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Originals

Exercise as a provocative test in early renal disease in Type 1 (insulin-dependent) diabetes: albuminuric, systemic and renal haemodynamic responses

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Summary. The value of exercise as a provocative test for early renal disease in Type 1 (insulin-dependent) diabetes was re-evaluated. Three carefully characterized groups of males were studied: 10 non-diabetic controls, 16 diabetic patients (group 1) with normal urinary albumin excretion (< 15 μg/min) and 14 Albustix-negative diabetics (group 2) with increased urinary albumin excretion (15-122 μg/min). Assignment to a study group was made on the basis of three 24-h urine collections, and the groups were well matched for age, weight, height, and serum creatinine concentration. The two diabetic groups were similar with regard to duration of disease (13 ± 6 versus 16 ± 3 years), metabolic control (HbA_{1c}: 8.4 ± 1.4 versus 8.7 ± 1.3%) and degree of diabetic complications (beat-to-beat variation and retinopathy). An exercise protocol of 450 and 600 kpm/min workloads was employed. In the resting state group 2 patients had elevated systolic blood pressure compared with the normal subjects (132 ± 13 versus 119 ± 9 mmHg), and their glomerular filtration rate was significantly reduced compared with group 1 (123 ± 19 versus 138 ± 15 ml/min per 1.73 m^2, $p < 0.05$). During exercise the urinary albumin excretion rate increased significantly in all three groups (normal subjects: 6 ± 0.7 to 8 ± 1.3 (μg/min); group 1: 6 ± 0.6 to 9 ± 1 μg/min and group 2: 48 ± 10 to 113 ± 23 μg/min), the relative increase being higher in group 2 ($p < 0.01$). The changes in systemic haemodynamics were similar in all three groups in spite of a reduced maximum working capacity in group 2 (949 ± 249 versus group 1: 1163 ± 200 and normal subjects 1267 ± 264 kpm/min ($p < 0.05$). The renal haemodynamic changes were qualitatively similar for the three groups, but the filtration fraction during exercise increased in groups 1 and 2 to almost identical values and were significantly higher than in normal subjects (group 1 + group 2: 0.29 ± 0.02 versus normal subjects: 0.26 ± 0.03, $p < 0.02$). These findings suggest that an elevated transcapillary pressure gradient, as obtained during moderate exercise, will not cause an abnormal increase in albumin excretion per se. A functional glomerular lesion, already recognisable at rest (elevated albumin excretion) must also be present.

Key words: Type 1 diabetes, incipient nephropathy, exercise, albuminuria, renal haemodynamics, glomerular filtration rate, blood pressure, working capacity.

The exercise provocative test was introduced for detection of early changes in diabetic renal disease by Mogensen and co-workers in the early 1970s [1]. Specifically, moderate physical exercise could cause increased urinary albumin excretion ($U_{alb}V$) in patients with Type 1 (insulin-dependent) diabetes, who had normal levels of $U_{alb}V$ in the resting basal state. Their observations were confirmed by others [2], but were also subject to criticism [3, 4]. Recently, the relative increase in $U_{alb}V$ during exercise was found to be equal in patients with either normal or elevated baseline $U_{alb}V$ [5]. This observation indicated that minor abnormalities in the glomerular handling of albumin might already be recognisable at rest. The discrepancies between the observations in these previous studies cannot readily be explained, but differences in the way the exercise test was administered and in the composition of the study groups make comparisons difficult.

The mechanism underlying exercise induced albuminuria is unknown. The glomerular filtration rate (GFR), the renal plasma flow (RPF) and the filtration fraction are signifcantly elevated in diabetic patients from the time of diagnosis compared with normal subjects [6-9]. It has been speculated that a further exaggeration of the abnormal renal haemodynamics may be responsible for the exercise-induced increase in $U_{alb}V$ [10]. Furthermore, a positive correlation between exercise-induced systolic pressure and exercise-induced $U_{alb}V$ has been demonstrated [5].

