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Universitätsklinikum Mannheim

Galectin-3, renal function, and adverse outcomes: results from the LURIC and the 4D Study

Graciela Delgado Msc[1,2,**], Christiane Drechsler MD PhD[3,4,**], Christoph Wanner MD[3,4], Katja Blouin[3, 4], Stefan Pilz MD PhD[5], Andreas Tomaschitz MD[6,7], Marcus E. Kleber PhD[1,2], Christoph Willmes PhD[3, 4], Vera Krane MD[3,4], Bernhard K Kraemer MD[1], Winfried März MD[1,8], Eberhard Ritz MD[9], Wiek H. van Gilst MD PhD[10], Pim van der Harst MD PhD[10], Rudolf A. de Boer MD PhD[10]

1) Vth Department of Medicine, Mannheim Medical Faculty, University of Heidelberg, Mannheim, Germany; 2) Mannheim Institute of Public Health, Social and Preventive Medicine, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany; 3) University of Würzburg, Department of Internal Medicine 1, Division of Nephrology, Würzburg, Germany; 4) Comprehensive Heart Failure Centre, University of Würzburg, Würzburg, Germany; 5) Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Metabolism, Graz, Austria; 6) Department of Cardiology, Medical University of Graz, Graz, Austria; 7) Specialist Clinic for Rehabilitation PV Bad Aussee, Bad Aussee, Austria; 8) Synlab Center of Laboratory Diagnostics, Heidelberg, Germany; 9) University Hospital Heidelberg, Department of Medicine, Division of Nephrology, Heidelberg, Germany; 10) Department of Cardiology, University Medical Center Groningen, The Netherlands

Background

Galectin-3, a 250 amino acid galactose-specific lectin, plays a role in tissue fibrosis, immunity and the inflammatory response. Experimental studies in models of cancer, heart failure, and inflammatory disease have convincingly shown that galectin-3 contributes to the pathophysiology of these diseases. Similarly, in renal disease, galectin-3 has been shown to play a role in the onset and development of diabetic and non-diabetic nephropathy. Recently it has been reported that elevated galectin-3 precedes the development of chronic kidney disease and is associated with a rapid decline of the estimated glomerular filtration rate (eGFR) (1). We determined and evaluated galectin-3 in 2578 patients from the Ludwigshafen Risk and Cardiovascular Health (LURIC) study and 1168 patients participating in the German Diabetes Dialysis study (4D study) to investigate if galectin-3 is associated with adverse outcome in patients with impaired kidney function.

Methods

In 4D, galectin-3 was determined using an enzyme-linked immunosorbent assay (ELISA) developed by BG Medicine (BG Medicine, Inc., Waltham, USA 20). In LURIC, galectin-3 concentration was measured in plasma samples on an ARCHITECT analyzer (Abbott Diagnostics, Abbott Park, IL) using the same antibodies and the same conjugate like for the manual ELISA. The association of log transformed galectin-3 with clinical outcomes was assessed by Cox regression analyses. Analyses were performed using SPSS version 20.0 and R version 3.0.2 (http://www.R-project.org)

Results

Galectin-3 concentrations were increasing in parallel to decreasing kidney function. Mean galectin-3 levels were 12.8±4.0 ng/mL, 15.6±5.4 ng/mL, 23.1±9.9 ng/mL, and 54.1±19.6 ng/mL in patients with normal kidney function (eGFR ≥> 90; G1), mildly impaired kidney function (eGFR 60-89; G2), advanced kidney failure (eGFR<60; G3) and in dialysis patients, respectively (Table 1).

The incidence of cardiovascular outcomes was higher in 4D as compared to LURIC and increased with rising galectin-3 concentration in both cohorts, except for a decrease in the group with galectin-3 concentration between 80 ng/µl and 100 ng/µl in 4D (Figure 1).

Galectin-3 concentrations at baseline were not significantly associated with any of the investigated endpoints in patients with normal kidney function (G1). In patients with mildly reduced kidney function (G2), galectin-3 concentrations were associated with all-cause mortality and death and death due to infection in fully adjusted models with HRs of 1.15 (1.04-1.28) and 1.49 (1.03-2.16) per 1 SD increase in log transformed galectin-3, respectively (Table 2). In G3, galectin-3 concentrations were significantly associated with all-cause mortality, cardiovascular mortality and death due to infection with HRs of 1.22 (1.06-1.41), 1.21 (1.01-1.44) and 1.71 (1.08-2.70) in fully adjusted models, respectively. In 4D patients, after adjustment for confounders only the association with cardiovascular events remained significant with a HR of 1.12 (1.01-1.24) (Table 2).

