

# Carotid-Femoral Pulse Wave Velocity Is Associated With Cerebral White Matter Lesions in Type 2 Diabetes

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**OBJECTIVE**—Patients with type 2 diabetes have a high incidence of cardiovascular events including stroke. Increased arterial stiffness (AS) predicts cardiovascular events in the general population. Cerebral white matter lesions (WMLs) are associated with an increased risk of stroke. It is unknown whether AS in patients with type 2 diabetes is associated with WMLs.

**RESEARCH DESIGN AND METHODS**—We examined 89 patients recently diagnosed with type 2 diabetes (<5 years) and 89 sex- and age-matched controls. AS was assessed with carotid-femoral pulse wave velocity (PWV). WMLs were identified using magnetic resonance imaging and graded qualitatively with the Breteler scale (no/slight changes = 0, moderate changes = 1, severe changes = 2) and semiquantitatively.

**RESULTS**—The diabetes population had excellent glycemic control (HbA<sub>1c</sub>, 6.5% [6.2–6.8]; median [interquartile range {IQR}]) and had, compared with the controls, lower office blood pressure (BP) (127 ± 12/79 ± 8 vs. 132 ± 14/84 ± 10 mmHg) and total cholesterol (4.3 [3.9–4.7] vs. 5.6 [5.1–6.4]; mmol/L; median [IQR]), (*P* < 0.01 for all). Despite this, PWV was higher in the patients with diabetes compared with controls (9.3 ± 2.0 vs. 8.0 ± 1.6 m/s; *P* < 0.0001). PWV was associated with Breteler score (OR 1.36 [95% CI 1.17–1.58]; *P* < 0.001) and WML volume (1.32 [1.16–1.51]; *P* < 0.001) per 1 m/s increase in PWV. These associations remained significant when adjusted for age, sex, diabetes, 24-h mean arterial BP, BMI, heart rate, and use of antihypertensives and statins (Breteler score: 1.28 [1.03–1.60]; *P* < 0.05 and WML volume: 1.30 [1.06–1.58]; *P* < 0.05).

**CONCLUSION**—PWV was higher among patients with well-controlled type 2 diabetes compared with controls and was independently associated with WMLs. PWV may represent a clinically relevant parameter in the evaluation of cerebrovascular disease risk in type 2 diabetes.

Despite intensified treatment, patients with type 2 diabetes have a significantly higher incidence of cardiovascular events, including stroke, compared with patients without diabetes (1–3). Identifying new risk factors for incident cardiovascular disease, which add prognostic information to established risk factors, is important to improve risk

stratification and enable timely initiation of individually tailored preventive measures in this high-risk population (4). Increased arterial stiffness, as indicated by increased pulse wave velocity (PWV), is an independent predictor of cardiovascular morbidity and mortality and total mortality in various nondiabetic populations (5–11). In patients with diabetes,

PWV independently predicts cardiovascular and total mortality (12). Several studies have found cerebral white matter lesions (WMLs) to be associated with the risk of stroke (13). Nevertheless, it remains unknown whether PWV in patients with type 2 diabetes is associated with the severity of WMLs. In this study of a sample of patients with recently diagnosed type 2 diabetes and a sex- and age-matched control group, our aims were to 1) compare PWV and established cardiovascular risk factors and 2) study the association between PWV and WMLs.

## RESEARCH DESIGN AND METHODS

### Subjects

One hundred patients with type 2 diabetes and 100 controls matched individually for sex and age were included in this study. The patients were recruited consecutively from the outpatient clinics at Aarhus University Hospital, Aarhus, Denmark. Inclusion criteria were age > 18 years, diagnosis of type 2 diabetes according to World Health Organization criteria (14), and known duration of diabetes <5 years. The control subjects were recruited by advertising in the local press, and undiagnosed diabetes was excluded by fasting glucose and oral glucose tolerance tests. Subjects with impaired fasting glucose (nine participants), impaired glucose tolerance (three participants), or both (two participants) were accepted as control subjects. Exclusion criteria for both patients with diabetes and controls were acute or chronic infectious disease, end-stage renal failure, pregnancy or lactation, prior or current cancer, and contraindications to magnetic resonance imaging (MRI) (claustrophobia, magnetic material in the body, and body weight >120 kg). PWV data were not recordable in four participants because of atrial fibrillation and in three participants because of obesity. MRI data were not available for four participants because of previously unrecognized claustrophobia (in two of these participants PWV was not recordable because of technical problems). Accordingly,

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Received 15 May 2012 and accepted 23 August 2012.

