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

M. ALAWNA[1,2], M. AMRO[2], A.A. MOHAMED[1]

[1]Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Istanbul Gelisim University, Istanbul, Turkey
[2]Department of Physiotherapy and Rehabilitation, Faculty of Allied Medical Sciences, Arab American University, Jenin, Palestine

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 VO_{2max} 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% VO_{2max} 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 countries[1]. On the 5th of September 2020, there were around 26,171,112 COVID-19 confirmed cases on the world[2]. 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 cough[5]. 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 patients[3]. 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 it[6]. Previously, we have demonstrated that increasing the aerobic capacity produces short-term effects on immune and pulmonary functions[7]. 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 airway[7].

Corresponding Author: Ayman Mohamed, Ph.D, MSc, PT;
e-mail: amohamed@gelisim.edu.tr; dr_ayman_pt@hotmail.com

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[8]. 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[9]), 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 PEPDro scale[10]. 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[10]. 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

Table I. PEDro scale quality assessment strategy of the included studies.

Included Studies	Eligibility criteria	Randomization	Concealed allocation	Baseline similarity between groups	Blinding of Participants	Blinding of therapists	Blinding of all assessors	Key outcome measurements	Intention to treat Analysis	Results of between-group comparisons	Measures of variability
Tzai-Li Li and Pei-Yun Cheng (2007)[20]	✓	×	×	✓	×	×	×	✓	✓	✓	×
Koichi Okita et al (2004)[13]	✓	×	×	×	×	×	×	✓	✓	×	✓
Gihan S. Mohamed, Mona M. Taha (2016)[14]	✓	×	×	✓	×	×	×	✓	✓	✓	✓
Fabio Santos Lira1 et al (2017)[15]	✓	✓	×	✓	×	×	×	✓	✓	✓	✓
Edwards et al (2006)[16]	✓	×	×	✓	×	×	×	✓	✓	✓	✓
LaPerriere et al (1994)[11]	✓	✓	×	✓	×	×	×	✓	✓	✓	✓
Moyna et al (1996a)[17]	✓	✓	×	✓	×	×	×	✓	✓	×	✓
Kurokawa et al (1995)[18]	✓	×	×	✓	×	×	×	✓	✓	×	✓
Mitchell et al (1996)[12]	✓	✓	×	×	×	×	×	✓	✓	✓	✓
Nehlsen-Cannarella et al (1991)[21]	✓	✓	×	✓	×	×	×	✓	✓	✓	✓
Moyna et al (1996b)[19]	✓	×	×	✓	×	×	×	✓	✓	✓	✓

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[11-15]. The physical characteristics of the included studies are shown in **Supplementary Table I**.

Intervention

The performed interventions in short-term studies were cycling[16-20] and walking[21]. The performed interventions in long-term studies were cycling[11,12], walking/running[14,15], and cycling/running[13]. 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_{2max}[17-20], one study used peak power output[16], and one study used both VO_{2max} and maximum heart rate (MHR)[21]. To determine the exercise intensity in the long-term studies, two studies used the VO_{2max}[12,15], and three studies used MHR[13,14].

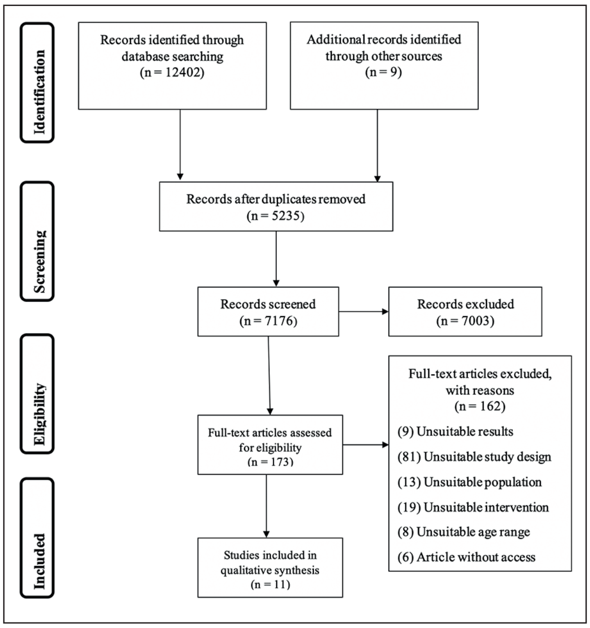

Figure 1. Search strategy findings.

