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Research Reviews on Effect of Exercise on DAMP's, HMGB1, Proinflammatory Cytokines and Leukocytes

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ABSTRACT
Intensive exercise can induce pro and anti-inflammatory cytokines, which is clearly seen with an increase in leukocytes in the circulation.DAMPs trigger massive cytokine release including tumor necrosis factor (TNF-α), interleukin (IL) -1, IL-6, IL-8, IL-12 and IFN types I and II. HMGB1 in human monocyte culture stimulates the release of some TNF-α, IL-1, IL-6, IL-8 and inflammatory protein macrophages (MIP)-1.Exercise can cause a high inflammatory response by increasing proinflammatory and anti-inflammatory cytokines (IL6, IL8, IL10, IL1β, and TNF-α). In Men IL1β and TNF-αhigher levels than women, both at baseline values and on the results of the examination after exercise. Exercise with an exercise program can increase IFN, TNF levels-α, IL-6, IL-8, IL1β, VEGF and MCP. In aerobic exercise there were no significant changes in TNF levels-αand IL-6 but there is an increase in the number of neutrophils. Intensity and aerobic exercise in experimental animals increased TNF levels-αand IL-6 in High Intensity Interval Training (HIIT) and Moderate Intensity Training (MIT) while in short-term aerobic exercise the HMGB1 level decreased. Conclusion: Exercise can affect DAMPs, HMGB1, proinflammatory cytokines, and blood leukocytes depending on variation, duration, intensity, type of exercise, and research subjects.

Keywords: Hmgb1, Proinflammatory Cytokines, Leukocytes
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INTRODUCTION

Physical exercise has 4 basic components, namely cardiac and pulmonary exercise (cardiopulmonary), muscle strength, flexibility and body composition.[1] Intensive exercise can induce pro-cytokines or anti-inflammatory, which is clearly seen with an increase in leukocytes in the circulation. However, it is known that neutrophils were one of the first immune cells released to respond to trauma, especially those caused by bacteria.[2] After doing exercise, the concentration of neutrophils in the blood will increase to 100 fold. While cytokines and chemokines induced by training activities include interleukin 6, 8, 10 and monotactic protein monocytes (MCP) -1.[3]The researchers agree that the athlete must examine also check the levels of several cytokine components in the process of checking the detection of chronic inflammation.[4]

Neutrophils play an important role in muscle tissue damage in the acute phase of muscle injury, whereas monocytes / macrophages regulate subsequent tissue regeneration. Neutrophils and monocytes / macrophages secrete various cytokines. Endothelial cells, pericytes, fibroblasts, neutrophils and monocytes / macrophages may all contribute to the expression of global cytokines in skeletal muscle.[5]

Muscle damage and injury is one of the risks when exercising, especially for athletes. One marker of muscle damage is creatinine kinase, which is released in response to damage to skeletal muscle and heart muscle in myocardial infarction. Despite its limitations, creatinine kinase levels are still used as biomarkers for muscle damage. After the biomarkers are released into the circulation, immune cells at the tissue level or naïve immune cells will migrate to the damaged target tissue and differentiate into mature proinflammatory macrophages and function to phagocyte, clean debris and degenerate damaged tissue. The mature macrophages will also release several growth factors, cytokines and other molecules as signals to start the inflammatory process. During this inflammatory process, macrophages turn into anti-inflammatory components and release growth factors and sitkoin with different types and functions from before to support the healing process.[4]

Muscle contraction directly induces the release of IL6 which is part of chemokine and plays a role and regulation of muscle growth.6 IL6 has a positive effect in glucose uptake and fat oxidation, besides, in its role as an anti-inflammatory cytokine, IL6 weakens the production of TNF alpha and IL1 beta where both have been known to form in the acute phase reaction and during cell proliferation.[7]

People who are overweight (obese) have higher levels of IL6 and TNF alpha than people with normal weight. This is because the accumulation of triglycerides in adiposity causes adiposity hypertrophy so that there will be an increase in pro-inflammatory cytokines, one of which is neutrophils which are the first immune cells respond when inflammation occurs by infiltrating into the adipose tissue and then stimulating the entry of M1 macrophages. These macrophages trigger an increase in IL6 and TNF alpha production.[8]

It is known that moderate intensity exercise (Moderate Intensity Training or MIT) is effective in reducing body fat. This low level of fat will prevent fat cell damage and the

possibility of cell hypoxia, so that it will reduce pro-inflammatory cytokines, namely IL6 and TNF, through increased adiponectin secretion and increased anti-inflammatory cytokines.[8]

