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Physical exercise as cytokine modulator in inflammatory immune response: a systematic review

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Abstract: Physical exercise contributes to maintain our health, through its role in inflammatory immune response. Cytokines are proteins that mediate communication between immune cells, either as pro- or anti-inflammation agents. Nonetheless, the dominance of pro- over anti-inflammatory cytokines during a workout, is harmful to health. This systematic review aimed at determining the effect of physical activity in modulating pro- and anti-inflammatory cytokines during immune response. Following Preferred Reporting Items for Systematic Reviews (PRISMA) guideline, literature searching was conducted in 3 databases which were PUBMED/MEDLINE, DOAJ and GARUDA, using keywords, citation tracking and snowballing. Inclusion and exclusion criterias were used to screen, while the Newcastle Ottawa Scale (NOS) was used to assess the quality of the articles. Data extraction and analysis were conducted descriptively. There were 376 articles identified, of which 329 were sorted and 82 were retrieved. Thirty articles underwent quality assessment, resulting to 12 inclusion studies. In conclusion, physical exercise influences the modulation of cytokine, whereby IL-6 and TNF-α (pro-) which increase at the beginning of exercise, are balanced by the increase of IL-10 (anti-inflammatory), which appears later in exercise or during recovery. For this purpose, physical exercise is recommended as a combination of aerobic and resistance exercise performed regularly at moderate intensity.

Keywords: sport, immune response, cytokine storm, IL-6 and -10, TNF-α

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INTRODUCTION

Covid-19 pandemic has taught us that taking care of our health and fitness is extremely important to build a proper and strong immunity against harmful pathogen (Nasrulloh et al., 2021). These could be achieved by consuming a balanced nutritious diet, having adequate rest and performing regular physical exercise (Adijaya & Bakti, 2021). Physical exercise is a form of physical activity, energy expenditure and calorie burning, which is planned, structured, and sustained by involving repetitive body movements, in order to improve physical fitness and immunity (Hayati, 2014).

Immunity is the body's ability to recognize (self/non-self), neutralize and eliminate, and metabolize foreign objects without causing damage to their own tissues (Maulana et al., 2020). Another term is the body's resistance which is the ultimate result of how immune system works through immune response (Widiastuti, 2020). The immune system consists of biological mechanisms (functional organs, tissues, cellular, molecular) used by individuals to fight against invading germs/pathogens (defense mechanism), to maintain stability of the internal environment (homeostasis), and to monitor abnormal cells (surveillance). There are two types of immune responses, namely natural/innate (nonspecific) and adaptive (specific). One of the important components in both innate and adaptive immune response is cytokine (Hayati, 2014).

Cytokines are small proteins (peptides with a molecular weight of 5-20 kDa) produced by various cells as mediators that regulate the immune response in intercellular signaling (communication), inflammation and the formation of blood cells (hematopoiesis). Cytokine is a general name and various cytokines are specifically named after the cell that produces them, for example lymphokines (cytokines produced by lymphocytes), monokines (cytokines produced by monocytes), chemokines (cytokines with chemotactic activity), and interleukins (cytokines produced by one leukocyte and act on other leukocytes). Cytokines are produced only when needed, are not stored and act on target cells either directly or indirectly. Cytokines play a role in the inflammatory response, activation of immune cells (macrophages and T lymphocytes) and the formation of antibodies. Based on their effects, there are two types of cytokines, namely pro-inflammatory cytokines, which function to support inflammation and destroy infected cells, for example tumor necrosis factor (TNF)-α, IFN (interferon), IL (interleukin)-1β, IL-2, IL-3, IL-5, IL-8; and anti-inflammatory cytokines, which function to control proinflammatory cytokine responses and limit the tissue damage due to immune response, such as IL-1ra, IL-4, IL-10, IL-11, and IL-13 (Taherkhani et al., 2020). Depending on the situation, IL-6 can act either as a pro or as an anti- inflammatory cytokine (Shehab Mahmoud Abd El-Kader et al., 2013).

