

## INCREASED NIGHT/DAY DIASTOLIC BLOOD PRESSURE RATIO IS ASSOCIATED WITH HIGH NORMAL URINARY ALBUMIN EXCRETION AND RETINOPATHY IN NORMOTENSIVE AND NORMOALBUMINURIC TYPE 1 DIABETIC PATIENTS

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*Key words:* type 1 diabetes mellitus, 24-h ambulatory blood pressure, 24-h urinary albumin excretion, nonproliferative retinopathy

### SUMMARY

The aim of the study was to determine whether a reduced nocturnal fall in blood pressure would increase the risk of microvascular complications in normoalbuminuric and normotensive type 1 diabetics. The study included 139 type 1 diabetic patients with urinary albumin excretion <30 mg/24 h and casual blood pressure <130/80 mm Hg. Direct ophthalmoscopy and 24-h ambulatory blood pressure were performed and patients divided according to the night/day diastolic and systolic blood pressure ratio <0.9 or >0.9 as dippers and nondippers. Significant differences were found in 24-h urinary albumin excretion ( $12.21 \pm 5.45$ ;  $18.78 \pm 4.73$ ;  $p=0.001$ ) and prevalence of nonproliferative retinopathy (44.24%; 76.9%;  $p=0.03$ ) between dippers ( $n=113$ ) and nondippers ( $n=26$ ) according to diastolic blood pressure ratio. Significant differences were also recorded in 24-h urinary albumin excretion ( $10.63 \pm 4.33$ ;  $16.76 \pm 5.8$ ;  $p=0.001$ ), prevalence of nonproliferative retinopathy (28.9%; 66.6%;  $p=0.04$ ) and duration of diabetes ( $9.55 \pm 8.84$ ;  $14 \pm 9.41$ ;

$p=0.004$ ) between dippers ( $n=76$ ) and nondippers ( $n=63$ ) according to systolic blood pressure ratio. The night/day diastolic blood pressure ratio was related to 24-h urinary albumin excretion and retinopathy ( $r=0.406$ ;  $r=0.23$ ). On stepwise multiple regression analysis, urinary albumin excretion was significantly associated with the night/day diastolic blood pressure ratio ( $\beta=0.794$ ), and retinopathy with the night/day diastolic blood pressure ratio ( $\beta=0.949$ ) and diabetes duration ( $\beta=0.04$ ). Accordingly, an impaired nocturnal diastolic blood pressure fall was concluded to be associated with high normal urinary albumin excretion and retinopathy in normoalbuminuric and strictly normotensive type 1 diabetic patients, and may be relevant for long-term development of microvascular complications.

### INTRODUCTION

Arterial hypertension is a well-recognized risk factor for progression of microvascular complications in type 1 diabetic patients (1). As many studies have demonstrated the beneficial effects of tight blood pressure (BP) control on target organ damage, the reduction of systolic and diastolic blood pressure to <130/80 mm Hg has been strongly recommended (2-6).

With the introduction of 24-h ambulatory blood pressure monitoring (AMBP), it has become evident that BP is characterized by a considerable degree of variability over a day-night period (7). Measurements

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made by conventional sphygmomanometer, although usually based on at least three separate examinations, are not representative of the BP over the 24-h period (7-9). The magnitude of BP variability has been shown to correlate independently with the range of target organ damage in patients with hypertension (5,7). The alternation in normal circadian BP rhythm with blunted vagal increase during the night was found in diabetic patients (10,11). The term "nondipping" has been applied to this abnormal nocturnal pattern and the night/day ratio of systolic (sBP) and diastolic (dBP) BP commonly used to define this status (12). The lack of nocturnal sBP or dBP fall in type 1 diabetic patients has been associated with microalbuminuria and retinopathy (10-16). However, in most of the published studies, type 1 diabetics were not selected for being normotensive, or only a small number of strictly normoalbuminuric and normotensive subjects were investigated. Considering the fact that the prevention of both nephropathy and retinopathy in these patients is a major clinical turning point, it would be of special interest to determine early BP changes related to the development of microalbuminuria and retinopathy in normotensive patients at the normoalbuminuric stage.

The present study was undertaken to characterize a large group of patients with normal casual BP and normal 24-h urinary albumin excretion (UAE) according to the night/day dBP and sBP ratio, and to establish the relationship between the night/day BP ratios and microvascular complications.

