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Research Article

The Effect of Resistance Training on The Changes in Serum Angiogenesis Stimulating Factors and The Progression of Retinopathy in Diabetic Patients

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Abstract

Background: Diabetic retinopathy is one of the most serious complications of Retina microvascular disorder, so the aim of this study was to investigate the effect of resistance training on changes in serum regressive stimulating factors and retinopathy progression in diabetic patients.

Materials and Methods: 24 men with type 2 diabetes without retinopathy symptoms were selected purposefully and randomly divided into two groups of 12 experimental controls. The experimental group performed 6 months of resistance training, three sessions per week with 65% intensity and 5% overload after all 6 sessions. Before and after 6 months, growth factor concentrations of vascular endothelium, nitric oxide and fasting blood sugar were measured and recorded, and finally the data were analyzed using correlated t-test, independent t and chi square. The meaning level was less than 0.05.

Results: Comparison of pre-test and post-test changes between the control and experimental groups showed that no (P=.001) and VEGF (P=.001) of the subjects after 6 months of resistance training had a significant difference with the control group, but there was no significant difference between the control and experimental groups.

Conclusion: A period of resistance training can increase growth factor derived from endothelium and plasma nitric oxide in diabetic patients and it may be hypothesized that exercise, in addition to controlling diabetes through increasing these factors, may also be effective in preventing retinopathy.

Keywords:
VEGF and NO, Endurance training, Retinopathy, Type 2 diabetes.

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1. Introduction

Diabetic retinopathy is the most common chronic complication of diabetes and the leading cause of visual impairment in patients between the ages of 25 and 74 (1). Although chronic hyperglycemia and hypertension are clearly effective in the pathogenesis of diabetic retinopathy, other risk factors and pathways to its pathogenesis have not been well clarified despite important researches. Overall, it seems that the total number of factors including hyperglycemia, duration of diabetes, onset age of diabetes, hypertension and inflammatory factors are involved (2). In general, diabetes causes abnormal glucose metabolism due to decreased levels or insulin activity, and increased blood glucose levels have structural and physiological effects on retinal capillaries and alter them both anatomically and functionally. Continuous increase in blood glucose levels causes it to be shanted into the Aldous-reductase pathway in certain tissues and the result of this pathway is the conversion of sugar to alcohol. The intra-walled pericytes of the retina capillaries are affected by these alcohols and are functionally impaired. These microorganisms are the primary symptoms of diabetic retinopathy (3). The tearing of microorganisms leads to superficial or deep retinal bleeding (4). Vascular endothelium growth factor (vegf) is one of the most important issues in this field (5). VEGF is a hemodymer protein bonded to heparin with a molecular weight of 45 kDa that is capable of proangogenic activity both in vivo and in vitro conditions and has 7 isoforms F, E, D, C, B, A and PIGF that are produced from VEGF gene as a result of different splicing. These isoforms differ in molecular weight and biological properties (6). It seems that VEGFA is the most important isoform attributed to VEGF. Overexposion of this isoform causes powerful angiogenic effects in different tissues. It also increases permeability and vasodilation. Different factors affect vegf production. The most important of which are hypoxication, shear pressure, contraction and muscle stretching, decreased blood glucose concentration, cytokines and HIF-1 (7).

One of the most important regulators is specific angiogenesis and performs their biological action on target cells through interaction with tyrosine kinase receptors in the plasma membrane of cells. After binding to their ligand, these receptors become dematrodes and autophospheric, which ultimately leads to an intracellulation cascade (8). VEGF-A is the main factor in the angiogenesis process and its effect is accomplished by activating vegfr-1 and VEGFR-2 receptors. VEGF is the oxide nitric synthesis by phosphorylation of AKT and phosphorylation of amp activating protein kinase (9).

VEGF plays a role in migration, proliferation, matrix degradation of endothelial cells, formation of vascular networks as well as nitrik oxid production and release of endothelial cells. In addition, it has an apoptive effect on endothelial cells and causes expression of antibiotics BCL2 and A1 in these cells. In vivo conditions, VEGF regulates vascular permeability that is necessary for the onset of angiogenesis, which is why it is called vascular penetrating factor and, in this case, acts 50,000 times stronger than histamine (10). Nitic oxid caused by endothelium, by creating continuous dilating tone in the bed, causes better blood supply of organs. Vascular endothelium plays a vital and complex role in regulating blood flow and producing chemicals such as nitrik oxid, prostacicline and endotheline. Skin vessels, in addition to nerve and humoral factors, are controlled by endothelium (11).

