Review Article

Can physical activity affects on Omicron mutation: Cross talk between skeletal muscle and the immune system

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Abstract

Omicron, a new type of SARS-CoV-2 was first reported by South Africa to the World Health Organization (WHO) on November 24, 2021. Two days after Africa was reported to the World Health Organization, the Omicron was identified as a global threat. Omicron has many genetic mutations, the potential effects of which are more dangerous than other SARS-CoV-2 genetic mutations. With the increase in vaccination in the world, the amount of physical activity to improve the functioning of the immune system decreased. Relying on vaccines alone cannot guarantee an improvement in the functioning of the immune system and the people of the world, given the lack of knowledge about the prevalence of omicron and its potential dangers, should look for ways to boost the immune system. In this study, we highlight the importance of increasing physical activity at the time of omicron outbreaks, along with the proposed protocols.

Key Words: **Immune system, Exercise, Physical activity, Myokines, Omicron**

Introduction

In late December 2019, an unknown disease called pneumonia with unknown effects spread in Wuhan, China (He et al., 2020). A few days later, the causative agent of this mysterious pneumonia was identified as a new coronavirus (nCoV) by several independent laboratories (Lu et al., 2020; P. Zhou et al., 2020). Finally, the World Health Organization named the virus "acute respiratory syndrome coronavirus-2" (SARS-CoV-2) (M. Zhou et al., 2020). Since that time, the virus has killed millions of people and spreads through airborne particles, so quarantine and staying at home to reduce the transmission of the disease was on the agenda of governments (Jiang et al., 2020). During the home quarantine period, it was discovered that the corona virus could affect the body's most vital part, that is, the immune system (Tay et al., 2020; Yang et al., 2020). Therefore, many studies have reported strategies to improve the functioning of the immune system, one of which is to increase physical activity (Ahmadi Hekmatikar & Molanouri Shamsi, 2020; Chagas et al., 2020; Fallon, 2020; Khoramipour et al., 2021; Lendacki et al., 2021).

Meanwhile, a year later, various COVID-19 vaccines were developed by scientists and introduced to the world, which could reduce the risks associated with coronavirus mortality (Callaway, 2021; Della Pia et al., 2021). The World Health Organization (WHO) had three general categories after the outbreak of COVID-19 to prioritize surveillance and research into the virus: variants of concern (VOCs), variants of interest (VOIs), and variants under monitoring (VUMs) (He et al., 2021). On November 26, 2021, a new type called Omicron (B.1.1.529) was designated as the fifth VOC by the WHO, which immediately raised global concerns (He et al., 2021). Omicron (B.1.1.529) is a rapidly spreading coronavirus in the world that most people are unaware of and can have many dangerous effects.

Due to the increase in vaccine production worldwide, people have reduced their physical activity and increased their vaccine doses (Ita, 2021). In this way, it can be stated that in absence

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of a vaccine, they increased the amount of physical activity while relying on the effects of the vaccine during its production means a decrease in physical activity. It has been almost two years since the outbreak of COVID-19 in the world and people have returned to their normal lives, however, recent reports have raised some concerns (Omicron is on its way) (Team, 2021). However, in this study, the goal of the researchers is to encourage people to continue physical activity, even during the return of COVID-19 in the form of Omicron (B.1.1.529) and its rapid spread in the world. Therefore, in this study, we will examine the effect of physical activity to counteract the possible effects of Omicron (B.1.1.529).

Omicron in the world?

On December 3, 2021, the World Health Organization (WHO) reported Omicron in 38 countries in all six WHO regions, and a growing trend in South Africa indicates a transferable increase (Kupferschmidt, 2021). On the other hand, a statement from the Dutch Ministry of Health showed that the COVID-19 (Omicron) mutant virus was present in Europe ten days before it was detected in Africa (Vaughan, 2021) The report found that two of the items discovered in the Netherlands were samples tested on November 19 and 23, 2021, which had been exposed to omicrons before warning from South Africa (Vaughan, 2021). On November 13 and 18 in Hong Kong, two patients became infected with Omicron while traveling and the first passenger transmitted the virus to another passenger despite being in the hotel quarantine in the opposite rooms (Gu et al., 2021). In addition, on December 19, Iran reported its first Omicron case on a passenger returning from the UAE. Therefore, what studies and reports show is that Omicron is spreading around the world, and where Omicron comes from and what effects it has can be important to us? Table 1 shows 89 countries that reported the number of patients with Omicron (It was discovered on all six continents. https://www.gisaid.org/hcov19-variants/.2021,").

