Arterial Stiffness Is Associated With Cardiovascular, Renal, Retinal, and Autonomic Disease in Type 1 Diabetes

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OBJECTIVE—In patients with type 1 diabetes, we investigated the association between arterial stiffness and diabetes complications.

RESEARCH DESIGN AND METHODS—Cross-sectional study including 676 Caucasian patients with type 1 diabetes (374 [55%] men, aged 54 ± 13 years [mean ± SD]) and 51 nondiabetic controls (28 [55%] men, aged 47 ± 13 years). Aortic pulse wave velocity (PWV) was measured with SphygmoCor (AtCor Medical, Sydney, Australia) for 635 patients and all 51 controls.

RESULTS—PWV (mean ± SD) in patients and controls were 10.4 ± 3.4 and 7.6 ± 1.9 m/s, respectively (P < 0.001). After multivariate adjustment, PWV correlated with age, diabetes duration, urinary albumin excretion rate, heart rate, and blood pressure (P < 0.05 for all). ANCOVA was used for comparisons between groups and adjusted for gender, age, estimated glomerular filtration rate, heart rate, HbA₁c, and 24-h mean arterial pressure. PWVs in normoalbuminuric, microalbuminuric, and macroalbuminuric patients were 9.5 ± 3.2, 11.0 ± 3.6, and 11.4 ± 3.0 m/s, respectively (adjusted P < 0.001). PWV in patients with previous cardiovascular disease, versus patients without, was 12.1 ± 3.5 vs. 10.0 ± 3.2 m/s, respectively (adjusted P < 0.001). PWVs in patients with high (≥140/90 mmHg) versus intermediate (130–140/80–90 mmHg) and low (<130/80 mmHg) blood pressure were 11.8 ± 3.6, 10.0 ± 3.0, and 9.8 ± 3.3 m/s, respectively (adjusted P < 0.001). Furthermore, PWV increased with increasing degree of retinopathy (P < 0.001). Finally, PWV increased with abnormal heart rate variability 11.5 ± 3.3 m/s vs. 10.1 ± 3.1 m/s (borderline and 8.1 ± 2.1 m/s (normal), (adjusted P = 0.027).

CONCLUSIONS—Arterial stiffness increased with presence and duration of type 1 diabetes. Furthermore, PWV increased with all the investigated diabetes complications (cardiovascular, renal, retinal, and autonomic disease) independently of other risk factors.

Arterial stiffness predicts cardiovascular disease (CVD) events in the general population (1), in hypertension (2,3), and in diabetes (4,5). A recent meta-analysis by Vlachopoulos et al. (6) showed pulse wave velocity (PWV) to predict both CVD and all-cause mortality. The gold standard for measurement of arterial stiffness is aortic PWV measurements (7,8), which have shown to be reproducible in the general population (9) and in patients with chronic kidney disease (10).

In hypertension, PWV is a marker of subclinical organ damage. Recent studies have shown PWV to be predictive of future changes in systolic blood pressure (SBP) development of hypertension (11) to potentially improve CVD risk scoring (12,13), and also to be higher among patients less responsive to antihypertensive medication (AHT) (14).

Furthermore, in patients with end-stage renal disease, elevated PWV is an independent predictor of all-cause mortality (15), and lowering PWV by AHT reduces the mortality independently of the blood pressure (BP) reduction (16).

In type 1 diabetes, PWV has been shown to be associated with cerebral microvascular disease, cardiac (17) and renal function (18), and in type 2 diabetes with microalbuminuria (19). These associations are suggestive of PWV being related to vascular dysfunction (20) and large artery alterations, thereby possibly engaging in the development of kidney impairment (21). Arterial stiffness also is associated with autonomic neuropathy in type 1 diabetes (22,23) and retinopathy in type 2 diabetes (24), further illustrating the association between arterial stiffness and microvascular disease.

The current study is the first in a relatively large and diverse group of patients with type 1 diabetes to investigate the association between PWV and a range of diabetes complications, including albuminuria, CVD, elevated BP, retinopathy, and autonomic neuropathy.

RESEARCH DESIGN AND METHODS

Patients
From September 2009 until June 2011, Caucasian patients with type 1 diabetes attending the outpatient clinic at Steno Diabetes Center were invited to enter a cross-sectional study investigating the associations between BP, arterial stiffness, and diabetes complications. Of 1,283 patients invited, 676 patients were included in the study. The cohort was selected to include patients with a wide range of albuminuria; hence, 316 patients with normalalbuminuria, 169 with microalbuminuria, and 191 with macroalbuminuria were included. A control group of 51 persons without diabetes was also included in the study for comparison with patients with normalalbuminuria and short duration of diabetes to investigate if presence of diabetes influenced PWV.

