Arch Clin Exp Med 2022;7(3):61-65.
e-ISSN: 2564-6567
DOI:10.25000/acem. 1145353
Araştırma makalesi / Research article

Effects of exercise on coronary flow reserve and biochemical parameters in patients with type 2 diabetes mellitus

Aerobic egzersizin tip 2 diyabet hastalarında koroner akım rezervi ve biyokimyasal parametrelere etkisi

Göksel Güz [1], Hüseyin Oflaz [2]

Abstract
Aim: Coronary, peripheral and cerebral vascular diseases are the most important causes of mortality and morbidity in diabetic patients. The aim of our study was to determine the dysfunction in the epicardial coronary arteries and microvascular circulation noninvasively by measuring the coronary flow reserve (CFR) by transthoracic echocardiography, and to examine the effect of regular aerobic exercise on CFR in diabetic patients.
Methods: Forty patients with diabetes mellitus and 20 healthy volunteers were included in the study. These patients were those who had been using oral antidiabetic drugs for at least 3 years, had no ischemia symptoms and did not exercise regularly. At the beginning of the study, the CFR obtained from the distal left anterior decendant artery (LAD) flow in the transthoracic echocardiography of diabetic patients was compared with the health control group. Diabetic patients were divided into two groups as those who were included in a regular exercise program and those who were not. The exercise group was given regular aerobic exercise for 8 weeks in the department of sports medicine. Post-exercise CFR values of diabetic patients included in aerobic exercise program were compared with pre-exercise values.
Results: Basal CFR values of diabetic patients were statistically significantly lower than healthy volunteers ($p<0.001$). A significant improvement was found in the post-exercise CFR values of the diabetic patients who were included in the exercise program compared to the pre-exercise levels ($p<0.001$).
Conclusion: Regular aerobic exercise can reduce the risk of cardiovascular complications by improving coronary flow reserve in diabetic patients.
Keywords: Exercise, coronary flow reserve, type 2 diabetes mellitus.

Öz
Amaç: Diyabetik hastalarda en önemli mortalite ve morbidite nedenleri koroner, periferik ve serebral hastalıklardır. Çalışmamızın amacı, epikardiyal koroner arterler ve mikrovasküler dolaşımdaki disfonksiyonu transtorasik ekokardiyografi ile koroner akım rezervinin (CFR) ölçülerek noninvaziv olarak belirlemek, düzenli aerobic egzersizin diabetik hastalarda CFR üzerindeki etkisini incelemekti.
Yöntemler: Çalışmaya 40 diabetus mellitus hastası ve 20 sağlıklı gönüllü dahil edildi. Bu hastalar en az 3 yıldır oral antidiyabetik ilaç kullanan, iskemi semptomu olmayan ve düzenli egzersiz yapmayan hastalardı. Çalışmanın başlangıcında diyabetik hastaların transtorasik ekokardiyografisinde distal LAD (left anterior decendan artery) akımından elde edilen CFR, sağlık kontrol grubu ile karşılaştırıldı. Diyabetik hastalar düzenli egzersiz programına alınanlar ve egzersiz konusunda yönlendirilmeyenler olarak iki gruba ayrıldı Egzersiz grubuna spor hekimliği anabilim dalında 8 hafta süreyle düzenli aerobik egzersiz verildi. Aerobik egzersiz programına alınan diyabetik hastaların egzersiz sonrası CFR değerleri egzersiz öncesi değerleri ile karşılaştırıldı.
Bulgular: Diyabetik grupların bazal CFR değerleri sağlıklı gönüllülere göre istatistiksel olarak anlamlı derecede düşüktü ($p<0.001$). Egzersiz programına alınan diyabetik hastaların egzersiz sonrası CFR değerlerinde egzersiz öncesi düzeylere göre anlamlı iyileşme tespit edildi ($p<0.001$).
Sonuç: Düzenli aerobic egzersiz, diyabetik hastalarda koroner akım rezervini düzelterek kardiyovasküler komplikasyon riskini azaltabilir.
Anahtar Kelimeler: Egzersiz, koroner akım rezervi, tip 2 diabetus mellitus.