## PATIENTS AND METHODS

One hundred and thirty-nine patients with type 1 diabetes (64 female and 75 male) hospitalized at the Vuk Vrhovac Clinic ward from January 2002 till October 2004 were included in the study. Type 1 diabetes was diagnosed according to the World Health Organization (WHO) criteria (<40 years of age at onset of diabetes, a previous episode of ketoacidosis or documented ketonuria, requirement of insulin therapy for life maintenance). The following inclusion criteria were used: diabetes duration >1 year, age >18 years, UAE <30 mg/24 h measured on three occasions, casual BP <130/80 mm Hg in supine position using disappearance of Korotkoff sound (phase V) to determine diastolic blood pressure, and absence of

cardiovascular and renal disease. None received or had earlier received antihypertensive or other medical treatment apart from insulin.

The 24-h BP was measured using an AMBP 630 (Nihon Colin, Komaki, Japan), which can measure sBP, dBP and heart rate (HR) by the oscillometric method in 20-minute interval. Only those recordings in which more than 85% of the programmed readings were successful were included in the analysis. Maximal, minimal and mean daytime (07:00-22:00), nighttime (22:00-07:00) sBP, dBP, and HR were calculated. The night/day sBP and dBP ratio was calculated for each patient and those with the ratio >0.9 were classified as nondippers (17).

Direct ophthalmoscopy was performed with dilated pupils by experienced ophthalmologists and retinopathy was classified according to the European Protocol (18).

Urinary albumin concentration was determined by an immunoturbidimetric assay (Olympus Diagnostics, Lismeehan, Ireland). Glycosylated HbA<sub>1c</sub> was determined on the same day as AMBP by immunoturbidimetry (Bayer, Tarrytown, USA). The normal reference range of HbA<sub>1c</sub> at our laboratory is 3.5%-5.7%.

Results were expressed as mean  $\pm$  SD. Statistical analysis was performed by Student's t-test (differences between the two groups), Pearson test (correlation), and multiple regression analysis (stepwise linear regression, beta indicating the regression coefficient). Statistical significance was set at  $p < 0.05$ .

UAE values were log-transformed to obtain parametric distribution. The study was approved by the local Ethics Committee and all participants signed an informed consent on entry to the study.

## RESULTS

Patients were classified according to the night/day dBP and sBP ratio as dippers and nondippers. Clinical and laboratory data are shown in Table 1. The groups divided according to the night/day dBP were similar according to age, sex, duration of diabetes, HbA<sub>1c</sub>, lipid profile, and smoking status. Nondippers showed a significantly higher 24-h UAE and prevalence of retinopathy than dippers. There was a significant

Table 1. Clinical characteristics of type 1 diabetic patients divided according to night/day dBP and sBP ratio

	Night/day dBP ratio			Night/day sBP ratio		
	Dippers (n=113)	Nondippers (n=26)	p	Dippers (n=76)	Nondippers (n=63)	p
Age (yrs)	34.53±10.99	36.23±11.6	NS	33.76±10.01	35.92±12.03	NS
Sex (F/M)	52/61	12/14	NS	39/37	25/38	NS
Diabetes duration (yrs)	11.32±9.09	13.96±10.45	NS	9.55±8.84	14±9.41	0.004
HbA <sub>1c</sub> (%)	7.9±1.74	8.47±2.02	NS	8.07±1.83	7.92±1.78	NS
HDL cholesterol (mmol/L)	1.56±0.39	1.51±0.48	NS	1.57±0.41	1.53±0.40	NS
LDL cholesterol (mmol/L)	3.06±1.13	3.09±1.04	NS	3.16±1.22	2.97±0.99	NS
Triglycerides (mmol/L)	1.24±0.69	1.4±0.63	NS	1.19± 0.73	1.35±0.61	NS
Smoking status (n of patients)		35	9	NS	19	17
UAE (mg/24 h)	12.21±5.45	18.78±4.73	0.001	10.63±4.33	16.76±5.8	0.001
Creatinine clearance	1.33±0.39	1.26±0.44	NS	90.95±11.9	94.02±17.12	NS
Nonproliferative retinopathy (n of patients)	50	20	0.03	22	42	0.04

Data are expressed as mean ±SD, percentage (%), or number of patients with the respective characteristic; dBP=diastolic blood pressure; sBP=systolic blood pressure; UAE=urinary albumin excretion.

