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Original Article

Cellular fibronectin response to supervised moderate aerobic training in patients with type 2 diabetes

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Abstract. [Purpose] Physical activity is one of the most pivotal targets for the prevention and management of vascular complications, especially endothelial dysfunctions. Cellular fibronectin is an endothelium-derived protein involved in subendothelial matrix assembly. Its plasma levels reflect matrix alterations and vessel wall destruction in patients with type II diabetes. This study investigated the influence of 12 weeks of supervised aerobic training on cellular fibronectin and its relationship with insulin resistance and body weight in type II diabetic subjects. [Subjects and Methods] This study included 50 men with type II diabetes who had a mean age of 48.8 ± 14.6 years and were randomly divided into two groups: an aerobic exercise group (12 weeks, three 50 minutes sessions per week) and control group. To examine changes in cellular fibronectin, glycosylated hemoglobin, insulin resistance, fasting insulin, fasting blood sugar, and lipid profile, 5 ml of blood was taken from the brachial vein of patients before and 48 hours after completion of the exercise period and after 12 hours of fasting at rest. Data analysis was performed using the SPSS-16 software with the independent and paired t-tests. [Results] A significant decrease was observed in body mass index and body fat percentage in the experimental group. Compared with the control group, the aerobic exercise group showed a significant decrease in cellular fibronectin, glycosylated hemoglobin, insulin resistance, fasting insulin, fasting blood sugar, and lipid profile after 12 weeks of aerobic exercise. The change in cellular fibronectin showed positive significant correlation with body mass index, diabetic biomarkers, and physical activity level. [Conclusion] The results showed that supervised aerobic exercise as a stimulus can change the levels of cellular fibronectin as matrix metalloproteinase protein a long with improvement of insulin sensitivity and glycosylated hemoglobin in order to prevent cardiovascular diseases in men with diabetes

Key words: Cellular fibronectin, Aerobic training, Type II diabetes

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INTRODUCTION

Diabetes is considered one the most serious results of metabolic disorders with major related complications worldwide, such as cardiovascular disease, nephropathy, retinopathy, and amputation[1)].

It has reported that the pathogenesis of vascular diseases accompanying diabetes such as endothelial dysfunction and atherosclerosis result from the imbalance between relaxing and contracting endothelial factor which ultimately are associated with future progression of vascular and end-organ damage[2)].

In diabetes mellitus, many factors affect the development of endothelial dysfunction such as elevated sugar levels and insulin resistance, which in turn increase the probability of cardiovascular risk and mortality, especially among diabetic patients with obesity, hypertension, and metabolic syndrome. On the other hand, insulin resistance was shown to be associated with

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the progression of endothelial dysfunction to atherosclerosis in individuals with type 2 diabetes[3].

Also, many research studies have reported that the most important step for progression of arterial diseases is endothelial dysfunction. So, it is very important to evaluate endothelial function clearly either with vascular function tests or estimation of the concentrations of specific endothelial proteins[4, 5]. Fibronectin (FN) is one of the most reliable proteins that can be estimated as a plasma indicator protein for endothelial function. It refers to a large category of glycoproteins (440–500 kD) that is considered to be one of the main constituents of the extracellular matrix and plays a potential role in cell to cell as well as cell to matrix adhesions[4]. Most studies have reported that FN protein has different specific variants that differ in the arrangement of their peptides. The major cellular fibronectin (CFN) type III variant present in the blood stream (soluble or plasma FN) is specifically produced and released by endothelial cells during pathological conditions[5–7].

Many studies have reported significant elevation of circulating cFN in many metabolic syndromes associated with endothelial activation, such as diabetes mellitus, and considered cFN a specific marker for endothelial cell injury[8–10]. So, the change in the levels of serum or plasma cellular fibronectin may reflect the extent of matrix changes and vessel wall damage in patients with diabetes.

Increases in the extracellular matrix glycoprotein fibronectin and calcification also may contribute to arterial stiffness with ageing[11, 12]. Previously, it was reported that regular exercise could enhance the hemostatic physiological changes that could provide significant protection against major thrombotic events[13–16], whereas alterations or impairment in all thrombotic factors, including fibrinogen and fibronectin concentration were enhanced by exercise[17, 18].

Habitual aerobic exercise is a first-line therapeutic strategy for reducing the risk of CVD with ageing[19–21]. Middle-aged and older adults who regularly perform aerobic exercise demonstrate less age-associated stiffening of large elastic arteries compared with their sedentary peers[22, 23].

However, the mechanisms by which regular aerobic exercise exerts its favorable effects on large elastic artery stiffening with ageing have not been established, partly because of lack of access to these tissues in humans. The limited available data in experimental animals (forced swimming in rats) do not support an influence of voluntary exercise on whole artery collagen or elastin[24–27]. Also, the mechanisms by which regular aerobic exercise exerts its effects on cFN in type 2 patients have not been established. So we aimed in this study to evaluate the effect of supervised aerobic training of moderate intensity on plasma levels of cFN and its relationship with insulin resistance and body weight in subjects with type 2 diabetes.

