Research Article

Brain-derived neurotrophic factor (BDNF) variation to aerobic exercise and aloe vera intake in women with type 2 diabetes

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Abstract

This study aimed to investigate the interactive effect of aloe vera intake and eight weeks' aerobic exercise on serum BDNF, glucose, and insulin levels in women with type 2 diabetes. In this experimental study, 32 women with type 2 diabetes were selected and randomly divided into four groups of control, supplement, and exercise, exercise + supplement. The exercise program was performed 3 sessions per week for 8 weeks (40 min of exercise with 50-60% of heart rate reserve in the first four weeks and 60 min of exercise with 60-80% of heart rate reserve in the second four weeks). The supplement taking groups received 400 mg/kg of oral aloe Vera 3 days per week for 8 weeks. The data were analyzed using analysis of covariance (ANCOVA). A significant increase was observed in BDNF levels, insulin sensitivity of patients in the supplement, exercise, and exercise + supplement groups (p=0.001). The glucose and insulin levels, insulin resistance, BMI, and body fat percentage significantly decreased in the supplement, exercise, and exercise + supplement groups (p=0.001). It seems aloe Vera intake and aerobic exercise to have protective effects against development of type 2 diabetes complications in women.

Key Words: **Glucose, Insulin resistance, Neurotrophic factor, Exercise training**

Introduction

Diabetic neuropathy is one of the most common and costly complications of type 2 diabetes. The prevalence of neuropathy in newly diagnosed patients and in those with a long history of diabetes are 8% and above 50%, respectively (Feldman et al.,2019). The pathologic mechanisms of diabetic neuropathy are not completely known; however, the disease is associated with degeneration of Schwann cells and myelinated nerve fibers, and loss of nerve populations. These neurodegenerative markers led researchers to investigate the effect of growth factors, as potential therapeutic agents, in the treatment of diabetic neuropathy (Feldman et al.,2017). The neurotrophin family is composed of these growth factors that play a huge role in nerve regeneration and protection. Neurotrophins are vital to the formation and functioning of the peripheral nervous system and loss of neurotrophin signaling will lead to devastating effects (Feldman et al.,2017). Brain-derived neurotrophic factor (BDNF) is a member of neurotrophin family with a molecular weight of 27 kDa and consists of two polypeptide chains. BDNF acts through two receptors of tyrosine kinase and LNGFR at cell surface. BDNF exists in the central and peripheral nervous system, endocrine system, lymphocytes, muscles, liver, heart, and endothelial system, and plays a regulatory role in glucose metabolism. Studies have shown significant decrease in BDNF levels in patients with glucose disorders, diabetes, and insulin resistance (Ansari et al.,2016). In fact, degeneration of neurons and Schwann cells in diabetic subjects causes changes in the levels of growth factors expression and synthesis in the peripheral nervous system. As reported, in streptozotocin-induced diabetic rats, the nerve growth factor (NGF) levels decrease in sympathetically innervated target organs. Compared to NGF, BDNF protects more sensory neurons, and plays a more important role in the survival and growth of motor neurons (Eslami et al.,2015).

Today, serious challenges associated with diabetes and its therapeutic strategies have resulted in great preventive efforts. Sport activities are among these preventive strategies that can improve the health of the whole body, as well as the brain's functioning. Salehi and Hosseini reported that eight weeks of moderate to high endurance training significantly increased serum BDNF levels in streptozotocin-induced diabetic rats (Salehi et al.,2017).

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According to researches, high-intensity exercise increases BDNF levels in people with diabetes (Tonoli et al.,2015). also reported that 9 months of aerobic training did not significantly affect serum BDNF levels in individuals with type 2 diabetes (Swift et al.,2012). Inadequate response to some traditional treatments has urged researchers to use complementary and alternative therapeutic methods (e.g., herbal and dietary treatment methods) for the treatment of diabetes. Due to their phenolic and flavonoid compounds, medicinal herbal extracts have antioxidant properties and can prevent the development of oxidative stress in diabetic patients. Aloe Vera with the scientific name of Aloe barbadensis is native to the Africa continent and has been used for many years due to its anti-inflammatory, antimicrobial, wound-healing, and anti-tumor effects. Aloe Vera gel is used for treatment of infectious wounds, burns, and cuts. Reducing blood glucose and cholesterol levels, relieving arthralgia, and improving the immune system are other notable properties of this plant (Alinejad et al.,2015). The hypoglycemic effect of aloe Vera gel depends largely on degeneration of pancreatic β-cells. The compounds available in aloe Vera extract prevent the death of beta cells (Ayoubi et al.,2015). Asgari Hazaveh et al reported that high intensity interval exercise accompanied with aloe Vera supplement significantly increases serum insulin in diabetic male rats (Asgari et al.,2018). Researchers have proposed the use of various exercises along with herbal supplements as a safe strategy for controlling obesity, diabetes, and their complications. However, due to the diversity of exercise programs and herbal supplements, contradictory and ambiguous results have been obtained. Although many studies have investigated the effect of aerobic exercise on BDNF and glycemic indices in diabetic patients, few studies have focused on the combined effects of aloe Vera intake and aerobic exercise on BDNF and glycemic indices in type 2 diabetic patients. This study aimed to investigate the combined effects of aloe Vera intake and eight weeks of aerobic exercise on serum BDNF, glucose, and insulin levels in women with type 2 diabetes.

