Controlling systolic blood pressure is difficult in patients with diabetic kidney disease exhibiting moderate-to-severe reductions in renal function

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Abstract
This study compared the use of antihypertensive treatment and blood pressure (BP) controls between patients with diabetic kidney disease (DK+) and patients with non-diabetic kidney disease (DK−) exhibiting moderate-to-severe chronic renal failure who did not need renal replacement therapy. A cross-sectional survey included all renal patients with s-creatinine at ≥200 μmol/l attending regular control sessions at six renal units in Norway. Of the 351 patients included, 73 (20.8%) were DK+. The proportion reaching a BP goal of <130/80 mmHg was similar in DK+ and DK− (14.1% vs 13.6%, p=0.92), while 38% and 39% achieved a BP of <140/90 mmHg, respectively. The systolic BP goal was more difficult to achieve than the diastolic BP goal in DK+ patients (35% vs 15%) despite a mean of three different types of drugs being used. Loop diuretics and beta-adrenergic-receptor antagonists were the most frequently prescribed drugs, and the use of angiotensin-converting enzyme inhibitors or angiotensin-II-receptor antagonists declined when renal function deteriorated, from 80% to 0% and from 66% to 20% in the DK+ and DK− groups, respectively (p=0.001). Thus, despite the use of multiple antihypertensive drugs, controlling BP – especially the systolic BP – is difficult in high-risk patients with chronic renal failure caused by diabetic kidney disease.

Key Words: Antihypertensive drugs, blood pressure control, chronic renal failure, diabetic kidney disease

Introduction
Hypertension is the most important risk factor for the progression of kidney disease and renal insufficiency. An additional renoprotective benefit beyond that obtained by blood pressure (BP) lowering has been provided in drugs blocking the renin–angiotensin system, both in diabetic (1–3) and non-diabetic (4–7) kidney disease. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-II-receptor antagonists (ARBs) are often used in conjunction with a diuretic or calcium-channel blocker (CCB), but there are increasing reports of the use of combination therapy with ACEIs and ARBs (8–11).

The choice of antihypertensive drugs is affected by comorbidity (e.g. coronary heart disease or congestive heart failure) and by specific pathophysiological changes in chronic renal failure, such as volume overload. The importance of sympathetic overactivity as a contributor to hypertension in renal patients has been emphasized (12), and hence beta-adrenergic-receptor blockers (BBs) are frequently used in these patients. It has been claimed that CCBs improve the survival of hemodialysis patients...
BP control in diabetic kidney disease

(13, 14), and this has been linked to a reduced risk of calcinosis due to a specific effect on intracellular calcium and disturbances in the calcium–phosphate balance (15). However, others have suggested that further trials are needed to substantiate the associated treatment decisions (16).

The major cause of morbidity and mortality in diabetes mellitus is cardiovascular disease, which occurs prematurely as well as in excess compared with non-diabetic subjects, and even more so when diabetes is complicated with chronic renal failure. Hypertension is a modifiable risk factor for cardiovascular disease in general, although this has not been convincingly observed in diabetic kidney disease (2, 3), while progression of renal function deterioration is delayed or halted (1–3).

Early studies provided evidence that diastolic BP (DBP) should be below 90 mmHg in progressive renal disease (17). Recent guidelines based mainly on observational data recommend that BP should be lowered to <130/80 mmHg in progressive chronic renal failure irrespective of its cause, and even lower in patients with marked proteinuria (18–21). There are few data on how well BP control is achieved in renal patients in clinical hospital practice (22, 23), particularly in diabetic kidney disease (24). We have previously reported results on controlling BP in patients with moderate-to-severe chronic renal failure receiving specialized care (25).

Given this background, the aim of the current study was to compare in a specialist setting how BP is controlled between chronic-renal-failure patients with diabetic kidney disease and those with non-diabetic kidney disease.