SUBJECTS AND METHODS

Fifty subjects diagnosed as having type 2 diabetes mellitus more than 5 years previously with normal or near normal body weights participated in this study. The diagnosis of diabetes mellitus (DM) was based on the American Diabetes Association criteria for DM2 (fasting plasma glucose level higher than 126 mg/dl and/or glucose level exceeding 200 mg/dl at 2 hours in the 75 g oral glucose tolerance test[28]). The subjects were divided into two groups: an aerobic exercise group (12 weeks, three 50 minutes sessions per week) and control group (sedentary lifestyle). General characteristics of the subjects are shown in Table 1. Standardized physical examination, demographic measures, and collection of serum samples were performed before and after the 12- weeks of moderate aerobic training program. Participants with obesity (body mass index [BMI] ≥ 30 (kg/m^2), type 1 diabetes, smokers, severe diabetic complications, metabolic syndromes, viral hepatitis, and obvious heart diseases were excluded from the study. Before starting the study, the participants were requested to provide an informed consent. This

Table 1. Demographic, clinical, and biochemical characteristics of the patients with type 2 diabetes in both the aerobic exercise and control groups (n=50)

Variables*	Aerobic exercise (n=25)	Control (25)
Age (years)	48.8 ± 14.6	48.7 ± 3.4
Height (cm)	165 ± 2.2	161.4 ± 2.1
Weight (kg)	71.9 ± 2.4	70.8 ± 3.8
BMI (kg/m^2)	26.41 ± 4.3*	27.18 ± 5.1
Body fat (%)	31.8 ± 2.3*	29.7 ± 1.85
Diabetes duration (years)	13.5 ± 9.8*	10.9 ± 8.6
HbA1c (%)	9.7 ± 1.2**	8.1 ± 0.9
Total cholesterol (mmol/l)	5.9 ± 0.9*	4.7± 0.8
HDL cholesterol (mmol/l)	1.8 ± 0.7*	1.7 ± 0.3
Triglycerides (mmol/l)	1.9 ± 1.3*	1.6 ± 1.2
LDL cholesterol (mmol/l)	3.7 ± 1.1*	3.1 ± 0.96
Treatment for hypertension	11 (25)	12 (25)

Data presented as the mean ±SD. The paired sample t-test revealed significant differences in within group comparisons (*p<0.05, **p<0.01, ***p<0.001)

study was approved by the ethics committee of Rehabilitation Research Chair (RRC), King Saud University, KSA, under file number/ ID: RRC- 2013-016.

The participants in the aerobic exercise group performed an exercise program designed according to Karvonen's formula[29] three times per week for 12 weeks. The training intensity of each intervention was selected according to the maximum and resting heart rate of each participant. The pre training heart rates (THR max; 60–70% for 45–60 min) of the participants were calculated after performing warm-up exercises for 5 to 10 minutes using a treadmill, bicycle, and stair master as previously reported[30, 31]. An automatic portable heart rate meter (Polar Electro, Kempele, Finland) was used to calculate the exact heart rate of each participant. An exercise test was performed to ensure that the participants' levels of physical activity corresponded to 30–45% of VO_2max uptake[32].

Physical activity scores were estimated as previously reported using a pre-validated short form of the International Physical Activity Questionnaire (IPAQ)[33, 34]. The levels of physical activity of all patients were estimated and calculated as metabolic equivalents consumed during moderate, vigorous or normal daily physical exercise[35, 36]. According to physical activity (PA), the subjects were classified into three groups; low PA (600 MET–min/week; n=25), moderate PA (≥ 600 MET- min/week; n=15), and high PA (≥ 3.000 MET- min/week; n=10).

All diabetes- related factors and cellular fibronectin were estimated from serum blood samples collected from all participants before and after the training program.

Fasting blood glucose and glycosylated hemoglobin (HbA1c) were measured by routine colorimetric techniques using commercial kits (for glucose, QuantiChrom Glucose Assay Kit, DIGL-100, BioAssay Systems, Hayward, CA, USA; for HbA1c, Bio-Rad, Richmond, CA, USA). An ELISA technique was used to estimate the level of insulin in serum of all subjects using an ELISA kit (Insulin ELISA kit human, KAQ1251, Invitrogen Corporation, Camarillo, CA, USA).

Homeostasis model assessment of insulin resistance (HOMA-IR) which has previously been validated was used to measure insulin resistance in fasting state. The results IR were significantly calculated in the fasting insulin (IF) and fasting glucose (GF) as follows: HOMA-IRZ (IF!GF)/22.5[37–39].