What is Omicron and why does it cause so much concern?

Table 1. 89 countries and the number of patients with Omicron

Countries	Total	In past 4 weeks	In past 4 weeks%	Countries	Total	In past 4 weeks	In past 4 weeks%	Countries	Total	In past 4 weeks	In past 4 weeks%
United Kingdom	43,156	42,658	29.7%	Russia	48	48	19.5%	Mauritius	7	0	0.0%
USA	15,037	14,824	15.9%	Zambia	46	42	100.0%	Bangladesh	7	7	20.6%
Denmark	3,318	3,270	11.5%	Lithuania	46	46	7.0%	Reunion	7	4	3.4%
South Africa	1,894	650	98.6%	Nigeria	45	27	81.8%	Pakistan	6	6	16.7%
Israel	1,259	1,241	26.7%	Czech	45	43	3.9%	Sri Lanka	5	4	2.2%
Australia	1,231	1,216	36.1%	Kenya	38	29	76.3%	Liechtenstein	4	4	3.8%
Austria	785	19	3.3%	Malawi	34	34	100.0%	Lebanon	4	4	100.0%
Belgium	696	676	17.9%	Malta	34	34	61.8%	Trinidad and Tobago	3	3	11.1%
Switzerland	686	611	15.3%	Poland	30	30	0.8%	Nepal	3	0	0.0%
Canada	629	576	18.3%	New Zealand	29	29	13.5%	Finland	3	0	0.0%
Spain	600	588	25.0%	Senegal	26	23	57.5%	Philippines	3	3	100.0%
Italy	425	399	7.7%	Ecuador	24	24	18.9%	Colombia	3	3	9.1%
Netherlands	399	327	11.4%	Georgia	22	19	11.2%	Maldives	2	1	1.8%
Botswana	382	321	97.6%	Thailand	20	16	4.7%	Algeria	2	1	50.0%
Sweden	376	355	13.8%	Cambodia	20	20	10.2%	Greece	2	1	5.3%
Germany	334	232	2.3%	Jordan	19	19	52.8%	Venezuela	2	2	100.0%
France	331	294	4.5%	Hong Kong	18	4	44.4%	Sierra Leone	1	0	0.0%
Chile	325	324	35.6%	Mozambique	17	0	0.0%	Egypt	1	1	100.0%
Norway	308	274	40.3%	Namibia	17	0	0.0%	Luxembourg	1	1	0.5%
Singapore	281	281	34.1%	Malaysia	16	15	7.9%	Iran	1	1	20.0%
Mexico	254	251	34.5%	Morocco	15	15	83.3%	Vietnam	1	1	1.2%
India	205	197	19.7%	Romania	15	13	7.9%	Ukraine	1	1	14.3%
Brazil	154	147	16.8%	Argentina	14	14	18.7%	Uganda	1	1	100.0%
Japan	152	143	46.0%	Peru	12	12	44.4%	Costa Rica	1	1	12.5%
Ireland	144	127	83.0%	Slovenia	12	11	1.0%	Panama	1	1	100.0%
Gibraltar	122	122	30.9%	Congo	10	10	100.0%	Mauritius	7	0	0.0%
Turkey	117	117	3.0%	Slovakia	10	9	1.7%				
Portugal	115	90	8.5%	Oman	9	8	38.1%				
Indonesia	67	67	19.6%	South Korea	9	6	0.8%				
Ghana	66	20	95.2%	Montenegro	8	8	16.3%				
Puerto Rico	60	59	60.2%	Brunei	8	8	40.0%				

After the COVID-19 vaccine was widely produced and distributed around the world and the people of the world started their daily lives African scientists have reported 'Omicron' as a worrying new strain of SARS-CoV-2 to the World Health Organization in recent weeks (Bai et al., 2021; Pulliam et al., 2021; Viana et al., 2021). The world is eagerly awaiting clues as to how the epidemic will change direction. However, a big conundrum is where and how the Omicron evolved and what lessons it has learned to avoid a dangerous species of the future (Kupferschmidt, 2021). Omicron has been found to have 50 genetic mutations, of which about 26 to 36 are related to Spike COVID-19 (Team, 2021; Roessler et al., 2021). These mutations in the spike are involved in the transmission, disease severity, and immune escape.

