Impaired aerobic work capacity in insulin dependent diabetics with increased urinary albumin excretion

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Abstract

To assess whether decreased aerobic work capacity was associated with albuminuria in insulin dependent diabetics aerobic capacity was measured in three groups of 10 patients matched for age, sex, duration of diabetes, and degree of physical activity. Group 1 comprised 10 patients with normal urinary albumin excretion (<30 mg/24 h), group 2 comprised 10 with incipient diabetic nephropathy (urinary albumin excretion 30-300 mg/24 h), and group 3 comprised 10 with clinical diabetic nephropathy (urinary albumin excretion >300 mg/24 h). Ten non-diabetic subjects matched for sex, age, and physical activity served as controls. Oxygen uptake was similar in the four groups at rest and during a 75 W workload. Maximal oxygen uptake was also similar in the control subjects and group 1 (median 41.7, (range 29.1-53.0) ml/kg/min *v* 38.5 (26.6-59.2) ml/kg/min, respectively), but was significantly lower in group 2 (27.7 (13.9-44.3) ml/kg/min) and group 3 (26.8 (22.6-36.7) ml/kg/min). The difference in maximal oxygen uptake between groups 1 and 2 was 10.8 ml/kg/min (95% confidence interval 3.6 to 23.4 ml/kg/min) and between groups 1 and 3, 11.7 ml/kg/min (4.9 to 22.5 ml/kg/min). These differences were not explained by differences in metabolic control or the degree of autonomic neuropathy.

Thus the insulin dependent diabetics with only slightly increased urinary albumin excretion had an appreciably impaired aerobic work capacity which could not be explained by autonomic neuropathy or the duration of diabetes. Whether the reduced capacity is due to widespread microangiopathy or another pathological process affecting the myocardium remains to be established.

Introduction

Insulin dependent as well as non-insulin dependent diabetic patients who develop diabetic nephropathy have a more than 30-fold increased relative mortality compared with diabetic patients who do not develop this condition.^{1,3} This excess mortality is substantially caused by cardiovascular diseases,⁴ and a high incidence of coronary heart disease within the first few years after the onset of proteinuria has been shown.⁵ Accordingly, reduced cardiac performance and work capacity have been shown in diabetics with renal failure.⁶ Indirect estimates of maximal oxygen uptake based on the response of the heart rate to work suggested a reduced capacity for aerobic work in diabetics at the early stage of diabetic nephropathy.⁷ In the present study a range of metabolic variables including oxygen

uptake, heart rate, and lactic acid concentration were studied in diabetics performing maximal exercise to determine whether patients in the very early stage of diabetic nephropathy have impaired work capacity.

Subjects and methods

SUBJECTS

We recruited from the outpatient clinic at Steno Memorial Hospital 30 patients aged 18-45 with insulin dependent diabetes mellitus who had been aged under 31 at the onset of the disease and had had the disease for more than five years. They did not have a history of non-diabetic renal disease, and in all of them bacterial cultures of urine yielded negative results. The patients were recruited from three groups according to the degree of albuminuria, which was based on the median urinary albumin excretion in three 24 hour urine collections taken at home during normal physical activity. Three collections were made to take into account the high (40%) day to day variation of the variable.

The three groups were defined as follows: group 1 comprised 10 patients (four women, six men) with normal urinary albumin excretion (<30 mg/24 h) selected at random; group 2 comprised 10 patients with raised urinary albumin (30-300 mg/24 h)—that is, patients with incipient diabetic nephropathy; and group 3 comprised 10 patients with overt diabetic nephropathy (urinary albumin excretion >300 mg/24 h). Patients in groups 2 and 3 were matched with those in group 1 for sex, age, duration of diabetes, and degree of physical activity. Ten healthy non-diabetic subjects matched for sex, age, and physical activity served as controls. Daily physical activity was graded from 0 to 5 based on employment, mode of transport to and from work, and participation in sport. Subjects were classified as non-smokers, smoking 1-15 cigarettes/day, and smoking >15 cigarettes/day according to their daily consumption.

We gave all patients conventional insulin treatment—that is, twice or thrice daily injections of intermediate acting insulin often mixed with short acting insulin; no other drugs were given. No patient or control had a history of angina pectoris, cardiac arrhythmias, or pulmonary disease. Auscultation of the heart and lungs and a nine lead electrocardiogram obtained at rest and during maximal exercise showed no abnormalities.

All subjects gave their informed consent, and the study was approved by the regional scientific ethics committee.