While exercise with heavy intensity (High Intensity Interval Training or HIIT) is known to be effective in increasing the lipid profile and the release of anti-inflammatory sitkoin because when someone does HIIT there is a muscle contraction that causes mitochondrial activity to be maximized in enzymatic reactions. This will increase glucose uptake in skeletal muscle which will eventually also cause an increase in adiponectin secretion.[8]

A study was conducted on 39 obese mice to observe differences in levels of alpha TNF and IL6 after exercise for 6 weeks with a frequency of 4 times a week between groups of rats with high intensity exercise (HIIT), groups of rats with moderate intensity training (moderate intensity training or MIT) and control groups that don't do the exercise. The results showed that the MIT and HIIT group had significantly higher alpha TNF levels than the control group, but there were no significant differences in the alpha TNF level between the MIT and HIIT groups. Whereas IL-6 levels in the HIIT group were significantly lower than the MIT and control groups.[8]

Research by Hildae et al. Of respondents with chronic inflammatory disease (type 1 diabetes, fibrosis cysts, and chronic obstructive pulmonary disease). The results show that groups with chronic inflammatory disease are more likely to trigger different inflammatory responses (for example, the inflammatory response becomes excessive after acute exercise and becomes weak after exercise) compared to the healthy group. Inflammatory marker levels, especially IL-6, and T cells, total leukocytes and lymphocytes, will remain high with a longer duration to the recovery phase after acute exercise in patients with chronic inflammatory diseases than in healthy individuals. Other than that,in her journal that was approved by previous studies proving a systemic endurance exercise program in patients with chronic heart failure and type 2 diabetes mellitus.[9]

Another study conducted on a group of respondents who did an exercise program for 4 weeks, showed that IFN gamma and TNF alpha levels in the group did not have a significant difference between before and after 4 weeks of training. In their journal, Marques et al said that the results of various studies on the relationship of exercise with cytokine levels were not so consistent, not all studies showed an increase in cytokines after exercise. Like a study of a group that did 32 weeks of training, the results actually showed no significant effect on cytoin levels in some older respondents.[10]

LaVoy et al in his journal stated that the results of studies consistently show that acute aerobic exercise in humans does not change the cytokine activity of T cells and the strength of exercise does not change the levels of TNF alpha and IFN gamma in individuals with type 2 diabetes. However, the results of Tierra et al. showed that swimming training for 12 weeks caused an increase in gamma IFN and TNF alpha in mice that were the study subjects. And the same study by Lamprecht et al with research subjects in the form of horses showed the results of increased levels of gamma IFN. These studies all show different and inconsistent results. This could be due to differences in types, duration, intensity and research subjects.[10]

Strength training induces leukocytosis especially neutrophils in the systemic circulation, damage to muscles and internal organs and immune suppression.[11] In contrast to the study of Huldani et al 2020 showed there were no significant differences in the number of leukocytes in the fitter and fatigue groups, with the average number of leukocytes in the group with VO2 max fit is 7.83 thousand / µl and 7.27 thousand / µl in the less fit group. This study was also supported by Tenorio in 2014 regarding the relationship of leukocyte counts, nutritional status, and fitness status in adolescents, which actually showed a negative correlation between leukocyte counts and adolescent fitness status.[12]

Various studies have shown that the effect of increasing neutrophils after strength training lasts several hours longer. However, cytokine response is not significant during and after intensive training with short duration. The accumulation of inflammatory cytokines, neutrophils and macrophages in the organs triggers the formation of tissue damage or organ dysfunction, not only muscle, but also the kidneys, liver and intestine.[11]

Research also shows that the magnitude of the IL6 response after strength training depends on decreasing cellular energy and increasing heat stress which is then related to stress hormones. This response will be suppressed by an increase in energy supply and cooling interventions of the body. According to Katsuhiko in his journal, exercises conducted at night will induce more IL6 release than morning exercises.[11]

Research by Richard et al of healthy young adults who underwent random aerobic exercise (cycling, swimming, etc.) for 12 weeks. The results showed a 15% increase in VO2 max and an increase in free fat mass in the group that did the exercise program and this did not occur in the control group who did not do the exercise. The hypothesis in this study is that exercise will reduce the induction of the release of TNF alpha, IL6 and TLR4. But apparently the results of the hypothesis are wrong. However, post hoc analysis shows that exercise triggers IL6 and TNF alpha responses to lipopolysaccharide stimulation, this is consistent with the possible positive effects of aerobic exercise on health.[13]

