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ORIGINAL RESEARCH

Pulse Pressure and Diurnal Blood Pressure Variation Associated with Micro- and Macrovascular Complications in Type 2 Diabetes

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ABSTRACT

Background: Pulse pressure (PP) is an independent predictor of cardiovascular disease microalbuminuria in non-diabetic people. Reduced circadian blood pressure (BP) variation has been identified as a risk factor for diabetic complications. In a sample of type 2 diabetic patients, we looked at the relationship between retinopathy, nephropathy, macrovascular disease, PP, and diurnal BP change.

Method: We performed a 24-hour ambulatory blood pressure (AMBP) and fundoscopy on 100 type 2 diabetes patients, and urine albumin excretion was measured using the urinary albumin / creatinine ratio. It was determined whether or not macrovascular disease existed.

Results: Out of 100 subjects, 15 had grade 2 retinopathy, and 24 had more severe retinopathy (grade 3-6). Those with grade 2 and 3-6 retinopathy exhibited larger PP and blurred diurnal BP fluctuation than patients without retinopathy (grade 1). Nephropathy group comparison (58 normal, 24 microalbuminuric, 18 macroalbuminuric patients). In comparison to individuals without macrovascular disease (n=69), patients with this consequence (n=31) had a higher AMBP score.

Conclusion: In type 2 diabetes mellitus, increased PP and blurred diurnal BP variation are hemodynamic abnormalities linked to micro and macrovascular complications.

Keywords: Pulse Pressure, Diurnal Blood Pressure, Nephropathy, Retinopathy

INTRODUCTION

Elevated blood pressure (BP) is a major risk factor for the development of diabetes complications.[1]Ambulatory blood pressure measurement (AMBP) has been demonstrated to be superior to conventional blood pressure measurement in predicting cardiovascular disease and death in nondiabetic, hypertensive people.[2,3] Pulse pressure (PP) has recently received attention as a predictor of cardiovascular risk in non-diabetic subjects.[4] In addition, higher PP has recently been linked to microalbuminuria in non-diabetic people.[5] There are no published research on the involvement of PP in diabetes and its complications at this time. There is mounting evidence that not only the average blood pressure, but also an irregular circadian BP rhythm with a reduced fall in night blood pressure (nondipping), influences the development of diabetic problems. In both type 1 (retinopathy[6] and nephropathy[7,8]) and type 2 diabetes, a link between altered diurnal BP variation and diabetic sequelae has been discovered (nephropathy[9,10] and macrovascular disease[11]). The researchers wanted to see if

there was a link between diabetic micro- and macrovascular problems and PP, as well as circadian BP variation, in type 2 diabetes patients.

MATERIAL AND METHODS

A total of 100 type 2 diabetic patients were identified from our hospital's emergency department, based on the following criteria: age at diagnosis >30 years, no requirement for insulin treatment for at least one year after diabetes diagnosis, and no history of ketoacidosis. A retinal examination was performed one month after a 24-hour AMBP assessment. High-performance liquid chromatography was used to determine haemoglobin A1c (HbA1c) (nondiabetic range <6.4 %). The patients were categorised as nonsmokers (those who had not used tobacco on a daily basis for the previous year) or smokers (daily use of tobacco).

24-Hour Blood Pressure Readings Measurements: These were taken during the course of a routine day at home or at work. Day and night BP were calculated using individually reported sleeping periods. The patient was ruled out if more than 3 hours were missing (four patients).

Retinopathy Grading: A normal 60-degree image was taken in each eye. The presence of laser scars or vascular abnormalities such as intraretinal microvascular abnormalities (IRMA vessels), venous beading, or neovascularizations was noted, as well as the number of each type of pathologic lesions: haemorrhages or microaneurysms, hard exudates, or cotton wool spots (truncated at 99). Two expert graders separately assessed each shot. When two graders disagreed on a photograph, the two graders worked together to reevaluate it. According to the principles used in the Wisconsin Epidemiologic Study of Diabetic Retinopathy[13], each eye was assigned an overall retinopathy grade on a scale of 1 to 6, 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[12,14]): 3a = 20 or more haemorrhages or microaneurysms, or 3b hard exudates combined with any number of haemorrhages or microaneurysms, or 3c less than 5 cotton wool spots combined with haemorrhages or microaneurysms or hard exudates; 4 = 5 or more cotton wool spots or IRMA vessels combined with haemorrhages or microaneurysms with or without hard exudate The analysis was based on the retinopathy grade of the patient's worse eye. AMBP readings were unknown to the ophthalmologists.