Methods

Study design

The study design and patient population are described in detail elsewhere (25), and are therefore only summarized here. This was a cross-sectional survey based on hospital charts of patients with chronic renal failure with serum creatinine at ≥200 μmol/l from six renal units in Oslo, Norway, and the surrounding area, which constitutes the nephrology referral area for approximately 1.8 million Norwegians. Only ambulatory patients were included, and they had to attend regular controls at least every 3rd month at the renal unit. Furthermore, the last visit had taken place at 1–120 days before the present survey. Acute renal failure with serum creatinine elevation of less than 3 months duration, previous dialysis or transplantation, and current dialysis were exclusion criteria. All consultants at the renal units were informed of the survey. The study has been approved by The National Committees for Research Ethics in Norway. The database was anonymized.

The time of first admission and laboratory measurements at different times including the last visit were recorded, as were the cardiovascular and macrovascular histories (e.g. myocardial infarction, stroke, peripheral vascular disease and aortic aneurism). The drug regimen at the time of the survey was registered using the classes of antihypertensive medication, and also the dosage for loop diuretics. ACEIs and ARBs were grouped together. No patient used a combination of the two classes. BP measurements at the time of admission to the hospital and at the last visit before the present survey were also entered into the database. The pulse pressure (PP) was calculated by subtracting DBP from SBP. Serum creatinine was used as a measure of kidney function. Creatinine clearance could be calculated in two-thirds of the patients using the Cockcroft–Gault formula (26). Patients were categorized according to the proposed US guidelines (21) based on the calculated creatinine clearance. Proteinuria status was often either lacking or obtained with variable methodology, which was mostly qualitative or semi-quantitative. These data were therefore not collected.

The diagnosis of diabetic nephropathy was based on the hospital records. Patients were designated hypertensive based on a BP of >140/90 mmHg at admission, the use of antihypertensive drugs, or a BP at the last visit of >140/90 mmHg. Controlled hypertension was defined as a BP of <130/80 mmHg, and uncontrolled hypertension was defined as BP>130/80 mmHg at the last consultation. The control rate was also assessed using <140/90 mmHg as the target.

Statistics

All data are presented as means ± standard deviations except where numbers and percentages are given. For skewed distributions, the median and 25th (Q1) and 75th (Q3) percentiles are given. Comparisons were made using the t-test, Student’s t-test, and one-way analysis of variance (ANOVA); Wilcoxon’s test, Kruskal–Wallis one-way ANOVA and Mann–Whitney U-test (p’) were also used for skewed distributions. A simple bivariate relationship was assessed by calculating Spearman’s correlation coefficients. All statistical analyses were performed using standard software (SPSS version 11.0, SPSS, Chicago, IL, USA). Two-tailed probabilities of p (p’ ≤ 0.05) were considered indicative of statistical significance.
Results

Data from 351 patients were used in the current analyses. Diabetic kidney disease was specified as the cause of chronic renal failure in 21.3% (73 patients), of which 62 (85%) had type 2 diabetes mellitus. There was no significant difference between patients with diabetic kidney disease and those with non-diabetic kidney disease with respect to age (62.5 ± 12.7 vs 65.0 ± 12.6 years, \( p = 0.23 \)), body weight (80.8 ± 20.1 vs 84.2 ± 18.6 kg, \( p = 0.29 \)) or creatinine clearance (24.8 ± 12.4 vs 24.5 ± 9.1 ml/min, \( p = 0.29 \)). The time from referral to the time of registration for the present study also did not differ significantly (median and Q1–Q3, 24 (8–58) vs 17 (9–35) months, \( p’ = 0.28 \)). There was also no difference in the K/DOQI stages of chronic renal failure between the two groups. Triglyceride levels were marginally higher in the patients with diabetic kidney disease (mean 2.1 ± 2.6 mmol/l, \( p = 0.059 \), \( p’ = 0.09 \)); otherwise, no differences were found in lipid levels between the two groups.

Macrovascular disease

Concomitant macrovascular disease was prevalent, and significantly higher in the patients with diabetic kidney disease than in the patients with non-diabetic kidney disease (51% vs 35%, \( p = 0.01 \)). A similar difference was observed for coronary heart disease (44% vs 26%, \( p = 0.003 \)).