[1] **Medicana International Hospital, Department of Cardiology, Beylikduzu, Istanbul, Turkey.**
[2] **Istanbul University, Istanbul Faculty of Medicine, Department of Cardiology, Istanbul, Turkey.**

GG: 0000-0002-8386-9160
HO: 0000-0003-1937-7038

Ethics Committee Approval: The present study was approved by Local Ethical Committee of Istanbul University Istanbul Faculty of Medicine (267690/2010).
Etik Kurul Onayı: Bu çalışma Istanbul Üniversitesi Istanbul Tıp Fakültesi Etik Kurulu tarafından onaylanmıştır (267690/2010).

Conflict of Interest: No conflict of interest was declared by the author.
Çıkar Çatışması: Yazar çıkar çatışması bildirmemiştir.

Financial Disclosure: The author declared that this case has received no financial support.
Finansal Destek: Yazar bu çalışma için finansal destek almadığını beyan etmiştir.

Geliş Tarihi / Received: 20.07.2022
Kabul Tarihi / Accepted: 07.12.2022
Yayın Tarihi / Published: 26.12.2022

Sorumlu yazar / Corresponding author:
Göksel Güz

Adres/Address: Beylikdüzü cad. No: 3, Beylikdüzü Medicana İnternational Hastanesi. Beylikdüzü, İstanbul, Türkiye

E-mail: gokselguz@yahoo.com

Tel/Phone: +90 05057748831

Atıf yazım şekli: / How to cite: Güz G, Oflaz H. Effects of exercise on coronary flow reserve and biochemical parameters in patients with type 2 diabetes mellitus. Arch Clin Exp Med 2022;7(3):61-65.

Introduction

Diabetes mellitus is one of the most important threats to human health in modern society. The most prominent mortality and morbidity causes in diabetic patients are coronary, peripheral and cerebral diseases [1]. Cardiovascular mortality is increased by 3 to 4 folds in diabetic patients compared to patients without diabetes [2]. Endothelial dysfunction, proinflammatory state, tendency to thrombosis, autonomic dysfunction and disruptions in lipoproteins are the mechanisms responsible for cardiovascular incidents [3, 4]. Insulin resistance has key importance on chronic inflammation followed by endothelial dysfunction, formation and development of atheroma plaque [5, 6]. Endothelial dysfunction seen in diabetes is the most important factor that initiates and promotes the macroangiopathic and atherosclerotic process. Due to major role of normal endothelium on blood vessel homeostasis, it is known that endothelial dysfunction has major effects in pathophysiology of vasospasm, thrombus for- mation and diseases progressing with blood vessel proliferation [7, 8]. Today, atherosclerosis is considered to be an inflammatory disease. Many cells (endothelial cells, smooth muscle cells, macrophages) and proteins (inflammatory cytokines, adhesion molecules) play a role in this inflammatory process and development of the lesion [9].

Coronary angiography used to detect coronary artery disease only reveals the atherosclerotic lesions narrowing towards the blood vessel lumen. Coronary angiography do not provide with sufficient data regarding physiology of coronary blood flow or endothelial function. In recent years, transthoracic echocardiography (TTE) or measurements of coronary flow reserve (CFR) obtained with invasive coronary angiographic methods, have been drawing attention in demonstrating coronary arterial endothelial function and level of microvascular circulation. Based on the principle that inability of coronary arteries to vasodilate during metabolic need indicates endothelial dysfunction, CFR measurements can confidently determine the status of both epicardial coronary arteries and microvascular coronary circulation [10].

The aim of our study was to non-invasively determine dysfunction in epicardial coronary arteries and microvascular circulation with measurement of coronary flow reserve using transthoracic echocardiography in patients with type 2 diabetes despite absence of ischemic symptoms, and to demonstrate the amelioration in endothelial functions, glycemic control and insulin resistance along with increase in coronary flow reserve after 8 weeks of regular exercise.