Nephropathy Classification: Albumin/creatinine ratios in three morning urine samples were used to assess urinary albumin excretion (UAE). When at least two of three urinary albumin/creatinine ratios were<2.5 mg/mmol (men) and <3.5 mg/mmol (women), patients were classified as normoalbuminuric, 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[15].

Macrovascular Disease Classification: If one or more of the following symptoms, history of myocardial infarction, coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, symptoms of or operation for intermittent claudication, amputations, or history of transient ischemic attack or stroke were present, the subject was classified as having macrovascular disease. AMBP readings were unknown to the physician who performed the macrovascular disease state classification. The local ethics commission approved the study.

STATISTICAL ANALYSIS

Anova and chi square test was used to analyse the significant difference. It was considered significant if the two-tailed P value was less than 0.05.

RESULTS

Table 1 shows the clinical characteristics and Table II the ambulatory blood pressure of the patients when classified by degree of problems. The AMBP was consistently greater in patients with retinopathy (grades 2 and 3–6) than in patients with no apparent retinal abnormalities (grade 1), whereas AMBP values in patients with retinopathy grades 2 and 3–6 were similar. Patients with retinopathy had lower diurnal BP variation, as evidenced by higher night/day ratios of systolic (P <.05) and diastolic BP (P =.07). Rise in BP with increasing severity of retinopathy was more pronounced in systolic night BP than in diastolic night BP, night PP was higher in the retinopathy groups than in the non-retinopathy groups (grade 2 grade 1, P<.05, grade 3–6 v grade 1, P = not significant). Most patients with no retinopathy (grade 1) had normal UAE (19 % microalbuminuric, 11 % macroalbuminuric), but this was not the case in patients with grade 2 (50 % microalbuminuric, 25 % macroalbuminuric) and 3–6 retinopathy (22 % microalbuminuric, 39 % macroalbuminuric), P<.05 for grades 2 and 3–6 grade 1. Patients with grade 3–6 diabetes had a considerably longer duration of diabetes than the other two groups. There were no significant differences between the groups in terms of age, sex, cigarette use, antihypertensive or antidiabetic therapy, BMI, HbA1c, or lipids (data not shown). The duration of diabetes had a mild, nonsignificant relationship with AMBP parameters; however, age associated considerably with specific AMBP parameters (night/day ratios, systolic night BP, and night PP), but albuminuria status correlated strongly with practically all AMBP measures (as described in detail in the next paragraph). When albuminuria status, age, and duration were included as covariates in the ANOVA, the effect of retinopathy grade on diastolic night BP remained significant (P =.03), whereas the effect of retinopathy grade on the other AMBP parameters barely reached statistical significance (e.g., P =.06 for systolic night BP).

All AMBP indicators, except diastolic day BP, and all PP, showed a statistically significant stepwise increase in BP with increasing degree of albuminuria. In the normo-, micro-, and macroalbuminuric groups, diurnal BP variation was more attenuated, with stepwise increases in systolic (P<.02) and diastolic (P<.05) night/day ratios. Figure 1 shows the mean values of systolic and diastolic night BP and night PP for the patients divided by albuminuria. The microalbuminuric group had higher systolic and diastolic nocturnal BP than the normoalbuminuric group (P =.08 for both), while the macroalbuminuric group had the highest (P<.001 for both). The macroalbuminuric group had the highest night PP (P<.001 compared to the normoalbuminuric group), but the difference between the micro- and normoalbuminuric groups was not statistically significant. Patients with macroalbuminuria were older and had had diabetes for longer than those with normo- and microalbuminuria. There were no significant differences between the groups in terms of sex, tobacco use, antihypertensive or antidiabetic medication, BMI, HbA1c, or lipids (data not shown). 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 when age and duration were included as covariates in a multivariate analysis (table 2).

