The effect of metabolic control on rate of decline in renal function in insulin-dependent diabetes mellitus with overt diabetic nephropathy

Henrik Mulec¹, Göran Blohme², Bo Grände¹ and Staffan Björck³

¹ Department of Nephrology, Northern Älvsborg County Hospital, Trollhättan; Departments of ² Internal Medicine, and ³ Nephrology, Sahlgrenska Hospital, University of Göteborg, Göteborg, Sweden

Abstract

Background. Strict glycaemic control has been shown to reduce the risk of developing diabetic nephropathy. However, the impact of glycaemic control on prognosis is less clear. Therefore we investigated the effect of long-term glycaemic control on the decline in renal function in insulin-dependent diabetic patients with overt nephropathy.

Methods. The study was performed at two hospital-based diabetes centres in western Sweden. The study was an observational retrospective follow-up study in 158 insulin-dependent diabetics with proteinuria with a mean (±SD) age of 36±9 years and a diabetes duration of 22±8 years. The change in glomerular filtration rate was measured as $^{51}$Cr EDTA clearance for a median of 8 years (range 1–17). Glycaemic control was determined with measurements of glycated haemoglobin $A_{1c}$.

Results. The decline in glomerular filtration rate was $3.8±3.7$ ml/min/year. The blood pressure was $143/82±15/7$ mmHg and the mean glycated haemoglobin was $8.7±1.6%$. The correlation coefficient between glycated haemoglobin and decline in glomerular filtration rate was $−0.39$ ($P<0.0001$) and between decline in glomerular filtration rate and systolic and diastolic blood pressure $−0.17$ ($P=0.03$) and $−0.29$ ($P=0.003$) respectively. In patients with glycated haemoglobin $<8.0%$ and diastolic blood pressure $<85$ mmHg the decline in glomerular filtration rate was $1.7±2.3$ ml/min/year.

Conclusions. In this retrospective observational study, effective blood-pressure control was associated with a low rate of decline in renal function and a low urinary albumin excretion. The correlation between glycaemic control and decline in renal function indicates that poor glycaemic control can accelerate the loss of renal function in diabetic nephropathy.

Key words: blood pressure; diabetic nephropathy; glomerular filtration rate; glycaemic control; insulin-dependent diabetes mellitus; renal failure

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collected overnight on three successive occasions. From the group of patients fulfilling one of these criteria, those whose glomerular filtration rate had been determined at least twice during a time period of at least 1 year were selected. Data was collected from the clinical records during the period from the first to the last glomerular filtration rate measurement, thus representing the period of change in renal function and follow-up period. The mean follow-up period was 8.0 ± 3.9 years (range 1–17).

One hundred and fifty-eight patients, 59 women and 104 men, were found. At entry the patients were 35.5 ± 9.0 years old, with a diabetes duration of 21.8 ± 8.0 years. Proliferative retinopathy was present in 78%, 63% had a smoking history, and 26% were smoking at the censoring date. All patients were on an ordinary diabetic diet without sodium or protein restriction. BMI at the end of the study was 23.3 ± 3.2 kg/m². Eighty per cent of the patients injected human insulin more than three times daily. The final insulin dose was 0.67 ± 0.2 U/kg body-weight daily. Self-monitoring of blood glucose was encouraged and all patients were instructed on how to adjust the insulin dose depending on the blood glucose result.

The glomerular filtration rate was determined as the plasma disappearance of 51Cr EDTA after a single injection [14]. Serum cholesterol and serum triglycerides were measured by routine automated methods. Data on cholesterol were missing for 22 patients and on triglycerides for 53. For each patient a mean of 8.5 cholesterol and 2.6 triglyceride measurements were made. Only urinary albumin excretion data, measured in timed overnight samples with an immunochemical turbidimetric assay, was used. Repeated urinary albumin excretion measurements were available for only 96 patients because of a change of methods.

Glycated haemoglobin was measured as haemoglobin A₁c (HbA₁c) using high-performance liquid chromatography with a mono S HR5/5 column (Pharmacia, Biotec). The correlation between samples analysed at the two hospitals was 0.99. The regression coefficient was 1.047 ± SEM 0.052. In the first 12% of 3876 samples, glycated haemoglobin was measured as haemoglobin A₁. To convert these haemoglobin A₁ values to haemoglobin A₁c for each patient, the last haemoglobin A₁ measurement was compared to the first haemoglobin A₁c value and a conversion formula was constructed using linear regression analysis.

Blood pressure was recorded in the supine position after frusemide. Calcium antagonists were used as third-line drugs. The final insulin dose was 0.67 ± 0.2 U/kg body-weight daily. Self-monitoring of blood glucose was encouraged and all patients were instructed on how to adjust the insulin dose depending on the blood glucose result.

