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Original Article

Biomarkers of endothelial function and insulin resistance response to aerobic exercise versus resistance exercises in obese type 2 diabetic patients

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ABSTRACT

Background: The risk of endothelial dysfunction and insulin resistance is higher in type 2 diabetes mellitus (T2DM) which could be modulated with exercise training. However, to our knowledge, there is no clinical studies have addressed which exercise specific type is superior in modulating biomarkers of endothelial dysfunction and insulin resistance for T2DM.

Objective: This study aimed to determine the differences in response of biomarkers of endothelial dysfunction and insulin resistance to aerobic versus resistance exercises in type 2 diabetic patients.

Materials and Methods: Eighty obese type 2 diabetic patients participated in this study and were included into two groups, group (A) received aerobic exercises; where group (B) received resistance exercises for 12 months.

Results: The mean values of Inter-Cellular Adhesion Molecule (ICAM-1), Vascular Cell Adhesion Molecule (VCAM-1), tissue plasminogen activator (tPA), E-selectin, glycosylated hemoglobin ($HBA_{1}c$) and Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) were significantly decreased in both groups at the end of the study. However, the mean values of ICAM-1, VCAM-1 and t-PA antigen were more significantly reduced in group (A), while the mean values of HBA1c and HOMA-IR were more significantly reduced in group (B) and there were significant differences between both groups at the end of the study.

Conclusion: Resistance exercise appears to be more beneficial than aerobic exercise for improving insulin resistance in T2DM. Also, aerobic exercise appears to be more beneficial than resistance exercise for improving endothelial function in T2DM.

Keywords: endothelial function biomarkers, aerobic exercise, type 2 diabetes mellitus, resistance training, insulin resistance, obesity

INTRODUCTION

Over the previous 2 decades, type 2 diabetes mellitus (T2DM) becomes a major health problem as globally about 366 million were affected in 2011 and it is expected to have 552 million of T2DM in 2030 (1,2). Globally, T2DM is considered a major chronic disorder leads to morbidity and mortality (3-5). However, the risk of obesity and T2DM is progressively increased and as a result of the insulin resistance risk, coagulation disorders, dyslipidemia and the cardiovascular complications (6,7) which considered the principal causes for the overall morbidity and mortality in obese diabetic subjects (8).

The endothelial dysfunction usually comes before the development of cardiovascular disorders (9), so early detection and correction of endothelial dysfunction should be done for appropriate prevention of atherosclerosis and as result cardiovascular disorders development (10,11). Aerobic exercise may enhance the endothelial function in obsess non-insulin dependent diabetes mellitus (12,13). Moreover, endothelial dysfunction was reversed by application of moderate intensity aerobic exercise for 60 minutes/ day for seven weeks in type 2 diabetic db/db mice (14).

There are many laboratory markers to measure the markers of endothelial dysfunction and increased levels of this biomarker indicate increased risk of cardiovascular diseases (15,16). Moreover, higher serum level of tissue plasminogen activator (tPA) is an indicator of activation of endothelial activities associated with increased risk of cardiovascular dysfunction (17).

Insulin resistance has a major role in increased risk of atherosclerosis and other cardiovascular disorders in type 2 diabetic patients (18). However, aerobic exercise modifies the metabolic risk factors for cardiovascular dysfunction through improving of insulin sensitivity (19,20).

Resistance exercise training displayed many health benefits as increasing glucose uptake and insulin sensitivity by skeletal muscles (21,22). Moreover, resistance exercise training modulates blood lipids profile disorders (23). However, recent studies documented the common benefits of both aerobic and resistance exercise training for cardiovascular disorders (24,25).

As it is less clear which is more beneficial aerobic or resistance exercise training for modulation of endothelial function and insulin resistance. So, the present study aims to compare impact of aerobic and resistance exercises on insulin resistance and markers of endothelial function in type 2 diabetic obese patients.