DOI: 10.2337/dc12-0942. Clinical trial reg. no. NCT00674271, clinicaltrials.gov.

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the 11 matches for these 11 participants also were excluded; thus, data from 178 participants were available for statistical analysis. The study was approved by the Research Ethics Committee of Central Region, Denmark, and by the Danish Data Protection Agency. All patients gave their written, informed consent to participate.

### Study protocol

**Pulse wave velocity measurements.** Examinations were conducted from 9 A.M. until 1 P.M. after a minimum of 5 min rest in a quiet room. The study subjects had abstained from smoking and intake of tea, coffee, or other caffeinated beverages for at least 3 h before the examinations. At least 2 h elapsed between breakfast and the examinations.

Measurements of PWV were performed using an applanation tonometer (Millar, SPT-301B, Houston, TX) and SphygmoCor equipment and software, version 8.0 (AtCor Medical, Sydney, Australia). After a minimum of 5 min of rest in the supine position, the carotid-femoral PWV was determined by sequential electrocardiogram-referenced recordings of the pulse wave at the carotid and the femoral artery by the tonometer. The transit time was determined by the intersecting tangent algorithm method (15), and the path length was calculated by subtracting the distance between the site of the carotid artery pulse measurement and the sternal notch from the distance between the site of the femoral artery pulse measurement and the sternal notch, all measured directly using a tape measure. The mean of two PWV measurements was calculated. Within-subject coefficient of variation for PWV was 5.1%.

Office blood pressure (BP) was measured on the right arm, and mean systolic and diastolic BPs were calculated as the average of three measurements obtained after a minimum of 5 min of rest in the seated position. Arm circumference was assessed using a tape measure and an appropriately sized cuff. BP was measured by a Riester Champion N automatic blood pressure monitor (Riester GmbH, Jungingen, Germany) or a Speidel & Keller mercury sphygmomanometer (Speidel & Keller, Welch Allyn, Jungingen, Germany). Pulse pressure was calculated as systolic BP minus diastolic BP, and mean arterial pressure as diastolic BP + (systolic - diastolic)/3.

Ambulatory BP was monitored for 24 h using Spacelabs 90217 (Spacelabs Healthcare, Issaquah, WA). BP was measured at 20-min intervals during the day and night.

The calculation of day and night BP was based on patients' individual diary recordings of awake and sleeping hours. Recordings with more than three missing hours (maximum of 1 h during the night) were excluded from the analysis. Visit-to-visit BP coefficients of variation are 2–5% (16,17).

**Brain MRI.** Brain MRI was performed with an eight-channel SENSE head coil on a 1.5-T MRI scanner (Achieva, Philips, Best, Netherlands) to obtain axial T2-flair-weighted scans with a slice thickness of 5 mm (T2-flair echo time, 130 ms; repetition time, 6000 ms; inversion time, 2200 ms; echo train length (number per repetition time), 19; flip angle, 90 degrees; number of averages, 2). The magnetic resonance images were evaluated by an experienced radiologist who was blinded to the subjects' diabetes/control status. WMLs were defined as areas of brain parenchyma with an increased signal on the T2-weighted scans but without significant volume loss. The WMLs were assessed both qualitatively and semiquantitatively. Qualitatively, the patients were graded 0–2 according to the scale introduced by Breteler et al. (18) (0–4 punctate WMLs = 0, >4 punctate WMLs but no confluent lesions = 1, presence of confluent WMLs regardless of number of punctate lesions = 2). This scale is simple and robust, with a high interrater reliability (19). In addition, the volume of the WMLs was assessed semiquantitatively as area of WMLs multiplied by the slice thickness. Measurements were performed using the Osirix 4.0 Dicom viewer (20). The radiologist and a biomedical engineer, both blinded to the diabetes/control status of the patients, in cooperation recorded the areas of the WMLs. The areas of all individual confluent lesions were measured. The size of a typical punctate WML was estimated by using the mean area of a representative sample (36 lesions). The areas of measured punctate WMLs from five randomly selected patients with diabetes and five controls were randomly distributed around the estimated mean area, with no obvious indication of difference in size of WMLs between the two groups. Hence, the total estimated WML volume in the individual patient was calculated as follows:

