Arterial stiffness predicts mortality in individuals with type 1 diabetes

Short running title: Arterial stiffness and mortality in diabetes

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OBJECTIVE Type 1 diabetes is accompanied by a significant burden of cardiovascular disease (CVD), which is poorly explained by traditional risk factors. We therefore aimed to explore whether arterial stiffness estimated by the augmentation index (AIx) predicts mortality in individuals with type 1 diabetes.

RESEARCH DESIGN AND METHODS After baseline examination comprising pulse wave analysis by applanation tonometry alongside assessment of traditional cardiovascular risk factors, 906 individuals with type 1 diabetes from the FinnDiane Study were followed up for a median of 8.2 (5.7–9.7) years. Associations between baseline hemodynamics, including AIx, and all-cause mortality as well as a composite of cardiovascular and/or diabetes-related mortality were investigated using multivariable Cox regression models.

RESULTS The 67 individuals who died during follow-up had higher baseline AIx (28% [21–33] vs. 19% [9–27], $P < 0.001$) compared to those alive. This association was independent of conventional risk factors (age, sex, BMI, HbA_{1c}, estimated glomerular filtration rate [eGFR] and previous CVD event) in Cox regression analysis (standardized hazard ratio 1.71 [1.10–2.65], $P = 0.017$) and sustained in a subanalysis of individuals with chronic kidney disease. Similarly, higher AIx was associated with the composite secondary endpoint of cardiovascular and diabetes-related death (N = 53) after adjustments for sex, BMI, eGFR, previous CVD event and height (standardized hazard ratio 2.30 [1.38–3.83], $P = 0.001$).

CONCLUSIONS AIx predicts all-cause mortality as well as a composite cardiovascular and/or diabetes-related cause of death in individuals with type 1 diabetes, independent of established cardiovascular risk factors.

Cardiovascular disease (CVD) is the leading cause of the excess morbidity and mortality observed in individuals with type 1 diabetes, and the standardized mortality ratio is known to increase by each stage of diabetic nephropathy (1,2). This predisposition is only partly attributable to traditional risk factors, and in fact, cardiovascular risk scores developed for the general population and type 2 diabetes are poorly applicable in type 1 diabetes (3). Thus, a unique risk factor profile is likely to prevail in these individuals and merits further characterization.

Arterial stiffness is a well-known predictor of mortality in the general population and in selected groups, including those with type 2 diabetes, yet no longitudinal studies have been carried out in individuals with type 1 diabetes (4,5). Interestingly, arterial stiffening seems to occur early in individuals with type 1 diabetes, as their pulse pressure, a crude estimate of arterial stiffness, increases up to 15–20 years earlier than in healthy controls (6). This phenomenon of early arterial ageing made us hypothesize that arterial stiffness may be an important mediating factor leading to premature death in type 1 diabetes. Since microangiopathy is a major manifestation of complicated type 1 diabetes, we further hypothesized that early signs of arterial stiffening could be detected by the augmentation index (AIx), which as a measure of arterial pulse wave reflections is particularly affected by stiffness in the small resistance arteries (7). We previously showed that AIx correlates with microvascular and macrovascular complications in type 1 diabetes in a cross-sectional setting (8). The aim of this study was therefore to explore whether AIx predicts all-cause as well as cardiovascular and/or diabetes-related mortality in type 1 diabetes.

RESEARCH DESIGN AND METHODS

The FinnDiane cohort

This prospective observational follow-up study is part of the ongoing nationwide Finnish Diabetic Nephropathy (FinnDiane) Study, in which more than 5400 individuals with type 1 diabetes have been characterized since 1997. The study protocol has been approved by the local ethics committees and written informed consent was obtained from each participant. The FinnDiane protocol has been previously described in detail (9). Briefly, baseline data on cardiovascular risk factors and diabetic complications are collected from standardized questionnaires and medical files, as well as through clinical examination and biochemical measurements. Since 2001, noninvasive assessment of arterial stiffness and central hemodynamics through pulse wave analysis has been included in the baseline examination of those individuals studied at the FinnDiane center in Helsinki.