The study conformed to the Declaration of Helsinki and was approved by the Danish National Committee on Biomedical Research Ethics (2009–056;
Pulse wave velocity in type 1 diabetes

NCT01171248). All patients gave written informed consent.

Baseline clinical and laboratory methods
Arterial stiffness was measured as carotid-femoral (aortic) PWV by the SphygmoCor (AtCor Medical, Sydney, Australia) device. Participants were placed in supine position and measurements were performed after 15 min of rest by trained laboratory technicians. Three PWV measurements were recorded, and the two measurements closest to each other were averaged and used in the analyses. A PWV ≥12 m/s was regarded as elevated according to current guidelines (25).

Urinary albumin excretion ratio (UAER) was measured in 24-h sterile urine collections by enzyme immunoassay. Patients were stratified as normoalbuminuric if they, in two out of three consecutive measurements, had persistent normoalbuminuria with UAER <30 mg/24 h and were considered microalbuminuric or macroalbuminuric if UAER was between 30 and 300 mg/24 h or >300 mg/24 h, respectively.

The estimated glomerular filtration rate (eGFR) was calculated by the four-variable Modification of Diet in Renal Disease formula (26). Patients with end-stage renal disease, defined as receiving dialysis or renal transplantation, or GFR/ eGFR <15 ml/min/1.73 m² were not included in the study.

Electrocardiographs were recorded with Cardiosoft version 6.51 (GE Healthcare).

All 24-h ambulatory BPs (AMBP) were recorded with a validated tonometric watch-like device (BPro; HealthStats, Singapore), which captures radial pulse wave reflection and calculates AMBP (27,28). The BPro device measures BP every 15 min during a 24-h period. In the current study, the BPro device was calibrated with an oscilometric device (UA 787; A&D Medical (29)) before BP measuring. The AMBP data were adequate if ≥14 and ≥7 BP recordings were obtained during day and night, respectively, according to present guidelines (30). The mean number of successful measurements in our cohort was 45 ± 7 and 18 ± 4 during the day and the night, respectively. Dipping was calculated as the percentage decrease in night (11:00 P.M.–7:00 A.M.) compared with day systolic BP (SBP) (7:00 A.M.–11:00 P.M.). Dipping <10% was classified as abnormal. Although the reproducibility of abnormal dipping is imperfect, abnormal dipping has been shown to be predictive of CVD events (31).

Heart rate variability (HRV) was measured during paced deep breathing (32). Abnormal HRV is one of the earliest signs of cardiac autonomic neuropathy and is highly reproducible (33,34). A HRV ≥15 was classified as normal, HRV of 11–14 was classified as borderline, and HRV <11 bpm was classified an abnormal value.

Retinopathy status was obtained from medical records. All patients attending Steno Diabetes Center have regular ophthalmological examinations, where retinopathy is assessed from retinal photographs taken through dilated pupils and graded as nil, simple, proliferative, or blind based on the worst eye.

HbA1c was measured by high-performance liquid chromatography (normal range: 4.1–6.4%, [21–46 mmol/mol]; Variant; Biorad Laboratories, Munich, Germany) and serum creatinine concentration by an enzymatic method (Hitachi 912, Roche Diagnostics, Mannheim, Germany). Based on standardized questionnaires, current users of ≥1 cigarettes or cigars or pipes per day were classified as smokers and all others were classified as nonsmokers. Previous CVD was history of myocardial infarction, coronary intervention, stroke, or peripheral arterial disease based on standardized World Health Organization questionnaires and patient records.

Statistical analysis
Normally distributed variables are given as mean ± SD. Non-normally distributed variables are given as median (range) and log10-transformed before analysis. Comparisons between groups were performed by unpaired Student t test or ANOVA. The χ² test was used to compare noncontinuous variables. Univariate linear regression models were used to compare PWV with covariates. All covariates independently associated with PWV (P < 0.05) from the univariate analyses were entered in a multivariate backward stepwise regression model. ANCOVA was used for multivariable adjustment when comparing groups. In all tests, a two-tailed P ≤ 0.05 was considered statistically significant.

