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Exercise capacity is a predictor of cardiovascular events in patients with type 2 diabetes mellitus

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Abstract

Peak exercise oxygen consumption (peak VO_2), as measured by expired gas analysis, is an accurate, reproducible and reliable method for determining exercise capacity. In this study, a cohort of 468 patients with type 2 diabetes underwent graded exercise testing to measure peak VO_2 at baseline; the cohort was followed for five years for the occurrence of cardiovascular disease (CVD) events. Patients who developed CVD events during the five-year follow-up period were found to have significantly lower baseline peak VO_2 , as compared to those who did not ($p=0.02$). Analysis by gender showed that the mean peak VO_2 in male patients who developed CVD events was significantly lower than the peak VO_2 in those who did not ($p<0.03$). Multiple Cox regression analysis also showed low peak VO_2 to be an independent factor.

In conclusion, patients with type 2 diabetes mellitus with reduced peak VO_2 during exercise have a greater tendency to develop future CVD events.

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Key words: exercise, peak VO_2 , diabetes mellitus, cardiovascular events.

Introduction

Cardiovascular disease is a leading cause of morbidity and

mortality in people with type 2 diabetes mellitus, accounting for a 2–4-fold increase in the overall mortality.¹ Various reports have shown that regular physical activity is associated with a reduced risk of coronary heart disease.^{2,5} Regular physical activity is in turn associated with higher levels of physical fitness, as measured by maximal oxygen uptake and heart rate response to submaximal exercise.^{6,7} Physical training increases the maximal oxygen uptake in the body. The increase in maximal O_2 uptake in healthy subjects is a result of an increase in peak cardiac output and an increased extraction of O_2 from the blood. Additionally, the beneficial effect of physical training has been attributed to changes in skeletal muscles and to an increase in arterial O_2 content.⁸

Some, although not all, previous studies have suggested that subjects with uncomplicated type 2 diabetes mellitus have an impaired peak exercise performance compared with healthy age-matched controls.^{9–13} The impairment in exercise is not associated with the degree of glycaemic control.¹³ However, the mechanism by which exercise performance is impaired in persons with type 2 diabetes is not known. Nevertheless, lifestyle modification, including exercise, remains an integral part of the management of diabetes mellitus and has been shown to prevent progression from impaired glucose tolerance to diabetes.¹⁴

Peak exercise oxygen consumption (peak VO_2) as measured by expired gas analysis serves as an accurate, reproducible and reliable method for determining exercise capacity. However, limited data are available on the relation between physical fitness as measured by exercise testing and subsequent cardiovascular morbidity and mortality.^{15–18} The purpose of this study was to determine the predictive value of baseline peak exercise oxygen consumption on subsequent development of cardiovascular events in a cohort of 468 patients with type 2 diabetes during a five-year follow-up period.

Research design and methods

Study population

The study subjects were participants in the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, a large, prospective, randomised, blinded clinical study designed to determine the effects of moderate versus intensive blood pressure control on the outcome of complications in type 2 diabetes. This trial has been described in detail previously.¹⁹ Participants in the ABCD trial between the ages of 40 and 74 years were identified from diagnosis-related group and phar-

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macy and billing lists from participating hospitals. Individuals found to be eligible after an initial phone screen and eligibility visit were enrolled into this study.

The diagnosis of type 2 diabetes mellitus for all patients enrolled in the ABCD trial was made according to criteria based on the World Health Organization report of 1985,²⁰ which followed the National Diabetes Group criteria of 1979.²¹ Institutional Review Board approval was obtained for the conduct of all aspects of the ABCD trial, and all eligible patients gave informed consent for participating in the study.

During the pre-randomisation period, participants were tapered off all pre-existing antihypertensive agents, and placebo was prescribed for a minimum of seven and a maximum of 11 weeks.²² During this period, all baseline examinations were performed. Thus, all baseline exercise tests and peak VO_2 measurements were performed after 7–11 weeks of wash-out from any antihypertensive medications. A structured interview with detailed questions regarding medications and history of cardiovascular disease also took place. Patients with a history of coronary artery disease at baseline were excluded from the study.

