ARTICLE

Ambulatory pulse pressure, decreased nocturnal blood pressure reduction and progression of nephropathy in type 2 diabetic patients

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Abstract

Aims/hypothesis We followed type 2 diabetic patients over a long period to evaluate the predictive value of ambulatory pulse pressure (PP) and decreased nocturnal BP reduction (non-dipping) for nephropathy progression.

Methods Type 2 diabetic patients ($n=112$) were followed for an average of 9.5 (range 0.5–14.5) years. At baseline, all patients underwent 24 h ambulatory BP measurement. Urinary albumin excretion rate was evaluated by three urinary albumin:creatinine ratio measurements at baseline and follow-up.

Results At baseline, patients who subsequently progressed to a more advanced nephropathy stage ($n=35$) had reduced diastolic night/day BP variation and higher 24 h systolic BP and PP values; they also had more advanced nephropathy and were more likely to smoke than those with no progression of nephropathy ($n=77$). In a Cox regression analysis, independent predictors of nephropathy progression were 24 h PP ($p<0.01$), diastolic night:day BP ratio ($p=0.02$) and smoking ($p=0.02$). The adjusted hazards ratio (95% CI) for each mmHg increment in 24 h PP was 1.04 (1.01–1.07), whereas the adjusted hazards ratio (95% CI) for each 1% increase in diastolic night:day BP ratio was 1.06 (1.01–1.11). Only one of 33 patients (3.0%) with both a diastolic night:day BP ratio and a 24 h PP below the median progressed, whereas 17 of 32 patients (53.1%) with both a diastolic night:day BP ratio and a 24 h PP equal to or above the median progressed to a more advanced nephropathy stage ($p<0.001$).

Conclusions/interpretation Ambulatory PP, impaired nocturnal BP decline and smoking are strong, independent predictors of nephropathy progression in type 2 diabetic patients.

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Introduction

An elevated pulse pressure (PP) is strongly associated with micro- [1–5] as well as macrovascular [1, 6–8] complications in type 2 diabetic patients. In a large observational study including 954 elderly type 2 diabetic patients [9], ambulatory PP was a strong and independent predictor of progression of nephropathy during a 2 year follow-up period. At present, no studies on the long-term predictive value of ambulatory PP for nephropathy progression in patients with type 2 diabetes have been published.

Impaired nocturnal BP decline ('non-dipping') is another BP abnormality that has been associated with micro- [1, 10–17] and macrovascular [1, 18] complications in type 1 and type 2 diabetic patients. In a recently published 3 year follow-up study in elderly patients with type 2 diabetes [19], patients with a reversed diurnal BP rhythm (nocturnal BP 'risers') had an increased risk of nephropathy progression compared with those who had a normal reduction in BP during the night ('dippers'). Data on the long-term prognostic significance of blunted circadian BP variation for progression of nephropathy in type 2 diabetic patients are sparse.

Hence, the aim of the present study was to evaluate the predictive value of 24 h ambulatory PP and diurnal BP variation for progression of nephropathy in type 2 diabetic patients in a long-term follow-up study.

Methods

Patients We randomly selected 118 type 2 diabetic patients from our outpatients clinic from March 1993 through October 2000 and included them in the study. Cross-sectional data from a subgroup of these patients have previously been published [1]. Patients were followed for a mean of 9.5 (range 0.5–14.5) years until death or until 1 April 2008. Six patients were excluded due to incomplete 24 h ambulatory blood pressure (AMBP) measurement (four patients) or migration (two patients), thus leaving 112 patients with available follow-up data.

All patients included in the study were of white ethnicity. The diagnosis of diabetes was established according to WHO criteria. Type 2 diabetes was defined as: (1) onset of diabetes after the age of 30 years; (2) no need for insulin treatment for ≥1 year after the diagnosis of diabetes; and (3) no history of ketoacidosis. Patients were classified as non-smokers (without daily use of tobacco for the preceding year) or smokers (daily use of tobacco). All patients gave their written informed consent to participate. The study adhered to the tenets of the Declaration of Helsinki and was approved by the local committee for biomedical ethics.

