Hypertension and Cardiovascular Risk Factors in Hemodialyzed Diabetic Patients

EBERHARD RITZ, CORNELIA STRUMPF, FRIEDER KATZ, ANTONY J. WING, AND EDUARD QUELLHORST

SUMMARY In a retrospective study, the cause of death and the cardiovascular risk conferred by hypertension and other risk factors were analyzed in 200 diabetic and 200 nondiabetic patients who were matched for age, sex, year of admission, and center of treatment. Total and cardiovascular mortality were considerably higher in diabetics, cardiovascular mortality being 4.8 times higher in patients with type I and 3.0 times higher in those with type II diabetes compared to matched controls. Cardiovascular mortality progressively increased with age and had not improved in recent years. In both types I and II diabetes, the rate (58%) and proportion (38%) of deaths from cardiovascular causes were significantly higher in diabetics than in matched controls. Myocardial infarction (13%) and stroke (7%) accounted only for a minority of cardiovascular mortality, the majority (80%) being due to “sudden death of unknown cause.” Autopsy was carried out in 33% of patients with sudden death. A documented history of long-standing hypertension increased cardiovascular death in diabetic more than in nondiabetic patients. Diabetic retinopathy (an index of microangiopathy) and absence of peripheral pulses, amputation, or history of myocardial infarction, stroke, or transient ischemic attacks (as evidence of macroangiopathy) caused surprisingly little increase in relative risk for cardiovascular death. In diabetics but not in nondiabetics, cardiomegaly, particularly in association with echocardiographic abnormalities, was a strong predictor of cardiovascular death. (Hypertension 7 [Suppl II]: 11-118-124, 1985)

KEY WORDS diabetes mellitus hemodialysis cardiovascular death macroangiopathy

In all studies reported to date, survival of patients with diabetic uremia who are receiving maintenance hemodialysis has been markedly inferior to that of those with nondiabetic uremia.1-5 One-year survival rates reported by the European Dialysis and Transplantation Association (EDTA) registry for diabetics treated solely by hemodialysis were 62% for those age 0 to 40 years at start, 67% for those 40 to 60 years, and 59% for persons over age 60. High cardiovascular mortality is the single most important factor for poor survival of diabetics receiving hemodialysis. The percentage of death from cardiovascular causes in diabetics varies from 23%2 to 54.2%.3

The overriding importance of hypertension in the prognosis of dialyzed diabetic patients has been recognized by many authors; however, quantitative information on the relationship of cardiovascular mortality in these patients to hypertension and other risk factors, as well as risk estimates with respect to nondiabetic persons, is currently not available. The present retrospective multicenter study was designed specifically to answer these questions. A preliminary report of the study was given elsewhere.6

Patients and Methods

Patient Population

All diabetic patients who entered uremia treatment programs in 17 German dialysis centers between January 1, 1972 and December 31, 1983 and who were recorded on the EDTA registry were entered into the study. In all, 228 diabetic patients were identified. The hospital records of 24 patients could not be traced and 4 were found to have been erroneously reported as having diabetes, leaving a total of 200 patients for
analysis. Patients who subsequently either underwent kidney transplantation (9 of 200, 8 of whom had type 1 diabetes) or received peritoneal dialysis (9 of 200, 3 of whom had type 1 diabetes) were excluded. Of the remaining 182 hemodialyzed diabetic patients, 2.7% received limited care dialysis, 2.7% home dialysis, and 94.6% center hemodialysis. Diabetes was classified as type I or type II according to the recommendations of the National Diabetes Data Group; classification was based on case histories obtained from interviewing the patients or their private physicians or analyzing patients' records.

Included in the final analysis were 58 patients with type I diabetes (median age at entry 41.1 years, range 21–67 years; 33 men, 25 women; median duration of diabetes 24 years, range 4–56 years); 111 patients with type II diabetes (median age at entry 61.2 years, range 37–67 years; 59 men, 52 women; median known duration of diabetes 12.7 years, range 0.25–27 years); and 13 patients with nonclassified diabetes (median age at entry 55.3 years, range 47–72 years; 6 men, 7 women). Case controls were obtained by a manual hierarchical search of the EDTA files. Patients were listed for each center according to dates of first treatment. This list was searched alternatively on either side of the diabetic patients until two patients were found of the same sex and age (± 5 years). The search was extended to only 1 year on either side. The first of the two patients whose records were retrieved was used as the control. Of the 200 controls entering treatment programs, 14 underwent transplantation and 3 received peritoneal dialysis, leaving a total of 183 patients for analysis. In unbalanced pairs where either the diabetic patient or matched control was lost for analysis because of transplantation or transfer to peritoneal dialysis, the remaining partner was used for further analysis. Of the 183 control patients included in the final analysis, 16 (8%) received limited care dialysis, 10 (6%) home dialysis, and 157 (86%) center hemodialysis. In the following discussion, the appropriate matched controls for patients with type I or II diabetes or the combined total controls for all diabetic patients are given as indicated in the tables.