Another reason why Omicron could be a dangerous virus is the receptor-binding domain (RBD). Spike receptor-binding domain (RBD) is a validated viral entity that detects ACE2 receptor as a mediator of virus entry (Lan et al., 2020; Yan et al., 2020). It is noteworthy that the RBD spike is the main target for neutralizing antibodies. Previous studies have shown that mutations in the coronavirus at the 484 and 417 spike positions are associated with immune escape (Zimerman et al., 2021). Since the Omicron type also contains the E484A and K417N mutations, it is likely that the Omicron will also resist these two antibodies and have a strong immune escape (He et al., 2021). These mutations in Omicron show an increase in transmissibility and pathogenicity and a decrease in the ability to be neutralized by monoclonal antibodies and escape immunity (He et al., 2021).

Moreover, one of the main concerns is to see what effects Omicron will have on the immune system. Omicron mutations help it escape antibodies, the body's first line of defense against infection (Keeton et al., 2022). New findings show that vaccinated people are about three to four times more likely to get the virus if a family member becomes infected with Omicron (Keeton et al., 2022). New studes shows that protection against SARS-CoV-2 virus is reduced even in people who have experienced both SARS-CoV-2 infection and are vaccinated against it, a compound that initially creates excessive immunity (Keeton et al., 2022). However, previous evidence suggests that the power of existing vaccines against other types of coronaviruses is gradually declining. Recent data suggest that re-infections and new infections are more likely to occur in the Omicron type, suggesting that combined or enhanced immunity is the key to preventing severe infection (Keeton et al., 2022).

Although, the exact effects of Omicron on the immune system have not yet been reported, strengthening the immune system is one of the most important and key strategies to combat this unpredictable mutant virus. It has been reported that the Omicron can cross the body's first line of defense but cannot cross the body's second line of defense, the T cells (Keeton et al., 2022). Well-maintained T cell immunity against Omicron is likely to help protect against severe COVID-19 (Keeton et al., 2022). In recent studies, researchers have emphasized the role of Omicron by influencing myokines. In this regard, Suzuki et al. (2022) in a study entitled "The Potential of Exerkines in Women's COVID-19: A New Idea for a Better and More Accurate Understanding of the Mechanisms behind Physical Exercise" reported that in Covid-19 and its mutations, its genes are affected like omicron myokines (Suzuki et al., 2022). These behavioral changes of myokines, which include ↑myostatin ↑TGF-β1 ↑IL-6 ↑IL-15 ↓decorin ↓irisin ↓BDNF ↓FGF↔SPARC, can lead to a decrease in immune system function (Suzuki et al., 2022). It seems that the binding of Omicron and its receptor on the muscle can lead to the entry of this virus into the muscle and behavioral changes in myokines (Suzuki et al., 2022). Another decrease in the function of body's immune system is the behavioral changes of myokines that can affect the body's immune system (Rogeri et al., 2020).

Table 2. Summary of the study recommendations for exercise during Covid-19

Type of exercise	Recommended protocols
Yoga, tai chi, walking, cycling, weight training	Low-intensity exercise includes: (30-45% Vo2max or Borg scale 1 to 3). This exercise is suitable for children and the elderly. Summary Studies have reported at least 100 to 150 minutes per week, which is appropriate for this age group of 150 minutes per week. The number of sessions per week between 2 to 3 weeks is sufficient.
Aerobic exercise (including walking, cycling, running, mountaineering, boxing, tai chi, rope, and weight training)	Moderate-intensity exercise: (45-65% Vo2max or Borg scale 4 to 6). This exercise is suitable for people between the ages of 18 and 40. 150 to 300 minutes per week can be suitable for this age group. The appropriate number of training sessions for this age group is 3-5 training sessions per week. The duration of each training session with cooling and warming is a total of 50 to 60 minutes.
Resistance training	Moderate-intensity exercise: (50-70% 1RM or Borg scale 4 to 6). This exercise is suitable for people between the ages of 18 and 40. 150 to 300 minutes per week can be suitable for this age group. Exercises in a circle or station in each session and the number of repetitions between 10 to 12 repetitions between 3 to 4 sets. The duration of each training session with cooling and warming is a total of 50 to 60 minutes.
Anaerobic exercises	High intensity training: (65-100% Vo2max or Borg scale 4 to 10). Avoid these exercises.

The relationship between skeletal muscle and the immune system occurs in different ways and includes different aspects. For example, the increase of TGF-β1 and IL-6 in the muscle can lead to a decrease in the function of the immune system (Rogeri et al., 2020). Therefore, it was hoped that strengthening the body's second line of defense might be able to prevent infections and side effects of Omicron. Apart from using vaccines, it is one of the best ways to do moderate-intensity physical activity.