Twenty-four hour AMBP measurements The 24 h AMBP was measured by an oscillometric technique with Spacelabs 90202 and 90207 devices (Spacelabs, Redmond, WA, USA) validated according to the British Hypertension Society protocol [20]. Spacelabs 90202 obtained readings every 20 min between 06:00 and 00:00 hours and once hourly between 00:00 and 06:00 hours, whereas Spacelabs 90207 measured at 20 min intervals throughout the 24 h period. Measurements were performed during a day with normal activities at home or at work. Individually reported

sleeping times were used in the calculation of day and night BP. If more than 3 h were missing, the patient was excluded (four patients). Nocturnal BP dipping was evaluated by systolic and diastolic night:day BP ratios, presented as percentages, calculated by dividing night-time BP (average of the hourly averages over the night-time period) by day-time BP (average of the hourly averages over the day-time period) and multiplying this value by 100. Office BP was measured with a Hawksley random zero sphygmomanometer (Hawksley, Sussex, UK). The mean of three measurements was calculated.

Nephropathy classification Urinary albumin concentration was determined by an immunoturbidimetric method (Roche Diagnostics, Basel, Switzerland). The urinary albumin excretion (UAE) was evaluated by albumin:creatinine ratios in three samples of morning urine at baseline as well as at follow-up. Patients were classified as normo-, micro- or macroalbuminuric when at least two of three samples had urinary albumin:creatinine ratios of <2.5 mg/mmol (men) and <3.5 mg/mmol (women), 2.5 to 25 mg/mmol (men) and 3.5 to 35 mg/mmol (women), or >25 mg/mmol (men) and >35 mg/mmol (women), respectively [21]. In patients with normoalbuminuria at baseline, progression of nephropathy was defined as the development of stable micro- or macroalbuminuria. In patients with micro- or macroalbuminuria at baseline, progression was defined as the development of stable macroalbuminuria, or a doubling of plasma creatinine level or development of end-stage renal failure, respectively [22–24].

Eye examinations In each eye a standard photograph of 60 degrees was taken. Each photograph was evaluated independently by two experienced graders. Patients were classified as having no, mild (grade 2) or advanced (grades 3–6) retinopathy as previously described [1].

Laboratory analyses HbA_{1c} was determined by high-performance liquid chromatography (non-diabetic range 4.4 to 6.4%). Total cholesterol, HDL-cholesterol and triacylglycerol were analysed using an enzymatic colorimetric method (Cobas Integra 700; Roche). LDL-cholesterol was calculated from the Friedewald equation: LDL-cholesterol = total cholesterol − HDL-cholesterol − triacylglycerol × 0.45.

Statistical analyses All variables were tested for normal distribution using the Kolmogorov–Smirnov non-parametric test. UAE and plasma creatinine level were logarithmically transformed prior to analysis in order to obtain normal distribution. Results are expressed as means ± SD (normally distributed variables) or as medians with interquartile range for skewed data. Differences between groups at baseline were tested by the Student's *t* test. For non-continuous

variables, the χ^2 test with Yates' correction was used. The predictive value of baseline variables for nephropathy progression is presented as HRs with 95% CIs.

The predictive value of baseline variables for nephropathy progression was evaluated by Cox proportional hazards multiple regression analyses. The analyses were performed with backwards selection including the following baseline variables that were significant at the 0.10 level in a bivariate analysis (log-rank test): smoking, plasma creatinine, 24 h systolic BP, 24 h PP and diastolic night:day BP ratio. In addition, sex, age, duration, baseline UAE and HbA_{1c} were included in the model because of their biologically plausible association with nephropathy progression. The following variables were excluded: baseline antihypertensive and glucose-lowering treatment modality, history of macrovascular disease, retinopathy severity, height, BMI, total cholesterol and HDL- and LDL-cholesterol, triacylglycerol, office BP values, 24 h diastolic AMBP values and systolic night:day BP ratio.

Data were analysed using SPSS (version 15.0) statistical software (Chicago, IL, USA). A two-tailed p value of less than 0.05 was considered statistically significant.