The exercise duration ranged between 18 min-60 min in ten studies. The remaining study performed aerobic exercise until exhaustion[15]. The duration used in short-term studies was approximately 18-60 min and they performed them for 1-2 times/week. Four studies performed aerobic exercise for one time[17-19,21], one study performed aerobic exercise for one week[20], and one study performed aerobic exercise for two weeks[16]. In long-term studies, the exercise duration ranged between 18-80 minutes. One study performed aerobic exercise for 30 minutes[12], one study performed aerobic exercise for 45 minutes[11], one study performed aerobic exercise for 50 minutes[14], one study performed aerobic exercise for 80 minutes[13], and one study performed aerobic exercise for 5 km running[15]. The physical characteristics of aerobic exercise in the included studies are shown in Table II.

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)[16-20]. One study showed significant increases in all immunomarkers except Mon and Gran[21]. Immunological markers differently increased in some of the included studies as follows: IL-6[16], CD16-56[17,19,21], CD16[18], CD3[19], CD4[19,21], CD8[19], and CD19[19]. CD3 and CD18 significantly decreased in one study[17]. CD4 and CD8 significantly decreased in one study[19]. Four studies had nonsignificant changes in CD3[21], CD4[18], CD8[18], or CD20[21].

In the long-term studies, Leuk nonsignificantly increased in one study[11]. Linf and Leuk nonsignificantly increased in two studies[11,12]. CD4, CD8, and CD20 significantly increased in one study[11]. CD4/CD8 and CD56 nonsignificantly increased in one study[11]. IL-6 and IL-10 significantly decreased in one study[15]. IgG, IgA, and IgM significantly increased in one study[14], and nonsignificantly increased in one study[12]. Serum C-reactive protein significantly decreased in one study[13]. 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-

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

Study	Mode	Intensity	Duration	Frequency
Li and Cheng (2007)[20]	Cycling	55% VO_{2max}	60 Min	1 day/week for 2 weeks
Koichi Okita et al (2004)[13]	Cycling or running	60% to 80% MHR	80 minutes dance + 30-60 min aerobic exercises	2 days a week for 8 weeks
Mohamed and Taha (2016)[14]	Walking/running on a treadmill	60-75% of the predicted MHR	50 min	3 sessions/week for 12 weeks
Fabio Santos Lira[1] et al (2017)[15]	Running intermittently	70% of VO_{2max} (MAS)	5 km run	3 sessions/week for 5 weeks
Edwards et al (2006)[16]	Cycling	55% of maximum power output	45 min	3 sessions /week for 1 week
LaPerriere et al (1994)[11]	Cycling	70-80% Age-PMHR	45 min	3 sessions/week for 10 weeks
Moyna et al (1996a)[17]	Cycling	55-85% of VO_2 peak	18 min	1 Session
Kurokawa et al (1995)[18]	Cycling	60% of VO_{2max}	60 min	1 Session
Mitchell et al (1996)[12]	Cycling	75% VO_2 peak	30 min	3 sessions/week for 12 weeks
Nehlsen-Cannarella et al (1991)[21]	Walking	60% of VO_{2max} or 70% of MHR	45 min	1 Session
Moyna et al (1996b)[19]	Cycling	55-85% of VO_{2max}	18 min	1 Session

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.

Immunological markers differently changed in the included short term studies. Leuk significantly increased in three studies[18,20,21]. Linf significantly increased in three studies[18,19,21]. Gran significantly increased in two studies[18,19]. Neut significantly increased in three studies[19-21]. Mon significantly increased in three studies[17,19,20]. Eo-

Table I. Table III. Post-aerobic exercise regulation and immunological markers.

