

# Association of Pulse Pressure and Diurnal Blood Pressure Variation with Micro- and Macrovascular Complications in Type 2 Diabetes in Rohilkhand Region

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## ABSTRACT

**Introduction:** In non-diabetic persons pulse pressure (PP) is an independent predictor of cardiovascular disease microalbuminuria. Reduced circadian blood pressure (BP) variation is a potential risk factor for the development of diabetic complication. We investigated association between retinopathy, nephropathy, macrovascular disease, PP and diurnal BP variation in a group of type 2 diabetes patients.

**Material and methods:** In 100 type 2 diabetic patients we performed 24 hr ambulatory BP (AMB BP) and fundoscopy, urinary albumin excretion was evaluated by urinary albumin/creatinine ratio. Presence and absence of macrovascular disease was assessed.

**Result:** 61 patients had no detectable retinal changes (grade 1), 15 had grade 2 retinopathy, 24 had more advanced retinopathy (grade 3-6). Compared to patients without retinopathy (grade 1), patients with grade 2 and 3-6 had higher PP and blurred diurnal BP variation. Comparing nephropathy group (58 normal, 24 microalbuminuric, 18 macroalbuminuric patients). Results are similar likewise compared to patients without macrovascular disease (n=69), patients with this complication (n=31) had higher AMBP value.

**Conclusion:** Increased PP and blurred diurnal BP variation are hemodynamic abnormalities associated with micro and macrovascular complication in type 2 diabetes mellitus.

**Keywords:** Pulse Pressure, Diurnal Blood Pressure, Micro and Macrovascular, Type 2 Diabetes

evaluate the association between pulse pressure and micro- and macrovascular complications of diabetes, as well as circadian BP variation, in patients with type 2 diabetes.

## MATERIAL AND METHODS

Hundred type 2 diabetic patients were identified from our hospital OPD, In present study age of diagnosis of diabetes is >30 years, with no need for insulin treatment for at least 1 year after the diagnosis of diabetes, and no history of ketoacidosis. Retinal examination was done within 1 month from an assessment of 24-h AMBP. Hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) was determined by high-performance liquid chromatography (non-diabetic range < 6.4%). The patients were classified as non smokers (without daily use of tobacco for the preceding year) or smokers (daily use of tobacco).

**Twenty-Four-Hour BP Measurements** The AMBP was measured are performed. If the measurements are found to be missing for more than 3 hrs the patient was excluded.

## Retinopathy Grading

In each eye a standard photograph of 60 degrees was taken. Each type of pathologic lesions like hemorrhages or microaneurysms, hard exudates, or cotton wool spots was counted, and the presence of laser scars or vascular abnormalities such as venous beading, or neovascularisations or intraretinal microvascular abnormalities (IRMA vessels) were counted, Every photograph taken was individually evaluated by two experienced graders. When the both evaluations of a photograph were discrepant it was reassessed by both the graders together. On the basis of the grading of all lesions present on a photograph each eye was assigned an overall retinopathy grade on a scale from 1 to 6 according to the principles used in the Wisconsin Epidemiologic Study of Diabetic Retinopathy<sup>19</sup> with a modification is considered to ensure that lesions implies the same risk of progression to proliferative diabetic retinopathy resulted in the same retinopathy level (ETDRS Report 12<sup>20</sup>): 1 = no retinopathy;

## INTRODUCTION

Blood pressure (BP) elevation is a key risk factor for the development of diabetic complications.<sup>1</sup> In non-diabetic, hypertensive subjects 24-h ambulatory BP measurement (AMB BP) has been shown to be superior to conventional BP measurement in predicting cardiovascular disease and death.<sup>2,3</sup> Recently,<sup>4</sup> focus has been directed toward pulse pressure (PP) as a predictor of cardiovascular risk in non-diabetic subjects.<sup>5-10</sup> Moreover, increased PP is associated with microalbuminuria in non-diabetic subjects.<sup>11</sup> There are no studies concerning the role of PP in diabetes and its associated complications. It is now being evident that not only the average level of BP, but also an abnormal circadian BP rhythm with a decreased fall in night BP, determines the development of diabetic complications. An association between impaired diurnal BP variation and diabetic complications has been found in both type 1 (retinopathy<sup>12</sup> and nephropathy<sup>13,14</sup>) and in type 2 diabetes (nephropathy<sup>15,16</sup> and macrovascular disease<sup>17</sup>). The aim of this study was to

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2a = less than 20 hemorrhages or microaneurysms, or 2b = cotton wool spots alone; 3a = 20 or more hemorrhages or microaneurysms, or 3b hard exudates combined with any number of hemorrhages or microaneurysms, or 3c less than 5 cotton wool spots combined with hemorrhages or microaneurysms or hard exudates; 4 = 5 or more cotton wool spots or IRMA vessels combined with hemorrhages or microaneurysms with or without hard exudates; 5 = venous beading combined with hemorrhages 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. The retinopathy grade on the worst eye was used for the analysis in all the patients. AMBP values were not known to the ophthalmologists.

