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24-h ambulatory blood pressure and retinopathy in normoalbuminuric IDDM patients

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Summary The role of blood pressure elevation in the incidence and progression of diabetic retinopathy is not clearly established and results have been conflicting. Blood pressure and urinary albumin excretion (UAE) are closely related. In order to evaluate the independent relationship between retinopathy and blood pressure elevation, precise information on UAE is essential, as confounding by renal disease (incipient or overt), cannot otherwise be excluded.The aim of the present study was to evaluate the association between diabetic retinopathy and 24-h ambulatory blood pressure (AMBP) in a group of well-characterized normoalbuminuric IDDM patients. In 65 normoalbuminuric (UAE < 20 μg/min) IDDM patients we performed 24-h AMBP (Spacelabs 90 207) with readings at 20-min intervals. Fundus photographs were graded independently by two experienced ophthalmologists. UAE was measured by RIA and expressed as geometric mean of three overnight collections made within 1 week. HbA_{1c} was determined by HPLC. Tobacco use and level of physical activity were assessed by questionnaire. Fifteen patients had no detectable retinal changes [grade 1], 35 had grade 2 retinopathy; and 15 had more advanced retinopathy [grade 3--6]. Diastolic night blood pressure was significantly higher in patients with diabetic retinopathy compared to patients without retinopathy (68 ± 8 mmHg [grade 3--6] and 65 ± 6 mmHg [grade 2], compared to 61 ± 4 mmHg [grade 1], $p = 0.02$). Diurnal blood pressure variation was significantly blunted in the patients with retinopathy as indicated by a higher night/day ratio of diastolic blood pressure (84.6 % ± 4 [grade 3--6], and 81.2 % ± 6 [grade 2] compared to 79.1 % ± 4 [grade 1], $p = 0.01$). Heart rate tended to be higher in patients in group 2 and 3--6 compared to patients without retinopathy with p values of 0.07 and 0.11 for day-time and 24 h values, respectively. Mean HbA_{1c} increased significantly with increasing levels of retinopathy ($p < 0.01$). Patients were similar regarding sex, age, tobacco use, and level of physical activity. Notably, UAE was almost identical in the three groups (5.0 ×/÷1.7 [grade 1], 3.9 ×/÷1.8 [grade 2], and 5.1 ×/÷1.6 μg/min [grade 3--6]). In conclusion, night blood pressure is higher and circadian blood pressure variation blunted in patients with retinopathy compared to patients without retinopathy despite strict normoalbuminuria and similar UAE levels in the groups compared. Our data suggest that the association between blood pressure and diabetic retinopathy is present also when coexisting renal disease is excluded. Disturbed diurnal variation of blood pressure is a pathophysiological feature related to the development of both retinopathy and nephropathy in IDDM patients. [Diabetologia (1998) 41: 105--110]

Keywords Diabetic retinopathy, 24-h ambulatory blood pressure, IDDM, urinary albumin excretion.

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Abbreviations: IDDM, Insulin-dependent diabetes mellitus; UAE, urinary albumin excretion; AMBP, ambulatory blood pressure; N/D ratio, night/day ratio.

Diabetic retinopathy can be expected to develop in the majority of insulin-dependent diabetic (IDDM) patients [1--4], and despite the beneficial effect of photocoagulation, this complication remains a leading cause of visual loss in young adults [5, 6]. Duration of diabetes and poor blood glucose control are established risk factors for the development of retinopathy [7--10], but the pathogenetic mechanisms underlying the initiation and progression of this complication are still poorly understood. Identification of other potentially modifiable clinical parameters associated with retinopathy, e.g. high blood pressure might have implications for understanding pathophysiology, and for preventing and managing retinopathy.

In diabetic nephropathy the close association between blood pressure increase and progression of kidney disease is now clearly established with important consequences for clinical practice: Antihypertensive treatment especially with angiotensin converting enzyme (ACE)-inhibitors has been demonstrated to impede progression of diabetic nephropathy [11--17]. In contrast, the role of blood pressure elevation for the incidence and progression of diabetic retinopathy has not been clearly demonstrated [18--20]. Several studies have been hampered by inadequate methods of establishing the presence and severity of retinopathy as well as insensitive assessment of systemic blood pressure. Furthermore, the characterization of patients with regard to urinary albumin excretion (UAE) has often been insufficient. The association between blood pressure and even minor elevations of UAE is well described [21--29]. Evaluation of a possible independent relationship between retinopathy and blood pressure elevation is rendered impossible without precise information on albumin excretion, since confounding by coexisting incipient renal disease cannot be ruled out.