Materials and Methods

Subjects

A pretest-posttest design and a control group were used to conduct this quasi-experimental study on 32 women with type 2 diabetes. The study population included women with type 2 diabetes, aged 40-55 years, admitted to Madaen Hospital, Tehran, among whom 32 individuals were selected using convenience and purposive sampling methods. The participants were randomly divided into four groups of control (n=8), supplement (n=8), exercise (n=8), and exercise plus supplement (n=8).

The patients were first briefed about the nature and structure of the research and their participation manner. The inclusion criteria included a history of type 2 diabetes (based on medical diagnosis and records) for at least 3 years, a fasting blood sugar of 162-250 mg/dL, and the use of similar medications (metformin and glibenclamide). The patients voluntarily participated in the research and signed informed consent forms.

Exercise protocol

The exercise protocol consisted of 8 weeks of aerobic exercise, 3 sessions per week. Each session included 40-60 min of activity on a step. In the first four weeks, 40 min of exercise was performed with 50-60% of heart rate reserve, while, in the second four weeks, 60 min of exercise was performed with 60-80% of heart rate reserve (Mendes et al.,2015). Heart rate reserve was calculated by the Karvonen formula. The supplement taking groups received 400 mg/kg of oral aloe Vera gel 3 days per week for 8 weeks. The aloe Vera gel was supplied from Barij Essence Company, Kashan (Asgari et al.,2018).

Measurements

Body fat percentages (BFP) were calculated by measuring skinfold thickness with Harpenden Caliper (measurement accuracy of 0.1 mm) using Jackson-Pollock 3-site formula for women (Jackson et al.,1980). VO2max was calculated using Rockport's walk test. Blood samples were taken 48 hours before and 48 hours after each exercise session. Samples were collected from 7 to 8 am, using the participants' left-hand veins. The participants were sitting and resting in the laboratory during the process. BDNF ELISA Kits (China, Wuhan) were used for measuring serum BDNF levels with a detection sensitivity of 0.06 ng/ml. Glucose levels were measured using glucose kit (Pars Aazmun Co., Iran) through the glucose oxidase method. The variation and sensitivity coefficients of the measurement method were 1.19% and 5 mg/100 mL, respectively. Insulin plasma levels were measured using Mercodia insulin ELISA kit (Sweden) with variation and sensitivity coefficients of 6.48% and of 0.15 µU/ dL, respectively.

Insulin resistance levels were calculated using the homeostatic model assessment (HOMA-IR) method with the following formula (da Silva et al.,2007):

HOMA-IR = Fasting Insulin (mU/mL) × Fasting Glucose (mmol/L)/22.5

Insulin sensitivity levels were also measured using the following formula:

QUICKI=1/ (log (fasting insulin, µL/mL) + log (fasting glucose, mg/dL))

Statistical analysis

The data distribution normality was tested by the Shapiro-Wilk test. ANCOVA was used to determine whether there are any significant differences between the exercise and control groups. in terms of various variables. The homogeneity and Levene's tests were conducted as prerequisites for the covariance test. The significance level was considered 0.05. All analyses were performed in SPSS 24. various variables.

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Results

The mean and standard deviation of the participants' demographic and anthropometric characteristics are presented in Table 1. The pre-test and post-test results of covariance analysis for the experimental and control groups in terms of BDNF, glucose, insulin, insulin resistance, insulin sensitivity, BMI, BFP, and VO2max are presented in Table 2. The results showed a significant increase in BDNF, Quicki, and VO2max levels of the middle-aged women with type 2 diabetes following eight weeks of aerobic exercise and aloe Vera intake ($p<0.05$). In addition, the glucose and insulin, insulin resistance, BMI, and BFP levels significantly decreased ($p<0.05$).