Study population

In this substudy, individuals with available baseline data on arterial stiffness by the year 2015 were included. Further inclusion criteria were age above 18 years, type 1 diabetes diagnosed by the age of 40 and insulin treatment initiated within 1 year of the diagnosis. The baseline population comprised 906 individuals (416 men) with a mean age of 43.2 years (standard deviation [SD] 12.2), including 134 individuals with chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2, ongoing hemodialysis or having received a renal transplant, as well as 98 individuals with a previous CVD event, defined as myocardial infarction, coronary revascularization, stroke, lower extremity revascularization or non-traumatic amputation.

Pulse Wave Analysis

Applanation tonometry (SphygmoCor, Atcor Medical, Sydney, NSW, Australia) is a noninvasive reproducible method to estimate central (aortic) blood pressure variables and arterial stiffness through pulse wave analysis (10,11). A high-fidelity micromanometer (SPC-301; Millar Instruments, Houston, TX) is used to record peripheral pressure waveforms from the radial artery of the right arm and three readings with a pattern of at least 20 valid waveforms are selected for the analysis. The software generates a central pressure waveform using a validated transfer function. This enables determination of central systolic (CSBP) and diastolic (CDBP) blood pressure, central pulse pressure (CPP = CSBP – CDBP), central mean arterial pressure (CMAP = 1/3 x CSBP + 2/3 x CDBP), central end-systolic pressure (CESP), ejection duration (ED), as well as subendocardial viability ratio (SEVR), which indirectly estimates myocardial perfusion. To assess stiffness in the small resistance arteries, AIx is calculated as a quotient of two measures – the difference of the second and the first systolic peak of the pressure waveform (corrected for heart rate) and CPP.

Clinical endpoints

Mortality data were obtained from the cause-of-death statistics and the archive of death certificates maintained by Statistics Finland. Cardiovascular deaths of individuals with diabetes are not uncommonly classified as diabetes-related deaths in Finland, especially in cases where no autopsy has been performed. Therefore, we combined cardiovascular and/or diabetes-related causes of death into one secondary endpoint in the survival analysis, alongside all-cause and cardiovascular mortality.

Statistical methods

Univariable analyses of established cardiovascular risk factors and hemodynamic variables from pulse wave analysis were run to detect differences between those who died during follow-

up and those who survived. Chi-squared tests were used for dichotomous variables and *t*-tests or Mann–Whitney U tests for continuous variables. Data are presented as mean ± SD (normally distributed) or median with interquartile range (non-normally distributed) for continuous variables and as percentages for dichotomous variables.

Longitudinal analysis was performed using Kaplan–Meier survival curves with log-rank tests. For multivariable analyses, covariates were standardized by dividing the difference of each value and the covariate mean by the standard deviation of that covariate. The best-fit regression model for each endpoint was selected using the Akaike information criterion and further adjusted for sex and the variable of interest from pulse wave analysis. Independent associations with mortality were determined by Cox regression analysis and are presented as standardized hazard ratios (sHR) with 95% CI. *P* values < 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

After a median follow-up of 8.2 (5.7–9.7) years, 67 (7.4%) individuals had died (Table 1). These individuals were older, had a longer diabetes duration, higher office systolic blood pressure, pulse pressure, HbA_{1c} and triglycerides, as well as lower BMI and eGFR at baseline, compared to those who survived. Similarly, those who died had more often antihypertensive and lipid-lowering medication as well as a previous CVD event at baseline. In the pulse wave analysis, AIx (28% [21–33] vs. 19% [9–27]), CSBP (138 [121–150] vs. 119 [109–131] mmHg), CMAP (96 [91–105] vs. 91 [85–98] mmHg), CPP (61 [44–80] vs. 41 [34–52] mmHg), and CESP (115 [106–125] vs. 105 [96–116] mmHg) were higher, whereas SEVR (116% [102–138] vs. 142% [123–164]) was lower at baseline in those who died during follow-up.