Results

Baseline clinical and laboratory characteristics of study participants are given in Table 1. During follow-up, 35 (19 of 71 patients with normo-, seven of 26 patients with micro-, and nine of 15 patients with macroalbuminuria) of 112 patients progressed to a more advanced stage of nephropathy. All patients progressing from normo- to micro- or from micro- to macroalbuminuria had an increase in UAE of at least 25%. Patients who subsequently progressed to a more advanced nephropathy stage tended to be older, had a slightly longer duration of diabetes, were more likely to be treated with insulin and tended to have more advanced retinopathy and macrovascular disease, higher office BP values, poorer glycaemic control and a higher plasma creatinine level than those with no progression of nephropathy ($n=77$). However, these differences were not statistically significant. The number of patients on antihypertensive therapy (AHT) at baseline was similar for those with and those without progression of nephropathy. Moreover, night:day BP ratios did not differ between subgroups of AHT (data not shown).

In contrast, among the patients who progressed to a more advanced nephropathy stage there was a significant preponderance of smokers and patients with a more advanced degree of nephropathy at baseline. Likewise, diastolic night:day BP ratio and 24 h systolic BP and PP, but not 24 h diastolic BP, were significantly higher in the group who subsequently progressed to a more advanced

Table 1 Baseline clinical and laboratory characteristics of 112 type 2 diabetic patients without (non-progressors) or with progression (progressors) of nephropathy at follow-up

Characteristic	Non-progressors ($n=77$)	Progressors ($n=35$)	p value
Sex (men/women)	45/32	23/12	0.53
Age (years)	57±10	59±8	0.21
Known duration of diabetes (years)	6±7	8±8	0.19
Antihypertensive treatment	40	19	0.84
ACE inhibitor/ARB	20	11	0.65
Beta-blocker	13	4	0.58
Calcium channel blocker	16	13	0.10
Diuretic	16	8	0.81
Glucose-lowering treatment			0.05
Diet	30	6	
Oral agent	34	18	
Insulin	13	11	
Smoking	19	17	0.01
History of macrovascular disease	19	13	0.18
Retinopathy			0.17
None	43	17	
Mild	25	9	
Advanced	9	9	
Nephropathy			0.02
Normoalbuminuria	52	19	
Microalbuminuria	19	7	
Macroalbuminuria	6	9	
BMI (kg/m²)	29±5	30±5	0.79
HbA_{1c} (%)	8.2±1.7	8.8±2.0	0.13
Plasma creatinine (μmol/l)	76 (66–87)	78 (67–99)	0.08
Urinary albumin: creatinine ratio (mg/mmol)	1.6 (0.8–4.0)	2.8 (1.5–23.8)	0.59
Total cholesterol (mmol/l)	5.9±1.0	5.8±1.7	0.71
HDL-cholesterol (mmol/l)	1.2±0.3	1.2±0.4	0.66
Triacylglycerol (mmol/l)	2.5±2.2	2.4±1.3	0.68
Office systolic blood pressure (mmHg)	155±23	161±20	0.17
Office diastolic blood pressure (mmHg)	92±10	93±17	0.63
Office PP (mmHg)	62±18	68±16	0.16
24 h systolic blood pressure (mmHg)	138±13	149±21	<0.01
24 h diastolic blood pressure (mmHg)	81±9	85±12	0.09
24 h PP (mmHg)	56±10	64±14	<0.001
Systolic night:day blood pressure ratio (%)	89.4±7.8	91.7±7.3	0.14
Diastolic night:day blood pressure ratio (%)	84.8±8.5	88.9±7.6	0.01

Values are n, mean ± SD or median (interquartile range)
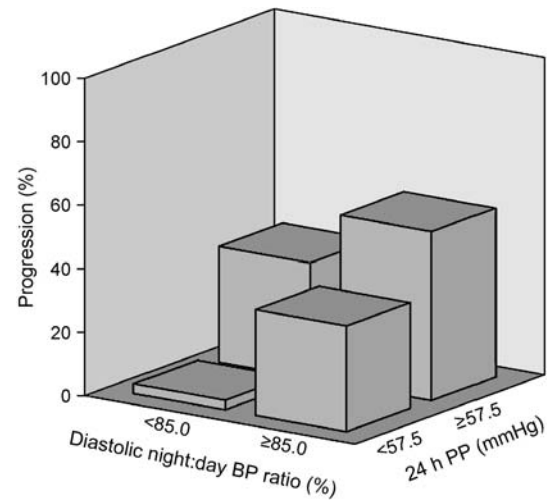
ARB, angiotensin 2 receptor antagonist

nephropathy stage. The proportion of patients who exhibited progression of nephropathy according to baseline smoking status and 24 h systolic BP, 24 h PP and diastolic night:day ratio below the median or equal to or above the median is presented in Table 2.