EXERCISE PROTOCOL

After a normal breakfast (and insulin injection in the case of the patients) at 0700 and a light meal at 1100 the subjects reported to the laboratory at 1300. A cannula was inserted into an antecubital vein, and the subjects rested for 60 minutes in the supine position. The exercise test was performed on a mechanically braked, electronically controlled bicycle ergometer (Monark Model 669-1, Varberg, Sweden). Subjects were allowed five to seven minutes to warm up at a workload of 75 W, and the load was then increased stepwise by 25 W until the subject became exhausted. Each workload was maintained for 90-120 seconds. Expired air was collected in Douglas bags while the patient was at rest on the bicycle and during the last 30-40 seconds of each workload.⁸ The volume of expired air was measured with a Tissot spirometer and the content of oxygen and carbon dioxide analysed by a Servomex paramagnetic oxygen analyser and a Beckman infrared carbon dioxide analyser, respectively. These instruments had been calibrated with gas mixtures whose oxygen and carbon dioxide contents had been determined by the Scholander technique. Heart rate was registered continuously by nine lead electrocardiography. If necessary blood glucose concentration was adjusted to 4-12 mmol/l with intravenously injected insulin or glucose before exercise. Venous blood for analysis of lactate was collected and precipitated in perchloric acid before exercise and at exhaustion.

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LABORATORY MEASUREMENTS

Serum and urinary albumin concentrations were measured with an enzyme linked immunosorbent assay (ELISA)⁹; haemoglobin A_{1c} concentration with a chromatographic technique (normal range 4.1-6.4%)¹⁰; serum

creatinine concentration with a reaction rate kinetic principle that eliminated pseudocreatinines¹¹; blood glucose concentration with a glucose meter (Hypocount, Suffolk, England); and blood lactate concentration fluorometrically by the lactate dehydrogenase method.¹² Blood pressure was measured with a standard clinical sphygmomanometer (cuff 25 x 12 cm);

TABLE I—Clinical characteristics of patients with insulin dependent diabetes and normal subjects. Values are medians (ranges) except when stated

	Normal subjects	Group 1 (normal urinary albumin (<30 mg/24 h))	Group 2 (incipient nephropathy; urinary albumin 30-300 mg/24 h)	Group 3 (clinical nephropathy; urinary albumin >300 mg/24 h)
No of patients	10	10	10	10
Ratio of men:women	6:4	6:4	6:4	6:4
Age (years)	33 (25-38)	32 (19-38)	30 (24-42)	29 (19-42)
Duration of diabetes (years)		16 (9-29)	16 (8-30)	18 (10-26)
Body mass index (kg/m ²)	22.8 (20.9-24.7)	22.6 (20.5-24.4)	22.6 (19.1-26.2)	22.2 (19.28-7)
Dose of insulin (IU/kg)		0.6 (0.4-1.0)	0.6 (0.3-1.1)	0.6 (0.4-1.2)
Blood glucose concentration (mmol/l)	4.4 (3.3-5.2)	6.7 (4.9-10.3)	7.2 (4.9-10.0)	7.3 (4.8-12.6)
Haemoglobin A _{1c} (%)	5.2 (4.7-5.6)†‡§	7.9 (5.5-8.7)*‡§	8.7 (6.6-10.8)*†	9.4 (7.5-10.9)*†
Blood pressure (mm Hg)	118/75 (110/70-160/78)	120/74 (95/70-140/75)	130/85 (110/65-150/88)	130/83 (110/70-150/90)
Serum creatinine (μmol/l)	74 (61-100)	84 (74-88)	80 (53-108)	83 (68-120)
Haemoglobin (g/l)	140 (106-153)	140 (131-153)	140 (119-150)	140 (111-148)
Physical activity	3 (2-4)	3 (1-4)	2 (1-4)	3 (1-4)
Daily consumption of cigarettes (0:1-15:>15)	5:5:0	8:2:0	6:2:2	6:2:2
Beat to beat variation (/min)	19 (10-31)§	17 (2-44)§	16 (6-29)§	10 (6-21)*†‡
No of subjects with abnormal beat to beat variation (<15 /min)	1	5	5	7
No of patients with retinopathy (<3 microaneurisms: simplex retinopathy:proliferative nephropathy)		8:2:0	6:3:1	1:6:3

||Graded from 0 to 5 on basis of employment, mode of transport to and from work, and participation in sport.

Significant difference ($p<0.05$) compared with *normal subjects, †group 1, ‡group 2, and §group 3.