All-cause mortality

When divided into tertiles based on AIx values, those in the highest tertile showed the highest rate of all-cause mortality (Figure 1). Furthermore, AIx was associated with all-cause mortality in an unadjusted Cox regression model (Table 2). After adjustments for sex, age, BMI and HbA_{1c}, AIx remained in the model with a sHR of 2.14 (1.42–3.23, $P < 0.001$). In the final model, after correcting for two additional strong predictors of mortality, eGFR and previous CVD event, AIx was still associated with all-cause mortality (sHR 1.71 [1.10–2.65], $P = 0.017$). Similarly, CSBP (sHR 1.29 [1.03–1.62], $P = 0.028$), CMAP (sHR 1.30 [1.05–1.62], $P = 0.019$) and SEVR (sHR 0.67 [0.47–0.94], $P = 0.022$) were independently associated with all-cause mortality in the final model. In a subanalysis including only individuals with CKD, AIx showed an even stronger association with all-cause mortality (sHR of 3.39 [1.66–6.91], $P = 0.001$), when adjusted for sex, BMI and previous CVD event.

No adjustments for peripheral blood pressure variables were made in the regression model to avoid multicollinearity. AIx correlated with systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse pressure (PP) with Pearson's correlation coefficients of 0.432, 0.284 and 0.344, respectively. For comparison with AIx, these variables where added separately to the final Cox regression model (sex, age, BMI, HbA_{1c}, eGFR and previous CVD event). Independent, yet weaker association with all-cause mortality was seen for SBP (sHR 1.34 [1.07–1.67], $P = 0.011$), DBP (sHR 1.28 [1.01–1.63], $P = 0.041$) and PP (sHR 1.28 [1.00–1.64], $P = 0.046$).

Cardiovascular and diabetes-related mortality

Of the deaths that occurred during the follow-up, 53 were classified as cardiovascular and/or diabetes-related. In an adjusted Cox regression model (Table 3), AIx was independently associated with the composite endpoint of cardiovascular and/or diabetes-related mortality

(sHR 2.30 [1.38–3.83], *P* = 0.001). When cardiovascular mortality (N = 36) was analyzed separately, AIx was associated with both cardiovascular mortality (sHR 2.36 [1.22–4.53], *P* = 0.010) and non-cardiovascular mortality (sHR of 2.11 [1.25–3.56], *P* = 0.005) in adjusted Cox regression analyses. For the other than cardiovascular and/or diabetes-related causes of death (N = 14), however, AIx was not a significant risk factor in a Cox regression model adjusted for sex (sHR 1.56 [0.82–2.99], *P* = 0.179).

CONCLUSIONS

In this study population of 906 individuals with type 1 diabetes followed up for a median of 8.2 years, AIx was an independent risk factor for all-cause mortality even after adjustments for well-known risk factors, including renal function. The same observation was made regarding cardiovascular and/or diabetes-related mortality as a composite secondary endpoint, as well as in a subanalysis of only individuals with CKD. Other measures of central hemodynamics that showed an independent association with all-cause mortality included CSBP, CMAP and SEVR. When comparing sHRs, AIx outperformed both the central and the office blood pressure variables in predicting all-cause mortality, when separately included in the final multivariable model.

While arterial stiffness indices have been increasingly studied in type 2 diabetes, this is the first study to investigate the association between AIx, a surrogate measure of stiffness in the small resistance arteries, and mortality in individuals with type 1 diabetes. Earlier studies in type 1 diabetes have evaluated how the pulse pressure, a crude estimate of stiffness in the large arteries, predicts CVD and mortality (12,13). Prospective studies utilizing the gold standard measure of arterial stiffness, pulse wave velocity (PWV), are so far limited to type 2 diabetes.