At baseline, smokers and non-smokers had similar diastolic night:day BP ratios and 24 h PP values ($p > 0.3$ for both comparisons). Similarly, diastolic night:day BP ratios and 24 h PP values did not correlate statistically ($r^2 = 0.004$, $p = 0.48$). The predictive value of combining the two BP indices is illustrated in Fig. 1. Only one of 33 patients (3.0%) with a diastolic night:day BP ratio and a 24 h PP below the median progressed, whereas 17 of 32 patients (53.1%) with both a diastolic night:day BP ratio and a 24 h PP equal to or above the median progressed to a more advanced nephropathy stage ($p < 0.001$).

In unadjusted bivariate analyses, 24 h PP was the baseline variable most strongly correlated with nephropathy progression; 46.3% of patients with a 24 h PP equal to or above the median value of 57.5 mmHg exhibited progression of nephropathy, whereas only 16% of patients with a 24 h PP below the median value subsequently progressed (log-rank test for differences between groups, $p < 0.001$) (Fig. 2). Cox proportional hazards models were used to test which baseline variables were independently predictive of subsequent nephropathy progression. The final model included sex, age, duration of diabetes, smoking, baseline UAE, HbA_{1c}, plasma creatinine, 24 h systolic BP, 24 h PP and diastolic night:day BP ratio. Independent predictors of nephropathy progression were smoking (HR 2.48, 95% CI 1.19–5.17, $p = 0.02$), 24 h PP (HR 1.04 [for each mmHg increase], CI 1.01–1.07, $p < 0.01$) and diastolic night:day BP ratio (HR 1.05 [for 1% increase], 95% CI 1.01–1.07, $p = 0.02$); the other variables in the model did not have a
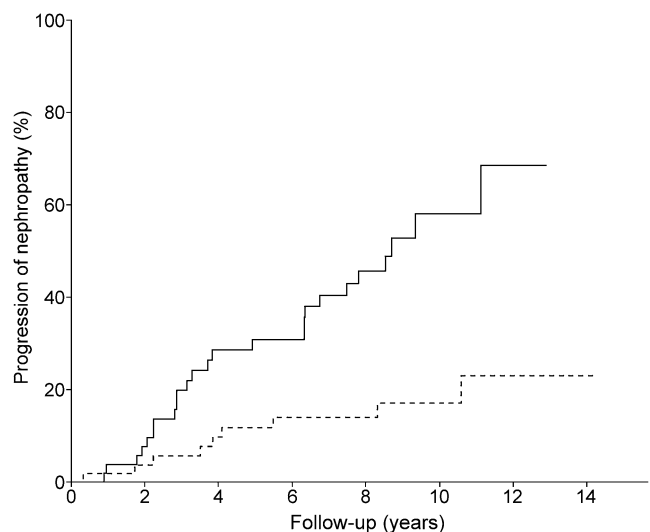

Fig. 1 Three-dimensional graph of the proportion of type 2 diabetic patients with progression of nephropathy according to categories of diastolic night:day BP ratio (<85.0% or ≥85.0%, the median value) and 24 h ambulatory PP (<57.5 mmHg or ≥57.5 mmHg, the median value). $p < 0.001$ (χ^2 test with Yates' correction)

significant independent predictive value for nephropathy progression.

Discussion

In this prospective observational study with a follow-up period of 9.5 years, high 24 h PP and impaired nocturnal diastolic blood pressure decline were both strong and independent predictors of nephropathy progression, thus confirming hypotheses generated from previous cross-

Table 2 Percentage of patients with progression of nephropathy at follow-up according to categories of baseline variables (below the median value or equal to or above the median value)

Variable	Progression of nephropathy (%)	p value
Smoking		0.01
No	24.7	
Yes	47.2	
24 h systolic blood pressure		0.02
<138.3 mmHg	19.6	
≥138.3 mmHg	41.1	
24 h PP		<0.001
<57.5 mmHg	16.1	
≥57.5 mmHg	46.4	
Diastolic night:day blood pressure ratio		<0.01
<85.0%	17.9	
≥85.0%	44.6	