Thus the exercise test may be of importance as a diagnostic test as well as a tool for investigating systemic

Table 1. Clinical characteristics of the study groups

	Age (years)	Height (cm)	Weight (kg)	Serum-creatinine (μmol/l)	Diabetes duration (years)	HbA_{1c} (%)	Beat-to-beat variation (per min)	Retinopathy[a]
Normal subjects ($n=10$)	35± 8 (28–53)	180± 6 (169–187)	71± 6 (64–83)	91± 10 (85–111)	–	–	–	–
Diabetic patients with urinary albumin excretion < 15 μg/min (Group 1) ($n=16$)	32± 6 (19–40)	178± 5 (177–188)	75± 7 (71–89)	88± 10 (77–108)	13± 6 (6–24)	8.4± 1.4 (6.0–11.0)	19± 8 (3–38)	7/9/0
Diabetic patients with urinary albumin excretion > 15 μg/min (Group 2) ($n=14$)	33± 7 (20–47)	178± 6 (171–185)	72± 7 (57–80)	88± 10 (77–105)	16± 3 (10–22)	8.7± 1.3 (6.7–11.3)	18±10 (4–33)	5/9/0

Values given as mean ± SD with range in parenthesis. No significant differences between the groups.
[a] < 3 microaneurisms/simplex retinopathy/proliferative retinopathy

and renal haemodynamic abnormalities in early diabetic renal diseases.

The present study was undertaken to re-evaluate the albuminuric response to exercise in Type 1 diabetic patients with normal and elevated $U_{alb}V$ compared with normal subjects. Systemic and renal haemodynamics were also studied.

Subjects and methods

Patient recruitment and selection

Thirty adult male Type 1 diabetic patients were studied. Ten age matched non-diabetic males served as controls. The patients were chosen on the basis of duration of diabetes (5–25 years), Albustix-negative urine, normal serum creatinine level, and negative urine culture. All patients gave informed consent for their participation, and the study was approved by the Regional Medical Ethics Committee.

The patients were subdivided into two groups according to their level of albuminuria, identified on the basis of the mean $U_{alb}V$ in three 24-h urine collections performed at home during normal activity. This was done to take into account the large (50%) coefficient of variation of the 24-h urinary albumin excretion rate ($U_{alb}V$) [11, 12]. Sixteen patients formed group 1 and were defined as normoalbuminuric, with a $U_{alb}V$ of < 15 μg/min. The 14 patients in group 2 were characterized by elevated $U_{alb}V$ with the mean $U_{alb}V$ of three 24-h urine samples ranging from 15–122 μg/min; 12 of these patients were in the lower range of microalbuminuria with $U_{alb}V < 60$ μg/min. The distribution of $U_{alb}V$ in 24-h urine samples of 239 normal subjects is skewed (median 6.1, 95% percentiles: 1.1–24 μg/min) [13]. The chosen level of 15 μg/min is the same as used recently by Christensen [5], slightly above the level used by Viberti et al. [2], but consistent with a previously suggested definition of incipient nephropathy [14]. Patient and control data are shown in Table 1. The groups were well matched for age, weight, height, and serum creatinine. The two diabetic groups did not differ significantly with regard to duration of disease, level of metabolic control, and degree of diabetic complications.

The exercise protocol

The exercise protocol of Mogensen et al. [14] was used for these studies. The patients reported to the exercise laboratory at 08.00 h in the fasting state, the most recent insulin dose having been given before supper the previous evening. Alcohol and tobacco were proscribed for at least 12 h before the study. A cannula was inserted into an antecubital vein in each arm. After careful attention to the achievement of steady state water diuresis [15], two basal timed urine specimens (20 min each) were collected. The patient was exercised at 450 kpm/min (W 450), and then at 600 kpm/min (W600) for 20 min; a timed urine was obtained at the end of each period. Two post-exercise recovery periods of 20 min were each accompanied by urine collections. The patients sat in chairs except when voiding or exercising. The exercise load was performed on a mechanically braked electronically controlled ergometercycle (Monark, model 669-1, Varberg, Sweden).

Systemic haemodynamics

The blood pressure was measured by the indirect auscultatory method, using a sphygmomanometer and cuff. The blood pressure was measured twice in the middle of each period, and also after 15 min of exercise at each of the two work loads. During exercise the diastolic pressure as assessed by this method is not reliable [16] and is therefore not reported. The heart rate was recorded from surface electrodes, and the mean heart rate in 20-s periods was calculated.

Renal haemodynamic measurements

The GFR was measured by the classical constant infusion technique with urinary collections [17] using ^{125}I-iothalamate as the filtration marker [18]. The results were corrected to a body surface area of 1.73 m^2. The intra-assay coefficient of variation in our laboratory was 4.1%. The RPF was defined as the extraction of hippuran, using ^{131}I-hippuran [18]. This has been shown to be a reliable technique for renal plasma flow, even during exercise [19]. These results were also corrected to a body surface area of 1.73 m^2. The intra-assay coefficient of variation was 4.3%. The filtration fraction was calculated as GFR/RPF.