Circulating cFN was measured with an immune assay technique using an ELISA kit (Sigma-Aldrich, St. Louis, MO, USA). The concentrations of cFN were measured calorimetrically according to the manufacturer's instructions.

The obtained data were analyzed using the SPSS-16 software. In this study, quantitative data are represented as the mean±SD. The paired sample t-test was used to compare changes within groups, and the independent sample t-test was used to compare changes between groups. $p<0.05$ was considered statistically significant.

RESULTS

Fifty men who had a mean age of 48.8 ± 14.6 years and had been diagnosed with type 2 diabetes were participated in this study to evaluate the effect of supervised aerobic training on the level of cFN. Clinical details of the subjects and the biochemical variables under study are summarized in Table 1. In the exercise group, the patients with type 2 diabetes were characterized by a significantly longer duration of diabetes and higher biochemical parameters compared with the control subjects. The mean HbA1c and lipid profile concentrations were significantly higher in the exercise group than in the control group (Table 1).

There was a significant decrease (p=0.001) in fasting blood sugar, fasting insulin, glycosylated hemoglobin (HbAc1), and insulin resistance following 12 weeks of moderate aerobic training (Table 2). Also, there was a significant decrease in BMI and the cFN level (p=0.001) in the patients following 12 weeks of moderate aerobic exercise. However, no significant changes were observed in the control group after 12 weeks (p>0.05), and there were significant correlation (p=0.01) between the decrease in cFN and the reductions in BMI, fasting blood sugar, fasting insulin, glycosylated hemoglobin (HbAc1), and

Table 2. Mean ± standard deviation (SD) and statistical comparison of the pre- and post-training values of the studied variables in the aerobic exercise and control groups

Variables	Groups					
	Aerobic exercise (n=25)			Control (n=25)		
	Pretest	Posttest	Mean Diff.	Pretest	Posttest	Mean Diff.
F.B. Sugar (mg/dl)	197 ± 92.8	146.3 ± 21	50.7 ± 15***	185 ± 65.7	184.3 ± 58.7	0.7 ± 0.08
HbAc1 (%)	8.7 ± 1.2	6.3 ± 0.6	1.40 ± 0.4** *	9.1 ± 0.9	8.9 ± 1.2	0.2 ± 0.03
F. insulin (μU/ml)	40.6 ± 9.3	25.7 ± 6.8	14.9 ± 3.5 ***	41.5 ± 3.7	38.7 ± 5.3	2.8 ± 0.8
IR (mU^*mmol/L^2)	5.9 ± 1.4	3.6 ± 0.9	2.3 ± 0.6***	4.3 ±1.9	4.19 ± 1.5	0.11 ± 0.06
Cellular fibronectin (cFN; μg/ml)	6.9 ± 2.9	3.2 ± 1.2	3.7 ± 0.9***	4.7 ± 2.7	4.6 ± 1.8	0.1 ± 0.05
BMI ($kg\backslash m^2$)	26.41 ± 4.3	23.5 ± 2.7	2.81 ± 1.4*	27.18 ± 5.1	26.9 ± 6.3	0.28 ± 0.7

F.B. sugar: fasting blood sugar; HbAc1: glycosylated hemoglobin, F.Insulin: fasting insulin, IR: insulin resistance; BMI: body mass index. Data presented as the mean ±SD. The paired sample t-test revealed significant differences in within group comparisons (*p<0.05, **p<0.01, ***p<0.001)

insulin resistance, as shown in Table 3.

In relation to the status of physical activity, there was positive significant correlation (p=0.001) between the fibronectin level and the intensity of physical activity (low, moderate, and high), as shown in Table 3. Furthermore, there was a significant decrease in the level of fibronectin in subjects with moderate to high physical activity compared with those with low physical activity (sedentary lifestyle).

DISCUSSION

The increasing prevalence of type 2 diabetes mellitus (T2DM) may relate to the increase in overweight and obesity among adults. Population-based studies showed that T2DM is the sixth-leading cause of death attributed to cardiovascular disease (CVD; nearly 70%)[40, 41].

Physical activity is one of the most pivotal targets for the prevention and management of type 2 diabetes in both genders[42]. It was reported that in patients with T2DM, physical activity can improve glycemic control, prevent cardiovascular disease, and reduce the risk of cardiovascular and total mortality[43, 44].

Several studies reported that exercise training improved metabolic disorders, as measured by HbA1c, blood glucose, or insulin sensitivity[45, 46], but the effect of exercise training on plasma cFN remains controversial. So, this present study aimed to investigate the effects of moderate intensity of aerobic exercise training for 12 weeks on plasma cFN and its relationship with reduction of body weight and improvements of insulin sensitivity among type 2 diabetic subjects.