PATIENTS AND METHODS

Subjects

Eighty obese patients with T2DM (50 males and 30 females), their age ranged between 40 and 55 years, without coronary arterial disease who visited the out clinic of diabetes at King Abdalaziz University Hospital, Saudi Arabia. All the participants were informed regarding the objectives of the study and about

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the possible risks and discomforts involved with their participation in the experiments, signing an informed consent. The study protocol was approved by the Ethics committee of Faculty of Applied Medical Sciences. The exclusion criteria included subjects receiving medicines with known effect on endothelial function, as angiotensin converting enzyme inhibitors, calcium channels blockers, nitrates, beta-blockers, anti-oxidizers, hormonal replacement and insulin; cigarette smoking history in the last 12 months; participation in a physical exercise program in the last 12 months; chronic obstructive pulmonary disease; hypertension (systolic blood pressure above 180 mmHg or diastolic blood pressure above 110 mmHg); osteoporosis and diabetic neuropathy, congestive heart failure, uncontrollable cardiac arrhythmias, and severe illness that precluded them from exercising.

A cardiologist conducts an initial clinical examination for all participants. However, initial rest electrocardiogram was made and the blood pressure was measured, also the electrocardiogram was continuously observed and the blood pressure was measured in each period. The participants were guided to keep the original dietary habits and behaviors. However, participants were randomized between two groups who received their hypoglycemic agents and the only difference in the intervention was that group (A) received aerobic exercise training, while group (B) received resistance exercise training that is why we didn't use a control group.

Measurements

All subjects underwent a laboratory examination, performed at Laboratory of King Abdalaziz University Teaching Hospitals, after a 12 h period of fasting.

A. Measurement of glycosylated hemoglobin and insulin resistance: Blood sample after fasting for 12 hours was taken from each patient in clean tubes containing few mg of K2EDTA, centrifuged and plasma was separated and stored frozen at -20° used for estimation of glycosylated hemoglobin (HBA_1c) using colorimetric method. Homeostasis Model Assessment-Insulin Resistance (HOMA) index for insulin sensitivity was computed following this equation: [fasting glycemia (mmol/L) · fasting insulin (mIU/L)]/22.5 (26).

B. Measurement of biomarkers of endothelial function: Adhesion molecules biomarker includes E-selectin, Inter-Cellular Adhesion Molecule (ICAM-1), Vascular Cell Adhesion Molecule (VCAM-1) and tissue plasminogen activator antigen (tPA:Ag) were measured from frozen serum samples stored at −80 °C. Enzyme-linked immunosorbent assays (ELISAs) were used to measure soluble levels of E-selectin, ICAM-1and CAM-1 (R&D Systems), however tissue plasminogen activator antigen (tPA:Ag) was determined using a commercial kit (Hyphen BioMed for t-PA, France).

All measurements were done at the beginning of the study and will be repeated after 3 months.

Procedures

Following the previous evaluation, all patients were divided randomly into the following groups:

A. Aerobic exercise: The aerobic exercise group completed a 12-week aerobic exercise training program. Each session of physical exercise was divided in: 5 min of warm up, with stretching exercises and circling of members and body; 30 min of aerobic exercise divided into row ergometer (15 min) and bicycle ergometer (15 min); and 5 min of cold down at the end, with stretching, flexibility and relaxation exercises, five sessions per week. The training program was performed at 70% of the individual age-predicted maximal heart rate (HR_{max}) according to Tanaka et al. [27]. The exercise sessions were supervised by one of the investigators and the determined intensity of exercise was monitored and registered for each patient by a watch of heart rate (Polar Vantage XL, Polar Electro Inc., Port Washington, NY). The alarms of the watches were programmed for the inferior and superior limits of the correspondent intensity, determined for each patient.

