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LITERATURE STUDIES

Molecular Mechanisms and Effectiveness of Sports On Hypertension Treatment

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Abstract: Hypertension is a serious global health problem. Exercise is an effective non-pharmacological intervention in the management of hypertension through several molecular mechanisms, including vascular endothelial regulation, oxidative stress modulation, and anti-inflammatory effects. This literature study aims to increase readers' knowledge about the molecular mechanism and effectiveness of exercise in the treatment of hypertension by conducting literature searches in national and international journals published in the last 5 years. The main pathological changes in hypertension are changes in the structure and function of arterial vessels, which are characterized by increased peripheral vascular resistance due to vascular remodelling. Regular aerobic exercise has been shown to increase the activity of antioxidant enzymes, including *superoxide dismutase* (SOD), which plays an important role in protecting cells from oxidative damage. The frequency and duration of exercise play a key role in the effectiveness of exercise programs to lower blood pressure in hypertensive patients.

Keywords: hypertension, exercise, physical exercise, blood pressure

INTRODUCTION

Based on the latest World *Health Organization* (WHO) report in 2023, hypertension is a serious global health problem with a prevalence of 1.28 billion adults aged 30-79 years worldwide, with two-thirds of cases occurring in low- and middle-income countries. This condition is even more worrying because about 46% of people with hypertension are unaware of the condition, less than half (42%) are diagnosed and receive treatment, and only 21% are well-controlled. Based on the 2023 Survey Kesehatan Indonesia (SKI), the prevalence

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of hypertension in the ≥18-year-old population in Indonesia reached 30.8% based on blood pressure measurements, down from 34.1% in Riskesdas 2018, but only 8.6% were diagnosed by doctors.[1,2]

Hypertension is a global health challenge that requires a comprehensive therapeutic approach to its management. As a major risk factor for cardiovascular disease, hypertension requires effective interventions to lower blood pressure and prevent complications. Exercise has proven to be one of the most effective non-pharmacological interventions in hypertension management.[3,4]

Recent studies have shown that the combination of aerobic exercise and *resistance training* can significantly reduce systolic blood pressure by 6.4 mmHg and diastolic by 3.7 mmHg in hypertensive patients. A recent meta-analysis revealed that each additional 30 minutes of aerobic exercise per week could lower systolic blood pressure by 1.78 mmHg and diastolic blood pressure by 1.23 mmHg, with optimal reductions achieved at a duration of 150 minutes per week.[3,5]

Although aerobic exercise remains the primary recommended approach for high blood pressure management, recent research shows that various exercise modalities such as *resistance training*, *combined training, high-intensity interval training*, and *isometric exercise training* are also effective in lowering resting blood pressure. Understanding the molecular and physiological mechanisms of the antihypertensive effects of exercise is essential for optimizing exercise recommendations for hypertensive patients.[4,6]

This literature study aims to improve readers' knowledge about the molecular mechanisms and effectiveness of exercise in the treatment of hypertension.

METHOD

This study was conducted by searching the literature using scientific publications in national and international journals published in the last 5 years.

RESULT

Molecular Mechanism

Vascular Endothelial Regulation

The main pathological changes in hypertension are changes in the structure and function of arterial vessels, which are characterized by increased peripheral vascular resistance due to vascular remodelling. Aerobic exercise triggers endothelial adaptation through anti-proliferative, anti-inflammatory, and antioxidant mechanisms and improves vascular structure through changes in vascular endothelial cells, vascular smooth muscle cells, and extracellular matrix synthesis. [7–9]

In this process, aerobic exercise plays an important role in increasing blood flow and shear pressure (*shear stress*), which then triggers the release of vascular protective molecules such as NO, as well as decreasing the expression of endothelial angiotensin

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type II receptors type 1 and reducing NADPH oxidase activity. Aerobic exercise for 16 weeks was shown to lower blood pressure and increase eNOS expression, as well as lower levels of IGF-1, PI3K, and phosphorylated B protein kinase (p-Akt). At the cellular level, eight weeks of aerobic exercise inhibited NF-κB p65 activity and decreased the increase in norepinephrine, and epinephrine as well as the expression of IL-1β and TNF-α in plasma. Aerobic exercise also affects the extracellular matrix by reducing the accumulation of excess collagen which can increase the stiffness of blood vessels, as well as regulating activity *matrix metalloproteinases* (MMPs) which play an important role in vascular remodeling. [7]

Another study showed that 12 weeks of aerobic exercise significantly lowered systemic vascular resistance and increased the elasticity index of small arteries. Aerobic exercise also increases angiogenesis in adipose tissue, improves blood flow and reduces hypoxia and macrophage infiltration, which contributes to the improvement of overall vascular function. Further research revealed that endothelial function assessed by [10] *flow-mediated dilations* (FMD) showed a decrease of 3.2% in hypertensive patients compared to normotension. Regular moderate-intensity exercise also plays a role in regulating hypertension through changes in immune cells, which is partly due to the anti-inflammatory effects of such physical exercise. [7,10]

