RESEARCH ARTICLE

Specifics of fetuin-A levels in distinct types of chronic heart failure

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Introduction: Fetuin-A has been described to correlate inversely with vascular calcification both in animal models but also in patients with heart and renal disease. In this current study, we sought to investigate whether fetuin-A might be a useful marker for the discrimination of ischemic (ICM) from dilated cardiomyopathy (DCM).

Methods: A total of 124 non-consecutive patients were included in this study, 59 patients suffered from ICM and 65 patients from DCM. Serum samples were obtained during out-patient visits and analyzed for fetuin-A by ELISA.

Results: Median fetuin-A concentration in the overall cohort was significantly lower in ICM patients compared to DCM patients ($62.2 \pm 16.4 \mu\text{g/mL}$ vs. $129.6 \pm 56.6 \mu\text{g/mL}$; $P < .001$). A positive correlation of fetuin-A levels was found with BMI, cholesterol, LDL/HDL ratio and triglycerides and an inverse correlation with age ($r = -.36$; $P < .001$). Moreover, patients suffering from (stable) angina pectoris evidenced lower fetuin-A levels compared to non-symptomatic patients ($73.1 \pm 22.7 \mu\text{g/mL}$ vs. $83.7 \pm 26.2 \mu\text{g/mL}$; $P = .047$).

Conclusions: Fetuin-A was shown to be a potential discriminator and biomarker for the differential diagnosis between ICM and DCM. Fetuin-A levels might also be helpful in the process of diagnostic decision-making in regards to invasive management or medical therapy.

KEYWORDS

biomarker, cardiomyopathy, ELISA, fetuin-A, heart failure

1 | INTRODUCTION

Heart failure (HF) with reduced ejection fraction constitutes an important reason for morbidity and increasing health care costs as prevalence in developed countries is as high as 10% of those older than 70 years.^{1,2} Whereas diagnosis and indications for treatment are based on simple algorithms taking clinical symptoms, biomarkers, echocardiography,

and coronary angiography into account, investigation of pathogenesis and underlying mechanisms in patients remain challenging in some cases.³⁻⁵

HF due to ischemic heart disease remains the most important HF entity, even with early reperfusion strategies being widely followed.⁶ During work-up for HF, indications for coronary angiography are angina pectoris, high pre-test probability of coronary artery disease (CAD) and positive non-invasive stress tests, but a normal coronary angiogram does not rule out ischemic heart disease as myocardial

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scars might still be present in cardiac magnetic resonance imaging and coronary microcirculation might be impaired.^{3,7-9} Another important HF entity is dilated cardiomyopathy (DCM), which is considered to be the final common pathway of diverse genetic influences and environmental influences, mainly due to inflammation.^{10,11}

Fetuin-A is a glycoprotein mainly expressed and secreted from the liver and adipose tissue.¹² In 1944, fetuin has been described for the first time in fetal calf serum.¹³ In the human setting, fetuin was initially named α 2-Heremans-Schmid glycoprotein after its two discoverers.^{14,15} Fetuin-A is known to be increased in obesity, type 2 diabetes mellitus and metabolic syndrome.¹⁶ On the other hand, fetuin-A is acting as an inhibitor of ectopic calcification and fetuin-A levels were reported to be inversely associated with calcification scores and both cardiovascular events and mortality.¹⁷⁻¹⁹

Fetuin-A has been shown to influence a broad spectrum of cellular mechanisms both via direct interaction by preventing the formation of large crystals and also by regulating energy and bone metabolism.²⁰⁻²³ Moreover, fetuin-A has also been described as an inhibitor of vascular smooth muscle cell apoptosis.²⁴ It can also counteract effects of transforming growth factor- β and bone morphogenetic protein-2 on the formation of calcified tissue.^{21,25} So far, low serum fetuin-A levels were found in many pathological conditions with vascular calcifications such as coronary artery disease and degenerative valvular heart disease.²⁶⁻²⁹

We, therefore, investigated and compared fetuin-A levels in cardiomyopathies of differential pathogenesis, to evaluate fetuin-A as a potential biomarker for the discrimination of the etiology of ischemic cardiomyopathy (ICM) and DCM.

