Natural History of Nephropathy in Type I Diabetes
Relationship to Metabolic Control and Blood Pressure

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SUMMARY In recent years, the respective roles of metabolic control and blood pressure on the
development of nephropathy in patients with type I diabetes have been studied intensively. Based on
our own retrospective analysis, we conclude that metabolic control, but not blood pressure, deter-
mines the onset of proteinuria in these patients. Once proteinuria has developed, concurrent metab-
olic control has little effect on the time interval to onset of renal failure. In contrast, blood pressure has
great predictive value for the time interval to onset of both renal failure and proliferative retinopathy.
(Hypertension 7 [Suppl II]: II-74-II-78, 1985)

KEY WORDS • hypertension • diabetic proteinuria • blood glucose

Much is known about nephropathy with respect to the numbers of patients with type I diabetes who develop the condition and the
time course of renal complications. In contrast, much less is known with respect to the factors determining the onset and evolution of nephropathy. In particular, the relative roles of metabolic control and hypertension remain controversial.

Determining the role of metabolic control on the evolution of renal damage in various stages of nephropathy is of paramount importance, because it influences indications for supercontrol using the insulin pump. In experimental studies, glycemic control clearly influenced the development of renal and retinal lesions, although the characteristics of diabetic glomerulosclerosis cannot be perfectly reproduced in experimental animals. Previous clinical studies suggested a role for metabolic control in the onset of nephropathy. However, in one of these, no difference was made between types I and II diabetes. The effects of metabolic control were detected in a Japanese study, in which the development of glomerular lesions in recent-onset, juvenile type I diabetes was investigated with histological techniques. As yet, the role of metabolic control in more advanced stages of nephropathy is the subject of controversy.

The influence of hypertension and renal hemodynamics on the development of nephropathy have been recognized only in recent years. Experimental studies suggested that, by virtue of sustained glomerular overperfusion, elevated arterial blood pressure may cause nonspecific progression of glomerular damage. This theoretical concept is also supported by some clinical observations. In prospective studies, a relationship was noted between blood pressure and decay of renal function, although this has not been observed by all investigators; furthermore, antihypertensive treatment was shown to decrease the rate of decay of renal function.

In view of these uncertainties, we tried to define further in a retrospective longitudinal study the respective roles of metabolic control and hypertension on the evolution of renal disease in precise stages of diabetic nephropathy. We are perfectly aware of the limitations of retrospective studies; however, these patients whose hypertension, according to modern standards, was virtually untreated provided unique information that cannot be obtained in prospective trials. The methodological details of the present study were published extensively elsewhere. This review discusses the major findings with respect to existing knowledge in the field.
Preproteinuric Stage of Type I Diabetes

We evaluated 324 patients with type I diabetes (153 men, 171 women) who were admitted between 1966 and 1983 to the Diabetes Outpatient Clinic of the Department of Internal Medicine, University of Heidelberg, and were subsequently seen for at least five consecutive consultations per year. The 220 (106 men, 114 women) patients with type I disease who were admitted to the Diabetes Clinic of the Academisch Ziekenhuis Leiden were evaluated in a similar fashion. Those observed in both clinics were comparable with respect to sex and age at onset of diabetes (data not given). Patients with known renal causes of proteinuria (e.g., polycystic kidneys, known glomerulonephritis) or onset of proteinuria before the seventh year of diabetes were not included. Onset of persistent proteinuria was defined as four consecutive positive urine tests during a 6-month period.

Proteinuria was evaluated semiquantitatively with Combur test strips (Boehringer Mannheim, Mannheim, West Germany). Blood pressure (phase 1 and phase 5) was measured after 5 to 10 minutes of rest in the sitting position. Measurements were made with a calibrated standard mercury manometer according to the recommendations of the League against High Blood Pressure.

As shown in Figure 1, the rate of development of clinical nephropathy, that is, persistent proteinuria, was lower in the Leiden than in the Heidelberg cohort (p < 0.05). This was not explained by differences of metabolic control or blood pressure. In contrast, median postprandial blood glucose levels were slightly higher in the Leiden than the Heidelberg patients (245 and 208 mg/100 ml respectively). In contrast to another study in which diabetic nephropathy occurred more frequently in male than in female patients, we found a higher frequency of persistent proteinuria in female than in male patients; the male/female ratio was 1:1.3 in the Leiden group and 1:1.6 in the Heidelberg group. The reasons for these different findings are unknown; genetic or environmental factors must be investigated. The following data refer only to the Heidelberg group.

In the past it was commonly accepted that development of hypertension in patients with type I diabetes heralded the onset of overt nephropathy. Recently, however, slightly but significantly higher blood pressure in preproteinuric patients with type I diabetes with microalbuminuria (Albustix-negative urine, positive for albumin on radioimmunoassay) was described. This finding is in excellent agreement with our own results (Table 1). Blood pressure of diabetic patients who subsequently developed proteinuria was compared with that of individuals from the general German population who were matched for age, sex, and body mass index (BMI); the data on the general population, based on the Munich blood pressure study, were kindly supplied by Dr. Keil, Munich. It is obvious that particularly in female patients, the prevalence of established hypertension in those with preproteinuric type I diabetes was higher than in individuals of the general population. This observation is compatible with the notion that blood pressure rises before overt (Albustix-positive) proteinuria is demonstrable.

