Decreasing glomerular filtration rate—an indicator of more advanced diabetic glomerulopathy in the early course of microalbuminuria in IDDM adolescents?

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Abstract

Background. Overt diabetic nephropathy is accompanied by a progressive decline in glomerular filtration rate (GFR). In this study we have investigated if a reduction of GFR already during the transition from normo- to microalbuminuria is associated with glomerular structural changes.

Methods. Seventeen adolescents (11 girls/6 boys) with 10.5 (3.3) (mean, SD) years of IDDM were studied. GFR was previously measured in the normoalbuminuric stage 2–5 years prior to the renal biopsy, and measured again at the time for the biopsy, after in mean 1.8 years of microalbuminuria (15–200 μg/min). HbAlc and albumin excretion rate were measured 3 or 4 times yearly and blood pressure 1–4 times yearly between the GFR examinations. The associations between the yearly rate of fall in GFR and basement membrane (BM) thickness, mesangial and matrix volume fractions, matrix star volume, mean capillary diameter (CAPD), area of filtration surface (peripheral BM per glomerulus, total capillary length per glomerulus, the ratio of peripheral BM to capillary surface, glomerular volume, and interstitial volume fraction were analysed.

Results. BM thickness and matrix star volume were increased in patients with, as compared to those without, a decline in GFR ≥ 6 ml/min per year (P < 0.005 respectively). Patients with previous glomerular hyperfiltration (≥ 135 ml/min per 1.73 m²) showed the steepest decline in GFR; 11 ml/min per year versus −0.8 ml/min per year in previously normofiltering patients, P < 0.001. The rate of fall in GFR was positively correlated to BM thickness (P < 0.001), interstitial volume fraction (P = 0.02) and CAPD (P = 0.04), mean HbAlc (P = 0.01), but not to the change in HbAlc between GFR examinations.

Conclusion. A decreasing glomerular filtration rate in the early stage of microalbuminuria may be due to more advanced diabetic glomerulopathy than in IDDM patients with stable GFR.

Key words: basement membrane thickness; diabetic glomerulopathy; glomerular filtration rate; mesangial matrix; microalbuminuria; renal interstitium

Introduction

The relative importance of sustained glomerular hyperfiltration on the development of diabetic nephropathy is under debate [1–5]. In an 8-year prospective study we previously reported elevated glomerular filtration rate (GFR) to be an independent predictor of the development of micro- and macroalbuminuria in adolescents with IDDM [1]. In diabetic rats increased GFR, in association with elevated intraglomerular pressure, was positively related to subsequent glomerulosclerosis [6,7]. No such results are available in humans. However, we have recently found that glomerular hyperfiltration, preceding the onset of microalbuminuria, adds to the prediction of the degree of morphometric glomerular changes in adolescents with IDDM and low-grade microalbuminuria [8]. In contrast, an inverse correlation between current GFR and glomerular structural quantities was previously reported in IDDM subjects within the microalbuminuric range [9]. Although it has been generally observed that GFR does not start to decline before the onset of macroalbuminuria, i.e. when albumin excretion (AER) is > 200 μg/min) [10], it was suggested that such an inverse relationship between GFR and morphological changes may indicate that the microalbuminuric patients with the most advanced structural changes have already started to decline in GFR [9].

Taken together, this challenged us to explore whether a reversed glomerular hyperfiltration may be an expression of more progressed diabetic glomerulopathy, already in the early stage of microalbuminuria.
Subjects and methods

Subjects

Seventeen adolescents (11 girls, 6 boys), ≥15 years old with >5 years of IDDM and with microalbuminuria, initially recruited for a long-term trial comparing the effect of enalapril and metoprolol on structural glomerular changes, were included in the present study. A previous examination of glomerular filtration rate (GFR) was performed in all study participants prior to onset of microalbuminuria. Microalbuminuria was defined as albumin excretion rate (AER) 15–200 μg/min in at least 2/3 consecutive overnight urine samples. Microalbuminuria was persistent for in mean 1.8 years at the time for the kidney biopsy. All patients had a prepubertal onset of IDDM.

In all patients signs of retinopathy were investigated by fundus photography within 1 year prior to the renal biopsy. Simplex retinopathy, defined as one or more microaneurysms or haemorrhages, was seen in 12 subjects. One patient had proliferative changes.