BP

Only one of the 73 patients with diabetic kidney disease was normotensive, compared with 11 of the 278 patients with non-diabetic kidney disease (\( p = 0.28 \)). In those who had hypertension, the PP was significantly higher in those with diabetic kidney disease than in those with non-diabetic kidney disease at the time of referral, but no difference in PP was apparent at the time of the survey (Table I). Thus, the decrement in PP during the follow-up at the renal unit was more pronounced in patients with diabetic kidney disease than in those with non-diabetic kidney disease (10.4 ± 20.1 vs 5.1 ± 19.6 mmHg, \( p = 0.05 \), \( p’ = 0.03 \)).

There was no difference between the two groups in the proportion reaching the target BP of <130/80 mmHg (14.1% vs 13.6%, \( p = 0.92 \), Figure 1), nor in the proportion reaching either an SBP of <130 mmHg (\( p = 0.50 \)) or a DBP of <80 mmHg (\( p = 0.86 \)). Fewer reached the SBP goal than the DBP goal in both groups (diabetic kidney disease, 35.2% vs 15.4%; non-diabetic kidney disease, 34.1% vs 18.9%). There was no difference between the groups when the BP target was set at <140/90 mmHg (39% vs 38%, \( p = 0.81 \)). The SBP goal of <140 mmHg was achieved in 45% and 41% of patients with diabetic and non-diabetic kidney disease, respectively (\( p > 0.05 \)), while the DBP goal of <90 mmHg was reached in 71% and 76%, respectively (\( p > 0.05 \)).

Antihypertensive therapy

The number of different types of drugs used was significantly higher in patients with diabetic kidney disease than in the other group (3.0 ± 1.2 vs 2.5 ± 1.3, \( p = 0.003 \)), and there were fewer patients using monotherapy in the diabetic group (Figure 2). Although a similar proportion of patients in the two groups used antihypertensive drugs, there were differences in treatment modality (Figure 3). Loop diuretics were more frequently used by the patients with diabetic kidney disease, and the mean daily dose of furosemide was higher (159 ± 149 vs 114 ± 111 mg, \( p = 0.02 \), \( p’ = 0.06 \)). The dosage of

Table I. Blood pressure levels in hypertensive patients with diabetic and non-diabetic kidney disease as a cause of chronic renal failure at the time of referral to the hospital, and at the time of the survey.

<table>
<thead>
<tr>
<th></th>
<th>Diabetic kidney disease (( n = 73 ))</th>
<th>Non-diabetic kidney disease (( n = 266 ))</th>
</tr>
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<tbody>
<tr>
<td>At admittance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>159 ± 28</td>
<td>156 ± 24</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>86 ± 17</td>
<td>89 ± 16</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>73.7 ± 19.0</td>
<td>67.6 ± 19.6*</td>
</tr>
<tr>
<td>At study time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>143 ± 19</td>
<td>143 ± 21</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>80 ± 11</td>
<td>81 ± 11</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>63.2 ± 18.0</td>
<td>62.4 ± 18.4</td>
</tr>
</tbody>
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DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure. *\( p = 0.024 \).
loop diuretics increased with the K/DOQI classification stage in the total study population ($p' = 0.27$), and the difference was significant between stages 3 and 5 ($87\text{ vs } 149\text{ mg}, p' = 0.023$). Looking separately at the patients with diabetic kidney disease, no difference appeared with increasing serum creatinine levels or with decreasing creatinine clearance. The median dose of furosemide in the patients with diabetic kidney disease was 80 mg (Q1–Q3 60–245 mg; range 20–560 mg). Furthermore, a substantially higher proportion of patients with diabetic kidney disease used BBs, while the proportions were similar for CCBs and ACEIs/ARBs. None of the patients in the current survey used a combination of ACEIs and ARBs. Thiazide diuretics were used by only a very small number of patients and are categorized here together with $\alpha_1$-receptor blocker, $\alpha$-methyldopa, and moxonidine. While statin therapy was prevalent in both groups, the rate was significantly higher in patients with diabetic kidney disease (61% vs 46%, $p = 0.016$). Statin use did not vary with advancing renal failure ($p = 0.57$).