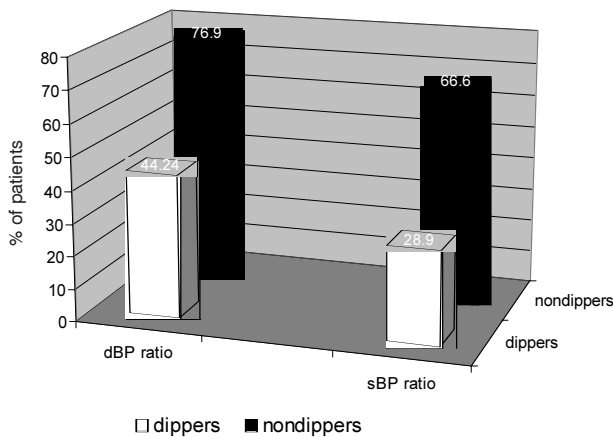
Table 2. Ambulatory blood pressure values and heart rate in type 1 diabetic patients divided according to night/day dBP and sBP ratio

	Night/day dBP ratio			Night/day sBP ratio		
	Dippers (n=113)	Nondippers (n=26)	p	Dippers (n=76)	Nondippers (n=63)	p
Mean night systolic BP (mm Hg)	106.16±8.69	115.04±7.61	0.001	103.6±8.12	112.8±7.6	0.001
Mean night diastolic BP (mm Hg)	60.23±6.4	68.38±6.18	0.001	59.05±5.71	64.78±7.27	0.001
Mean day systolic BP (mm Hg)	119.66±7.96	119.14±8.02	NS	120.01±8.3	119.01±7.48	NS
Mean day diastolic BP (mm Hg)	74.08±6.82	72.8±6.88	NS	74.42±6.39	73.15±6.97	NS
Mean night heart rate (beats/min)	64.04±10	68.29±12.29	NS	65.08±10.26	65.18±11.54	NS
Mean day heart rate (beats/min)	75.75±10.14	77.1±11.37	NS	71.94±9.76	72.83±11.19	NS
Night/day diastolic BP ratio (%)	0.73±0.20	1.28±0.21	0.001			
Night/day systolic BP ratio (%)				0.85± 0.03	0.94±0.03	0.001

Data are expressed as means ± SD; dBP=diastolic blood pressure; sBP=systolic blood pressure.

difference in 24-h UAE, prevalence of retinopathy and duration of diabetes between dippers and nondippers classified according to the night/day sBP. Nondippers showed higher values of the mean nocturnal systolic and diastolic blood pressure compared to dippers. During the day, dipper and nondipper patients showed similar levels of the mean sBP and dBp. There was no significant between-group difference in either nocturnal or diurnal HR (Table 2). The prevalence of nonproliferative retinopathy in type 1 diabetic patients is shown in Figure 1.

Figure 1. Prevalence of nonproliferative retinopathy in type 1 diabetic patients divided according to night/day dBp and sBP ratio



The night/day dBp ratio was related to 24-h UAE and retinopathy (Figs. 2 and 3). A stepwise multiple regression analysis was performed with UAE as a dependent variable and the following variables as possible predictors: sex, age, duration of diabetes, HbA<sub>1c</sub>, night/day dBp ratio, and night/day sBP ratio. UAE was significantly associated with night/day dBp ratio ( $\beta=0.794$ ). When retinopathy was entered as a dependent variable and the following variables as possible predictors: sex, age, duration of diabetes, HbA<sub>1c</sub>, night/day dBp ratio, night/day sBP ratio, and UAE, retinopathy was significantly associated with night/day dBp ratio ( $\beta=0.949$ ) and duration of diabetes ( $\beta=0.04$ ).

## DISCUSSION

In order to prevent the development of nephropathy and retinopathy in type 1 diabetics, many investigations have been performed in the last decade. It is

Figure 2. Correlation between night/day dBp ratio and nonproliferative retinopathy in type 1 diabetic patients ( $r=0.23$ )

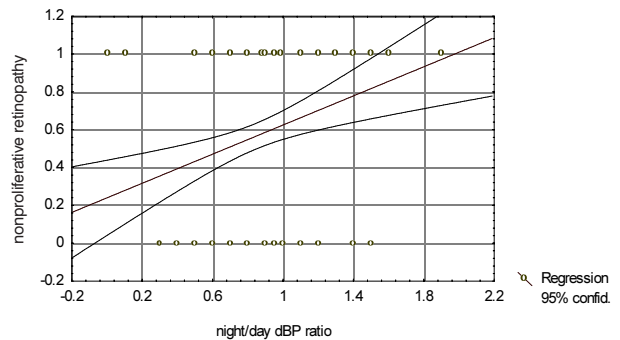
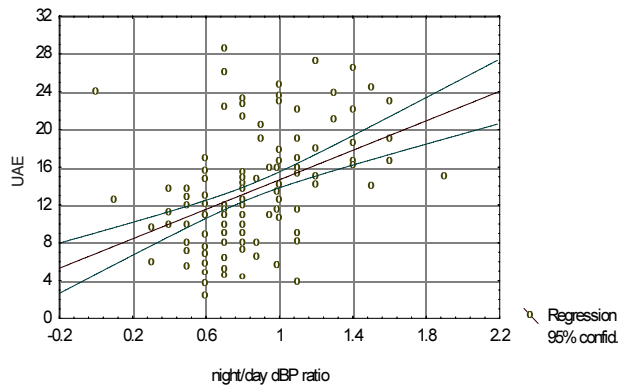