The aim of the present study was to evaluate the association between diabetic retinopathy and 24 h ambulatory blood pressure as well as circadian blood pressure variation in a group of well-characterized normoalbuminuric IDDM patients.

Subjects and methods

Patients. We selected 65 patients from among 120 patients participating in an ongoing prospective study addressing identification of risk factors for the development of complications in IDDM. The following criteria were applied: participants had to be normoalbuminuric (UAE < 20 μg/min in at least two out of three overnight urine collections) and without other chronic diseases. Retinal examination had to be performed within 6 months of the assessment of UAE and blood pressure. None received (or had earlier received) antihypertensive or other medical treatment apart from insulin. UAE was measured by RIA and expressed as geometric mean of three overnight collections made within 1 week. HbA_{1c} was determined by HPLC (non-diabetic range 4.4--6.4%). Blood glucose was determined by Reflolux II, Boehringer Mannheim (Mannheim, Germany).

Patients were classified according to participation in leisure-time physical activity as: *Passive* (not participants), *Moderate* (physical exercise once or twice a week), and *Active* (Physical exercise more than twice a week). Tobacco consumption was graded as *Non-smokers* (without daily use of tobacco for at least the last year), *Moderate smokers* (less than 15 cigarettes per day) and *Heavy smokers* (More than 15 cigarettes per day).

The study was approved by the local ethics committee and patients gave their written informed consent.

Grading of retinopathy. After induction of cycloplegia and mydriasis by phenylephrin 10% and tropicamid 1% eye drops, fundus photography was performed with a Canon 60UV fundus camera on Kodak ectachrome 64 colour diapositive film. In each eye a standard photograph of 60 degrees was taken centered on the foveal region, thus covering and area corresponding approximately to fields 1--5 of the standard fields used in the Early Treatment For Diabetic Retinopathy Study [30]. For the grading each photograph was projected to a size of 1×1 meter on a wall board. The number of each type of pathological lesion, haemorrhages and/or microaneurysms, hard exudates, or cotton wool spots was counted (truncated at 99), and the presence of laser scars or vascular abnormalities such as intraretinal microvascular abnormalities (IRMA vessels), venous beading, or neovascularizations was noted. Furthermore, the presence of diabetic maculopathy was noted, defined as hard exudates within one disk diameter of the fovea. Each photograph was evaluated independently by two experienced graders. When the two evaluations of a photograph were discrepant it was reassessed by the two graders together. In case there was still discrepancy the opinion of the most senior grader was used.

On the basis of the grading of all lesions on a photograph each eye was assigned an overall retinopathy grade on a scale from 1--6 according to the principles used in the Wisconsin Epidemiologic Study of Diabetic Retinopathy [1] with a modification to ensure that lesions implying the same risk of progression to proliferative diabetic retinopathy resulted in the same retinopathy level (ETDRS Report 12 [31]). Consequently, the assignment of retinopathy grade was made according to the following guidelines:

1) No retinopathy. 2) a. Less than 20 haemorrhages and/or microaneurysms, or b. Cotton wool spots alone. 3) a. More than or = 20 haemorrhages and/or microaneurysms, or b. Hard exudates combined with any number of haemorrhages and/or microaneurysms, or c. Less than 5 cotton wool spots combined with haemorrhages and/or microaneurysms or hard exudates. 4) More than or = 5 cotton wool spots or IRMA vessels combined with haemorrhages and/or microaneurysms with or without hard exudates. 5) Venous beading combined with haemorrhages and/or microaneurysms with or without hard exudates, IRMA vessels or cotton wool spots. 6) Proliferative diabetic retinopathy, or scars of photocoagulation known to have been directed at new vessels.

In each patient the retinopathy grade on the worst eye was used for the analysis. The ophthalmologists had no knowledge of the subjects' blood pressure or their glycaemic control and, thus, graded the eye findings in an unbiased way.