Exercise testing and measurement of peak oxygen consumption (peak VO_2)

An exercise treadmill test was administered during the pre-randomisation period using a Half Bruce protocol.²³ The electrocardiogram was monitored continuously (Q5000 Exercise Monitor; Quinton, Seattle, WA) and blood pressure was measured at the end of each stage by an automated blood pressure cuff (model 412 automated blood pressure cuff; Quinton). Patients exercised until symptoms forced them to stop. Measurements of oxygen consumption and carbon dioxide production, with calculations of the respiratory exchange ratios, were performed continuously using an automated gas exchange measuring system (Q-plex Metabolic Cart; Quinton). Values were recorded at 15-second intervals. The respiratory exchange ratio (RER), the ratio of carbon dioxide production to oxygen consumption, was used as a measure of exercise intensity. Peak VO_2 was defined as oxygen consumption ($\text{ml kg}^{-1} \text{min}^{-1}$) at peak exercise and was calculated as the mean of values during the last minute of exercise. To ensure an adequate effort, only patients who reached $\text{RER} \geq 1.0$ were included in the analysis; 43 patients who were not able to reach RER of 1.0 were excluded. Thus, the cohort study population was 468 patients with type 2 diabetes mellitus.

CVD events

An independent end point committee, which was blinded to the study intervention arms, reviewed all cardiovascular events. Cardiovascular disease (CVD) events were defined as follows: 1) death due to cardiovascular events (sudden death, progressive heart failure, myocardial infarction, arrhythmias, cerebral vascular accidents, and ruptured aortic aneurysm); 2) non-fatal myocardial infarction; 3) non-fatal cerebral vascular accident; 4) heart failure requiring hospital admission; and 5) pulmonary infarction. The end point committee reviewed and confirmed all cardiovascular events.

Table 1. Baseline clinical and laboratory profile of 468 patients with type 2 diabetes according to subsequent development of cardiovascular event

Variable	No CVD (n=397)	CVD (n=71)	P value
Clinical profile			
Gender (M/F)	256/141	51/20	0.2300
Age (years)	57.1±0.4	60.2±0.9	0.0272
Duration of diabetes (years)	8.6±0.4	12.1±0.8	0.0001
Duration of hypertension (years)	10.0±0.5	11.7±1.3	0.2061
Systolic blood pressure (mmHg)	144.1±0.9	150.2±2.0	0.0052
Diastolic blood pressure (mmHg)	91.3±0.4	91.6±1.0	0.7485
BMI (kg/m^2)	31.3±0.3	30.9±0.6	0.7668
Smoking (pack years)	19.1±1.4	20.2±3.5	0.7668
Left ventricular mass (g/m^2)	215.2±4.4	220.5±9.7	0.6174
Prevalence peripheral vascular disease (%)	10.4	18.3	0.0696
Prevalence retinopathy (%)	49.7	65.7	0.0116
Prevalence nephropathy (%)	12.1	31.9	0.0374
Laboratory profile			
Cholesterol (mg/dL)	218.5±2.6	221.3±6.4	0.6842
HDL (mg/dL)	41.6±0.6	38.3±1.5	0.0413
LDL (mg/dL)	130.9±1.7	138.9±4.4	0.0909
Triglycerides (mg/dL)	267.7±13.3	274.5±31.5	0.8435
Glycosylated haemoglobin (%)	11.6±0.2	12.5±0.4	0.0451

Key: CVD = cardiovascular disease; M = male; F = female; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein

To convert cholesterol from mg/dL to mmol/L, multiply by 0.02586
To convert triglycerides from mg/dL to mmol/L, multiply by 0.01129

Albuminuria and retinopathy were classified as described in earlier reports.²⁴

Statistical analysis

Univariate analysis was performed relating peak O_2 consumption with cardiovascular events that developed over time and with various other clinical factors. Multiple regression analysis was performed, controlling for age, sex, duration of diabetes, hypertension and body mass index. All results were reported as means + or - standard error (SE).