### Nephropathy Classification

The three samples of morning urine were taken for urinary albumin excretion (UAE) and was evaluated by albumin/creatinine ratios. Patients were classified as normoalbuminuric, when at least two of three urinary albumin/creatinine ratios were <2.5 mg/mmol (men) and <3.5 mg/mmol (women), microalbuminuric (between 2.5 and 25 mg/mmol (men) and between 3.5 and 35 mg/mmol (women)), or macroalbuminuric (>25 mg/mmol (men) and >35 mg/mmol (women) or dip stick positive proteinuria in at least two of three samples).<sup>21</sup>

### Macrovascular Disease Classification

Macrovascular disease is considered if one or more of the following was present: symptoms of angina pectoris, history of myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, symptoms of/ or operation for intermittent claudication, amputations, or history of transient ischemic attack or stroke. The AMBP values were not known to the physician who performed the classification of macrovascular disease. The study was approved by the ethical committee of our hospital.

### STATISTICAL ANALYSIS

Pair wise comparisons were assessed with significance levels appropriately modified using the method of Dunnett (two-sided), when analysis of variance (ANOVA) indicated significant differences between groups. For noncontinuous variables the X<sup>2</sup> test with Yates' correction was used. A two-tailed P value of less than .05 was considered significant. Results are expressed as mean +/- SD. Multiple regression analysis was performed by stepwise linear regression analysis.

### RESULTS

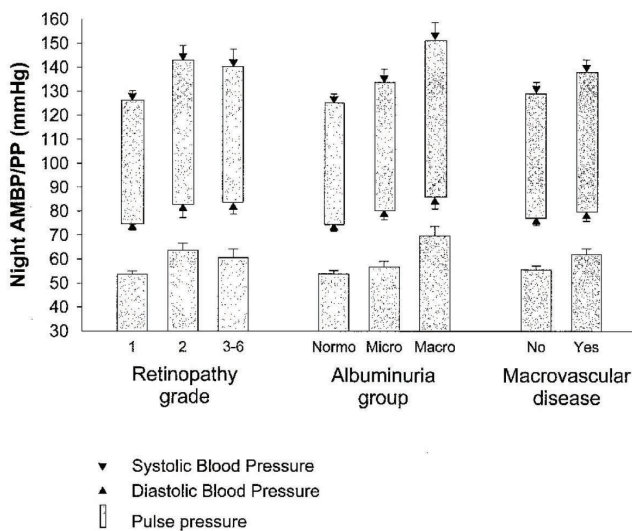
#### Retinopathy

Sixty one patients had no detectable retinal changes (grade 1), 15 had grade 2 retinopathy, and 24 had advanced retinopathy (grades 3–6). They were grouped together due to the very small numbers present in each group. The clinical characteristics and AMBP values of the patients when grouped together according to severity of complications are given in (Table 1). In patients with retinopathy (grades 2 and 3–6) the