In the ANCOVA, adjustments were made for gender, age, eGFR, HbA1c, heart rate (HR), and 24-h mean arterial pressure (MAP). Covariates used in the ANCOVA were those that were significantly associated with PWV in the multiple linear backward stepwise regression analysis. eGFR was used instead of logUAER, because albuminuric groups were compared, and 24-h MAP was used instead of 24-h pulse pressure (PP) to not adjust for arterial stiffness. In additional models, we substituted 24-h MAP with 24-h SBP (see Table 2). Finally, age was chosen at the expense of diabetes duration to not exclude the controls in the multivariate analysis. However, in additional adjustment models (Table 2), we substituted age with diabetes duration because age also is included in the equation for eGFR. When comparing patients with controls, HbA1c was not included because it would entail a degree of adjustment for diabetes. All statistical calculations were performed using SPSS for Windows, version 15.0 (SPSS, Chicago, IL).

RESULTS
Baseline characteristics
Attainment of three PWV measurements on all participants was attempted, but only 635 (94%) patients and 51 (100%) controls had PWV measurements available. Overall, participants with successful PWV measurements were younger, with shorter diabetes duration, lower HR, lower 24-h PP, lower BMI, higher eGFR, had less previous CVD, and received less AHT (P < 0.05 for all) versus patients without PWV measurements. In contrast, gender distribution, 24-h SBP, DBP, MAP, albuminuria group, UAER, HbA1c, total cholesterol, smoking status, retinopathy status, and prevalence of autonomic neuropathy were similar among participants with and without PWV measurements (P > 0.05 for all).

In 13 patients, only one PWV measurement was obtained. These patients were included in the calculations, using the single measurement as mean value. However, if excluding the 13 patients from the calculations, similar results were obtained.

Baseline characteristics of the 635 patients and 51 controls with PWV measurements are shown in Table 1. Patients with PWV measurements were 54 ± 13 years old, with 32 ± 16 years of diabetes duration, and 349 (55%) were men. Overall, 304 (48%), 152 (24%), and 179 (28%) had normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively.
Table 1—Baseline characteristics for patients according to albuminuria group for the 635 patients and 51 controls