Statistical analysis

Results are presented as means (SD) unless otherwise stated except for urinary albumin excretion, which is given as a geometric mean (antilog. 95% confidence interval of the logarithms). Values are means of the individual means when appropriate. Differences between groups were tested with the Mann–Whitney unpaired sample test because of a skewed distribution of rate of decline in GFR. The rate of decline in glomerular filtration rate over time was calculated by linear regression analysis for the entire follow-up period for each patient. To overcome an eventual problem with non-linearity in change in glomerular filtration rate over time, a renal end-point was defined as a fall in glomerular filtration rate of 40% during the observation period for each patient. This level was arbitrarily chosen to give a sufficient number of events during the follow-up period. The exact time for the end-point date was calculated from the surrounding two glomerular filtration rate measurements, assuming that the decline in glomerular filtration rate between these points was linear. Proportional hazard regression analysis was used to identify interactions between the renal end-point and clinical and laboratory characteristics. The occurrence of events in groups was estimated by the Kaplan–Meier product limit method and compared between groups by the Mantel–Cox log-rank test (Figure 3). Proportional hazards regression analysis was used to determine interactions between groups and covariates (Figure 2). Spearman’s rho was used for correlations with decline in glomerular filtration rate. Statview statistical software (Abacus concepts, Inc., Berkeley, California, USA) was used for calculations.

Results

The 158 patients were followed for 8.0 ± 3.9 years, which represents 1259 patient-years. The characteristics of the patients and results are summarized in Table 1.

The average decline in glomerular filtration rate over time was 3.8 ± 3.7 ml/min/year. The fall in glomerular filtration rate was greater for those with normal glomerular filtration rate (> 70 ml/min/1.73 m²) at entry than in those with reduced renal function (4.3 ± 3.9 vs 2.7 ± 2.9 ml/min/year respectively, P = 0.01). Glycated haemoglobin and blood pressure did not differ between these groups. The albumin excretion rate during follow-up was lower than that usually associated with diabetic nephropathy. In patients with reduced glomerular filtration rate it was 184 (97–347) µg/min and in those with normal glomerular filtration rate 167 (112–249) µg/min. Urinary albumin excretion was less than 200 µg/min in 53% of the patients. Nine patients had urinary albumin excretion below 20 µg/min; four of these had a reduced glomerular filtration rate at entry.

Antihypertensive treatment varied throughout the follow-up period and evaluation of the effect of different drugs was therefore not possible. Most (90%) of the patients were treated with an angiotensin-converting enzyme inhibitor, usually combined with frusemide. Calcium antagonists were used as third-line drugs.

The change in glomerular filtration rate was significantly correlated to glycated haemoglobin, systolic and diastolic blood pressure, urinary albumin excretion, baseline GFR, and insulin dose per kilogram

| Table 1. Clinical and laboratory results in 158 patients with diabetic nephropathy |
|---------------------------------|-----------------|
| Initial GFR (ml/min/1.73 m² BSA) | 82 ± 27         |
| HbA₁c (%)                       | 8.7 ± 1.6       |
| Systolic blood pressure, (mmHg) | 143 ± 15        |
| Diastolic blood pressure, (mmHg) | 82 ± 7         |
| Mean arterial blood pressure (mmHg) | 102 ± 8    |
| Serum cholesterol (mmol/l), (n = 141) | 6.3 ± 1.5   |
| Serum triglycerides (mmol/l), (n = 110) | 2.2 ± 1.8   |
| Urinary albumin excretion, (µg/min), (n = 96) | 172 (123–240)* |
| Change in GFR (ml/min/1.73 m² BSA/year) | −3.8 ± 3.7   |

Values are means of the individual means of all values for each patient.

*Geometric mean and 95% confidence interval.
Glycaemic control and progression of diabetic nephropathy

Table 2. Spearman’s rank correlation coefficients with rate of change in GFR for patients with diabetic nephropathy

<table>
<thead>
<tr>
<th></th>
<th>rho</th>
<th>P value</th>
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<tbody>
<tr>
<td>Haemoglobin A1c</td>
<td>−0.385</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>−0.29</td>
<td>0.0003</td>
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<tr>
<td>Albumin excretion</td>
<td>−0.276</td>
<td>0.007</td>
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<tr>
<td>Baseline GFR</td>
<td>−0.239</td>
<td>0.003</td>
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<tr>
<td>Insulin dose (per kg body-weight)</td>
<td>−0.21</td>
<td>0.011</td>
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<tr>
<td>Systolic blood pressure</td>
<td>−0.17</td>
<td>0.034</td>
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<tr>
<td>Serum triglycerides</td>
<td>−0.16</td>
<td>NS</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>−0.08</td>
<td>NS</td>
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NS, not significant.