Results

Baseline clinical and laboratory characteristics

A cohort of 468 patients with type 2 diabetes, 307 (65.6%) males and 161 (34.4%) females, was followed for a period of five years. Table 1 shows the baseline clinical and laboratory characteristics, categorised according to subsequent development of CVD events. The mean age of those who subsequently developed CVD events was higher when compared to those who did not. Duration of diabetes, level of systolic

Table 2. Baseline clinical and laboratory profile by gender

Variable	Males (n=307)	Females (n=161)	P value
Clinical profile			
Age (years)	58.6±0.5	57.5±0.6	NS
Duration of diabetes (years)	9.1±0.4	9.1±0.6	NS
Duration of hypertension (years)	6.3±0.6	6.9±0.8	NS
Systolic blood pressure (mmHg)	134.1±0.7	137.4±1.0	0.0099
Diastolic blood pressure (mmHg)	81.5±0.4	81.3±0.5	NS
BMI (kg/m ²)	30.6±0.3	32.2±0.4	0.0016
Smoking (pack years)	24.8±1.7	8.9±2.3	0.0001
Left ventricular mass (g/m ²)	231.6±4.6	186.7±6.4	0.0001
Prevalence peripheral vascular disease (%)	9.8	14.6	0.0067
Prevalence retinopathy (%)	54.8	48.4	NS
Prevalence nephropathy (%)	43.8	31.7	0.0247
Laboratory profile			
Cholesterol (mg/dL)	211.7±2.5	226.2±3.4	0.0007
HDL (mg/dL)	38.5±0.7	45.4±0.9	0.0001
LDL (mg/dL)	130.5±2.0	133.3±2.9	NS
Triglycerides (mg/dL)	259.9±15.2	285.4±20.9	NS
Glycosylated haemoglobin (%)	11.4±0.2	12.1±0.2	0.0302

Key: BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein

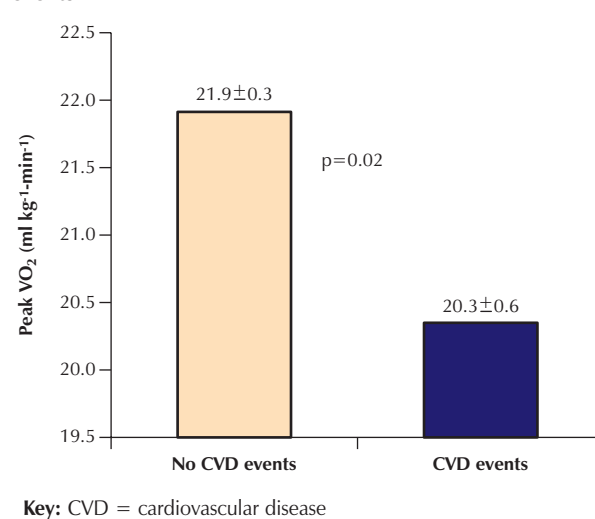
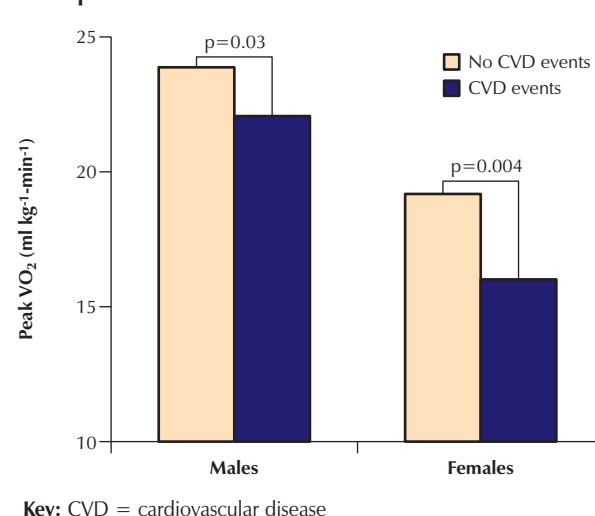
To convert cholesterol from mg/dL to mmol/L, multiply by 0.02586
To convert triglycerides from mg/dL to mmol/L, multiply by 0.01129

