Renal Involvement in Type 2 Diabetes Mellitus: A Clinicopathologic Study of the Henry Ford Hospital Experience

Francis Dumler
Vijay Kumar
Raymond N. Romanski
Pedro Cortes
Nathan W. Levin

Follow this and additional works at: https://scholarlycommons.henryford.com/hfhmedjournal
Part of the Life Sciences Commons, Medical Specialties Commons, and the Public Health Commons

Recommended Citation
Dumler, Francis; Kumar, Vijay; Romanski, Raymond N.; Cortes, Pedro; and Levin, Nathan W. (1987) "Renal Involvement in Type 2 Diabetes Mellitus: A Clinicopathologic Study of the Henry Ford Hospital Experience," Henry Ford Hospital Medical Journal: Vol. 35 : No. 4 , 221-225.
Available at: https://scholarlycommons.henryford.com/hfhmedjournal/vol35/iss4/13

This Article is brought to you for free and open access by Henry Ford Health System Scholarly Commons. It has been accepted for inclusion in Henry Ford Hospital Medical Journal by an authorized editor of Henry Ford Health System Scholarly Commons.
Renal Involvement in Type 2 Diabetes Mellitus: A Clinicopathologic Study of the Henry Ford Hospital Experience

Francis Dumler, MD,* Vijay Kumar, MD,† Raymond N. Romanski, MD,‡ Pedro Cortes, MD,* and Nathan W. Levin, MD*

To better understand renal dysfunction in type 2 diabetes mellitus, we studied the clinical and autopsy findings in comparable cohorts of 108 diabetic and 77 nondiabetic patients. In the diabetic group, no differences were noted between black and white patients in blood glucose concentrations, mean blood pressure, or the prevalence of diabetic glomerulosclerosis. However, the prevalence of renal insufficiency was significantly greater (P = 0.002) in black diabetics (58%) than in white diabetics (35%), black controls (28%), and white controls (20%). Logistic regression analysis demonstrated a significant association of renal insufficiency with diabetes (P = 0.006) and race (P = 0.032), but not with mean blood pressure, age, or sex. An additional nonspecific glomerular lesion commonly found was global sclerosis. The occurrence of this lesion was significantly greater (P = 0.001) in black diabetics (42% ± 5%) than in white diabetics (26% ± 5%), black controls (19% ± 4%), and white controls (21% ± 4%), and was highly correlated (P = 0.001) to serum creatinine concentrations. In patients with serum creatinine concentrations lower than 1.6 mg/dL, kidney weight was significantly greater (P = 0.03) in diabetics with diabetic glomerulosclerosis (405 ± 32 g) as compared to those without it (300 ± 25 g) or to control patients (329 ± 13 g). This study demonstrates that the overall prevalence of diabetic glomerulosclerosis in this group of type 2 diabetics is 45%, and that renal enlargement is present in these patients prior to the development of significant renal insufficiency. In addition, renal insufficiency and end-stage renal failure are more common in black than in white diabetics. (Henry Ford Hosp Med J 1987;35:221-5)

Renal disease in type 1 (insulin-dependent) diabetes mellitus is well characterized and has been the subject of intense study (1-9). That clinical renal disease may differ in type 1 and type 2 (noninsulin-dependent) diabetes is suggested by a tenfold difference in the prevalence of diabetic renal disease as the cause of death in patients younger (20%) and older (2%) than 40 years of age. Although abnormal proteinuria may occur in 50% of patients with type 2 diabetes, the glomerular filtration rate does not decrease progressively in most of these patients (10). While the vast majority of patients with type 1 diabetes mellitus who develop renal insufficiency have diabetic nephropathy (8), the extent to which diabetic nephropathy is responsible for renal insufficiency in type 2 diabetics is not well defined. Because the relationship between renal insufficiency and diabetic nephropathy requires histological confirmation, a retrospective autopsy study of 108 consecutive cases of type 2 diabetes mellitus was undertaken to address this issue. In addition, comparisons were made between blacks and whites in view of apparent racial differences in the prevalence of end-stage renal failure from various causes (11).