Material and methods

Fourty patients diagnosed with type 2 diabetes in Istanbul Facuty of Medicine, Department of Diabetes, who were on follow-up for at least three years due to diabetes, without ischemic symptoms, on oral antidiabetics and who had sedentary lifestyles were included in our study. All patients were included in the study after receiving their written consents. For this study Istanbul Faculty of Medicine's Ethics Committee approval was obtained. Diabetic patients included in the study were divided into two groups. Patients in the first group were put under a regular exercise program of 5 times per week by the Department of Sports Medicine and were encouraged to exercise regularly in the remaining days. Patients in the second group were not given any exercise program nor any additional information about exercise. Exclusion criteria for patients were presence of untreated (uncontrolled) hypertension (systolic blood pressure >160 mmHg, diastolic blood pressure >90 mmHg), known or suspected coronary artery disease, rhythm disorder (chronic or permanent atrial fibrillation etc.), chronic diseases such as chronic kidney failure and liver disease, bundle block in basal echocardiography, lung disease such as chronic obstructive pulmonary disease (COPD) that would limit effort capacity and absence of appropriate physical conditions to exercise. Patients whose left anterior descending artery (LAD) flow tracings were not ideal or unable to be seen with pulse wave Doppler were excluded from the study. Moreover, in order to compare features of diabetic patients such as CFR and insulin resistance with the healthy population, twenty healthy participants with similar age and sex characteristics with the patient group were included in the study.

Before starting the exercise program, a Burdick model treadmill stress test machine was used to perform exercise stress test to diabetic patients who would be included in the exercise program. All patients and those in healthy control group were given cardiopulmonary exercise test by the department of sports medicine using "Quinton 65 treadmill", "Quinton 5000" effort test system, "Cortex Metalyzer 3B" metabolic assessment device and "Metasoft 2.7" software support. To assess metabolic parameters of the participants, "Rudolph Mask 2 way 7910" was used during testing. Patients in the exercise group received 5 days a week of exercise for a duration of 8 weeks.

To all individuals that participated to the study, routine transthoracic echocardiographic mea- surements in left lateral decubitus position were performed with a 3 MHz probe using VIVID 7 (GE, General Electric) device. M-mode echocardiography and two-dimensional measurements were done in accordance with methods stated by American Society of Echocardiography [14]. Left ventricular conventional echocardiographic measurements were performed in all individuals.

Investigation of coronary flow reserve was done using the same device and a 3 mHz probe. LAD mid-distal flow was imaged using color Doppler in left lateral decubitus position, at the point of intersection of midclavicular line with 4-5th intercostal space, in longitudinal apical 2 chamber view of the left ventricle, with optimal velocity of 12-15 cm/s. The cursor was placed on the LAD flow. First, basal value [PDV (peak diastolic flow velocity)] of the coronary flow velocity (CFV) was measured with pulsed- wave Doppler. Then, the subjects received 0.56 mg/kg of dipyridamole infusion for 4 minutes. In case of less than 10% of increase in heart rate compared to basal values, an additional 0.28 mg/kg of dipyridamole infusion for 2 minutes was given. 2 minutes after the dipyridamole infusion was over, hyperemic peak diastolic flow velocity was measured. CFR was calculated via the formula: hyperemic peak diastolic flow velocity/basal peak diastolic flow velocity. During dipyridamole infusion and until the procedures were over, patients were monitorized and their blood pressures were followed.

After 12 hours of fasting, morning plasma glucose and insulin levels, cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglyceride, pro-brain natriuretic peptide (pro-BNP), highly sensitive C-reactive protein (hs-CRP), HbA1c, C- peptide, fructosamine and fibrinogen levels of patients and control group were measured.

In our study, the first step was to compare values of the healthy control group and those of diabetic patients were statistically compared at first. Basal values before exercise of diabetic patient who did not exercise regularly. Values obtained after exercise of these patients were compared with values before exercise and those of diabetic patients who did not exercise. Parameters that ameliorated after exercise of diabetic patients enrolled in the exercise program were likewise compared with those of the healthy group.

Statistical Analysis

Continuous variables with parametric distribution were expressed as mean + standart sapma deviation. Categroical data were expressed as frequncies and their differences were analyzed using the Chi-square test. Variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether they were normally distributed. Continuous variables were compared using Student's t test or the Mann-

Whitney U test as appropiate. The ANOVA test or Kruskall Wallis Test was used to compare basal basal peak diastolic velocity (BPDV), hyperemic peak diastolic velocity (HPDV), CFR values of the groups. Statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, Illinois, USA). Statistical significance was taken as p<0.05.

Results

Comparison of basal blood chemistry values and physical features such as age, height and weight of healthy volunteers and patient volunteers who participated in the study is given in Table1.

Table 1. Comparison of basal values of the groups.