Analysis of Cardiovascular Risk Factors

Taking the date of admission to the dialysis program as the reference point, information concerning the following items was obtained from available written patient records and/or interview of the physician in charge. All data were not available for every patient; the number of patients for whom the respective information was lacking is given in parentheses.

1. Documented history of long-standing hypertension: This was assumed to be present if at least 5 years prior to dialysis blood pressure was documented to be above 160/95 mm Hg on three separate occasions or if antihypertensive medication was given (information missing in 34 patients and 37 controls).

2. Systolic blood pressure (phase I) at time of admission into dialysis: The mean of 5 measurements at the time of first dialysis was taken (information missing in 5 patients and 6 controls).

3. Electrocardiographic (ECG) evidence of left ventricular hypertrophy (LVH): Information was obtained either from records or from inspection of the electrocardiogram when available; LVH was defined as positive Sokolow index and/or at least 5 points on the Romhilt-Estes scale (information missing in 19 patients and 11 controls).

4. Additional ECG abnormalities: Evidence of ECG abnormalities other than LVH, such as bundle branch block, depression of ST segment, inverted T wave, and so on was obtained from reports or electrocardiograms when available (information missing in 12 patients and 8 controls).

5. Documented cardiomegaly at the time of first dialysis, defined as cardiothoracic ratio greater than 0.5 (information missing in 12 patients and 15 controls).

6. Presence of diabetic retinopathy as diagnosed by a written record of an ophthalmologist (record missing in 27 patients); records did not permit unequivocal distinction between background and proliferative retinopathy.

7. Documented absence of one or more peripheral pulses on physical examination (information missing in 21 patients and 44 controls).

8. Recorded amputation (information missing in 19 patients).

9. Documented history of myocardial infarction (ECG or enzyme changes), stroke, or transient ischemic attacks (TIA).

10. History of angina pectoris reported by the patient and documented in the patient records at the time of admission to dialysis (no information in 16 patients and 19 controls).

11. Serum cholesterol below 260 mg/dl (SMA-12 autoanalyzer technique) (no information in 20 patients and 22 controls).

End Points

The times and causes of death were taken from records or consultations with family members or private physicians. The following events were classified as cardiovascular mortality: sudden death (sudden defined as less than 1 hour, cardiac arrest, cause unknown), death after documented myocardial infarction (ECG changes and/or enzyme changes), or death after stroke. Autopsy records were available for 23 (25%) of 93 deceased diabetics and 13 (29%) of 45 deceased controls. Autopsy was performed on 3 of 7 diabetic patients with the diagnosis of myocardial infarction, none of the 4 with stroke, and 14 (33%) of the 42 with sudden death. In controls, autopsy records were available for 1 of 3 dying from myocardial infarction, none of 2 dying from stroke, and 4 of 12 dying from sudden death.

Statistical Evaluation

Actuarial survival was calculated using standard techniques. The relative risk was calculated as $R = a/n_1 \cdot c/n_2$ from a contingency table, where $a$ equals the number of dead with risk factor; $c$ equals the number of dead without risk factor; $n_1$ equals the number of all individuals with risk factor; and $n_2$ equals the number of all individuals without risk factor. Significances for relative risks $P_r/P_d$ were calculated as $R = a/n_1 \cdot c/n_2$ from contingency tables. The statistical significance of relative risks was evaluated according to Sachs. Comparison of contingency tables (between diabetic and nondiabetic patients) was carried out according to Le Roy and the differential interpretation according to Steingruber. To avoid a Bonferroni type of error from
multiple testing, the findings were considered significant only when $p < 0.01$.

