used VO\(_{2\max}\), one study used peak power output, and one study used both VO\(_{2\max}\) and maximum heart rate (MHR). To determine the exercise intensity in the long-term studies, two studies used the VO\(_{2\max}\), and three studies used MHR.

**Immunological Markers**

In the short-term studies, six of them showed significant increases in leukocytes (Leuk), lymphocytes (Linf), neutrophils (Neut), monocytes (Mon), eosinophils (Eosin), IL-6, CD16-56, CD16, CD4, CD3, CD8, CD19, and granulocytes (Gran). One study showed significant increases in all immunomarkers except Mon and Gran. Immunological markers differently increased in some of the included studies as follows: IL-6, CD16-56, CD16, CD3, CD8, and CD19. CD4/CD8 and CD56 nonsignificantly increased in one study. IL-6 and IL-10 significantly decreased in one study. IgG, IgA, and IgM significantly increased in one study, and nonsignificantly increased in one study. Serum C-reactive protein significantly decreased in one study.

The regulation of immunological markers in the included investigations is shown in Table III.

**Discussion**

This review aimed to systematically analyze the studies that investigated the effects of aerobic exercise on immune functions among non-ath-
letes to provide evidence-based aerobic exercise recommendations for patients with COVID-19. This study is unique because it is the first one that provided safe aerobic exercise prescriptions for patients with COVID-19 to improve their immune functions and help to decrease the disease severity and death rate without any exhaustion.

Table II. Association of circ_001680 expression with clinicopathologic characteristics of glioma.

<table>
<thead>
<tr>
<th>Study</th>
<th>Mode</th>
<th>Intensity</th>
<th>Duration</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li and Cheng (2007)²⁰</td>
<td>Cycling</td>
<td>55% VO₂ max</td>
<td>60 Min</td>
<td>1 day/week for 2 weeks</td>
</tr>
<tr>
<td>Koichi Okita et al (2004)²¹</td>
<td>Cycling or running</td>
<td>60% to 80% MHR</td>
<td>80 minutes dance + 30-60 min aerobic exercises</td>
<td>2 days a week for 8 weeks</td>
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<tr>
<td>Mohamed and Taha (2016)²⁴</td>
<td>Walking/running on a treadmill</td>
<td>60-75% of the predicted MHR</td>
<td>50 min</td>
<td>3 sessions/week for 12 weeks</td>
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<tr>
<td>Fabio Santos Lira et al (2017)²⁵</td>
<td>Running intermittently (MAS)</td>
<td>70% of VO₂ max</td>
<td>5 km run</td>
<td>3 sessions/week for 5 weeks</td>
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<tr>
<td>Edwards et al (2006)²⁶</td>
<td>Cycling</td>
<td>55% of maximum power output</td>
<td>45 min</td>
<td>3 sessions /week for 1 week</td>
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<tr>
<td>LaPerriere et al (1994)²⁷</td>
<td>Cycling</td>
<td>70-80% Age-PMHR</td>
<td>45 min</td>
<td>3 sessions/week for 10 weeks</td>
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<tr>
<td>Moyna et al (1996a)²⁸</td>
<td>Cycling</td>
<td>55-85% of VO₂ peak</td>
<td>18 min</td>
<td>1 Session</td>
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<tr>
<td>Kurokawa et al (1995)²⁹</td>
<td>Cycling</td>
<td>60% of VO₂ max</td>
<td>60 min</td>
<td>1 Session</td>
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<tr>
<td>Mitchell et al (1996)³⁰</td>
<td>Cycling</td>
<td>75% VO₂ peak</td>
<td>30 min</td>
<td>3 sessions/week for 12 weeks</td>
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<tr>
<td>Nehlsen-Cannarella et al (1991)³¹</td>
<td>Walking</td>
<td>60% of VO₂ max or 70% of MHR</td>
<td>45 min</td>
<td>1 Session</td>
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<tr>
<td>Moyna et al (1996b)³²</td>
<td>Cycling</td>
<td>55-85% of VO₂ max</td>
<td>18 min</td>
<td>1 Session</td>
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Table III. Post-aerobic exercise regulation and immunological markers.