B. Resistance exercise: The aerobic resistance group completed a 12-week of resistance exercise training program. Each session of physical exercise was divided in: 5 min of warm up, with stretching exercises and circling of members and body; 30 min of specific resistance training; and 5 min of cold down at the end, with stretching, flexibility and relaxation exercises, five sessions per week (28). The resistance exercise protocol aimed to develop muscle mass and strength in the following muscle groups: (1) quadriceps (leg press and leg extension), (2) hamstrings (seated leg curl), (3) gluteal (hip abduction), (4) trunk and arms (double chest press, lateral raise and overhead press), and (5) abdominal wall (abdominal machine). Subjects exercised on variable resistance machines (Nautilus Sports/Medical Industries, Independence, VA). Training intensity was gradually increased during the first four weeks. The intensity of the training stimulus was initially set at 50% to 60% of one-repetition maximum (1RM) with a work range of two sets of 10 to 15 repetitions. Subjects then progressed from 65% to 75% of 1RM at a work range of six to eight repetitions (two sets) and remained at this level until the end of the program. 1RM tests were performed every two weeks for the first month and then every four weeks until the end of the program. Between these tests, the load was increased for those subjects who were able to easily complete 12 or more repetitions for both sets; The exercise sessions were supervised by one of the investigators and the determined intensity of exercise was monitored and registered for each patient by a watch of heart rate (Polar Vantage XL, Polar Electro Inc., Port Washington, NY). The alarms of the watches were programmed for the inferior and superior limits of the correspondent intensity, determined for each patient.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS version 17.0 for Windows (Statistical Package for the Social Sciences, SPSS Inc. Chicago, IL, USA). For descriptive purposes, mean values of untransformed and unadjusted variables are presented (mean ± SD). The mean values of the investigated parameters obtained before and after three months in both groups were compared using paired "t" test. Independent "t" test was used for the comparison between the two groups. A two-tailed value of $P < 0.05$ was considered statistically significant.

RESULTS

Eighty patients with T2DM completed the screening evaluation. The baseline characteristics of the participants are shown in Table (1). Most participants (65%) were men. Forty participants were assigned to the aerobic exercise intervention group (n = 40; 26 males and 14 females) and resistance exercise group (n =40, 24males and 16 females). None of the baseline characteristics differed significantly between the two groups is listed in Table 1.

The mean values of ICAM-1, VCAM-1, tPA:Ag, E-selectin, HBA1c and HOMA-IR were significantly decreased in both groups at the end of the study (Tables 2 and 3). However, the mean values of ICAM-1, VCAM-1 and tPA:Ag were more significantly reduced in group (A), while the mean values of HBA1c and HOMA-IR were more significantly reduced in group (B) and there were significant differences between both groups at the end of the study (Table 4).

Table 1: *Mean value of baseline characteristics of all participants*

	Group (A)	Group (B)	P-value
Age (year)	43.76 ± 4.32	45.12 ± 3.98	0.587
Gender (male/female)	26/14	24/16	0.761
BMI (kg/m^2)	35.52 ± 3.48	34.19 ± 4.23	0.393
Duration of diabetes (years)	11.32 ± 4.77	10.12 ± 3.95	0.241
HbA1c (%)	8.11 ± 0.76	7.85 ± 0.91	0.418
Systolic blood pressure (mmHg)	138.37 ± 10.31	135.84 ± 9.57	0.926
Diastolic blood pressure (mmHg)	81.24 ± 7.41	79.73 ± 8.12	0.872
High-density lipoprotein cholesterol (mg/dl)	47.35 ± 6.22	48.65 ± 7.16	0.715
Low-density lipoprotein cholesterol (mg/dl)	108.78 ± 9.34	106.92 ± 8.51	0.644
Triglycerides (mg/dl)	146.82 ± 12.15	143.13 ± 11.64	0.615

BMI: Body Mass Index; HBA1c: glycosylated hemoglobin.