TABLE II—Median (range) oxygen uptake, heart rate, and blood lactate concentrations in diabetic patients with or without nephropathy and normal subjects

	Normal subjects	Group 1 (normal urinary albumin (<30 mg/24 h))	Group 2 (incipient nephropathy; urinary albumin 30-300 mg/24 h)	Group 3 (clinical nephropathy; urinary albumin >300 mg/24 h)
Oxygen uptake (ml/kg/min):				
At rest	4.3 (3.7-5.1)	4.7 (3.7-6.2)	4.4 (2.8-6.2)	4.7 (3.6-6.1)
At 75 W	16.8 (12.1-20.6)	17.5 (16.2-24.5)	16.1 (7.5-22.2)	20.0 (14.3-22.1)
At exhaustion	41.7 (29.1-53.0)†‡§	38.5 (26.6-59.2)†§	27.7 (13.9-44.3)*†	26.8 (22.6-36.7)*†
Heart rate (beats/min):				
At rest	72 (65-94)	86 (75-104)*	86 (68-100)*	90 (75-112)*
At 75 W	103 (94-140)	120 (96-154)*	121 (94-160)*	130 (110-144)*
At exhaustion	182 (170-194)	185 (155-192)	180 (130-192)	173 (145-185)
Blood lactate (mmol/l) at exhaustion	8.4 (5.6-13.3)	7.0 (5.5-12.6)	6.9 (3.9-8.9)	6.5 (3.4-8.2)

Significant difference ($p<0.05$) compared with *normal subjects, †group 1, ‡group 2, and §group 3.

Maximal oxygen uptake in normal subjects and diabetic patients with or without nephropathy (group 1=patients with normal urinary albumin excretion (<30 mg/24 h); group 2=patients with incipient nephropathy (urinary albumin 30-300 mg/24 h); group 3=patients with clinical nephropathy (urinary albumin >300 mg/24 h). ●=Five patients with best long term metabolic control; ○=five patients with poorest long term metabolic control. Horizontal bars indicate median values.

Groups 2 and 3 v normal subjects and group 1: $p<0.01$.

diastolic blood pressure was measured at the disappearance of the Korotkoff sounds (phase V). Eye background was examined by ophthalmoscopy through the dilated pupil and classified as normal or showing background or proliferative retinopathy. Autonomic neuropathy was assessed from the beat to beat variation in heart rate during forced respiration.¹³ Body mass index was calculated as weight/height² (kg/m²).

STATISTICAL METHODS

Results are expressed as medians and ranges. Groups were compared by the Kruskal-Wallis range test and, when significant differences were found, by the Mann-Whitney test. Correlations were sought by multiple regression analysis. Results were considered to be significant if $p<0.05$ (two tailed).

Results

Table I shows the clinical characteristics of the diabetics and normal controls and the excellent match of sex distribution, age, duration of diabetes, and physical activity among the groups. The figure shows that maximal oxygen uptake was similar in the controls and group 1 and was significantly reduced in groups 2 and 3 ($p<0.01$); it was not significantly different between groups 2 and 3.

In the diabetic patients beat to beat variation and maximal oxygen uptake were not significantly correlated ($r=0.28$); the numbers of patients with

autonomic neuropathy were identical in groups 1 and 2 (table I). The heart rate was significantly higher at rest and during baseline (75 W) exercise in the diabetic groups compared with the controls ($p < 0.05$), but the maximal heart rate was similar in the four groups (table II). Multiple regression analysis did not disclose any correlation between maximal oxygen uptake and resting heart rate ($r = 0.12$), or maximal heart rate ($r = 0.17$). Blood glucose concentrations were similar in the diabetic groups during work (table I). Long term metabolic control as reflected by the haemoglobin A_{1c} concentration was significantly worse in groups 2 and 3 than group 1 (table I), but there was no significant correlation between maximal oxygen uptake and haemoglobin A_{1c} concentration and when patients with similar haemoglobin A_{1c} concentrations in the three diabetic groups were compared the maximal oxygen uptake was still significantly reduced in groups 2 and 3 compared with group 1 ($p < 0.05$).

