Hypertension as Related to Renal Function in Diabetes Mellitus
FRANÇOIS C. REUBI, KATHRIN A. FRANZ, AND FRITZ HORBER

SUMMARY The relationships between blood pressure and renal function were investigated in 78 hypertensive patients with diabetes mellitus type I or II. Renal function was assessed by determining the glomerular filtration rate and the para-aminohippurate clearance in 32 and serum creatinine in 46 subjects. In the latter, the reciprocal serum creatinine, corrected for age and changing creatinine/insulin clearance ratio, was used as an estimate of glomerular filtration rate. In the 54 patients with serial determinations, the duration of follow-up averaged 10.5 years. In older patients with type II diabetes without clinical proteinuria, hypertension developed either before or after the onset of diabetes. When it appeared, renal function was only slightly reduced. During follow-up, the decline in reciprocal serum creatinine averaged 2.7% per year, a figure very similar to that found in nondiabetic patients with benign essential hypertension. It did not correlate with the blood pressure. In patients with a proteinuria greater than 2.5 g per day and histologic and/or clinical evidence of diabetic glomerulosclerosis, the severity of hypertension correlated inversely with the level of renal function. The rate of decline in function averaged 11% per year but varied widely. It was not significantly related to the blood pressure. These data suggest that different types of hypertension (essential, diabetic, and nephrogenic) may be associated with diabetes mellitus. The rate of decline in renal function is closely related to the presence or absence of clinical proteinuria but not to the level of blood pressure. (Hypertension 7 [Suppl II]: II-21-II-28, 1985)

KEY WORDS • blood pressure • glomerular filtration rate • serum creatinine

HYPERTENSION is very common in diabetic patients. In younger subjects with insulin-dependent diabetes, hypertension develops during the course of diabetic glomerulosclerosis (DGS) and tends to become more severe as renal function decreases. In older patients with type II diabetes and no clinical proteinuria, hypertension may be present several years before the diabetes becomes manifest. Alternatively, it may appear after the diagnosis of diabetes has been made. In patients with maturity-onset diabetes, impaired renal function is not a prerequisite for the development of hypertension.

In older hypertensive diabetics without proteinuria, the decrease in renal function is slow. In certain patients with DGS, it may be very rapid, and it has been suggested recently that early antihypertensive treatment may slow renal deterioration. The present study was designed to assess the relationships between blood pressure and renal function in various forms of diabetes mellitus and to evaluate to what extent the level of blood pressure (BP) determines the rate of progression of diabetic nephropathy.

Patients and Methods

Group 1
Twenty-nine hypertensive patients with type II diabetes and no clinical proteinuria had repeated measurements of serum creatinine and blood pressure (Table 1). The average duration of the follow-up was 14 years (range 7–21 years). Mean age at the beginning of the observation period was 59 years (range 30–74 years). There were 4 male and 25 female patients. Serum creatinine and blood pressure values were usually measured on several occasions every year and were averaged for each successive year. Reciprocal serum creatinine (100/cr) was used as an estimate of glomerular filtration rate (GFR).

When the 100/cr values were plotted against time, the decrease was approximately linear or exponential. Decline in function was assessed by drawing a straight line by visual approximation. The absolute decrease in milliliters per milligram per year was obtained by dividing the total decrease by the number of years; the
There were 25 patients with type I and 7 with type II diabetes. They were not receiving antihypertensive treatment prior to and during the clearance examinations. In eight of these patients (six women and two men, mean age 34 years, range 19–47 years), serial clearance determinations were performed over 3 to 6 years (subgroup 2B). These subjects did not receive effective antihypertensive treatment during follow-up.

**Group 3**

Seventeen proteinuric patients (13 men, 4 women) with DGS had repeated measurements of serum creatinine and BP. In five patients DGS was confirmed by renal biopsy; in 12 the diagnosis was made clinically (proteinuria > 2.5 g/day, often nephrotic syndrome, diabetic retinopathy, insulin-dependent diabetes of long duration, and progressive hypertension). There were 13 patients with type I and 4 with type II diabetes. Mean age at the time diabetes was discovered was 32 years (range 7–64 years). Mean age at the beginning of the observation period was 44 years (range 20–64 years). The average duration of follow-up was 7.5 years (range 2–17 years). In some patients hypertension was never treated adequately. The remaining subjects were given various antihypertensive drugs, which they took at least intermittently. The corrected 100/\(c_r\) values were used as an estimate of GFR.