Results

Survival and Cardiovascular Death

Actuarial survival was lower in patients with type I and type II diabetes than in their respective matched controls. In the observation period, 55.9% of female (median age 53.9 years) and 46.9% of male patients (median age 54.9 years) died.

Figure 1 shows actuarial rate of loss of patients due to cardiovascular death for those with types I and II diabetes and controls. It is obvious that the number of deaths from cardiovascular causes in diabetics of all groups vastly exceeded that of controls. As shown in Figure 2, cardiovascular mortality progressively increased with age in diabetic patients who received hemodialysis. The overall proportion of patients with type I diabetes who died from cardiovascular causes was 4.8 times higher than in matched controls ($p < 0.001$); for those with type II diabetes the respective proportion was increased 3.0 times ($p < 0.01$).

Causes of Death

Table I lists the causes of death for patients with types I and II diabetes and for all diabetic patients and their controls. It is obvious that the rate and number of deaths from cardiovascular causes among all causes of death was significantly higher in patients with both types of diabetes than in controls. Further analysis showed that in the first 18 months of dialysis, 61.4% (35 of 57 deaths) were due to cardiac causes, whereas in diabetic patients dialyzed for more than 18 months the percentage decreased to 41.6% (15 of 36 deaths). In nondiabetic controls, the respective percentages were 28.0% in those dialyzed for less and 40% in those dialyzed for more than 18 months. There were no significant sex differences in either patients or controls.

Risk Factor Profile in Diabetic Patients

Treatment of hypertension in diabetic patients admitted to hemodialysis was unsatisfactory. Of 200 diabetic patients, 184 (92%) had hypertension. Of these 184, 7 (3.8%) had no antihypertensive treatment and only 24 (13%) patients achieved systolic pressure less than 160 mm Hg with antihypertensive therapy. Hypertension tended to be treated better in nondiabetic controls. Of the 200 controls, 116 (78%) had hypertension. Of these 150 controls, 11 (7.1%) had no antihypertensive medication and 101 (64.7%) had insufficient antihypertensive treatment, but 44 (28.2%) achieved a systolic pressure less than 160 mm Hg with antihypertensive therapy. There was a strong relationship between age and clinical evidence of macroangiopathy (Table 2).

Hypertension was interrelated with other risk factors. A higher proportion of patients with angina pectoris was hypertensive (90.2%) than those without angina pectoris (67.5%), but angina pectoris was unrelated to hypercholesterolemia or overweight, according to the Broca formula. Peripheral arterial disease was not significantly related to hypertension (present in 83.3% of patients with and 78.4% without peripheral arterial disease). Hypertension was not related to overweight (present in 89.1% of patients with and 78.9% without overweight).

Relationship Between Cardiovascular Risk Factors on Admission for Dialysis and Subsequent Cardiovascular Death

Table 3 gives the relative risk for cardiovascular death with respect to patients’ clinical status on admis-
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TABLE 1. Causes of Death in Diabetic Patients and Controls

<table>
<thead>
<tr>
<th>Cause</th>
<th>Diabetic patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type I</td>
<td>Type II</td>
</tr>
<tr>
<td>Sudden death</td>
<td>17/34</td>
<td>21/50</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0/34</td>
<td>5/50</td>
</tr>
<tr>
<td>Stroke</td>
<td>2/34</td>
<td>2/50</td>
</tr>
<tr>
<td>Total cardiovascular deaths</td>
<td>19/34</td>
<td>28/50</td>
</tr>
<tr>
<td>Infection</td>
<td>2/34</td>
<td>7/50</td>
</tr>
<tr>
<td>Other</td>
<td>7/34</td>
<td>2/50</td>
</tr>
<tr>
<td>Unknown causes</td>
<td>6/34</td>
<td>13/50</td>
</tr>
<tr>
<td>Total dead</td>
<td>34</td>
<td>50</td>
</tr>
<tr>
<td>Total observed</td>
<td>58</td>
<td>111</td>
</tr>
</tbody>
</table>

TABLE 2. Macroangiopathy and Age in Diabetic Patients (Types I and II) Admitted to Dialysis

<table>
<thead>
<tr>
<th>Peripheral vascular disease (absent pulses or amputation)</th>
<th>History of myocardial infarction, stroke, or TIA</th>
<th>Angina pectoris</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>n</td>
<td>21-40</td>
</tr>
<tr>
<td></td>
<td>41-50</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>51-60</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>58</td>
</tr>
<tr>
<td>Totals</td>
<td>182</td>
<td>79</td>
</tr>
</tbody>
</table>

