

Original investigation

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Cardiovascular adaptations to exercise training in postmenopausal women with type 2 diabetes mellitus

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Abstract

Background: Type 2 diabetes mellitus (DM-2) is one of the most prevalent chronic diseases of the aged and contributes to a significant amount of cardiovascular disease morbidity and mortality. Exercise training may be beneficial in attenuating the cardiovascular maladaptations associated with DM-2. The purpose of this study was to examine the effects of exercise training on left ventricular (LV) and vascular function in a sample of postmenopausal women with DM-2.

Methods: Twenty-eight postmenopausal women with DM-2 (age: 59 ± 7 yrs) were assigned to either an exercise training (ET) ($n = 17$) or control group (CT) ($n = 7$). Cardiorespiratory fitness ($\dot{V}O_{2peak}$), LV filling dynamics and arterial compliance were assessed at baseline in all participants. The ET group performed a supervised aerobic and resistance training intervention three days per week for a period of 10 weeks, while the CT group continued normal activities of daily living.

Results: Body mass index, $\dot{V}O_{2peak}$, age and duration of diabetes were similar between the ET and CT groups at baseline. $\dot{V}O_{2peak}$ (21.3 ± 3.3 to 24.5 ± 4.2 ml·kg⁻¹·min⁻¹, $p < 0.05$) and large artery compliance (1.0 ± 0.4 to 1.2 ± 0.4 mL·mmHg⁻¹, $p < 0.05$), increased significantly in the ET group following training despite no change in LV filling dynamics, blood pressure, lipid profile or insulin sensitivity. All variables remained unchanged in the CT group.

Conclusions: Exercise training improves large artery compliance and cardiorespiratory fitness in postmenopausal women with DM-2, without any appreciable changes in LV filling dynamics or conventional risk factors for cardiovascular disease.

Background

One of the most common chronic diseases associated with aging is type 2 diabetes mellitus (DM-2). The increasing number of older individuals developing DM-2 in North America [1] is an enormous clinical concern, as this disease is associated with excessive mortality from cardiovascular disease (CVD) [2]. The increased CVD-related morbidity and mortality associated with DM-2 may be attributed to the clustering of synergistic co-morbidities such as hypertension, dyslipidemia and obesity. However, recent evidence suggests that cardiac [3] and vascular [4] maladaptations, such as impaired left ventricular (LV) filling dynamics [5] and increased arterial stiffness [4], may also contribute to these observations.

Exercise training has been shown to reduce CVD mortality and morbidity with senescence possibly by attenuating age-associated declines in LV filling dynamics [6], arterial compliance [7] and endothelial control of vascular tone [8]. As such, it has been hypothesized that the cardiovascular maladaptations associated with aging are secondary to reduced physical activity patterns rather than senescence. Several lines of evidence suggest that the cardiovascular and metabolic maladaptations to DM-2 may also be attenuated with increased physical activity patterns. Specifically, remarkably similar improvements in glucose uptake [9], cardiorespiratory fitness [9,10] and oxygen uptake kinetics [10] have been documented following exercise training between individuals with DM-2 and age-matched healthy controls. Furthermore, data from our laboratory suggests that low cardiorespiratory fitness is associated with a decline in arterial compliance and significantly elevated C-reactive protein expression in postmenopausal women with DM-2 [11]. We therefore proposed that exercise training favorably modulates cardiovascular parameters associated with CVD in individuals with DM-2.

The primary purpose of this investigation was to examine the effects of exercise training on known correlates of cardiorespiratory fitness, mainly LV filling dynamics and arterial compliance, in women with DM-2. The primary hypothesis was that a 10-week exercise training intervention in women with DM-2 would improve cardiorespiratory fitness subsequent to improvements in LV diastolic filling properties and arterial compliance.

Methods

Subjects

A total of 28 postmenopausal women with clinically documented DM-2, free from diabetic complications, were screened for underlying coronary artery disease with resting and maximal exercise electrocardiograms. Exclusion criteria for this investigation included: evidence of ischemic heart disease by history or positive resting or

exercise electrocardiogram; angina or any other cardiac symptoms potentially limiting exercise capacity; and/or presence of musculoskeletal or peripheral vascular abnormalities that would limit exercise capacity. Written informed consent was obtained from all subjects prior to the investigation and the Research Ethics Review Board within the Faculty of Medicine at the University of Alberta approved the study protocol.

