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# Increases in Central Aortic Impedance Precede Alterations in Arterial Stiffness Measures in Type 1 Diabetes Mellitus

Nancy K Sweitzer,MD,PhD[1*], Mohan Shenoy,MD[1], James H. Stein,MD[1], Sunduz Keles,PhD[1], Mari Palta,PhD[1], Tamara LeCaire,MS[1], Gary F Mitchell,MD[2]

[1]University of Wisconsin, Madison, WI [2]Cardiovascular Engineering, Inc., Waltham, MA
600 Highland Avenue, MC 5710, E5/582 CSC, Madison, WI 53792. E-mail: nks@medicine.wisc.edu

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## Abstract

**Objective:** Increased pulse pressure (PP) has been associated with increased cardiovascular risk in persons with diabetes. Changes in central aortic properties can increase central PP and may adversely affect microvascular perfusion and cardiac performance. This study was performed to define early changes in central arterial properties in a group of young persons with type 1 diabetes mellitus (T1DM).

**Research and Design Methods:** Seventeen persons with type 1 diabetes mellitus and their non-diabetic controls who were participating in the Cardio-Diab Study had arterial stiffness and pulsatile hemodynamics measured using calibrated tonometry and pulsed Doppler. Aortic characteristic impedance ($Z_c$) was calculated from the ratio of change in carotid pressure and aortic flow in early systole. Pulse wave velocity was assessed from tonometry and body surface measurements.

**Results:** Mean duration of T1DM was 15.3±0.7 years. In T1DM, central PP was elevated (45±11 vs. 36±10 mmHg in controls, p=0.02), as was peripheral PP (54±13 vs. 43±10 mmHg, p=0.002). $Z_c$ was elevated in T1DM (179±57 vs. 136±42 dynes x sec/cm$^5$ in controls, p=0.004) whereas pulse wave velocity was not different (5.9±0.9 m/s in T1DM vs. 5.9±0.7 ms/ in controls, p=NS). There was a moderate correlation between $Z_c$ and urinary albumin excretion (coefficient = 0.39, p = 0.02).

**Conclusions:** $Z_c$ appears to be increased early in T1DM, prior to elevation of pulse wave velocity, and is associated with higher PP, which may contribute to renal microvascular damage in diabetes.

Cardiovascular disease (CVD) claims the lives of 65% of persons with diabetes mellitus, approximately 150,000 deaths per year in the US.[1] Pulse pressure (PP) is a non-traditional marker of increased CVD risk that strongly predicts cardiovascular events in type 2 diabetes mellitus.[2-4] Because stiffening of central arteries is associated with increased PP, understanding aortic change in the natural history of diabetes is of interest. This is of particular importance since CVD risk in diabetes is not completely predicted by traditional cardiovascular risk factors and occurs at an early age.[5] Improved understanding of the role played by central arterial stiffening in the pathophysiology of diabetes may shed light on the excess CVD mortality faced by these individuals.

There are multiple measures of arterial stiffness, reflecting different properties of the aorta and peripheral vessels. Prior studies have demonstrated conflicting results for stiffness changes in diabetic populations.[6-14] This has been attributed to technical differences in studies, different ages and durations of diabetes in studied participants, and the presence of confounding conditions, such as hypertension.[13, 15] In addition, data on stiffness may differ depending on whether regional or global measures of stiffness or wave reflection are assessed. In hypertensive patients, it has been shown that increased aortic impedance ($Z_c$) correlates to increased pulse pressure, with changes in pulse wave velocity (PWV) due primarily to changes in mean arterial pressure (MAP) rather than vessel stiffening.[16] We sought to comprehensively assess arterial hemodynamics in a small cohort of young people with Type 1 diabetes mellitus (T1DM). We hypothesized that early changes in proximal aortic impedance in T1DM may play an important etiological role in later development of vascular complications.