TABLE 3. Relative Risk for Cardiovascular Death

<table>
<thead>
<tr>
<th>Total</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>diabetic controls</td>
<td>controls</td>
</tr>
<tr>
<td>History of hypertension &gt; 5 years</td>
<td>2.3 (89.7%)</td>
</tr>
<tr>
<td>BP at start of dialysis &lt; 160 mm Hg</td>
<td>0.4* (21.9%)</td>
</tr>
<tr>
<td>BP at start of dialysis &gt; 160 mm Hg</td>
<td>2.5* (78.1%)</td>
</tr>
<tr>
<td>Combination of 1 and 3</td>
<td>2.8† (72.0%)</td>
</tr>
<tr>
<td>ECG evidence of LVH</td>
<td>1.5 (52.1%)</td>
</tr>
<tr>
<td>Additional ECG abnormalities</td>
<td>1.7* (29.5%)</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>1.7* (63.5%)</td>
</tr>
<tr>
<td>Combination of 6 and 7</td>
<td>2.3† (23.5%)</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>2.0 (82.7%)</td>
</tr>
<tr>
<td>Absence of lower extremity pulses</td>
<td>1.4 (37.1%)</td>
</tr>
<tr>
<td>Amputation</td>
<td>1.7 (18.4%)</td>
</tr>
<tr>
<td>History of myocardial infarction, stroke, or TIA</td>
<td>1.6 (20.1%)</td>
</tr>
<tr>
<td>Combination of 10, 11, and 12</td>
<td>0.9 (15.2%)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>1.8* (38.3%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1.2 (31.9%)</td>
</tr>
</tbody>
</table>

Significant increase or decrease of relative risk (in groups of diabetic or controls respectively). Numbers in parentheses represent prevalence of risk factor.

*Nominal \( p < 0.05 \)
†Nominal \( p < 0.01 \)
patients but not in controls. Sixty-four percent of diabetic patients and 51% of controls had cardiomegaly. Cardiomegaly significantly increased the proportion of deaths from cardiovascular causes in diabetics (1.73 times) but not in controls (0.83 times).

The presence of both peripheral arterial disease (absent pulses or amputation) and history of end organ damage in the coronary or cerebral circulations (i.e., myocardial infarction, stroke, or TIA) increased the relative risk of cardiovascular death 4.0 times in controls but failed to change the relative risk significantly (0.86 times) in diabetic patients.

**Discussion**

The present study documented that hypertension is almost uniformly present when diabetic patients are in terminal renal failure. This is in agreement with numerous other reports.\(^3,4,13-16\) Of particular note is the finding that hypertension was much less effectively controlled in diabetics than in matched controls admitted for hemodialysis. In a previous study,\(^13\) we noted that of those receiving hemodialysis, a considerably higher proportion of diabetic (50%) than nondiabetic (27.7%) patients required antihypertensive medication. Such medication was mostly needed because patients did not comply with fluid restriction and/or because ultrafiltration was not well tolerated. Similar problems of hypertension control prior to and during dialysis may explain, at least in part, why a history of hypertension tended to affect cardiovascular prognosis more adversely in diabetic persons than in matched controls. The finding that hypertension at entry into dialysis predicted the risk of cardiovascular mortality was in agreement with findings of Rostand et al.\(^17\)

The high cardiovascular mortality noted in dialyzed diabetics agreed with previous reports.\(^2,8\) In our series, myocardial infarction accounted for only 7 of 54 cardiovascular deaths in diabetic patients, none occurring in those with type I diabetes. The low proportion of documented myocardial infarction agreed with recent studies\(^4\) recording only 4 cases of myocardial infarction among 35 deaths in insulin-dependent dialyzed diabetics. In our study, "sudden death of unknown cause" was the major cause of death. Although admittedly, this category may include some patients with unrecognized suicide, hyperkalemia (particularly after omission of insulin injections), or unanticipated death secondary to advanced autonomic polyneurop-
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athy, it is unlikely that many myocardial infarctions were missed because 33% of the patients had a postmortem examination. Sudden death was equally frequent in patients with insulin-dependent and noninsulin-dependent diabetes, thus rendering unlikely hyperkalemia secondary to withdrawal of insulin. Furthermore, it would be difficult to explain why suicide or hyperkalemia should be predicted by hypertension and other risk factors.