Cytokine is also a hot topic in the course of the Covid-19 disease. The immune response to coronavirus infection (SARS CoV2) can trigger an excessive and uncontrolled production of pro-inflammatory cytokines, resulting to an aggressive immune response that causes systemic inflammation and damage to body tissues. This condition, called as a cytokine storm, eventually became the cause of death for Covid-19 patients due to respiratory failure and multi-organ damage (Pertiwi, 2021). Cytokine release can be triggered by a variety of stimuli including hormonal stress, oxidative stress, and physical exercise (Nasrulloh et al., 2021). Physical exercise can increase immune response , including the production of cytokines (Taherkhani et al., 2020). Pro-inflammatory cytokines (IL-2, IL-5, IL-6, IL-8, TNF-α) are needed to boost the immune system during the acute phase of pathogen infection. On the other hand, anti-inflammatory cytokines (IL-1ra and IL-10) are needed to limit the inflammatory reaction so that there is no significant damage to tissues, including the skeletal muscles during exercise (Ostrowski et al., 1999). Therefore, the immune response triggered by physical exercise can have both positive and negative impacts (Maulana et al., 2020). Depending on intensity and duration, strenuous physical exercise has been reported to be associated with a compromised immune response (immune dysfunction) (Widiastuti, 2020).

All in all, the link between physical exercise and immunity has two opposing sides, the helpful and the harmful ones, just like a knife. In one side, physical exercise can strengthen the immune response, but at the other side, physical exercise is also known to be a stressor to the immune system. Thus, ideally, physical exercise can be a potential modulator of the immune system by regulating the release of pro-inflammatory and anti-inflammatory cytokines. This study is a systematic review of current literatures, which purposes to determine the effect of physical exercise in modulating pro and anti-inflammatory cytokines cytokines during immune response.

METHODS

This research is designed as a narrative systematic review, following the *Preferred Reporting Items for Systematic Reviews* (PRISMA) protocol (Figure 1) (Parums, 2021). The PICO was determined to formulate keywords and facilitate literature searching. They are as follow: P (population) i. e. humans, healthy; I (intervention) namely physical exercise; C (comparison) which is a comparison between the type, duration and/ or frequency, and intensity of physical exercise and/or a comparison with sedentary control; and O (outcome), the measured parameter, in this case is cytokine, the mediator of immune response. Based on this PICO, the keywords were formulated as a combination of: 1) "physical-exercise OR physical-activity OR exercise OR training" AND "immune OR immunity OR immune response OR ressistance" AND "cytokine OR cytokines OR inflammation"; and 2) "*latihan-fisik* OR *aktivitas-fisik* OR *olahraga* OR *training* OR *exercise"* AND "*imun* OR *immunitas* OR *kekebalan* OR *respon-imun"* AND *"sitokin* OR *inflamasi*".

