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The Impact of Different Types of Exercise Training on the Angiopoietin Family

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Abstract

Purpose: The objective of this study is to analyse various articles on the effect of various types of exercise on the angiopoietins family and angiopoietin-like proteins (ANGPTLs). **Methods:** PubMed, Science Direct, Scopus and Google Scholar databases were searched from 2000 to September 2020. After screening the articles, 19 articles that met the inclusion criteria were studied and analysed. **Results:** In our body, four types of angiopoietin and eight types of angiopoietin-like proteins have been identified, the functional method of some of them which are still not entirely understood. Angiopoietin-1 and angiopoietin-2 are essential regulators of vascular formation and maintenance. Angiopoietin-1 is found in perivascular and vascular cells within and around smooth muscle cells and plays an important role in growth, vascular stability, and pathological angiogenesis. On the other hand, angiopoietin-2 and angiopoietin-3 are mainly involved in inducing vascular regression, cell death, and inflammation. Angiopoietin-4, like angiopoietin-1, is responsible for the maturation, stabilization, and stasis of blood vessels. **Conclusion:** Studies show that exercise has a significant effect on increasing capillary density in the human body by increasing angiopoietin as one of the angiogenesis factors. In addition, there are many other benefits such as contribution to fat burning and treatment of coronary artery disease, cancer, asthma, and ischemia. More research is needed on the effects of different types of exercise training on angiopoietins.

Keywords: Exercise Training, Physical Activity, Angiogenesis, Angiopoietin

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INTRODUCTION

Angiogenesis has a significant effect on the cure of cardiovascular disease. Therefore, it is important to study the function of endothelial cells (ECs), the mechanism of angiogenesis, and the factors that enhance and inhibit angiogenesis. Angiogenesis refers to the formation of new blood vessels from existing blood vessels, including the differentiation of endothelial progenitor cells and the regulation of cytokines (Memczak et al. 2013). Capillaries are present in almost all organs; their structure is different according to the demand for function. In skeletal muscle, their main role is exchanging gases and metabolites at the level of blood and tissue (Roger et al. 2019). The basic signals of exercise-induced angiogenesis are multifaceted in origin and effects. A significant increase in capillary content requires at least four weeks of exercise in humans (Eslami et al. 2021; Hoier et al. 2012; Holloway et al. 2018)

Angiopoietin is one of the growth factors in the human body that is especially effective in the process of angiogenesis. The gene for this protein is located on chromosome 8 (Bahremand et al. 2014; William et al. 2005). Angiopoietin (Ang) does not initiate the process of angiogenesis but causes changes in the direction of stabilization and destabilization of blood vessels. The angiopoietin family has four members (Karkkainen et al. 2004): Ang1, Ang2, Ang3, Ang4. Angiopoietin-like proteins (ANGPTL) are also an extraordinary family of secretory proteins that are structurally associated with angiogenesis-modulating factors. This family consists of eight protein members encoded by eight genes (ANGPTL1 to ANGPTL8). Three members of this family, ANGPTL3, ANGPTL4, and ANGPTL8, have been extensively studied as important regulators of lipid metabolism in the heart, skeletal muscle, white adipose tissue (WAT), and brown adipose tissue (BAT). In particular, these ANGPTL proteins have been shown to mediate the hydrolysis of triglycerides (TG) by lipoprotein lipase (LPL). Evidence suggests that modulation of these three ANGPTL proteins is promising in reducing circulating lipoprotein levels as well as reducing the risk of cardiovascular disease (Morelli et al. 2019). All proteins have a co-amino-terminal domain as well as a carboxy-terminal fibrinogen-like domain except ANGPTL8, which lacks the next domain (Mattijssen & Kersten. 2012; Quagliarini et al. 2012).