Study protocol

Prior to exercise training, subjects were evaluated over the course of two separate visits. Initially, participants reported to the University of Alberta Hospital, Division of Cardiology for a history and physical examination as well as a resting and exercise electrocardiogram. A graded exercise test was performed on an electronically braked cycle ergometer to determine ventilatory threshold and cardiorespiratory fitness. On the second visit, subjects reported to the Metabolic Unit following an overnight fast for blood work, applanation tonometry and resting echocardiograms. A period of at least 48 hours separated the two visits, to allow for complete recovery of the acute effects of the exercise test. Following baseline testing, participants were assigned to either control (CT) or exercise training (ET) groups. The data reported here are a combination of pilot data collected in 10 subjects and a second study in which 18 patients were randomly distributed into two groups (exercise or control). Of the 28 originally screened patients, four women were initially excluded due to either positive stress test or inability to perform the exercise training requirements of the investigation. Therefore 24 women were included in the initial investigation (ET = 17, CT = 7). Six women were excluded from the analysis due to poor adherence to the exercise intervention. Adherence was determined by attendance and completion of 80% of the prescribed exercise training. Therefore data from 18 women were included in the final analysis of this investigation (ET = 11; CT = 7). The remaining eleven participants in the ET group completed $92 \pm 3\%$ of the exercise sessions. Individuals in this investigation were treated for diabetes through diet and exercise ($n = 5$) or oral hypoglycemic agents ($n = 13$), while no participants were on insulin therapy.

Graded maximal exercise test

Oxygen consumption, carbon dioxide production and minute ventilation were sampled every five seconds at rest and during exercise using a Parvo Medics TrueMax 2400 Metabolic Cart (Parvo Medics, East Sandy, UT). The graded exercise test was performed on a cycle ergometer. The stress test began at an exercise intensity of 30 watts and increased by 20 watts every two minutes. Heart rate (electrocardiogram), blood pressure (auscultation) and ratings of perceived exertion were recorded at the end of every two-minute stage. Peak rate of oxygen consumption

($\dot{V}O_{2peak}$) was determined from the average rate of oxygen consumption over the final 60 s of the exercise test. The heart rate response to graded exercise was used to prescribe exercise intensity during the exercise intervention.

Assessment of arterial compliance and resting hemodynamics

Resting measurements of vascular function were performed in the morning with the participants fasted, lying supine in a dimly lit room, having refrained from vasoactive medications for a period of 48 hours prior to testing. Arterial compliance was assessed using computerized arterial pulse waveform analysis by a trained investigator. This technique involves 30-s recordings of signal-averaged arterial pulse waves by applanation tonometry using a surface residing pressure transducer on the radial artery (Hypertension Diagnostics Inc., Egan MN). A single investigator performed all measurements of arterial compliance. Two components of arterial compliance were calculated based on a modified Windkessel model of circulation: capacitive compliance (large artery), and oscillatory (or reflective) compliance [12]. This technique has been validated previously [12].

Echocardiographic measurements

Imaging of the LV was performed as previously described [5,13]. In brief, all images were captured using a commercially available ultrasound instrument (Hewlett Packard, Sonos 5500) with a 3.5 MHz transducer by a trained technician. The same technician acquired and analysed pre and post-intervention images for each participant. Subjects were required to lie quietly for a period of 5–10 minutes, in a dimly lit quiet room prior to imaging. Two-dimensional transthoracic images of the LV were obtained from the parasternal short-axis view at the level of the mid-papillary muscles according to American Society of Echocardiography guidelines [13]. LV diastolic filling dynamics were assessed using pulsed-wave Doppler analysis of transmitral and pulmonary venous flow patterns recorded in the apical four-chamber view [5]. All echocardiographic images were averaged over three cardiac cycles.

Blood collection and analysis

Blood was drawn in the fasted state prior to ultrasound imaging. The following haematological parameters were determined using common laboratory procedures [14–17]: glucose, insulin, glycosylated hemoglobin (HbA_{1c}), total cholesterol, high and density low lipoproteins and triglycerides. Insulin was measured using a Roche Diagnostics Elecsys 2010 System using the sandwich principle [14]. Plasma lipids [15–17], glucose and HbA_{1c} were determined on a Synchron LX20 analyzer (Beckman Coulter, Fullerton CA). The homeostasis model assessment (HOMA index) was used as an estimate of insulin sensitivity [18].