$$\begin{aligned} &(\text{total number of punctate lesions in the} \\ &\text{patient} \times \text{average area of punctate lesion}) \\ &+ (\text{total areas of confluent lesions in the} \\ &\text{individual patient}) \times \text{slice thickness.} \end{aligned}$$

Cerebral infarctions were defined as areas with volume loss surrounded by signals

consistent with gliosis and were classified as lacunar when the size was less than 15 mm. **Urinary albumin excretion.** Urinary albumin excretion was evaluated by albumin-to-creatinine ratios in three morning urine samples. Patients were classified as microalbuminuric when at least two of three samples had urinary albumin-to-creatinine ratios of 2.5:25 mg/mmol (men) and 3.5:35 mg/mmol (women).

### Statistics

Differences in means were assessed by paired *t* tests. Assumption of normal distributions was tested by histograms and Q–Q plots. Skewed data (HbA1c, total cholesterol, triglycerides, and urine albumin-to-creatinine ratio) were log-transformed before *t* tests were performed. The estimated volumes of WMLs were not normally distributed even if log-transformed. Thus WML volumes were categorized as low, medium, or high (operationalized as 1st to 50th percentile, 51st to 75th percentile, and 76th to 100th percentile, respectively, because of the skewed distribution of WMLs, with a substantial part of the sample having no or few WMLs) to enable ordinal regression analysis with adjustment for matching and confounders. Test for trend was calculated by the nptrend-test in Stata software. Difference in Breteler score between the two groups was tested with a signed rank test. Baseline data are presented as means ± SD or median (25th percentile; 75th percentile) for skewed data. A two-tailed *P* value of less than 0.05 was considered statistically significant. Data were analyzed with software from Stata (version 11, StataCorp LP, College Station, TX).

**RESULTS**—Patient characteristics are presented in Table 1. The patients with diabetes were recently diagnosed and were overweight, but had good glycemic control. There was no difference between the two groups regarding smoking habits, but a significantly higher proportion of the diabetes population was taking antihypertensive and cholesterol-lowering treatment (Table 1). Accordingly, the diabetes group had significantly lower office BP and cholesterol levels.

Twenty-four hour ambulatory (ABPM) systolic and diastolic BP were comparable between the two groups, whereas 24-h ABPM of pulse pressure was significantly higher in the diabetes group, primarily because of a higher pulse pressure at night in the diabetes group (Table 1). The diabetes group also was characterized by a