In contrast to group 1, mBP varied during follow-up depending on the stage of DGS (increasing with the progression of the disease) and on the effectiveness of antihypertensive therapy. In addition, the slope of the decline in function varied in many patients. Therefore shorter periods were used for studying the possible correlations between rate of progression and blood pressure. When clear-cut differences could be observed in a patient, the whole follow-up was divided into two or three periods with either different slopes of decreasing function or different levels of mBP. The data of the eight patients in group 2 who had serial clearance determinations (subgroup 2B) were handled similarly. All together there were 43 well-individualized periods ranging from 2 to 11 years in 25 patients. Possible relationships between the rate of protein excretion and mBP were not investigated in this study.

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**Table 1. Synopsis of the Groups of Diabetic Patients**

<table>
<thead>
<tr>
<th>Group</th>
<th>Diabetes type</th>
<th>Glomerulosclerosis</th>
<th>Hypertension</th>
<th>Proteinuria</th>
<th>Mean duration of follow-up (yr)</th>
<th>Mean age at entry (yr)</th>
<th>Antihypertensive treatment</th>
</tr>
</thead>
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<tr>
<td>I*</td>
<td>II (29)</td>
<td>Unlikely</td>
<td>Yes</td>
<td>No</td>
<td>14</td>
<td>59</td>
<td>Variable</td>
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<td>A</td>
<td>(16)</td>
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<tr>
<td>B</td>
<td>(13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2†</td>
<td>I (25), II (7)</td>
<td>Biopsy-proved</td>
<td>Yes</td>
<td>Yes</td>
<td>47</td>
<td>34</td>
<td>No</td>
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<tr>
<td>A</td>
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<tr>
<td>B</td>
<td>(8)</td>
<td></td>
<td></td>
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<td>5.2</td>
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<td>3</td>
<td>I (13), II (4)</td>
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<td>Yes</td>
<td>Yes</td>
<td>7.5</td>
<td>44</td>
<td>Variable</td>
</tr>
</tbody>
</table>

*Hypertension preceded diabetes in subgroup 1A; diabetes preceded hypertension in subgroup 1B.
†Single clearance determinations were performed in subgroup 2A, and serial clearance determinations were performed in subgroup 2B.
As in group 1, the $100/C_r$ values were corrected for age-related changes in serum creatinine and increase in the creatinine/inulin clearance ratio with decreasing GFR. Since the patients were younger and the fall in GFR was more rapid, correction factors were modified accordingly.

The diagnosis of diabetes mellitus was based on the presence of definitely elevated fasting blood sugar values on repeated occasions. Patients with borderline disease were excluded. The histological diagnosis of DGS was made by an independent pathologist and based on the presence of nodules and/or extensive intercapillary deposits together with arteriolar hyalinization.

Proteinuria was measured by the biuret method. Serum creatinine was determined with the Greiner Selective Analyser GSA II by the alkaline picrate method. The GFR and effective renal plasma flow (PAH clearance, $C_{PAH}$) were measured by the conventional clearance technique using either inulin or $51$Cr-EDTA and sodium PAH as indicators. Blood pressure was measured in supine position after 3 minutes of rest by the cuff method, using phase 5 for the diastolic BP. The mBP was calculated by adding one-third of the pulse pressure to the diastolic pressure. Informed consent was obtained from the patients for the clearance studies.

**Results**

**Group 1 — Hypertensive Patients with Type II Diabetes Without Proteinuria**

The 16 patients of subgroup 1A with antecedent hypertension had a mean age of 61 years at the beginning of the observation period. Their average mBP for the entire observation period was $113 \pm 8$ mm Hg (mean $\pm$ SD, range 103–132 mm Hg). The mean decline in $100/C_r$ was $2.46 \pm 2.26$ ml/mg/yr or $2.07 \pm 1.72$%/yr. When the decline was corrected for the age-related decrease in serum creatinine and the changing creatinine/inulin clearance ratio, these values were $3.11 \pm 2.85$ ml/mg/yr or $2.62 \pm 2.17$%/yr.