2 | METHODS

2.1 | Study population

One hundred and twenty-four, non-consecutive patients were included in this study at the University Hospital Jena, Germany. Patients were recruited during follow-up visits in our specialist outpatient clinic for patients suffering from HF. Patients were examined by an experienced physician in the treatment of HF; patients with signs of acute HF were not enrolled. Fifty-nine patients suffered from ICM and 65 patients from DCM. Diagnosis of ICM was made according to European society of cardiology (ESC)-guidelines by coronary angiogram after initial evaluation by thorough examination, medical taking, laboratory analysis, and echocardiogram. Likewise, DCM was defined by ESC guidelines as left ventricular dilatation, diagnosis of HF and no evidence of relevant coronary artery disease. Coronary angiography and echocardiography was also performed in all DCM patients to exclude CAD and other reasons of myocardial dysfunction (valvular heart disease, systemic disease involving the myocardium). All patients suffered from HF with reduced ejection fraction. Serum samples were obtained from study patients after informed consent. Aliquots of obtained serum samples were stored at -80°C until ELISA measurements were conducted. Patients suffering from active infection, malignant disease, or advanced renal failure (as indicated by a

glomerular filtration rate <30 mL/min) were not included. The study was approved by the local ethics committee and conducted according to the Universal Declaration of Helsinki.

2.2 | Laboratory analysis

Laboratory parameters were measured by routine laboratory analysis. Fetuin-A concentration was determined by a commercially available ELISA kit (Human fetuin-A/AHSG DuoSet ELISA, DY1184; R&D Systems, Minneapolis, MN, USA). Analyses were performed according to manufacturer's instructions. In brief, patient samples and standard fetuin-A protein were added to the wells of the ELISA plate and incubated for two hours. Plates were then washed using a Tween 20/phosphate-buffered saline solution (Sigma Aldrich, St. Louis, MO, USA). Then, a biotin-labeled antibody was added to each well and incubated for another two hours. Plates were washed again and Streptavidin-horseradish-peroxidase solution was added. After adding tetramethylbenzidine (TMB; Sigma Aldrich) a color reaction was achieved. Values of optical density were determined at 450 nm on an ELISA plate-reader (iMark Microplate Absorbance Reader, Bio-Rad Laboratories, Vienna, Austria).

2.3 | Statistical analysis

Statistical analysis was performed using SPSS (22.0; SPSS Inc., Armonk, NY, USA) and GraphPad-Prism software (GraphPad-Software, La Jolla, CA, USA). Kolmogorov-Smirnov testing was used to assess for normal distribution. Normally distributed values are given as mean $\pm$ standard error of the mean. Means were compared by student's *t* test. As fetuin-A was not normally distributed, fetuin-A concentrations are given as median $\pm$ interquartile range and medians were compared by Mann-U test. Correlations were assessed by Spearman's rank-correlation coefficient. Differences between New York Heart Association (NYHA) functional classification stages were compared using the Kruskal-Wallis test with Dunn's post-test for multiple comparisons. A $P<.05$ was considered to be statistically significant.

3 | RESULTS

Baseline characteristics are shown in Table 1. Patients suffering from ICM were significantly older compared to those suffering from DCM (64 ± 2 years vs. 55 ± 1 years; $P<.001$) and evidenced lower total cholesterol (152 ± 10 mg/dL vs. 182 ± 9 mg/dL; $P=.04$) and LDL (81 ± 9 mg/dL vs. 107 ± 7 mg/dL; $P=.03$) levels. Brain natriuretic peptide (BNP) (448.9 ± 76.4 pg/mL vs. 734 ± 127.8 pg/mL; $P=.06$) was in trend lower in ICM patients. Regarding cardiovascular risk factors ICM patients suffered from arterial hypertension more often (77% vs. 43%; $P<.001$). There were no differences in medication, NYHA stadium or clinical symptoms such as angina and peripheral edema.

Fetuin-A levels correlated positively with BMI ($r=.34$; $P<.001$) and inversely with age ($r=-.36$; $P<.001$) as well as positively with cholesterol, LDL/HDL ratio as well as triglyceride concentration, as seen in

TABLE 1 Baseline characteristics of patients suffering from ICM and dilated cardiomyopathy (DCM)