ANGPTL proteins have also been shown to play different physiological roles in metabolism, inflammation, and cancer (Hato et al. 2008; Wang et al. 2015)

Numerous studies have investigated the changes in vascular endothelial growth factor under pathological conditions as well as the effects of various exercise training on angiogenesis under physiological conditions. Regular physical exercise declines mortality, risk of cardiovascular disease and the progression of coronary heart disease (CAD), furthermore, improves function (Metsios et al. 2020). Globally, regular exercise increases life expectancy, even in patients with cardiovascular disease, several mechanisms seem to underlie the beneficial effects of exercise (Park and Kim. 2020). Exercise postpones blood pressure and aortic stiffness with age, improves lipid profile and endothelial function, decreases oxidative stress, and by reducing the production of cytokines and proinflammatory proteins such as interleukins, molecules, adhesion molecules, fibrinogen or C-reactive protein (CRP) causes an anti-inflammatory effect. Thus, exercise-induced health mechanisms comprise interconnected systems, but the signalling pathways of these effects are uncertain (Tartibian et al. 2021; Barnard et al. 2020; Larouche et al. 2015). One of the most common factors in improving exercise capacity or performance through exercise is increased capillary density (Heidary and Mehdipour. 2021; Higashi and Murohara. 2017). As mentioned before, the tremendous impact of angiogenesis on the improvement of cardiovascular disease is significant, and many studies have investigated the effect of exercise on angiogenesis. It is evident that aerobic exercise can enhance cardiac angiogenesis, in which vascular endothelial growth factors play a key role (Roya et al. 2018). Exercise training can also cause vascular tissue in the brain and heart muscle, which reduces the risk of stroke and heart attack, respectively (Taheri Chadorneshin et al. 2017). Moreover, studies have shown that exercise at the same time has beneficial effects on all cardiovascular risk factors and its role along with medication is well known (Thiagarajan et al. 2017)

According to what was said, the purpose of this review article is to analyse different articles on the effect of various types of exercise training on the angiopoietin family and angiopoietin-like proteins and

investigate the basic mechanisms of angiopoietin and activating and inhibiting factors of it.

METHOD

This research is a systematic review study. Based on this, using a systematic search strategy in the databases of PubMed, Science Direct, and Scopus, the desired articles were extracted. The keywords "Exercise", "Training", "Physical Activity", "Angiopoietin" and "ANGPT" were also used in this search and all articles published between 2000 and 2020 were extracted. It should be noted that the Google Scholar database was used as a supplementary search and several articles were added to this research project. It should also be noted that the search process in this study was completed on September 12, 2020.

Regarding the exclusion criteria of all review articles, case reports, articles of conferences and seminars that were presented only with the abstract of the article, articles with irrelevant or unsportsmanlike titles, articles in a language other than English or the exact angiopoietin factor in them was not investigated were removed. Other articles met the inclusion criteria.

Then, after a comprehensive review, complete information about the articles that were eligible for the study, including the type of study, sample size, characteristics of subjects (age, gender, and health status), data on angiopoietin factor before and after exercise intervention, and the characteristics of the exercise program (a type of exercise, intensity, and duration of exercises) was extracted from the articles. This information was classified based on the type of study, the type of exercise training, and the type of subjects (human or animal), and all of them are reported in this article.

Also, the quality of the articles was assessed using the Down and Black checklists. This checklist consists of 27 items, of which 25 items have a score of zero or one, one item has a score of zero to two, and the last item has a score of zero to five, and the maximum score based on this checklist is 31, in which Among them, articles that scored between 20 and 25 were considered as medium quality articles and articles that scored above 25 as high-quality articles were included in the research. It is worth mentioning that the validity and reliability of this checklist has been confirmed in previous studies (Edwards and Pilutti, 2017).

Besides, the evaluation of the quality of the articles and the extraction of the data were done separately by the two authors; In case of disagreement, the issue was discussed between the two authors, and the final opinion was applied (as shown in Figure 1).