<table>
<thead>
<tr>
<th></th>
<th>Controls, n = 51</th>
<th>Normal albuminuria, short duration, n = 211</th>
<th>Normal albuminuria, long duration, n = 304</th>
<th>Microalbuminuria, n = 152</th>
<th>All patients, n = 635</th>
<th>P Normal albuminuria, short vs. controls</th>
<th>P Normal albuminuria, long vs. all vs. controls</th>
<th>P Normal albuminuria, vs. microalbuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, men/women, %</td>
<td>55/45</td>
<td>59/41</td>
<td>50/50</td>
<td>50/50</td>
<td>55/45</td>
<td>0.293</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>47 ± 13</td>
<td>44 ± 15</td>
<td>50 ± 11</td>
<td>53 ± 13</td>
<td>54 ± 13</td>
<td>0.258</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes duration, y</td>
<td>Not available</td>
<td>6 ± 3</td>
<td>28 ± 17</td>
<td>35 ± 15</td>
<td>38 ± 11</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>5.4 ± 0.3</td>
<td>37.7 ± 9</td>
<td>37.7 ± 0.9</td>
<td>8.1 ± 1.2</td>
<td>8.3 ± 1.2</td>
<td>0.014</td>
<td>0.593</td>
<td>0.024</td>
</tr>
<tr>
<td>HbA1c, mmol/mol</td>
<td>35 ± 3</td>
<td>63 ± 9</td>
<td>61 ± 10</td>
<td>62 ± 11</td>
<td>65 ± 13</td>
<td>68 ± 13</td>
<td>64 ± 13</td>
<td>0.379</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.0 ± 0.7</td>
<td>4.7 ± 0.7</td>
<td>4.7 ± 0.7</td>
<td>4.7 ± 0.8</td>
<td>4.6 ± 1.0</td>
<td>0.144</td>
<td>0.593</td>
<td>0.024</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.6 ± 3.8</td>
<td>24.6 ± 3.1</td>
<td>24.4 ± 3.7</td>
<td>24.7 ± 3.5</td>
<td>25.5 ± 4.0</td>
<td>0.096</td>
<td>0.740</td>
<td>0.247</td>
</tr>
<tr>
<td>p-Creatinine, μmol/L</td>
<td>74 ± 11</td>
<td>72 ± 14</td>
<td>74 ± 14</td>
<td>81 ± 13</td>
<td>121 ± 59</td>
<td>0.311</td>
<td>0.181</td>
<td>0.367</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73m²</td>
<td>95 ± 14</td>
<td>103 ± 22</td>
<td>90 ± 19</td>
<td>94 ± 21</td>
<td>85 ± 27</td>
<td>64 ± 29</td>
<td>83 ± 28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UAER, mg/24 h</td>
<td>8 (2–157)</td>
<td>11 (3–44)</td>
<td>7 (2–236)</td>
<td>11 (3–152)</td>
<td>131 (4–527)</td>
<td>0.030</td>
<td>0.002</td>
<td>0.016</td>
</tr>
<tr>
<td>*Previous CVD, %</td>
<td>4</td>
<td>3</td>
<td>12</td>
<td>10</td>
<td>28</td>
<td>29</td>
<td>19</td>
<td>&lt;0.009</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>6</td>
<td>23</td>
<td>18</td>
<td>18</td>
<td>17</td>
<td>24</td>
<td>19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AHT, %</td>
<td>8</td>
<td>25</td>
<td>54</td>
<td>45</td>
<td>89</td>
<td>98</td>
<td>71</td>
<td>&lt;0.009</td>
</tr>
<tr>
<td>Renin angiotensin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aldosterone system, %</td>
<td>4</td>
<td>25</td>
<td>50</td>
<td>42</td>
<td>81</td>
<td>94</td>
<td>66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium blocker, %</td>
<td>0</td>
<td>9</td>
<td>19</td>
<td>16</td>
<td>45</td>
<td>44</td>
<td>31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium blocker 1 or</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>calcium blocker 3</td>
<td>0</td>
<td>13</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>7</td>
<td>8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Betablocker</td>
<td>2</td>
<td>3</td>
<td>9</td>
<td>7</td>
<td>13</td>
<td>17</td>
<td>11</td>
<td>0.555</td>
</tr>
<tr>
<td>Statin, %</td>
<td>6</td>
<td>33</td>
<td>44</td>
<td>41</td>
<td>67</td>
<td>84</td>
<td>59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>†Antiplatelets, %</td>
<td>6</td>
<td>33</td>
<td>44</td>
<td>41</td>
<td>67</td>
<td>84</td>
<td>59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin dose, IU</td>
<td>0</td>
<td>50 ± 24</td>
<td>45 ± 47</td>
<td>47 ± 41</td>
<td>47 ± 24</td>
<td>51 ± 26</td>
<td>48 ± 34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>65 ± 10</td>
<td>69 ± 11</td>
<td>70 ± 12</td>
<td>70 ± 12</td>
<td>71 ± 12</td>
<td>76 ± 12</td>
<td>72 ± 12</td>
<td>0.031</td>
</tr>
<tr>
<td>24-h AMBP SBP, mmHg</td>
<td>130 ± 21</td>
<td>125 ± 14</td>
<td>129 ± 14</td>
<td>128 ± 15</td>
<td>131 ± 15</td>
<td>129 ± 15</td>
<td>129 ± 15</td>
<td>0.063</td>
</tr>
<tr>
<td>24-h AMBP DBP, mmHg</td>
<td>82 ± 14</td>
<td>77 ± 10</td>
<td>77 ± 10</td>
<td>73 ± 9</td>
<td>75 ± 10</td>
<td>75 ± 10</td>
<td>0.18</td>
<td>0.552</td>
</tr>
<tr>
<td>24-h AMBP PP, mmHg</td>
<td>48 ± 11</td>
<td>48 ± 9</td>
<td>53 ± 11</td>
<td>51 ± 12</td>
<td>56 ± 12</td>
<td>53 ± 12</td>
<td>0.719</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-h AMBP MAP, mmHg</td>
<td>98 ± 15</td>
<td>93 ± 11</td>
<td>94 ± 10</td>
<td>94 ± 11</td>
<td>94 ± 10</td>
<td>94 ± 11</td>
<td>93 ± 11</td>
<td>0.024</td>
</tr>
<tr>
<td>Dipping, %</td>
<td>10.9 ± 6.0</td>
<td>11.0 ± 6.0</td>
<td>9.5 ± 5.2</td>
<td>9.9 ± 5.5</td>
<td>9.5 ± 5.5</td>
<td>7.8 ± 5.6</td>
<td>9.2 ± 5.6</td>
<td>0.929</td>
</tr>
<tr>
<td>HRV, bpm</td>
<td>19 ± 8</td>
<td>18 ± 8</td>
<td>11 ± 7</td>
<td>13 ± 8</td>
<td>9 ± 7</td>
<td>7 ± 5</td>
<td>11 ± 8</td>
<td>0.381</td>
</tr>
<tr>
<td>Pulse wave velocity, m/s</td>
<td>7.6 ± 1.9</td>
<td>7.8 ± 1.9</td>
<td>10.2 ± 3.3</td>
<td>11.0 ± 3.6</td>
<td>11.4 ± 3.0</td>
<td>10.4 ± 3.4</td>
<td>0.656</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse wave velocity</td>
<td>&gt;12 m/s, %</td>
<td>4</td>
<td>2</td>
<td>24</td>
<td>17</td>
<td>32</td>
<td>39</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are percentage (%) and mean ± SD or median(range). Some patients with previous microalbuminuria or macroalbuminuria receiving antihypertensive treatment had values <30 mg/24 h at time of investigation.

