Renal Histopathology in Hypertensive Diabetic Patients

Gerhard Ditscherlein

Summary A total of 250 renal biopsy specimens from diabetic patients and from the kidneys of 400 autopsy cases were examined histologically and compared to kidneys from 160 autopsied nondiabetics. The morphological findings were assessed in relation to hypertension. There was a high prevalence of arteriolosclerosis, glomerulosclerosis, and pyelonephritis; in addition, early diabetic glomerulopathy and glomerulonephritis, particularly of the membranous type, were noted in a remarkably high percentage of diabetic patients. Ninety-three percent of patients with hypertension had arteriolosclerosis, and a good correlation existed between the extent of this lesion and the level of blood pressure. Even in 66% of normotensive patients, however, arteriolosclerosis was found. This fact and the involvement of the vas efferens argue against the notion of arteriolosclerosis being exclusively a sequela of hypertension. More than 70% of patients with glomerulosclerosis suffered from hypertension, compared to less than 50% of patients without either that condition or early diabetic lesions. The majority of diabetic patients with pyelonephritis and glomerulonephritis were hypertensive. We conclude that hypertension in diabetic patients with renal involvement may result from different renal lesions that can be differentiated only by histological examination.

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Key Words • biopsy specimens • autopsy • arteriolosclerosis • glomerulosclerosis • glomerulonephritis

During recent years, some reviews have dealt with hypertension in diabetic patients, particularly in relation to diabetic nephropathy. [1-3] There is little information, however, on the relationship of hypertension to morphological lesions in the kidney. Renal lesions are usually summarily diagnosed as "diabetic nephropathy." This term may be useful for physicians who have to rely on clinical information, such as persistent proteinuria and decline in glomerular filtration rate, to assess renal involvement, but pathohistological examination may more precisely specify the renal lesion or detect superimposed pathology. Consequently, histological studies are important not only for evaluating renal prognosis but for clarifying the pathogenesis of hypertension.

Material and Methods

Biopsy specimens taken from 250 diabetic patients and kidney tissue obtained from 400 autopsy cases were examined histologically. In 131 biopsy cases semithin sections (cut with Ultramicrotome OmU2 of C. Reichert AG, Vienna, Austria) were also investigated with Movat's silver impregnation method, which permits one to recognize lesions in fine detail, such as moderate basement membrane thickening, slight mesangial expansions (i.e., the early stage of diabetic glomerulosclerosis), as well as spike formation along the basement membrane (e.g., in membranous glomerulonephritis). The autopsy and biopsy series differed in some important respects (Table 1). In the biopsy series, 88 patients had type I diabetes, 108 patients type II diabetes, and the rest could not be classified with certainty. This was also true for a large percentage in the postmortem series.

Hypertension was diagnosed according to WHO criteria (> 160 mm Hg systolic, > 95 mm Hg diastolic). Statistical evaluation was performed using the t test and the chi-square test respectively. Only statistically significant differences are discussed.

Results

Diabetic glomerulosclerosis (GS) was found in the autopsy series in 45.3% and in the biopsy material in 37.2% of patients. Information on hypertension in patients with GS is given in Table 2. The numbers with hypertension were similar in the autopsy and biopsy...
The relationship between AS and hypertension in diabetes. We observed this in 79.5% of the autopsy cases with GS and in 18% of the other series. More than 70% of the patients with GS had hypertension, compared with 40 to 50% of other diabetics. In contrast, in patients with early diabetic glomerular lesions, the prevalence of hypertension was lower than in those with manifest GS, but not significantly different from the prevalence in patients without glomerular lesions. We also noted that in patients below 40 years of age, 67% with GS had hypertension. This was certainly more than the expected prevalence of essential hypertension in this age group.

A frequent finding in kidneys of diabetics is arteriolosclerosis. We observed this in 79.5% of the autopsied diabetics compared with 48% in 160 nondiabetics of the same age distribution. In 68% of the biopsy series, arteriolosclerosis (AS) was observed. The relationship between AS and hypertension in diabetics in our material is presented in Table 3.

An important finding was the involvement of the postglomerular vas efferens, which was noted in 60% of our autopsy cases with GS and in 18% of the other diabetics. In postmortem examination of supposed nondiabetics, this lesion was very rarely found. Hypertension was documented in 74% of diabetics with AS of the vas efferens.

We found chronic pyelonephritis (PN) in 90 (22.5%) autopsy cases; in 43 patients, acute inflammatory lesions were present. Sixty-nine percent of the 90 autopsy cases had a history of hypertension, but further evaluation was difficult because of the frequent combination of PN with GS and/or AS respectively (Table 4).

### Table 1. Comparison of Biopsy and Autopsy Series

<table>
<thead>
<tr>
<th>Series</th>
<th>Autopsy</th>
<th>Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>400</td>
<td>250</td>
</tr>
<tr>
<td>Female/Male ratio (%)</td>
<td>68.8/31.2</td>
<td>44/56</td>
</tr>
<tr>
<td>Age at examination (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40</td>
<td>2%</td>
<td>42%</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>84%</td>
<td>12%</td>
</tr>
<tr>
<td>Age at manifestation (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>3%</td>
<td>41%</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>81%</td>
<td>19%</td>
</tr>
<tr>
<td>Duration of diabetes (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6</td>
<td>55%</td>
<td>37%</td>
</tr>
<tr>
<td>&gt; 15</td>
<td>13%</td>
<td>21%</td>
</tr>
</tbody>
</table>

### Table 2. Hypertension in Diabetic Patients with and without Glomerulosclerosis

<table>
<thead>
<tr>
<th>Series</th>
<th>Autopsy material</th>
<th>Biopsy material</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Patients</td>
</tr>
<tr>
<td></td>
<td>with hypertension</td>
<td>with hypertension</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Without GS</td>
<td>172</td>
<td>71</td>
</tr>
<tr>
<td>With GS</td>
<td>153</td>
<td>112</td>
</tr>
<tr>
<td>Early glomerular lesions</td>
<td>(not proved in all cases)</td>
<td>37</td>
</tr>
</tbody>
</table>

In a biopsy series, glomerulonephritis (GN) was found in a remarkable percentage (15.3%) of specimens that could be examined in semithin sections. Noteworthy was the relatively high prevalence of membranous GN (Table 5); however, various other GN types were also observed. Most of the patients with GN were hypertensive. Combination with GS was apparent in eight specimens with membranous GN; six of these patients were hypertensive.