No patient was on antihypertensive treatment, low-protein diet, or insulin pump treatment. At the time for the renal biopsy two patients had a diastolic (but not systolic) blood pressure >90th percentile for age and sex. Otherwise patients were normotensive. All subjects were on 4–5 daily insulin injections, with a mean daily insulin dose of 0.95 (0.17) U/kg. No patient had ketonuria at the time for the renal function investigations. Clinical data at the time for renal biopsy are presented in Table 1.

Procedure

An initial examination of GFR, HbAlc, blood glucose, AER, and systolic and diastolic blood pressure was performed in all while still normoalbuminuric, i.e. 2–5 (mean 3) years prior to the renal biopsy. HbAlc and AER were thereafter measured 3 or 4 times yearly, and blood pressure 1–4 times yearly. Measurements of GFR, HbAlc, blood glucose, AER and blood pressure were finally repeated at the time for the renal biopsy.

Ultrasound-guided transcutaneous kidney biopsies were taken using an automated biopsy device with an 18-gauge needle (PresicionCut® AB, Becton Dickinson and Co, New Jersey, USA). Tissue was fixed in 2% glutaraldehyde in modified Tyrode buffer and immediately mailed to the electron-microscopy laboratory in Arhus, where it was sectioned into smaller blocks, dehydrated, and embedded into epoxy.

Clinical and laboratory methods

The initial examination of GFR was carried out by $^{51}$Cr EDTA clearance (2uCi$^{51}$Cr/kg body weight) using two-compartment analysis. At follow up GFR, renal plasma flow (ERPF) and filtration fraction (FF) were measured using the continuous infusion technique of inulin (Inutest, Laevosan-Gesellschaft, Linz, Austria) [11] and $\text{p}$-aminohexane puric acid (PAH, Merck Sharp and Dohme, Rahway, New Jersey, USA) [12]. Patients were then orally hydrated with 20 ml/kg during 1 h and with 5 ml/kg body weight every 30 min during the clearance study, to obtain spontaneous micturition. No simultaneous comparisons between the two methods for analysis of GFR were performed in our laboratory in IDDM patients, but there was a close correlation ($r = 0.93, P < 0.001$) between the single inulin injection technique and the two-compartment analysis of $^{51}$CrEDTA clearance in healthy subjects [13]. Furthermore, in a subset of six patients included in the present study, both inulin (continuous infusion) and CrEDTA clearances were performed within a 6-month period. Among these only one patient was missclassified regarding glomerular hyperfiltration ($\geq 135$ ml/min). This patient showed a GFR $> 135$ ml/min by the use of inulin clearance but a GFR $< 135$ ml/min by the use of CrEDTA clearance.

Timed overnight AER was measured on fresh specimens by immunoturbidimetry [14]. Intra- and interassay coefficients were 3 and 4.7% respectively in the range 10–50 mg/l. Blood pressure measurements were performed by a conventional sphygmomanometer with a cuff of appropriate size, in the supine position after 5 min rest. Diastolic blood pressure was read at the disappearance of the Korotkoff sounds. HbAlc was analysed by HPLC (Auto-A, Kyotofuka, Kagaku, Kyoto, Japan). Reference levels were 4–6%.

Fasting blood glucose levels were determined by a glucose dehydrogenase method (Gluk-DH, Merck, Darmstadt, Germany)

Morphometric methods

Morphometric data were obtained by light- and electron-microscopy. Calculations were performed combining the estimates at three different levels of magnification [15].

\textit{Quantitation by light microscopy.} This was carried out after systematically sectioning of the tissue blocks. The first section of the block having full tissue was the baseline section. The block was then sectioned exhaustively in 1-μm thick sections. All sections were picked up on slides and stained with toluidine blue. Sections with 10-μm intervals were used to estimate the volume of new appearing glomeruli. In mean, 15 glomeruli were used for the estimation of glomerular volume and analysed by the Cavalieri’s method [15]. The areas of glomerular profiles, defined as the minimal circumscribed convex polygon (A), were measured by point counting at $390 \times$ magnification. A regular square grid with point