The group with macrovascular disease had continuously higher systolic AMBP values, which reached statistical significance for systolic night BP (Table 2). Conversely, diastolic day BP was slightly lower in the macrovascular disease group, whereas diastolic night BP was slightly higher. As a result, when compared to the group without macrovascular disease, PP and night/day ratios were much greater in this group. Figure 1 shows the mean values of systolic and diastolic night BP and night PP for the two groups. The figure shows that systolic night BP and night PP (both P<.05) were greater in the group with macrovascular disease than in the group without macrovascular disease, but diastolic night BP did not differ significantly between the groups. Patients with macrovascular disease were older and had

diabetes for a longer time than those who did not have this consequence. When age and duration were included as factors in the analysis, the effect of macrovascular disease group remained significant for the systolic and diastolic night/day ratios (P<.05 for both), but not for the other AMBP indicators. Albuminuria (P<.001) and age (P<.001) were significant predictors of systolic night BP when retinopathy, albuminuria, and macrovascular disease groups were combined with age, sex, duration, antihypertensive treatment, BMI, and HbA1c in a multivariate analysis, whereas the effect of retinopathy grade was borderline significant (P =.06, for the total multivariate analysis: r Age, albuminuria, and macrovascular disease group were all predictors of systolic night/day ratio (P<.05 for all, total analysis r2 = 0.25, P<.001), while albuminuria group (P<.001) and age (P<.05, total analysis r2 = 0.28, P<.001) were predictors of night PP. For these BP metrics, none of the other criteria indicated had a significant predictive value.

Table 1: Demographic profile among the study subjects according to complications

Complications	M/F	Age (in years)	Duration (in years)	AHT (%)	HbA1c (%)
Retinopathy grade					
1	32/29	54.5±10.2	3.3±2.8	56	8.5±1.6
2	11/4	58.3±7.86	2.7±2.6	54	8.2±2.1
3-6	16/8	59.4±8.73	8.5±7.2	72	8.4±1.8
p value	0.09	0.28	<0.01	0.43	0.46
Albuminuria Group					
Normo	32/26	52.8±9.4	3.4±2.1	52	8.3±1.4
Micro	15/9	54.1±8.81	3.83±2.2	61	8.6±2.2
Macro	12/6	61.7±9.98	8.1±7.4	74	8.4±1.4
p value	0.09	0.007	<0.01	0.56	0.77
Macrovascular Disease					
No	35/32	53.9±9.2	3.7±4.2	54	8.5±2.1
Yes	24/9	60.6±10.47	5.5±4.9	78	8.9±1.9
p value	0.24	0.004	0.07	0.32	0.81

Table 2: Clinical characteristics of patients grouped according to severity of complications

Complications	Systolic AMBP (mm Hg) Day	Systolic AMBP (mm Hg) Night	Systolic AMBP (mm Hg) N/D ratio (%)	Diastolic AMBP (mmHg) Day	Diastolic AMBP (mmHg) Night	Diastolic AMBP (mmHg) N/D ratio (%)	Pulse Pressure (mm Hg) Day	Pulse Pressure (mm Hg) Night
Retinopathy grade 1 2 3-6 P	144 ±14 154 ±19 154 ±21 <.05	128 ±14 145 ±16 142± 23 <.01	89.3± 7 94.6 ±8 92.0± 6 <.05	86 ±9 90 ±15 91± 9 NS	73 ±8 81± 14 82 ±11 <.01	85.1± 9 90.8 ±10 89.0 ±7 <.07	57 ±11 64± 11 63± 15 NS	55± 10 64 ±10 61± 15 <.05

Albuminuria group Normo Micro Macro P	143± 13 147± 15 162 ±22 <.001	127 ±13 136 ±16 153 ±20 <.001	88.9 ±7 92.0 ±7 94.9± 7 <.02	86± 9 89 ±10 93 ±12 NS	73± 8 79 ±11 84 ±12 <.01	84.8 ±9 88.9 ±7 91.0 ±10 <.05	57 ±9 59 ±11 70 ±16 <.001	54± 9 57 ±10 70 ±15 <.001
Macrovascular Disease No Yes P	147± 17 149 ±17 NS	131± 19 140 ±16 <.05	89.2± 6 94.1± 9 <.01	89 ±10 86 ±11 NS	76± 11 78 ±11 NS	85.0 ±7 91.0 ±11 <.01	58 ±12 63 ±12 .07	57 ±12 63 ±11 <.05