Figure 3. Correlation between night/day dBp ratio and UAE in type 1 diabetic patients ( $r=0.406$ )



widely accepted that blunted diurnal BP variations are pathophysiologically related to the development of microvascular complications (1,4,7,19,20). Disturbed circadian BP variability has been identified as an early sign of incipient nephropathy in type 1 diabetic patients (10,11,14,15,21,22,23). It has recently been confirmed that nondipping status is related to more renal morphological changes and long-term hyperfiltration in normoalbuminuric adolescents and young adult type 1 diabetics with a short duration of the disease (24).

However, only a few studies were conducted to investigate BP variation between normotensive type 1 diabetics with high normal and low normal UAE. As high normal UAE is considered the best way to predict microalbuminuria, demonstration of a significant association of blunted BP rhythm with high normal UAE would be of great importance (19). Two studies found that increased UAE levels within the normal

range were associated with blunted nocturnal dBP fall in type 1 diabetic patients who did not fulfill the criteria of normotension (11,13).

Poulsen et al. documented a higher night/day dBP ratio in normoalbuminuric and normotensive type 1 diabetics who progressed to microalbuminuria, but concluded that this pattern could not be used as a marker of renal disease because the BP difference disappeared when diabetes duration was taken into account (25).

Our study revealed an association between impaired nocturnal BP fall and higher normal UAE in a large group of type 1 diabetic patients, strictly normoalbuminuric and normotensive by both clinical and AMBP measurements. The inclusion of a large number of normoalbuminuric patients enhanced the discriminatory power between the low normal and high normal UAE levels.

In contrast to the study of Poulsen et al., no significant difference in diabetes duration was found between the two groups of patients divided according to dBP ratio. The duration of diabetes does not represent a confounding factor in the evaluation of the relationship between dBP and UAE. Although patients with a higher sBP ratio showed a significantly higher UAE and prevalence of retinopathy than patients with a lower sBP ratio, on multiple regression analysis only the night/day dBP ratio was related to UAE. According to our results, the early stage in the natural course of diabetic nephropathy seems to be characterized by nocturnal increase in diastolic BP. This is in contrast with the study documenting that an increase in sBP predicted the progression to microalbuminuria in normotensive and normoalbuminuric type 1 diabetics (26).

We also found a significant association between higher night/day BP and the prevalence of nonproliferative retinopathy. Many studies have shown that elevated BP represents a risk factor for the development and progression of retinopathy in type 1

diabetics (1,20,27,28). Little information is available with regard to diurnal BP rhythm and retinopathy in normotensive and normoalbuminuric patients, when the confounding influence of renal disease is excluded. A previously reported study showed that in normoalbuminuric type 1 diabetics a higher night dBP was associated with increasing levels of retinopathy, but the patients were not normotensive according to recent criteria (16). Our results confirmed that nonproliferative retinopathy was already present in type 1 diabetic patients with BP <130/80 mm Hg and was significantly associated with dBP. The level of night dBP related to retinopathy was significantly lower than previously reported (16,27,28). However, the results of multiple regression analysis indicated the relationship between dBP and retinopathy to be influenced by the duration of diabetes.

## CONCLUSIONS

In type 1 diabetic patients with normal clinical BP, high normal UAE and nonproliferative retinopathy, the night sBP and dBP are higher and diurnal variability is reduced in comparison to patients with low normal UAE and without retinopathy. The night/day dBP ratio appears to be a stronger predictor of microvascular complications than the night/day sBP ratio. The rise in night dBP in type 1 diabetic patients may represent an early abnormality in the natural course of diabetic nephropathy and could be relevant for the development of retinopathy. The identification of increased night dBP as a modifiable parameter related to the development of microvascular complications might have implications for therapeutic approach. Performing AMBP in type 1 diabetic patients at the normoalbuminuric stage and with normal clinical BP should be strongly recommended. The abnormal circadian dBP variability may be involved in the development of microvascular complication in type 1 diabetics, which needs to be clarified in future longitudinal studies.

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