Discussion

This study aimed to investigate the effects of aloe Vera intake and eight weeks of aerobic exercise on serum BDNF, glucose, and insulin levels in women with type 2 diabetes. The results showed a significant increase in BDNF levels following aloe Vera intake and eight weeks of aerobic exercise. Recent evidence suggests that physical activity can increase neuronal plasticity, which is associated with increased neurotrophic factors, such as BDNF. However, its scientific mechanism has not yet been fully understood. Few studies conducted on the impact of physical activity on BDNF have yielded ambiguous and contradictory results; they have mostly shown an

Table 1: Mean and standard deviation of the participants' demographic and anthropometric characteristics.

Group		Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	BFP (%)	VO_{2max} (mL/kg/min)
Control	Pre-test	45.50±3.42	159±1.98	71.48±3.09	27.93±1.31	34.08±0.802	27.08±1.37
	Post-test			71.68±2.92	28±1.91	34.24±0.714	26.86±3.07
Supplement	Pre-test	47.75±3.84	161±1.60	72.45±3.84	27.96±1.78	34.28±1.80	27.53±1.69
	Post-test			73.65±3.74	28.42±1.71	33.07±1.75	29.44±1.37
Exercise	Pre-test	48.50±4.62	161±2.69	70.59±5.12	26.94±2.06	33.82±2.01	26.07±0.871
	Post-test			67.88±5.79	25.76±2.31	31.20±1.76	27.45±0.924
Exercise plus Supplement	Pre-test	47.25±5.07	159±1.55	72.49±5.03	29.17±1.91	33.88±1.65	26.13±1.14
	Post-test			67.88±5.12	26.26±2.38	30.27±1.66	28.27±2.01

Table 2: Descriptive indicators of research variables in the pre-test and post-test stages.

Variable		Control	Supplement	Exercise	Exercise+ Supplement	Sig.	Effect size
BDNF (ng/L)	Pre-test	161.1 ± 5.01	158.9±5.21	160.7±3.68	160.5±2.81	0.001*	0.678
	Post-test	161.7 ± 5.30	187.1±6.82	177.6±7.36	215.9±9.39		
Glucose (mmol/L)	Pre-test	10.46±0.693	10.71±0.789	10.69±0.789	10.94±0.929	0.001*	0.895
	Post-test	10.87±0.773	9.98±0.764	9.48±0.855	8.48±0.749		
Insulin (mU/mL)	Pre-test	7.296±0.445	7.32±0.679	7.26±0.632	7.46±5.65	0.001*	0.426
	Post-test	7.76±0.914	6.54±0.485	6.68±0.522	5.77±0.400		
Insulin resistance	Pre-test	3.38±0.354	3.50±0.563	3.50±0.486	3.64±0.587	0.001*	0.682
	Post-test	3.75±0.517	2.90±0.357	2.83±0.424	2.18±0.340		
Insulin sensitivity	Pre-test	0.530±0.012	0.528±0.018	0.529±0.015	0.525±0.019	0.001*	0.735
	Post-test	0.520±0.016	0.550±0.017	0.554±0.024	0.592±0.024		
BMI (kg/m^2)	Pre-test	27.93±1.31	27.96±1.78	26.94±2.06	29.17±1.91	0.001*	0.418
	Post-test	28±1.19	28.42±1.71	25.76±2.31	26.26±2.38		
BFP (% of body weight)	Pre-test	34.08±0.802	34.28±1.80	33.82±2.01	33.88±1.65	0.001*	0.852
	Post-test	34.24±0.714	33.07±1.75	31.20±1.76	30.27±1.66		
VO_{2max} (mL/kg/min)	Pre-test	27.08±1.37	27.53±1.69	26.07±0.871	26.13±1.14	0.001*	0.307
	Post-test	26.86±3.07	29.44±1.37	27.45±0.924	28.27±2.01		