The pool of all uncorrected $100/C_r$ values was plotted against time (Figure 1) and the regression line was calculated. The best fit was a flat exponential curve given by the following equation: $\ln 100/C_r = -0.016$ year + 4.63. After correction for the changes in creatinine level and clearance the equation became: $\ln 100/C_r = -0.042$ year + 4.64. Assuming linearity (an approximation justified by the almost linear shape of the curve), the mean decline in $100/C_r$ would be $3.1$ ml/mg/yr.

The 13 patients of subgroup 1B with late hypertension had a mean age of 55 years when they entered the study. Their average mBP for the entire observation period was $111 \pm 4$ mm Hg (range 104–117 mm Hg). The mean decline in $100/C_r$ was $2.46 \pm 1.36$ ml/mg/yr or $2.21 \pm 1.04$%/yr. After correction for the changes in creatinine level and clearance, the decline was $3.11 \pm 1.72$ ml/mg/yr or $2.79 \pm 1.13$%/yr.

The regression line calculated from the pool of all uncorrected observations (Figure 2) was again a flat exponential given by the following equation: $\ln 100/C_r = -0.009$ year + 4.58, or after correction: $\ln 100/C_r = -0.036$ year + 4.6. Assuming linearity, the mean decline in $100/C_r$ would be $2.56$ ml/mg/yr.

There was no statistical difference in the rate of decline between the subgroups. For the whole group (29 patients) it averaged $2.7$%/yr. For each subgroup the individual rates of decline were plotted against the corresponding mBP. There was no significant correlation between the variables.

**Figure 1.** Plot of uncorrected $100/C_r$ data and regression lines in 16 patients with type II diabetes without clinical proteinuria with antecedent hypertension.
Group 2 — Single or Serial Determinations of GFR and C_PAH in Patients with DGS Not Receiving Antihypertensive Treatment

The 57 data in 32 patients clearly showed that mBP increased progressively with the decline in GFR (Figure 3) and PAH clearance. The two correlations were highly significant (mBP vs GFR: \( r = -0.632, p < 0.001 \); mBP vs C_PAH: \( r = -0.627, p < 0.001 \)). The filtration fraction (GFR/C_PAH ratio, FF), was variable (mean 0.19 ± 0.055, range 0.119-0.336). It tended to increase with increasing mBP and decreasing GFR, but did not correlate significantly with either variable.

The results of the serial clearance determinations performed in the eight patients of subgroup 2B are reported with group 3.

Group 3 — Serial Measurements of either GFR and C_PAH or Serum Creatinine in Patients with DGS

In the eight patients who had repeated determinations of GFR and C_PAH (subgroup 2B), mBP ranged from 97 to 150 mm Hg. The GFR decreased from a mean of 79.4 ± 37.8 to 29.2 ± 18.5 ml/min within 3.9 ± 2.0 years, corresponding to a decrease of 12.8 ml/min/yr or 16.2%/yr (range 1.3-44 ml/min or 2.6-56.1%). There were marked interindividual differences in the rate of decline (Figure 4). The effective renal plasma flow (C_PAH) decreased from 471 ± 234 to 177 ± 154 ml/min, that is, 16.0%/yr (range 6.8-51.4%). From the pooled GFR data (Figure 5) a linear regression line was calculated. The equation was GFR = -13.1 years + 85.3 (\( r = 0.651, p < 0.001 \)),

**Figure 2.** Plot of uncorrected 100/Cr data and regression lines in 13 patients with type II diabetes without clinical proteinuria with late hypertension.

**Figure 3.** Inverse correlation between mBP and GFR in 32 patients with diabetic glomerulosclerosis (57 determinations).
corresponding to a decrease of 13.1 ml/min/yr or 15.3%/yr. The correlation was not improved ($r = -0.648$) by using the logarithms of GFR.