Table 2 shows the time interval between onset of diabetes and onset of persistent proteinuria in persons with type I diabetes with different blood pressures or different levels of metabolic control. It is obvious that in three groups with different blood pressure status there was no difference with respect to the time interval of onset of persistent proteinuria. In contrast, the time interval was significantly (p < 0.05) shorter in those with poorer than those with better metabolic control. A dose-effect relationship between postprandial glucose and time to onset of proteinuria could be established. Median postprandial glucose (mmol/L) and time interval (years) were significantly correlated (r = 0.40, p < 0.01). The relationship between postprandial blood glucose and time to onset of proteinuria was not due to associated differences in blood pressure, since we found no such difference of significance among patients with poor, fair, or acceptable metabolic control.

In agreement with previous findings, these observations establish a relationship between metabolic control in early type I diabetes and subsequent development of proteinuria. Although median levels of postprandial glucose in patients with long-standing diabetes (over 20 years) who did not develop proteinuria (n = 30) were significantly lower (median 189 mg/100 ml, range 135–285 mg/100 ml) than in those

![Figure 1. Cumulative incidence of diabetic nephropathy in relation to duration of type I diabetes in 324 patients from Heidelberg (*) and 220 patients from Leiden (*).](image-url)
TABLE 2. Effect of Metabolic Control and Blood Pressure Status on the Onset of Persistent Proteinuria in 52 Patients with Type I Diabetes

<table>
<thead>
<tr>
<th>Metabolic control</th>
<th>Blood glucose (mmol/L)</th>
<th>Blood pressure (mm Hg)</th>
<th>Onset of proteinuria (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good (n = 19)</td>
<td>10.3 (6.1–11.0)</td>
<td>150/88 (118–184/80–110)</td>
<td>23 (11–32)</td>
</tr>
<tr>
<td>Moderate (n = 21)</td>
<td>12.2 (11.1–12.7)</td>
<td>148/85 (122–190/75–103)</td>
<td>19 (10–30)</td>
</tr>
<tr>
<td>Poor (n = 12)</td>
<td>14.1 (12.8–15.9)</td>
<td>154/85 (130–202/76–110)</td>
<td>14 (8–25)</td>
</tr>
<tr>
<td>Blood pressure status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No hypertension (n = 27)</td>
<td>11.7 (8.3–15.7)</td>
<td>137/80 (118–156/75–86)</td>
<td>19 (12–32)</td>
</tr>
<tr>
<td>Intermittent hypertension (n = 16)</td>
<td>12.8 (9.9–13.9)</td>
<td>150/89 (139–160/80–100)</td>
<td>19 (8–29)</td>
</tr>
<tr>
<td>Persistent hypertension (n = 9)</td>
<td>11.4 (7.9–12.9)</td>
<td>175/95 (157–207/90–115)</td>
<td>19 (9–30)</td>
</tr>
</tbody>
</table>

Results given as mean with range in parenthesis.

Metabolic control was classified according to annual median blood glucose levels: good, < 200 mg/100 ml; moderate, 200–230 mg/100 ml; poor, > 230 mg/100 ml. Blood pressure status was classified according to the frequency of blood pressures > 160 mm Hg systolic or > 95 mm Hg diastolic per year: no hypertension, all readings < 160/95 mm Hg; intermittent hypertension, repeatedly but not constantly > 160/> 95 mm Hg; persistent hypertension, continuously > 160/> 95 mm Hg.

who did, the overlap was quite considerable (median 219 mg/100 ml, range 120–270 mg/100 ml). This implies that some patients with type I diabetes may fail to develop proteinuria despite poor metabolic control. Since follow-up of the populations who did and did not develop proteinuria was comparable (data not given), a lead-time artifact is excluded. This observation demonstrates that factors other than metabolic control most probably play a role in the genesis of proteinuria.

Animal studies clearly established the overriding importance of glomerular overperfusion on the development of glomerular damage in experimental diabetes mellitus.12 In view of these findings it is surprising that blood pressure had no apparent effect on the onset of proteinuria. This shows that results of animal experiments cannot be readily extrapolated to clinical human diabetes. Potential explanations for a deleterious role of hypertension in late diabetes include progressive development of arteriolar lesions interfering with autoregulation of glomerular capillary pressure, and progressive mesangial expansion interfering with autoregulatory adaptation of renal perfusion.

Determinants for the Clinical Evolution of Nephropathy and Retinopathy in Proteinuric Type I Diabetes

Of 14 normotensive patients with proteinuric type I diabetes, 20% had elevated serum creatinine levels after 10 years of follow-up. In contrast, out of 34 hypertensive patients with proteinuric type I diabetes, 95% had renal insufficiency after 10 years of follow-up (Figure 2). These groups are comparable with respect to metabolic control (median postprandial glucose in normotensive persons 10.4 mmol/L, in hypertensive patients 10.9 mmol/L). This would establish hypertension as an important risk factor for the onset of renal insufficiency in those with proteinuric type I diabetes.