Maximal working capacity

The maximal working capacity was determined at the end of the formal exercise study, approximately 60 min after completion of the 600 kpm/min work load. The patients were allowed 5 min to warm up at a work load of 450–600 kpm/min. The work load was then increased stepwise until the patient became exhausted. Each work load was maintained for 2 min, or until the heart rate was stable in consecutive 20-s periods. At high work loads, this procedure ensures the achievement of steady state conditions, and a good correlation between heart rate and oxygen uptake [20]. The work load at which maximal oxygen uptake will occur ($W_{max}O_2$) was calculated from the following equation:

$$W_{max}O_2 = W\,600 \times \frac{\text{maximal heart rate - basal heart rate}}{\text{heart rate at 600 kpm/min - basal heart rate}}$$

Table 2. Urinary albumin excretion rate in the three groups in 24-h urine and during water diuresis before and after exercise

Patient no.	Normal subjects				Group 1 (albumin excretion < 15 μg/min)					Group 2 (albumin excretion ≥ 15 μg/min)				
	Basal[a] (μg/min)	Exercise[c] (μg/min)	Change during exercise[d] (μg/min)	Relative change (%)	24-h urine[b] (μg/min)	Basal[a] (μg/min	Exercise[c] (μg/min)	Change during exercise[d] (μg/min)	Relative change (%)	24-h urine[b] (μg/min)	Basal[a] (μg/min)	Exercise[c] (μg/min)	Change during exercise[d] (μg/min)	Relative change (%)
1	3.0	4.8	1.8	60	5	6.7	4.5	−1.2	−18	15	18.1	38.5	20.4	113
2	3.4	4.4	1.0	29	6	4.0	7.0	3.0	75	19	34.5	70.0	35.5	103
3	3.8	6.2	2.4	63	6	2.9	4.3	1.4	48	21	31.0	29.0	−2.0	−6
4	4.6	5.4	0.8	17	7	2.6	7.8	5.2	200	22	15.6	27.3	11.7	75
5	5.7	9.1	3.4	60	7	3.5	4.7	1.2	34	23	9.7	18.4	8.7	90
6	6.2	13.1	6.9	111	7	11.8	8.8	−3.0	−25	23	30.6	55.0	24.4	80
7	6.3	5.6	−0.7	−11	7	4.9	8.6	3.7	76	27	25.5	59.0	33.5	131
8	6.3	7.5	1.2	19	8	4.1	5.0	0.9	22	39	39.5	112.0	72.5	184
9	8.7	15.6	6.9	79	11	7.9	13.9	6.0	76	49	59.5	139.0	83.5	140
10	8.7	12.3	3.6	41	11	6.3	8.7	2.4	38	53	65.5	180.0	114.5	175
11					12	7.5	9.2	1.7	23	56	58.5	280.0	221.5	379
12					12	6.0	6.8	0.8	13	57	33.5	139.0	105.5	315
13					12	9.4	18.9	9.5	101	99	150.5	252.0	101.5	67
14					12	9.1	15.0	5.9	65	122	105.0	182.0	77.0	73
15					13	4.3	11.6	7.3	155					
16					14	3.6	11.4	7.8	22					
Mean ± SEM	5.7 ± 0.6	8.4 ± 1.3	2.7 ± 0.8	47 ± 11	9.0 ± 0.7	5.9 ± 0.7	9.1 ± 1.0	3.8 ± 0.7	57 ± 15	44.6 ± 8.5	48.4 ± 10.3	113 ± 22.8	65.2 ± 15.9	137 ± 27

[a] Urinary albumin excretion, mean of the two pre-exercise periods; [b] urinary albumin excretion, mean of three 24-h outpatient urine collections; [c] maximum urinary albumin excretion either during exercise or in the post-exercise period; [d] urinary albumin excretion provoked by exercise (maximum minus basal)

Laboratory measurements

HbA_{1c} was measured by a chromatographic technique [21]; values for the non-diabetic for this procedure are 4.1%-6.4%. *Urinary albumin* was measured by radioimmunoassay [22]. *Beat-to-beat variation* was assessed according to Ewing and Clark [23]. *Classification of retinopathy* was done on the basis of ophthalmoscopy through the dilated pupil.