Can physical activity really be effective in combating Omicron?

Looking at the history, scientists have stated that exercise is a free medicine for human health (Johnson, 1960). Due to the mechanization of living standards and reduced physical activity, the rate of various diseases had increased (Ehrman et al., 2009). When people were going about their daily lives, the spread of COVID-19 in the world came as a huge shock to people who were not physically active. Because regular physical activity can improve the immune system (Brolinson & Elliott, 2007), and on the other hand, COVID-19 directly fights the immune system (Fontanet & Cauchemez, 2020). Therefore, in the first months of the outbreak of coronavirus in the world, many studies were published which stated that regular physical activity can improve the immune system and be effective in combating COVID-19 (Ahmadi Hekmatikar & Molanouri Shamsi, 2020; Hekmatikar et al., 2021; Khoramipour et al., 2021).

Further studies reported exercise at home, which was moderate to low in intensity (Ahmadi Hekmatikar & Molanouri Shamsi, 2020; Hekmatikar et al., 2021; Khoramipour et al., 2021). The importance of physical activity increased dramatically during the COVID-19 pandemic due to the improvement of the immune system through exercise (Fontanet & Cauchemez, 2020; Khoramipour et al., 2020). Therefore, improving the immune system during the COVID-19 pandemic through moderate-intensity exercise can be one of the main ways to fight the Coronavirus. The study recommendations for training during dangerous COVID-19 surges are summarized in Table 2.

With the production of vaccines in the world, the amount of physical activity decreased and the reliance on vaccines increased. Studies have found that increasing physical activity during the COVID-19 pandemic and receiving the vaccine and reducing physical activity levels would lead to increased depression and anxiety (Farhani et al., 2022; Puccinelli et al., 2021). On the other hand, the relationship between physical activity and behavioral changes of myokines in muscle can also be very effective in controlling Omicron. For example, it is mentioned in a study that resistance training with an intensity of 50 to 70% 1RM and aerobic exercises with an intensity of 55 to 60 % Vo2max can lead to behavioral changes of myokines and improve the functioning of the immune system (Suzuki et al., 2022). Other studies have also confirmed that aerobic and moderate-intensity resistance training can be a suitable strategy for improving positive behavioral changes in muscle myokines, and this can lead to improved immune system function (Goh et al., 2014; Leal et al., 2018; Pedersen et al., 2007).

Although, the studies stated that high-intensity training cannot be a suitable strategy for improving the immune system function through positive behavioral changes of myokines (Goh et al., 2014; Leal et al., 2018; Pedersen et al., 2007; Suzuki et al., 2022), what is important is to probe the time physical activity can be beneficial for Omicron patients. Suzuki and colleagues were able to show that during viral diseases such as Covid-19, only low-intensity resistance training (30-40% 1RM) can be a relatively good solution to reduce the negative changes of myokines in the muscle (Suzuki et al., 2022). In confirmation of these findings, another study stated that low-intensity resistance training in a patient with Covid-19 could lead to the improvement of physiological changes in the patient (Hekmatikar et al., 2021). On the other hand, it appears that the best training strategies for producing positive changes in myokines in the muscle are after hospital discharge (Ahmadi Hekmatikar et al., 2022; Suzuki et al., 2022).

Finally, for a better impact of physical activity on myokine, resistance training can be effective first in a chronic form and then aerobic training (Ahmadi Hekmatikar et al., 2022; Suzuki et al., 2022). Although, it seems that resistance training may be effective in an acute form, these exercises are more effective during low-intensity disease in order to control the disease (Ahmadi Hekmatikar et al., 2022; Suzuki et al., 2022). Thus, the focus of studies is the importance of the effect of chronic training on myokines and the improvement of immune system function from the point of view of omicron control (Ahmadi Hekmatikar et al., 2022; Suzuki et al., 2022).

Why can the immune system improvement be effective in the Omicron wave?

It has been found that the host immune system itself determines the severity of COVID-19 in the body (Agha-Alinejad et al., 2022; Ahmadi Hekmatikar et al., 2022; Merad & Martin, 2020). The body has two immune systems including: I) Innate immune system, and II) adaptive immune system. The innate immune system is the body's first line of defense against the corona virus (Schultze & Aschenbrenner, 2021; Tayebi et al., 2020). One of

One of the main components of the innate immune system is natural killer cells. New studies have shown that natural killer cells change their nature and lose their cytotoxicity due to the entry of COVID-19 (Schultze & Aschenbrenner, 2021; Suzuki et al., 2022). COVID-19 has been shown to bypass the innate immune system, but recent studies have shown that the role of the adaptive immune system in counteracting COVID-19 is more prominent than the innate immune system (Sette & Crotty, 2021).