- **Table 1.** Clinical data on IDDM adolescents with microalbuminuria, and with (group 1) or without (group 2) an estimated decline in GFR $> 6$ ml/min per year during 2–5 years prior to renal biopsy. Mean (SD)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (f/m)</td>
<td>8/5</td>
<td>9/5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>19.7 (2.9)</td>
<td>18.4 (3.1)</td>
</tr>
<tr>
<td>Duration of IDDM (years)</td>
<td>9.9 (2.6)</td>
<td>11.1 (3.9)</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>24.9 (1.4)</td>
<td>24.0 (1.7)</td>
</tr>
<tr>
<td>Insulin dose (U/kg)</td>
<td>0.98 (0.19)</td>
<td>0.93 (0.15)</td>
</tr>
<tr>
<td>Current HbAlc (%)</td>
<td>9.5 (1.4)</td>
<td>8.3 (1.8)</td>
</tr>
<tr>
<td>Current systolic blood pressure (mmHg)</td>
<td>123 (8)</td>
<td>127 (24)</td>
</tr>
<tr>
<td>Current diastolic blood pressure (mmHg)</td>
<td>85 (6)</td>
<td>77 (11)</td>
</tr>
<tr>
<td>Current glomerular filtration rate (ml/min per 1.73 m$^2$)</td>
<td>119 (20)</td>
<td>125 (28)</td>
</tr>
<tr>
<td>Current effective renal plasma flow (ml/min per 1.73 m$^2$)</td>
<td>594 (75)</td>
<td>596 (111)</td>
</tr>
<tr>
<td>Current filtration fraction (%)</td>
<td>20.2 (2.0)</td>
<td>21.8 (3.1)</td>
</tr>
<tr>
<td>Current albumin excretion rate (μg/min) (geometric mean, 95% confidence interval)</td>
<td>50 (24–97)</td>
<td>32 (21–49)</td>
</tr>
<tr>
<td>Retinopathy (yes/no)</td>
<td>7/1</td>
<td>6/3</td>
</tr>
</tbody>
</table>
distance of 34 μm was used. Glomerular volume equals \( t \times \Sigma A \) where \( t \) is the distance between levels. To measure \( t \) in the individual biopsies in the individual blocks a notch was cut at the right-hand side of the tissue block at the start of sectioning, and the distance between sectioning plane and the bottom of the notch measured by counting 1 μm steps with the microtome. A repeat measure was done after having cut the block, and the average distance between levels was calculated as the difference between two measurements divided by the number of levels in between.

For measurement of interstitial volume fraction fields of vision were projected onto a computer screen attached to a Zeiss microscope at the magnification of \( \sim 700 \times \). A point grid with coarse and fine points (ratio 1:9) was projected by the computer to the screen. The distance of fine points corresponded to 50 μm. An independent position of the grid with respect to the visual field was ensured by moving the stage by step motors attached to the microscope. The point counting included coarse points hitting any cortex tissue, and fine points hitting interstitium, defined as the space in between tubular epithelial cells, outside Bowman’s capsule and outside larger blood vessels, including connecting tissue, capillaries, and cells. Further, fine points hitting glomeruli including Bowman’s capsule and larger blood vessels were not counted. The interstitium was expressed as volume fraction of tubular cortex, \( V_v \) (interstitium/tubular cortex), i.e. cortex tissue excluding glomeruli and larger blood vessels. The estimate was obtained by sum of points from five blocks of tissue.