Table 2: *Mean value and significance of ICAM-1, VCAM-1, tPA:Ag , E-selectin, HBA1c and HOMA-IR in group (A) before and after treatment*

	Mean + SD		T-value	P-value
	Pre	Post		
ICAM-1 (ng/ml)	95.87 ± 8.16	80.93 ± 7.94	9.15	0.002*
VCAM-1 (ng /ml)	828.33 ± 36.42	731.81 ± 29.13	10.61	0.001*
E-selectin (ng/ml)	15.18 ± 4.12	9.17 ± 3.19	8.21	0.003*
t-PA antigen(ng/ml)	7.11 ±1.87	5.03 ±1.61	7.84	0.005*
HBA1c (%)	8.43 ± 1.93	7.24 ± 1.72	4.43	0.014*
HOMA-IR	4.52 ± 1.75	3.43 ± 1.42	3.92	0.025*

ICAM-1: Inter-Cellular Adhesion Molecule; VCAM-1: Vascular Cell Adhesion Molecule; HBA1c: glycosylated hemoglobin; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance Index; tPA:Ag: tissue Plasminogen Activator Antigen; (*) indicates a significant difference between the two groups, P < 0.05.

Table 3: *Mean value and significance of ICAM-1, VCAM-1, tPA:Ag , E-selectin, HBA1c and HOMA-IR in group (B) before and at the end of the study*

	Mean + SD		T-value	P-value
	Pre	Post		
ICAM-1 (ng/ml)	94.31 ± 7.56	87.74 ± 7.32	5.19	0.021*
VCAM-1 (ng /ml)	824.93 ± 37.81	782.32 ± 32.43	6.14	0.015*
E-selectin (ng/ml)	14.72 ± 4.54	12.23 ± 4.26	4.13	0.026*
t-PA antigen(ng/ml)	6.94 ±1.59	6.01 ±1.48	3.75	0.038*
HBA1c (%)	8.22 ± 1.72	6.14 ± 1.63	8.27	0.006*
HOMA-IR	4.11 ± 1.63	2.33 ± 1.42	7.62	0.009*

ICAM-1: Inter-Cellular Adhesion Molecule; VCAM-1: Vascular Cell Adhesion Molecule; HBA1c: glycosylated hemoglobin; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance Index; tPA:Ag: tissue Plasminogen Activator Antigen; (*) indicates a significant difference between the two groups, P < 0.05.

Table 4: *Mean value and significance of ICAM-1, VCAM-1, tPA:Ag , E-selectin, HBA1c and HOMA-IR in group (A) and group (B) at the end of the study*

	Mean + SD		T-value	P-value
	Pre	Post		
ICAM-1 (ng/ml)	80.93 ± 7.94	87.74 ± 7.32	4.08	0.011*
VCAM-1 (ng /ml)	731.81 ± 29.13	782.32 ± 32.43	4.51	0.016*
E-selectin (ng/ml)	9.17 ± 3.19	12.23 ± 4.26	4.07	0.015*
t-PA antigen(ng/ml)	5.03 ±1.61	6.01 ±1.48	4.11	0.013*
HBA1c (%)	7.24 ± 1.72	6.14 ± 1.63	3.68	0.027*
HOMA-IR	3.43 ± 1.42	2.33 ± 1.42	3.57	0.028*

ICAM-1: Inter-Cellular Adhesion Molecule; VCAM-1: Vascular Cell Adhesion Molecule; HBA1c: glycosylated hemoglobin; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance Index; tPA:Ag: tissue Plasminogen Activator Antigen; (*) indicates a significant difference between the two groups, P < 0.05.

DISCUSSION

Exercise is recognized as a cornerstone for T2DM prevention and treatment due to its ability to regulate blood sugar levels, with minimal undesired side effects (29). Along with glycemic control and improving endothelial function (30). Despite these general benefits there is a gap in the knowledge regarding the best exercise intervention in order to achieve maximal enhancements with lowest risks, such that exercise can be used in a primary care recommendation (31).

The main finding of the present study was the fact that patients with T2DM have a significantly accentuated insulin resistance and abnormal endothelial function. Physical exercise training also improved the glycemic profile and markers of endothelial function. Resistance exercise appears to be more beneficial than aerobic exercise for improving insulin resistance in T2DM. Also, aerobic exercise appears to be more beneficial than resistance exercise for improving endothelial function in T2DM.