Due to different pathophysiological characteristics and the accumulation of CVD at a younger age in type 1 diabetes, extrapolating findings from studies of non-diabetic populations or even individuals with type 2 diabetes should be made with caution (14). It is of note that in type 1 diabetes the macrovascular complications may in part have a microvascular origin. In fact, small vessel disease is the major underlying cause of ischemic stroke in individuals with type 1 diabetes, and interestingly, more common compared to individuals with type 2 diabetes (15). In the absence of symptomatic CVD, a reduced coronary vascular reactivity has been shown in young individuals with type 1 diabetes, and another study demonstrates differences in the atherosclerotic morphology of the coronary arteries between the two types of diabetes (16,17). Recently, even an autoimmune component has been proposed to play a role in the pathogenesis of CVD in type 1 diabetes (18). Although the exact pathogenic mechanisms remain to be uncovered, current knowledge implies that type 1 diabetes needs to be considered a separate entity when the risks and prevention of cardiovascular complications are studied (14).

As AIx reflects stiffness in the small resistance arteries, our findings may support the hypothesis of small vessel disease contributing to the pathogenesis of macrovascular complications and premature mortality seen in type 1 diabetes. The DCCT/EDIC study demonstrated the long-standing effects of hyperglycemia on the risk of diabetic complications and cardiovascular disease in type 1 diabetes, a phenomenon referred to as “metabolic memory” (19). Whether this is partly mediated by small vessel disease and arterial stiffness is an open question to be addressed in future research.

Although noninvasive and applicable for clinical practice, applanation tonometry is operator-dependent and can be considered time-consuming and costly. However, new operator-independent technologies to capture central hemodynamics by pulse volume plethysmography have been developed in recent years and may improve the feasibility of measuring arterial stiffness (20). Indeed, novel clinical risk markers are needed to be able to predict the increased

risk of CVD and mortality in type 1 diabetes. Given our findings, AIx could be a useful tool to detect such high risk of cardiovascular complications, enabling intensive cardiovascular risk control at an early stage for these individuals. Nevertheless, clinical implications require further investigation of the added value of AIx in risk prediction models, especially compared to the traditional blood pressure variables. This study did show a higher risk of mortality per SD increment in AIx as compared to that of SBP, DBP or PP in separate multivariable models.

The prospective study setting in a large cohort with comprehensive phenotypic data constitutes a major strength in our study, whereas its observational design only allows speculations about causality. With increasing age, there are some limitations to the reliability of AIx. Following a nonlinear pattern, AIx steeply increases in the young while reaching a plateau at older age (21). This could partly be explained by the formula itself – concurrent increases in both augmentation pressure and CPP could result in AIx remaining stable or even declining (22). Central PWV increases later in life, whereas AIx may be preferable in younger populations, which is essential when considering the applicability for early detection and prevention of CVD. It is not clear, how AIx changes over time in individuals with type 1 diabetes, or whether there should be a transfer function specifically validated in type 1 diabetes. However, based on the early increase in pulse pressure in type 1 diabetes, one could assume earlier plateauing of AIx. Our study population was relatively young, which may have contributed to the predictive value of AIx in this study. As PWV measured by applanation tonometry was introduced to the FinnDiane protocol at a later stage, complete data powered for prospective analysis are still on the way.

To summarize, AIx as an estimate of stiffness in the small resistance arteries is independently associated with all-cause mortality, as well as the composite of cardiovascular and/or diabetes-related mortality in type 1 diabetes. These results together with our earlier findings suggest that detection of early vascular aging in individuals with type 1 diabetes could have complementary

value in clinical risk assessment when targeting a more aggressive treatment approach for high-risk individuals.

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Conflict of interest. P-H.G. is an advisory board member of AbbVie, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, Sanofi, and has received lecture honoraria from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Elo Water, Genzyme, Medscape, MSD, Mundipharma, Novartis, Novo Nordisk, Sanofi and SCIARC. D.G. has received lecture or advisory honoraria from AstraZeneca, Boehringer Ingelheim, Fresenius, GE Healthcare and Novo Nordisk, as well as support to attend medical meetings from CVRx. and Sanofi Aventis. The other authors declared no conflict of interest.