blood pressure, prevalence of microvascular complications (retinopathy and nephropathy) and high-density lipoprotein (HDL)-cholesterol levels were significantly different at baseline among the two groups; on the other hand, duration of hypertension, levels of diastolic blood pressure, body mass index, pack years of smoking, prevalence of peripheral vascular disease and low-density lipoprotein (LDL)-cholesterol were similar in the two groups.

When these profiles were analysed by gender (table 2), the mean age, duration of diabetes, duration of hypertension, diastolic blood pressure and prevalence of retinopathy were similar among males and females. The pack years of smoking, left ventricular mass and prevalence of nephropathy were significantly higher in males than in females. However, females had higher body mass index (BMI), total cholesterol, HDL-cholesterol, and glycosylated haemoglobin levels (table 2).

Peak exercise oxygen consumption and CVD

Patients in the total cohort who developed cardiovascular events during the five years of follow-up demonstrated significantly lower peak exercise oxygen consumption at baseline than patients who did not (20.3 ± 0.6 ml kg⁻¹ min⁻¹ versus 21.9 ± 0.3 ml kg⁻¹ min⁻¹) (figure 1). For the entire

Figure 1. Peak exercise oxygen consumption (VO₂) at baseline in patients who did not or who did develop CVD events**Figure 2. Peak exercise oxygen consumption (VO₂) at baseline in males and females who did not or who did develop CVD events**

cohort of patients, male subjects had a significantly higher peak VO₂ at baseline than female subjects (23.3 ± 0.27 ml kg⁻¹ min⁻¹ in males versus 18.5 ± 0.37 ml kg⁻¹ min⁻¹ in females, $p < 0.0001$) (data not shown). Of the 307 male patients, 51 (16.6%) and of the 161 female patients, 20 (12.4%) patients developed CVD events during the five-year follow-up period. The difference in incidence of CVD events among the males and females was not statistically significant ($p > 0.05$). Figure 2 shows that the mean peak VO₂ at baseline in the male patients who developed CVD events was significantly lower than in those who did not develop CVD events (21.9 ± 0.7 ml kg⁻¹ min⁻¹ versus 23.6 ± 0.3 ml kg⁻¹ min⁻¹, $p < 0.03$). Similarly, the mean peak VO₂ in the female patients who developed CVD events was significantly lower than in those who did not

Table 3. Multiple Cox proportional hazards regression analysis for the development of CVD events

	Hazard ratio	95% CI	P value
Peak VO ₂	0.931	0.879–0.987	0.0165
Gender (male)	1.766	0.959–3.252	0.0680
Duration of diabetes	1.047	1.016–1.079	0.0027
Duration of hypertension	1.014	0.988–1.041	0.2991
Systolic blood pressure	1.012	0.993–1.031	0.2247
Diastolic blood pressure	0.964	0.921–1.009	0.1182
Overt albuminuria	2.174	1.244–3.798	0.0064
Cholesterol	1.001	0.995–1.007	0.7330

Key: VO₂ = exercise oxygen consumption; CVD = cardiovascular disease

(16.2±0.9 ml kg⁻¹ min⁻¹ versus 18.8±0.3 ml kg⁻¹ min⁻¹, $p < 0.004$) (figure 2).

To evaluate the relative influence of several concurrent variables on the development of CVD events, multiple Cox proportional regression analysis was performed. The model included age, gender, duration of diabetes, duration of hypertension, blood pressure, overt albuminuria and total serum cholesterol. The results (table 3) showed that, in addition to duration of diabetes and overt albuminuria, peak VO₂ is also an independent factor in predicting CVD events ($p = 0.0165$).

