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Tumor Necrosis Factor Alpha (TNF- α), Nuclear Factor of kappa B (NF- κ B) p65 and calcineurin expression play a role in the regulation of muscle regeneration process through aerobic exercise in HIV patients



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ABSTRACT

Background: Human Immunodeficiency Virus infection is a chronic disease with inflammatory conditions and experience progressive muscle wasting with increasing of tumor necrosis factor alpha. Physical exercise is a non-pharmacological therapy which stimulates the muscle regeneration. Moderate intensity of aerobic exercise is safe for human immunodeficiency virus patients. Whether tumor necrosis factor-alpha plays a role in the process of muscle regeneration in human immunodeficiency virus infection who have had tumor necrosis factor alpha level higher. Objective: To explain the role of tumor necrosis factor alpha, NF-kappaB, and Calcineurin expression in the regulation of muscle regeneration process.

Methods: Research subjects are population with clinical stage II human immunodeficiency virus infection. Subjects were grouped into two: I

(n = 9) as subjects who got aerobic exercise for 8 weeks and C (n = 9) as subjects who were observed for 8 weeks. Muscle samples were taken from the vastus lateralis muscle biopsies that were performed 24 hours after the last physical exercise. And the immunohistochemical examination was done with anti- tumor necrosis factor alpha monoclonal antibody, anti- NF-kappaB, and anti-calcineurin.

Results: The relationship of muscle contraction to Tumor necrosis factor alpha and calcineurin expression, and to the other myogenic factors was significant, but not to NF-kappaB p65 expression.

Conclusion: Muscle regeneration process needs TNF-alpha and NF-kB p65 expression as regulators with TNF-alpha, NF-kB p65, myogenic factors as the path of exercise and calcineurin expression as a regulator with calcineurin myogenic factors as the path of exercise.

Keyword: Human Immunodeficiency Virus, aerobic exercise, muscle regeneration process, Tumor Necrosis Factor Alpha

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INTRODUCTION

Infection causes muscle wasting in Human Immunodeficiency Virus (HIV) or immunological failure and secondary infection. Human immunodeficiency virus infection is a condition of chronic immune activation that causes the release of pro-inflammatory markers¹ so that an increase of pro-inflammatory cytokines occurs in blood circulation, especially Tumor Necrosis Factor Alpha (TNF-alpha). Some research showed the molecular data that TNF-alpha is an activator of NF-kappaB (NF-kB) in muscle, and even known as a specific activator of NF-kB in HIV infection.²

Research of Chazaud and his colleagues (2003) suggested that the increased TNF-alpha at a certain level is required in the process of muscle regeneration, whereas calcineurin (CaN) plays an important role in the regulation of growth, and skeletal muscle plasticity.³ Skeletal muscle plasticity requires stimulation in the form of physical exercise. Based on the dual function of TNF-alpha in muscle regeneration, this study was conducted to elucidate the function

as well as other factors that play a role in the muscle regeneration in a population of HIV infection.

MATERIALS AND METHODS

The subjects in this study were male of HIV infection clinical stage II. The subjects were screened with WHO criteria,⁴ aged 21–50 years, in the outpatient clinic of infectious unit Dr. Soetomo General Hospital. Participants were screened with a medical questionnaire to affirm that they had not suffered from the opportunistic disease. Bleeding risk was screened with the bleeding time. Potential risks and requirements of this study were outlined in an informed consent form, and a written consent was obtained from the participants before their participation in the study. The Ethics committee approved the study at Dr. Soetomo General Hospital.

The subjects in the intervention group were given aerobic exercise with the frequency of 2 times per week, intensity 60–70% of maximum heart rate, duration of 23 minutes (warm-up and stretching 6 minutes, the core exercise 13 minutes, and

cooling-down 4 minutes) for 8 weeks. The time is adjusted with moderate intensity.

Vastus lateralis muscle biopsy was done by an orthopedic surgeon at the point of the bottom third of the line connecting the SIAS-patella, using a reusable Medcore gun and Unicore needle size 16G.

Materials for immunohistochemical examination: anti-TNF-alpha monoclonal antibody clone 52B83 product of Novus Biological (NB600-1422), anti-NF- κ B p65 monoclonal antibody clone 112A1021 product from Novus Biological (NB100-56712), and anti-CaN monoclonal antibody clone 2G8 product of Novus Biological (H0005530-M03).

Statistical Analysis

Path analysis.

RESULTS

The results of statistical analysis between variables TNF-alpha, NF- κ B p65, CaN, and others myogenic factor with aerobic exercise shows that all paths have positive correlation values except TNF-alpha to NF- κ B p65 has a negative correlation. The results of path analysis showed that standardized coefficient values, and its significance in [Table 1](#).