Alarmin is an endogenous molecule that plays a role in the physiological function of homeostasis, but can be produced quickly as a result of cell damage due to stress, infection or trauma. There are several types of alarmin based on the location of the cellular compartment where it is located. Aalarmin which is in the nucleus is called High Mobility Group Box-1 (HMGB1), it binds to DNA. HMGB1 circulating in circulation forms heterocomplex with 12 CXC motif chemokines (CXCL12).[3] Activated HMBG1 will bind to PRR in immune cells to contribute to proinflammatory signals. inducing cytokines, such as the release of TNF alpha, TLR-4 and the CXC receptor 4 chemokine receptor (CXCR4). Then, it is CXCR4 that induces microglial activation, phosphorylation of MAPK p42 / 44 and expression of interleukin 6 and TNF alpha.[14]

A person who exercises with severe intensity has the possibility to experience injury or muscle breakdown, although it is rare, or life-threatening conditions such as rhabdomyolisis.3 In the case of such an injury, there will be a condition called secondary inflammatory response as a result of the release of inflammatory factors intracellular to extracellular parts. This will then cause an endogenous danger signal called damage-associated molecular patterns (DAMP). One of the proteins of this DAMP is high mobility group box 1 (HMGB1).[15] It is released as a danger signal of damage to muscle cells so that it activates and triggers the mobilization of immune cells toward the target location. HMGB1 levels will return to their original concentration after 30 minutes of rest after exercise.

Not all exercises can trigger a meaningful increase in HMGB1 systemically. One of the studies that looked at HMGB1 levels in plasma respondents who did exercise in the form of bicycle racing as far as 1200 km, obtained results that were exactly the opposite of the results of other studies. Although there are technical errors in plasma examination and the influence of biological phenomena in this study cannot be ruled out.[3]

RESEARCH ON HUMAN

Some research comparisons based on the subject, training methods and research results based on acute exercises:

No	Title (Author)	Research subject	Method of Subject Training	Conclusions / Research Results
1.	The effects of acute and chronic exercise on inflammatory markers in children and adults with a chronic inflammatory disease: a systemic review (Hilde E. Ploeger, Takken Team, Mathieu HG de Greef, Brian W. Timmons, 2009)	Adult and child groups, each with chronic inflammatory disease (type 1 diabetes mellitus patients, fibrosis cysts and chronic obstructive pulmonary disease)	7 children doing acute training, 8 adults doing acute training, 5 other adults doing chronic strength training, 1 person doing resistance training (weight training)	• An exercise program can reduce chronic inflammation in some patients in the study subjects. However, if only doing one single exercise will actually cause a worse inflammatory response. Inflammatory response arising from exercise training can be higher, depending on the type and severity of the disease, as well as the frequency, duration and intensity of the exercise performed.
2.	Changes in cytokine levels after prolonged and repeated moderate intensity exercise in middle-aged men and women (R. Terink, CCWG Bongers, RF Witkamp, M. Mensink, TM Eijsvogels, JMT Klein Gunnewiek, MTE Hopman, 2018)	50 men (mean age 58.9 ± 9.9 years) and 50 women (average age 50.9 ± 11.2 years).	The research subject groups were monitored for 4 consecutive days and had to walk for about 9 hours each day at their own pace. The first blood sample is taken one to two days before the exercise begins as a reference value or baseline, the next sample is taken every day immediately after the exercise is completed.	• All cytokine concentrations observed after exercise (IL6, IL8, IL10, IL1 beta, and TNF alpha) experienced an increase in baseline values (P> 0.001). Then the concentration decreased from the first day to the second day (P <0.01). • Baseline values of cytokines in the group of men and women have different. And IL1 beta and TNF alpha are the 2 types of cytokines with the highest levels in the group of male respondents, both at baseline values and on the results of the examination after exercise. • Exercise induces an increase in cytokines, but these levels will go down in the following days while still doing the same intensity and training load

Some research comparisons by subject, training methods and research results by type of exercise:

No	Title (Author)	Research subject	Method of Subject Training	Conclusions / Research Results
1.	The effect of a fourweek exercise	10 taekwondo athletes were male,	All research subjects underwent	• The levels of gamma