Nassis et al. proved that 12 weeks of aerobic training improved insulin sensitivity in overweight and obese girls (32). Similarly, moderate to heavy-intensity aerobic training (ie, 60%-95% of maximal heart rate) that was done 3 times a week for 6 months was shown to improve insulin sensitivity in both younger (n = 14; mean [SD] age, 29.1 [4.6] years) and older (n = 8; mean [SD] age, 62.3 [4.7] years) women (33). Duncan et al. demonstrated that 30 minutes of walking exercise 3 to 7 days per week for 6 months--reversed the pre-diabetic state of individuals without a change in their diets or any loss of body weight (34). Also, In 8 healthy young men, 18 to 25 years of age, 6 weeks of moderate-intensity cycling performed for 1 hour 5 days a week was capable of increasing their insulin sensitivity and glucose effectiveness (35).

Ibaftez et al, conducted a study of twice-weekly progressive resistance training for 16 weeks by 10 older men with newly diagnosed T2DM resulted in a 46.3% increase in insulin sensitivity, along with a 7.1% reduction in fasting glycemia and a significant loss of visceral fat (36). Dunstan et al**,** showed that 18 men with T2DM aged 60 to 80 years successfully progressed over 6 months of resistance training to completing 3 sets of 8 to 10 repetitions done at 75% to 80% of maximal on 8 to 10 exercises thrice weekly (37).

In this study, improvement in endothelial cell function was noticed as a result of aerobic and resistance exercise. Also, aerobic exercise appears to be more beneficial than resistance exercise for improving endothelial function in T2DM. In line with our data, Zoppini et al. demonstrated that vascular endothelial cell function improved in obese T2DM subjects who performed aerobic exercise for 6 months (50% to 70% heart rate reserve, 60 minutes/session, 2 times per week) (38). Also, Hamdy et al. performed a 6-month study on T2DM subjects with impaired glucose tolerance in which participants performed aerobic exercise (60% to 80% HRmax, 30 minutes, 3 times per week, or at least 150 minutes per week) and reported a significant improvement in endothelial cell function (39). The current study had a higher frequency of aerobic exercise per week than the study conducted by Zoppini et al., and the exercise periods and overall frequency were higher than in the study performed by Hamdy et al. Despite our short study period (12 weeks), the exercise programs appear to have had an effect on vascular endothelial cell function. When we examine studies where no change in endothelial cell function was observed, such as the 10-week aerobic exercise study performed by Ostergard et al. (40), we note that their study period was shorter than the current study, and that the exercise was less frequent.

In line with our results, Kwon et al. conducted a study on 40 overweight Korean women with T2DM and were assigned into 3 groups: an aerobic exercise group, resistance exercise group and control group, 60 minutes per day, 5 days per week for 12 weeks and assessed endothelial function by flow-mediated dilation (FMD) and found that aerobic exercise appears to be more beneficial than resistance exercise for improving endothelial function in T2DM (41). Also, Okada et al. found endothelial function improvement in 38 diabetic subjects after practicing aerobic physical exercise with resistance, independently of glycemic control and increased insulin sensitivity (42). Although Cohen et al. conducted a resistance exercise study on obese T2DM subjects in which progressive resistance exercise (75% to 85% 1RM, 3 sets, 8 reps) was employed. No significant change in endothelial cell function was observed after 2 months; however, after 14 months they reported an improvement in endothelial cell function (43).

Explanation for the endothelial function improvement could be the changes in the lipid profile after aerobic physical exercise training, specifically low density lipoprotein (LDL) cholesterol. The LDL cholesterol had a significant improvement as an effect of low and of high intensity aerobic physical exercise in the present study. Other studies showed that the improvement in lipids profile is associated with vascular function improvement (44).

Our study has certain limitations. First, the study did not include a control group. Second, the participants were motivated men and women who were asked to exercise in a semi-supervised setting; therefore, the results might not generalize to a non-supervised group in the general population. Also, our study has a strength point as a large number of subjects leading to excellent statistical power to detect exercise exposure effects across groups

CONCLUSION

Resistance exercise appears to be more beneficial than aerobic exercise for improving insulin resistance in T2DM. Also, aerobic exercise appears to be more beneficial than resistance exercise for improving endothelial function in T2DM.

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