**Quantitation by electron-microscopy.** Thin sections for electron-microscopy were cut with a random, independent position within new appearing glomeruli in the block. The levels for thin sectioning were predetermined to be at 50 μm and multiples thereof from the baseline section. In each new appearing glomerulus the first three levels were thin sectioned. **Low magnification.** At 2300 × magnification the entire glomerular profile was photographed. Micrographs were fitted together to produce photomontages, i.e. three complete cross-sections in each of three glomeruli. On the montages the following parameters were estimated, the volume fraction of mesangium to glomerulus (the circumscribed polygon) using a double grid (1:8) with a point distance between fine points of \( \sim 8 \) μm; the surface density of capillary walls; the peripheral basement membrane towards urinary space, and mesangial capillary interface. Surface density was estimated by intersection counting with test lines in the grid. \( S_v = 2 \times 1/P \) glomer × test line per P, where \( I \) is number of intersections between test lines and the trace of surface and \( P \) number of points hitting glomerular space. The ratio of intersections with individual interfaces gives directly the ratio between surface areas. Finally, the number of profiles of glomerular capillaries was counted for estimation of capillary length density, \( L_v = 2 \times Q/glomerular \) area, where \( Q \) is the number of profiles. An estimate of average capillary diameter was obtained from the ratio of \( S_v/L_v \), giving an average circumference. **High magnification.** From the largest of the three profiles in each glomerulus a subsample of the area (~24%) was photographed at a magnification of 9800 × (Figure 1). On the micrographs the basement membrane thickness (BMT) was estimated by orthogonal intercepts [16], and the matrix volume fraction within mesangium estimated with a 2:1 grid. Finally the matrix star volume was measured by classifying point sampled intercepts in a predetermined direction as described elsewhere [17].

**Statistical methods**

Comparisons between groups were performed by the unpaired Student’s \( t \) test. The Pearson correlation coefficients were calculated to estimate interrelations between variables. The estimated yearly rate of reduction in GFR was calculated as the change in GFR divided by number of years between the initial and follow-up examinations of GFR. Group division was arbitrarily based on an estimated rate of fall in GFR > 6 ml/min per year. This limit was chosen as a decline in GFR > 5.3 ml/min per year was recently reported in patients with nephropathy without antihypertensive treatment [18]. Due to a skewed distribution, AER values were log normalized prior to calculations. Results are presented as mean (SD) except for AER where geometric mean (95% confidence interval) is given. A \( P \) value ≤ 0.05 was considered statistically significant.

**Results**

**Renal structure and function, blood pressure and metabolic control in patients with and without a decline in glomerular filtration rate**

Patients were grouped according to a rate of fall in GFR ≥ 6 ml/min per year (group 1) or < 6 ml/min per year. Age, sex, duration of IDDM, current HbA1c, systolic and diastolic blood pressure, AER, GFR, and renal plasma flow and filtration fraction were similar between groups at the time for the renal biopsy. (Table 1).

Previous GFR was significantly higher in group 1 than in group 2, and all but one patient in group 1 was previously hyperfiltering, i.e. with a GFR > 135 ml/min per 1.73 m\(^2\) (Table 2). AER was...
similar between groups at the time for previous GFR measurement, whereas HbAlc was higher in group 1 (Table 2). Mean HbAlc between previous and current GFR was also higher in group 1, and so was mean diastolic, but not systolic, blood pressure (Table 3).

Baseline membrane thickness (BMT) and matrix star volume were significantly increased in group 1 as compared to group 2 (Table 4). Other morphometric measures, i.e. matrix [Vv(mat/glom); Vv(mat/mes)] and mesangial [Vv(mes/glom)] volume fractions, glomerular volume, Vv(interstitium/tubular cortex), mean capillary diameter (CAPD), surface area of peripheral BM per glomerulus (FS per glom), total capillary length per glomerulus (LCAP per glom) and the ratio of peripheral BM to capillary surface (SPBM/CAPS) did not differ between groups (Table 4).

Table 2. Previous glomerular filtration rate 2–5 years prior to renal biopsy and concomitant albumin excretion rate and HbAlc values in subjects with (group 1) and without (group 2) a decline in glomerular filtration rate ≥6 ml/min per year. Mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular filtration rate (ml/min per 1.73 m²)</td>
<td>152 (13)</td>
<td>122 (19)***</td>
</tr>
<tr>
<td>Albumin excretion rate (µg/min) (geometric mean, 95% confidence interval)</td>
<td>8 (4–13)</td>
<td>6 (2–10)</td>
</tr>
<tr>
<td>HbAlc (%)</td>
<td>10.2 (1.8)</td>
<td>8.3 (1.7)*</td>
</tr>
</tbody>
</table>

*P < 0.05, ***P < 0.001.