Hypertension may cause cardiovascular death in diabetics by one of several mechanisms. More severe coronary atherosclerosis in diabetics has been shown in studies using coronary angiography and in case control autopsy studies using both coronary angiography and histology. Diabetic persons with angina pectoris have poorer prognosis, and those with myocardial infarction have greater immediate and delayed mortality. In addition, the frequency of myocardial infarction is presumably higher, although this has been questioned.

Previous reports documented high prevalence and poor prognosis of coronary lesions in diabetic patients with uremia admitted to hemodialysis. Weinrauch et al. noted 2-year survival of 88% in 12 patients with type I diabetes without coronary lesions and only 20% in 9 dialyzed patients with type I diabetes with coronary lesions. Kjellstrand et al. found that cardiovascular mortality was much higher in initial months of dialysis than later on, which was confirmed in the present study. They suggested that a cohort of patients with preexisting coronary lesions die soon after beginning hemodialysis.

Several findings of our study, however, are compatible with the role of additional factors other than coronary lesions. In a prospective study, using Doppler measurements of lower leg arterial pressure, 9.6 times higher cardiovascular mortality was found in nonuremic diabetic patients with peripheral vascular disease. No such increase was found in dialyzed diabetic patients with evidence of macroangiopathy. Furthermore, in dialyzed diabetics, a history of myocardial infarction, stroke, TIA, or angina pectoris increased the risk of subsequent cardiovascular death much less than in nondiabetic persons, and in dialyzed patients, cardiovascular mortality was high even in the absence of documented risk factors (see Table 4).

Evidence for noncoronary cardiac disease in diabetics comes from the demonstration of periodic acid-Schiff (PAS)—positive hyaline material in extramural and intramural coronary arteries and the interstitial deposition of PAS-positive material and collagen in the myocardium of diabetic patients. Further evidence of cardiomyopathy was provided by Regan et al. who found elevated left ventricular end-diastolic pressure and diminished stroke volume index in diabetic patients even in the absence of coronary lesions, ischemia, or myocardial dyskinesia. Cardiomyopathy as a result of hypertension, diabetes, or both might explain our finding that cardiomegaly on admission to dialysis predicted subsequent cardiovascular death in diabetic (but not in nondiabetic) patients. Overhydration as an alternative cause of cardiomegaly is not excluded, but it would be difficult to see why at admission to dialysis that should have had adverse consequences only in dialyzed diabetics. The hypothesis of an important role of noncoronary cardiomyopathic mechanisms of cardiac death in dialyzed diabetic persons would explain the rarity of myocardial infarction and the predictive value of cardiomegaly; it would also have interesting implications for treatment modalities. Decreased left ventricular compliance from diabetic cardiomyopathy, as demonstrated in experimental and clinical studies, would render dialyzed diabetics more susceptible to left ventricular underfilling and hypotension during ultrafiltration. Hypotensive episodes are more common in these patients and might even cause more severe myocardial ischemia because of impaired autoregulation in diabetes. We have been struck by anecdotal observations of widespread myocardial fibrosis in dialyzed diabetic patients who had patent coronary arteries (unpublished observations, 1984).

As reported elsewhere, actuarial 5-year survival of diabetic patients was 70% for those receiving hemofiltration, 56% CAPD, and only 34% hemodialysis, but patients were not randomly allotted to treatment modalities. Sudden death of unknown cause accounted for 4 of 11 fatalities of subjects undergoing hemodialysis, but only 1 of 7 for hemofiltration. It has been proposed that electrical instability might explain adverse cardiac effects of hemodialysis in diabetics, since in the same patients, episodes of cardiac arrhythmia (Holter monitoring) were more prevalent after hemodialysis, despite control of serum potassium, than after hemofiltration. Posttreatment cardiac arrhythmia was related to hypotensive episodes during treatment irrespective of treatment modality. Cardiomyopathy in dialyzed diabetics may predispose to intradialytic hypotension, posthypotensive arrhythmia, and sudden death. Better survival of patients receiving hemofiltration may be due to fewer hypotensive episodes. This interpretation is clearly hypothetical and must be tested in controlled prospective studies.

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