DISCUSSION

Increased TNF-alpha as a result of aerobic exercise

Tumor necrosis factor-alpha is a major cause of HIV muscle wasting. In research Magauda, et al. (2004) discussed the concept that physical exercise is effective for the prevention or treatment of some chronic diseases, can reduce TNF-alpha and NF- κ B in patients with HIV infection so as to prevent muscle wasting. Muscle wasting that occurs in patients with HIV infection involves several factors that are associated with secondary infections or gastrointestinal disease,⁵ and is also caused

by a decrease in energy intake, the side effects of drug therapy, or due to malabsorption, also due to the level of HIV replication. The production of pro-inflammatory cytokines increases, especially TNF-alpha,⁶ as well as biological adaptation is still unclear.⁷ Anorexia is caused by tumor necrosis factor-alpha and IL-1, which inhibits the appetite center in the hypothalamus.

TNF-alpha expression results in this study showed that the I group is higher, meaning that aerobic exercise causes an increase in TNF-alpha in skeletal muscle. Research Gielen and colleagues (2003), analyzed the effect of regular physical exercise on cytokine expressions of skeletal muscle in patients with chronic heart failure. Skeletal muscle biopsies before doing physical exercise showed an increased expression of TNF-alpha, IL-1, and IL-6. On immunohistochemical examination after exercise showed decreased expression of TNF-alpha, IL-1, and IL-6 in the local into myocyte. A decrease in cytokine expression was obtained after physical exercise for 6 months. Increased expression of TNF-alpha in skeletal muscle could occur without infiltration of macrophages, suggesting that skeletal muscle myocytes produce cytokines paracrine/autocrine.⁸

Several studies by Hoffman-Goetz and Pedersen (1994) shows that physical exercise followed by an increase in cytokine responses in the blood along with the stress of bioactive molecules. The response is the same as in sepsis, and injury.⁹ Other researchers reported that there was an increase in cytokines and also reported that there was no change in the production of TNF-alpha after strenuous physical exercise.¹⁰

Researchers Spate and Schulze (2004) explained an increase in TNF-alpha is probably caused by local inflammation which is often found in the condition of chronic diseases or inflammatory reactions that are triggered by muscle damage mechanics.¹¹ Increased expression of TNF-alpha in the muscles after physical exercise happens possibly because physical exercise can trigger TNF-alpha spending muscle through post-transcriptional regulatory mechanisms. Regulation of TNF-alpha at the molecular level can be determined through the expression of TNF-alpha in the vastus lateralis muscle.¹² Peak expression of TNF-alpha at 24 hours after injury. In this study taking muscle biopsies 24 hours after the last physical exercise showed an increase in TNF-alpha, which can trigger the regeneration process. According to the research, Hawke and Garry (2001) report that TNF-alpha may modulate the regenerative process of skeletal muscle¹³ and the research of Moresi and colleagues (2006) show that TNF-alpha have the effect of bimodal causing

Table 1 Standardized coefficient value, and significance between variables

Variable	(b)	(p)
Muscle contraction to TNF- α	0.487	0.047
TNF- α to NF κ B p65	- 0.032	0.822
NF κ B p65 to Pax7	0.690	0.002
NF κ B p65 to MyoD1	0.714	0.001
NF κ B p65 to myogenin	0.540	0.037
Muscle contraction to CaN	0.901	0.000
CaN to Pax7	0.709	0.001
CaN to MyoD1	0.598	0.011
CaN to myogenin	0.591	0.012

p < 0.05

atrophy and hypertrophy in cultured muscle cells depending on the time when TNF-alpha is given.¹⁴

Results of the vastus lateralis muscle biopsies in this study showed an increased expression of TNF-alpha in the muscle groups doing the aerobic exercise of moderate intensity, the possibility for a biopsy performed 24 hours after the last aerobic exercise. According to the timing diagram of cellular responses, the first 24 hours after injury or exercise, the invasion of macrophages which shows TNF-alpha is still increasing.¹⁵ The production of ROS in muscle occurred 45 minutes after exercise and reached a maximum in 120 minutes.¹⁶ In the first 45 minutes of ROS has not been countered by SOD because SOD production occurred 48 hours after the injury/exercise, and lack of antioxidants in the muscle of patients with HIV infection.