24-h blood pressure measurements and circadian blood pressure variation. Ambulatory blood pressure (AMBP) was measured by an oscillometric technique (Spacelabs 90 207, validated by the British Hypertension Society [32]). Readings were

Table 1. Clinical characteristics of patients grouped according to severity of retinopathy

Eye category	*n*	Sex (% ♂)	Age (years)	Duration (years)	HbA_{1c} (%)	Insulin (U/kg body weight)	UAE (μg/min ×/÷ TF)	Height (m)	Weight (kg)	Smoking (Non-smoking-Moderate-Heavy)	Physical activity (Not active-Moderate-Active)
1	15	67 %	33.2 ± 9.0	9.8 ± 5.3	7.7 ± 1.0	0.71 ± 0.22	5.0 ×/÷ 1.7	1.80 ± 8	75.4 ± 8.0	73--7--20 %	67--27--6 %
2	35	71 %	38.9 ± 10.4	21.1 ± 9.8	8.3 ± 1.2	0.64 ± 0.19	3.9 ×/÷ 1.8	1.75 ± 8	73.9 ± 10.1	65--0--35 %	70--27--3 %
3--6	15	73 %	37.5 ± 6.3	21.4 ± 6.2	9.1 ± 0.9	0.67 ± 0.14	5.1 ×/÷ 1.6	1.75 ± 10	78.5 ± 11.7	54--6--40 %	65--31--4 %
ANOVA		NS	NS	< 0.01	< 0.01	NS	NS	NS	NS	NS	NS

Data are mean ± SD except for UAE presented as geometric mean ×/÷ tolerance factor

Table 2. Ambulatory blood pressure and heart rate

Eye category	Systolic AMBP (mm Hg)				Diastolic AMBP (mm Hg)				Heart rate (beats/min)			
	24-h	Day	Night	N/D ratio (%)	24-h	Day	Night	N/D ratio (%)	24-h	Day	Night	N/D ratio (%)
1	120 ± 7	125 ± 8	108 ± 6	86.1 ± 4	72 ± 5	77 ± 6	61 ± 4	79.1 ± 4	73 ± 12	77 ± 12	63 ± 13	80.4 ± 9
2	124 ± 10	129 ± 10	113 ± 11	87.6 ± 5	75 ± 6	80 ± 6	65 ± 6	81.2 ± 6	76 ± 7	81 ± 8	66 ± 9	81.3 ± 8
3--6	124 ± 10	128 ± 11	114 ± 8	88.9 ± 5	76 ± 7	80 ± 7	68 ± 8	84.6 ± 4	80 ± 10	86 ± 10	69 ± 11	80.3 ± 6
ANOVA	NS	NS	NS	NS	NS	NS	0.02	0.02	0.11	0.07	NS	NS

Data are means ± SD

obtained at 20-min intervals throughout 24 h. Measurements were performed during a day with normal activities at home or at work. Individually reported sleeping times were implemented in the calculation of day and night blood pressure. Records with more than 2 missing hours were excluded (two patients).

Statistical analysis. Before analysis, UAE values were log transformed to approximate normal distribution. When analysis of variance (ANOVA) indicated significant differences between groups, pairwise comparisons were assessed with significance levels appropriately modified using the method of Bonferroni. For non-continuous variables the chi-square test with Yates correction was used. A two-tailed p value of less than 0.05 was considered significant. Results are expressed as mean ± SD except for UAE, which is presented as geometric mean ×/
÷tolerance factor.

Results

Fifteen patients had no detectable retinal changes (grade 1), 35 had grade 2 retinopathy, and 15 had more advanced retinopathy (grades 3--6). The latter were grouped together due to the small numbers in each group [9]. Clinical characteristics of the patients when grouped according to severity of retinopathy are given in Table 1. The mean HbA_{1c} increased significantly with increasing levels of retinopathy ($p < 0.01$).The patients were similar regarding UAE, smoking habits, level of physical activity, and insulin consumption. Duration of diabetes was significantly longer in patients in category 2 and 3--6 compared to patients with no retinopathy and body mass index was slightly higher in patients in category 3--6 compared to patients with no retinopathy. Data on AMBP and heart rate are given in Table 2. AMBP was consistently higher in the groups with retinopathy (group 2 and 3--6) compared to the group with no detectable retinal changes, reaching statistical significance for diastolic night blood pressure ($p < 0.02$). Furthermore, diurnal variation was significantly blunted in the patients with retinopathy as indicated by a higher night/day ratio of diastolic blood pressure ($p < 0.01$). Individual values of diastolic night blood and diastolic night/day ratio for the three groups are depicted in Figure 1 and 2. As apparent from the figures there was a stepwise increase in both diastolic night blood pressure and diastolic night/day ratio with increasing eye involvement and tests for linear trend were statistically significant for both night blood pressure and night/day ratio ($p < 0.01$ for both). Heart rate tended to be higher in patients in group 2 and 3--6 compared to patients without retinopathy with p values of less than 0.06 and 0.11 for day-time and 24 h, respectively. There was no association between duration of diabetes and circadian blood pressure variation ($r = 0.1$, $p = 0.66$), and the differences in night blood pressure and circadian variation persisted after entering diabetes duration as a covariate in the ANOVA, thus adjusting for the differences in duration between the groups ($p < 0.02$ for the effect of retina grade). As the three groups were significantly different in respect to metabolic control, we analysed whether part of the differenses in blood pressure and circadian blood pressure variation was explained by differences in HbA_{1c}. There was no correlation between HbA_{1c} and diastolic night blood pressure or diastolic night/day ratio ($r = 0.15$