Complications	n (♂/♀)	Age (y)	Duration (y)	AHT (%)	HbA <sub>1c</sub> (%)	Systolic AMBP (mm Hg)		Diastolic AMBP (mm Hg)		Pulse Pressure (mm Hg)			
						Day	Night	N/D ratio (%)	Day	Night	N/D ratio (%)	Day	Night
Retinopathy grade													
1	61(25/24)	55 ± 11	3.4 ± 4.4	55	8.8 ± 1.8	144 ± 14	128 ± 14	89.3 ± 7	86 ± 9	73 ± 8	85.1 ± 9	57 ± 11	55 ± 10
2	15(10/3)	59 ± 10	2.4 ± 3.0	54	8.3 ± 2.2	154 ± 19	145 ± 16	94.6 ± 8	90 ± 15	81 ± 14	90.8 ± 10	64 ± 11	64 ± 10
3-6	24(14/4)	58 ± 9	8.8 ± 7.5	78	8.3 ± 2.0	154 ± 21	142 ± 23	92.0 ± 6	91 ± 9	82 ± 11	89.0 ± 7	63 ± 15	61 ± 15
P	NS	NS	<.001	NS	NS	<.05	<.01	<.05	NS	<.01	<.07	NS	<.05
Albuminuria group													
Normo	58(23/22)	55 ± 9	3.5 ± 4.1	53	8.9 ± 2.1	143 ± 13	127 ± 13	88.9 ± 7	86 ± 9	73 ± 8	84.8 ± 9	57 ± 9	54 ± 9
Micro	24(13/6)	53 ± 11	3.9 ± 5.5	68	8.5 ± 1.7	147 ± 15	136 ± 16	92.0 ± 7	89 ± 10	79 ± 11	88.9 ± 7	59 ± 11	57 ± 10
Macro	18(12/3)	62 ± 10	8.2 ± 8.0	73	8.1 ± 1.5	162 ± 22	153 ± 20	94.9 ± 7	93 ± 12	84 ± 12	91.0 ± 10	70 ± 16	70 ± 15
P	NS	<.05	<.05	NS	NS	<.001	<.001	<.02	NS	<.01	<.05	<.001	<.001
Macrovascular disease													
No	69(30/25)	54 ± 9	3.8 ± 5.4	53	8.8 ± 2.1	147 ± 17	131 ± 19	89.2 ± 6	89 ± 10	76 ± 11	85.0 ± 7	58 ± 12	57 ± 12
Yes	31(19/6)	60 ± 11	5.8 ± 5.9	76	8.3 ± 1.5	149 ± 17	140 ± 16	94.1 ± 9	86 ± 11	78 ± 11	91.0 ± 11	63 ± 12	63 ± 11
P	NS	<.05	NS	NS	NS	NS	<.05	<.01	NS	NS	<.01	.07	<.05

Table-1: Clinical characteristics and ambulatory blood pressure of patients grouped according to severity of complications

AMBP = ambulatory blood pressure; AHT = receiving antihypertensive treatment; HbA<sub>1c</sub> = hemoglobin A1c; N/D = night/day; NS = not significant; Normo = normoalbuminuria; Micro = microalbuminuria; Macro = macroalbuminuria. Data are mean ± SD.



**Figure-1:** Mean values of night ambulatory blood pressure (AMBP) and night pulse pressure (PP) in relation to the three complication types (□ diastolic blood pressure; ▾ systolic blood pressure; shaded bar, PP). Error bars indicate SE.

AMBP was found to be consistently higher compared to the group with no detectable retinal changes (grade 1), whereas in patients with retinopathy grades 2 and 3–6 AMBP values were similar. Diurnal BP variation was found to be blunted in the patients with retinopathy as indicated by higher night/day ratios of systolic ( $P < .05$ ) as well as diastolic BP ( $P = .07$ ). Mean values of systolic and diastolic night BP and night PP for the three groups are depicted in Fig. 1. As apparent from the figure particularly systolic ( $P < .01$  for grades 2 and 3–6 v grade 1) but also diastolic night BP ( $P < .05$  for grades 2 and 3–6 v grade 1) were found higher in patients with retinopathy compared to patients without retinopathy, whereas there was no significant difference between grades 2 and 3–6.

As the increase in BP with increasing severity of retinopathy was more pronounced in systolic than in diastolic night BP, night PP was higher in the groups with retinopathy compared to the group without retinopathy (grade 2 v grade 1,  $P < .05$ , grade 3–6 v grade 1,  $P =$  not significant). Patients with no retinopathy (grade 1) had nearly normal UAE (19% were micro- and 11% macroalbuminuric), whereas in patients with grade 2 (50% micro- and 25% macroalbuminuric) and 3–6 retinopathy (22% micro- and 39% macroalbuminuric) are having these results,  $P < .05$  for grades 2 and 3–6 v grade 1. Diabetes duration was significantly longer in patients with grade 3–6 compared to patients in the rest two groups. No significant differences were found regarding tobacco consumption, age, sex, antihypertensive or anti-diabetic treatment, body mass index (BMI), HbA<sub>1c</sub>, or lipids between the groups (data not shown). There was a weak, non significant association between AMBP parameters and duration of diabetes, Age is correlating significantly with some AMBP parameters (night/day ratios, systolic night BP and night PP), whereas albuminuria status correlated strongly with almost all AMBP parameters. When covariates like albuminuria status, age, and duration were entered in the ANOVA, there was still a significant effect of retinal grade

on diastolic night BP ( $P = .03$ ), whereas on the rest of the AMBP parameters the effect of retinopathy grade barely reached any statistical significance (eg,  $P = .06$  for systolic night BP).