Statistical methods

Albumin data were $\log_{10}$ transformed and then, as with the systemic and renal haemodynamic results, analyzed using the paired and unpaired t-test (two tailed). A linear regression analysis was used to examine correlations.

Results

Baseline data

All values presented represent the mean of two preexercise basal periods. The patients had been characterized according to $U_{alb}V$ levels in 24-h urine collections. This value correlated with $U_{alb}V$ during water diuresis on the day of study ($r = 0.93$, $y = -3.0 + 1.1x$). In consequence, the albuminuric levels in the two groups were confirmed except for patient 5, group 2, found to be excreting 10 μg/min at the time of the study (Table 2). The basal heart rate in group 1 was elevated compared with the normal subjects ($p < 0.02$). The heart rate in group 2 was between the other two groups and statistically indistinguishable (Table 3). The systolic blood pressure in group 2 was significantly elevated compared with the control group (Table 3).

The GFR values at rest are shown in Figure 1. The GFR was elevated in both diabetic groups compared with the normal subjects. The GFR in the normoalbuminuric group was significantly above that seen in the microalbuminuric group (138 ± 15 versus 123 ± 19 ml/min per 1.73 m^2, $p < 0.05$). The three patients in group 2 with the lowest GFR values had mean 24-h $U_{alb}V$ levels of 19, 54, and 27 μg/min. These patients and the three group 1 patients with the lowest GFR values all had autonomic neuropathy (beat-to-beat variations < 15 per min), but were in better metabolic control compared with the other patients (all six patients had HbA_{1c} levels < 8.3%). The RPF values differed between groups 1 and 2 (603 ± 61 versus 543 ± 74 ml/min per 1.73 m^2, $p < 0.05$); the calculated filtration fraction (GFR/RPF) was similar in the two groups.

Systemic haemodynamic response to exercise

Five of the diabetic patients, four in group 1 and one in group 2, failed to initiate voiding within the first minute after the 600 kpm/min workload. Since urine albumin excretion is high in both the exercise void and the first post exercise urine, $U_{alb}V$ is not very sensitive to this delay. On the other hand, renal haemodynamics change

Table 3. Basal clinical data and data on maximum working capacity test

	Age (years)	Diabetes duration (years)	Heart rate		Basal Blood Pressure		Maximum work load (kpm/min)	$W_{max}O_2$ (kpm/min)
			basal (beats/min)	maximal (beats/min)	systolic (mmHg)	diastolic (mmHg)		
Normal subjects ($n=10$)	35±8	-	58±7	176±15	119±9	81±6	1501±234	1267±264
Diabetic patients with urinary albumin excretion <15 µg/min (Group 1) ($n=12$)	31±7	11±4[c]	70±8[a]	177±12	126±9	85±7	1352±127[a]	1163±200
Diabetic patients with urinary albumin excretion ⩾15 µg/min (Group 2) ($n=13$)	34±7	16±3[c]	64±12	162±12[c b]	132±13	82±8	1162±322[b]	949±949[c b]

Values given as mean ± SD. Differences between groups considered significant when $p<0.05$ (two tailed).
[a] Significant differences between normal subjects and group 1; [b] significant differences between normal subjects and group 2; [c] significant differences between group 1 and group 2
This table includes normal subjects and the 25 patients who completed the renal haemodynamic study (five patients are missing (compare Tables 1 and 2) as explained in the text)

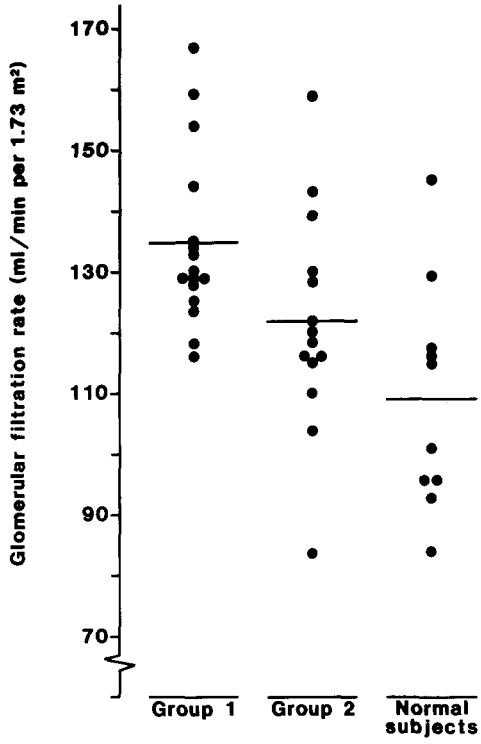

Fig. 1. Basal glomerular filtration rate in young Type 1 diabetic patients with (group 1, $n=14$) and without (group 2, $n=16$) microalbuminuria (urinary albumin excretion rate > 15 µg/min), and in healthy subjects ($n=10$). Horizontal bars indicate mean values. Difference between group 1 and group 2, $p<0.05$. Difference between normal subjects and group 2, $p<0.05$