Expression of TNF-alpha in skeletal muscle in this study was higher in the intervention group, but also showed activation of satellite cells through the expression of myogenic factors higher, meaning that macrophage inflammation produces TNF-alpha and muscle contraction can affect the activity of satellite cells. According to research by Chazaud, et al. (2003) on the behavior of muscle progenitor cells (MPC) which depends on the conditions of activation of macrophages; the results show that the inflammation of macrophage stimulate the growth, proliferation, differentiation, and fusion of MPC.³

This condition is consistent with research by Langen, et al. (2001) which states that administration of TNF-alpha in myoblast will inhibit differentiation, but after differentiating into myocytes, become more resistant to a cytokine, and then fuses into muscle fibers. Tumor necrosis factor-alpha cannot directly work on the mature muscles to accelerated protein degradation.¹⁷ Myocyte enhancer factor 2 (MEF2) that have been activated by CaN will trigger a hypertrophic gene expression such as myosin and actin, resulting in increased muscle mass.¹⁸ The process of differentiation seems to be modulated by the signal TNFalpha_NF-kB.¹⁷

This study showed that expression of TNF-alpha in vastus lateralis muscle biopsy increased in the intervention group.

Increased nuclear factor kappa beta p65 (NF-kB p65) as a result of aerobic exercise

Nuclear factor kappa-B is a regulator kappa-B, is expressed in virtually all types of cells and tissues. It plays an important role in mediating responses to outside stimuli, as a central mediator of the immune response, inflammation, apoptosis, and proliferation.

Acute physical exercise activates NF-kB. Ji, et al. (2004) state that in mice on giving physical exercise to fatigue, increased NF-kB levels than control.⁷

Ho, et al. (2005) also reported an increase in activity of NF-kB 1–3 hours after running on the treadmill for 60 minutes.¹⁹ Other studies have reported that regular physical exercise increases levels of glutathione in skeletal muscle that can decrease the activity of NF-kB,²⁰ but few studies which state that physical exercise lowers the activity of NF-kB.²¹

The majority states that physical exercise triggers NF-kB activity, whereas aerobic exercise causes a mitochondrial biogenic response which is an increase in the number and volume of muscle mitochondria, along with changes in the composition of the organelle. After 6 weeks of physical exercise, the mitochondrial muscle density increased 50–100%. The changes occur in three types of muscle fibers, type IIA greater than in type I and type IIX. Performance against physical exercise improves 5–20%.²²

Aerobic exercise can activate and increase the expression of NF-kB in skeletal muscle. Increased expression of NF-kB was induced by ROS generated by muscle contraction. At the time when muscle contraction occurs translocation of p65 follows phosphorylation of IκBα into the nucleus.²³

This study did not measure the production of ROS in muscle, but there have been previous studies on rats given physical exercise on a treadmill, showed a 38% increase in ROS from the ROS levels at rest.²⁴

Increased production of ROS after physical exercise is followed by an increase in protein SOD (superoxide dismutase), which occurs 48 hours later, the antioxidant capacity that protects muscle cells from the cytotoxic effects.²⁵ Oxidative stress can increase the activity of caspase 3 induced degradation of actin-myosin, NF-kB activation relationship with the degradation or apoptosis is a homeostatic regulation.²⁶

Expression of NF-kB is greater in the intervention group, meaning that aerobic exercise activates NF-kB response to mechanical strain mechanism. Nuclear factor kappa beta regulators are known as growth factor for a number of endogenous and exogenous expression that increases skeletal muscle regeneration, especially the proliferation of satellite cells, the condition is consistent with research by Bottex-Gauthier, et al. (2003).²⁷

The expression of NF-kB in this study showed significant improvement. This increase is likely due to the provision of aerobic exercise, muscle contraction which is the source of ROS, and activation by TNF-alpha increased. But TNF-alpha to NF-kB p65 expression show $b = -0.032$, $p = 0.822$ means that the activation of NF-kB is not because of the stimulation of TNF-alpha but due to exercise which causes the production of ROS and inflammation

are needed for regeneration. Several years ago ROS was considered as a toxic species that causes oxidative stress, pathogenesis, and aging, but it is now evident that ROS in a certain concentration is a molecule which signals in the regulation of physiological processes in some tissues, including the skeletal muscle. The balance between the positive effects, and negatively influenced by the source, the activity, and the concentration of ROS, antioxidant capacity, the level of energy in muscle cells, the ability of adaptation to oxidative stress, inflammatory conditions, and signal plasticity induced by ROS. In muscles, ROS may trigger different signaling pathways leading to diverging responses, from adaptation to cell death.²⁸ Increased activity of NF- κ B causes skeletal muscle adaptations dependent strength, speed, and duration of the contraction of the muscle, which further activates SOD, and inhibits ROS. Oxidative stress is an important modulator of skeletal muscle regeneration after injury/exercise. The balance between ROS production and expression of antioxidant enzymes, and its activity play an important role in maintaining the homeostasis of muscle. Besides the importance of ROS in the regeneration of skeletal muscle, it also plays a role in cleaning the muscle fibers necrosis and improves muscle injury.²⁹

Aerobic exercise of moderate intensity for 8 weeks showed an increase in the number of satellite cells, and satellite cell activation in the intervention group was expressed by the increasing of myogenic regulatory factors.