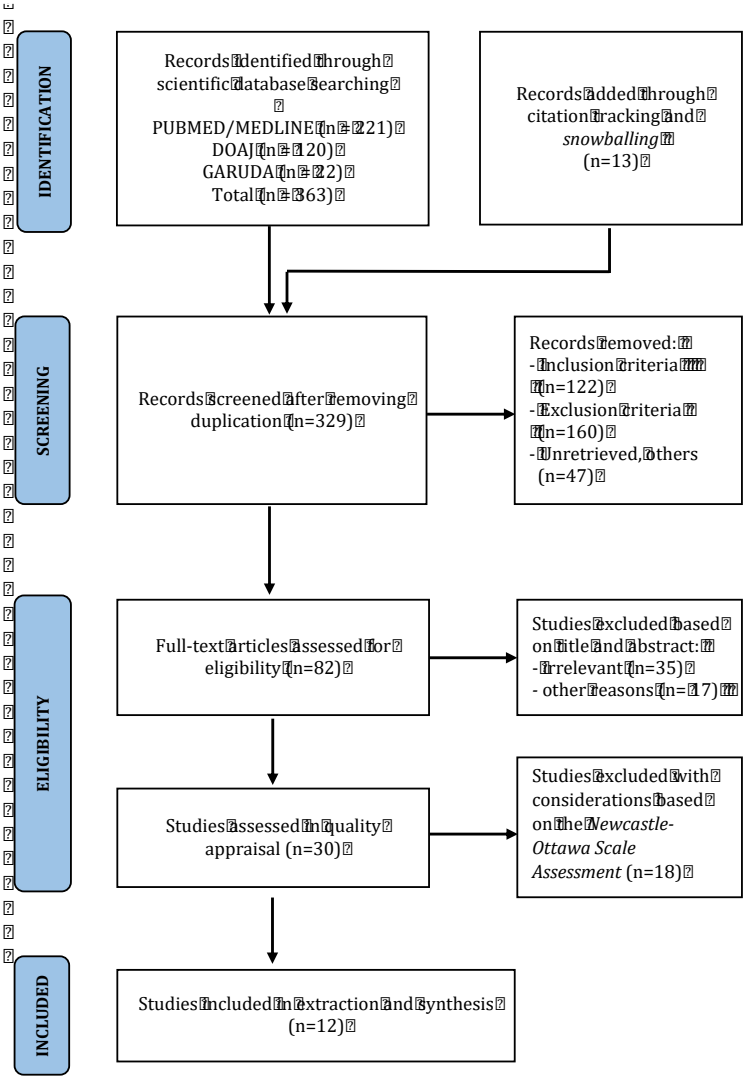

Figure 1. Flowchart for this review

Literature searching was then conducted in three scientific databases: MEDLINE (Pubmed), *Directory of Open Access Journal* (DOAJ) and GARUDA (Indonesian Database) with a combination of keywords searching, citation tracking, and snowballing for published articles during the last 10 years (2012-2022). At the identification stage, there were a total of 376 literatures (with additional records from citation tracking and snowballing) (Figure 1). The identified articles were then sorted for duplication and were screened for the accessibility and relevancy according to the inclusion and exclusion criterias (Table 1).

Table 1. Inclusion and Exclusion Criteria for Records Screening

Inclusion Criteria	Exclusion Criteria
Articles are original articles based on research	Review articles, research reports, bachelor and master thesis, dissertation.
The reported study is an experimental design on healthy human subjects / participants	Animal studies, human studies on certain patients and/ or non healthy individuals, also human studies designed as in vivo or vitro and/ or using samples other than blood
There is clear information about the exercise intervention such as type, intensity, frequency and/ or duration of exercise	The study intervention combines exercise with supplement, specific diet, and/ or certain tested drugs.
The study purposes to investigate the levels of cytokines, either pro or anti-inflammatory, or both types of cytokines.	The study measures other parameters, whereby the cytokines are not the primary object.

The next step was the eligibility screening, whereby title and abstract were used to removed irrelevant studies. There were 30 eligible studies which underwent quality assessment with the *Newcastle-Ottawa Scale* (NOS) (Figure 1) (Luchini, 2017). The NOS instrument is used to assess quality of the reported studies according to the following criterias: 1) participant selection (S), comparability (C), and the certainty of either intervention (E) or significant outcome (E), depending on the type of study (Table 2). A star is awarded when the study meets the criteria for each of the three categories. The final remark is denoted by the average count of stars and their interpretation. In this study, two researchers conducted the assessment, when a dispute occurred, the disagreement was solved with in-depth discussion. Based on the NOS remarks (Table 2), twelve studies graded as good and fair, were finally selected as the inclusion studies for data extraction and data synthesis (Figure 1). The data extraction was done with mapping and classifying the articles to answer the research questions. Afterward, descriptive analysis was used to synthesis and interpret the extracted data.