Prior publication. Parts of this study were presented at the 32nd Annual Meeting of the European Diabetic Nephropathy Study Group, Paris, France 24–25 May 2019, as well as at the 55th Annual Meeting of the European Association for the Study of Diabetes, Barcelona, Spain, 16–20 September 2019.

Author contributions. A.T., C.F., P.-H.G. and D.G. conceived and designed the analysis. A.T., C.F., V.H. and D.G. collected the data. A.T., C.F. and D.G. analyzed and interpreted the data. A.T., C.F., P.-H.G. and D.G. wrote the manuscript. A.T., C.F., V.H., P.-H.G. and D.G. revised and edited the manuscript. P.-H.G. is the guarantor of this study 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.

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Table 1. Baseline characteristics according to survival status.

	Alive	Dead	*P* value
N	839	67	
Male sex (%)	381 (45.4)	35 (52.2)	0.280
Age (years)	42.5 ± 12.0	52.9 ± 11.4	< 0.001
Diabetes duration (years)	26.5 ± 12.6	37.4 ± 13.1	< 0.001
Age at onset (years)	14.0 (9.8–21.9)	13.2 (8.6–21.3)	0.533
Height (cm)	171.8 ± 9.6	169.5 ± 10.2	0.059
BMI (kg/m^2)	25.1 (22.9–27.6)	23.9 (21.5–26.3)	0.011
Systolic blood pressure (mmHg)	134 (123–146)	151 (135–166)	< 0.001
Diastolic blood pressure (mmHg)	76 ± 9	77 ± 10	0.632
Pulse pressure (mmHg)	57 (48–69)	76 (56–93)	< 0.001
Antihypertensive medication (%)	368 (44.1)	53 (79.1)	< 0.001
RAAS-blockers (%)	321 (38.4)	38 (56.7)	0.003
HbA_{1c} (%) / (mmol/mol)	7.9 (7.2–8.7) / 63 (55–72)	8.3 (7.7–9.3) / 67 (61–78)	0.005
Total cholesterol (mmol/l)	4.5 (4.0–5.1)	4.6 (4.0–5.3)	0.619
HDL-cholesterol (mmol/l)	1.53 (1.29–1.86)	1.57 (1.41–2.03)	0.162
LDL-cholesterol (mmol/l)	2.5 (2.0–3.0)	2.4 (1.9–3.0)	0.337
Triglycerides (mmol/l)	0.92 (0.70–1.31)	1.10 (0.84–1.55)	0.003
Statin therapy (%)	213 (25.5)	30 (45.5)	< 0.001
eGFR (ml/min/1.73m^2)	103 (87–115)	64 (39–92)	< 0.001
Ever smoked (%)	354 (43.6)	35 (53.8)	0.111
Previous cardiovascular event* (%)	66 (7.9)	32 (48.5)	< 0.001
Augmentation index (%)	19 (9–27)	28 (21–33)	< 0.001
Subendocardial viability ratio (%)	142 (123–164)	116 (102–138)	< 0.001
Central systolic blood pressure (mmHg)	119 (109–131)	138 (121–150)	< 0.001
Central diastolic blood pressure (mmHg)	77 ± 9	78 ± 10	0.661
Central mean arterial pressure (mmHg)	91 (85–98)	96 (91–105)	< 0.001
Central pulse pressure (mmHg)	41 (34–52)	61 (44–80)	< 0.001
Ejection duration (ms)	326 ± 22	329 ± 27	0.432
Central end-systolic pressure (mmHg)	105 (96–116)	115 (106–125)	< 0.001

Data presented as N (%), means ± SD or medians (interquartile range). RAAS-blockers = renin-angiotensin-aldosterone-system blockers, eGFR = estimated glomerular filtration rate (by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula). *Previous cardiovascular event defined as myocardial infarction, coronary revascularization, stroke, lower extremity revascularization or non-traumatic amputation.