Table 3. Mean values of HbAlc, systolic and diastolic blood pressure between the two measurements of glomerular filtration rate (2–5 years) in patients with (group 1) and without (group 2) a decline in GFR ≥6 ml/min per year. Mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HbA1c</td>
<td>10.0 (0.9)</td>
<td>8.1 (0.9)**</td>
</tr>
<tr>
<td>Mean systolic blood pressure</td>
<td>121 (7)</td>
<td>118 (7)</td>
</tr>
<tr>
<td>Mean diastolic blood pressure</td>
<td>85 (6)</td>
<td>77 (5)**</td>
</tr>
</tbody>
</table>

**P = 0.01.

Table 4. Morphometric data in IDDM adolescents with (group 1) or without (group 2) a decline in GFR ≥6 ml/min per year during 2–5 years prior to renal biopsy. Mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMT (nm)</td>
<td>651 (119)</td>
<td>535 (77)*</td>
</tr>
<tr>
<td>Vv(Mat(mes)) (%)</td>
<td>55.6 (3.5)</td>
<td>54.1 (5.1)</td>
</tr>
<tr>
<td>Vv(Mat/glom) (%)</td>
<td>12.1 (4.1)</td>
<td>10.6 (1.9)</td>
</tr>
<tr>
<td>Vv(Mes/glom) (%)</td>
<td>21.8 (6.0)</td>
<td>19.7 (3.4)</td>
</tr>
<tr>
<td>Matrix star volume (µm³)</td>
<td>34.1 (7.0)</td>
<td>24.2 (10.0)*</td>
</tr>
<tr>
<td>CAPD (µm)</td>
<td>6.9 (1.8)</td>
<td>7.0 (0.8)</td>
</tr>
<tr>
<td>SPBM/CAPS (%)</td>
<td>68.4 (7.9)</td>
<td>73.6 (5.2)</td>
</tr>
<tr>
<td>FS per glom (mm²)</td>
<td>0.37 (0.14)</td>
<td>0.37 (0.11)</td>
</tr>
<tr>
<td>LCAP per glom (mm)</td>
<td>23.2 (8.7)</td>
<td>23.2 (7.3)</td>
</tr>
<tr>
<td>Glomerular volume (10⁶ µm³)</td>
<td>3.72 (1.15)</td>
<td>3.07 (0.83)</td>
</tr>
<tr>
<td>Vv(interstitium/tubular cortex) (%)</td>
<td>23 (4)</td>
<td>20 (3)</td>
</tr>
</tbody>
</table>

Fig. 2. Correlation between basement membrane thickness and the estimated yearly fall in glomerular filtration rate (r = 0.70, P < 0.001).

Discussion

A negative association between GFR and BMT earlier reported in IDDM patients with microalbuminuria, implicated that glomerular hyperfiltration may not be a risk factor for the development of diabetic nephropathy [9]. However, no such conclusion can be drawn based on cross-sectional data. An alternative explanation to this inverse correlation is that microalbuminuric patients with the most advanced glomerular structural changes are those who have already started to decline in GFR [9].

In the present study of microalbuminuric adolescents we found an inverse, albeit non-significant, association between current GFR and morphometric glomerular
changes. This lack of significance may be explained by the fact that most GFR values were concentrated within a narrow and normal range. On the other hand, there was a positive correlation between previous GFR in the normoalbuminuric stage, and BMT in the microalbuminuric stage. Furthermore, mainly patients with previous glomerular hyperfiltration exhibited a fall in GFR, and this decline seemed to be independent of a reduction in HbA1c. In fact, mean HbA1c during follow-up was highest in patients with the most pronounced decline in GFR. Taken together, this indicates that the resolution of glomerular hyperfiltration was not primarily due to improved metabolic control. In contrast, it suggests that a poor metabolic control may promote the decline in GFR already in the transitional stage from normo- to microalbuminuria.

Mean diastolic blood pressure was higher in patients with a decline in GFR and was correlated to the rate of fall in GFR. It cannot be excluded that an elevated blood pressure may have enhanced the rate of fall in GFR. This is in accordance with findings in hypertensive patients with established diabetic nephropathy, where long-term antihypertensive treatment may reduce the decline in GFR by >50% [19–21].

BM thickness, Vv(interstitium/tubular cortex), and mean capillary diameter were highly correlated to the rate of fall in GFR. Thus we hypothesise that resolved glomerular hyperfiltration may not necessarily reflect a ‘normalised’ GFR, but rather implicate a pathological loss of filtration capacity in patients with microalbuminuria.