	program on the secretion of IFN-γ, TNF-α, IL-2 and IL-6 cytokines in elite Taekwondo athletes (Oktay Kaya, 2016)	with an average age of 20.67 ± 0.24 years and weight 65.45 ± 1.69 kg, in good health, studying at a high school level Physical and Sports Education, Selcuk University, Konya, Turkey.	taekwondo training programs every day for 4 weeks. The exercise program starts with warming up for 20 minutes, each exercise is repeated 3 times, and ends with cooling.	IFN and alpha TNF did not differ significantly between before and after the 4 week exercise program. • The highest IL6 level was found in the fatigue phase after exercise (P <0.05). • A 4-week exercise program resulted in a decrease in IL6 levels (P <0.05)
2.	Effect of Intense Exercise on Inflammatory Cytokines and Growth Mediators in Adolescent Boys (and Nemet, Youngman Oh, Ho-Seong Kim, MaryAnn Hill, Dan M. Cooper, 2002)	11 healthy men of high school age, ranging from 14 to 18.5 years old, took 1.5 hours of single wrestling	Subjects must attend a single and special wrestling exercise program for 1.5 hours.	• There was a significant decrease in anabolic mediator after exercise, i.e. total IGF1, IGF1 bound and insulin. Whereas free IGF-1 does not change. • An increase in proinflammatory cytokines after exercise, namely IL6. Alpha TNF and IL1 beta.
3.	Circulating Inflammatory Cytokine Responses to Endurance Exercise in Female Rowers. (Jürimäe, J., Vaiksaar, S., & Purge, P., 2018).	Fifteen female rowers (18.3 ± 1.6 years; 172.0 ± 5.0 cm; 67.5 ± 8.8 kg; maximum oxygen consumption [VO2 max]: 47.2 ± 7.9 ml. .-1 kg-1)	All study subjects completed 1 hour endurance exercise (distance: 12.1 ± 1.1 km; energy expenditure [EE]: 639 ± 69 kcal; heart rate: 151 ± 7 beatsmin-1; intensity: 79.6 ± 3.5% of the second ventilation turning point).	• Cardiorespiratory fitness as measured by VO2 max correlates with changes in IL-6 (r = -0.55; P <0.05) l • improvement (P <0.05) in IL-6, IL-8, VEGF and MCP

Some research comparisons by subject, training methods and research results based on aerobic exercise:

No	Title (Author)	Research subject	Method of Subject Training	Conclusions / Research Results
1.	Aerobic Exercise Training and Inducible Inflammation: Results of a Randomized Controlled Trial in Healthy, Young Adults (Richard P. Sloan, PhD; Peter A. Shapiro, MD; Paula S. McKinley, PhD; * Matthew Bartels, MD; † Daichi Shimbo, MD; Vincenzo Lauriola, MS; Wahida Karmally, RD; Martina	119 young adults (ages 20-45 years), healthy, not smoking, low activity, do not have good exercise habits.	All research subjects took part in running for 2 weeks then underwent the first blood sample (T1). Individuals who meet the first program can go on to the next session for 12 weeks (aerobic exercise program) and after that a second sample (T2) is taken. Then, given 4 weeks to not do the exercise, only the third sampling (T3)	• There were no changes in the inflammatory markers even though during exercise there was a maximum increase in oxygen consumption by fifteen percent. • Aerobic exercises with different longitudinals also produce different polysaccharide effects in inducing TNF alpha san IL6, conditions in T1 and T2 trigger polysaccharides to increase their induction of the release of TNF alpha (P = 0.041) and IL6 (P = 0.11), and significantly the phase between T2 to T3 triggers polysaccharides to reduce their induction in the release of TNF alpha (P = 0.007)

	Pavlicova, PhD; C. Jean Choi, MS; Tse-Hwei Choo, MS; Jennifer M. Scodes, MS; Pamela Flood, MD; ‡ Kevin J. Tracey, MD, 2018)		was conducted.	and IL6 (P <0.001) • There were no significant changes in TNF alpha and IL6 between each phase when lipopolysaccharide levels were 0.0 ng / mL
2.	Effects of mild and moderate aerobic exercise on levels of interleukin 8 and total neutrophils in adolescents (Huldani, 2016)	31 male students of SMAN 1 Banjarbaru, with an age range of 15-18 years, physically fit, do sports at least once a week at least jogging for 30 minutes, cooperative, not smoking, not taking drugs that affect the number of neutrophils and levels IL8 at least 2 days before blood draw, normal body mass index (20-25), VO2 max value ≥ 38.4	9 people underwent mild aerobic exercise, 12 people underwent moderate aerobic exercise, and 10 people did not undergo training or as controls	• An increase in the number of neutrophils after doing aerobic exercise, can be seen from the average number of neutrophils in the mild and moderate aerobic group compared to the control group. • There was no difference between the mild aerobic and control groups (P = 0.519). • There was a difference between the moderate aerobic group and the control group (P = 0,000) • There was no difference in the number of neutrophils between the group of adolescents who did light aerobic exercise with the control group (P = 0.519) • Moderate aerobic exercise causes an increase in the number of neutrophils in the group of study subjects.