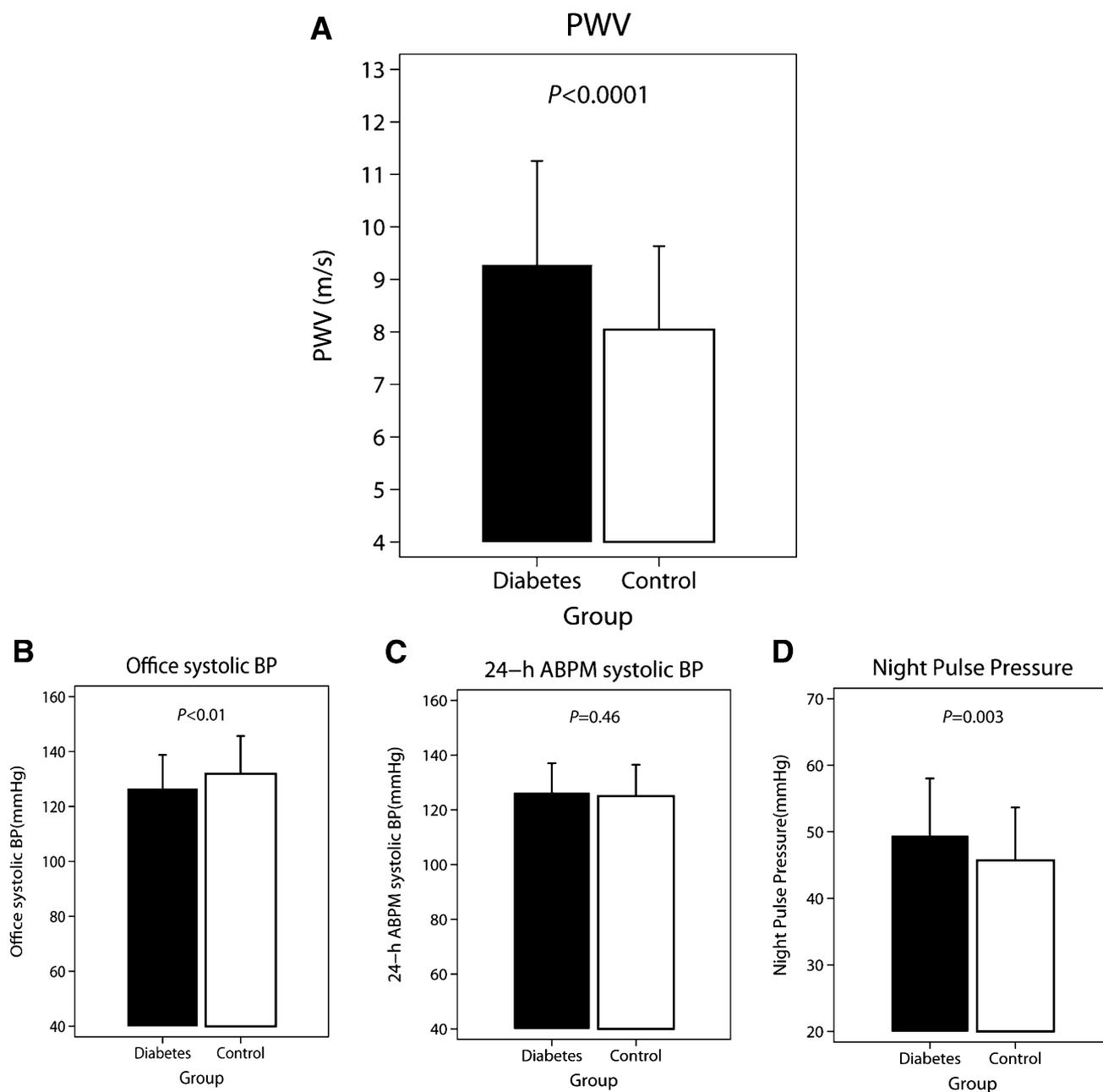
Table 1—Patient characteristics

	Patients with diabetes	Controls	P value
Sex, n			—
Men	46	46	
Women	43	43	
Age (years)	59 ± 10	59 ± 10	—
Diabetes duration (years)			—
Median	1.8	—	
25th percentile	0.8	—	
75th percentile	3.1	—	
HbA1c, %			<0.0001
Median	6.5	5.7	
25th percentile	6.2	5.5	
75th percentile	6.8	5.8	
BMI (kg/m <sup>2</sup> )	30 ± 5	26 ± 4	<0.0001
Smoking, n			0.95
Current	18	18	
Previous	32	30	
Never	39	41	
Statin use, n			<0.001
Yes	68	16	
No	21	73	
Antihypertensive treatment, n			<0.001
Yes	56	25	
No	33	64	
Total cholesterol (mmol/L)			<0.0001
Median	4.3	5.6	
25th percentile	3.9	5.1	
75th percentile	4.7	6.4	
LDL-cholesterol (mmol/L)	2.2 ± 0.7	3.4 ± 1.0	<0.0001
HDL-cholesterol (mmol/L)	1.4 ± 0.3	1.7 ± 0.6	0.0001
Triglycerides (mmol/L)			0.03
Median	1.4	1.2	
25th percentile	1.1	1.0	
75th percentile	1.6	1.6	
Urine albumine/creatinine ratio (mg/mmol)			0.0001
Median	0.40	0.25	
25th percentile	0.28	0.17	
75th percentile	0.98	0.40	
Office measurement (mmHg)			
Systolic BP	127 ± 12	132 ± 14	<0.01
Diastolic BP	79 ± 8	84 ± 10	<0.001
Pulse pressure	47 ± 10	48 ± 10	0.72
24-h ABPM (mmHg)			
Systolic BP	126 ± 11	125 ± 12	0.46
Diastolic BP	76 ± 7	76 ± 7	0.17
Pulse pressure	52 ± 8	49 ± 9	0.03
Mean arterial pressure	92 ± 8	93 ± 8	0.72
Daytime ABPM (mmHg)			
Systolic BP	131 ± 11	130 ± 12	0.78
Diastolic BP	78 ± 8	80 ± 8	0.11
Pulse pressure	53 ± 9	50 ± 9	0.08
Nighttime ABPM (mmHg)			
Systolic BP	116 ± 11	112 ± 11	0.02
Diastolic BP	66 ± 7	66 ± 7	0.97
Pulse pressure	49 ± 9	46 ± 8	0.003
Heart rate (bpm)			
Office	67 ± 10	62 ± 11	0.001
24 h	73 ± 10	68 ± 9	0.002