Immunological memory is the basis for lasting protective immunity after infection or vaccination. Immunological memory can include memory B cells, antibodies, memory CD4+ T cells, and / or memory CD8+ T cells (Dan et al., 2021). Studies in patients with acute and recovering COVID-19 have found that T cell responses are associated with reduced disease (Liao et al., 2020; Moderbacher et al., 2020). Indicates that the response of SARS-CoV-2-specific CD4+ T and CD8+ T cells may be important for its control and resolution (Laing et al., 2020; Zhang et al., 2020). Therefore, increasing the level of T cells can be effective in controlling coronavirus disease. It has also been shown that an increase in T cells could possibly protect the body against Omicron (Keeton et al., 2022). During moderate-intensity physical activity, an increase in T cells can be one of the main factors in improving the adaptive immune system (Keeton et al., 2022). Body activity does not appear to have an effect on the immune system in the short term, and chronic immune system changes can be much more appropriate (Sellami et al., 2018). Of course, this is not surprising, because after the death and negative effects of Covid-19, scientists finally realized that the body's adaptive immune system and T cells are the hope for humans to fight COVID-19 (Grifoni et al., 2021). However, given that Omicron is new and has not been studied much, it is not yet possible to say how physical activity and changes in the immune system can actually fight the mutated virus.

Discussion

As the world faces its third year of coronavirus outbreak and its prevalence has increased by the most infectious strain ever, many scientists are optimistic that the death toll from this epidemic on global health will be reduced by 2023. The increase in Omicron cases in Europe and North America has been very rapid, and we may see an equally rapid decline in the next month or two, although it may take four to six months for this species to resonate around the world. Immunity to the Omicron type of coronavirus has been shown to decrease with both the Moderna and Pfizer / BioNTech vaccines - but not to the extent that reduced after a normal infection (Tzenios et al., 2023). Some experts see Omicron as an indicator of the future evolution of the Sars-Cov-2 virus. Because natural selection helps mutations to pass as quickly and efficiently as possible between people who already have immune protection. Mutations in the Omicron make it much more infectious than previous species in the nasopharynx and upper respiratory tract - aiding rapid transmission - but conversely less likely to penetrate deep into the lungs, where it is most damaged (Grifoni et al., 2021).

In this study, it was verifies that Omicron is very dangerous, but its effects are still unknown. When the corona virus was first known in the world, millions of people died because their immune systems were low due to inactivity. Three years after the start of the corona virus in the world, the worrying news about the Omicron mutant virus has caused a great deal of concern. Therefore, in this study, it is recommended that before the virus regains power in the world, it is better to warn the people to increase physical activity to improve the functioning of the immune system. Omicron can bypass the innate immune system, but a review of the articles showed that Omicron is likely to be weakened against T cells. Therefore, in addition to receiving the third dose of the vaccine, moderate physical activity can help improve the functioning of the immune system and strengthen T cells. Finally, it can be stated that the danger is near and it is better to strengthen your immune system to fight against this virus.

Conclusions

In general, the results of the present study along with previous ones showed that Omicron is one of the most dangerous mutant viruses that can lead to physiological behavioral changes and decreased immune system function by binding to its receptors throughout the muscle. It seems that one of the reasons for the decrease in the immune system's function is the behavioral changes of myokines. However, one of the important strategies to deal with and control Omicron is physical activity. It seems that physical activity can be effective in two aspects from a muscular perspective: On the one hand, the importance of physical activity and low-intensity resistance training during the Covid-19 as a good strategy; and on the other hand, physical activity in the form of moderate intensity exercise is suggested after the discharge from the hospital . However, the effect of physical activity on myokines is more chronic from the point of view of Omicron control. It seems that after chronic physical activity, myokines start to undergo positive changes, and these positive changes can create adaptation, which is an excellent strategy for improving immune system function. Ultimately, this improvement in immune system function can lead to Omicron control.

What is already known on this subject?

The risks of Omicron along with the increase in mortality, the prevalence of which has recently increased again.

What this study adds?

Highlighting the importance of Omicron in the body's immune system, especially changes in myokines and the importance of physical activity to control and deal with it.

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Compliance with ethical standards

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