	Diabetics with exercise (n=20)	Diabetics without exercise (n=20)	Healthy group	p
Age (year)	56.45 ± 4.72	55.25 ± 3.44	54.4 ± 4.08	0.29
Weight (kg)	79.3 ± 10.8	81.2 ± 9.18	82.1 ± 8.9	0.77
Height (cm)	165 ± 5.2	166 ± 7.1	169 ± 7.4	0.70
Insulin (uU/ml)	8.17 ± 5.1	10.2 ± 3.07	6.26 ± 2.1	0.004
Fasting blood glucose (mg/dL)	151 ± 44.65	143.3 ± 32.13	84.8 ± 7.9	<0.001
Basal hsCRP (mg/L)	3.36 ± 1.25	3.2 ± 1.09	1.99 ± 0.9	<0.001
Basal HOMA-IR	3.93 ± 1.85	3.45 ± 0.62	<1.3 ± 0.4	0.001
Basal Pro-BNP (ng/ml)	65.7 ± 80.5	53.2 ± 52	31.05 ± 17.6	0.037
Basal C-Peptide (ng/ml)	2.38 ± 1.15	2.33 ± 1.49	-	0.90
Triglyceride (mg/dl)	210.6 ± 113.7	231.5 ± 51.09	-	0.61
LDL cholesterol (mg/dl)	117.75 ± 23.56	116.9 ± 20.59	-	0.90
HDL cholesterol (mg/dl)	40 ± 11.69	38.95 ± 8.12	-	0.83
Basal HbA1c	7.46 ± 1.2	7.32 ± 0.4	-	0.65
Basal fructosamine (mmol/L)	3.01 ± 0.6	3.25 ± 0.59	-	0.24
Basal fibrinogen (mg/dl)	409.4 ± 117.6	400.7 ± 118.8	-	0.81
Basal VO_2 max	24.1 ± 2.66	25.3 ± 2.25	32.6 ± 6.67	<0.001

HsCRP: high sensitive c reactive protein, HOMA-IR: Insulin resistance calculated via homeostasis model assessment method, LDL: low density lipoprotein, HDL: high density lipoprotein, HbA1c: hemoglobin A1c, VO2 max: maximal oxygen consumption- maximal aerobic capacity

Comparison of basal peak diastolic flow velocity, hyperemic peak diastolic flow velocity and coronary flow reserves of diabetic patients that followed an exercise program, diabetic patients who did not follow an exercise program and healthy adult group is given in Table 2. According to this, while basal peak diastolic flows did not significantly differ between the three groups, there was a statistically significant difference in hyperemic peak diastolic flow velocity and coronary flow reserve between healthy adults and both groups of diabetic patients (Table 2). There are 20 people in the group of those who exercise. Of the 20 participants, 15 (75%) were able to complete the exercise program. Values of 15 patients before and after exercise were evaluated.

Table 2. Comparison of basal BPDV, HPDV, CFR values of the groups

Coronary flow	Diabetics with exercise (n=20)	Diabetics without exercise (n=20)	Healthy group	Test value	P
Basal BPDV (cm/s) †	32.70 ± 8.298	32.65 ± 5.071	33.45 ± 7.373	F=0.081	0.922[a]
Basal HPDV (cm/s) †	54.75 ± 10.120	53.55 ± 7.112	75.15 ± 17.315	$\chi 2$=23.467	0.0001[b]
Basal CFR (cm/s) †	1.68 ± 0.186	1.66 ± 0.239	2.25 ± 0.232	F=47.332	0.0001[a]

†: mean ± standard deviation.
a: ANOVA; b: Kruskal Wallis Test. BPDV: Basal peak diastolic flow velocity, CFR: Coronary flow reserve, HPDH: Hyperemic peak diastolic flow velocity.

Comparison of BPDV, HPDV and CFR values before and after exercise of the group of diabetic patients who exercise are given in Table 3; and HPDV and CFR values are statistically significantly higher after exercise compared to before. Blood chemistry values before and after exercise of the group under the exercise program is given in detail in Table 4, values before and after exercise of maximum oxygen intake (VO_2 max) were compared, and maximum oxygen intake was found to be statistically significantly lower before exercise than after (23.8 ± 2.9 vs 27.6 ± 2.9, p= 0.0001).

Table 3. Comparison of BPDV, HPDV, CFR values before and after exercise of the group of diabetics who exercise.