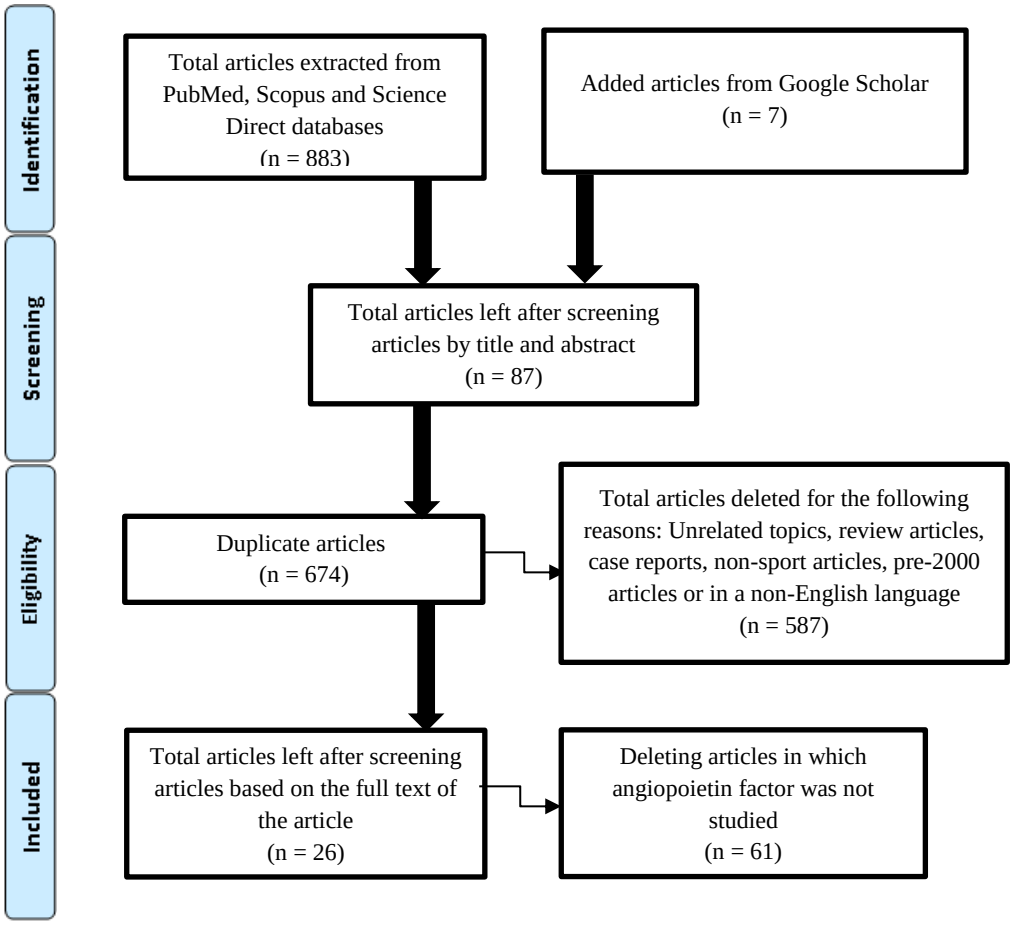

Figure 1 - Flow diagram of the study selection process

RESULTS

Angiopoietins

Angiopoietins, including adipose-derived proteins, comprise of nine proteins that form the second endothelial growth factor receptor

signalling pathway, which, after the active VEGF-VEGFR angiogenesis phase, performs an important function in regulating blood and lymphatic vessels. They help regulate endothelial function, angiogenesis, inflammation, regeneration of blood vessels and vascular homeostasis in adult tissues (Lee et al. 2009; Soori et al. 2018). The family of angiopoietins has four members, angiopoietin-1, angiopoietin-2, angiopoietin-3, angiopoietin-4 (Scott. 2010).

All angiopoietins bind with the same affinity to the protein kinase receptor, a protein specific to endothelial cells. Angiopoietin-1 and angiopoietin-2 are the basic regulators of vascular formation and maintenance which their activity begin with fetal growth and development and continues throughout life. Angiopoietin-1 is found in perivascular and vascular cells within and around smooth muscle cells and plays an important role in growth, vascular stability, and pathological angiogenesis. On the one hand, angiopoietin-2 and angiopoietin-3 contribute to vascular regression, cell death, and inflammation. On the other hand, Angiopoietin-2 can strengthen new blood vessels when combined with vascular endothelial growth factors. It also promotes healthy adipose tissue, resistance to weight gain due to a high-fat diet, improved metabolic functions, and glucose tolerance, and insulin sensitivity. Obstruction of angiopoietin-2 also leads to a decrease in vascular density in subcutaneous white adipose tissue and the spread of unhealthy adipose tissue. Angiopoietin-4, like angiopoietin-1, is also responsible for vascular maturation, stabilization, and stasis (Isidori et al. 2016; Fagiani and Christofor. 2013; Salajegheh. 2016; Akwii et al. 2019). Also, there are several proteins known as angiopoietin-like proteins (Angl), (angiopoietin 1-like protein to angiopoietin 8-like protein) and are widely used in many tissues, including the liver, vascular system, and blood system (Carbone et al. 2018). Indeed, they play an important role in inflammation, lipid metabolism, and angiogenesis. Angiopoietin-1-like protein has been identified as an anti-angiogenic agent, which inhibits endothelial cell proliferation, migration, and endothelial cell adhesion, by inhibiting angiogenesis, invasion, and metastasis, as a tumor-inhibiting gene improves clinical outcomes in patients. Its expression causes the balance of angiogenesis and permeability (Chen et al. 2016). Angiopoietin-2-like protein is a secretory glycoprotein derived from