Table 2. Results of the Quality Asseement with the *Newcastle-Ottawa Scale*

Author, Year	**Types of Exercise**	**Participants**	***Newcastle-Ottawa Scale Assessment****			
			S	**C**	**O - E**	**T**
Vijayaraghava & Radhika, 2014	Acute (moderate versus strenuous) versus Chronic exercise	18 healthy subjects (10 male and 8 female), aged 18-25 y.o.	★★★	★★	★★★	★★☆ Fair
Nielsen et al., 2016	Moderate versus strenuous exercise	22 men and 8 women aged 27-56 y.o., were divided into moderate (n=16) and severe (n=14) group.	★★★	★★★	★★★	★★★ Good
Verbickas et al., 2017	Acute exercise (metabolic-demand exercise versus muscle-damage exercise)	12 healthy men aged 20-30 y.o. were divided into two groups: *sprint interval cycling exercise* (SIE) and *sretch-shortening cycle exercise* (SSE).	★★	★★	★★★	★★☆ Fair
Shehab M. Abd El-Kader & Al-Shreef, 2018	Aerobic versus resistance exercise	86 elderly persons aged 61-66 y.o., rarely exercise, were divided into aerobic (n=42) and resistance (n=44) group.	★★★	★★★	★★★	★★★ Good
Bachi et al., 2019	Combination of aerobic and moderate intensity of resistance training versus sedentary control	54 elderly women, aged 60-80 y.o., divided into training (n=27) and sedentary (n=27) group.	★★★	★★★	★★★	★★★ Good
Fitria et al., 2019	Cardio exercise in various frequency groups	25 healthy elderly people (13 women and 12 men) aged 64-75 y.o., divided into 3 frequency group.	★★★	★★★	★★★	★★★ Good
Sampaio et al., 2019	Combination of aerobic and moderate-intensity resistance	32 elderly women, aged 60-70 y.o.	★★★	★★	★★★	★★☆ Fair
Bloigu et al., 2020	Extreme physical exercise, acute exercise at three different intensities	12 active volunteers (10 men and 2 women) and 30 controls (25 men and 5 women)	★★★	★★	★★★	★★☆ Fair
Pozzolo et al., 2020	Moderate versus strenuous aerobic exercise	14 healthy volunteer students	★★★	★★★	★★★	★★★ Good
Despeghel et al., 2021	Combination of resistance and endurance versus control	40 participants were divided into two groups: training (n = 30) and control (n = 10)	★★★	★★★	★★★	★★★ Good
Fonseca et al., 2021	Acute exercise, aerobics of moderate to severe intensity,	12 untrained young men	★★★	★★	★★★	★★☆ Fair
Middelbeek et al., 2021	*Moderate intensity continuous training* (MIT) versus *Sprint interval training* (SIT)	22 inactive healthy men, aged 40–55 y.o., were divided into MIT (n=10) and SIT (n=12) group.	★★★	★★	★★★	★★☆ Fair

RESULTS AND DISCUSSION

Exersice has been widely promoted as important contributors for physical and emotional health. While there are many benefits to immunity, certain types of exercise can also cause significant physiological stress and thus suppress the immune system. Several studies have documented an association between exercise and immune modulation, either activation or inhibition. Activation of the innate immune system occurs in response to exercise and is largely mediated by cytokine signaling (Zheng et al., 2015).

Characteristics of Inclusion Studies

There are 12 literatures reporting the effect of physical exercise on cytokine included in this study (Table 2), and the summary of those studies is presented in Table 3. Five studies reported a single type of exercise intervention, such as aerobic endurance (Fitria et al., 2021; Vijayaraghava & Radhika, 2014) or anaerobic endurance (Bloigu et al., 2020; Fonseca et al., 2021; Nielsen et al., 2016). Four studies compared aerobic with anaerobic endurance (Middelbeek et al., 2021; Pozzolo et al., 2020; Verbickas et al., 2017; Vijayaraghava & Radhika, 2014), one study compared aerobic versus resistance training (El-Kader & Al-Jiffri, 2019). Three studies compared an exercise intervention versus sedentary controls (Bachi et al., 2019; Bloigu et al., 2020; Despeghel et al., 2021) while three others investigated a combination of aerobic and resistance exercise versus sedentary controls (Bachi et al., 2019; Despeghel et al., 2021; Sampaio et al., 2019).