rapidly. These measurements are dependent on a close time relationship between exercise and urine collections. Therefore, patient 5, 9, 11, and 13 in group 1 and patient 3 in group 2 (Table 2) were excluded from the analyses of the renal haemodynamics during exercise. The duration of diabetes of these patients was slightly longer (10-24 years). They did not differ with regard to the other variables, nor with regard to metabolic control during exercise.

During exercise, blood glucose levels were basically unchanged, between the diabetic groups (Table 4). Two patients vomited before exercise due to excess water load. They had no ketonuria and felt comfortable enough to continue the test.

Urine flow was very similar in the three groups at rest, but was significantly reduced during exercise in all three groups ($p<0.01$). There was no difference between the two diabetic groups (Table 4).

When tested for maximal working capacity, the microalbuminuric group achieved a maximal heart rate of 162±12 beats/min ($p<0.05$) lower than seen in the normoalbuminuric group (177±12) or the non-diabetic subjects (176±15). However, the fixed work load of 600 km/min represented a significantly greater stress for the patients in group 2 (Table 5). The actual maximal work load performed by group 2 was 1162± 322 kpm/min, which was significantly lower than seen in normal subjects (1501±234, $p<0.05$). In this instance, group 1 (1352±127 kpm/min) was also significantly different from normal, but calculation of $W_{max}O_2$, a more reliable indicator of maximal working capacity, revealed that group 2 (949±249 kpm/min) was significantly lower than both group 1 (1163±200) and the control subjects (1267±264); the differenze between group 1 and non-diabetic subjects was no longer significant (Table 3).

During the exercise provocative test, the 600 kpm/min workload elicited almost identical heart rates (126±17, 127±21 beats/min) and systemic blood pressures 164±12, 167±17 mmHg) in groups 1 and 2, respectively. These values were not significantly higher, than those obeobserved in normal subjects (115±10 beats/min, 155±17 mmHg).

Furthermore, the changes in heart rate and systolic blood pressure were similar for all groups (Table 5).

Table 4. Urine flow and blood glucose concentrations before and during exercise

	Urine flow (ml/min)		Blood glucose (mmol/l)		
	Resting	600 kpm/min	Resting	at 600 kpm/min	Post-exercise
Normal subjects ($n=10$)	12.0±3.6	8.0±3.4	-	-	-
Diabetic patients with urinary albumin excretion <15 μg/min (Group 1) ($n=12$)	11.3±4.6	5.6±3.2	12.9±3.0	13.9±2.6	14.1±2.8
Diabetic patients with urinary albumin excretion ≥15 μg/min (Group 2) ($n=13$)	10.8±1.5	5.4±2.9	14.8±3.5	15.6±3.9	15.6±4.1

Table 5. Systemic and renal haemodynamic responses to exercise (600 kpm/min)

	Urinary albumin excretion basal ($U_{alb}V$) (μg/min)	Δ $U_{alb}V$ (μg/min)	600 kpm/min as relative work load (%)	Δ Heart rate (beats/min)	Δ Systolic blood pressure (mmHg)	Δ GFR (%)	Δ RPF (%)	Δ Filtration fraction(%)
Normal subjects ($n=10$)	5.7±2.0	2.8±2.5	49±11	57±9	36±12	12±12	27±12	19±9
Diabetic patients with urinary albumin excretion <15 μg/min (Group 1) ($n=12$)	5.5±2.7	2.9±3.3	53±11	56±16	38±12	18±10	34±11	25±14
Diabetic patients with urinary albumin excretion ≥15 μg/min (Group 2) ($n=13$)	49.7±39.7[a b]	70±59[a b]	68±20[a b]	62±15	36±13	21±9[a]	36±9[a]	28±7[a]

Values given as mean ± SD. Differences between groups considered significant when $p<0.05$ (two tailed).
[a] Significant differences between normal subjects and group 2; [b] significant differences between group 1 and group 2

Albuminuric response

The $U_{alb}V$ seen after exercise provocation was the same in group 1 as in the normal group (Table 2, $p<0.01$). In group 2 the abnormal basal $U_{alb}V$ was further exacerbated by exercise. Both maximum $U_{alb}V$ and absolute as well as relative change in $U_{alb}V$ provoked by exercise were higher in this group compared with either of the other two groups ($p<0.01$). A significant correlation was found between the basal $U_{alb}V$ and exercise-induced increase in $U_{alb}V$ in group 2 ($r=0.89$, $p<0.001$).