### Nephropathy

Fifty eight patients were normoalbuminuric (median urinary albumin/creatinine ratio 1.5 mg/mmol, mean plasma ([p]-creatinine) 77  $\mu$ mol/L), 24 patients were microalbuminuric (median albumin/creatinine ratio 7.1 mg/mmol, mean p-creatinine 75  $\mu$ mol/L), and 18 patients were macroalbuminuric (median albumin/creatinine ratio 124.2 mg/mmol, mean p-creatinine 95  $\mu$ mol/L); in 1 patient it was not possible to obtain information on UAE. In normal UAE patients AMBP values were consistently lowest, They were somewhat higher in the microalbuminuric group, and highest in the group with macroalbuminuria (Table 1).

This increment in BP with increasing degree of albuminuria was statistically significant for all AMBP parameters, except for diastolic day BP, as well as for all PP. Diurnal BP variation was increasingly abrupt, with stepwise augmentation in night/day ratios of systolic ( $P < .02$ ) and diastolic BP ( $P < .05$ ), in the normo-, micro- and macroalbuminuric groups. Mean values of systolic and diastolic night BP and night PP for the patients divided according to albuminuria are depicted in Fig. 1. Systolic and diastolic night BP tended to be higher in the micro- than in the normoalbuminuric group ( $P = .08$  for both) and was highest in the macroalbuminuric group ( $P < .001$  v the normoalbuminuric group for both). Night PP was highest in the macroalbuminuric group ( $P < .001$  v normoalbuminuric group), whereas the difference between the normo and microalbuminuric groups was not statistically significant. Patients with macroalbuminuria were having longer duration of diabetes and were older than patients in the normo- and microalbuminuric groups. There were no significant differences regarding antihypertensive or anti-diabetic treatment, sex, tobacco consumption, BMI, HbA<sub>1c</sub>, or lipids between the groups. When age and duration were included as covariates in a multivariate analysis, the effect of albuminuria status on systolic day ( $P < .01$ ) and night ( $P < .001$ ) BP, diastolic night BP ( $P < .01$ ), systolic and diastolic night/day ratio ( $P < .05$  for both), and day and night PP ( $P < .05$  and  $P < .001$ , respectively) was still statistically significant.

### Macrovascular Disease

Sixty nine patients had no history or symptoms of macrovascular disease, whereas the remaining 31 patients fulfilled at least one of the above-mentioned criteria for this condition. In the group with macrovascular disease, systolic AMBP values were consistently higher, reaching statistical significance for systolic night BP (Table 1). Whereas, diastolic day BP tended to be a little lower in the group with macrovascular disease, whereas diastolic night BP tended to be a little higher. Consequently, PP and night/day ratios were significantly higher in this group, compared to the group without macrovascular disease. Mean values of systolic and diastolic night BP and night PP for the two groups are depicted

in Fig. 1. It is apparent that systolic night BP and night PP ( $P < .05$  for both) were higher in the group with macrovascular disease than in the group without macrovascular disease, whereas no significant difference in diastolic night BP was seen between the groups. Patients with macrovascular disease were having longer duration of diabetes and are mostly older than patients without this complication. In patients with macrovascular disease (24% were micro- and 28% macroalbuminuric) albuminuria is found to be higher than in patients without macrovascular disease (23% micro- and 15% macroalbuminuric), but this difference was not statistically significant. There were no differences regarding sex, tobacco consumption, antihypertensive or anti-diabetic treatment, BMI,  $HbA_{1c}$ , or lipids between the groups. When age or duration were introduced as covariates in the analysis, the effect of macrovascular disease group was still significant for systolic and diastolic night/day ratios ( $P < .05$  for both), but not for the rest of the AMBP parameters. When entering retinopathy, albuminuria, and macrovascular disease groups together with age, sex, duration, antihypertensive treatment, BMI, and  $HbA_{1c}$  into a multivariate analysis, predictors of systolic night BP were albuminuria ( $P < .001$ ) and age ( $P < .01$ ), whereas the effect of retinopathy grade was borderline significant ( $P = .06$ , for the total multivariate analysis:  $r^2 = 0.33$ ,  $P < .001$ ). Predictors of systolic night/day ratio were age, albuminuria, and macrovascular disease group ( $P < .05$  for all, total analysis  $r^2 = 0.25$ ,  $P < .001$ ), and predictors of night PP were albuminuria group ( $P < .001$ ) and age ( $P < .05$ , total analysis  $r^2 = 0.28$ ,  $P < .001$ ). All other factors mentioned had no significant predictive value for these BP parameters.