Fig. 1. The mean (SEM) rate of decline in 158 patients with diabetic nephropathy divided into three equally sized groups depending on HbA1c. P=0.002 ANOVA difference between groups.

Fig. 2. Probability of progression to a 40% reduction in glomerular filtration rate in patients with diabetic nephropathy. The patients are divided in two equally sized groups according to HbA1c. The cut-off level became 8.6%. Thick line are patients with HbA1c above 8.6% and thin line patients with HbA1c below 8.6%. Number of patients at risk are given below graph. P=0.0005 for difference between groups.

Fig. 3. Risk of nephropathy progression (decline in glomerular filtration rate of 40%) for clinical and laboratory characteristics based on proportional hazards regression analysis. The relative risk of each risk factor (or specified increase) is shown with corresponding 95% confidence interval. A point on the left of the axis indicates a reduced risk while a point on the right side corresponds to an increased risk of progression.

Discussion

In this retrospective study, the rate of deterioration in renal function was found to be related to the degree of hyperglycaemia, measured as the mean level of glycated haemoglobin during the follow-up period of 1–17 years, for patients with overt diabetic nephropathy. This indicates that strict metabolic control improves the prognosis in overt diabetic nephropathy.

This finding is consistent with previous findings from studies on the value of glycaemic control on incidence of incipient and overt nephropathy in IDDM populations at different degree of glycaemic control [5–11]. It can be concluded that strict blood glucose control can reduce the risk of developing incipient nephropathy and that it will at least delay the progression to overt diabetic nephropathy [12]. In contrast to this, a recent study failed to show reduced progression of albuminuria of improved metabolic control [11].

Regarding established diabetic nephropathy, a common opinion is that there is a point of no return when the renal function has entered a downhill course. In one study there was an impact of metabolic control...
on the initiation but not on the progression of renal disease [2]. It has even been argued that attempts to further improve diabetic control during this stage of the disease may convey risks that exceed any positive effects [13].

The concept of different importance of glycaemic control in different stages of diabetic nephropathy is based on a number of small studies in overt nephropathy that failed to show a beneficial effect of improved metabolic control on the decline in renal function [15–21]. Several of these studies were carried out when higher blood pressure levels were tolerated. In only one of these older studies [22] and in two recent studies a correlation between metabolic control and decline in glomerular filtration rate was found [23,24]. A reduced sensitivity to hyperglycaemia is difficult to reconcile since that would mean that still functioning nephrons for unknown reason would have developed resistance to hyperglycaemia.

Another explanation could be that intraglomerular hypertension in the advanced stages of nephropathy would constitute a self-maintaining destructive process independent of metabolic control [25,26]. Therefore, strict control of hypertension may be necessary to enable detection of other risk factors such as increased blood glucose.

In the present study hypertension was effectively treated during the whole follow-up period mainly with angiotensin converting enzyme inhibitors and frusemide. The blood pressure was lower than the present recommendations for the start of antihypertensive treatment [27].

The albuminuria, although not measured in all patients, was low, which shows that combined efforts to improve blood pressure and metabolic control can reduce proteinuria to the microalbuminuric range in a substantial proportion of patients, even when renal function is reduced. This indicates that during effective antihypertensive treatment the classification of patients as having micro- or macro-albuminuria has a reduced relevance.

Although there was a trend, no significant correla-
tion between cholesterol, triglycerides and fall in glom-
erular filtration rate was found. One explanation for
this could be that serum cholesterol was lower than in a previous study of ours showing such a relationship [28]. Another explanation might be that the number of measurements was comparatively small for each patient and that they are therefore not representative.

The overall rate of change in glomerular filtration rate of \(-3.8\, \text{ml/min/year}\) in an unselected population of insulin-dependent diabetes mellitus patients with nephropathy, is comparable to \(-4.7\pm1.4\, \text{ml/min/year}\) in several study populations of other European investiga-
tors [29]. It is substantially lower than the progressi-
\(on\) of untreated diabetic nephropathy \(-10\) to
\(-14\, \text{ml/min/year}\) [30]. In a recent large study, where blood pressure was controlled in a manner similar to that in the present study, the rate of decline in glomerular filtration rate was calculated to be \(-9.2\, \text{ml/min/year}\) [31]. An explanation for this differ-
ence might be that blood glucose was less well con-
trolled, or the selection of a group of diabetic patients with poorer prognosis indicated by a higher urinary protein excretion.

Recently, a threshold for an increasing risk of micro-
albuminuria was found at glycated haemoglobin values exceeding 8.1% [32]. The present study was not conclusive in this respect. A threshold has also been claimed to exist for renal changes at a glycated haemoglobin level of about 8.5–9.0% [33,34].

In conclusion, we found that the degree of glycaemic control, expressed as a mean glycated haemoglobin level, was closely related to the rate of decline in glomerular filtration rate during effective blood press-

\[References\]

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