Coronary flow	n	Before exercise	After exercise	t	Pα
BPDV †	15	32.27 ± 9.384	34.80 ± 5.454	-0.881	0.393
HPDV †	15	54.27 ± 2.892	76.07 ± 13.771	5.261	0.0001
CFR †	15	1.69 ± 0.203	2.15 ± 0.253	6.082	0.0001

†: mean ± standard deviation.
BPDV: Basal peak diastolic flow velocity, CFR: Coronary flow reserve, HPDH: Hyperemic peak diastolic flow velocity.

Table 4. Comparison of biochemistry parameters before and after exercise of the group of diabetics who exercise.

	n	Before exercise	After exercise	t	p[a]
Insulin †	15	8.19 ± 5.715	8.38 ± 3.958	-0.231	0.820
C-Peptide †	15	2.09 ± 1.191	2.61 ± 1.792	-1.739	0.104
FBG †	15	150.67 ± 47.566	123.0 ± 31.173	3.126	0.007
HbA1c †	15	7.47 ± 1.406	6.88 ± 0.989	4.171	0.001
Fructosamine †	15	3.02 ± 0.736	2.66 ± 0.479	3.065	0.008
HDL †	15	40.73 ± 13.21	48.53 ± 14.784	-5.706	0.0001
Triglyceride †	15	210.40 ± 127.26	147.2 ± 63.493	2.367	0.033
LDL †	15	115.67 ± 26.161	97.73 ± 20.800	4.142	0.001
Fibrinogen †	15	410.80 ± 133.27	368.9 ± 117.62	2.617	0.020
CRP †	15	3.29 ± 1.39	2.49 ± 1.039	2.644	0.019
HOMA-IR †	15	4.20 ± 1.93	2.42 ± 1.208	3.714	0.002
Pro-BNP †	15	73.53 ± 91.	44.40 ± 32.758	1.818	0.091

†: mean ± standard deviation.
[a]: Paired Sample t-Test. FBG: fibrinogen, HbA1c: Hemoglobin A1c, HDL: high density lipoprotein, LDL: low density lipoprotein, CRP: C reactive protein, HOMA-IR: Insulin resistance calculated via homeostasis model assessment method, pro-BNP: pro brain natriuretic peptide

Discussion

It is known that diabetes leads to atherosclerosis, hypertension, coronary artery disease and certain problems in the heart free of valvular disease [11-13], that it increases cardiovascular mortality and that cardiovascular mortality in diabetic population is significantly higher compared to general population [14]. In our study, the positive effects of exercise on glycemic control, cholesterol panel, and inflammatory markers in diabetic patients as well as its positive effect on endothelial functions were demonstrated by the CFR method. CFR values of diabetic patients were found to be lower than the healthy group in accordance with the literature.

In diabetes, aerobic exercise is as efficient as pharmacotherapy. Exercise not only attains glucose control, it also prevents cardiovascular complications of diabetes [15, 16]. According to duration and intensity of physical exercise, production of free radicals and activations of the antioxidant system can increase [17, 18]. Oxidative stress depends on the balance between production of free radicals and anti- oxidant activity. While excessively intense exercise plasma 8-hydroxyguanosine (8- OHdG) and serum malondialdehyde concentrations indicating oxidative stress; regular, conscious exercise decreases plasma levels of these oxdative stress markers. Effects of exercise on oxidative stress are shaped with duration and intensity of the exercise. Regular, conscious exercise is highly important in diabetic patients in order to achieve metabolic control and decrease oxidative stress [19, 20]. In a study by Nojima et al. [21] regular exercise for one year was shown to decrease oxidative stress leading to a visible drop in urinary 8- OHdG levels that indicate total oxidative stress.

It is known that oxidative stress disrupts glycemic control by causing insulin resistance and that it leads to micro and macrovascular complications [22]. Regular physical activity applied to diabetic patients improves glycemic control by decreasing oxidative stress. It decreases the frequency of complications encountered in diabetes. It mends endothelial dysfunctions seen in early stages of atherosclerosis: the most common and deadly complication of diabetes.