*Previous CVD events were myocardial infarction, coronary revascularization, stroke, or peripheral vascular disease. †Antiplatelets are acetylsalicylic acid and clopidogrel.
Correlations between PWV and covariates in patients
In the patients, PWV correlated positively with age \((r = 0.63)\), diabetes duration \((r = 0.54)\), 24-h PP \((r = 0.50)\), HRV \((r = 0.48)\), 24-h SBP \((r = 0.33)\), UAER \((r = 0.24)\), HR \((0.21)\), and dipping \((r = 0.10)\), and inversely correlated with eGFR \((r = 0.33; P < 0.001\) for all\) and, to a lesser degree, with 24-h DBP \((r = 0.10; P = 0.021)\) and 24-h MAP \((r = 0.06; P = 0.07)\). PWV was higher in men, patients with previous CVD, and patients receiving AHT \((P < 0.05\) for all\) (Table 2). In contrast, PWV was similar in smokers and nonsmokers (Table 2) and did not correlate with total daily insulin dose, total cholesterol, BMI, height, or weight (data not shown). The final model after selection of significant covariates showed that PWV correlated with age, diabetes duration, gender, logUAER, HR, and 24-h PP \((P < 0.05\) for all).

Patients with normoalbuminuria versus controls
Mean \(\pm\) SD PWV in normoalbuminuric patients \((n = 304)\) versus controls \((n = 51)\) was 9.5 \(\pm\) 3.2 vs. 7.6 \(\pm\) 1.9 m/s, respectively \((P < 0.001)\). After adjustment, PWV remained significantly higher in patients versus controls \((P < 0.001)\) (Table 1). Entering use of AHT in the adjusted analysis did not alter the result (data not shown).

Overall, 52 (17\%) normoalbuminuric patients compared with 2 (4\%) controls had elevated PWV \((\geq 12 \text{ m/s})\) \((P = 0.008)\) (Table 1). Patients with increased PWV were more often male, older, had longer diabetes duration, higher 24-h SBP, higher UAER, and higher total cholesterol, lower eGFR, received more often AHT, and had more previous CVD \((P < 0.001\) for all\). HbA1c, BMI, and smoking status were similar in patients with and without elevated PWV \((P > 0.05\) for all).

Patients with normalalbuminuria and short versus long duration of diabetes
Among the normoalbuminuric patients, 93 (31\%) had short diabetes duration \((<10\text{ years})\), whereas 211 had long duration \((\geq 10\text{ years})\). PWVs in normoalbuminuric patients with short versus long duration were 7.8 \(\pm\) 1.9 and 10.2 \(\pm\) 3.3 m/s, respectively \((P < 0.001)\) (Table 1). The difference attenuated after multivariate adjustment (adjusting for age, gender, eGFR, HbA1c, HR, and 24-h MAP) \((P = 0.082)\); however, if substituting age with diabetes duration \((P < 0.001)\) (Table 2). Overall, 2 (2\%) patients with short duration compared with 50 (24\%) with long duration had elevated PWV \((\geq 12 \text{ m/s})\) \((P < 0.001)\) (Table 1).

Patients with different degrees of albuminuria
PWVs in patients with normalalbuminuria, microalbuminuria, and macroalbuminuria were 9.5 \(\pm\) 3.2 m/s, 11.0 \(\pm\) 3.6 m/s, and 11.4 \(\pm\) 3.0 m/s, respectively \((P < 0.001)\) (Table 1). For the different albuminuria groups, PWV tended to increase with both albuminuria and age. This finding is consistent with earlier vascular aging in patients with increasing albuminuria. After adjustment, PWV still increased with albuminuria group \((P < 0.001)\). Entering use of AHT in the adjusted analysis did not alter the result (data not shown). In addition, PWV was increased \((\geq 12 \text{ m/s})\) in 32 (17\%), 49 (32\%), and 70 (39\%) of patients with normalalbuminuria, microalbuminuria, and macroalbuminuria \((P < 0.001)\).