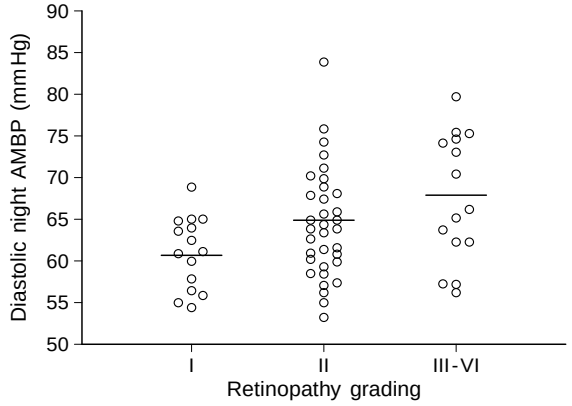

Fig. 1. Diastolic night ambulatory blood pressure according to retinopathy grading (bars indicate mean values)

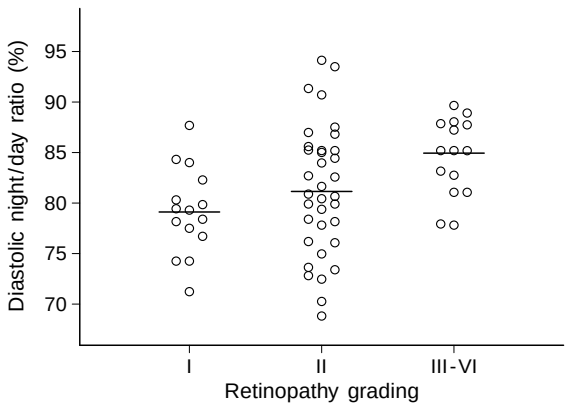

Fig. 2. Diastolic night ratio according to retinopathy grading (bars indicate mean values)

and 0.10 $p > 0.40$ for both), and when HbA_{1c} was included as a covariate in the ANOVA, the differences in both diastolic night blood pressure and diastolic night/day ratio persisted ($p < 0.05$ and $p < 0.03$, respectively). When in addition to HbA_{1c}, weight, age, duration, and cigarette consumption were included as covariates, the effect of retinal stage on diastolic night/day ratio barely reached statistical significance ($p = 0.07$).

Comparing patients without diabetic retinopathy (group 1, $n = 15$) with patients with all grades of retinopathy (group 2 and group 3--6, $n = 50$) showed higher diastolic night blood pressure (61 ± 4 compared to 66 ± 7 mmHg, $p < 0.01$) and higher diastolic night/day ratio (79.1 ± 4 vs $82.2 \pm 6\%$, $p < 0.03$) in the group with diabetic retinopathy. In addition, 24-h systolic and diastolic AMBP also tended to be higher in the group with diabetic retinopathy compared to patients without diabetic retinopathy: 124 ± 10 / 75 ± 6 vs 120 ± 7 / 72 ± 5 mmHg, $p = 0.07$ and $p = 0.09$, respectively.

Discussion

We present data for a group of patients examined with 24-h AMBP -- a technique not previously implemented in the study of retinopathy in IDDM. In comparison with clinical blood pressure measurement, 24-h AMBP offers several advantages: a multitude of measurements, a lower intrapatient variation [33], a superior correlation with both the degree of target-organ lesions in essential hypertensive patients [34] and with microalbuminuria in IDDM patients [25]. Moreover, AMBP provides an integrated blood pressure profile over time and includes night measurements, thus allowing for an exploration of circadian blood pressure patterns. In IDDM patients with diabetic nephropathy, cross-sectional studies have shown disturbances in diurnal variation characterized by a blunted diurnal rhythm, and this has been shown to increase when diabetic nephropathy increases from microalbuminuria to overt nephropathy [35]. The patients included in the present study all had normal clinical blood pressure and normal. In spite of this, we found higher night blood pressure and blunted diurnal variation (increased night/day ratio) with increasing levels of retinopathy. Thus, the two major complications of IDDM, nephropathy and retinopathy, seem to share this pathophysiological feature. The groups were similar regarding age, sex, and level of physical activity. Notably, UAE was almost identical in the three groups excluding this potential confounder. Furthermore, we found an association between poorer glycaemic control as indicated by higher HbA_{1c} and retinopathy. Our data could be seen in context with the haemodynamic hypothesis proposed by Patel and Kohner [36, 37]: blood pressure elevation increases perfusion pressure, and in the presence of hyperglycaemia, the autoregulatory adaption of vessels is inhibited. This induces hyperperfusion, which by increasing shear stress leads to capillary damage and closure, causing retinal ischaemia with subsequent additional hyperperfusion. The higher heart rate in patients with retinopathy would also -- *ceteris paribus* -- tend to increase perfusion. Although both day, 24-h, and night blood pressure numerically were higher with higher grades of retinopathy, only night blood pressure reached statistical significance. It is noteworthy that an association between impaired reduction of night blood pressure has been described for other organ lesions (left ventricular cardiac mass [38], cardiovascular episodes in women [39]).