Exercise intervention

The 10-week exercise intervention consisted of three supervised exercise sessions per week and included a combination of aerobic and resistance training. The aerobic component of the exercise program was performed on a cycle ergometer for 30–55 minutes at intensities between 65 and 75% of heart rate reserve. The intensity and duration of the aerobic component of the exercise intervention increased weekly so that each participant was performing 55 minutes of aerobic exercise at ~75% of heart rate reserve in the final week of the training program. Resistance training consisted of three sets of 10–15 repetitions at a resistance between 50 and 65% of one-repetition maximum in large muscle groups, using the following exercises: chest press, latissimus dorsi pull down, shoulder press, biceps curls, leg press, leg curl and leg extension. The resistance applied to each apparatus was increased each week so that each participant was performing three sets of 10 repetitions at 65–70% of the original one-repetition maximum. Control subjects were asked to continue their previous physical activity patterns throughout the 10-week intervention period.

Statistical analysis

All statistical analyses were performed using SPSS software (Version 11.0, SPSS, Chicago, IL). A repeated measures ANOVA was used to compare the effects of an exercise and control condition on LV filling dynamics, arterial compliance and risk factors for CVD. Tukey post-hoc analyses were performed to determine group differences. A p value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Baseline characteristics of both groups are provided in Table 1. At baseline, there were no significant differences in conventional risk factors for CVD, such as age, body mass index, systolic blood pressure, lipid profile, hormone replacement therapy or fasting insulin or glucose levels between the two groups. No differences in peak exercise variables were observed between the ET and CT groups at baseline. The average respiratory exchange ratio values at peak exercise in both groups did not exceed 1.10, however they were not significantly different between the groups (1.06 ± 0.04 vs 1.05 ± 0.05 in the ET and CT groups respectively).

Exercise training data

Resting hemodynamics prior to and following the exercise intervention are provided in Table 2. After 10 weeks of exercise training, $\dot{V}O_{2peak}$ increased by approximately 15% (21.3 ± 3.3 to 24.5 ± 4.2 $ml \cdot kg^{-1} \cdot min^{-1}$; $p < 0.05$) in the ET group. Maximal heart rate and respiratory exchange ratio values at follow-up testing were similar to baseline

Table 1: Subject characteristics prior to and following the intervention time period.

Variable	ET (n = 11)		CT (n = 7)	
	Pre	Post	Pre	Post
Age (yrs)	58 ± 7	---	59 ± 5	---
Weight (kg)	89.8 ± 12.0	86.9 ± 10.9	84.6 ± 16.5	85.1 ± 16.9
BMI (kg/m ²)	34.2 ± 4.6	32.8 ± 3.6*	33.6 ± 7	33.4 ± 7.3
TC (mmol/L)	5.0 ± 1.1	5.2 ± 1.0	5.2 ± 0.8	5.0 ± 0.4
HDL (mmol/L)	1.3 ± 0.3	1.30 ± 0.2	1.3 ± 0.2	1.3 ± 0.2
LDL (mmol/L)	2.9 ± 0.9	2.9 ± 1.0	3.0 ± 0.6	2.9 ± 0.4
HbA _{1c} (%)	6.6 ± 0.9	6.4 ± 0.6	7.4 ± 1.1	7.4 ± 0.8
Insulin (mmol/L)	11.7 ± 5.9	10.5 ± 4.8	11.9 ± 5.6	13.8 ± 7.3
HOMA	3.5 ± 2.1	3.0 ± 1.5	3.75 ± 1.6	3.9 ± 2.0
$\dot{V}O_{2peak}$ (mL·kg ⁻¹ ·min ⁻¹)	21.3 ± 3.3	20.02 ± 4.9	---	---
Therapy				
Diabetes (D/O)	4/7	---	1/6	---
Hypertension	5	---	4	---
Lipid	2	---	1	---

Means ± SD. BMI = Body mass index; TC = Total cholesterol; HDL = High density lipoprotein; LDL = Low density lipoprotein; HbA_{1c} = glycosylated hemoglobin; HOMA = Homeostasis model assessment of insulin sensitivity; D/O = Diet and exercise / oral diabetic therapy * = p < 0.05 vs pre-training

Table 2: The impact of exercise training on resting hemodynamics in postmenopausal women with type 2 diabetes.