**Research Design and Methods**

The Wisconsin Diabetes Registry Project was a population-based cohort of individuals with T1DM.[17-21] The Cardio-Diab Study cohort included 155 of these individuals with no known CVD. Each subject with T1DM invited a gender- and race-matched non-diabetic sibling or cousin, and if not, a friend, within 5 (preferably) or 10 years of their age to serve as a control. Twenty consecutive pairs participating in the Cardio-Diab Study June 2004 through January 2005 were enrolled. The primary endpoint was the difference in aortic characteristic impedance between groups. The sample size gave us greater than 80% power to detect a 30% difference in aortic impedance.[16] The protocol was approved by the University of Wisconsin Human Subjects Committee, and each participant gave separate informed consent for this sub-study.

Participants were studied supine after quiet rest.[22-24] With a semiautomated, computer controlled cuff, auscultatory BP was obtained at 2-minute intervals with a goal of obtaining 3 sequential readings within 5 mm Hg for systolic blood pressure (SBP) and diastolic blood pressure (DBP). Arterial tonometry was obtained from the brachial, radial, femoral, and carotid arteries in quick succession with a custom transducer. A limb-lead electrocardiogram (ECG) was recorded. Echocardiographic images of the left ventricular outflow tract were obtained in a parasternal long-axis view. Body surface measurements were assessed from suprasternal notch to brachial, radial, femoral, and carotid recording sites.[22] Data were digitized during the primary acquisition, transferred to CD-ROM and shipped to Cardiovascular Engineering, Inc. (Waltham, MA), for analysis.

Non-contrast computerized tomography (CT) scans of the chest were performed using a GE HiSpeed Advantage spiral CT scanner (GE, Milwaukee, WI) using

ECG gating. Scans were used to assess outer diameter of the aorta 2 cm above the aortic valve. When the aorta was non-circular, the smallest dimension was used. A single timed urine collection was performed for determination of albumin concentration and creatinine clearance.

Tonometry waveforms were signal-averaged with the ECG used as a fiducial point.[25] Average systolic and diastolic cuff pressures were used to calibrate the peak and trough of the signal-averaged brachial pressure waveform. Diastolic and integrated mean brachial pressures were used to calibrate other pressure tracings.[26] Carotid-femoral PWV was calculated from transit time and body surface measurements corrected for parallel transmission as described previously.[23] LVOT diameter was measured and used to compute cross-sectional area and used to convert flow velocities to volume flows.[27] Augmentation index (AI) was calculated using carotid waveforms.[28] Aortic characteristic impedance ($Z_c$) was estimated in the time domain as the pressure change associated with an increase in flow from 0 to 95% peak flow ($\triangle P/\triangle Q$). Proximal aortic compliance per unit length was calculated as described previously.[29]

Baseline characteristics and hemodynamic data were compared using paired student's t tests and pearson correlations. Multivariable regression analyses were performed two ways. Correlations between impedance and other clinical variables of interest were explored in a regression analysis using matched pairs and thus controlling for diabetes effect. An unmatched multivariable regression analysis was also performed to determine which variables contained independent predictive value with regard to impedance and pulse pressure. Classical assumptions of linear regression analysis were satisfied for all analyses.

**Results**

Forty participants, twenty matched pairs, were sequentially studied. Complete arterial hemodynamic data was obtained from 17 pairs of participants. Seven T1DM subjects had related controls. The remaining 10 T1DM subjects had unrelated controls. Clinical characteristics of the participants are shown in Table 1. Although diabetes had been present on average for 15 years in the patients, the aggressiveness of diabetes management and control were demonstrated by the low prevalence of hypertension and microalbuminuria.

Arterial hemodynamic data are shown in Table 2. SBP and mean arterial pressure (MAP) were not statistically different in the two groups. DBP was lower in T1DM ($p=0.05$). Both brachial and carotid PP was significantly elevated in the group with T1DM. Aortic $Z_c$ was markedly elevated in patients with T1DM. Those with T1DM had larger forward pressure amplitude despite comparable peak flow. (Figure 1) PWV and augmentation index, however, did not differ between persons with T1DM and controls.