The combination of higher heart rate and blunted diurnal blood pressure variation with disproportionate elevation of night blood pressure could also indicate autonomic dysfunction in patients with retinopathy, and a connection between autonomic dysfunction and poor autoregulation of retinal vessels could be considered [40]. In addition, the risk of early onset proliferative retinopathy has been reported to be closely related to cardiovascular autonomic neuropa-

thy [41]. It is however important to notice that the retinal vessels, unlike most other vessels in the circulation do not possess any functioning sympathetic innervation [42]. Thus, neuropathy may be a risk indicator of yet unknown aetiologic processes underlying the development of diabetic retinopathy. Sinclair et al. [43] has described increasing impairment in autoregulation of retinal blood flow with increasing grades of diabetic retinopathy. This produces a situation, where even discrete elevations in systemic blood pressure are readily transmitted to the retinal microcirculation, resulting in capillary hypertension and hyperperfusion. In a study by Parving et al. [44] the effect of antihypertensive treatment (ACE inhibitors and diuretics) on blood-retinal barrier leakage was assessed. The results suggested that systemic blood pressure elevation contributes to an increased leakage of fluorescein across the blood-retinal barrier, and that this leakage can be reversed by antihypertensive treatment. No controlled studies evaluating the effect of antihypertensive treatment on the initiation and progression of diabetic retinopathy have been performed, although preliminary reports [44, 45] seem to indicate a possible positive effect.

N|orgaard et al. [46] attempted to separate the possible effects of hypertension and of increased urinary albumin loss on diabetic retinopathy by comparing hypertensive, normoalbuminuric IDDM patients with normotensive, normoalbuminuric patients and found no statistically significant difference in prevalence of diabetic retinopathy, thus claiming that hypertension *per se* is not associated with increased retinal changes. However, since the conclusion is based on a negative finding, the risk of a type 2 error must be taken into consideration; indeed the prevalence of advanced retinopathy was 17 % among the hypertensive patients ($n = 51$) compared to 9 % among the normotensive patients ($n = 55$). Furthermore, the methods used for eye examination (ophthalmoscopy by physicians) and blood pressure measurements (single standard sphygmomanometer measurements to the nearest 5 mmHg) may also add to the risk of missing a difference.

In a recent large population-based study employing retinal photographs, diastolic blood pressure remained a significant risk factor for moderate-severe retinopathy in IDDM after adjusting for age, duration, HbA_{1c}, and UAE [47]. As indicated in our analysis taking cigarette smoking and HbA_{1c} into account it is possible that part of the blood pressure elevation is explained by these two factors. However, in the light of the well-known difficulties in obtaining better glycaemic control and smoking cessation we think that the finding of higher blood pressure is potentially important from a clinical point of view.

In non-diabetic patients with mild essential hypertension, Dimmitt et al. [48] found no association between AMBP and retinopathy assessed by fundal photographs. However, only daytime measurements were performed and potential differences in night blood pressure could thus not be accounted for. In a population-based study [49] Stephenson et al. recently described a retinopathy-dependent difference in the relationship between blood pressure and UAE: in IDDM patients with retinopathy UAE increased steeply with blood pressure as opposed to those without retinopathy who exhibited virtually no rise in UAE with increasing blood pressure.

In conclusion, our data suggest that in IDDM patients, the relationship between retinopathy and blood pressure may not be confined to patients with elevated UAE but could be present independent of renal disease. Prospective studies are needed in order to further evaluate the association between blood pressure elevation and diabetic retinopathy and controlled studies designed to evaluate whether antihypertensive therapy may impede or prevent development and progression of diabetic retinopathy would be of interest.

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