Table 3. Summary of Inclusion Studies on Exercise as Cytokine Modulators

AUTHOR, YEAR	EXERCISE (Type, intensity, duration) *	CYTOKINES AND MEASUREMENT	IMPORTANT RESULTS
Vijayaraghava & Radhika, 2014	*10m Shuttle Walking test* as acute exercise with maximum heart rate (MHR) increased to 50% (day 1) and until 100% from baseline (day 2). *Chronic exercise*: regular exercise from 3 to 30 days at moderate intensity.	Serum IFN-γ was measured by ELISA before, after session 1, session 2, and after the last exercise routine.	Plasma IFN-γ decreased in acute moderate and decreased further in severe exercise and increases in regular moderate exercise.
Nielsen et al., 2016	*Full marathon* (n=14): running time 3 hours 30 mins. *Half marathon* (n=16): running time 1 hour 30 mins (men) and 1 hour 45 mins (women).	Serum IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL12, TNF-α, and IFN-γ was measured by ELISA before and after the marathon.	Moderate and vigorous physical exercise showed a significant increase in IL-6, IL-8, and IL-10, while TNF-α level and IL-1β did not change or decreased.
Verbickas et al., 2017	*Sprint interval cycling exercise*/SIE: 12 stationary bike sessions @5 seconds with intervals of 3 minutes at a load of 7.5% body weight. *Stretch-shortening cycle exercise*/SSE: 200 cycles of repeated drop-jumps from a height of 0.5m with a 30 second delay between jumps.	IL-6 and IL-10 was measured with ELISA before and 2 minutes, 1 hour, 12 hours and 24 hours after exercise.	IL-6 increased more after SIE than SSE, but IL-10 levels did not differ between the two groups.
Shehab M. Abd El-Kader & Al-Shreef, 2018	Long duration (6 months) of aerobic exercise (n=42) with 40 minutes of treadmill versus resistance exercise (n=44) with 40 minutes of weight training, consisting of 3 sets @8-12 repetitions.	Serum IL-6 and IL-10 were measured by "immunoassay analyzer" and TNF- by ELISA, before and after intervention (6 months).	Long duration of aerobic and resistance exercise decreases TNF-α and IL-6, but only of aerobic increases IL-10, significantly.
Bachi et al., 2019	Combination of aerobic and resistance exercise 3x/week compared to sedentary group (as a control) for 18 months. *Low impact aerobics*: coordination and rhythmic motion at 60 to 70% MHR. *Moderate-intensity resistance training*: 5 different exercises for different muscle groups performed slowly in 2 series with 10-20 repetitions.	IL-1β, IL-6, and TNF-α serum were measured with "multiplex assays", 24 hours after the last session.	IL-1β, IL-6, and TNF- were lower in the exercise group than in the sedentary group.
Fitria et al., 2021	Cardio aerobic exercise (*Senam Jantung Sehat*), divided into 3 groups based on frequency 3x, 4x and 5x/week for 4 weeks	Plasma levels of TNF-α were measured with ELISA before and after treatment	Cardio with 3x/ can reduce TNF-α plasma in the elderly compared to 4x/ and 5x/ week.
Sampaio et al., 2019	A combination of aerobic and resistance exercise in moderate intensity 2x/week for 24 weeks	IL-1β, IL-1ra and IL-6 were measured by ELISA kit before and 24 hours after the last exercise.	Moderate intensity exercise 2x/week for 24 weeks decreased IL-6 (37%), IL-1β (16%) and IL-1ra (32%).
Bloigu et al., 2020	Extreme exercise: *full marathon* (n=4, distance 42.2 km, pace 4:43 ± 0:13), *half-marathon* (n=7, distance 21.1 km, pace 5:37 ± 0:50) or *skiing* for 24 hours (n= 1, pace3:32) versus *healthy subjects* as control.	Pro-inflammatory cytokines (IL-6, IL-8, TNF-α) and anti-inflammatory (IL-10, TGF-β) were measured by ELISA, before, and at 3 and 48 hours after exercise.	Extreme physical exercise increased IL-6, IL-8, and IL-10 significantly (before vs. 3 hours-post-exercise), which gradually decreased after 48 hours. Significant increases in TNF-α and IL-8 were seen at more intense activity.
Pozzolo et al., 2020	Static bicycle in two different training zones: at 65-70% MHR and at 80-85% MHR.	IL-6 and IL-10 were measured by ELISA before and after the training session.	IL-6 did not decrease significantly in both exercises, while IL-10 decreased significantly in the lower exercise zone.
Despeghel et al., 2021	Combination of endurance and light resistance exercises, 1 hour/session, 2x/week for 6 weeks. *Endurance*: stationary bike for 20 mins until 100%	Plasma levels of IL-1ra, IL-2, IL-6, IL-8, IL-10, IL-18, TNF-α were measured using immunoenzymatic assay, before	The decrease in IL-6, IL-8, IL-10 was significant in the training group than in the control group.