A decrease in aortic diameter could explain increased $Z_c$ with no difference in PWV, given the strong dependence of impedance on vessel diameter. LVOT diameter determined by echocardiography and proximal aortic diameter determined by CT scan were both smaller in the group with T1DM, reaching statistical significance in the LVOT measurement (Table 2).

Correlation analysis was used to determine relations between both aortic impedance and pulse pressure and other clinical variables. Initial correlations were performed preserving matched pairs in the analysis, in effect controlling for diabetes. In addition to the presence of diabetes, urine albumin excretion, HbA1c and female sex were significantly correlated with $Z_c$(Table 3). Multivariable analysis was performed using unmatched pairs but including diabetes as a

variable. Urine albumin and LVOT diameter had independent predictive power in this model, with an F statistic of 5.3, p = 0.003, however none of the individual p values in this model meet the Bonferroni standard of p=0.0125 for 4 comparisons. In multivariable analysis only diabetes, impedance and BMI remained independent predictors of central pulse pressure.

**Conclusions**

This study investigated changes in the large and medium arteries of young people with T1DM and demonstrated an increase in $Z_c$ in T1DM, independent of MAP. Increased $Z_c$ was associated with a higher level of pressure pulsatility in the diabetic aorta for a given level of flow. This increase in $Z_c$ occurred prior to changes in more traditional measures of central arterial stiffness such as PWV, which has been shown to be elevated in more advanced stages of diabetes.[6-8] The increase in $Z_c$ was associated with increased central and peripheral PP in the patients with diabetes, and was accompanied by a decrease in LVOT diameter. While an increase in PWV and earlier return of reflected waves to the proximal aorta can cause an increase in central PP particularly in younger people, premature wave reflection was not the mechanism of increased central or peripheral PP in our T1DM patients. Rather, the primary finding was an increase in incident pressure wave amplitude, indicating changes in the proximal aorta leading to greater pressure change for a given flow from the left ventricle.

Increased central arterial stiffness has been demonstrated previously in patients with Type 2 diabetes mellitus.[8-10] Early changes in diabetes and in T1DM in particular have not been as well characterized.[11] Post-mortem analysis demonstrated that the aortas from individuals with T1DM were intrinsically stiffer than those from age-matched controls.[12] In another study of participants with T1DM, diabetes was associated with increased aortic augmentation index in men but not women.[6] However, use of generalized transfer functions to calculate central pressure waveforms in diabetics has been questioned, and changes in PWV and AI have not always correlated in studies of patients with diabetes.[13, 15] Furthermore, none of the foregoing studies measured $Z_c$.

Increased PP is known to be a marker of adverse clinical events in patients with diabetes mellitus,[2, 3] and is increased when impedance rises. From the waterhammer equation, $Z_c$ is directly proportional to PWV, and inversely proportional to vessel area ($Z_c$ = PWV*rho/Area, where rho is the density of blood). Impedance will thus be sensitive to changes in vessel diameter. Because PWV is not different between the two groups in our study, we suggest that a small decrease in aortic diameter could explain our data. This is supported by the decrease in LVOT area noted in the diabetic group in this study, which maintains significance in multivariable modeling. The failure to note a decrease in aortic diameter may be because CT scans were non-contrast, allowing visualization of only external vessel diameter. Eutrophic aortic remodeling results in decreased internal lumen diameter due to vessel wall thickening, without a change in outer vessel diameter. If this sort of aortic remodeling were to occur in diabetes, leading to increased pulsatile pressure in the proximal aorta, it would be missed on a non-contrast scan. Decreases in internal aortic diameter have been noted previously in patients with diabetes[14] as well as in hypertension.[16] This decrease in aortic diameter with pathologic conditions contrasts with the modest age-related increase in aortic diameter that has been observed in relatively healthy individuals. With aortic wall stiffening and aortic diameter increases, as in healthy aging, a predominant increase in PWV is observed because the increase in diameter offsets the effect of wall stiffening

on $Z_c$.[16] The present findings suggest that factors responsible for proper matching between aortic diameter and resting flow may be impaired in T1DM, indicating an active and potentially plastic vascular remodeling process at work in young patients with this disease process.

