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Associations between plasma fibulin-1, pulse wave velocity and diabetes in patients with coronary heart disease

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ABSTRACT

Background: Diabetes is related to increased risk of cardiovascular disease, and arterial stiffness and its consequences may be the factor connecting the two. Arterial stiffness is often measured by carotid-femoral pulse wave velocity (cf-PWV), but no plasma biomarker reflecting arterial stiffness is available. Fibulin-1 is an extracellular matrix protein, up-regulated in arterial tissue and in plasma in patients with type 2 diabetes. We aimed to evaluate the association between plasma fibulin-1 and arterial stiffness measured by cf PWV in a group of patients with diabetes, and one without, all undergoing coronary artery bypass grafting.
Methods: Pulse wave velocity (PWV) and pulse wave analysis including augmentation index (Aix75) was measured in 273 patients, who subsequently underwent a coronary by-pass operation. Plasma samples were drawn and information was gathered on diabetes status, HbA1c, lipids, medication, body mass index, co-morbidities and smoking status. Carotid artery intima–media thickness, as well as estimation of carotid artery plaque burden, and distal blood pressure was also obtained.
Results: Sixty three patients had diabetes, and this group had significantly higher levels of plasma fibulin-1, PWV and Aix75, compared to the 210 patients who did not have diabetes. In univariate analysis fibulin-1 and pulse wave velocity were not correlated in either group whereas fibulin-1 in patients without diabetes was correlated to Aix75.
Conclusion: Fibulin-1 and arterial stiffness indices are not directly related in patients with cardiac disease, despite the fact that both measures are increased among patients with diabetes.

1. Introduction

Patients with diabetes are at high risk of developing cardiovascular diseases (CVD). The risk cannot be explained by other well-known risk factors such as smoking, high LDL-cholesterol and hypertension (Emerging Risk Factors Collaboration et al., 2010; Spencer, Pirie, & Stevens, 2008; Schramm, Gislason, & Kober, 2008), and the patho-physiologic background for this is unknown. Large, elastic arteries stiffen in response to aging, believed to be a consequence of a shift in collagen/elastin ratio, towards a higher collagen extent and elastin fragmentation, non-enzymatic collagen cross-linkage, reduced nitric oxide bioavailability, increased oxidative stress and perhaps also due to media calcification (Jacob, 2003; Brooke, Karnik, & Li, 2003; Nilsson et al., 2013). It has been proposed that patients with diabetes suffer from early vascular aging, and this group of patients can present with stiffer large arteries even when adjusting for age, compared to a background population (Nilsson, 2008). Increased arterial stiffness has been suggested as one element in the link between diabetes and the increased risk of CVD. Pulse wave velocity is a well-recognized marker of large artery stiffness (Van Bortel et al., 2012), but to date there is no available plasma biomarker reflecting arterial stiffness.

Fibulin-1 is an extracellular matrix and plasma glycoprotein found up-regulated in the arterial wall and in plasma from patients with diabetes with CVD, and is also an independent predictor of long term mortality in patients with diabetes. Moreover it was found correlating to arterial pulse pressure, a surrogate measure of arterial stiffness, and to carotid compliance as well (Cangemi et al., 2011). Attention has therefore been on this protein, and whether or not plasma fibulin-1 levels reflect arterial stiffness measures, such as pulse wave velocity and aortic augmentation index.

The aim of this study was to investigate whether fibulin-1 and large artery stiffness are increased among diabetes patients with significant cardiovascular disease and to explore possible connections between fibulin-1 and arterial stiffness, measured by carotid-femoral pulse wave velocity (cf-PWV) and augmentation index standardized at pulse frequency 75 (Aix75).

Conflicts of interest: Maria Lyck Hansen and Lars Melholt Rasmussen declare that they have no conflicts of interests.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

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Table 1
Clinical patient characteristics. Mean ± SEM.

	Patients with diabetes (N = 63)	Patients without diabetes (N = 209)	*p-value*
Male sex, %	84	80	0.35
Age, years	67 ± 1.1	66 ± 0.6	0.46
BMI, kg/m^2	29 ± 0.7	28 ± 0.3	0.20
Currently smoking, %	20	15	0.34
Statin treatment, %	92	89	0.29
Antihypertensive treatment, %	83	68	0.02
Total cholesterol, mmol/l	3.9 ± 0.1	4.0 ± 0.1	0.45
LDL-cholesterol, mmol/l	2.1 ± 0.1	2.3 ± 0.1	0.11
HDL-cholesterol, mmol/l	1.1 ± 0.0	1.1 ± 0.0	0.56
Triglycerides, mmol/l	1.7 ± 0.2	1.4 ± 0.0	0.005
Creatinine, μmol/l	86 ± 3.8	89 ± 1.4	0.37
GFR, ml/min per 1.73 m^2	78 ± 2.6	73 ± 1.0	0.02
Brachial systolic blood pressure, mmHg	139 ± 2.4	136 ± 1.4	0.25
Brachial diastolic blood pressure, mmHg	73 ± 1.5	77 ± 0.8	0.04
Brachial pulse pressure, mmHg	68.5 ± 3.1	60.2 ± 1.3	0.006
Brachial mean blood pressure, mmHg	93 ± 1.7	95 ± 1.0	0.37
Central systolic blood pressure, mmHg	127 ± 2.3	124 ± 1.4	0.32
Central diastolic blood pressure, mmHg	74 ± 1.6	77 ± 0.9	0.13
Aix75, %	26.9 ± 1.3	23.1 ± 0.7	0.015
Cf-pulse wave velocity, m/s	13.2 ± 1.0	10.7 ± 0.2	0.001
Size left atrium, cm	4.0 ± 0.1	3.8 ± 0.1	0.07
Left ventricle posterior wall, cm	1.1 ± 0.04	1.1 ± 0.02	0.07
Left ventricle internal diameter, diastole, cm	5.4 ± 0.2	5.1 ± 0.1	0.19
Ejection fraction, %	54 ± 1.5	54 ± 0.7	0.94
Fibulin-1, μg/ml	63 ± 2.5	54 ± 1.1	<0.001

