

Extracellular matrix protein fibulin-1 plasma levels are associated with increased cardiovascular risk in chronic kidney disease

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Background

Fibulin-1 is one of the few extracellular matrix proteins present in blood in high concentrations. We aimed to define the relationship between plasma fibulin-1 levels and risk markers of cardiovascular disease in patients with chronic kidney disease.

Methods

Plasma fibulin-1 was determined in patients with chronic kidney disease (n=32; median age, 63 years; interquartile range, 51 to 73 years). Serological biomarkers related to cardiovascular disease (fibrinogen, interleukin 6, C-reactive protein) were measured. Arterial applanation tonometry was used to determine central hemodynamic and arterial stiffness indices.

Results

The characteristics of chronic kidney disease study participants are shown in **Table 1**. Biochemical, hemodynamic and vascular variables of chronic kidney disease study participants are given in **Table 2**. We observed a positive correlation of fibulin-1 levels with age ($r=0.38$; $p=0.033$), glycated hemoglobin ($r=0.80$; $p=0.003$), creatinine ($r=0.35$; $p=0.045$), and fibrinogen ($r=0.39$; $p=0.027$). Glomerular filtration rate and fibulin-1 were inversely correlated ($r=-0.57$; $p=0.022$). There was a positive correlation between fibulin-1 and central pulse pressure ($r=0.44$; $p=0.011$) and central augmentation pressure ($r=0.55$; $p=0.001$). In a multivariable regression model, diabetes, creatinine, fibrinogen and central augmentation pressure were independent predictors of plasma fibulin-1 (**Table 3**).

Table 1. Population characteristics of chronic kidney disease study participants. Values are medians (25% - 75% percentile) or numbers (percentages), n = 32. Abbreviations: ACE = angiotensin converting enzyme, AT = angiotensin, eGFR = estimated glomerular filtration rate, Kt/V = dialysis dose. * n = 16, eGFR determination only in patients without hemodialysis therapy. † n = 8.

Age, years	62.5 (51 – 73)
Sex, men, n (%)	25 (78)
Body mass index, kg/m ²	24.8 (21.7 – 28.1)
Smoking, n (%)	18 (56)
Underlying kidney disease, n (%)	
Diabetic nephropathy	2 (6)
Nephrosclerosis	9 (28)
Glomerulonephritis	4 (13)
Others	17 (53)
Disease prevalence, n (%)	
Diabetes	11 (34)
Hypertension	25 (78)
Peripheral artery disease	2 (6)
Coronary artery disease	9 (28)
Stroke	5 (16)
eGFR, mL/min/1.73 m ² , *	39.9 (23.3 – 58.3)
Kt/V [†]	1.1 (0.9 – 1.4)
Medication, n (%)	
Phosphate binder	16 (50)
Erythropoietin analog	15 (47)
Platelet aggregation inhibitor	8 (25)
Diuretic	7 (22)
ACE inhibitor /AT antagonist	14 (44)
Calcium antagonist	15 (47)
β-Blocker	12 (38)

Conclusions

Increased plasma fibulin-1 levels were associated with impaired kidney function and diabetes. Fibulin-1 levels were also associated with hemodynamic cardiovascular risk markers. We conclude, that fibulin-1 is involved in the pathogenesis of cardiovascular disease observed in chronic kidney disease

Table 2. Biochemical, hemodynamic and vascular variables of chronic kidney disease study participants. Values are medians (25%-75% percentile), n=32. Abbreviations: HbA_{1c}=glycated hemoglobin, IL6=interleukin 6, CRP=C-reactive protein, SBP=systolic blood pressure, DBP=diastolic blood pressure, PP=pulse pressure, CAP=central augmentation pressure, Aix=augmentation index, Aix@75 = augmentation index at a heart rate of 75 beats/min, PWV=pulse wave velocity. *n=12

P-Fibulin-1, µg/mL	73.9 (54.9 – 85.3)
HbA _{1c} , %	7.2 (5.6 – 8.2)
P-Fibrinogen, µmol/L	11.7 (10.0 – 13.4)
P-IL6, pg/mL	5.03 (3.50 – 8.36)
P-CRP, mg/L	4.30 (1.52 – 11.86)
S-Albumin, g/l	41 (39 – 44)
P-Creatinine, µmol/L	380 (171 – 701)
P-Urea, mmol/L	15.2 (11.7 – 19.4)
SBP _{brachial} , mmHg	138 (130 – 152)
DBP _{brachial} , mmHg	77 (70 – 86)
SBP _{aortic} , mmHg	128 (115 – 140)
DBP _{aortic} , mmHg	79 (71 – 87)
PP _{aortic} , mmHg	49 (34 – 59)
Heart rate, beats/min	70 (63 – 82)
CAP, mmHg	13 (8 – 21)
Aix _{aortic} , %	31 (23 – 35)
Aix @75 _{aortic} , %	26 (21 – 32)
PWV _{aortic} , m/s	10.1 (7.9 – 13.3)

Table 3. Multivariable regression analysis of plasma fibulin-1. Age, presence of diabetes, creatinine, central augmentation pressure, and logarithmically transformed plasma fibrinogen concentration were used in a stepwise backward selection process (n = 32). Abbreviations: CAP = central augmentation pressure.

Independent variable	Adjusted r ²	F	β	p
Model	0.59	11.98		<0.001
Diabetes			0.40	0.005
Creatinine			0.43	0.002
CAP			0.25	0.073
Fibrinogen _{log}			0.32	0.011



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