	ICM	DCM	P
Age	64±2	55±1	<.001*
BMI	28±1	29±1	.41
Ejection fraction (%)	38±2	36±2	.41
LVEDd (mm)	59±1	59±1	.62
Cholesterol (mg/dL)	152±10	182±9	.04
LDL (mg/dL)	81±9	107±7	.03*
HDL (mg/dL)	39±3	43±2	.26
LDL/HDL ratio	2.2±0.2	2.6±0.1	.13
Triglycerides (mg/dL)	209±49	177±22	.50
c-reactive protein	4.8±1.1	6.8±1.5	.44
BNP (pg/mL)	448.9±76.4	734.1±127.8	.06
Heart rate (bpm)	66±2	74±2	.13
Creatinine (μmol/L)	109.8±6.9	99.1±4.1	.16
Urea (mmol/L)	9.1±1.0	8.2±0.7	.45
Thrombocytes (×10 ⁹ /L)	199.4±7.0	211.4±6.0	.19
Leucocytes (×10 ⁹ /L)	7.4±0.3	7.7±0.2	.26
Symptoms since (months)	14±3	15±3	.70
Betablocker	100%	100%	1.00
ACE-I/Sartans	96%	92%	.46
Aldosteron antagonists	63%	66%	.85
Diuretics	79%	91%	.11
NYHA I	33%	29%	.26
NYHA II	39%	27%	.23
NYHA III	23%	30%	.41
NYHA IV	5%	14%	.22
Edema	27%	25%	.83
Angina pectoris	8%	3%	.40
Adiposity	35%	41%	.55
Smoking	41%	50%	.34
Arterial hypertension	77%	43%	.001*
Type 2 diabetes mellitus	37%	38%	1.00

*indicates statistical significance.

Table 2a. In the ICM subgroup fetuin-A correlated positively with BMI, but not with age (Table 2b). In the DCM subgroup fetuin-A correlated positively with BNP and BMI (Table 2c).

The median fetuin-A concentration in the overall cohort was 76.8±20.6 μg/mL and significantly higher in the DCM group compared to patients suffering from ICM (129.6±56.6 μg/mL vs. 62.2±16.4 μg/mL; $P<.001$). As fetuin-A positively correlated with age and there was a significant age difference between those two groups, we also compared fetuin-A concentrations in those patients aged younger than 65 years (patient demographics see Table S1). Again, fetuin-A concentration in patients suffering from ICM was significantly lower compared to DCM patients (62.2±10.2 μg/mL vs. 153.4±58.7 μg/mL, $P<.001$). Except for creatinine levels and smoking status no significant differences were found between patients < or > 65 years of age.

TABLE 2 Correlation analysis of clinical parameters with levels of fetuin-A in the whole cohort (a), in ICM patients (b) and dilated cardiomyopathy patients (c)

Fetuin-A vs.	r	P
(a)		
Ejection fraction (%)	-.04	.70
LVEDd (mm)	.12	.22
Cholesterol (mg/dL)	.37	.008*
LDL (mg/dL)	.24	.11
HDL (mg/dL)	.05	.76
LDL/HDL ratio	.25	.09*
Triglycerides (mg/dL)	.39	.005*
c-reactive protein (mg/L)	-.01	.91
BNP (pg/mL)	-.16	.13
BMI	.34	<.001*
Age	-.36	<.001*
Heart rate (bpm)	.21	.03
Creatinine (μmol/L)	.003	.98
Urea (mmol/L)	-.11	.33
Thrombocytes (×10 ⁹ /L)	.13	.18
Leucocytes (×10 ⁹ /L)	.14	.14
Symptoms since (months)	.15	.19
(b)		
Ejection fraction (%)	.011	.44
LVEDd (mm)	.15	.29
Cholesterol (mg/dL)	.37	.17
LDL (mg/dL)	.15	.59
HDL (mg/dL)	.02	.94
LDL/HDL ratio	.20	.48
Triglycerides (mg/dL)	.45	.09
c-reactive protein (mg/L)	.14	.56
BNP (pg/mL)	-.02	.88
BMI	.36	.01*
Age	-.19	.19
Heart rate (bpm)	.22	.13
Creatinine (μmol/L)	.15	.38
Urea (mmol/L)	-.09	.63
Thrombocytes (×10 ⁹ /L)	.14	.35
Leucocytes (×10 ⁹ /L)	.29	.05*
Symptoms since (months)	.01	.96
(c)		
Ejection fraction (%)	.02	.88
LVEDd (mm)	.15	.25
Cholesterol (mg/dL)	.29	.09
LDL (mg/dL)	.16	.38
HDL (mg/dL)	-.08	.67
LDL/HDL ratio	.24	.17
Triglycerides (mg/dL)	.47	.005

(Continues)

TABLE 2 (Continued)

Fetuin-A vs.	<i>r</i>	<i>P</i>
c-reactive protein (mg/L)	.002	.99
BNP (pg/mL)	.32	.02*
BMI	.38	.004*
Age	-.16	.24
Heart rate (bpm)	.06	.65
Creatinine (μmol/L)	.11	.43
Urea (mmol/L)	-.07	.62
Thrombocytes (×10 ⁹ /L)	.07	.60
Leucocytes (×10 ⁹ /L)	.05	.73
Symptoms since (months)	.26	.09

*indicates statistical significance.