**Use of ACEIs or ARBs in relation to stage of chronic renal failure**

Staging based on estimated creatinine clearance was possible in 214 of the 339 patients categorized as hypertensive (including 46 of the 72 with diabetic nephropathy). None of the patients was categorized as being in stage 1, while only three patients were categorized as stage 2. Stages 2 and 3 are therefore grouped together. Most of the total study sample (54%) were classified as having severely reduced renal function (i.e. stage 4), while the proportions were similar for stages 3 and 5 (26% and 20%, respectively); the proportions were 30%, 52% and 18%, respectively, in patients with diabetic kidney disease.

There was a sharp decline in the use of ACEIs or ARBs with advancing renal failure ($p < 0.001$). The finding was slightly different in patients with diabetic kidney disease (Figure 4a), as none classified as stage 5 used ACEIs or ARBs. In both groups, the proportion using loop diuretics increased with more advanced renal failure (Figure 4a and 4b), but the mean dosage of loop diuretics did not differ significantly with the stage of chronic renal failure.
Discussion

Findings in clinical trials do not necessarily translate to clinical practice, but the overall mean SBP in the patients with diabetic kidney disease in the current survey was similar to that observed in the randomized RENAAL study (3). However, the BP control was far from optimal in this population as only 14% of the patients reached the target BP of <130/80 mmHg after a median follow-up time at renal units of approximately 2 years. This result mirrors the findings from a large US database in which only 11% of diabetic patients achieved an SBP goal of <130 mmHg (27). In a recent study from Finland, 19% of type 1 diabetic patients with overt nephropathy achieved a BP of <130/85 mmHg (24). Those patients had not reached end-stage renal disease, and detailed data regarding renal function were not provided. Furthermore, while the majority of patients in our study had type 2 diabetes mellitus, the Finnish study included only patients with type 1 diabetes mellitus and overt nephropathy. The failure to obtain the goal BP is especially discouraging given that diabetic kidney disease is a major contributor to the increasing prevalence of end-stage renal failure in both the US and Europe. A recent (albeit small) prospective study looked specifically at the effectiveness of a stepped-care program in the treatment of diabetic nephropathy, and found that only one-third of patients reached a BP target of <130/80 mmHg in clinical practice (23). The patients in that study had serum creatinine levels 52–395 µmol/l, and they differed substantially from our patients in comorbidities.

A total of 39% of the patients with diabetic kidney disease in the present study reached a target BP of <140/90 mmHg. In a recent study conducted among normotensive patients with type 2 diabetes, intensive antihypertensive therapy aimed at a DBP of <80 mmHg had little beneficial effect on the progression of kidney disease in the group with overt albuminuria. The estimated creatinine clearance was reduced from 82 to 52 ml/min in the intensively treated group, compared with a reduction of 76 to 57 ml/min in those with a more modest reduction in BP (28). The BP goal to aim for in this population is clearly still debatable.

Our inclusion criteria differed from those used in other studies. Our patients had been transferred to specialist clinics in nephrology due to their kidney disease. Patients with serum creatinine levels of >200 µmol/l have traditionally been identified as a group requiring referral from general practice to more specialized care. Furthermore, our patients were required to attend regular control sessions, i.e. only patients who attended such a session at least every 3rd month were included. Although the care could therefore be assumed to be the best available, there were clearly still problems achieving a BP goal of <130/80 mmHg. However, there was a substantial decline in BP from the time of referral to the last visit. Moreover, the number of patients obtaining acceptable BP control in the present survey may be underestimated due to some patients receiving specialist care for only a short time. Notwithstanding that limitation, the number reaching a BP of <140/90 mmHg is better than what has been achieved in patients with essential hypertension in general practice in Norway (29). Furthermore, there was no difference in BP control between patients with diabetic and non-diabetic kidney disease.