Values provided as mean ± SD unless otherwise indicated.

higher urinary albumin-to-creatinine ratio than the control group. The patients with diabetes had significantly higher resting heart rate and 24-h ABPM heart rate than the controls (Table 1). Three patients in the diabetes group and two patients in the control group were classified as microalbuminuric. PWV in the diabetes group was significantly higher than in the control group ( $9.3 \pm 2.0$  vs.  $8.0 \pm 1.6$  m/s;  $P < 0.0001$ ), as shown in Fig. 1, which also depicts office and 24-h ABPM of systolic BP and night pulse pressure. PWV increased with Breteler score ( $P < 0.001$  for trend; Fig. 2). In unadjusted ordinal regression analysis, PWV predicted Breteler score, both overall and in the diabetes and control groups (Table 2). The association remained significant after adjustment for age, sex, diabetes, 24-h mean arterial BP, BMI, 24-h heart rate, and use of antihypertensives and statins (Table 2). Adjustment for mean office BP, systolic BP (24-h ABPM or office measurement), or pulse pressure (office measurement, 24-h ABPM, day or night values) instead of 24-h mean BP did not alter this association. Similarly, adjustment for resting heart rate instead of 24-h heart rate or additional inclusion of smoking status or urinary albumin-to-creatinine ratio did not alter the associations significantly. In stratified analysis, PWV independently predicted Breteler score in the diabetes group but not in the control group (Table 2). In the diabetes group, the association remained significant even after inclusion of HbA1c, duration of diabetes, or treatment modality in the model ( $P < 0.05$  for all). Testing for interaction between PWV and diabetes/control group, however, was not significant ( $P = 0.67$ ).

PWV independently predicted increasing WML volume in unadjusted ordinal logistic regression analysis, both overall and in the diabetes and control groups (Table 2). The association remained statistically significant after adjustment for age, sex, diabetes, 24-h mean arterial BP, BMI, 24-h heart rate, and use of antihypertensive treatment and statins (Table 2). Adjustment for mean office BP, systolic BP (24-h ABPM or office measurement), or pulse pressure (office measurement, 24-h ABPM, day or night values) instead of 24-h mean BP did not alter this association. Similarly, inclusion of smoking or urinary albumin-to-creatinine ratio did not alter the associations significantly. In stratified analysis, PWV was independently associated with WML volume in the diabetes group but



**Figure 1**—PWV and BP in 89 patients with type 2 diabetes and 89 sex- and age-matched controls. A: PWV. B: office systolic BP. C: 24-h ABPM. D: Night pulse pressure.