Table 2. Central hemodynamic variables in association with all-cause mortality in multivariable Cox regression models.

	AIx	CSBP	CMAP	SEVR
Model 1	2.765 (1.966–3.889) $P < 0.001$	1.921 (1.601–2.306) $P < 0.001$	1.608 (1.301–1.988) $P < 0.001$	0.410 (0.299–0.561) $P < 0.001$
Model 2	2.565 (1.707–3.854) $P < 0.001$	1.535 (1.219–1.933) $P < 0.001$	1.379 (1.099–1.730) $P = 0.006$	0.493 (0.351–0.691) $P < 0.001$
Model 3	2.139 (1.418–3.227) $P < 0.001$	1.467 (1.177–1.828) $P = 0.001$	1.346 (1.079–1.679) $P = 0.008$	0.551 (0.390–0.778) $P = 0.001$
Model 4	1.709 (1.100–2.654) $P = 0.017$	1.290 (1.029–1.618) $P = 0.028$	1.301 (1.045–1.621) $P = 0.019$	0.666 (0.470–0.944) $P = 0.022$

Data presented as standardized hazard ratios (95% confidence interval) and *P* values. AIx = augmentation index, CSBP = central systolic blood pressure, CMAP = central mean arterial pressure, SEVR = subendocardial viability ratio.

Model 1: unadjusted

Model 2: age and sex

Model 3: age, sex, BMI, HbA_{1c}

Model 4: age, sex, BMI, HbA_{1c}, estimated glomerular filtration rate (eGFR), previous cardiovascular event (myocardial infarction, coronary revascularization, stroke, lower extremity revascularization or non-traumatic amputation)

Table 3. Augmentation index (AIx) in association with cardiovascular and diabetes-related mortality in multivariable Cox regression models.

Cardiovascular/diabetes-related mortality			
yes (N = 53)		no (N = 14)	
Added variable	AIx sHR (95% CI)	Added variable	AIx sHR (95% CI)
	3.469 (2.315–5.199) *P* < 0.001		1.426 (0.779–2.609) *P* = 0.250
+ Male sex	4.402 (2.896–6.691) *P* < 0.001	+ Male sex	1.561 (0.815–2.991) *P* = 0.179
+ BMI	4.338 (2.843–6.619) *P* < 0.001		
+ eGFR	2.794 (1.767–4.419) *P* < 0.001		
+ CVD event	2.743 (1.674–4.493) *P* < 0.001		
+ Height	2.296 (1.378–3.825) *P* = 0.001		
Cardiovascular mortality			
yes (N = 36)		no (N = 31)	
Added variable	AIx sHR (95% CI)	Added variable	AIx sHR (95% CI)
	3.410 (2.085–5.578) *P* < 0.001		2.234 (1.396–3.574) *P* = 0.001
+ Male sex	4.209 (2.522–7.022) *P* < 0.001	+ Male sex	2.754 (1.668–4.546) *P* < 0.001
+ Diabetes duration	2.686 (1.505–4.792) *P* = 0.001	+ HbA_{1c}	2.514 (1.525–4.143) *P* < 0.001
+ eGFR	2.157 (1.197–3.887) *P* = 0.010	+ CVD event	2.213 (1.317–3.716) *P* = 0.003
+ CVD event	2.355 (1.224–4.530) *P* = 0.010	+ Total cholesterol	2.105 (1.247–3.555) *P* = 0.005

AIx = augmentation index, eGFR = estimated glomerular filtration rate (by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula), CVD event = previous cardiovascular event (myocardial infarction, coronary revascularization, stroke, lower extremity revascularization or non-traumatic amputation), sHR = standardized hazard ratio, CI = confidence interval.

Figure 1. Kaplan–Meier survival curves with log-rank tests for all-cause mortality (N = 67) by augmentation index (AIx) tertiles.