Discussion

Our main findings were impaired aerobic capacity in diabetics with persistent but only slightly increased urinary albumin excretion and normal aerobic capacity in diabetics with normal albumin excretion. Furthermore, the reduction in aerobic capacity did not correlate with reduced beat to beat variation, which is an index of autonomic neuropathy. The reliability of these observations is based on the assumption that a valid determination of maximal oxygen consumption was made, which is supported by four observations. Firstly, all subjects were exercised to complete exhaustion. Secondly, the mean maximal heart rate was in the range expected for subjects of this age¹⁴ and was not significantly different among the four groups. Thirdly, the respiratory quotient determined at exhaustion was higher than one in all but one subject. Fourthly, "levelling off"—that is, no further increase in heart rate and oxygen uptake at increasing workloads—was seen in most subjects. In subjects in whom levelling off did not occur the heart rate, respiratory quotient, and blood lactate concentration at exhaustion were similar to values obtained in the subjects in whom it did occur, indicating that true maximal oxygen uptake was measured in all subjects. One patient in each group had an appreciably reduced maximal heart rate, but these patients had severe autonomic neuropathy, and the finding of respiratory quotients above one and blood lactate concentrations above 6.3 mmol/l indicated that their maximal aerobic capacity had been reached.

Impaired aerobic work capacity has been described in diabetic renal failure⁶ and, on the basis of indirect evidence, has been suggested to occur in patients with incipient diabetic nephropathy,⁷ but our finding of a 40% reduction in maximal oxygen consumption in patients with incipient diabetic nephropathy is new. We also found that aerobic work capacity was reduced to the same extent in patients with incipient and overt clinical nephropathy.

The reduced work capacity of our patients was not explained by ischaemic heart disease as all had normal electrocardiograms at rest and during exercise. Thus from the relation oxygen uptake = heart rate $\times$ stroke volume $\times$ (arterial oxygen concentration - mixed venous oxygen concentration) it seems that as the maximal heart rate was similar the difference in oxygen uptake between groups 1 and 2 might be explained by either reduced stroke volume or reduced extraction of oxygen in muscles or both; either possibility might be caused by diabetic microangiopathy. Cardiovascular limitations to exercise have previously been suggested in patients with non-diabetic renal disease,¹⁵ but our patients had fairly well preserved renal function with serum creatinine concentrations below 120 μ mol/l (table I). Our findings could not be explained by anaemia, and none of the patients had electrolyte disorders or acidosis (data not shown).

Metabolic control tended to be worse with increased urinary albumin excretion; aerobic capacity was not however correlated with haemoglobin A_{1c} concentration in any of the groups and the blood glucose concentration at the time of the exercise test was similar in all three diabetic groups. The impaired aerobic capacity in the patients with increased urinary albumin excretion could not be explained by a higher prevalence of autonomic neuropathy. In contrast to previous findings^{16 17} we found no correlation between autonomic neuropathy and decreased aerobic capacity. Some of the

patients with autonomic neuropathy studied by Hilsted *et al* had clinical nephropathy,^{16 17} and consequently their reduced work capacity might be explained by a higher prevalence of clinical and incipient nephropathy rather than autonomic neuropathy.

We believe that reduced oxygen uptake at exhaustion in diabetics with albuminuria is due to cardiomyopathy or reduced oxygen extraction in peripheral tissues affected by microangiopathy, or both. If this is the case our study shows that young diabetics with persistently increased urinary albumin excretion suffer not only from early renal disease but also from potentially serious non-renal complications. Such patients have reduced functional capacity of the cardiovascular system even from the earliest stage of diabetic nephropathy, which might well contribute to their considerable mortality from cardiovascular diseases.

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ONE HUNDRED YEARS AGO

MR. PUNCH, in his playful wisdom, has lately aimed his shafts, not a day too soon, at the system which must be held responsible for the woeful miseries endured by the those who, at seasons like the present, desire loyally to show their dutiful allegiance to the Throne. Whosoever conventionalism is allowed, at the risk of health and of human life, to usurp the place of common sense, it is clearly the duty of the medical profession to let its voice be heard. When fair daughters of Eve, in so-called full dress, ingeniously display to the utmost their shapely arms and backs and busts; when, with the help of the modiste and the undressmaker, they approach as nearly to the nude as may be; when the young and beautiful, after a brief season of gaslight gaiety, are seen to be careworn and haggard; when matrons, beautified with feathers and paint, complacently smile at the sight of their daughters thus victimised; when modesty is thus shocked and common sense outraged, then we come to know that we are in the halls of modern fashion and enjoyment. Is the medical profession justified in witnessing such vagaries of human judgment without protest? Perchance the counsel of the wise, if properly directed, might yet succeed in coming to the rescue of long-suffering and half-clothed humanity.

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