Endothelial dys- function in diabetic patients is directly associated with the duration and intensity of hypergly- cemia. In a study conducted by Yokoyama et al., longterm glycemic control was shown to signifi- cantly improve coronary flow reserve in patients with asymptomatic diabetes [23]. Nemes et al. [24] stated in their publication that there was a negative correlation between insulin resistance and CFR. Endothelial dysfunction was considered to be one of the reasons of insulin resistance in this study. In our study, we have observed that regular exercise leads to a significant decrease in insulin resistance. Decrease in insulin resistance brings on the improvement in endothelial functions. By decreasing insulin resistance, exercise ameliorates endothelial functions and increases coronary flow reserve. One of the mechanisms responsible for the improvement in endothelial functions in our patient group is the decreased insulin resistance in the physical activity and exercise group. Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) values after regular and intense physical activity of patients in this group were significantly lower than initial HOMA-IR values of these patients and HOMA-IR values of 8 weeks after of the diabetic group that did not exercise.

In a study conducted by Ilercil et al. [25] patients with impaired glucose tolerance, association between left ventricle mass, left ventricle wall thickness and insulin resistance was investigated and an independent association between insulin resistance and increased left ventricle wall thickness was revealed. Similar to current literature, compared to healthy control group, left ventricle wall thickness in diabetic patients was likewise greater in our study. In a study by Sung et al., relation between increased left ventricle mass and endothelium dependent vasodilation in peripheral arteries was investigated and endothelium dependent vasodilation in peripheral arteries was found to be insufficient in those with increased left ventricle mass [26]. Davis et al. [27] stated in their study that increase in left ventricle mass was a component of metabolic syndrome and an important cardiovascular risk factor. There are much evidence supporting the existence of insulin resistance in pathogenesis of left ventricle hypertrophy.

It is known that diabetic patients do not have enough physical activities and that more than 80% of the diabetic patient population follows a sedentary lifestyle. Compared to general population, rate of having an inactive, sedentary lifestyle is higher in diabetic patients [28]. Within the lifestyle changes suggested to diabetic patients, along with diet, exercise is known to cause a significant decrease in morbidity and mortality [29]. It has been shown that regular exercise improves cardiac autonomic and contraction functions. Deficiency of insulin in diabetics leads to decreased activity of Na/Ca exhancer protein. With increased physical activity, in diabetic patients, insulin resistance decreases and intracellular calcium metabolism improves through the increase in the activity of Na/Ca exhancer protein. This is reflected as the increase in functional capacity in the clinical status of the patient. In our study, VO2 max values of the patients after 8 weeks of exercise showed significant improvement.

In diabetic patients, due to increased oxidative stress, endothelium is eroded and damaged. There is decrease in Nitric oxide (NO) dependent vasodilator system, increase in vasoconstrictor system along with a worsened ability of the coronary arteries to dilate due to endothelial dysfunction and decreased CFR values. CFR is a parameter with a prognostic value. Cortigiani et al. [30] followed 1130 patients with coronary artery disease, 270 of whom were diabetics, for a period of 16 months. Analyses regarding development of cardiovascular incidents showed that age ($p=0.02$), wall motion abnormalities ($p=0.05$), abnormal CFR value ($p<0.0001$) were the independent prognostic parameters. Compared to patients with CFR >2, those with CFR ≤2 had a significantly higher risk ($p<0.0001$) of having a cardiovascular incident regardless of being a diabetes status. In patients with normal CFR value, risk of having a cardiovascular incident was found to be 2.2% in diabetics and 2.0% in non-diabetics ($p=0.8$). While rate of cardiovascular incidents in diabetic patients with low CFR levels was 9.3%; annual rate of cardiovascular incidents in non-diabetic patients with low CFR levels was 5.1% [30].

In the current study, in accordance with the other studies in literature, comparison of control and diabetic groups CFR levels in diabetic patients' group were statistically lower compared to control group. After 8 weeks of exercise, there was significant improvement in coronary flow reserve of diabetic patients who exercised. Although initially there was no significant difference in coronary flow reserves between diabetic patient groups, at the end of 8 weeks, those who were not informed about physical activity had significantly lower coronary flow reserve than those who exercised. Comprehensive studies investigating the effects of exercise on CFR in diabetes arequite few. A study by Sebastian Sixt et al. [31] demonstrated that regular exercise improved coronary endothelial functions. Response of coronary arteries to acethylcholine after six months of exercise was invasively measured, and significant improvement in coronary endothelial functions was observed. In this study, coronary arteries of the patients were examined before and after exercise with an intravascular ultrasound, and no increase in coronary plaque burden with regular exercise was found. In our study, the argument that endothelial functions significantly improve in diabetic patients who exercise regularly was proven using transthoracic echocardiography, which is a non-invasive method easier to use in clinical practice. Endothelial dysfunction overlooked with coro- nary angiography or stress test can therefore be recognized with decrease in CFR, and detection of atherosclerosis in earlier stages will be possible.