Variable	ET (n = 11)		CT (n = 7)	
	Pre	Post	Pre	Post
Heart rate	72 ± 10	71 ± 13	83 ± 11	78 ± 10
SBP (mmHg)	133 ± 15	136 ± 20	139 ± 17	136 ± 20
DBP (mmHg)	76 ± 9	76 ± 10	74 ± 11	72 ± 10
C ₁ (mL/mmHg)	1.0 ± 0.4	1.2 ± 0.4*	0.75 ± 0.23†	0.79 ± 0.29
C ₂ (mL/mmHg)	0.05 ± 0.04	0.03 ± 0.01	0.03 ± 0.02	0.03 ± 0.02
SVR (dynes·sec·cm ⁻⁵)	1846 ± 471	1712 ± 247	1910 ± 336	1794 ± 291

SBP = Systolic blood pressure; DBP = Diastolic blood pressure; $\dot{V}O_{2peak}$ = cardiorespiratory fitness; C₁ = Large artery compliance; C₂ = Small artery compliance; SVR = systemic vascular resistance. * = p < 0.05 vs Pre † = p < 0.05 vs ET

values, suggesting similar effort for both tests. Cardiorespiratory fitness was not assessed in the CT group during follow-up testing.

Fasting blood glucose, insulin and lipid profile before and after the 10-week intervention period are presented in Table 1. Hematological variables were not significantly different in either group following the intervention time period. The HOMA index of insulin sensitivity decreased by ~17% in the ET while it did not change in CT. These changes in the HOMA index however, did not reach statistical significance.

LV filling dynamics, estimated from Doppler-derived transmitral and pulmonary venous flow profiles, were not significantly different following the intervention time period in either group (Table 2). In the ET group, large artery compliance increased by ~16% in response to exercise training (p < 0.05), while small artery compliance remained unchanged. Large and small artery compliance were unchanged in the CT group.

Discussion

The major novel finding of this investigation is that 10 weeks of exercise training elicited an increase in both large artery compliance and cardiorespiratory fitness in women

with DM-2 without any appreciable change in LV filling dynamics or conventional CVD risk factors.

Significant negative correlations have been observed between cardiorespiratory fitness and arterial stiffness [7,19], suggesting that exercise training may modulate central arterial compliance in healthy older individuals. More importantly, regular physical activity has been shown to attenuate the age-related decline in arterial compliance in healthy older men and women [7,19]. The findings from this investigation support the concept that exercise training favorably alters arterial stiffness in older women and extends these findings to women with DM-2.

Improvements in arterial compliance have been observed following lipid lowering therapy [20], however any appreciable changes in lipids following exercise training were not observed in this sample of women with DM-2. Although a slight improvement in the HOMA index (a marker of insulin sensitivity [18]) was observed following exercise training, the changes in the HOMA index were unrelated to changes in arterial compliance following the exercise intervention. Therefore the observed improvement in arterial compliance with exercise training in women with DM-2 in this investigation cannot be attributed to changes in lipid or glucose metabolism. Improved endothelium-mediated vasodilatation or a reduction in intima-media wall thickness [21] may explain enhanced arterial compliance with exercise training in older individuals. It is possible that the changes in large artery compliance observed with exercise training in this study were observed secondary to an improvement in endothelial dependent dilatation as exercise training-mediated improvements in flow mediated dilatation of the brachial artery have recently been documented in persons with DM-2 [22].

LV diastolic function is believed to be an important determinant of cardiorespiratory fitness in healthy individuals [23]. Data from cross-sectional and intervention studies examining the role of exercise training on LV filling dynamics (a surrogate of LV diastolic function) in older individuals are inconclusive [6,24-26]. While some demonstrate that exercise training attenuates age-related declines in LV filling dynamics [26] others do not [6,24]. Contrary to the findings reported here, Poirier and colleagues [27] have demonstrated a relationship between cardiorespiratory fitness and LV filling dynamics in normotensive men with DM-2. The data presented here support and extend the findings of Spina and associates [24], demonstrating that LV adaptations to exercise training are limited in post menopausal women and extend them to women with DM-2.

Several differences between this investigation and that of others may explain discrepant findings with regards to the LV adaptation to exercise training. First, the training stimulus employed in this investigation may not have been of sufficient duration (10 weeks) or frequency (three days/week) to elicit appreciable changes in the structure or cellular properties of the LV detectable with Doppler-derived transmitral flow patterns. Had the intervention been extended to 12 months, as others have done [26] it is possible that LV filling dynamics may have been altered. It is apparent however that gender differences in the LV adaptation to exercise training exist [6,24,25]. The findings presented here support the concept of a limited LV adaptation to aerobic exercise training in older women and extend them to older women with DM-2.