adipose tissue, expressed in the heart, adipose tissue, kidney, lung, and skeletal muscle, which is involved in metabolic syndrome, angiogenesis, and inflammation (Carbone et al. 2018). Angiopoietin-3-like protein is a liver-specific secretory factor, which is mainly involved in the metabolism of triglyceride-rich lipoproteins by inhibiting lipoprotein lipase (LPL) activity. Angiopoietin-3 protein, like angiopoietin-4 protein, appears to play an important role in regulating fat storage and breakdown (Carbone et al. 2018; McQueen et al. 2017) and is mainly produced and secreted by the liver and adipose tissue. Reversible binding of the angiopoietin-4-like protein to LPL lipoprotein lipase leads to remain in the subcutaneous space, resulting in temporary inhibition of enzyme activity. Angiopoietin-4 protein inhibits the absorption of triglyceride-rich lipoproteins by inhibiting lipoprotein lipase, thereby increasing blood triglyceride levels and hepatic triglyceride stores (Mattijssen and Kersten. 2012). It is also contributes to energy homeostasis, redox regulation, inflammation, endothelial cell integrity, angiogenesis, and cancer. This factor has been recognized as an anti-angiogenic protein that can regulate vascular integrity and angiogenesis (Tan et al. 2012; Xu et al. 2015). Angiopoietin-5 and 6-like proteins, like angiopoietin-3 and 4-like proteins, contribute to fat metabolism, triglycerides, and growth. Angiopoietin-5-like protein is expressed in adipose tissue and the adult human heart. Another family member of angiopoietin-like proteins has also been shown to directly regulate fat, glucose, and energy metabolism (Carbone et al. 2018; Sharma. 2017; Namkung et al. 2011).

Signaling pathway of angiopoietin

Collective interactions between angiopoietins, tyrosine kinase receptors, vascular endothelial growth factors, and their receptors create two signaling pathways. Tie-1 and Tie-2. Angiopoietin proteins 1 to 4 are all Tie-2 receptor ligands.

Tie-2 is a tyrosine kinase receptor that is expressed almost exclusively on endothelial cells. The best of these are Ang-1 and Ang-2. Signal transmission by Tie2 activates the PI3K / Akt cell survival signal pathway and activates endothelial nitric oxide synthase (eNOS). Which in turn leads to vascular stabilization, cell survival and cell proliferation. By activating this pathway, FOXO1, which is predominantly expressed in endothelial cells and is a negative regulator

of angiogenesis, is inhibited, which ultimately leads to a significant increase in Ang2 mRNA levels. Tie2 activation also inhibits NF-κB-dependent expression of inflammatory genes (Eklund et al. 2017; Akwii et al. 2019) (as shown in Figure 2).