The present study has the following limitations. First, our modest sample size obtained from a single center may make the generalizability of the observed results difficult. Second, an assessment of additional markers of endothelial dysfunction besides CFR, which could have supported the study results, was not performed. Third, we did not perform coronary angiography on the patients. Fourth, is the absence of a long-term follow-up of the participants.

To summarize, regular exercise and physical activity are highly important in diabetic patients for primary and secondary protection against cardiovascular incidents. Physical activity increases insulin sensitivity in diabetic patients, and has many positive effects on glucose metabolism. In the current study we found that regular aerobic exercise improved CFR in patients with diabetus mellitus. In light of these findings, exercise should be highly recommended to diabetic patients and those with a risk of developing diabetes mellitus.

References

1. Htay T, Soe K, Lopez-Perez A, Doan AH, Romagosa MA, Aung K. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. Curr Cardiol Rep. 2019;21:45.
2. Viigimaa M, Sachinidis A, Toumpourleka M, Koutsampasopoulos K, Alliksoo S, Titma T. Macrovascular Complications of Type 2 Diabetes Mellitus. Curr Vasc Pharmacol. 2020;18:110-116.
3. Poznyak A, Grechko AV, Poggio P, Myasoedova VA, Alfieri V, Orekhov AN. The Diabetes Mellitus-Atherosclerosis Connection: The Role of Lipid and Glucose Metabolism and Chronic Inflammation. Int J Mol Sci. 2020;21(5):1835.
4. Lefrandt JD, Smit AJ, Zeebregts CJ, Gans RO, Hoogenberg KH. Autonomic dysfunction in diabetes: a consequence of cardiovascular damage. Curr Diabetes Rev. 2010;6:348-58.
5. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuñiga FA. Association between insulin resistance and the development of cardiovascular disease. Cardiovasc Diabetol. 2018;17:122.
6. Willerson JT, Ridker PM. Inflammation as cardiovascular risk factor. Circulation 2004;109 Suppl 1: II2-10.
7. Arcaro G, Cretti A, Balzano S, Lechi A, Muggeo M, Bonora E, Bonadonna RC. Insulin causes endothelial dysfunction in humans: sites and mechanisms. Circulation 2002;105:576-582.
8. Festa A, Agostino Jr, Howard G, Mykkänen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000;102:42-7.
9. Rigo F. Coronary flow reserve in stress-echo lab. From pathophysiologic toy to diagnostic tool. Cardiovasc Ultrasound 2005;3:8.
10. Brainin P, Frestad D, Prescott E. The prognostic value of coronary endothelial and microvascular dysfunction in subjects with normal or non-obstructive coronary artery disease: A systematic review and meta-analysis. Int J Cardiol. 2018;254:1-9.
11. Tibaut M, Petrovič D. Oxidative Stress Genes, Antioxidants and Coronary Artery Disease in Type 2 Diabetes Mellitus. Cardiovasc Hematol Agents Med Chem. 2016;14:23-38.
12. Duan J, Zhang HY, Adkins SD, Ren BH, Norby FL, Zhang X, Benoit JN, Epstein PN, Ren J. Impaired cardiac contractile function and IGF- 1 Response in myocytes from calmodulin dia- betic mice: role of Akt and RhoA. Am J Physiol Endocrinol Metab. 2003;284:E366-76.
13. Nojima H, Watanabe H, Yamane K, Kitahara Y, Sekikawa K, Yamamoto H, Yokoyama A, Inamizu T, Asahara T, Kohno N; Hiroshima University Health Promotion Study Group. Effect of aerobic exercise training on oxidative stress in patients with type 2 diabetes mellitus. Metabolism. 2008; 57:170-176.
14. Strain WD, Paldánius PM. Diabetes, cardiovascular disease and the microcirculation. Cardiovasc Diabetol. 2018;17:57. Erratum in: Cardiovasc Diabetol. 2021;20:120.