There are important implications of increased central arterial pulsatility early in the disease process of diabetes. The increased pulsatility with the change in $Z_c$ is carried into the periphery, as manifest by increased brachial PP. The presence of higher PP in the central and peripheral circulation may lead to transmission of pressure pulsatility farther into the microcirculation than normally found, and may precipitate microvascular damage. Evidence for microvascular damage is suggested by the correlation between increased $Z_c$ and urine albumin levels in our study. Increased glomerular perfusion pressure, as might be seen if pressure pulsatility increases, is known to lead to renal microvascular damage.[30] Our data suggest that changes in the central aorta may precipitate renal microvascular change or conversely, that early microvascular damage in the kidney may contribute to increases in pressure and flow pulsatility at all levels of the circulation. The fact that the correlation with urine albumin is seen in the absence of overt microalbuminuria suggests that the aortic changes, which were substantial, may precede and contribute to the renal changes. In addition, our data suggest that once microalbuminuria develops, the relationship between arterial hemodynamics and renal vascular function may be altered, a concept supported by others.[31] A similar relationship between PP or measures of central aortic stiffness and urine albumin excretion has been noted previously in T2DM,[7, 32, 33] while urine albumin does not necessarily correlate to hyperinsulinemia,[34] again suggesting the importance of hemodynamic changes in the development of renal microvascular disease. The link between PP or central arterial stiffness and urine albumin levels has also been demonstrated in patients with hypertension,[16, 35-41] and in healthy adults.[42, 43] In addition to damaging microvessels, the higher degrees of pressure pulsatility seen in T1DM may also increase tensile and shear stresses in the large and medium vessels and could contribute to early atherogenesis.

There are limitations to our study. The group studied is small, and may not be representative of people with T1DM. In addition, by necessity, this exploratory analysis of stiffness involved multiple comparisons and spurious significant values are possible. The study was powered for the primary endpoint only, and other significant findings must be interpreted as exploratory rather than definitive. With the small sample size, outliers may significantly influence the data and lead to spurious findings. The urine albumin determination is based on a single timed collection, rather than averaging repeated collections. Our conclusion that aortic diameter is reduced because Zc is increased but PWV is not assumed that Zc and PWV are measured at the same point. Zc assesses the proximal aortic root whereas CFPWV evaluates the spatially averaged properties of the descending thoracic and abdominal aorta and iliac artery. Thus, regionally heterogeneous changes in arterial properties, rather than a difference in aortic diameter, may explain elevated Zc with unchanged CFPWV. These data are cross-sectional. Longitudinal data on a larger group of subjects would be required to demonstrate aortic remodeling and the relationship to changes in impedance and other measures of stiffness over time.

*Summary and Clinical Significance*

In summary, we have shown increased PP in young persons with T1DM, resulting from changes in aortic characteristic impedance at similar MAP. The changes in $Z_c$ may be related to decrease aortic diameter.

$Z_c$ correlates with urine albumin levels, which suggests a link between central arterial properties, increased central and peripheral PP, and microvascular damage at an early stage in the pathophysiology of diabetic vascular disease. We suggest that increased vessel pulsatility, delivered distally in the circulation, may expose organs to greater degrees of small vessel pulsatile flow than is optimal, leading to microvascular damage and organ dysfunction.