Fig. 2 Progression of nephropathy in type 2 diabetic patients with a 24 h ambulatory PP below (dashed line, $n = 56$) or equal to or above (solid line, $n = 56$) the median (57.5 mmHg). $p < 0.001$ (log-rank test)

sectional and short-term observational studies. In the proportional hazards analysis, a 1 mmHg increase in 24 h PP and a 1% increase in diastolic night:day BP ratio conferred an increased risk of nephropathy progression of 4 and 5%, respectively, whereas smoking more than doubled the risk of nephropathy progression, even after adjustment for multiple other potential risk factors.

During the last decade, numerous studies have established PP as a strong, independent predictor of cardiovascular morbidity and mortality in non-diabetic patients [25–30]. In 2002, we published baseline data from the middle-aged Danish type 2 diabetic patients participating in the present follow-up study [1]. In this cross-sectional study, we were the first to demonstrate strong associations between ambulatory PP values and micro- and macrovascular complications; in particular, the association between PP and albuminuria was very strong [1]. Although the cross-sectional design did not allow any firm conclusions regarding causality, we hypothesised that PP could be a risk factor for the progression of albuminuria in this patient group. Subsequently, several studies have associated an elevated PP with both micro- [3, 5] and macrovascular [6–8] complications in diabetic patients.

In 2006, Palmas et al. published a very significant longitudinal study including 1,040 elderly type 2 diabetic patients followed for 12 to 24 months [9]. In that study, 164 of 954 patients without macroalbuminuria at baseline progressed at least one level from normo- or microalbuminuria to micro- or macroalbuminuria. After adjustment for other clinical covariates, ambulatory PP was a strong and independent predictor of albuminuria progression, above and beyond office BP. The study had considerable statistical power, due to a large number of participants and the employment of 24 h AMBP, whereas its limitations included the relatively short follow-up period of only 1 to 2 years, considering the fact that diabetic nephropathy typically evolves over a decade or more [31]. Moreover, albuminuria status was evaluated on the basis of a single urine sample, even though three samples are usually recommended due to the considerable intra-individual day-to-day variability of this key variable [21]. Finally, these important results from elderly participants (mean age around 71 years) cannot necessarily be extrapolated to other age groups with less arterial stiffness and, consequently, a less pronounced elevation of PP. In the present study, we confirm the results from the Palmas study and extrapolate them to a group of middle-aged (mean age 58 years) type 2 diabetic patients followed for 9.5 years with a more precise assessment of nephropathy status (based on three urine samples per patient at baseline as well as at follow-up).

Numerous previous studies have established the superiority of 24 h AMBP over conventional office BP measurement for the association with [1, 5, 15, 32, 33] and

prediction of hypertensive end-organ damage in diabetes [9, 34, 35]. Moran et al. found that office and 24 h systolic AMBP were independently associated with albuminuria in elderly type 2 diabetic patients [4]; however in the longitudinal study mentioned above [9], ambulatory PP predicted progression of albuminuria above and beyond office BP. In the present study, none of the office BP values had any significant predictive value for the progression of nephropathy, whereas 24 h systolic AMBP and PP values were strong predictors of nephropathy progression in type 2 diabetic patients. Obviously, the shortcomings of office BP measurement in the present study can be ascribed to lack of power, but it is striking that this commonly used diagnostic modality had no predictive value in a 9.5 year follow-up study in a high-risk group of type 2 diabetic patients. These results suggest that more widespread use of 24 h AMBP measurements could significantly improve our ability to identify patients at increased risk of developing microvascular complications.