Increasing the level of blood lipids in the long term, especially in old age, causes sedimentation in the vascular system and hardening of the vascular artery. It also increases blood pressure and can cause heart attack, brain attack and death by vascular obstruction (12).

Andothelia cells that cover the internal surface of the vessels create an active relationship between blood and smooth muscle cells and perform this operation in response to mechanical and chemical stimuli such as vasoactive. Nitric oxid (NO) and oxygen-derived free radicals (OFR) are among the substances and compounds produced from these cells. Oxidation is responsible (5), the growth factor of vascular endothelials releases the dependent nitric oxid, which is due to an increase in cytosolic calcium and nitrite nitrite nitrite oxidation. Nitrik oxide synthesis shows less endothelia (Kim, 2014), which produces less nitrik oxid, decreases nitrix oxid production can be associated with increased activity of blood platelets and arterical thromboses, as well as increased arthrogenesis (11).

Several studies have been conducted in this area that can be done to research Prado et al. (2017) in a research titled The relationship between exercise and diabetic retinopathy(13), Ren et al. (2019) in a study entitled Physical Activity and Retinope Risk Diabetics(14), Shamsol et al. (2015) in a study entitled The Effect of Diet and Exercise on Diabetic Retinopathy(15), and Toloui et al. (2019) in a study titled Comparing the Effect of Eight Weeks of Aerobic Training And resistance to angiogenic factors dealt with angiogenic factors(16). Vizvari et al. (2018) in a study titled the effect of intense aerobic training on changes in serum levels of some inhibitory and stimulating angiogenesis indices in women with type 2 diabetes (17). Mohammadi et al. (2018) investigated the effect of eight weeks of aerobic interval training on serum levels of nitric oxide and endotheline-1 in overweight elderly men. Since exercise has an effective role in physical and mental health through reducing or modifying health risk factors, it has always been considered by experts, so that the American Diabetes Association recommends regular physical exercises with moderate or high intensity for diabetic patients, after exercise training, major biochemical and physiological adaptations occur in the human body. One of the most important adaptations is vascular dilation and increased capillary density or angiogenesis, which is exerted by increasing the stress valve caused by increased blood flow during physical activity. Sequential changes in shear stress lead to increased bioactivity of VEGF and NO. Due to limited researches on the effect of resistance training on nitrik concentration of oxid and vascular endothelial growth factor, this study was conducted (18). Therefore, the aim of this study was to investigate the effect of resistance training on changes in reggae stimulation and retinopathy progression in diabetic patients.

2. Materials and Methods

In this quasi-experimental field study, 24 men with type 2 diabetes aged 45-50 years who did not have retinopathy according to retinal fellowship were included in this study. The selected subjects had no history of participating in any resistance training and did not have any heart disease or specific diseases and all patients were under the supervision of an internist during the study to control diabetes. At first, the general health questionnaire, physical activity level and medical background were completed by the subjects to assess the initial condition and 48 hours before and after 6 months of resistance training, 5 cc blood was taken from the anterior arm venous volunteers. After taking blood samples, VEGF plasma concentration was obtained using the QUALITY ELISA of BOSTER Company made in the United States with the accuracy of 10th of picogram/millimeter (Pg/ml), nitrik oxid concentration. Using ELIZA kit, GLORY company made in the United States was measured with the accuracy of 100 μmol/l (μmol/l) and FBS concentrations were measured by phenometric method using Pars Test kits made in Iran.

Resistance Training Program:

After evaluating the level of physical well-being of the subjects, the experimental group participated in resistance training for 6 months, 3 sessions per week and about 60 minutes per session. The training program consisted of 10 minutes of warm-up with a variety of stretching and leniency movements and then 10 stationary movements in circles for 30 to 40 minutes. At the end, 10 minutes of cooling was considered. Stations consisted of 10 types of resistance training (leg press, chest press, shoulder press, front arm, back arm, let's money, knee extension (quadriceps), knee bending (serene and hamstring), heel lifting (strengthening twin muscle), and leakage.The training program in each session consisted of three rounds with twelve repetitions and with intensity of 40-65% of one repetition maximum, rest time between stations, 45 to 60 seconds and Rest time between each round was 90 seconds. The principle of overload was designed in such a way that after every 6 training sessions, one test was performed one repetition maximum for each person in each station and 5% of weight was added to it (Williams, 2002). The following formula was used to determine a repeat of the limit (Williams, 2002).