In patients who developed renal insufficiency, however, a correlation was found between concurrent blood glucose values and the time interval between onset of persistent proteinuria and elevation of serum creatinine (Figure 3). Therefore metabolic control apparently modulates the rate of appearance of renal insufficiency in those destined finally to develop renal insufficiency primarily on the basis of high blood pressure. There was a clear-cut inverse relationship between mean arterial blood pressure (diastolic value plus one-third of the systolic value) and the interval between onset of proteinuria and onset of proliferative
retinopathy (Figure 4). This seems to establish hypertension as an important risk factor also in the genesis of proliferative retinopathy in diabetics with nephropathy. In contrast, metabolic control had no influence on the above time interval (data not given).

Evolution of Renal Failure in Type I Diabetes

There is consensus that at the time of onset of renal insufficiency, virtually all diabetic patients are hypertensive. In our own study, the prevalence of hypertension rose progressively with advancing stages of nephropathy, 92% of patients being hypertensive when serum creatinine was above 133 \( \mu \text{mol/L} \) (Table 3). The role of hypertension in the progression of renal insufficiency is clearly depicted in Figure 5, which shows the decay of renal function after serum creatinine had risen to greater than 133 \( \mu \text{mol/L} \) in patients with intermittent or persistent hypertension. As illustrated, the decay was more rapid in patients with persistent hypertension.

It is of note that at this stage of renal failure, postprandial glucose was no longer related to the development of nephropathy. There was no relationship between median postprandial glucose and the slope of \( 1/\text{serum creatinine} \) versus time. These observations further illustrate the notion of a "point of no return," indicating that the progression of renal lesions is independent of metabolic control once an advanced stage of nephropathy is reached.

Table 3. Quality of Antihypertensive Treatment at Different Stages of Diabetic Nephropathy

<table>
<thead>
<tr>
<th>Stage of nephropathy</th>
<th>Prevalence of hypertension</th>
<th>Not treated BP &gt; 160 mm Hg</th>
<th>Treated BP &gt; 160 mm Hg</th>
<th>Treated BP &lt; 160 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preproteinuria</td>
<td>12/37 (32%)</td>
<td>8 (62%)</td>
<td>5 (38%)</td>
<td></td>
</tr>
<tr>
<td>Persistent proteinuria</td>
<td>35/52 (67%)</td>
<td>25 (71%)</td>
<td>10 (29%)</td>
<td></td>
</tr>
<tr>
<td>Elevated serum creatinine*</td>
<td>184/200 (92%)</td>
<td>7 (4%)</td>
<td>153 (83%)</td>
<td>24 (13%)</td>
</tr>
</tbody>
</table>

\[ BP = \text{blood pressure.} \]

*Data from Ritz et al., 1984.25
The Challenge of Antihypertensive Therapy of Nephropathic Type I Diabetes

The high prevalence of hypertension in our patients with diabetic nephropathy clearly illustrates past failure to appreciate the importance of effective blood pressure control. Antihypertensive therapy was ineffective due to the local arrangement of diabetes care in which metabolic control was delegated to the diabetes clinic and antihypertensive therapy to the private physician. To the extent that today the necessity of antihypertensive treatment is more clearly perceived by the medical profession, the following data are, it is hoped, of only historical interest.

As shown in Table 3, the prevalence of hypertension progressively rose with advancing stages of nephropathy, but only a minority of patients in the stages of persistent proteinuria, renal insufficiency, or prerenal failure had effective antihypertensive medication lowering blood pressure to normal levels. Since a strong relationship exists between blood pressure and development of nephropathy, the necessity to normalize blood pressure cannot be overemphasized. Even in terminal renal failure, however, the subsequent fate of patients on dialysis will strongly depend on their history of hypertension. We showed that in diabetic persons receiving hemodialysis, the relative risk of cardiovascular death increased 2.5-fold for those with a long (over 5 years) history of hypertension. Such an increase was much more marked than in nondiabetic patients (1.3-fold) who received hemodialysis.

As reviewed recently by us and others, antihypertensive medication in diabetic patients poses numerous problems related to metabolic or other side effects. Better understanding of conventional drugs, such as beta blockers, and availability of new agents, such as calcium antagonists, converting enzyme inhibitors and minoxidil, should facilitate management of these patients in the future.

It is obvious that several questions still cannot be answered. To which level must blood pressure be reduced in order to halt progression of nephropathy? With respect to development of retinal exudates, a prospective study showed a blood pressure-dependent increment of risk at readings within the normotensive range. Similar considerations may apply not only to retinal but also to renal lesions. As shown by one group, when mean arterial blood pressure is lowered, microalbuminuria will be reduced in parallel. Whether or not this indicates a more benign subsequent evolution of nephropathy when blood pressure is aggressively reduced into the lower normotensive range remains to be established.

References
Natural history of nephropathy in type I diabetes. Relationship to metabolic control and blood pressure.
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Hypertension. 1985;7:II74
doi: 10.1161/01.HYP.7.6_Pt_2.II74

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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