Increased CaN due to aerobic exercise

The CaN is a myogenesis regulator; it regulates the gene expression of myogenin at the level of transcription. This study showed a significant improvement in the intervention group that CaN due to muscle contraction would increase intracellular Ca²⁺. This signal activates adaptation response and transcriptional regulation. The relationship between CaN with the activation of satellite cells is very strong. The results of this study showed that CaN contributes to the expression of myogenin (as a marker of myotube) but weaker than the contribution to the expression Pax7, it can happen because the myogenesis process is a dynamic process so that the phases of activation, proliferation, differentiation, and fusion is always changing. Data showed the greatest increase in myogenin expression; it means there are fusions already or the addition of new muscle fibers in the biopsy 24 hours after moderate intensity exercise for 8 weeks. Myogenin expression increased significantly from the results of the biopsy were performed after 8 weeks of aerobic exercise. Research shows that myogenin

increased within 1 week after physical exercise, these data are similar to those reported by Carson, and Booth (1998).³⁰

The role of TNF-alpha expression to NF-kB in regenerating skeletal muscle

Tumor necrosis factor alpha as a regulator of the immune response and inflammation which is synthesized by macrophages, and immune cells, it is also synthesized by the muscles, i.e., by the myoblast, and activity is increasing differentiation and fusion.³¹ The response to injury will enhance the expression of TNF-alpha and its receptor. The skeletal muscles produce TNF-alpha in response adaptation and create environments with high TNF-alpha. In research with mice, TNF-alpha stimulates chemotactic response myogenic cell; thus, increasing myogenesis.³¹ Possible activation of NF- κ B by TAK1 (transforming growth factor-beta-activated kinase 1), which is very important in the function and homeostasis of satellite cells.³² The results of path analysis in this study showed that in the regeneration of skeletal muscle, the TNF-alpha did not activate NF- κ B, possibly because (1) TNF-alpha have a bimodal effect on myogenesis which depends on its concentration.³³ The research by Donati, et al. (2007) report that low doses of TNF-alpha increase myogenesis of myoblast.³⁴ (2) The effect of TNF-alpha causes chemotactic macrophages to the area of injury which stimulates myogenesis. (3) Tumor necrosis factor alpha-mediated activation of p38 in muscle cells in response to muscle injury.³⁴ The results of in vivo studies in contrast to in vitro for their control physiological effects, such as physiological temperature, blood circulation which meets the needs of O₂, the supply of substrate, a physiological environment, the interaction between the muscle fibers, and the dynamics of ions in cells.¹⁸

Mechanisms of physical exercise-induced muscle regeneration

Homeostatic processes in adult humans are very important in regenerating skeletal muscle. Giving stimuli will lead to responses that activate the muscle compartment, i.e., satellite cells and other precursor cells. Satellite cells are important in muscle regeneration, but this process needs to be supported with good environmental quality. Aspects of cellular and molecular activity of muscle regeneration, i.e., degeneration, inflammation, regeneration, remodeling, and maturation/repair function.¹⁷ Increased regeneration of musculoskeletal in patients with HIV infection clinical stage II as a result of the aerobic exercise of moderate intensity through the mechanism of muscle contraction,

caused an increase in the influx of Ca^{2+} . And the production of IGF-1 in muscle increased the activation of CaN. And further enhanced the myogenic regulatory factors, increasing satellite cell activation, and proliferation, and also myogenin as a marker of differentiation, and fusion of new fibers.

So, exercise causes an increase in skeletal muscle regeneration through increased expression of myogenic regulatory factors as a result of vastus lateralis muscle biopsy. The provision of aerobic exercise repeatedly was able to improve the regeneration of skeletal muscle that indicated with activation, proliferation (increased expression of Pax7, and MyoD1), and satellite cell differentiation (increased expression of myogenin).

The regeneration process requires the interaction of intracellular signal, proteins that regulate the function of muscle-specific genes and extracellular signals. Mutual interaction activates satellite cells triggering proliferation, differentiation, fusion, and form new muscle fibers. Path analysis showed that TNF- α did not contribute to the activation of NF- κ B p65, whereas activation of NF- κ B p65 contributed in determining the condition of the satellite cells.

CONCLUSION

Muscle regeneration process needs TNF- α , and NF- κ B p65 expression as regulators with the path of exercise as TNF- α , NF- κ B p65, myogenic factors as the path of exercise and calcineurin expression as a regulator with calcineurin myogenic factors as the path of exercise.

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