Methods

Patient population
The Medical Records Department at Henry Ford Hospital identified in its computerized index 650 patients who were older than age 50 at death and whose complete medical and autopsy records were available for study. Of these 650 patients, 145 had been classified by their primary physician as having diabetes mellitus. The diagnosis of type 2 diabetes was retrospectively confirmed, and patients were included in the study only if the following criteria were documented: 1) a negative history of diabetic ketoacidosis; 2) age at onset of diabetes of 40 years or older; and 3) body weight not less than 95% of the calculated ideal body weight based on sex, age, and height. A total of 108 patients with type 2 diabetes as defined by these criteria were entered in the study. The remaining 505 nondiabetic patients were entered into the control group only if 1) plasma glucose concentrations were consistently lower than 180 mg/dL, and 2) body weight was at least 95% of the calculated ideal body weight. A total of 77 patients fulfilled these criteria.
Clinicopathologic evaluation

The following information was recorded for each patient: duration of diabetes, mode of diabetes therapy, mean blood pressure, blood glucose, degree of proteinuria, and serum creatinine concentrations at diagnosis and during the last admission. Blood pressure and blood glucose measurements during the last hospital admission were reviewed, and mean values utilized for analysis. Renal insufficiency was arbitrarily defined as a serum creatinine concentration consistently greater than 2 mg/dL, and end-stage renal failure as a serum creatinine concentration consistently greater than 8 mg/dL or by the use of maintenance dialysis procedures. To ensure that renal function was documented during a representative steady state, if sudden changes in renal function occurred, the stable serum creatinine concentration preceding the acute event was used for analysis. Cardiac weight and left ventricular thickness measurements were recorded.

All renal histological material was analyzed in a blind manner by an independent observer who had no knowledge of the clinical or autopsy findings. Autopsy material for light microscopic studies was considered adequate for reexamination in 134 patients because postmortem alterations did not interfere with the evaluation of the following: 1) presence and degree of global glomerular sclerosis, 2) presence and degree of hyaline arteriosclerosis and intimal thickness of interlobular and arcuate arteries, and 3) presence of diabetic glomerulosclerosis. All glomeruli in each kidney section were examined while avoiding areas of infarction. Global glomerular sclerosis was defined as a rounded, solid scar replacing the entire glomerular tuft, Bowman's space, and blending with or obscuring Bowman's capsule. The degree of diabetic glomerulosclerosis and of arteriosclerosis was graded by using a 0 to 4+ scale at the end of each slide examination. Diabetic glomerulosclerosis lesions were further classified as diffuse or nodular.

Data management and statistical analysis

Identification of all patients eligible for the study was conducted by the Medical Records Department without prior knowledge of the presence or absence of diabetes. All statistical analyses were carried out with the Statistical Analysis System (12). Results are expressed as mean ± SEM or in frequency distributions. Comparison of means was carried out by analysis of variance followed by Duncan's multiple-range test. Frequency distributions were compared by chi-square analysis. The effects of risk factors for the development of renal insufficiency were analyzed by logistic regression.

Results

The characteristics of the patient populations are shown in Table 1. No differences were noted in age, duration of diabetes, or in the prevalence of insulin therapy between black and white diabetics (Table 1). There were no differences in sex distribution or body weight between groups. Body mass index was also similar in all groups (39 ± 1, 39 ± 1, 39 ± 1, and 40 ± 1 kg/m² in black diabetic, white diabetic, black control, and white control patients, respectively). Black control patients had a lower mean age (P = 0.03) than the other groups. Mean blood pressures were significantly higher (P = 0.02) in diabetic than in control patients, but blood pressure differences were not observed between races in diabetic or control patients (Table 1). No differences in cardiac weights were noted between groups: black diabetics (485 ± 30 g), white diabetics (488 ± 11 g), black controls (508 ± 24 g), and white controls (498 ± 22 g). Left ventricular thickness was greater (P = 0.005) in white controls (1.69 ± 0.06 cm) than in black controls (1.59 ± 0.06 cm), white diabetics (1.41 ± 0.09 cm), or black diabetics (1.43 ± 0.10 cm).