* Significance level ($P \leq 0.5$) was considered

increase in BDNF levels (Salehi et al.,2017: Brinkmann et al.,2017). However, some studies have shown that exercise does not affect BDNF (Mackay et al.,2017). These contradictory results may be due to the differences in exercise protocols, the type of participants, duration of studies, initial BDNF levels, measurement methods, supplements, or controlling the participants' nutrition and physical activity. The present results are consistent with those obtained by Brikman et al. (2017) and Salehi and Hoseini (2012), which may be due to the fact that the participants were diabetic in all these studies. BDNF levels are lower in diabetic patients than in others; thus, physical activities can better improve BDNF levels in these patients. The exact effects of physical activities on neurotrophies are unknown; however, these activities affect BDNF through several mechanisms. Physical activities in human subjects can lead to the survival of dopaminergic neurons, thereby increasing the synthesis of dopamine. Neurogenesis is one of the mechanisms that can explain this improvement. Neurogenesis is the result of moderate-intensity aerobic exercises. Binding of BDNF to tyrosine receptor kinase B (TrkB) produces various intracellular signaling pathways including reversed antisense (RA) and mitogen activated protein kinase (MAPK) (Fallah et al.,2016). Exercise increases BDNF gene expression through TrkB in the brain and especially in hippocampus. In addition, moderate-intensity exercise upregulates the hippocampal BDNF-TrkB signaling pathway (Babaei et al.,2013). Studies have shown that daily exercise leads to the release of various neurotransmitters (e.g., dopamine, norepinephrine, and in particular BDNF) (Fallah et al.,2016). On the other hand, anti-oxidative supplements can affect synaptic plasticity and cognition through mechanisms involved in energy homeostasis. Mechanisms that affect energy metabolism and synaptic plasticity are considered as frameworks for the effects of cellular stress on cognitive function. For example, neurotrophies are considered the main factors in this equation that can link environmental factors to mental health. Aloe Vera can reduce oxidative damage and morphological changes in the brain (Heshmati et al.,2015). Therefore, the increased BDNF level in the present study can be attributed to the reduction in oxidative stress (resulting from the use of aloe Vera and exercise).

Another finding of the study was a significant decrease in insulin resistance due to the use of aloe Vera and eight weeks of aerobic exercise. The results are in line with the study of Abdi and Mohajer Iravani who reported that six weeks of aerobic exercise can reduce insulin resistance in women with type 2 diabetes (Abdi et al.,2018). However, the results are inconsistent with the study of Hosseini (Hosseini et al.,2017). Activation of AMPK and increased activity of phosphoinositide-3-kinase and Akt/PKB are possible mechanisms involved in the reduction of insulin resistance. Clinical studies have shown a decrease in insulin and phosphoinositide-3-kinase signals in skeletal muscles of insulin-resistant and type 2 diabetic patients. However, the post-exercise improved absorption of glucose in the entire body is associated with an increase in insulin receptor substrate 1 and 2 (IRS1 and IRS2) and phosphoinositide-3-kinase in the skeletal muscle. AMPK upregulation is another mechanism through which physical activity can improve insulin resistance. Physical activity increases the gene expression of GLUT-4 and its transfer from cytoplasm to cell membrane through AMPK, and thereby, improves the entry of glucose into muscle cells (Kadoglou et al.,2013). Finally, aerobic exercise makes specific biochemical changes in muscles, and increases capillary density and the number of oxidative enzymes to improve glucose transport and metabolism. This will increase insulin binding to muscle cell receptors, which in turn will reduce the need for insulin. Aloe vera, due to its antioxidant properties, seems to play an important role in preventing oxidative stress. Studies have shown that the flavonoid compounds available in aloe Vera can reduce the complications of diabetes. Recent studies on medicinal plants have shown that some plants have insulin-like properties and can prevent complete absorption of carbohydrates and lipids by small intestine. On the other hand, previous results have shown that polysaccharides, flavonoids, glycoproteins, polypeptides, steroids, alkaloids, and pectin available in medicinal plants (like aloe vera) can well justify possible hypoglycemic properties of these plants (in terms of preventing blood biochemistry changes) in the treatment of diabetes (Farah et al.,2005).

Another result of this study was a significant increase in the quantitative insulin sensitivity check index (QUICKI) due to the use of aloe Vera and eight weeks of aerobic exercise. Evidence suggests that improving insulin sensitivity due to exercise is associated with changes made in the expression or activity of the proteins involved in the transmission of insulin signals in skeletal muscle, such as AMPK and protein kinase B (Akt) substrate of AS160 (Yamamoto et al.,2014). Following an exercise session, increased synthesis of adenosine triphosphate and increased activity of the mitochondrial biogenesis factor will enhance insulin sensitivity. In addition, increased permeability of the membrane and increased stimulation of the capillaries by insulin may promote glucose uptake, and subsequently increase insulin sensitivity. With its antioxidant potential, aloe Vera gel can reduce blood glucose levels through suppression of excessive free radical formation and reduction of glycation enzymes. The anti-inflammatory property of aloe Vera may be the second explanation for its anti-diabetic effect. Diabetes may be considered as an inflammatory disease, where inflammation is involved in the progression of diabetes. Many researchers attribute the anti-inflammatory property of aloe Vera to many of its components like emodin and mannose-6-phosphate (Robertson.,2010).