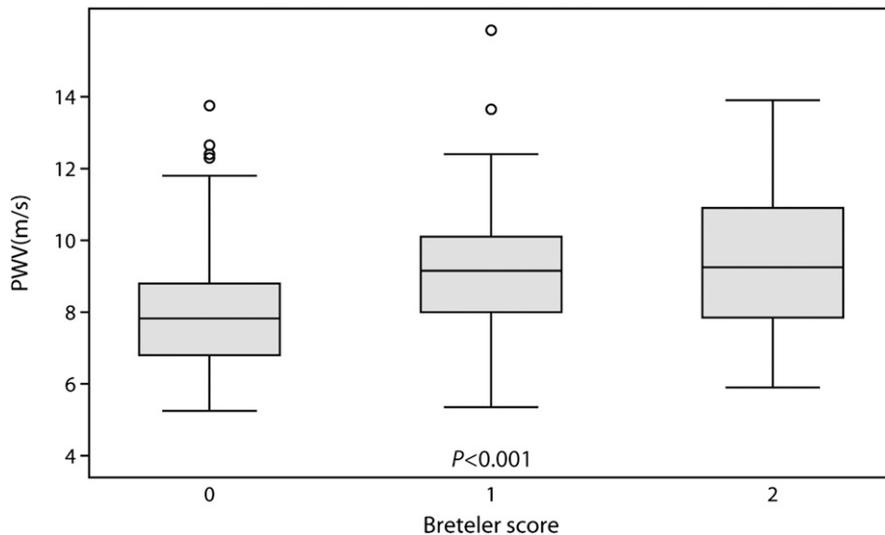
not in the control group (Table 2). However, test for interaction between PWV and diabetes/control group was nonsignificant ( $P = 0.85$ ).

There was no significant difference between the diabetes group and the control group with regard to Breteler score (48/31/10 vs. 50/26/13;  $P = 0.64$ ). Similarly, the volume of WMLs was not significantly different between the diabetes and the control groups (mean difference  $-0.3 \text{ cm}^3$  [95% CI  $-1.2$  to  $0.7 \text{ cm}^3$ ];  $P = 0.55$ ). In the control group, when comparing participants with impaired fasting

glucose or impaired glucose tolerance with participants with normoglycemia, there was neither a significant difference in Breteler score or WML volume ( $P = 0.86$  and  $P = 0.80$ , respectively).

Nineteen participants (11 patients with diabetes and 8 controls) had evidence of cerebral infarctions on the MRI scans. In the diabetes group, 6 of the 11 infarctions had been symptomatic; 5 were silent and only identified on the MRI scans. In the control group, three of the eight infarctions had had been symptomatic, and five were silent and only identified

on the MRI scans. Subjects with cerebral infarctions had significantly higher PWV than subjects without ( $9.9 \pm 1.7$  vs.  $8.5 \pm 1.9 \text{ m/s}$ ;  $P = 0.002$ ). The prevalence of infarctions was significantly higher in patients with PWV above versus below the median value of  $8.4 \text{ m/s}$  ( $P = 0.001$ ). Infarctions were present in 16 of 88 participants with a PWV above versus 3 of 90 participants with a PWV below the median value. Hence, the prevalence of infarctions was 5.5 times higher in participants with PWV above the median value compared with patients with PWV below the median value.



**Figure 2**—Box-and-whiskers plot of the association between PWV and Breteler score among all 178 subjects. *P* for trend is shown. The whiskers represent the highest value within 1.5 times the interquartile range (IQR) from the upper quartile and the lowest value within 1.5 times the IQR from the lower quartile.

**CONCLUSIONS**—The first main finding of this study was a significantly higher PWV in the diabetes group compared with the control group, despite optimal regulation of blood glucose, BP, and cholesterol levels in the diabetes sample and comparable smoking habits between the two groups. PWV is a well-established risk marker for cardiovascular disease, and our findings illustrate that assessment of PWV may provide additional information about patients' cardiovascular risk profile above and beyond what is revealed by conventional risk markers. Because glycemic control, BP, and cholesterol levels are modifiable over a short to medium time frame, the

information carried by these factors regarding the current risk status of the patient is reduced. In contrast, PWV presumably reflects accumulated damage to the arterial wall and is a robust marker of the working conditions of the heart and vascular system. A recent metaanalysis found that a 1-m/s increase in PWV corresponded to an age-, sex-, and risk factor-adjusted increase in risk of 14% (95% CI 9–20%) for total cardiovascular events, a 15% (9–21%) increase for cardiovascular mortality, and a 15% (9–21%) increase in all-cause mortality (21). Accordingly, a 1.3-m/s higher PWV in the diabetes group would correspond to an approximately 18% increase in total cardiovascular risk and a

20% increase in both cardiovascular mortality and total mortality risk compared with the control group.