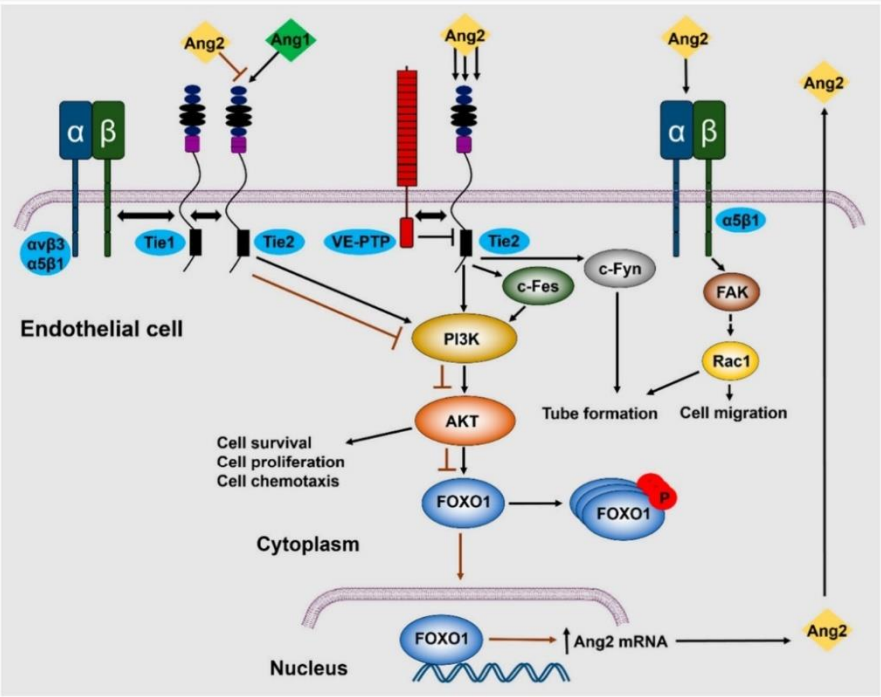

Figure 2: Angiopoietin 1 and 2 signaling pathway (Akwii et al. 2019)

DISCUSSION

The objective of this study is to review of the studies on the effect of various exercise training on angiopoietin levels and angiopoietin-like proteins. Studies show that exercise has a significant effect on increasing capillary density in the human body by acting on angiopoietin as one of the angiogenesis factors. Moreover, there are many other benefits such as involvement in fat burning and cure of coronary artery disease, cancer, asthma, and ischemia.

Angiopoietins do not play a direct role in the process of angiogenesis but stabilize and destabilize blood vessels. Exercise has no significant effect on the expression of Ang1 and Ang2 and most changes occur in Ang2 and Tie2 receptors (Taheri Chadorneshin and

Nourshahi. 2017). Angiogenesis is also a marker of cancer progression that has long been considered as a therapeutic target and since Ang1 and Tie2 are the most important signaling pathways of tumor angiogenesis, it seems that decreased expression of angiopoietin 1 leads to inhibit and impairs the function of the Ang1 and Tie2 signaling pathways in tumor tissue (DeBusk et al. 2003).

In a study with 11 healthy men, was found that aerobic exercise with and without restricting blood flow increased basal levels of the angiopoietin 2 (Ang-2 mRNA) gene, while Angiopoietin 1 (Ang-1 mRNA) gene levels are significantly reduced. Angiopoietin 2 (Ang-2) protein expression was determined following mRNA changes (Gustafsson et al. 2007). Zheng et al., By investigating the effect of aerobic exercise on 36 rats that suffered cerebral ischemia injury through right cerebral artery occlusion (MCAO) surgery, were randomly divided into 3 groups of 12 subjects before surgery and showed that the exercise training can have neuroprotective effects directly against ischemic / perfusion damage in stroke. The technique of middle cerebral artery occlusion surgery was adjusted to correct Ang-1 and Tie-2, and physical exercise increased its expression. As a result, increased Ang-1 and Tie-2 expression by exercise improved brain function in MCAO rats. Their results show the importance of angiogenesis in rehabilitation for post-ischemic brain injury and help explain the underlying mechanism (Zheng et al. 2011). In Ahmadian et al.'s study of continuous endurance training in 12 mice with breast cancer, which was divided into two groups of 6 mice (continuous endurance training group: 6, rest group: 6) and the results showed continuous endurance training reduced angiopoietin-1 gene and protein Tie-2 expression compared with the control group. Also, after 10 weeks of exercise training, the tumor size was lower in endurance training than in the control group. It seems that endurance training can inhibit some angiogenic factors and indirectly have a positive effect on the inhibition of breast cancer and this type of exercise can be used as a treatment for breast cancer (Ahmadian et al. 2018). In a study, 12 BALA / c rats after cancer induction (subcutaneous injection of MC4-L2 to the right side of rats) were randomly assigned to the intense exercise group (n = 6) and the inactive group (n = 6). Frequency of high-intensity interval exercise was five days a week for 11 weeks

which significantly reduced the expression of STAT-3 and angiopoietin-1, and the change in tumor volume and Tie-2 levels in the exercise group compared to the control group. It sounds high-intensity exercise can decline the progression of the tumor (Ahmadian et al. 2019).