Finally, three patients with slight to moderate amyloidosis were not hypertensive.

### Discussion

The demographic composition of our autopsy series corresponded to available information on the diabetes population of East Berlin and was therefore representative of the population of diabetics in general. In contrast, the biopsy series had a preponderance of male patients, younger patients, and patients with earlier stages of diabetes. This reflects patient selection for renal biopsy. In a way, however, the two series complemented each other. In assessing the relationship of hypertension and renal lesions, the high percentage of younger patients in the biopsy series was useful.

Our results demonstrate that the morphological features of diabetic nephropathy are quite heterogeneous. Moreover, the combination of several lesions, particularly GS, AS, and/or PN, was relatively frequent. This point was emphasized decades ago.7,9 Finally, glomerular lesions other than glomerulosclerosis or arteriolosclerosis must be taken into consideration — indeed, glomerulonephritis was unexpectedly frequent in our series. The occurrence of such combinations makes it difficult to assess the relationship between hypertension and specific renal lesions.

The proportion of cases of GS in our postmortem series corresponded to what was reported in the total of 8141 diabetic autopsy cases described in the literature. Our findings on hypertension in diabetic patients with and without GS (see Table 2) were also in agreement with postmortem data in the literature; no investigator found hypertension in all patients who had GS, but its prevalence in diabetics with GS was always higher than in diabetics without GS (for survey, see ref. 7). Furthermore, in our series, hypertension was more frequent in the nodular than in the diffuse type of GS. This supports the notion that nodular GS is a more advanced type of lesion. Moreover, in patients with early diabetic glomerular lesions, the prevalence of
hypothesis was lower than in those with manifest GS, but not different from patients without GS. Consequently, GS is presumably not the result of hypertension; the observations support the conclusion of Christlieb that hypertension in GS originates in the renal parenchyma.

Arterio-arteriolosclerosis is a very frequent finding in diabetics. Usually, the most impressive lesions are found in the vas afferentia; they are often advanced, with only a small lumen being left. The massive inudation of plasma into the intima and media with concomitant reduction of the muscle cells also involves the juxtaglomerular apparatus; this lesion may have deleterious effects on the function of both vascular smooth muscle cells and myoepithelial cells in the juxtaglomerular apparatus. Arteriolosclerosis tended to be more severe in diabetics than in a control group of 160 nondiabetic autopsy cases. Malignant nephrosclerosis in diabetics was extremely rare, which agrees with clinical experience.

A high frequency of AS was expected in our hypertensive diabetics (see Table 3). More remarkable was the high prevalence of AS in normotensive diabetics. This finding suggests that at least in many patients, hypertension does not play a role in the genesis of this vascular lesion. Certainly in hypertensive diabetics the probability for AS to occur is very high.

In a previous study we described a positive correlation between the level of blood pressure and the severity of AS; however, this must not be interpreted to indicate a cause-effect relationship. It cannot be excluded that AS is the first lesion that triggers the rise of blood pressure, although it certainly may also be the result of hypertension. An important clue in this respect may be AS of the vas afferentia, which is said to be specific for diabetes. This finding was remarkably common in middle-aged patients and those with diabetes of long duration. It is difficult to conceive, but not altogether impossible, that hypertension in the arterial tree could be transmitted into the postglomerular vessel. Besides, even in malignant hypertension, we never observed involvement of the vas efferens.

From all these facts we conclude that hypertension is not the primary disturbance leading to AS in diabetic patients. It seems more likely that diabetes initiates vascular lesions, which in turn initiate or aggravate hypertension, thus creating a vicious circle.

For several reasons we cannot assess whether pyelonephritis contributes to hypertension in diabetics:

1. Biopsy specimens are not representative, because PN as a focal lesion can never be excluded in small biopsy samples.
2. In the autopsy material, PN was frequently combined with other lesions, for instance about 40% of patients with nodular GS and AS also had chronic PN. This was a higher percentage than in patients with PN who had neither GS or AS (12%).
3. The group with pure chronic PN in the absence of GS or AS was so small that no general conclusions could be drawn.

We share the view of Heptinstall, who questioned the relationship of chronic PN to hypertension because of controversial findings.

There are few reports on GN in diabetics, and its occurrence in these patients is generally considered coincidental. Our biopsy results, however (see Table 5), clearly indicated that GN is by no means infrequent in diabetics, if adequate morphological techniques are applied. We found mostly GN of the membranous type, which agreed with recent anecdotal observations. Until now, we had observed a total of 12 diabetics with membranous GN; in 8 patients this was combined with GS mostly of modest intensity. Other types of GN are more rare. At any rate, the differential diagnosis of glomerulopathy in diabetic patients must take into consideration the presence of GN. Hypertension in diabetic patients with membranous GN and GS is presumably due principally to the concomitant presence of GS.

References

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