$$1RM = \frac{w}{1.0287 - 0.0278r}$$

Data analysis was performed using 21 SPSS edits. Central description and dispersion indices were used to describe the statistics and inferential statistics were used to compare the averages. For this purpose, the normal distribution of data was investigated using Kolmogrov-Smirnov test. Considering the natural nature of the data distribution, it was used to investigate the intergroup differences and the results and findings of the independent, dependent t-research and also to use the squared kai.

3. Results

Comparison of pre-test and post-test changes between the control and experimental groups showed that no (P=.001) and VEGF (P=.001) of the subjects after 6 months of resistance training had a significant difference with the control group, but there was no significant difference between fasting blood sugar in the control and exercise groups (P=.121) (Table 1). The results also showed that after 6 months of resistance training, none of the retinopathy symptoms were found in the training group, but in the control group, 3 subjects had mild retinopathy, and the results of the squared chi test showed that there was no significant difference between the control and training groups (p=0.06).

Table (1): Table 1 Compares changes before and after 6 months of intervention in variables measured in the exercise and control groups on VEGF and NO resting levels

Variable	Group	Pretest	Post-Test	Intergroup	Between Groups
VEGF)Picogram Per Milliliter(	Control	437.64+83.008	437.64+75.06	0.339	0.001
	Experimental	445.47+0.77	498.32+66.73	0.001	
NO Micromole(	Control	19.1+36.34	18.2+87.01	0.264	0.001
	Experimental	19.1+57.71	21.1+86.43	0.001	
FBS Mg/Dl)(	Control	145.58+14.29	142.13+58.99	0.001	0.121
	Experimental	151.10+67.20	148.10+41.54	0.001	

4. Discussion

As the results of this study showed, 6 months of resistance training had a significant effect on increasing growth factor derived from endothelium and nitric oxide plasma, and according to the adjustment of glucose level in the control group compared to the training group to eliminate the effect of fasting blood glucose on retinopathy progression, there was no significant difference between fasting blood glucose level in the control and training group.

The results of this study showed that 6 months of resistance training had a significant effect on the increase of endothelium-derived growth factor, which results from the results of Prado et al. (2017) research in a research titled the relationship between exercise and R Diabetic tinopathy achieved the results that physical activity decreased in patients with diabetic retinopathy compared to the control group and also showed negative correlation between diabetic retinopathy severity and physical activity(13). . In a study titled Physical Activity and Diabetic Retinopathy Risk, Ren et al. (2019) concluded that in diabetic patients, there was a relationship between physical activity and PA, and inactivity could also increase the risk of DR(14). Shamsol et al. (2015) in a study titled The Effect of Diet and Exercise on Diabetic Retinopathy achieved the results that lifestyle and nutrition have a positive effect on preventing or slowing the progression of DR, especially in order to protect nerve damage in the diabetic retina, and in addition, the benefits of physical activity have a positive effect on improving retinal neural function and inhibiting DR progression(19). In 2008, Yu et al. investigated the role of preinflammatory cytokines from vascular endothelial growth factor in pathogenesis in patients with rheumatoid arthritis. Yu et al. stated that VEGF is the best factor for regulating angiogenesis and have proposed VEGF-ANTI factors as angiogenesis inhibitors(20). The effect of exercise on serum VEGF has contradictory results as Toloui et al. (2019) in a study titled Comparing the effect of eight weeks of aerobic and resistance training on angiogenic factors achieved these results that there was no significant change.(16). Emilein et al. (2008) showed that following acute exercise, serum VEGF levels increased. This activity was performed on a bicycle meter and the results were so close to the significant level (P=0.055). None of the VEGF levels remained unchanged and changes were evident at all levels(21).

Also, the results of this study showed that 6 months of resistance training had a significant effect on NO, which results with the results of researches: mohammadi et al. (2017) that achieved these results, aerobic training increased nitric levels. Oxide can be matched(18), as well as the results of the Research of vazwari et al. (2017) that achieved intense aerobic training, which increased serum levels of some inhibitory and stimulating angiogenesis indices in women with type 2 diabetes. Be consistent (17).