Interestingly, patients suffering from (stable) angina pectoris (73.1 ±22.7 μg/mL vs. 83.7 ±26.2 μg/mL; *P*=.047) revealed lower fetuin-A levels compared to those not suffering from angina pectoris. Patients with pacemakers did not show altered fetuin-A concentrations compared to those without pacemakers (73.7±25.3 μg/mL vs.77.7±19.3 μg/mL; *P*=.45). Comorbidities of cardiovascular disease such as type 2 diabetes (74.1±20.0 μg/mL vs. 97.2±40.0 μg/mL; *P*=.13) and arterial hypertension (76.4±19.2 μg/mL vs. 97.2±41.1 μg/mL; *P*=.56) were not associated with significantly altered fetuin-A concentrations. Smokers had higher levels of fetuin-A (97.2±34.8 μg/mL vs.73.1±22.7 μg/mL; *P*=.049). Patients in different NYHA stages did not reveal significant differences in fetuin-A concentrations.

4 | DISCUSSION

Here, we demonstrate that fetuin-A concentrations differ between patients suffering from ICM and DCM, with patients suffering from ICM showing lower levels. Fetuin-A might, therefore, constitute a valuable biomarker for the evaluation of etiology of cardiomyopathies.

In our overall cohort, fetuin-A negatively correlated with age. As this correlation could not be shown in the distinct sub-cohorts, we think that this correlation is mainly due to the fact that patients suffering from ICM were older than those suffering from DCM and mainly driven by the different pathologies and etiologies underlying the cardiomyopathies. Although fetuin-A was reported to correlate with risk factors for coronary artery disease such as metabolic syndrome and obesity, lower fetuin-A levels in ICM patients corresponds to the finding of this protein being an inhibitor of ectopic calcification.¹⁸

In the overall cohort but also in the ICM and DCM subgroups, fetuin-A positively correlated with BMI. As obesity and obesity-related diseases are known to be associated with cardiovascular diseases, this finding is somehow puzzling. Mathews et al.³⁰ have shown that fetuin knockout mice evidenced improved insulin sensitivity, lower blood glucose levels, and also a higher resistance against diet-induced obesity. Moreover, fetuin knockout mice demonstrated lower body

weights compared to wild-type littermates. These in vivo animal data correspond nicely with the results obtained in our analysis of clinical data as a significant correlation with BMI (*r*=.34; *P*<.001) was found in our patient cohort. Moreover, patients with type 2 diabetes showed a trend toward higher fetuin-A concentrations (*P*=.1).^{31,32}

We can only speculate that there might be an U-shaped relationship between fetuin-A and cardiovascular disease, with fetuin-A first being elevated due to sub-clinical inflammation^{33,34} and atherogenesis and consequently fetuin-A being decreased as formerly inflammatory soft plaques and vascular lesions get calcified. The evaluation of the relation between fetuin-A and cardiovascular disease over the time course of pathogenesis is an endeavour certainly worth pursuing, but beyond the scope of this study.

Interestingly, in the overall cohort fetuin-A was positively correlated with cholesterol levels. But, as cholesterol as well as LDL concentrations were lower in the ICM sub-group, we think that this relation might be distorted by lipid lowering treatment, eg, by statin therapy.

With fetuin-A being a potential biomarker for prediction of pathogenesis of cardiomyopathy, one could speculate about several roles in diagnosis and even treatment of HF: In patients evidencing high fetuin-A levels, invasive work-up by coronary angiography could be avoided in case of uncertain non-invasive stress tests or low risk scores for coronary artery disease. Also in elderly or very fragile patients where one might be cautious performing invasive diagnostic measurements, determination of fetuin-A levels could be helpful for the diagnostic decision-making in patients with suspected coronary artery disease. On the other hand, in case of uncertain coronary angiogram and low fetuin-A levels one might tend to a more aggressive treatment for coronary artery disease by both invasive and conservative/medical therapy.

In conclusion, fetuin-A might be a promising biomarker for cardiovascular disease but further studies before any clinical application are warranted.

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SUPPORTING INFORMATION

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