	MHR; *Resistance*: strength training on 6 tools for 15 repetitions @ 1 min	and 24 hours after the last session.	
Fonseca et al., 2021	Static bicycle up to the anaerobic threshold (75% VO_2) 3x/week for 6 weeks, gradually from 24 to 39 minutes per session.	IL-6, IL-10, and TNF-α were measured by ELISA before, after the last exercise and at 10, 30, and 60 minutes of recovery.	Anaerobic acute exercise to exhaustion increased IL-6, TNF-, IL-10, significantly, but only the increase in IL-6 was dependent on the intensity and duration of exercise.
Middelbeek et al., 2021	*Moderate intensity continuous training*/ MIT (n=10) consists of 6 cycling sessions (60% of VO_2). *Sprint interval training*/ SIT (n=12) consists of 6 sessions of all out static bike for 30 seconds/session. The training lasted 2 weeks	Serum IL-6, IL-8, and TNF-α were measured by ELISA kit before and 48 hours after the end of the last session.	There was a 49% (SIT) and 11% (MIT) reduction in IL-6.

**When applicable*

In general, the inclusion studies compared type, duration and/ frequency, and intensity of exercise in relation to cytokine release. Kinds of exercise intervention in relation to cytokine release and vice versa are displayed in Figure 2A and 2B, respectively. It reveals that static bike accounts for majority of exercise intervention, while IL-6, IL-10 and TNF-α represent the most cytokines studied in order.

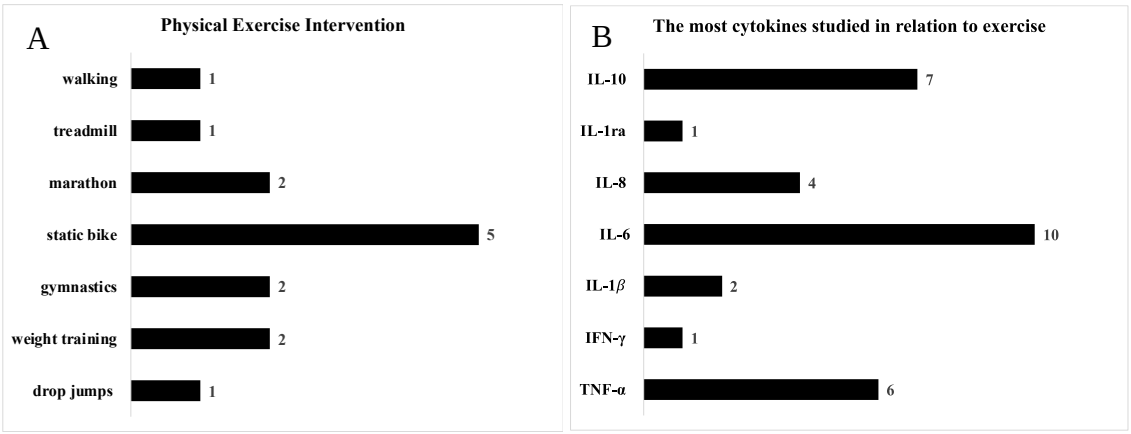

Figure 2. Types of exercise intervention in relation to cytokine release (A) and vice versa (B) as reported by inclusion studies. Graphs are presented as number.