The results also indicate a significant decrease in anthropometric indices such as BMI and BFP, and a significant increase in VO2max following aloe Vera intake and eight weeks of aerobic exercise. Aerobic exercise increases the intake of lipid reserves; hence, it is the best exercise for losing fat and some weight. Aerobic exercises

increase fat oxidation in exercised muscles. In these exercises, an increase in the activity of lipoprotein lipase enzyme increases the fatty acid β-oxidation capacity. This will increase the intake of fat and reduce the glucose contribution to energy metabolism in aerobic exercises (Lakka & Laaksonen.,2007). This has probably contributed to the participants' weight loss, and decreases in their BFP and BMI. In addition, aloe Vera controls the distribution of fatty acids in blood by controlling the metabolism of lipids in the liver. In fact, aloe Vera constructs unsaturated fatty acids that probably remove free radicals from blood stream and control the metabolism of lipids in the body (Hęś et al.,2019). Aerobic exercises seem to be effective in increasing the VO2max due to using more muscles, reducing BFP, and improving BMI. The significant increase in the VO2max may also be due to the decreased BFP, because studies have attributed the differences in VO2max values to differences in BFP (Shahidi et al.,2015). Most studies have shown that aerobic exercise increases aerobic power and decreases BFP. Aerobic exercises adjust muscle activation patterns to make cardiovascular, muscular, and metabolic systems compatible with physical activities. This will significantly increase VO2max. On the other hand, aerobic exercises increase the number of muscle capillaries, and develop muscle cross-sections, which will in turn improve the muscle blood flow. Moreover, they increase the number and size of the skeletal muscle mitochondria and improve muscle metabolism, which will enhance the muscle's aerobic capacity (Shahidi et al.,2015). In addition, antioxidant supplements increase the brain's oxygen intake, reduce fatigue, and prevent blood vessel clotting. Therefore, they improve the blood flow and skeletal muscle oxygen supply and increase oxygen intake (Lee et al.,2020).

Conclusion

Considering the participants' BMI, BFP, serum insulin, fasting glucose, and insulin resistance levels decreases, it is concluded that eight weeks of aerobic exercise and aloe Vera intake significantly increase serum BDNF levels. In general, it can be said that co-administration of aloe Vera and aerobic exercise has made positive improvements to the health of patients with type 2 diabetes through changing their body weight, BMI, and BFP. Therefore, diabetic patients can perform regular exercises (under the supervision of physicians and exercise physiologists) and take aloe Vera supplements to control their insulin resistance, as well as insulin and blood glucose levels.

What is already known on this subject?

Although the amount of BDNF (Key factor in brain-muscle cross talk) measures has increased with exercise training, to date, it remains an open question that BDNF change with aerobic exercise and aloe vera intake in women with type 2 diabetes.

What this study adds?

BDNF is produced and secreted by human skeletal muscles and other organs. BDNF has antidiabetic effect and associate with circulating anti-inflammatory cytokines in T2DM. This study shows increase BDNF with aerobic exercise and aloe Vera intake in T2DM.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The research was conducted with regard to the ethical principles (Ethic Code: IR.IAU.TMU.REC.1398.083) and Clinical trial (IRCTID: 20190505043476N1).

Informed consent Informed consent was obtained from all participants.

Author contributions

Conceptualization: S.R.M., H.R.; Methodology: H.R., S.K.M.S.; Software: S.R.M..; Validation: H.R., S.K.M.S.; Formal analysis: H.R., S.R.M., S.K.M.S.; Investigation: H.R., S.K.M.S., S.R.M.; Resources: S.R.M.; Data curation: H.R., S.R.M.; Writing - original draft: H.R., S.K.M.S.; Writing - review & editing: H.R., S.K.M.S., S.R.M.; Visualization: S.R.M..; Supervision: H.R.; Project administration: S.R.M..; Funding acquisition: H.R., S.K.M.S.

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