AMBP = ambulatory blood pressure; AHT = receiving antihypertensive treatment; HbA1c = hemoglobin A1c; N/D = night/day; NS= not significant; Normo = normoaalbuminuria; Micro= microalbuminuria; Macro = macroalbuminuria. Data are mean SD

DISCUSSION

We offer evidence for a link between AMBP and three type 2 diabetic complications: retinopathy, nephropathy, and macrovascular disease. The degree of problems was consistently linked with the AMBP readings. When comparing patients with issues to patients without complications, night BP was greater than day BP, indicating a disrupted circadian BP variation in these patients. Similarly, systolic BP increments were larger than diastolic BP increments, resulting in higher PP in groups with complications compared to groups without issues. We also discovered a robust link between the prevalence of retinopathy and nephropathy, but no statistically significant link between these two microvascular problems and the existence of macrovascular disease. However, because no invasive tests for macrovascular disease were conducted, precision in classifying people based on this consequence may be limited, thereby creating dilution bias and supporting the null hypothesis. Despite this possible lack of power, significant differences in AMBP levels were found between participants with and without clinically obvious macrovascular disease. The link between high blood pressure and diabetic complications is widely understood.[16]

PatelV et al[17] and Kohner et al[18]present a plausible explanation for the link between hypertension and retinopathy. Elevated blood pressure creates higher perfusion pressure, which causes hyperperfusion, especially when combined with hyperglycemia, which affects autoregulation. As a result of the increased capillary shear stress, these tiny arteries are damaged and close, resulting in additional hyperperfusion and the formation of a real circulus vitiosus. These hemodynamic alterations in the kidney could lead to glomerular hypertension and subsequent glomerular leakage of plasma proteins, resulting in a rise in albuminuria.[19] Increased shear stress in bigger arteries may facilitate atherosclerosis and endothelial dysfunction, two pathophysiologic pathways in macrovascular disease development. Our patients with problems had higher AMBP values than those without complications, confirming this notion. Furthermore, in individuals with problems, blood pressure decreased significantly less during the night. Previous investigations in both type 1 and type 2 diabetic patients have found a link between abnormal diurnal BP variation (nondipping) and diabetic problems.[6-8] Autonomic dysfunction, which has been linked to other diabetes problems, could be indicated by a reduced diurnal BP variation.[20–22] Autonomic nerve dysfunction in

resistance arteries may impair their ability to prevent the transmission of increased systemic BP to the microcirculation, putting additional load on capillary perfusion autoregulation and exacerbating capillary hypertension and hyperperfusion, as previously indicated. However, because no data on autonomic nerve function in these patients is available, this link remains conjectural.[23]

Until recently, the focus was on diastolic rather than systolic blood pressure changes. The PP widens as systolic blood pressure rises and diastolic blood pressure stays the same or falls with age. Until recently, these alterations were assumed to be physiologic and benign, and were thought to be caused by arteriosclerosis-induced stiffness of the arteries. Recent randomised trials have demonstrated that treating isolated systolic hypertension in elderly people has significant benefits[24–26], and multiple investigations have recently revealed that PP is a strong, independent predictor of cardiovascular events in nondiabetic subjects. Furthermore, PP and isolated systolic hypertension have recently been linked to microalbuminuria in middle-aged non-diabetic patients.[5]

Our research is the first to show a link between PP increases and diabetic complications. If an increased PP is an epiphenomenon resulting from lower flexibility of big and middle-sized arteries, one may assume that the ability of these vessels to absorb changes in BP is reduced, and as a result, these vessels are more likely to enable increased BP to reach the microcirculation. Capillary/glomerular hypertension and the development of micro- and macrovascular complications result from the increased BP amplitude, which imposes a steep increase in shear stress on the microvasculature, especially if resistance vessel innervation and autoregulation are impaired as described above.

CONCLUSION

In conclusion, our findings reveal that the presence of retinopathy, nephropathy, and macrovascular disease in type 2 diabetic individuals is consistently linked with increased PP and decreased nocturnal BP fall. These hemodynamic anomalies could be a cause or a contributing factor in the development of diabetes complications. Prospective studies are needed to further investigate these correlations and to determine the practicality of commencing antihypertensive medication based on PP or diurnal BP change.

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