In addition, use of 24 h AMBP as opposed to office BP measurement provides the opportunity to study diurnal BP fluctuations. In particular, focus has been directed towards a blunted nocturnal BP reduction ('non-dipping'), a pattern that has been consistently associated with diabetic vascular complications in previous studies [1, 10–17, 35]. In a 3 year follow-up of the same elderly type 2 diabetic patients mentioned above [4, 9], the investigators found that patients with a reversed diurnal BP rhythm (nocturnal BP 'risers') had an increased risk of nephropathy progression compared with patients with a normal reduction in BP during night-time ('dippers'), whereas patients with a reduced nocturnal BP decline ('non-dippers') had an intermediate risk of progression [19]. Nocturnal BP rising was an independent predictor of albuminuria progression in the multivariate analysis, whereas non-dipping did not independently predict albuminuria progression. In the present study, we found that a reduced diastolic nocturnal BP decline was an independent predictor of nephropathy progression; moreover, we found a strong and intriguing additive effect of combining diastolic night:day BP ratio and 24 h PP. Thus, in the group of patients with diastolic night:day BP ratio and 24 h PP below the median, only one of 33 patients progressed, whereas 17 of 32 patients in the group with these BP variables equal to or above the median progressed to a more advanced nephropathy stage.

Several questions remain unanswered.

First, what are the underlying pathophysiological mechanisms connecting the haemodynamic abnormalities, elevated PP and blunted nocturnal BP decline, with the development of microvascular complications, in casu progression of nephropathy in type 2 diabetes? We have previously demonstrated strong associations between endothelial perturbation and both non-dipping [17] and elevated PP [5], suggesting that an

enhanced level of endothelial cell activation could represent a link between these haemodynamic abnormalities and the development of microvascular complications in type 2 diabetes, possibly by promoting inflammation and atherosclerosis and by increasing the tendency of blood clotting. However, we were unable to make firm conclusions regarding causality due to the cross-sectional design of the studies.

Second, could pharmacological intervention against elevated PP or reduced nocturnal BP decline lead to a reduced incidence of microvascular complications? We have recently demonstrated that 12 months dual blockade with an angiotensin 2 receptor antagonist (candesartan) and an ACE inhibitor (lisinopril) was more effective in lowering 24 h ambulatory PP than monotherapy with high-dose lisinopril in type 2 diabetic patients [36]. However, it is as yet unknown whether this narrowing of PP induced by dual blockade of the renin–angiotensin system will translate into a long-term reduction in microvascular complications. Several researchers have demonstrated that it is possible to restore the normal circadian BP pattern in 'non-dipper's with selective antihypertensive therapy directed towards an elevated night BP [37–40]. Interestingly, this approach has been reported to reduce 24 h albumin excretion rate in microalbuminuric patients with essential hypertension, thus suggesting an increased organoprotective effect of re-establishing the normal diurnal BP rhythm [39]. These results are interesting and promising, but long-term intervention studies are needed to resolve whether antihypertensive treatment should be directed towards restoring the normal diurnal BP variation in 'non-dipping' patients and reducing an elevated PP.

The strengths of the present study include the long follow-up period of 9.5 years, the precise assessment of nephropathy status at baseline and follow-up, as well as the employment of 24 h AMBP measurement. There are several limitations to this study. First, the study was a clinically based observational study; hence, all types of pharmacological intervention were allowed during the follow-up period. Indeed, most patients received additional pharmacological (antihypertensive, lipid-lowering, antithrombotic etc.) therapy during this period, and we do not have the possibility to statistically correct for this intercurrent medication. However, during the follow-up period patients with high baseline BP levels would have been more likely to receive intensified antihypertensive therapy (including ACE inhibitors and angiotensin 2 receptor antagonists) than patients with low BP levels at baseline, thus reducing their risk of nephropathy progression and introducing a bias towards the null hypothesis. In spite of these pharmacological interventions during follow-up, high 24 h PP and reduced diastolic night BP decline were strong predictors of nephropathy progression, suggesting that these variables are useful for risk assessment in everyday clinical practice. Second, the number of patients participating in the study was limited, thus limiting statistical power. As previously discussed, this could explain the lack of predictive value of office BP variables for nephropathy progression in the present study, whereas the very significant results for smoking, 24 h ambulatory PP and diastolic night:day BP ratio despite the limited size of the study indicate that these variables are strong and important predictors of this serious complication.

In the present 9.5 year observational study, 24 h ambulatory PP, impaired nocturnal diastolic BP decline and smoking were strong, independent predictors of nephropathy progression in type 2 diabetic patients. These potentially modifiable risk factors could represent important targets for pharmacological and non-pharmacological intervention aiming at reducing the incidence of this serious complication of type 2 diabetes.

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