The types of drugs used differed somewhat in the group with diabetic kidney disease in our study compared with the diabetic population in the RENAAL study at baseline (3), especially regarding the use of BBs. However, in our study population, macrovascular disease was prevalent among patients with diabetic kidney disease. This is also the most likely explanation for the frequent use of statins. The use of loop diuretics in the RENAAL population increased to over 80% during the study period (3), which is close to the proportion we observed. Approximately half of our patients with diabetic kidney disease used either ACEIs or ARBs, a similar proportion to that in the RENAAL study at baseline (3). This contrasts with a Finnish study that found that 78% and 12% of patients with overt diabetic nephropathy used ACEIs and ARBs, respectively (24). However, the study populations were different as only type 1 diabetics were included in the Finnish study, and we do not know how well kidney function was preserved. In our study, 80% of patients with diabetic kidney disease with the best-preserved kidney function used ACEIs or ARBs. Moreover, a significantly larger number of different types of drugs were used by patients with diabetic kidney disease than by those with non-diabetic kidney disease, and the proportions were in the same range as those observed in clinical randomized trials. None of the patients in the present study used combination therapy with ACEIs and ARBs despite the recent reports of a possible favorable effect (8–11).

The higher use of BBs in patients with diabetic kidney disease than in those with non-diabetic kidney disease can be explained by an increased prevalence of coronary heart disease in the former group. Sympathetic overactivity in chronic renal failure (12) might also favor the use of BBs, but this should have affected both groups in a similar manner.
manner. The most likely explanation for the increased use and higher dosage of loop diuretics in the group with diabetic kidney disease is the volume load frequently seen in proteinuric kidney disease (30). In the total study population, a modest increase in the dose of loop diuretics was observed with more advanced renal failure. This was not apparent in the group with diabetic kidney disease, and therefore the use of larger doses of loop diuretics should be encouraged in order to enhance the BP-lowering effect.

As renal function deteriorates, the pattern of antihypertensive medication changes with a sharp decline in the use of ACEIs and ARBs. This was apparent in all patients, and may be attributable to a fear of adverse events, including an accelerated decline in renal function or serious hyperkalemia (31–33). The renoprotective effect of the inhibition of angiotensin-converting enzymes is independent of the severity of renal failure, and has actually been shown to be better in patients with a lower glomerular filtration rate (33).

This study is subject to some limitations. The study was cross-sectional, with data being collected retrospectively. The numbers of patients included in the two groups was limited to 73 patients with diabetic kidney disease and 278 patients with non-diabetic kidney disease. The general recommendation in Norway is that all patients with renal insufficiency should be seen by a specialist and referred to renal units. Thus, the results may not be applicable to patients with less advanced renal failure, those with kidney disease without renal function deterioration, those who attend control sessions less frequently, or those who are not attending renal units at all but are instead controlled in another setting. The six renal units that participated cover a referral area constituting more than one-third of all Norwegian inhabitants, and should therefore be representative of all the renal units in Norway. The proportion of urban dwellers is higher in our study population compared with the other two-thirds of Norwegians, and this could affect our results. There were, on the other hand, no significant differences in treatment strategy between the different hospitals (data not shown). Nearly all the patients in the current survey were Caucasian. The data are based on the hospital charts, leading to the possibility of shortcomings in registration. We had no data on compliance or adherence to the medication. The cause of chronic renal failure was based on a clinical assessment rather than a renal biopsy in the majority of patients, which could lead to an over-estimation of diabetic nephropathy. When patients are referred to a hospital with diabetic nephropathy, biopsies are rarely performed unless clinical signs and symptoms indicate another kidney disease.

To summarize and conclude, the present analysis of obtained BP levels and use of antihypertensive drug in patients with diabetic kidney disease regularly attending specialist care has clearly shown that it is difficult to control BP in this population, especially SBP. However, this was also the case in patients with non-diabetic kidney disease, although their use of antihypertensive drugs was slightly lower. The drug regimen differed somewhat between the two groups, with the use of loop diuretics and BBs being more prevalent in patients with diabetic kidney disease. The use of ACEIs and ARBs declined markedly with advancing renal failure, thereby suggesting the presence of an underuse of beneficial drugs in those patients who might benefit the most in terms of renal protection. Although all diabetic patients with the most advanced chronic renal failure used loop diuretics, there also appeared to be an underuse even of loop diuretics, and hence a higher dosage should be considered in order to improve BP control. Further prospective studies are warranted, especially into the possibility of obtaining better BP control in those patients at very high risk of not only the progression of renal disease, but also cardiovascular morbidity and mortality.

Acknowledgement

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References