New data suggest that aortic stiffness is reduced by long-term antihypertensive treatment beyond BP lowering, whereas the effect of aortic destiffening on cardiovascular events remains to be elucidated (22).

The second finding in this sample of patients with type 2 diabetes and sex- and age-matched controls was that PWV was associated with the severity of WMLs, both when WMLs were assessed on a visual rating scale or semiquantitatively. The association remained after adjustment for well-established risk factors for cardiovascular events and potential confounders of PWV including heart rate. The increased heart rate found in the diabetes group (Table 1) may indicate autonomic neuropathy, reduced fitness, or both, compared with the control group. Increased heart rate induces increased functional arterial stiffness (23). Activity levels and exercise are important determinants of arterial stiffness (24), and low fitness levels with resulting higher heart rate may contribute to the increased arterial stiffness seen in patients with diabetes (25). It is interesting that there was no significant difference in Breteler score or estimated WML volume between the two groups. We have no obvious explanation for this finding. It might reflect the multifactorial pathophysiology underlying the development of WMLs. A higher prevalence of some unidentified risk factors for WMLs in the control group could have influenced the WML burden in this group, yet the exact nature of these remain elusive given the well-matched groups (Table 1). The third finding was an increased prevalence of cerebral infarctions in patients with PWV above the median value (8.4 m/s). The relatively low number of cerebral infarctions (19 subjects), however, precluded adjustment for confounders; hence these findings should be interpreted cautiously and the results should be confirmed in a larger sample before conclusions regarding the predictive ability of PWV for nonfatal stroke in patients with diabetes can be made.

Several studies have shown that WMLs, especially confluent WMLs, are associated with an increased risk of cerebral infarctions (13,26,27). The pathogenesis of cerebral WMLs and the chain of events causing clinical infarctions are multifactorial and remain incompletely elucidated (26,28). However, ischemic

**Table 2**—Association of carotid-femoral PWV with qualitative (Breteler) and semiquantitative (WML volume) grading of cerebral WMLs in ordinal logistic regression analysis

	Unadjusted odds ratio (95% CI) per 1 m/s increase in PWV	<i>P</i> value	Adjusted odds ratio (95% CI) per 1 m/s increase in PWV	<i>P</i> value
<b>Breteler score</b>				
All	1.36 (1.17–1.58)	<0.001	1.28 (1.03–1.60)	<0.05
Patients with				
diabetes	1.42 (1.13–1.79)	0.002	1.39 (1.02–1.88)	<0.05
Controls	1.37 (1.10–1.71)	0.005	1.1 (0.78–1.59)	0.56
<b>WML volume</b>				
All	1.32 (1.16–1.51)	<0.001	1.30 (1.06–1.58)	<0.05
Patients with				
diabetes	1.37 (1.13–1.67)	0.001	1.43 (1.08–1.91)	<0.05
Controls	1.38 (1.11–1.73)	0.004	1.10 (0.76–1.61)	0.60

\*Adjusted for age, sex, diabetes, 24-h mean arterial BP, BMI, 24-h heart rate, and use of antihypertensives and statins.