Recently, angiopoietin-1 has been shown to stabilize capillaries and prevent their secretion, while angiopoietin-2 is an angiopoietin-1 antagonist and increases vascular permeability. The respiratory tract microcirculation has the potential to contribute to the pathogenesis of exercise-induced bronchoconstriction (EIB) in people with asthma. In a study that paid attention to the role of angiopoietin-2 in EIB in patients with asthma treated with inhaled corticosteroids, the levels of angiopoietin-1 and angiopoietin-2 in 32 patients who had been treated with Inhaled corticosteroids were surveyed. There were 14 subjects in the control group. All patients with asthma performed a treadmill exercise test that was set for 6 minutes with a fixed workload to increase the heart rate to 90% of the maximum predicted value based on the patient's age. Angioputin-2 levels in the respiratory tract of asthma patients were increased by inhaled corticosteroid therapy (Kanazawa et al. 2008)

ANGPTL4 protein was first discovered in skeletal muscle tissue by ELISA with immunofluorescence staining (Catoire et al. 2014). Interactions between ANGPTL4 and LPL were also observed intracellularly (Dijk et al. 2014; Robciuc et al. 2012). ANGPTL4 may has a regional interaction on LPL which is increased in skeletal muscle along with UCP3, PDK4, and CPT1 genes (Pilegaard et al. 2003). ANGPTL4 also inhibits LPL activity at the levels of capillary endothelial cells within muscle tissue (Chi et al. 2016). Another possible function of muscle ANGPTL4 production is to regulate angiogenesis which is suggested in connection with neovascularization and tendon repair (Mousavizadeh et al. 2016). On the other hand, information on the regulation of ANGPTL4 mRNA in human skeletal muscle during exercise is contradictory (Catoire et al. 2014; Norheim et al. 2014)

Angiopoietin-like protein 1 (ANGPTL1) is not well-known yet. Angiopoietin-like protein 2 (ANGPTL2), is associated with fat, insulin resistance and the development of type 2 diabetes (Kadomatsu et al.

2011). Besides, ANGPTL 3, 4, and 8 have been shown to play an important role in regulating lipid metabolism by inhibiting lipoprotein lipase. Similarly, ANGPTL6 is higher in patients with metabolic syndrome and is positively correlated with HDL levels. Recently, ANGPTL8 levels are higher in obese and diabetic individuals and are positively related to insulin resistance and fasting blood sugar in non-diabetic individuals. In the study of Abu Farha et al, A total of 144 subjects were recruited in this study to complete three months of exercise. Participants were classified according to BMI, 82 were non-obese and 62 were obese, and for the first time found that obesity increased ANGPTL7 levels in plasma and adipose tissue. Increased ANGPTL7 expression may play a minor role in regulating triglyceride (TG) levels in obese individuals, directly or through interaction with other members of the ANGPTL protein. Combined exercise training (moderate-intensity aerobic exercise and resistance training) reduces ANGPTL7 levels and shows the potential for targeting this protein as a therapeutic target for the regulation of hyperlipidaemia (Abu-Farha et al. 2017). Larouche et al (The study included 54 sexually mixed participants) found that in patients with cardiovascular disease (CAD), the level of ANGPTL2 in the serum level after high-intensity interval exercise (HIIE) decreases significantly and increases gradually after moderate to moderate-intensity exercise (MICE). A stable decrease in circulating ANGPTL2 can contribute to the chronic cardiometabolic effects of high-intensity interval exercise in patients with cardiovascular disease (Larouche et al. 2015). Also, 3 months of aerobic exercise reduces serum ANGPTL2 levels in patients with the acute coronary syndrome (ACS) (Thorin-Trescases et al. 2016). Gorecka has suggested that increased plasma free fatty acids (FFA) during mountain marathon running might play a role in releasing plasma ANGPTL4 and increasing secretion ANGPTL4 that may be is a compensatory mechanism against oxidative stress caused by fatty acids. The increase in HDL-C in plasma that occurs immediately after administration likely due to the protective effect of ANGPTL4 on HDL (Górecka et al. 2020). In another study, 18 sedentary obese postmenopausal women were randomly divided into experimental (n = 10) and control (n = 8) groups. Subjects in the experimental group were recruited to perform endurance training session for 30 minutes (running