Renal haemodynamic response

The renal haemodynamic changes during exercise were qualitatively similar for the three groups (Fig. 2). The percentage reduction in GFR and RPF was greater in the diabetic groups, especially in group 2, where it reached statistical significance ($p<0.05$, Table 5). This corresponds to the higher relative work load represented by 600 kpm/min in this group (68±20% of maximum work capacity) when compared with group 1 (53±11%) or normal subjects (49±11%) (Table 5). This relationship (Δ GFR and Δ RFP versus 600 kpm as a relative work load) appeared to be consistent, although it could not be expressed as a liniear correlation.

As previously noted, the filtration fraction in the basal state was slightly elevated in the diabetic group, but not significantly so when compared with the normal subjects. During exercise, however, the filtration fraction seen in the diabetic patients was significantly higher than that recorded for the non-diabetic control subjects (0.292±0.02 versus 0.260±0.012, $p<0.03$). The filtration fraction for group 2 (0.294±0.02) was virtually identical to that seen in group 1 (0.290±0.03), despite the large difference between the two groups in the absolute and relative changes in the urinary albumin excretion rate (Δ $U_{alb}V$) provoked by exercise (Tables 2 and 5).

No significant correlations were found between the Δ $U_{alb}V$ and any of the renal haemodynamic variables. There was also no correlation between Δ $U_{alb}V$ and Δ blood pressure. The only significant correlation between systemic and renal haemodynamic changes was found in the Δ blood pressure and Δ RPF in group 2 ($r=0.66$, $p<0.05$).