injury to the white matter presumably plays an important role in the development of WMLs. Cross-talk between the macro- and microcirculation seems to be central to this process. When the pulse wave travels along the arterial tree, reflected waves are generated at sites of impedance mismatch. This occurs at bifurcations and at the interface between arteries with low and high impedance, such as between the elastic aorta and the stiffer carotid arteries. This mechanism protects the microcirculation from excessive transmission of pulsatile energy. Nevertheless, with increasing aortic stiffness, the central pulse pressure increases and the impedance mismatch decreases, resulting in a higher transmission of pulsations into the low-impedance microvasculature of the brain (29,30). This may promote arterial wall remodeling (arteriosclerosis) with resulting smaller lumen and reduced vasodilatory reserve. Increased vascular resistance in response to increased pulse pressure with unchanged mean arterial pressure will reduce mean blood flow, potentially causing chronic hypoperfusion in the supplied areas of the brain. Furthermore, the concurrence of reduced vasodilatory reserve and the labile BP, often seen with increasing arterial stiffness, increases the risk of episodes of transient reductions of mean arterial pressure below the autoregulatory range, with ensuing episodes of microvascular ischemia (26,29). The potential combined effect of chronic and acute episodes of hypoperfusion and ischemia can induce damage to the white matter and disrupt the blood brain barrier, with leakage of plasma into the white matter. These alterations may manifest as diffuse areas of myelin rarefaction (i.e., WMLs) and localized areas of necrosis and cavitation (i.e., lacunes) (13,26,29). A recent meta-analysis of population studies found high levels of WMLs to be associated with a significantly increased risk of stroke (OR 3.1 [95% CI 2.3–4.1];  $P < 0.001$ ), which is even higher in high-risk populations with established atherosclerotic disease (7.4 [2.4–22.9];  $P = 0.001$ ) (13). Specific data for diabetes patients have not been published.

The association between PWV and WMLs has, to the best of our knowledge, not previously been studied in a well-defined sample of patients with type 2 diabetes and compared with nondiabetic controls. Previous studies have investigated the association between PWV and WMLs in other patient groups and have not found a uniform tendency. In some

studies, PWV was reported to be independently associated with WMLs (31–35), whereas in others it was not (36–40). These results probably reflect both the multifactorial pathophysiology underlying the development of WMLs and the methodological differences regarding assessment of PWV and WML. Overall, it seems that the association between PWV and WMLs is most pronounced in high-risk populations (elderly people, patients with cerebral infarctions, and patients with type 1 diabetes). We extend this association to patients with newly diagnosed type 2 diabetes. In stratified analysis, the association between PWV and WMLs was statistically significant only in the diabetes population, but it should be stressed that testing for interaction between diabetes and PWV was not significant. The implication of the nonsignificant interaction term is that no firm conclusions regarding differences in the strength of the association between PWV and WMLs in the diabetes group versus the control group can be made based on this study. However, the data do suggest that the underlying pathophysiology associating PWV and WMLs might be different in patients with diabetes compared with those without diabetes, potentially with a closer association in patients with diabetes than in controls. Further clarification of the differences in this association must await future studies.

In conclusion, we found increased PWV in a well-regulated sample of patients with type 2 diabetes compared with a sex- and age-matched control group. Moreover, increased PWV was independently associated with severity of WMLs even after adjustment for established cardiovascular risk markers. Thus, our findings support the potential added predictive value of PWV in risk stratification above conventional risk factors.

**Acknowledgments**—This work was supported by research grants from The Novo Nordisk Foundation, The A.P. Møller Foundation for the Advancement of Medical Science, The Beckett Foundation, and The Aase and Ejnar Danielsen Foundation.

No potential conflicts of interest relevant to this article were reported.

E.L. generated the study hypothesis, developed the study design, acquired, analyzed, and interpreted data, and drafted and revised the manuscript. P.H. developed the study design, acquired data, critically revised the manuscript, and obtained funding. B.S.-G. analyzed and interpreted data, provided technical support, and critically revised the manuscript. A.M. analyzed

data, provided technical support, and critically revised the manuscript. S.T. developed the study design, provided technical support, and critically revised the manuscript. M.E. provided statistical support, interpreted data, and critically revised the manuscript. J.S.C. developed the study design, provided administrative support, obtained funding, and critically revised the manuscript. S.T.K. and K.W.H. interpreted data and critically edited and revised the manuscript. W.Y.K. developed the study design, interpreted data, provided technical support, and critically edited and revised the manuscript. T.K.H. developed the study hypothesis and design, obtained funding, interpreted data, provided administrative support, and critically revised the manuscript. P.L.P. developed the study hypothesis, analyzed and interpreted data, handled supervision, provided administrative support, and critically revised the manuscript. E.L. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors thank laboratory technicians Merete Møller and Lisa Buus, from the Medical Research Laboratory at the Department for Endocrinology and Internal Medicine, Aarhus University Hospital, for excellent technical assistance.

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