Patients with or without previous CVD
Previous CVD was present in 121 (19\%) patients, and the PWV was 12.1 \(\pm\) 3.5 compared with 10.0 \(\pm\) 3.2 m/s in patients without previous CVD \((P < 0.001)\). Patients with previous CVD were older, had longer diabetes duration, higher HbA1c, higher UAER, higher 24-h DBP, and received more AHT. However, gender distribution, total cholesterol, BMI, 24-h SBP, and smoking status were similar between groups. After multivariate adjustment, PWV remained higher in patients with previous CVD \((P = 0.017)\). Entering use of statins, total cholesterol, or AHT in the adjusted analysis or excluding patients receiving class 1 or 3 calcium blockers or beta blockers did not alter the results (data not shown).

Patients with different levels of BP
A total of 623 patients had both PWV and 24-h AMBP measurements available.

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**Table 2—Comparison of PWV between groups in all 635 patients**

<table>
<thead>
<tr>
<th></th>
<th>PWV (m/s)</th>
<th>(P)</th>
<th>(P) Adjusted model 1§</th>
<th>(P) Adjusted model 2†</th>
<th>(P) Adjusted model 3‡</th>
<th>(P) Adjusted model 4¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male vs. female)</td>
<td>10.7 (\pm) 3.5 vs. 10.0 (\pm) 3.2</td>
<td>0.006</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (yes vs. no)</td>
<td>10.2 (\pm) 3.1 vs. 10.4 (\pm) 3.4</td>
<td>0.555</td>
<td>0.193</td>
<td>0.355</td>
<td>0.243</td>
<td>0.270</td>
</tr>
<tr>
<td>Normoalbuminuria, short vs. long</td>
<td>7.8 (\pm) 1.9 vs. 10.2 (\pm) 3.3</td>
<td>&lt;0.001</td>
<td>0.082</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normoalbuminuria vs. microalbuminuria vs. macroalbuminuria</td>
<td>9.5 (\pm) 3.2 vs. 11.0 (\pm) 3.6 vs. 11.4 (\pm) 3.0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.181</td>
<td>0.151</td>
<td>0.008</td>
</tr>
<tr>
<td>Previous CVD (yes vs. no)</td>
<td>12.1 (\pm) 3.5 vs. 10.0 (\pm) 3.2</td>
<td>&lt;0.001</td>
<td>0.017</td>
<td>0.006</td>
<td>0.009</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AHT (yes vs. no)</td>
<td>11.2 (\pm) 3.3 vs. 8.4 (\pm) 2.5</td>
<td>&lt;0.001</td>
<td>0.015</td>
<td>0.001</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BP (low, intermediate, and high)</td>
<td>9.8 (\pm) 3.3, 10.0 (\pm) 3.0, and 11.8 (\pm) 3.6</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.015</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HRV (normal, borderline, and abnormal)</td>
<td>8.1 (\pm) 2.1, 10.1 (\pm) 3.1, and 11.5 (\pm) 3.3</td>
<td>&lt;0.001</td>
<td>0.027</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dipping (normal vs. abnormal)</td>
<td>9.8 (\pm) 3.3 vs. 11.0 (\pm) 3.3</td>
<td>&lt;0.001</td>
<td>0.174</td>
<td>0.144</td>
<td>0.287</td>
<td>0.007</td>
</tr>
<tr>
<td>Retinopathy (nil, simplex, proliferative, and blind)</td>
<td>8.0 (\pm) 2.5, 10.0 (\pm) 2.8, 12.1 (\pm) 3.5, and 12.7 (\pm) 2.4</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.01</td>
<td>0.01</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Previous CVD events were myocardial infarction, coronary revascularization, stroke, or peripheral vascular disease. BP groups defined as low \(<130/80\), intermediate 130–139/80–89, and high: \(\geq 140/90\) mmHg. HRV defined as normal \(\geq 15\), borderline 11–14 and abnormal \(<11\) bpm. *Model 1: Adjusted for age, gender, eGFR, HbA1c, HR and 24-h MAP. †Model 2: same as model 1 but adjusted for diabetes duration instead of age. ‡Model 3: same as model 2 but adjusted for 24-h SBP instead of 24-h MAP. ¶Model 4: same as model 1 but excluding age because it is also a factor in the equation for eGFR. §Adjustments did not include gender.
These patients were divided into three groups based on 24-h ABP, resulting in 280 (45%) with low (<130/80 mmHg), 192 (31%) with intermediate (130–139/80–89 mmHg), and 151 (24%) patients with high (>140/90 mmHg) BPs. Mean ± SD 24-h AMBP measurements of the three groups were 116 ± 9/68 ± 7, 132 ± 6/79 ± 7, and 147 ± 8/84 ± 9 mmHg, respectively (P < 0.001). In comparison, PWVs in patients with low, intermediate, and high BP were 9.8 ± 3.3 m/s, 10.0 ± 3.0 m/s, and 11.8 ± 3.6 m/s, respectively (P < 0.001). Patients with the highest BP had lower eGFR, higher PP, and were more often smokers, but had similar gender distribution, age, diabetes duration, CVD, HbA1c, BMI, total cholesterol, UAER, and previous CVD. After multivariate adjustment, patients with higher BP still had significantly higher PWV than patients with intermediate and low BP (P = 0.001), whereas PWV was similar in patients with low and intermediate BP (P = 0.174). This did not change if adjusting for statins, total cholesterol, or AHT, or if excluding patients receiving class 1 or 3 calcium blockers or beta blockers (data not shown).