Oxidative Stress Regulation

Activation of endothelial cell mechanical sensors during aerobic exercise stimulates the production of eNOS and NO, reduces vascular oxidative stress, improves antioxidant response and improves NO bioavailability. *Manganese Superoxide Dismutase* (Mn-SOD) in the perivascular adipose tissue or *Perivascular Adipose Tissue* (PVAT) reduce the production of ROS networks. [7]

Regular aerobic exercise has been shown to increase the activity of antioxidant enzymes, including *superoxide dismutase* (SOD), which plays an important role in protecting cells from oxidative damage by converting superoxide into hydrogen peroxide. [10]

Aerobic exercise also lowers malondialdehyde (MDA) levels and increases the bioavailability of NO in blood vessels. Another study showed that 12 weeks of aerobic exercise significantly improved the expression and activity of Mn-SOD in the heart, which correlates with decreased blood pressure and oxidative stress. Physical exercise also activates ROS-sensitive signalling pathways in skeletal muscle, which in turn increases the capacity of endogenous antioxidants. In addition, moderate-intensity exercise consistently increases NO production through eNOS activation, which not only improves endothelial function but also reduces vascular oxidative stress. This increase in the bioavailability of NO contributes to the

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cardioprotective effect of exercise on hypertension.[11,12,13,8]

Modulation of Inflammation

Aerobic exercise can reduce low-level inflammation in obese people and lower plasma inflammatory cytokine levels. Physical exercise also prevents or weakens the infiltration of immune cells into the PVAT, thereby improving blood vessel function. Studies show that 16 weeks of aerobic exercise significantly lowers CRP, IL-6, and TNF-α levels in people with obesity.[7,8]

An 8-week aerobic exercise program was shown to inhibit NF-κB p65 activity and decrease the increase in norepinephrine, and epinephrine as well as the expression of IL-1β and TNF-α in plasma. Aerobic exercise also increases the expression of anti-inflammatory proteins such as adiponectin and IL-10, which play a role in improving vascular endothelial function. In addition, consistent moderate-intensity physical exercise can lower immune cell infiltration into PVAT and reduce systemic inflammation through decreased expression of adhesion molecules such as ICAM-1 and VCAM-1.[15,16,17]

Effectiveness of Sports Interventions

Types of Exercises

Isometric exercise is the most effective in lowering systolic and diastolic blood pressure compared to other types of exercise. [4] *Wall squat* and hand isometric exercises showed a decrease in systolic blood pressure of up to 8.33 mmHg and diastolic blood pressure of 3.9 mmHg in hypertensive patients. Aerobic exercise such as walking, running, or swimming lowered systolic blood pressure by 4.7 mmHg and diastolic by 3.1 mmHg. This blood pressure-lowering effect is equivalent to the use of one antihypertensive drug.[18,19,20]

Intensity and Duration

Moderate-intensity training (40-60% of maximum capacity) for 30-60 minutes per session provides optimal results. An increase in intensity above 70% VO2 max does not provide any additional benefit in lowering blood pressure. The frequency and duration of exercise play a key role in the effectiveness of exercise programs to lower blood pressure in hypertensive patients. An optimal exercise program requires a regular commitment with a frequency of 2-3 sessions per week, which must be maintained consistently for at least 8-24 weeks to get significant results.[18,19,21]

Research shows that the blood pressure-lowering benefits of a single exercise session can last up to 24 hours after physical activity is complete, a phenomenon known as *post-exercise hypotension.*[22] The optimal effect is usually achieved at the duration of the 24-week program, during which the physiological adaptations of blood vessels and the cardiovascular system have been well formed. An 8-12 week aerobic exercise program with 3 sessions per week significantly lowered systolic (-9.9 mmHg) and diastolic (-5.0 mmHg) blood pressure1.

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It is important to note that these blood pressure-lowering effects are cumulative, and each exercise session contributes to long-term blood pressure improvement.[21,22]

CONCLUSION

Exercise is an effective non-pharmacological intervention to lower blood pressure in hypertensive patients. This effectiveness is achieved through a variety of interrelated molecular mechanisms, including improved endothelial function, reduction of oxidative stress, and modulation of inflammation. An optimal exercise program requires a frequency of 2-3 sessions per week with a minimum duration of 8-24 weeks. Isometric exercise and a combination *of aerobic-resistance exercise* showed the highest effectiveness in lowering blood pressure. It is important to pay attention to the proper intensity and duration of exercise to maximize the benefits of lowering blood pressure, with moderate intensity (40-60% of maximum capacity) providing optimal results.

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