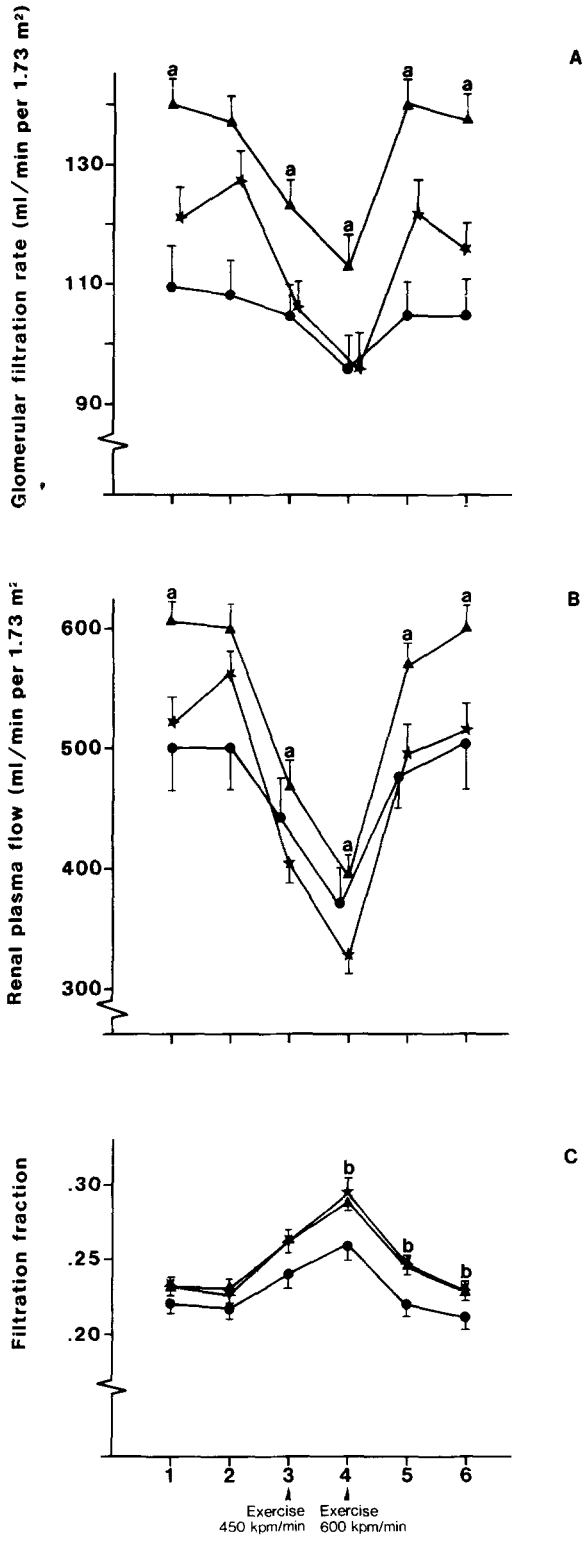

Fig. 2. **A** Glomerular filtration rate. **B** Renal plasmaflow and **C** filtration fraction before, during and after physical exercise in young Type 1 diabetic patients and normal subjects (mean ± SEM). On the horizontal axis 20-min periods are marked. ● Normal subjects ($n = 10$). ▲ Diabetic patients with normal urinary albumin excretion < 15 μg/min (group 1, $n = 12$). ✶ Diabetic patients with urinary albumin excretion ⩾ 15 μg/min (group 2, $n = 13$). [a] Difference between group 1 and group 2 ($p < 0.05$), [b] Difference between normals and group 1 as well as group 2 ($p < 0.05$). **A** Group 1 and the normal subjects differ significantly throughout the test ($p < 0.05$). **B** No significant difference between normal subjects and group 2

Discussion

The data in this study indicate that those diabetic patients who demonstrate a $U_{alb}V$ which is normal (< 15 μg/min) respond to exercise with an increase in $U_{alb}V$ which is not significantly different from that seen in non-diabetic individuals. Normal subjects have often been reported not to increase $U_{alb}V$ at this exercise level [1, 2, 5]. This may be due to differences in the interpretation of the exercise induced $U_{alb}V$.

The maximal $U_{alb}V$ may occur when patients are resting during the first post-exercise periods, as well as immediately following the 600 kpm/min workload. We have reported the highest value obtained in any of these periods. If this procedure is applied to the data in the study by Viberti et al. [2], his normal subjects also increased $U_{alb}V$ significantly. Data are not available for the other studies cited. The reason why maximal $U_{alb}V$ may occur in the post-exercise period is unknown. It could be speculated that some of the albumin filtered in excess during exercise (when urine production is low) is retained in the tubular system and then washed out, when urine production is rapidly increased following exercise. A washout phenomenon is described during the initiation of water-diuresis in the resting state [15]. Exercise did appear to exaggerate further albuminuria in patients who already were known to demonstrate an increased $U_{alb}V$ during basal conditions, thus confirming the work of Christensen [5]. However, even in this group some of the patients demonstrated a very modest increase in $U_{alb}V$, not distinguishable from the increase observed in group 1. Thus group 2 patients, who from several studies [24, 25, 26, 27] are known to be at high risk for the later development of overt diabetic nephropathy, in many cases have a "normal" albuminuric response to exercise. The diagnostic value of an abnormal response among group 1 patients would, on these grounds, be difficult to interpret. We therefore believe that this laborious test has no place in diagnosing early diabetic renal disease. However, our results indicate that exercise is an interesting tool. Group 2 had a significantly higher maximal $U_{alb}V$ compared with the other groups, both in absolute and relative terms. Christensen [5] found no difference in the relative increase of $U_{alb}V$ between patients with normal and elevated $U_{alb}V$. We cannot offer any explanation for this discrepancy, but the renal disease in his patients was more advanced, as judged from their basal $U_{alb}V$ levels.

The difference in the response to exercise observed in our study between the two diabetic groups might be explained by the fact that the fixed work-load of 600 kpm/min constituted a greater fraction of the maximal working capacity in group 2 patients. The 600 kpm/min work-load therefore represented a significantly greater stress for them. However, the difference in working capacity was not reflected in a differential increase in heart rate or systolic blood pressure. On the contrary, the systemic haemodynamic response to exercise was

similar in both diabetic groups (Table 5). It might be speculated that this indicated impaired sympathetic outflow in the group 2 patients, but the only objective data regarding this issue demonstrate no differences between the diabetic groups in beat-to-beat variation.