The results presented here have several clinical implications. Up to 80% of all deaths in persons with DM-2 are cardiovascular in nature [2], possibly secondary to an increase in arterial stiffness [28] that has been reported in this population [4]. The results of this study demonstrate that a brief exercise intervention in women with DM-2 enhances arterial compliance. As increased arterial stiffness is considered a risk for CVD, these data suggest that exercise may reduce the risk for CVD in women with DM-2 by reducing arterial stiffness. More importantly, these adaptations occurred despite little or no change in blood pressure, cholesterol profile or insulin sensitivity. Therefore, the non-invasive determination of arterial compliance may be an important adjunct in the assessment of CVD risk and/or treatment efficacy in individuals with DM-2 [28]. Finally, low cardiorespiratory fitness in men with DM-2 is associated with increased mortality, independent of conventional CVD risk factors [29]. Therefore, the observed increase in cardiorespiratory fitness in women with DM-2 following chronic exercise training could also be interpreted as a reduction in the risk for CVD-related mortality. These data lend support to the need for exercise training in the prevention and treatment of CVD-related morbidity and mortality in persons with DM-2.

A few limitations of this investigation need to be addressed. Firstly, although most demographic data were similar between both groups at baseline, a significant difference in arterial compliance was observed (Table 2). These baseline differences may be explained by the baseline differences in disease severity between the groups, as there were more individuals in the ET group whose diabetes was being controlled with diet and lifestyle and subsequently had slightly better glycemic control (Table 1). Although it is possible that these differences may have affected the results, one would expect the ET group to have less adaptive reserve relative to the CT group with lower arterial compliance at baseline. It is

Table 3: The impact of exercise training on left ventricular filling dynamics in postmenopausal women with type 2 diabetes. Mean \pm SD

Variable	ET (n = 11)		CT (n = 7)	
	Pre	Post	Pre	Post
Early (m/s)	87 \pm 10	88 \pm 15	97 \pm 23	91 \pm 22
Atrial (m/s)	95 \pm 29	92 \pm 20	93 \pm 11	87 \pm 23
E:A	1.0 \pm 0.3	1.0 \pm 0.3	1.0 \pm 0.2	1.1 \pm 0.3
E- Dec time (ms)	256 \pm 39	253 \pm 54	206 \pm 29	223 \pm 27
Pvs:Pvd	1.5 \pm 0.1	1.5 \pm 0.2	1.4 \pm 0.2	1.5 \pm 0.2
Pva (m/s)	28 \pm 7	29 \pm 5	28 \pm 4	29 \pm 7
Mad-Pad (ms)	-43 \pm 56	-31 \pm 33	0.1 \pm 2.3†	-3.7 \pm 17†

E/A = ratio of early to late transmitral filling velocities; Pvs:Pvd = Ratio of pulmonary venous flow in systole to pulmonary venous flow in diastole; Pva = pulmonary venous flow during atrial systole; Mad-Pad = Duration of transmitral atrial wave – duration of pulmonary venous atrial wave. † = p < 0.05 vs ET

therefore unlikely that these baseline differences contributed to the observed improvement in arterial compliance following exercise training. Secondly, LV or arterial function was not assessed under physiological stress such as exercise or β -adrenergic stimulation. Therefore it is unclear whether exercise training elicited improvements in inotropic or lusitropic LV reserve in women studied. Several investigations have demonstrated impaired cardiac inotropic responsiveness in both healthy aged [26] and aged individuals with DM-2 [30]. Although it is possible that an exercise-induced improvement in cardiorespiratory fitness occurred secondary to enhanced LV inotropic reserve, to our knowledge, this adaptation is limited to the male gender [26,27].

In conclusion, 10 weeks of exercise training improves both cardiorespiratory fitness and large artery compliance in postmenopausal women with DM-2. These adaptations were achieved without any significant changes in LV filling dynamics or conventional CVD risk factors, such as blood pressure, lipid profile or insulin sensitivity.

List of abbreviations

CT – Control group

CVD – Cardiovascular disease

DM-2 – Type 2 diabetes mellitus

ET – Exercise training group

HOMA index – Homeostasis model assessment index of insulin sensitivity

LV – Left ventricular

VO_{2peak} – Peak rate of oxygen consumption

Authors' contributions

JM – Conceived of the study, designed the investigation, participated in data collection, administered the intervention and drafted the manuscript

SM – Participated in the data collection, administered the intervention and preparation of the manuscript.

RL – Participated in the design of the investigation and was involved in the collection of the arterial compliance data.

MK – Participated in the data collection and the intervention administration.

IVM – Was involved in the stress testing/screening of participants.

AQ – Was involved in the design and coordination of the investigation.

DT – Was involved in the cardiac ultrasound imaging and analysis.

RW – Was involved in the screening of patients and cardiac ultrasound imaging.

MH – Was involved in the design and coordination of the investigation and participated in the echocardiographic analysis and interpretation.

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