15. Bassuk SS, Manson JE. Epidemiological evidence for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease. J Appl Physiol. 2005; 99:1193-204.
16. Davies KJ, Quintanilha AT, Brooks GA, Packer L. Free radicals and tissue damage produced by exercise. Biochem Biophys Res Commun 1982;107:1198-205.
17. Viguie CA, Frei B, Shigenaga MK, Ames BN, Packer L, Brooks GA. Antioxidant status and indexes of oxidative stress during consecutive days of exercise. J Appl Physiol. 1993;75:566-72.
18. Albright A, Franz M, Hornsby G, Kriska A, Marrero D, Ullrich I, Verity LS. American College of Sports Medicine position stand. Exercise and type 2 diabetes. Med Sci Sports Exerc. 2000;32:1345-60.
19. Sigal RJ, Kenny GP,Wasserman DH, Castaneda-Sceppa C. Physical activity/exercise and type 2 diabetes. Diabetes Care. 2004;27:2518-39.
20. Nojimaa H, Watanabea H, Kiminori Y, Yoshihiro K, Kiyokazu S. Effect of aerobic exercise train- ing on oxidative stress in patients with type 2 diabetes mellitus. Metabolism. 2008;57:170-6.
21. Urakawa H, Katsuki A, Sumida Y, Gabazza EC, Murashima S, Morioka K, Maruyama N, Kitagawa N, Tanaka T, Hori Y, Nakatani K, Yano Y, Adachi Y. Oxidative stress is associated with adiposity and insulin resistance in men. J Clin Endocrinol Metab. 2003;88:4673-6.
22. Yokoyama I, Ohtake T, Momomura S, Nishikawa J, Sasaki Y, Omata M. Reduced coronary flow reserve in hypercholesterolemic patients without overt coronary stenosis. Circulation. 1996;94:3232-8.
23. Nemes A, Lengyel C, Forster T, Várkonyi TT, Takács R, Nagy I, Kempler P, Lonovics J, Csanády M. Coronary flow reserve, insulin resistance and blood pressure response to standing in patients with normoglycaemia: is there a relationship? Diabet Med. 2005;22:1614-8.
24. Paranicas M, O'grady MJ, Welty TK, Robbins DC, Fabsitz RR, Howard BV, Lee ET. Relationship of impaired glucose tolerance to left ventricular structure and function. Am Heart J. 2001;141:992-8.
25. Sung J, Ouyang P, Bacher AC, Turner KL, DeRegis JR, Hees PS, Silber HA, Shapiro EP, Stewart KJ. Peripheral endothelium-dependent flow-mediated vasodilatation is associated with left ventricular mass in older persons with hypertension. Am Heart J. 2002;144:39- 44.
26. Davis CL, Kapuku G, Snieder H, Kumar M, Treiber FA. İnsülin resistance syndrome and lef ventricular mass in healthy young people. Am J Med. 2008;324:72-5.
27. Krug LM, Haire-Joshu D, Heady SA. Exercise habits and exercise relapse in persons with non–insulin-dependent diabetes mellitus. Diabetes Educ. 1991;17:185-8.
28. Look AHEAD Research Group, Gregg EW, Jakicic JM, Blackburn G, Bloomquist P, Bray GA, Clark JM, Coday M, Curtis JM, Egan C. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes Endocrinol. 2016;4:913-21.
29. Cortigiani L, Bombardini T, Corbisiero A, Mazzoni A, Bovenzi F, Picano E. The additive prognostic value of end-systolic pressure-vol- ume relation in patients with diabetes mellitus having negative dobutamine stress echocardiography by wall motion criteria. Heart. 2009;95:1429-35.
30. Cortigiani L, Bombardini T, Corbisiero A, Mazzoni A, Bovenzi F, Picano E. The additive prognostic value of end-systolic pressure-volume relation in patients with diabetes mellitus having negative dobutamine stress echocardiography by wall motion criteria. Heart. 2009;95:1429-35.
31. Sixt S, Beer S, Blüher M, Korff N, Peschel T, Sonnabend M, Teupser D, Thiery J, Adams V, Schuler G, Niebauer J. Long- but not short-term multifactorial intervention with focus on exercise training improves coronary endothelial dysfunction in diabetes mellitus type 2 and coronary artery disease. Eur Heart J. 2010;31:112-9.