The results of this study showed a significant reduction of fasting blood sugar, fasting insulin, glycosylated hemoglobin, and insulin resistance after 12 weeks of moderate aerobic training combined with a significant reduction in BMI. However, there was no significant change in control diabetic patients. The results of this study came are in agreement with some previous studies that reported that cardiovascular-based moderate physical activity along with modest weight loss of 5–7% appeared to improve glycemic control and lowered the risk of developing diabetes by 58% in overweight people with pre-diabetes[46–48]. Also, many studies have shown positive health benefits with moderate-intensity exercise in patients with T2DM, whereas a considerable improvement in HbA1c and cardiorespiratory fitness was reported in diabetic subjects who performed cardio respiratory exercise with varying intensities[49–51].

Hyperglycemia is the major causal factor in the development of endothelial dysfunction in diabetes mellitus through changes in extracellular matrix proteins including cellular fibronectin[52, 53], whereas elevated plasma levels of circulating cFN have been described in diverse clinical syndromes with endothelial activation, including diabetes mellitus, and cFN has been reported as a specific marker for endothelial cell injury[10].

Cellular fibronectin is important as a marker of endothelial dysfunction in diabetes, and the present study showed a significant increase in the level of cFN among patients with T2DM. The data obtained matched with previous studies that reported the elevation of cFN levels and suggested that circulating cellular fibronectin may be a marker protein for endothelial cell activation, especially in diabetes[10].

In the exercise group, a significant decrease in cFN concentration was reported in the patients following 12 weeks of moderate aerobic training compared with the control diabetic patients. The decrease in cFN levels showed significant positive correlations with the reduction s in fasting blood sugar, fasting insulin, glycosylated hemoglobin, insulin resistance, and body weight. The data are in line with previous studies that reported the importance of regular exercise in evoking hemostatic changes against major thrombotic events, especially improvement of the fibronectin level[13, 14, 17]. Also, modulation of plasma fibronectin (PF) was reported in men subjected to various intensities of physical exercise, whereas the PF level was

Table 3. Correlation between cellular fibronectin, BMI, and diabetic biomarkers in patients with type 2 diabetes (n= 50)

Variables	Pre-training value		Post-training value	
	Cellular fibronectin (cFN)		Cellular fibronectin (cFN)	
	R	(95% CI)	R	(95% CI)
F.B. Sugar	0.01	75 (73–98)	0.25**	94 (87–100)
HbAc1	0.06	80 (75–100)	0.53**	89 (77–100)
F. insulin	0.09	68 (56–100)	0.21**	90 (86–100)
IR	0.16	71 (65–100)	0.41**	94 (87–100)
BMI (kg\m^2)	0.11	78 (66–100)	0.31**	89 (75–100)
Physical activity				
Low	0.16	84 (65–100)	0.18***	78 (65–100)
Moderate	0.13	94 (85–100)	0.12***	92 (85–100)
High	0.11	91 (75–100)	0.14***	93 (75–100)

**p < 0.01; *** p < 0.001. 95% CI: 95% confidence interval

suppressed in men subjected to a long term exercise program for 8 weeks[54]. Expression of fibronectin, a glycoprotein that influences stiffness by binding to extracellular matrix proteins including integrins, collagen, and proteoglycans[55], has been reported to increase in the whole aorta with ageing in rats[56, 57].

It was reported that individuals who perform regular aerobic exercise experienced less age-associated stiffening of large elastic arteries compared with their sedentary peers[18, 19], as a result of the reduction in cFN protein level or modulation of the mechanical function of fibronectin in muscle oxygenation during exercise, which dilates the blood vessels and increases blood flow through the muscles[58].

In this study, patients showed significant increase in insulin sensitivity following 12 weeks of moderate aerobic training. This improvement may related to an increase in signaling process of post-receptor insulin[59] or by an increase in the levels of glucose transporter protein and mRNA[60], or activation of both glycogen syntheses and hexokinase[61], or by increasing delivered glucose to muscles and finally by changes in muscle composition[62].

The improvement of insulin resistance noted in this study could be also related to the improvement of cFN ; fibronectin binds to insulin-like growth factor binding protein-5 (IGFBP-5), and this binding negatively regulates the ligand-dependent action of IGFBP-5 by triggering its proteolysis[63–66], On the other hand, the reduction in expression of insulin receptor (InsR) was reported to be associated with enhanced activity of the insulin-like growth factor-1 receptor (IGF-1R)/PI3 K/Akt signaling pathway, which contributed in part to the attenuation of cellular FN accumulation via an increasing in its degradation by the action of matrix metalloproteinase enzymes (MMPs)[66, 67].

In conclusion, the findings of this study showed that supervised aerobic exercise for 12 weeks may improve endothelial dysfunction by reducing plasma levels of cellular fibronectin and improve of HbA1c, blood glucose, insulin sensitivity, and body weight in men with T2DM. The data also suggested a significant correlation between cellular fibronectin level and diabetic biomarkers along with body weight in men with T2DM.

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