Several studies have demonstrated various cytokines expressed in response to exercise. They may act to propagate, modulate or reduce inflammation in musculoskeletal health (Teschler & Mooren, 2019). Cytokines that are synthesized and released by muscle cells during muscular contractions are known as myokines (Pedersen et al., 2007). Not only affecting the muscle metabolism, myokines are also affecting the autocrine regulation of metabolism in muscles as well as in the para/endocrine regulation of other tissues and organs including the adipose tissue, liver, and brain (Seelaender et al., 2019). The release of either proinflammatory (of which TNF-α, and IL-6 are the most cytokines investigated in sport field), or anti-inflammatory cytokines (of which IL-10 is the most cytokine reported in exercise), can all be influenced by the type, frequency and/ or duration, and intensity of exercise.

Type of Exercise

In general, the inclusion studies commonly reported two types of exercise, namely aerobic or endurance and resistance exercises, whereby they are studied alone or as a combination of both. Aerobic exercise is known to improve cardiovascular function, increasing the heart rate or peak oxygen consumption without significantly changing muscle strength (Villareal et al., 2017); whereas resistance exercise improves neuromuscular adaptations as well as muscular fitness by training one single or a a group of muscles against external resistance so that muscle strength increaases without significantly changing peak oxygen consumption (He et al., 2018). When the two types are compared, Shehab M. Abd El-Kader & Al-Shreef (2018) demonstrated that 6 months of aerobic but not of resistance training significantly increased the anti-inflammatory cytokine, IL-10. Aerobic exercise training is reported to prevent the development of chronic inflammation in diabetes by reducing the production of pro-inflammatory cytokines TNF- alpha and IL-6 (Shehab Mahmoud Abd El-Kader et al., 2013).

Nonetheless, if the two types of exercise are combined, the physiological effects may potentiate one another (Lundberg et al., 2016). Combined exercise is known to exhibit greater anti- inflammatory effects than aerobic or resistance exercise alone, as evidenced by the decrease of CRP, IL-6, TNF alpha, leptin, and resistin and by the increase of anti-inflammatory cytokines such as IL-4, IL-10, and adiponectin (Middelbeek et al., 2021). In line with those previous studies, three studies (Table 3) demonstrated that aerobic together with muscle-strength exercise can enhance cardio-respiratory function (Sampaio et al., 2019), decrease the hallmark of immuno aging (IL-6, IL-8 and IL-10) (Despeghel et al., 2021) and provides protection against the complications of ischemic cardio- and cerebrovascular disease by improving markers of lipid and glycemic levels, anti-inflammatory actions, and anti-oxidative stress, particularly in elderly (Bachi et al., 2019).

Frequency and/ or Duration of Exercise

Acute exercise is defined as a single bout of exercise, whereas the chronic one is described as a repeated amount of bouts of exercise during a short or long-term period of time (Sellami et al., 2018). In healthy young individuals, acute exercise has influenced cytokines and inflammation (Vijayaraghava & Radhika, 2014). Acute exercise is reported as an important immunoadjuvant to stimulate the in- and out of leukocyte between circulatory system and tissues (Sellami, Bragazzi, et al., 2021). IL-6, IL-8 and TNF-α are reported to increase during acute streneous exercise (Sellami, Bragazzi, et al., 2021). In contrast, our inclusion studies showed that acute exercise reduces IL-6 by 49% (Middelbeek et al., 2021) and decreases IFN-γ (Vijayaraghava & Radhika, 2014). During short-duration moderate-intensity exercise, stress hormones can suppress immune cell function, and proinflammatory cytokines, so that an endurance exercise training program may reduce IL-6 concentrations or decrease the magnitude of the acute exercise IL- 6 response (Sellami et al., 2018). Therefore, the comparison between the effect of acute and chronic exercise are still conflicting. In this regard, age could be one of the influencing factors.

Chronic exercise is suggested to prevent immunosenescence, and to exert a positive effect on cardiovascular health as well as on the immune system (Sellami et al., 2018). In this study, we found that aerobic and resistance exercise for 6 to 18 months, decrease TNF-α, IL-6, IL-1β, and IL-1ra (Shehab M. Abd El-Kader & Al-Shreef, 2018; Bachi et al., 2019; Sampaio et al., 2019), while 6 months of aerobic exercise significantly increased the anti-inflammatory cytokines IL-10 (Shehab M. Abd El-Kader et al., 2016) and IFN-γ (Vijayaraghava & Radhika, 2014). But, a single bout of body weight resistance training also showed that age impacted moderate changes in IL-10, IL-6, and TNF-a in the middle-aged than young-aged group (Sellami, Al-Muraikhy, et al., 2021).