In the 17 patients (group 3) who had only serial serum creatinine determinations (follow-up 7.5 ± 4.5 years), the rate of decrease in $100/C_r$ was also variable (Figure 6). The $100/C_r$ decreased from 95.8 ± 36.0 to 49.8 ± 23.8 ml/mg, corresponding to a decrease of 6.13 ml/mg/yr or 6.4%/yr. After correction for the changes in serum creatinine and creatinine clearance, these values became 8.3 ml/mg/yr and 8.6%/yr respectively.

Since most patients were followed for at least 6 years, a first regression line was calculated for this initial period from the pool of data (Figure 6). The equation was $100/C_r = -4.83$ years + 81.3 ($p < 0.05$). The rate of decrease was 4.8 ml/mg/yr or 5.9%/yr; the corrected values were 6.5 ml/mg/yr and 8.0%/yr respectively.

In five patients with relatively high initial values and a rather slow decrease in function (mean initial age 45 years), $100/C_r$ determinations were available during longer follow-up periods (10–17 years). A second linear regression line was calculated for this subgroup over 14 years. It was $100/C_r = -2.26$ years + 107 ($p < 0.005$), yielding a mean corrected decrease in $100/C_r$ of 3.7 ml/mg/yr or 3.5%/yr.
The possible relationships between the rate of decline and mBP were investigated by analyzing 43 shorter periods. Because of the variable length and number of periods in individual patients, the mean rates of decline were different from the above-reported values. They were used only for comparison. The mean decrease in function per year was calculated for three levels of mBP: for mBP values less than 110 mm Hg it was 15.3 ± 14.8 ml/min (or ml/mg); for mBP 110 to 130 mm Hg, 11.5 ± 10.8 ml/min (ml/mg); for mBP greater than 130 mm Hg, 12.1 ± 12.9 ml/min (ml/mg). The percentages of changes were 13.7 ± 9.9, 15.1 ± 14.4, and 21.6 ± 17.5 respectively. There were no significant differences in the rates of decline among the three groups. In addition, the 43 individual rates of decrease in function were plotted against the individual mBP. Neither the absolute nor the percentage rates of decline correlated with mBP (absolute decrease vs mBP: r = 0.02; percentage of decrease vs mBP: r = 0.269, p < 0.1 > 0.05). The mean rates of decrease in function observed in group 3 (25 patients with DGS) and group 1 (29 patients without proteinuria) were compared and found to be significantly different (p < 0.001).

Discussion

In many patients with chronic renal disease the GFR decreases linearly with time, suggesting that every year the same number of nephrons undergo destruction. When patients are followed for a long time, however, activity of the disease is not always constant. Thus many curves consist of several segments with different slope. In some patients, a more or less regular exponential decrease indicates that a constant proportion of the remaining nephrons lose their function. In still other conditions, progression accelerates with time.\(^{11}\)

According to Rutherford et al.,\(^{12}\) the decrease in GFR can be estimated by plotting reciprocal serum creatinine against time. Aging and chronic renal failure cause a decrease in muscle mass and creatinine production, however, resulting in depression of serum creatinine.\(^{7}\) In addition, the creatinine/inulin clearance ratio increases with decreasing renal function.\(^{3,8}\) These two factors may produce a significant distortion of the 100/Cr falling curve. This distortion may simulate an exponential decrease or even no decrease at all in patients with a slow linear decline in function. For that reason, we have attempted to correct our 100/Cr data; however, we must admit that there is no entirely reliable way of adjusting the values, since in individual patients the relationships between serum creatinine and the other variables cannot be predicted accurately.

In many older diabetics without clinical evidence of DGS, mild to moderate hypertension was already present when the diagnosis of diabetes was first made. It would seem that they were suffering from essential hypertension, unless one assumes that persons prone to diabetes may develop "diabetic" hypertension before the appearance of the metabolic disorder. In these patients (subgroup IA) the corrected decline in 100/Cr was very slow (2.62%/yr) and almost identical with that found in benign essential hypertension.\(^{13,14}\) It was unrelated to the level of BP. Similarly, in benign essential hypertension, antihypertensive treatment may prevent in part the decrease in \(C_{\text{PAH}}\),\(^{13,14}\) but does not influence the rate of decrease in GFR.