Routine urinalysis was negative for protein in 47% of control and 16% of diabetic patients (P = 0.001). A qualitative urinary protein excretion greater than 300 mg/dL was found in three (4%) control patients and in ten (3%) diabetic patients without diabetic nephropathy. Serum creatinine concentrations were significantly higher (P = 0.02) in black diabetic patients than in white diabetic or control patients (Table 1). The prevalence of renal insufficiency was significantly greater (P = 0.002) in black diabetics (58%) as compared to white diabetics (35%), black controls (28%), or white controls (20%), as shown in Fig 1. Similarly, the prevalence of end-stage renal disease was significantly greater (P = 0.05) in black diabetics (27%) than in white diabetics (10%), black controls (14%), and white controls.
Prevalence (%) of Histological Diabetic Renal Disease

<table>
<thead>
<tr>
<th></th>
<th>DIABETICS</th>
<th></th>
<th>CONTROLS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Black</td>
<td>White</td>
<td>Black</td>
<td>White</td>
</tr>
<tr>
<td>Number of patients</td>
<td>35</td>
<td>29</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>Diabetic glomerulosclerosis</td>
<td>45</td>
<td>40</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Grade 3 to 4 + arteriosclerosis</td>
<td>38</td>
<td>24</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Percent of glomeruli with global sclerosis</td>
<td>42 ± 5*</td>
<td>26 ± 5</td>
<td>19 ± 4</td>
<td>21 ± 4</td>
</tr>
</tbody>
</table>

*P = 0.001 when compared to the other groups.

The prevalence of diabetic glomerulosclerosis was similar in black and white diabetic patients (Table 2), and the prevalence of renal insufficiency was 66% in patients with diabetic glomerulosclerosis and 36% in patients without it ($\chi^2 = 4.95; P = NS$). No differences were noted in blood glucose concentrations between black (277 ± 22 mg/dL) and white (269 ± 20 mg/dL) diabetic patients or between patients with and without diabetic glomerulosclerosis (265 ± 25 mg/dL and 282 ± 18 mg/dL, respectively).

Grade 3 and 4 + diabetic glomerulosclerosis were similarly present in black and white diabetics. Although the prevalence of grade 3 to 4 + lobular and arcuate arteriosclerosis was greater in black diabetics than in any other group, the differences were not statistically significant. However, the occurrence of global glomerular sclerosis was significantly greater ($P = 0.001$) in black diabetics than in white diabetics, black controls, or white controls (Table 2).

A significant correlation was found between the degree of global sclerosis and the logarithm of serum creatinine concentrations in all patient groups ($R = 0.729; P = 0.001$).

No differences in kidney weights between groups were noted: black diabetics (271 ± 17 g), white diabetics (313 ± 18 g), black controls (303 ± 19 g), and white controls (291 ± 15 g). However, when control and diabetic patients with and without diabetic nephropathy were grouped according to their serum creatinine concentrations, a significant increase in kidney weight ($P = 0.03$) was demonstrated at serum creatinine concentrations between 0.5 to 1.5 mg/dL in diabetics with diabetic nephropathy (405 ± 32 g) when compared to those without it (300 ± 25 g) or to control patients (329 ± 13 g) (Fig 2). In patients with serum creatinine concentrations greater than 1.6 mg/dL, this difference was not apparent (Fig 2).

The effects of diabetes, race, mean blood pressure, age, and sex in the development of renal insufficiency (including end-stage renal failure) were assessed by logistic regression. The logistic regression model demonstrated significant effects only for diagnosis (diabetic or control) and race (Table 3). The relative risk for developing renal insufficiency was increased 36 times if diabetes was present and was fourfold greater in black patients. The other variables studied (mean blood pressure, age, and sex) resulted in no added risk.
Nevertheless, mean glucose concentrations during the last hospital admission for diabetics; however, this study cannot appropriately evaluate whether the prevalence of renal insufficiency is different in black and white type 2 diabetic patients. A longitudinal prospective study would be ideal in providing data on renal function, blood pressure, and blood glucose control, but would require a long follow-up period. A cross-sectional design could provide adequate data on the prevalence of renal insufficiency in the study population. However, histological confirmation of diabetic nephropathy would require a substantial number of kidney biopsies, even in patients without apparent renal disease, which poses a serious ethical problem. For these reasons, a retrospective cross-sectional autopsy study was chosen.