Patients with different degrees of autonomic dysfunction

Of the 635 patients with PWV measurements, 617 also had HRV measured, whereas the 623 patients with 24-h AMBF measurements had information on dipping status available. Patients with normal, borderline, and abnormal HRV had PWV of 8.1 ± 2.1 m/s, 10.1 ± 3.1 m/s, and 11.5 ± 3.3 m/s, respectively (P < 0.001). After adjustment, PWV remained higher in patients with abnormal HRV (P = 0.027). Entering use of statins, total cholesterol, or AHT in the adjusted analysis or excluding patients receiving class 1 or 3 calcium blockers or beta blockers did not alter the results (data not shown).

Of the 623 patients with both dipping and PWV measurements available, 304 (49%) had normal dipping, whereas 319 (51%) had abnormal dipping. Patients with normal dipping had lower PWV compared with patients with abnormal dipping 9.8 ± 3.2 m/s and 11.0 ± 3.3 m/s, respectively (P < 0.001). However, this was not significant after multivariate adjustment (P = 0.174).

Patients with different degrees of retinopathy

A total of 632 patients had both PWV measurements and information on retinopathy status available. Of these patients, 136 (21%) had no retinopathy, 265 (42%) had simple retinopathy, 215 (34%) had proliferative retinopathy, and 16 (3%) patients were blind. PWV increased with degree of retinopathy 8.0 ± 2.5 m/s, 10.0 ± 2.8 m/s, 12.1 ± 3.5 m/s, and 12.7 ± 2.4 m/s, respectively (P < 0.001), which remained significant after multivariate adjustment (P < 0.001). Entering use of statins, total cholesterol or AHT in the adjusted analysis or excluding patients receiving class 1 or 3 calcium blockers or beta blockers did not alter the results (data not shown). We measured arterial stiffness by PWV in an observational cross-sectional study including 635 patients with type 1 diabetes and 51 nondiabetic control subjects. PWV was independently associated with gender, age, diabetes duration, BP, HR, and kidney function. Patients with increased PWV were male, older, with longer diabetes duration, higher 24-h SBP, higher total cholesterol, higher UAER, lower eGFR, received more often AHT, and had more previous CVD.

PWV was significantly higher in normoalbuminuric patients compared with controls, even after adjustment for covariates, suggesting early arterial stiffening associated with the presence of diabetes. Overall, 17% of normoalbuminuric patients and 4% of controls had abnormal PWV >12 m/s.

PWV predicted degree of albuminuria, previous CVD, 24-h ABP ≥140/90 mmHg, retinopathy, and autonomic neuropathy, even after adjustment for covariates.