In the patients of subgroup IB, hypertension appeared after the onset of diabetes, but the overall pattern of blood pressure and renal function was hardly
distinguishable from that of patients in subgroup 1A (see Figures 1 and 2). Hypertension was possibly due to diabetes itself, but since renal function was not more depressed than in the "essential" subgroup, it was presumably not caused by an alteration in renal hemodynamics. We may conclude that when hypertension develops in older diabetics without clinical proteinuria, its effects on renal function are not more deleterious than those of essential hypertension.

In patients with DGS and marked proteinuria, the rate of decrease was significantly faster than in those without proteinuria ($p < 0.001$), but there was great interindividual variation. The differences cannot be ascribed to age alone. Although progression was faster in patients in subgroup 2B (mean age 34 years) than in those in group 3 (mean age 44 years), there was no age difference in the latter among the five patients with slow progression and the other subjects (see Figure 6).

One crucial question is whether or not the variability in progression is related to blood pressure levels. The negative impression gained from review of all the charts was confirmed by analysis of the 43 short periods. Although the greatest percentage of decrease in function per year was observed during the periods with mBP greater than 130 mm Hg, the differences among the three mBP ranges were not significant. Similarly, the correlation between individual percentage rates of decline and mBP did not reach the level of significance.

Therefore our data seem to indicate that once DGS is established, the level of blood pressure is not an important determinant for the rate of decrease in function, provided hypertension is not malignant. In 1979 Jones et al. came to the same conclusion. Since more recent reports have emphasized the beneficial effects of antihypertensive treatment on the course of DGS, we should like to examine the possible reasons for this lack of agreement.

Antihypertensive treatment might be more beneficial in juvenile-onset diabetics than in older patients with DGS, and the subjects in Parving's and Mogensen's series were younger than ours. Differences in the quality of diabetes control may also play a role, although established DGS does not seem to benefit even from insulin pump therapy.

In DGS the decline in GFR has generally been assumed to be linear. It was clearly exponential in a group study by Goldstein extending over 5 years in 112 diabetic patients, but this author used uncorrected reciprocal serum creatinine values. We found that at least in some subjects, the falling curve was closer to an exponential than to a straight line (Figure 7). An exponential decline can also be observed in three of the charts published by Parving et al. Under these conditions, comparing short periods in the same subjects may be misleading when antihypertensive treatment is applied after the control period. What seems to be a change in slope due to treatment may in fact represent continuation of the exponential decrease. Furthermore, when antihypertensive therapy is initiated in patients with stable renal function, the fall in BP is usually paralleled by a transient drop in GFR, which tends to rise again during sustained treatment. In patients with DGS with a linear decrease in function, this phenomenon may alter the slope of decline. Such a change, as seen in two patients of the Parving's series.

**Figure 7.** Course of uncorrected and corrected $100/Cr$ in three patients with diabetic glomerulosclerosis. The decline is roughly exponential and unrelated to mBP.
series, does not necessarily mean that the rate of decline has been lowered by therapy. The same remarks apply to the study of five patients published in 1982 by Mogensen.4

To summarize, the data on BP and renal function in 78 subjects with either type I or type II diabetes indicate that different types of hypertension may be associated with diabetes and that the grade of renal impairment varies widely. In older patients with type II diabetes and no proteinuria, hypertension may precede or follow the clinical onset of diabetes. Renal function is relatively well preserved and the relationships between GFR and mBP are similar to the pattern observed in benign essential hypertension. In other words, the decrease in renal function is slow and not related to the level of mBP.

In patients with established DGS (most but not all of whom are insulin dependent), BP rises progressively with decreasing renal function. In these persons, hypertension is probably largely due to DGS. Although it has been suggested that hypertension per se might accelerate the development of DGS, we found no correlation between the level of BP and the rate of decrease in GFR and 100/o. It is still possible that early and aggressive antihypertensive treatment might delay the development of DGS. It is also likely that if the hypertension accompanying DGS becomes malignant, it will produce secondary renal lesions; however, benign hypertension has little influence on the rate of progression in DGS. This does not mean that hypertension in diabetics needs no treatment. Blood pressure control is highly recommendable in every type of hypertension since it may prevent, delay, or alleviate cardiovascular complications and improve the overall prognosis.

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