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**TABLE 1. Characteristics of Participants With and Without Type 1 Diabetes Mellitus**

| Clinical Characteristic | T1DM | No T1DM |
|---|---|---|
| Number of subjects | 17 | 17 |
| Females, n (%) | 13 (76) | 13 (76) |
| White, % | 17 (100) | 17 (100) |
| Sibling control, n (%) | NA | 6 (35) |
| Age, years | 27.3 ± 7.7 | 28.2 ± 8.9 |
| Duration of T1DM, years | 15.3 ± 0.7 | NA |
| HbA1c, % (Normal range 4.3-6.0)* | 7.8 ± 1.5 | 5.0 ± 0.3 |
| Hypertension (>140/90), n (%) | 1 (6) | 1 (6) |
| Above BP target for T1DM (130/80), n (%) | 1 (6) | 4 (23) |
| Height, cm | 166.9 ± 14.0 | 170.0 ± 8.5 |
| Weight, kg | 72.0 ± 19.7 | 72.6 ± 12.3 |
| Body mass index, $kg/m^2$ | 25.7 ± 5.7 | 25.1 ± 3.6 |
| Waist-to-hip ratio | 0.78 ± 0.04 | 0.77 ± 0.06 |
| Current smokers, n (%) | 7 (41) | 6 (35) |
| Use of anti-hypertensive medications, n (%) | 2 (12) | 0 |
| Use of lipid lowering medications, n (%) | 1 (6) | 0 |
| Normalbuminuria, n (%) ** | 16 (100) | 17 (100) |
| Urine albumin, mcg/min ** | 4.9 ± 2.2 | 4.2 ± 2.5 |

* n = 15 for no T1DM
** n = 16 for T1DM

**TABLE 2. Arterial Hemodynamics of Participants With and Without Type 1 Diabetes Mellitus**

| Hemodynamic Parameter | T1DM | No T1DM | p value |
|---|---|---|---|
| Heart rate, bpm | 69 ± 13 | 66 ± 13 | 0.52 |
| Brachial systolic pressure, mmHg | 113 ± 13 | 108 ± 12 | 0.30 |
| Brachial diastolic pressure, mmHg | 59 ± 9 | 65 ± 10 | 0.05 |
| Mean pressure, mmHg | 79 ± 9 | 81 ± 11 | 0.48 |
| Brachial pulse pressure, mmHg | 54 ± 13 | 43 ± 10 | 0.002 |
| Carotid pulse pressure, mmHg | 45 ± 11 | 36 ± 10 | 0.02 |
| PWV, m/s | 5.9 ± 0.9 | 5.9 ± 0.7 | 0.83 |
| Augmentation index, % | -1.5 ± 15.4 | -4.8 ± 16.7 | 0.45 |
| Aortic characteristic impedance, $Z_c$, dyne x sec/cm$^5$ | 179 ± 57 | 136 ± 42 | 0.004 |
| Stroke volume, nl | 69 ± 12 | 72 ± 17 | 0.41 |
| Peak aortic flow, ml/s | 329 ± 59 | 340 ± 67 | 0.60 |
| Forward pressure wave amplitude (mmHg) | 43 ± 11 | 34 ± 10 | 0.013 |
| Reflected wave amplitude (mmHg) | 12 ± 3 | 11 ± 3 | 0.21 |
| Ratio of reflected to forward pressure wave amplitude | .29 ± .06 | .32 ± .72 | 0.17 |
| Mean peripheral resistance (dyne*sec/cm$^5$) | 1395 ± 299 | 1427 ± 277 | 0.72 |
| LVOT diameter (cm) | 2.04 ± 0.18 | 2.17 ± 0.19 | 0.01 |
| Aortic diameter (cm) | 2.70 ± 0.27 | 2.85 ± 0.28 | 0.30 |

Data expressed as mean ± SD.
p value determined by paired student's t test.