Interstitial changes may be of greater importance than glomerular changes for the decline in renal function in IDDM. It has been suggested that changes in interstitial composition and interstitial pressure may profoundly influence the glomerular function [22]. This is most certainly the case in advanced diabetic nephropathy when interstitial expansion is extremely marked. Whether the much more subtle changes that we have described here may also influence the glomerular function by changing interstitial osmotic and hydraulic pressure cannot be determined. The observation of the association between the slight interstitial changes and the fall in GFR underlines the importance of taking all renal compartments into account when considering the clinical consequences of the structural changes in the kidney.

No evident physiological explanation to the positive correlation between the rate of fall in GFR and mean capillary diameter exists. It should be underlined that the average capillary diameter is not a precisely estimated measure, although the estimate with the present technique shows only a very small variation among cases. It may be speculated that a previous glomerular hyperfiltration, associated with a high intraglomerular pressure may result in an increased capillary diameter and that the elevated perfusion may stimulate extracellular matrix formation [23], promoting a decline in glomerular filtration. Whether the average diameter remains when perfusion declines is not known at all. Further, it may be speculated that the increased capillary diameter may be a consequence of an injured afferent arteriole being unable to protect the glomeruli from damage, provided the efferent arteriole is contracted. These arteriolar structural and functional changes may occur in parallel with the development of glomerulopathy.

The mechanism by which glomerular structural abnormalities may lead to functional derangements are unclear. The structural variable relevant to GFR is the total area of filtration surface in the kidney. Filtration surface has been used to denote the surface capillary—urinary interface. Loss of surface area of glomerular capillaries in advanced nephropathy, to a large extent dependent on glomerular occlusion, is likely to explain the decrease in GFR. Irrespective of the mesangial expansion which is prominent in advanced stages, the total filtration surface per open glomerulus is retained due to compensatory mechanisms [24]. Therefore, glomerular occlusion becomes the determinant factor. In our series, mesangial expansion was hardly detectable and glomerular occlusion is not prominent in this early phase. We did not find a correlation between GFR and filtration surface per glomerulus, which is probably due to the absence of extreme values in the present series. Thus we do not have a mechanistic explanation by size of filtration surface why the GFR has decreased in some patients.

It has earlier been found that a subgroup of IDDM patients may show a decline in renal function even without elevated AER [25]. Further, in a group of IDDM females with low creatinine clearance, diabetic glomerulopathy was evident also in the absence of microalbuminuria [26]. No association between sex and the degree of morphometric changes was seen in the present study. Chavers et al. [27] found that a part of microalbuminuric patients with a falling GFR and/or with hypertension had more progressed glomerular structural changes than patients with microalbuminuria only, which partly agrees with our findings. Despite a similar degree of low-grade microalbuminuria during the last year in most of our patients, a rather great variation in BM thickness was seen. This is somewhat compatible with earlier reports, indicating that already in the normoalbuminuric stage, glomerular structural changes have started to develop and may vary between individuals [27,28].

The circumstances that two different methods for measurements of GFR were used in the initial and the follow-up investigation, could have rendered the interpretation difficult regarding the decline in GFR. This would especially have been the case if the CrEDTA clearance tended to overestimate GFR as compared to the inulin clearance. A more marked decline in GFR than expected would then have been implicated. However, several studies have previously demonstrated that the clearance of CrEDTA underestimates GFR by approximately 5% as compared to that of a single injection of inulin [29–31]. Clinical experience also indicates that the continuous clearance of inulin tends to overestimate GFR as compared to the clearance of CrEDTA (Bo-Lennart Johansson, Department of
Clinical Physiology, Karolinska Hospital, Stockholm, personal communication). This was also the fact when comparing these two methods within a 6-month period in a subset of the patients in the present study. Thus, if anything, the true decline in GFR would be more, rather than less pronounced in the present study. Most important though, is probably the fact that the same method was used in all patients at the initial examination (i.e. clearance of CrEDTA) as also at follow-up (i.e. clearance of inulin).

In conclusion, the present data suggest that in adolescents with IDDM and with glomerular hyperfiltration in the normoalbuminuric stage, a decline in GFR, still not to subnormal limits, may be an expression of more advanced diabetic glomerulopathy in the early stage of microalbuminuria.

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