The renal haemodynamic responses to exercise was similar in the two diabetic groups. The somewhat larger changes in GFR and RPF in group 2 did reach statistical significance when compared with the normal control group, and probably reflect the greater relative work-load experienced by these patients. Mogensen and colleagues found that diabetic patients who demonstrated a significant increase in $U_{alb}V$ upon exercise provocation had a filtration fraction which was significantly elevated when compared with non-diabetic subjects [10]. The data presented here confirm that the filtration fraction during exercise in the diabetic subjects was significantly above that found in normal subjects. However, despite the enormous difference between groups 1 and 2 in terms of the functional consequences of exercise ($\Delta U_{alb}V$), the filtration fraction in these two groups at 600 kpm/min was nearly identical. If the elevation during exercise of the filtration fraction can reasonably be interpreted as representing an increase in transglomerular pressure, then these data indicate that an elevation of transglomerular hydraulic pressure to the levels achieved at 600 kpm/min will only be followed by a significant increase in $U_{alb}V$ when the glomerular membrane has already demonstrated impaired properties of permeability (i.e. an elevated basal $U_{alb}V$). The fact that the two diabetic groups had levels of filtration fractions which were nearly identical, both in the basal state and with exercise, also indicates that the increase in $U_{alb}V$ seen in diabetic patients with incipient nephropathy is not dependent on a transglomerular pressure which is increased above that seen in patients with normal rates of albumin excretion. The elevation of the filtration fraction during exercise (or during normal daily activity) may play an important role in the progression of diabetic nephropathy in those patients who already demonstrate abnormalities in the glomerular handling of albumin. This would be in agreement with the observations of Parving et al. [28] and Mogensen [29]. They were able to lower $U_{alb}V$ in patients with diabetic nephropathy who were aggressively treated for hypertension. In these patients renal autoregulation is impaired [30]. Therefore it is likely that a lowered systemic blood pressure is also accompanied by reduced transglomerular pressure resulting in reduced $U_{alb}V$.

The state of diabetic renal disease preceding overt nephropathy has been termed "incipient nephropathy" [14]. It is characterized by an elevation of basal $U_{alb}V$ at a time when the serum creatinine level is normal and the Albustixtest for urinary protein is negative. Retrospective studies suggest that these patients are at a much higher risk for developing full-blown clinical nephropathy than subjects whose basal $U_{alb}V$ is normal [24–27]. Our data extend these observations further and suggest that patients with incipient nephropathy may be different from age- and duration-matched diabetic patients with normal $U_{alb}V$ in several important aspects other than the rate of albumin excretion. The patients in this study with incipient nephropathy had a significantly lower maximum working capacity, and a significnatly elevated basal systolic blood pressure when compared with normal subjects. This observation concerning the significant elevation of blood pressure (while still within the normal range) corroborates our findings in a previous cross-sectional study [25] and those of Wiseman et al. [31]. In addition, the levels of GFR and RPF in these microalbuminuric patients were significantly lower than those observed in those with a normal $U_{alb}V$, even though the levels were still elevated when compared with controls. This difference could not be explained on the basis of sex, age, height, weight, duration of diabetes, degree of diabetic control, or presence of other diabetic complications. Patients with normoalbuminuria under the usual insulin treatment programs demonstrated an elevated GFR [6–9]; patients with early overt diabetic nephropathy (persistent proteinuria > 0.5 g/24 h, but normal serum creatinine concentration) generally have normal GFR values [28, 29]. If hyperfiltration is a primary factor in the initiation of diabetic nephropathy as suggested by others [32, 33], then the data presented here suggest that a change in renal function (from hyperfiltration to normal rates of filtration to deterioration) may occur as the patient passes across an important threshold into the stage of incipient nephropathy characterized by persistent microalbuminuria. This finding is different from what has been previously reported. In our own cross sectional study of the GFR of a smaller group of patients [25], no significant difference was observed when comparing patients with normal $U_{alb}V$ versus those with microalbuminuria. Wiseman et al. [31] also found that the GFR of patients with microabluminuria was not significantly different from that observed in patients with normal rates of urinary albumin excretion, although the mean values was lower. This difference in results might be due to the more rigorous approach (mean $U_{alb}V$ of three 24-h urine collections) used in this study to classify patients into groups with normal or elevated $U_{alb}V$. In planning future studies to confirm this important observation it would seem prudent to categorize patients only on the basis of several (at least three) 24-h urine collections over a period of 1–3 months. Patients who demonstrate persistent microalbuminuria under these conditions should be used in prospective studies to trace the true natural history of incipient nephropathy.

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