on a treadmill with 60% of maximum heart rate), and as a result, acute endurance training session did not result in significant changes in ANGPTL4 levels, however, cholesterol levels Significantly decreased. Also, no significant relationship was reported between pre- and post-ANGPTL4 levels and levels before and after TG, cholesterol, HDL, LDL, and VLDL test. Serum ANGPTL4 levels increased by only 2.9% after one endurance training session (Gholijani et al. 2016). Ingerslev et al. 2017, found out an interesting findings showing that exercise-induced ANGPTL4 is secreted from the liver and guided by a glucagon-cAMP-PKA pathway in humans. Participants were 27 healthy men and training protocols was muscular endurance training and aerobic exercise on an ergometer bike. These findings link the liver, insulin, glucagon, and lipid metabolism, suggesting that ANGPTL4 may be involved in metabolic diseases.

On the other hand, in another study, the effect of lifestyle intervention on ANGPTL8 concentration was investigated. 384 obese / overweight adults with newly diagnosed type 2 diabetes were randomly divided into diet (n = 128), diet + activity (n = 128) and control (n = 128) groups. Exercise activity consisted of 30 minutes of walking, 5 times a week, in which a 6-month intervention that resulted in weight loss by a calorie-restricted diet or diet + activity resulted in a significant reduction in ANGPTL8 concentration (Ingerslev et al. 2017). The results of the Kersten et al, show that plasma ANGPTL4 levels increase with fasting, calorie restriction, and endurance exercise, possibly resulting in increased plasma free fatty acids (Hu et al. 2019). A study also found that ANGPTL4 mRNA levels Increases in skeletal muscle during and after acute exercise which likely because of increased levels of free fatty acids and circulating cortisol. In this study The exercise protocol was a combination of endurance and strength training. The subjects were twenty-six healthy inactive men, and there was evidence that muscle-secreted ANGPTL4 had a limited effect on serum levels, and that muscle and adipose tissue contained two isoforms similar to ANGPTL4 mRNA (Kersten et al. 2009). ANGPTL4 is also significantly produced in response to a combination of endurance and strength exercises in muscle. However, liver and adipose tissue may be more involved in increasing exercise-induced ANGPTL4 serum levels (Norheim et al. 2014).

In a human study, serum ANGPTL4 levels were decreased in adenosine monophosphate (AMPK)-stimulated protein kinase-stimulated muscles during exercise, and plasma triglycerides were used as muscle fuel. Their study results refer to that muscle without local regulation of ANGPTL4 via AMPK and free fatty acids play a major role in controlling fat homeostasis during exercise (Catoire et al. 2014). Another study was designed to surveys the effect of aerobic exercise in addition to weight loss diet intervention on ANGPTL4 expression and its relationship with metabolic health. Thirty-five obese and sedentary people (sedentary obese men (n = 18) and obese and sedentary postmenopausal women (n = 17) recruited to a 6-month program that includes 3 weeks of aerobic exercise and 1 week of dietary instructions for Induction weight loss. Observed the expression of the angiopoietin 4-like protein gene (ANGPTL4 mRNA) of muscle is associated with ANGPTL4 body fat and glucose utilization (Li et al. 2020).

Another study reported that a period of physical activity could lower ANGPTL2 levels in patients and found that chronic exercise reduced ANGPTL2 in patients with the acute coronary syndrome (ACS). In addition, it has been provided that 3-month exercise-based prevention program, low-plasma ANGPTL2 levels, obtained after exercise, may be reflect endogenous and cardiopulmonary function (Thorin-Trescases et al. 2016).

Despite our research, we still have many unanswered questions about angiopoietins, angiopoietin-like proteins, and the effect of exercise on them, which could be a good topic for future studies. Angiopoietin 3 and 4 (Ang3 and Ang4) are still unknown to us, and the effect of different exercise training on angiopoietin-like protein levels can be investigate by researchers in the future.

CONCLUSIONS

Studies show that exercise has a significant effect on increasing capillary density in the human body by acting on angiopoietin as one of the angiogenesis factors. In addition, there are numerous other benefits like contribute to fat burning and treatment of coronary artery disease, cancer, asthma, and ischemia. More research is needed on the effects of different types of exercise training on angiopoietins.

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