RESEARCH ON ANIMALS

Some research comparisons based on subject, training methods and research results:

No	Title (Author)	Research subject	Method of Subject Training	Conclusions / Research Results
1.	Effect of High Intensity Interval Training (HIIT) and Moderate Intensity Training (MIT) on TNF-α and IL-6 levels in rats (Hadiono and BM Wara Kushartanti, 2018)	Thirty Nine white Rattus norvegicus rats wistar strain, male sex, aged 2-3 months with fat body weight (> 160 grams).	Rats were divided into three groups: 13 control groups without any exercise intervention, 13 were given high intensity interval training (HIIT) and 13 were undergoing moderate intensity physical training (MIT)	• Blood test results showed that the group that had done HIIT and MIT had significantly higher levels of TNF alpha compared to the control group (P = 0.003 and P = 0.001, respectively). • Both groups undergoing HIIT and MIT training did not have significant differences in alpha TNF levels. • The group undergoing HIIT had the lowest IL-6 levels compared to the MIT and control groups.
2.	Aerobic training normalizes autonomic dysfunction, HMGB1 content, microglia activation	SHR (spontaneously hypertensive rat) mice and Wistar-Kyoto (TWK) mice, aged 12 weeks, were	SHR and TWK mice were divided into two groups. The first group did not undergo training (sedentary	• Short-term aerobic exercise reduced HMGB1 levels in the paraventricular nucleus (NPV), cerebrospinal fluid (CSS (P <0.01) and plasma (P <0.01) in the SHR rat group.

	and inflammation in the hypothalamic paraventricular nucleus of SHR (Gustavo Santos Masson, Anand R. Nair, Pedro Paulo Silva Soares, Lisete Compagno Michelini and Joseph Francis, 2015)	placed at room temperature of 22 degrees Celsius and regulated light cycles 12 hours bright and 12 hours dark, accompanied by free access to food and water.	rats) and the second group underwent moderate intensity training (50-60% of maximum training capacity), carried out as many as 5 days per week, duration of 1 hour for each exercise, routine for 2 weeks.	• HMGB1 expression in NPV in SHR mice was higher than in TWK. • Doing aerobic exercise can reduce HMGB1 levels in NPV to normal levels in the SHR group (P <0.01). • However, HMGB1 levels in NPV in the TWK group were not significantly affected by aerobic exercise.

DISCUSSION

In the table above it can be seen that the results of acute exercise with exercise training programs can cause a high inflammatory response with an increase in proinflammatory and anti-inflammatory cytokines (IL6, IL8, IL10, IL1 beta, and TNF alpha). The levels of IL1 beta and TNF alpha are higher in men than women, both at baseline and after exercise. Exercise with an exercise program can increase levels of IFN, TNF alpha, IL-6, IL-8, IL1B, VEGF and MCP. In aerobic exercise there was no significant change in TNF alpha and IL-6 levels but there was an increase in neutrophil counts.

Previous studies have reported that prolonged single endurance exercise can cause acute increases in various variants of inflammatory cytokines, such as IL-2, IL-6, IL-8, IL-8, IL-10, IL-1β, TNF-α , gamma interferon (IFN-γ), monocyte-1 monocyte protein (MCP-1) and granulocyte-macrophage colony stimulating factors in male endurance athletes. However, there is only very limited information available for physically active women, where a single aerobic exercise has been reported to have no effect or can cause an increase in post-exercise in some inflammatory cytokines. The most studied inflammatory cytokines are IL-6, TNF-α and IL-1β, which usually increase as a result of a single training session that produces an acute inflammatory response. However, other investigations did not find changes in these inflammatory cytokine levels after acute exercise.[16]

Overall, DAMPs trigger the release of massive cytokines including TNF-α, IL-1, IL-6, IL-8, IL-12 and IFN types I and II. This mediator strengthens activation, maturation, proliferation, and recruitment of immune cells at the site of trauma, causing indirect activation of innate and adaptive immune cells such as DC or T cells.[17]

Exposure to HMGB1 in human monocyte culture stimulates the release of several proinflammatory cytokines including tumor necrosis factor (TNF), interleukin (IL) -1, IL-6, IL-8 and inflammatory protein macrophages (MIP) -1.The kinetic response to TNF release mediated by HMGB1 and LPS is very different. The release of TNF induced by HMGB1 is biphasic with the second wave being delayed, whereas the release of TNF mediated by LPS only occurs in the initial monophasic mode.[18,19,20,21,22]

CONCLUSION

Exercisecan affect DAMPs, HMGB1, proinflammatory cytokines, and blood leukocytes depending on variation, duration, intensity, type of exercise, and research subjects.

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