Intensity of Exercise

Pro- and anti-inflammatory cytokines are released by muscle contraction to varying degrees during exercise. Despite of the contractile mass involved and duration of exercise, the intensity of exercise is also a determinant factor. Measurement of intensity is based on the amount of energy consumption during activity, namely metabolic equivalents (METs=kcal/kg/min). It is categorized into inactive, light, moderate (3-6 MET), and high (> 6 MET). The intensity of exercise can also be determined by calculating the maximal percentage of oxygen consumption during a particular activity (VO_2max), either low intensity (<40% VO_2max), moderate (40-69%VO_2max), vigorous (70-90% VO_2max), or very high intensity (>90% VO_2max) (Sellami et al., 2018). Due to the strong correlation between oxygen consumption and pulse rate during exercise, the percentage of maximum pulse rate is often used to measure oxygen consumption (measured as 220 minus age). According to *American College of Sport Medicine* (ACSM) recommendations, light, moderate, high, and very high intensity refers to <40%, 40-55%, 55-70%, 70-90% and >90% of the maximum pulse, respectively (Miles, 2007).

Mild, or moderate exercise with appropriate rest periods is known to benefit immune system. Although moderate aerobic exercise modulates inflammatory cytokines more than rather than mild in obese type 2 diabetic patients (Shehab Mahmoud Abd El-Kader et al., 2013), but low intensity was reported to be as good as moderate intensity in regulating immune response (Middelbeek et al., 2021). In contrast, strenuous exercise is associated with robust inflammatory responses and greater oxidative stress, increasing the risk of injury and organ damage. During a strenuous workout, numerous cytokines are released. Some studies reported that TNF-α, IL-6, and IL-8 can increase up to 100-fold with IL-6 levels appear to increase more than the others (Bloigu et al., 2020; Fitria et al., 2021; Maulana et al.,

2020). Strenuous exercise triggers the hypothalamus gland to produce ACTH by the adrenal glands and thus increase the output of IL-6 production. In addition, Bloigu et al. (2020) observed that the less intense the exercise, the higher the decrease in anti-inflammatory response. Similarly, significant IL-10 reduction was observed in the 65-70% HR range, which was not observed in the 80-85% HR range. Anti-inflammatory cytokines, such as IL-10, appear later in exercise or during recovery as a compensatory mechanism to counteract the rising pro-inflammatory cytokines during a workout (Pozzolo et al., 2020). Furthermore, following an extreme or streneous workout, there is a suspicion that a broad decrease of immunity may occur or several hours after exercise, termed as the "open-window theory of susceptibility to infections," whereby the excessive training weaken the immune system (Bloigu et al., 2020). If this heavy exercise is prolonged, there will be a decline in innate immune cells' function to respond to acute stressor, and thus the risk of infection is even higher.

CONCLUSIONS

To conclude, we found that physical exercise does influence the modulation of pro- and anti-inflammatory cytokines with IL-6, TNF-α and IL-10 are the most cytokines affected, respectively. In addition, our findings also demonstrate that modulation of pro- and anti- inflammatory cytokines during exercise is varied, depending on the type, duration, and intensity of the exercise. In this regard, hyper increased level of pro-inflammatory cytokine, for example IL-6 and TNF-α during acute strenuous, heavy and/ or resistance exercise are deleterious to health, if they are not counteracted by the increased level of anti-inflammatory cytokine such as IL-10. Therefore, it is essential to organize the exercise regimen carefully in such manner that balances the production of pro- and anti- inflammatory cytokines, so that exercise can ultimately benefit our health and immunity. Furthermore, the exact chronological time of the increase/decrease of pro and anti-inflammatory cytokines during different types, intensities and duration/frequency of exercise still need to be further investigated. It will also be of interest to study how different type, intensity and duration/frequency of exercise influence the immune response of patients with infectious and non-infectious diseases and/ or acute and chronic diseases.

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