As in type 1 diabetes (13), an increase in renal size occurred in type 2 diabetic patients with diabetic nephropathy while renal function was preserved (Fig 2). The prevalence of histologically documented diabetic glomerulosclerosis was 45%, which correlates to previously reported prevalences of 25% to 60% (14-18). In addition, the 36% prevalence of renal insufficiency in diabetic patients without nephropathy indicates that a significant number of patients with type 2 diabetes mellitus have renal dysfunction not related to diabetic renal disease. Hypertensive and atherosclerotic renal disease accounted for the majority of renal dysfunction in patients without diabetic glomerulosclerosis. While the prevalence of renal insufficiency and end-stage renal failure (35% and 10%, respectively) in the white population is similar to that in other studies on type 2 diabetes (4,8,14,19-21), it is more frequent in black than in matched white diabetics (Fig 1) and approached that seen in type 1 diabetes (8). Observations from the Michigan Kidney Registry also indicate a fourfold increase in the occurrence of end-stage renal failure in black diabetics over age 40 when compared to white diabetics, with no differences in younger age groups (21). The prevalence of renal insufficiency in this study is a minimum estimate, since renal insufficiency was arbitrarily defined as a serum creatinine concentration greater than 2 mg/dL to ensure that all patients included in this category had reduced renal function.

Age, insulin requirement, and duration of diabetes (Table 1) do not account for the differences between black and white diabetics; however, this study cannot appropriately evaluate the possible relevance of the degree of diabetic control (22). Nevertheless, mean glucose concentrations during the last hospitalization did not differ between black and white diabetic patients or between diabetic patients with and without renal insufficiency.

The possible role of hypertension in the progression of renal insufficiency in diabetes has attracted much attention (5,6,23-26). In this study, logistic regression analysis did not demonstrate an effect of mean blood pressure, age, or sex on the prevalence of renal insufficiency. Although mean blood pressure was greater in diabetic patients, only race and the presence or absence of diabetes were associated with a significant increased risk for renal insufficiency. Several possibilities may account for the absence of a blood pressure effect on renal function in this study. The severity of hypertension throughout the overall duration of diabetes might not have been adequately represented by blood pressure measurements during the last hospital admission. However, cardiac weights were similar, and no differences were noted in left ventricular thickness between black and white diabetics. Patient selection is another important possibility. However, diabetic patients were drawn from an autopsy population that included all patients identified as diabetic independent of race. In addition, the distribution by race in the population studied is similar to the race distribution in Detroit. Finally, blacks may have an intrinsic predisposition for developing more severe glomerulosclerosis than whites at any given degree of hypertension. This difference could be further enhanced by the presence of diabetic microvascular disease. The combination of diabetes and race would then be a much stronger predictor of renal insufficiency than blood pressure alone, as demonstrated in this study. Indeed, black hypertensive patients have more severe nephrosclerosis and a lower renal blood flow than whites matched for age and degree of hypertension (27,28). In keeping with this, black diabetic patients had significantly more global sclerosis than white diabetic or control patients (Table 2), and a significant correlation was found between the degree of global sclerosis and serum creatinine concentrations. Global sclerosis is also commonly observed in patients with focal glomerular sclerosis (29), which is one of the most characteristic lesions observed in heroin nephropathy (30). With equal exposure to nephrotoxic factors, the prevalence of end-stage renal failure is also significantly greater in black than in white heroin abusers (31).

A racially determined response pattern of the renal microvasculature to various factors which include diabetes and hypertension may result in more severe global sclerosis and greater loss of renal function in black patients with diabetes mellitus independent of the prevalence of diabetic nephropathy. Further prospective studies are required to better define the effects of adequate control of diabetes and hypertension on diabetic-induced renal disease in black and white patients. The implication that end-stage renal failure occurs more frequently in the black type 2 diabetic may be relevant in the planning of end-stage renal failure treatment programs.

### Table 3

**Logistic Regression Analysis Data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>1.028</td>
<td>0.0065</td>
</tr>
<tr>
<td>Race</td>
<td>0.772</td>
<td>0.0317</td>
</tr>
<tr>
<td>Mean blood pressure</td>
<td>0.016</td>
<td>0.1646</td>
</tr>
<tr>
<td>Age</td>
<td>-0.03</td>
<td>0.918</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.19</td>
<td>0.6048</td>
</tr>
</tbody>
</table>

*The estimated regression coefficient for each variable in the model (maximum likelihood estimates).