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<tr>
<th>Study</th>
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<th>IL-1</th>
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<th>IL-6</th>
<th>IL-8</th>
<th>IL-10</th>
<th>CD3</th>
<th>CD4</th>
<th>CD8</th>
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↑: increased, ↓: decreased, ↔: not changed.
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Immunological markers differently changed in the included long-term studies. IL-1ra, IL-6, IL-8, and IL-10 significantly increased in one study 19. IL-6 significantly increased in one study 14. CD3 significantly increased in one study 19. CD4 significantly increased in two studies 19,21. CD16-56 significantly increased in three studies 17,19,21. CD16 significantly increased in one study 28. CD19 significantly increased in one study 19.

The exercise intensities in the included investigations were determined using VO2max or MHR. The short-term studies used VO2max to determine their intensities and they performed the exercise at an intensity of 55%-85% VO2max, or 60%-80% MHR 13, 16-20. While one short-term study used the MHR to determine the exercise intensity and it performed the exercise at an intensity of 60%-80% MHR 13, 60%-75% MHR 14, or 70%-80% MHR 11. Based on these findings, an aerobic exercise at an intensity of 55%-85% VO2max should be recommended for patients with COVID-19 because it increases immune functions. Besides, patients with COVID-19 should feel “somewhat light” exertion during the exercise and should be able to continue a conversation without breathlessness. In conclusion, patients with COVID-19 should feel “fairly light” during warming-up and cooling-down periods and “somewhat hard” during the main time of the exercise session 27,28.

The duration of aerobic exercise in all the included investigations ranged from 18-80 minutes. In the short-term studies, exercise durations were 18 min 11,19, 45 min 16,23, and 60 min 18,20. In the long-term studies, the exercise durations were 30 min 12, 45 min 11, 50 min 14, and 60 min 13. One study did not perform the exercise at a specific time instead, it used a distance of 5km running 25. Thus, 18-60 minutes of aerobic exercise would be a suitable exercise duration for patients with COVID-19. If the patients are sedentary or cannot handle the session time, daily multiple short bursts of aerobic exercise, with avoiding over exhaustion and fatigue, can be an effective way to increase the time of exercise 29.

The frequencies of aerobic exercise ranged from one session/week to three sessions/week. In the short-term studies, exercise frequencies were one session/week for one week 27, one session/week for two weeks 20, and three sessions/week for one week 16. In the long-term studies, the exercise frequencies were two sessions/week for eight weeks 13, three sessions/week for five weeks 25, three sessions/week for nineweeks 22, three sessions/week for ten weeks 21, and three sessions/week for twelve weeks 24. Based on these findings, an exercise frequency of three sessions/week would be a safe and helpful frequency for patients with COVID-19. If the patients are active and did not feel any exhaustion during aerobic exercise sessions, the frequency could be increased to five sessions/week 29.

There were some limitations in these reports. Some of the included studies investigated the effect of aerobic exercise on immune biomarkers response by recruiting both males and females in the same group 30,31. This may affect their results because males and females differently respond to aerobic exercise 25. Some researches included only females without considering the use of contra-
Conclusions

This review demonstrated that patients with COVID-19 should follow a regular program of aerobic exercise for 20-60 min. This program should be in the form of cycling or walking with an intensity of 55%-80% VO\textsubscript{2\text{max}} or 60%-80% of maximum heart rate. This program should be repeated 2-3 sessions/week. These previous parameters could safely enhance immune functions without producing any exhaustion.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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2) World Health Organization. Corona-virus disease (COVID-19) outbreak. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=CjwKCAjw_NX7BRAEiwA2dp-g0hCSX5jaxF1vgawdkp_pQINqBmv7m5wV-Gh-JlKe9uk1ee_qmrKkaohCi50QAvD_BwE.