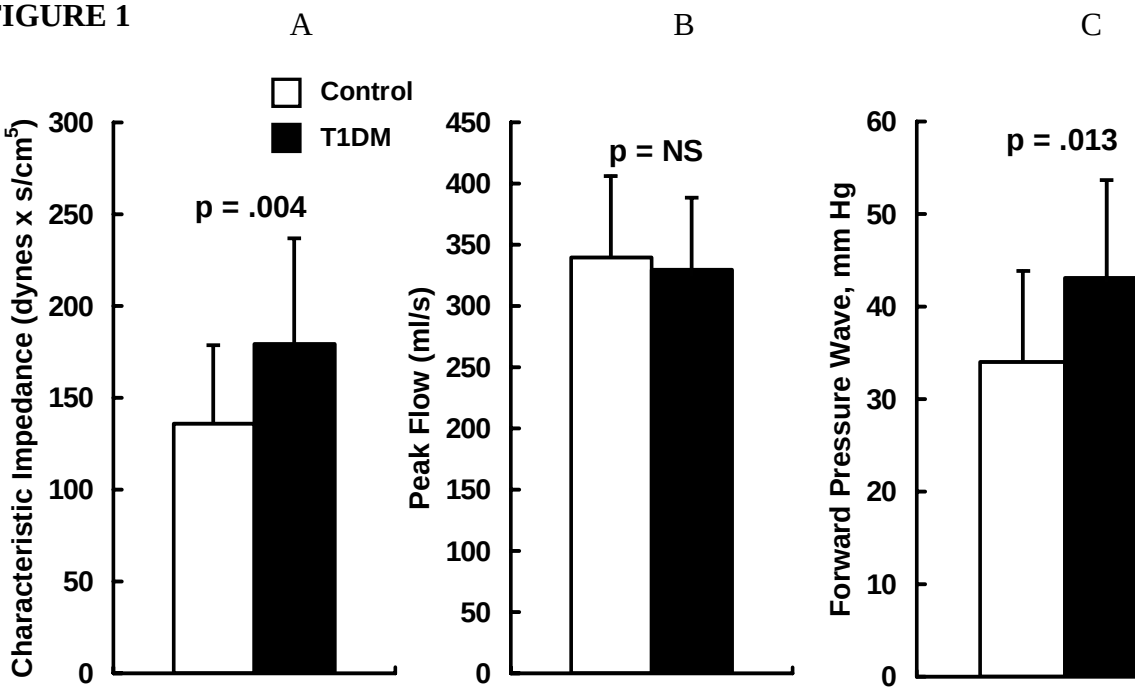
**TABLE 3. Regression Analysis of Associations Between Characteristic Impedance ($Z_c$ ) of the Aorta and Clinical Variables, Analyzed as Matched Pairs**

| Variable | Regression Coefficient (Adjusted for Diabetes) | Standard Error | p value |
|---|---|---|---|
| Type 1 Diabetes | 43.4 | 13.0 | 0.004 |
| Urine albumin excretion, mcg/min | 17.1 | 6.2 | 0.01 |
| HbA1C, % | 12.9 | 5.0 | 0.02 |
| Female Sex | 121.0 | 47.8 | 0.02 |
| LVOT diameter, cm | -141.5 | 71.4 | 0.06 |
| BMI, $kg/m^2$ | 3.0 | 2.8 | 0.30 |
| Carotid-femoral PWV, m/s | 16.3 | 17.1 | 0.35 |
| Current smoking | -3.3 | 3.8 | 0.39 |
| Augmentation Index, % | -0.5 | 1.0 | 0.64 |
| Heart rate, bpm | 0.2 | 1.1 | 0.85 |

**Figure Legend**

**Figure 1.** Increased characteristic impedance ($Z_c$) is present in type 1 diabetes mellitus (A), despite similar aortic flow (B). The increase in $Z_c$ is explained by greater pressure development for a given amount of flow in the diabetic aorta (C).

**FIGURE 1**


A
B
C
Control
T1DM
Characteristic Impedance (dynes x s/cm5)
300
250
200
150
100
50
0
p = .004
Peak Flow (ml/s)
450
400
350
300
250
200
150
100
50
0
p = NS
Forward Pressure Wave, mm Hg
60
50
40
30
20
10
0
p = .013