2. Methods

Two hundred and seventy two patients, who were referred to elective coronary artery bypass grafting at Odense University hospital between 2012 and 2014, were included in the present study.

Individuals were assigned as having type 2 diabetes diagnosis, if this diagnosis was registered in the patients file, or if at least one HbA1c measurement was above 48 mmol/mol.

The day before surgery, measures of PWV and Aix75 were made using the Sphygmocor system under standardized conditions (Van Bortel et al., 2012). All measurements were done in the morning between 9 and 11.30 a.m., while patients had been fasting for at least two hours. Measures were performed in a quiet room after patients had been resting for 5 min in the supine position. Brachial blood pressure was performed on the right arm using a typical sphygmomanometer. Pulse pressure was calculated by subtracting diastolic from systolic blood pressure, and mean blood pressure by the formula: diastolic blood pressure + pulse pressure/3. Several measurements of PWV were made on each patients and a mean of these was used for analysis. Central arterial blood pressure as well as the degree of Aix 75 was also obtained by several measurements with applanation tonometry, and the one with the highest operator index was used for analysis. Carotid artery intima–media thickness as well as carotid artery plaque burden was assessed by ultrasound with a semi-automatic system (Siemens syngo arterial health package), bilaterally at the site of one centimeter proximal of the carotid bifurcation. Distal toe pressure was measured by the Systoe system (Atys Medical) and indexed relative to the brachial systolic blood pressure. Index below 0.65 was registered as peripheral atherosclerotic disease (PAD). When distal toe pressure was not possible to measure, ankle–arm index was used instead and an index below 0.9 registered as PAD. Information on other diseases such as diabetes and hypertension was registered the day prior to surgery; smoking status, medical treatment, body mass index (BMI) and echocardiographic size measures were also noted.

Plasma fibulin-1 levels were performed by ELISA as described elsewhere (Cangemi et al., 2011).

Patients were excluded if any other rhythm than sinus rhythm was revealed by the ECG. In some patients PWV measurement was not possible due to difficulties in assessing sufficient quality of the femoral artery pulse wave. Pulse wave analysis (PWA) was therefore only performed in these patients. Patients were excluded if any significant valve disease was recognized by echocardiography.

The study was approved by the local ethics committee and all patients gave informed consent.

2.1. Statistics

Data are controlled for normal distribution by p-p plots, as well as by Kolmogorov–Smirnov test, and are presented as mean ± SEM or percentage. Differences between groups were tested by student's t-test. Categorical data with chi square test. Univariate correlation was performed by Pearson correlation analysis. A multiple regression was performed in order to determine the determinants of PWV and Aix75 in patients with diabetes as well as in patients without. A p value < 0.05 was considered statistical significant. All statistical analysis was performed by IBM SPSS Statistics 22. Figures are made with GraphPad Prism 5.

3. Results

Sixty three patients with diabetes and 209 patients without were included in the study. In the diabetes group the majority (82%, N = 58) were classified as type 2 and 8% (N =5) as type 1 diabetes.

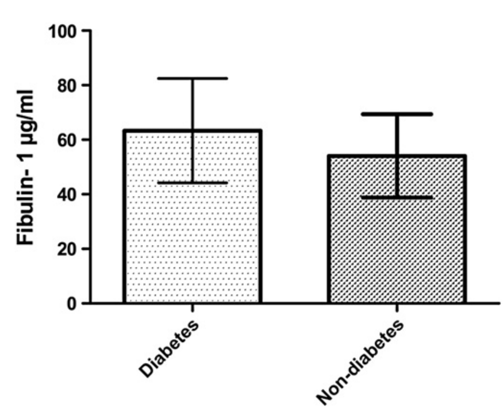

Fig. 1. Plasma concentrations of fibulin-1 in patients with and without diabetes undergoing coronary artery bypass grafting. Data presented as mean ± SEM. P < 0.001.