Discussion

In this study, we have demonstrated that lower peak VO₂ at baseline is associated with a higher rate of subsequent cardiovascular events when the entire cohort of patients with type 2 diabetes was analysed (figure 1). Male patients who subsequently developed CVD events had significantly lower baseline peak VO₂ than those who did not develop CVD events. Similarly, females who developed CVD events also had lower peak VO₂ than those who did not develop CVD events (figure 2). Overall, male patients had significantly higher peak VO₂ than females whether they did or did not develop CVD events (figure 2).

Exercise capacity is determined by the interplay of the fundamental physiological processes of the body. The micro- and macro-vascular complications observed in the patient with diabetes dictate the subject's capacity to perform exercise, which is manifest with lower peak VO₂ consumption and eventually signals future clinical cardiovascular events. In this regard (as shown in table 1), patients who developed CVD events were significantly older, with longer duration of diabetes, higher systolic blood pressure and higher prevalence of microvascular complications than those patients who did not develop CVD events. Thus, the lower peak VO₂ at baseline in such subjects most likely represents pre-existing sub-clinical micro- and macro-vascular disease. Nonetheless, we have demonstrated in the multiple Cox proportional hazards model that, after adjusting for other variables, low peak

VO₂ is an independent and significant predictor of future clinical CVD events.

Exercise is a major component in the management of patients with type 2 diabetes and peak VO₂ can be a reliable method for determining exercise capacity. Exercise increases insulin sensitivity and peripheral tissue glucose disposal, which helps to achieve optimum metabolic control. Peak VO₂ is directly correlated with insulin-stimulated glucose disposal.^{25–27} Decreased peak VO₂ has been observed in patients with insulin resistance and in their relatives; however, this trend can improve with intensive and regular physical training.²⁸ In exercise, both an increase in peak cardiac output and an increased extraction of oxygen from the blood increase maximal oxygen uptake. The increase in cardiac output in trained normal subjects occurs because of an increase in stroke volume.^{13,29} However, the beneficial effect of physical training in persons with coronary heart disease has been attributed primarily to peripheral mechanisms^{30,31} such as changing adaptive mechanisms, which increase arterial oxygen content, and to increases in muscle oxygen extraction.⁸

Urinary albumin excretion is associated with left ventricular dysfunction,^{32,33} and has also been reported to predict future cardiovascular events in European patients with type 2 diabetes^{34,35} and to impair exercise capacity in patients with diabetes.³⁶ However, there have been no reports to demonstrate the predictive power of peak VO₂ in future cardiovascular events in patients with type 2 diabetes mellitus. In the present study, those patients who developed cardiovascular events not only had lower peak VO₂ at baseline but also a higher prevalence of retinopathy and nephropathy. Thus, decreased peak VO₂ is one of several pathophysiological mechanisms leading to the time-dependent development of cardiovascular events in patients with type 2 diabetes mellitus.

Our group has previously reported that increasing urinary albumin excretion was directly associated with a decrease in exercise capacity.³⁷ This microvascular diabetic complication was associated with a decrease in exercise performance as measured by peak VO₂, independent of age, gender, race, duration of diabetes, duration of hypertension, BMI and glycosylated haemoglobin levels. In another study where assessments of demographic and cardiovascular risk factors were undertaken, the results revealed that age, obesity, systolic blood pressure, smoking and African-American race were independently associated with an impairment of exercise capacity.³⁸ Thus, decreased peak VO₂ appears to be associated with multiple factors involved in the complications of diabetes. While macrovascular disease in general and CVD in particular represent the leading causes of morbidity and mortality in type 2 diabetes,¹ there are currently limitations in the ability to assess the risk for further clinical events non-invasively.

The present study has demonstrated that low peak VO₂ at baseline is independently associated with the future development of cardiovascular events. Since diabetes mellitus is a multi-organ disease, peak VO₂ is likely to be dependent on various other concurrent factors involved in the microvascular and macrovascular complications of the dis-

ease. Further prospective studies would be required to determine the utility of peak VO_2 measurement during exercise as an indicator for future cardiovascular events in patients with type 2 diabetes.

Conflict of interest

None declared.

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