PWV is a measure for arterial stiffness, which previously has been shown to be associated with some microvascular and macrovascular complications in type 1 diabetes and to predict mortality and CVD outcome in various populations including patients with diabetes (1–4,6,35). Previously, we and others have shown PWV augmentation index, other indirect measures of arterial stiffness, to predict CVD, decline in kidney function and mortality (5), and presence of microvascular and macrovascular complications (35) in type 1 diabetes. However, this study is the first to investigate the association between PWV and kidney function, previous CVD, different BP levels, retinopathy, and autonomic dysfunction in type 1 diabetes. Complications with diabetes often co-occur, although the overlap is incomplete and presence of, e.g., CVD does not entail, e.g., kidney disease. Complications with diabetes are likely brought on by a complicated array of factors, and identifying single markers predictive of all or most complications could be beneficial. PWV may be one such marker, because we now show it to be elevated in the presence of several different complications to diabetes.

PWV has been shown to be associated with albuminuria in type 2 diabetes (19). We now demonstrate the same association for type 1 diabetes, which accords with evidence of arterial damage and endothelial dysfunction being involved in development of microalbuminuria, im paired kidney function, and CVD (20,21,36).

In the current study, we find PWV to be higher in patients with previous CVD, independently of AHT and BP. This finding is suggestive of lasting pathological arterial damage after CVD, which is either only partially reversible by treatment or persistent because of incomplete treatment.

PWV was similar in patients with 24-h ABMPS <130/80 vs. 130–139/80–89 mmHg. However, patients with 24-h ABMPS ≥140/90 mmHg had significantly higher PWV as compared with patients with 24-h ABMPS <140/90 mmHg. Thus, AMBPs in the range of 130–139/80–89 mmHg is associated with increased arterial stiffness, whereas AMBPs ≥140/90 mmHg are more likely to be pathological.

Others have shown PWV to predict outcome in various populations, and we now demonstrate an association between PWV and baseline characteristics in type 1 diabetes. Prospective follow-up studies on this current cohort potentially could prove interesting, with regard to PWV as predictor of outcome.

Because arterial stiffness is involved in the development of diabetes complications, debating if PWV reduction may prevent or even counteract progression of diabetes complications is warranted. Reversal of arterial stiffness is achieved by altering arterial morphology, endothelial activity, and/or smooth muscle tone. The impact of AHT on arterial stiffness is by reduction of smooth muscle tone and HR. However, few studies have shown AHT to reduce adverse outcome by reduction in arterial stiffness. The REASON trial found different effects of calcium blockers and beta blockers on central and peripheral PP (37), suggesting differences in the AHT impact on arterial stiffness. The CAFE study, a substudy of the ASCOT trial, also found calcium blockers versus beta...
patients included in the current study were
strengths and limitations
"Patients included in the current study were recruited from a pool of approximately 3,500 patients with type 1 diabetes attending the outpatient clinic at Steno Diabetes Center. Thus, almost 20% of patients followed-up at Steno Diabetes Center were investigated, representing a broad segment of the Steno population, which covers an unselected population of adult type 1 diabetic patients in the region. However, to ensure a broad spectrum of albuminuria, we sought to include a substantial number of patients with impaired kidney function. Therefore, patients with microalbuminuria and macroalbuminuria were overrepresented, and this may explain why the cohort, on average, had such a high PWV.

PWV measurements were performed by four different laboratory technicians. It would have been optimum if they had been performed by the same investigator. However, all four laboratory technicians were trained to obtain measurements with similar quality-control measures, and measurements were performed at a single center under uniform conditions.

All 24-h ABPs were measured with a tonometric device (BPro). We have previously shown BP measurements obtained with tonometry by BPro correlate well with measurements obtained with standard sphygmomanometric devices used at Steno Diabetes Center (28). Furthermore, because the arterial pulse wave changes morphology depending on site of recording and body position, the calculated BP will represent the brachial BP regardless of arm or body position. Moreover, others have validated it for 24-h ambulatory measurements (27). Furthermore, because PWV is measured by tonometry, BP measured by tonometry would only be favorable.

No restrictions to current medications were made, and thus some patients were using AHTs and others were using cardiovascular medication. Patients were not fasting before PWV measurements because of their diabetes.

CONCLUSIONS—In summary, in the present cohort of patients with type 1 diabetes, we found PWV to be independently associated with age, diabetes duration, gender, UAER, BP, and HR. Arterial stiffness was higher in patients as compared with controls, and in patients with increased kidney impairment and previous CVD, independently of covariates. Furthermore, arterial stiffness was increased in patients with 24-h ABPs ≥140/90 mmHg, and increased with retinopathy and autonomic neuropathy. Thus, type 1 diabetes, kidney impairment, CVD, elevated BP, retinopathy, and autonomic neuropathy are all associated with increased arterial stiffness.

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References