Study	Leuc	Linf	Gran	Neut	Mon	Eosin	IL-1	IL-2	IL-6	IL-8	IL-10	CD3	CD4	CD8	CD4 CD8	CD16-56	CD16	CD56	CD18	CD19
Li and Cheng (2007)[20]	↑	↑		↑	↑															
Koichi Okita et al 2004[13]																				
Mohamed and Taha (2016)[14]																				
Fabio Santos Lira1 et al (2017)[15]									↓		↓									
Edwards et al (2006)[16]									↑											
LaPerriere et al (1994)[11]	↔	↔			↔								↑	↑	↔			↔		
Moyna et al (1996a)[17]		↑			↑							↓				↑				↓
Kurokawa et al (1995)[18]	↑	↑	↑										↔	↔			↑			
Mitchell et al (1996)[12]		↔																		
Nehlsen-Cannarella et al (1991)[21]	↑	↑	↔	↑	↔							↔	↑			↑				
Moyna et al (1996b)[19]		↑	↑	↑	↑	↑						↑	↑	↑	↓	↑				↑

↑: increased, ↓: decreased, ↔: not changed.

sin 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[18]. CD19 significantly increased in one study[19].

Immunological markers differently changed in the included long-term studies. IL-1ra, IL-6, IL-8, and IL-10 significantly increased in response to an aerobic exercise that lasts for more than 2 hours, like cycling, marathons, and triathlons[23,24]. Neuts, Leuk, TNF-a, adhesion molecules (ICAM-1), and interleukins (IL-6, IL-10, IL-8, IL-12) significantly increased in response to long-running for 42.2 km[25]. Mon, Neut, and Leuk significantly increased in response to 21.1 km half-marathon[22]. Neut, Mon, and NK cells significantly increased in response to moderate cycling for 2 hours, while IL-6 remained high in response to the same exercise[26]. Immunoglobulins significantly increased in response to moderate walking for 45 min[21], while interleukin-2 and T-cell (CD5 and CD25) increased insignificantly in response to the same exercise. Lymphocytes significantly increased in response to cycle ergometer sessions (70-80% of MHR intensity, 45min/ week, for 10 weeks)[15]. Lymphocytes nonsignificantly increased in response to cycle ergometer sessions (75% of VO_{2max}, 30 min/ session, 3 times/week for 12 weeks)[12].

The modes of aerobic exercise were mainly cycling or walking. Seven studies performed cycling on an ergometer[11,12,16-20]. Two studies performed running on a treadmill[14,21]. Two studies performed cycling on an ergometer and running on a treadmill[13,15]. Based on these findings, treadmill walking or cycling (recumbent bike or upright with minimal resistance) would be a suitable exercise method for sedentary patients with COVID-19. Also for older adults with balance problems, cycling may be a good choice for them[27].

The exercise intensities in the included investigations were determined using VO_{2max} or MHR. The short-term studies used VO_{2max} to determine their intensities and they performed the exercise at an intensity of 55% VO_{2max}[16,20], 55%-85% VO_{2max}[17,19], or 60% VO_{2max}[18]. While one short-term study used the MHR to determine the exercise intensity and it performed the exercise at 60%-70% MHR[21]. Two long-term studies used VO2max to determine their intensities and they performed the exercise at an intensity of 70% VO_{2max}[15], or 75%VO_{2max}[12]. The other three long-term studies 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% VO_{2max} 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. Inconclusion, 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[17,19], 45 min[16,21], 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[15]. 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[17], 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[15], three sessions/week for nineweeks[12], three sessions/week for ten weeks[11], and three sessions/ week for twelve weeks[14]. 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[32]. Some researches included only females without considering the use of contraceptives[21]. Contraceptives can induce changes in immune biomarkers such as raising the absolute count of leukocytes and other biomarkers above their normal levels in healthy individuals[33]. The number of the included investigations was small because there are a small number of studies that investigated the effect of aerobic exercise on healthy individuals. Future systematic reviews are required to investigate the effect of aerobic exercise to improve immune biomarkers in patients with COVID-19 and other diseases, such as diabetes mellitus, hypertension, or obesity. Also, systematic reviews are highly required to investigate the effect of aerobic exercise to improve immune biomarkers in older patients with COVID-19.

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_{2max} 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.

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