### Discussion

The purpose of this study was to determine 1) the relationship between the presence of diabetic nephropathy and renal insufficiency, and 2) whether the prevalence of renal insufficiency is different in black and white type 2 diabetic patients. A longitudinal prospective study would be ideal in providing data on renal function, blood pressure, and blood glucose control, but would require a long follow-up period. A cross-sectional design could provide adequate data on the prevalence of renal insufficiency in the study population. However, histological confirmation of diabetic nephropathy would require a substantial number of kidney biopsies, even in patients without apparent renal disease, which poses a serious ethical problem. For these reasons, a retrospective cross-sectional autopsy study was chosen.

As in type 1 diabetes (13), an increase in renal size occurred in type 2 diabetic patients with diabetic nephropathy while renal function was preserved (Fig 2). The prevalence of histologically documented diabetic glomerulosclerosis was 45%, which correlates to previously reported prevalences of 25% to 60% (14-18). In addition, the 36% prevalence of renal insufficiency in diabetic patients without nephropathy indicates that a significant number of patients with type 2 diabetes mellitus have renal dysfunction not related to diabetic renal disease. Hypertensive and atherosclerotic renal disease accounted for the majority of renal dysfunction in patients without diabetic glomerulosclerosis. While the prevalence of renal insufficiency and end-stage renal failure (35% and 10%, respectively) in the white population is similar to that in other studies on type 2 diabetes (4,8,14,19-21), it is more frequent in black than in matched white diabetics (Fig 1) and approached that seen in type 1 diabetes (8). Observations from the Michigan Kidney Registry also indicate a fourfold increase in the occurrence of end-stage renal failure in black diabetics over age 40 when compared to white diabetics, with no differences in younger age groups (21). The prevalence of renal insufficiency in this study is a minimum estimate, since renal insufficiency was arbitrarily defined as a serum creatinine concentration greater than 2 mg/dL to ensure that all patients included in this category had reduced renal function.

Age, insulin requirement, and duration of diabetes (Table 1) do not account for the differences between black and white diabetics; however, this study cannot appropriately evaluate the possible relevance of the degree of diabetic control (22). Nevertheless, mean glucose concentrations during the last hospitalization did not differ between black and white diabetic patients or between diabetic patients with and without renal insufficiency.

The possible role of hypertension in the progression of renal insufficiency in diabetes has attracted much attention (5,6,23-26). In this study, logistic regression analysis did not demonstrate an effect of mean blood pressure, age, or sex on the prevalence of renal insufficiency. Although mean blood pressure was greater in diabetic patients, only race and the presence or absence of diabetes were associated with a significant increased risk for renal insufficiency. Several possibilities may account for the absence of a blood pressure effect on renal function in this study. The severity of hypertension throughout the overall duration of diabetes might not have been adequately represented by blood pressure measurements during the last hospital admission. However, cardiac weights were similar, and no differences were noted in left ventricular thickness between black and white diabetics. Patient selection is another important possibility. However, diabetic patients were drawn from an autopsy population that included all patients identified as diabetic independent of race. In addition, the distribution by race in the population studied is similar to the race distribution in Detroit. Finally, blacks may have an intrinsic predisposition for developing more severe glomerulosclerosis than whites at any given degree of hypertension. This difference could be further enhanced by the presence of diabetic microvascular disease. The combination of diabetes and race would then be a much stronger predictor of renal insufficiency than blood pressure alone, as demonstrated in this study. Indeed, black hypertensive patients have more severe nephrosclerosis and a lower renal blood flow than whites matched for age and degree of hypertension (27,28). In keeping with this, black diabetic patients had significantly more global sclerosis than white diabetic or control patients (Table 2), and a significant correlation was found between the degree of global sclerosis and serum creatinine concentrations. Global sclerosis is also commonly observed in patients with focal glomerular sclerosis (29), which is one of the most characteristic lesions observed in heroin nephropathy (30). With equal exposure to nephrotoxic factors, the prevalence of end-stage renal failure is also significantly greater in black than in white heroin abusers (31).

A racially determined response pattern of the renal microvasculature to various factors which include diabetes and hypertension may result in more severe global sclerosis and greater loss of renal function in black patients with diabetes mellitus independent of the prevalence of diabetic nephropathy. Further prospective studies are required to better define the effects of adequate control of diabetes and hypertension on diabetic-induced renal disease in black and white patients. The implication that end-stage renal failure occurs more frequently in the black type 2 diabetic may be relevant in the planning of end-stage renal failure treatment programs.

### References

Renal Involvement in Type 2 Diabetes—Dumler et al