Several factors are involved in the stimulation of angiogenesis factors, among which nitric oxide and vascular endothelium growth factor are involved in reduced production and biological activity in diabetes and are the main factors in the incidence of diabetic retinopathy. NO is a regulatory molecule with wide metabolic, vascular and cellular effects and is secreted in tissue in response to stimuli such as hypoxyicity. Resistance training causes hyperglycemia-related pathways to activate proinflammatory mediators by activating oxidative stress, thereby releasing proinflammatory cytokines, chemokines and other inflammatory mediators. Increased levels of these proinflammatory cytokines in the network of diabetic patients are associated with failure of BRB, retinal leukostasis and apoptosis associated with diabetic retinopathy. Inflammatory chemokines, including MCP, which activates macrofa and monocytes, are involved in the pathogenesis of retinopathy through pathways including VEGF. Other inflammatory proteins, including nitric oakside, cause cell damage to the retina under diabetic conditions. As the results of previous studies have shown, increased concentrations of VEGF and NO in blood serum levels are associated with fewer complications of diabetic retinopathy (5).

Resistance training also plays a role in stimulating and deforming the VEGF network of vessels, if the blood flow is low in the vessels, the endothelial cells will eventually be destroyed due to apoptosis. Regular exercises, especially resistance training, causes andothelial cells to be constantly exposed to mechanical pressure due to muscle contraction and stress on andothelial is one of the factors causing VEGF release and causes (13). VEGF increases muscles that are exposed to overload, contraction and hypermia since they are stretched during resistance exercise of andothelial cells, vegf release rate increases. Also, during exercise, the blood flow of active muscles increases about 10 to 20 times, which causes shear stress in the vessels. Also, resistance training causes mechanical pressures induced by muscles, stimulates no release and increases ENOS, which consequently reduces retinopathy and subsequently many researches have shown that No plays a key role in activating vegf signal pathway. No is one of the most important factors that are released from endothelium No free radical, which is made of L-arginine by the enzyme No synthesis and is involved in various processes such as neurotransmitter, vascular actions, defense and inflammation. (9). No, it dilates the veins, prevents platelet accumulation and also prevents the adhesion of lococytes. No is also an important factor in the creation of angiogenesis. Studies have reported that increased shear stress during endothelial cell proliferation and angiogenesis process causes no release in increasing VEGF. Many studies have shown that No plays a key role in activation of VEGF signal pathway (17). Also, it is likely that stretching of endothelial cells causes the breakdown of the base membrane and extracellular matrix and facilitates the necessary angiogenesis conditions, since most studies have highlighted the significant role of exercises in increasing the angiogenesis process, it is likely that resistance training due to further changes in the peripheral circulatory system and activation of stretching pathways and mechanical pressures of vessels in the angiogenesis process is more effective in the angiogenesis process. The result reduces the progression of retinopathy in diabetic patients, but since muscular analysis and atrophy occur in diabetic patients to compensate for these muscle injuries, the implementation of resistance training is one of the training requirements in these patients (22-24), so resistance training improves glucose profile and counteracts the serum decline of VEGF and NO due to inactivity and diabetes improves the regression process in these patients.

Conclusion

A period of resistance training can increase serum regressive factors and although the difference between diabetic retinopathy between the two groups was not significant, but due to the increase in VEGF and No and the lack of diabetic retinopathy in the training group, it can be suggested that exercise in addition to controlling blood sugar through VEGF and No increase can also help to prevent and control diabetic retinopathy.

To prove this, it is needed to study with more patients, patients with different stages of retinopathy, and longer duration of fallopian.

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Compliance with ethical standards

Conflict of interest None declared.

Ethical approval the research was conducted with regard to the ethical principles.

Informed consent Informed consent was obtained from all participants.

Author contributions

Conceptualization: A.B, I.B.; Methodology: A.B, I.B.; Software: A.B, I.B.; Validation A.B, I.B.; Formal analysis: A.B, I.B.; Investigation: A.B, I.B.; Resources: A.B, I.B.; Data curation: A.B, I.B.; Writing - original draft: A.B, I.B.; Writing - review & editing: A.B, I.B.; Visualization: A.B, I.B.; Supervision: A.B, I.B.; Project administration: A.B, I.B; Funding acquisition: A.B, I.B.

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