## DISCUSSION

We present data on the association between three complications of type 2 diabetes: retinopathy, nephropathy, and macrovascular disease and AMBP. The severity of complications correlates consistently with AMBP values. Night BP were increased to a higher extent than day BP in patients with complications compared to patients without complications, this reflects a disturbed circadian BP variation in these patients. Likewise, Increase in systolic BP was larger than diastolic BP, resulting in higher PP in groups with compared to groups without complications. We have also found a strong association between the presence of nephropathy and retinopathy, whereas the association between these two microvascular complications and the presence of macrovascular disease was not statistically significant. Precision may be limited in the classification of individuals as no invasive test has been performed for macrovascular complications, thus possibly introducing dilution bias, favoring the null hypothesis. But, despite of all this potential lack of power we were able to demonstrate significant differences in AMBP values between subjects with and without clinically evident macrovascular disease. The association between elevation in BP and diabetic complications is well known through many studies.<sup>22</sup> A possible reason for the association between retinopathy and hypertension is proposed by Kohner and Patel.<sup>23,24</sup> Blood

pressure elevation leads to increased perfusion pressure, which causes hyperperfusion, especially in the presence of hyperglycemia, as this condition impairs auto regulation. The resulting increase in capillary shear stress leads to damage and closure of these small vessels with subsequent additional hyperperfusion, thus establishing a true *circulus vitiosus*. In the kidney these hemodynamic changes might result in glomerular hypertension and subsequent glomerular leakage of plasma proteins, forming the basis for the increase in albuminuria.<sup>25</sup> In larger arteries increased shear stress might facilitate endothelial dysfunction and atherosclerosis that are two pathophysiologic mechanisms in the development of macrovascular disease. In accordance with this hypothesis our patients with complications had higher values of AMBP, than with those without complications. Likewise, BP dropped significantly less during the night time in patients with complications. This association between disturbed diurnal BP variation (non dipping) and diabetic complications is in accordance with previous studies in both type 1 and type 2 diabetic patients.<sup>12-17</sup> A blunted diurnal BP variation could be an indicator of autonomic dysfunction,<sup>26</sup> a condition that has been related to the other diabetic complications.<sup>26-28</sup> Dysfunction of autonomic nerves to resistance vessels might adversely affect their ability to prevent the propagation of an elevated systemic BP to the microcirculation, thus putting further strain on the auto regulation of capillary perfusion and aggravating the capillary hypertension and hyperperfusion, as mentioned previously. However, lack of data on autonomic nervous function in these patients makes this association speculative.

Till now focus has been directed toward increase in diastolic BP rather than systolic BP. Systolic BP often increases with age, whereas diastolic BP remains unchanged or declines,<sup>29</sup> causing a widening of the PP. These changes, thought to be due to the development of arteriosclerosis-induced stiffness of the arteries were, until recently thought to be physiologic and benign in nature. However, recent randomized trials have shown substantial benefits of treating isolated systolic hypertension in elderly patients,<sup>30-32</sup> and lately several studies have shown PP to be a major, independent predictor of cardiovascular events in non-diabetic subjects.<sup>5-10</sup> Moreover, in middleaged, non-diabetic subjects PP and isolated systolic hypertension has recently been shown to be associated with microalbuminuria.<sup>11</sup>

Our study is the first to report an association between increments in PP and diabetic complications in our region. If an augmented PP to some extent is an epiphenomenon, reflecting a decreased elasticity of large- and middle-sized arteries, one can imagine that the capability of these vessels to absorb changes in BP is decreased, and consequently, these vessels would be more likely to allow the propagation of an increased BP to the microcirculation. The resulting increased BP amplitude imposes a steep increase in shear stress on the microvasculature, especially if resistance vessel innervation and autoregulation is impaired as described above, resulting in capillary/glomerular hypertension and development of micro- and macrovascular complications.

In conclusion, our data show that in type 2 diabetic patients the presence of retinopathy, nephropathy, and macrovascular disease is consistently associated with increased PP and decreased fall in night BP. These hemodynamic abnormalities might be a result of or a contributor to the development of diabetic complications.

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