Table 1: Patients characteristics in LURIC (stratified according to eGFR) and 4D (means ± SD or median (25th to 95th percentile))

	LURIC			4D
	G1	G2	G3	Hemodialysis
	n = 1209	n = 1642	n = 456	n = 1168
Galectin-3 ng/ml	12.8±4.0	15.6±5.4	23.1±9.9	54.1±19.6
Age (years)	55.8±10.2	65.5±8.4	70.8±8.4	66±8
Gender (%men)	78.2	66.5	58.1	54.4
Smoker/Ex-smoker (%)	71.2	61.4	57.7	40.3
Systolic BP (mmHg)	136±22	143±24	145±26	146±22
Diastolic BP (mmHg)	80±11	82±12	79±12	76±11
BMI (kg/m²)	27.2±4.0	27.7±4.0	27.5±4.4	27.5±4.8
CAD (%)	72.9	79.9	83.8	29.8
CHF (%)	13.0	19.0	34.5	35.8
Hypertension (%)	62	78	84	88.7
eGFR (ml/min)	101±8.0	77±8.5	46±11.5	-
Albumin (g/dL)	4.4±0.5	4.4±0.5	4.3±0.6	3.82±0.3
C-reactive protein (mg/L)	2.4(1.0-6.7)	3.5(1.4-8.7)	6.5(2.5-14.9)	10.6±17.2
LDL cholesterol (mg/dL)	117±35	117±34	111±34	126±29
HDL cholesterol (mg/dL)	39±11	39±11	37±11	36±13
Triglycerides (mg/dL)	176±138	169±102	182±110	262±165
HbA1c (%)	6.1±1.2	6.4±1.2	6.7±1.4	6.7±1.3
Phosphate (mmol/L)	3.5±0.5	3.5±0.5	3.7±0.7	6.0±1.6
Creatinin (mg/dl)	0.8±0.1	1.0±0.1	1.4±0.8	6.9 ± 2.3
NT-pro-BNP (pg/mL)	143(63-385)	329(138-935)	1157(450-2795)	8139±13615

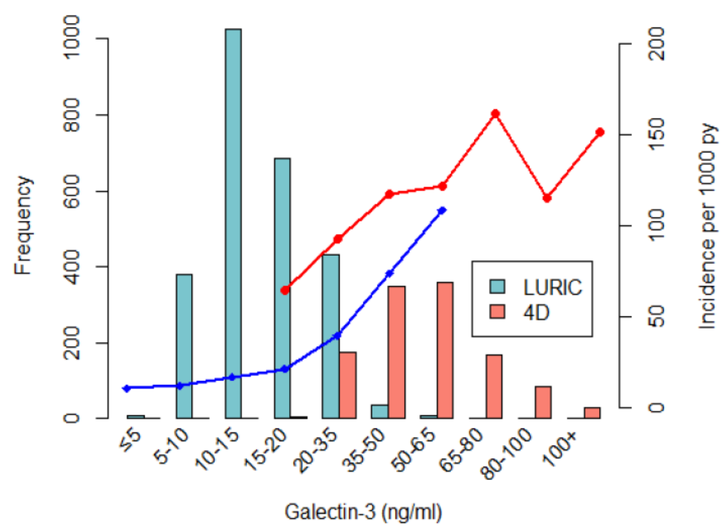

Figure 1: Relationship between the incidence of fatal cardiovascular events (lines) and galectin-3 concentration (columns).; py indicates person-years.

Table 2: Association of galectin-3 concentration with clinical endpoints in different stages of renal disease

	LURIC						4D	
OUTCOME	G1: eGFR 90+		G2: eGFR 60-89		G3: eGFR <60		Hemodialysis	
	HR (95% CI)	P§	HR (95% CI)	P§	HR (95% CI)	P§	HR (95% CI)	P§
All-cause mortality								
MODEL 1	1.05 (0.89-1.23)	0.586	1.22 (1.10-1.36)	<0.001	1.30 (1.12-1.50)	<0.001	1.10 (1.00-1.20)	0.043
MODEL 2	0.99 (0.84-1.18)	0.948	1.15 (1.04-1.28)	0.008	1.22 (1.05-1.41)	0.009	1.07 (0.98-1.17)	0.127
Cardiovascular events*								
MODEL 1	1.01 (0.81-1.25)	0.946	1.19 (1.04-1.35)	0.010	1.25 (1.05-1.48)	0.012	1.12 (1.01-1.23)	0.031
MODEL 2	0.96 (0.76-1.20)	0.704	1.10 (0.97-1.25)	0.155	1.21 (1.01-1.44)	0.038	1.12 (1.01-1.24)	0.026
Death due to infection								
MODEL 1	1.79 (0.64-5.00)	0.268	1.67 (1.14-2.44)	0.008	1.75 (1.13-2.73)	0.013	1.20 (0.99-1.46)	0.064
MODEL 2	2.27 (0.70-7.36)	0.171	1.49 (1.03-2.16)	0.037	1.71 (1.08-2.70)	0.023	1.14 (0.93-1.39)	0.200

* fatal and non-fatal events in 4D, only fatal events in LURIC; model 1: adjusted for age and sex; model 2: additional adjustments for smoking, systolic blood pressure, BMI, LDL cholesterol, statin treatment, diabetes, triglycerides and CRP

Discussion

The main findings of this study are first that circulating galectin-3 levels increase with decreasing kidney function up to extreme elevation in patients on dialysis, exceeding the normal range 4-5 fold, and second that circulating galectin-3 levels are associated with clinical outcomes only in patients with impaired kidney function.

The reasons for the extreme elevation in dialysis patients may be various. Possibly, galectin-3 is, at least in part handled or cleared by the kidney. The kidney is also in charge of maintaining a normal pH of about 7.4 in the blood. Decreasing kidney function may lead to acidosis and this may affect the binding affinity of galectin-3. Furthermore, extracellular galectin-3 is capable of binding, internalization, and degradation of Advanced Glycosylation End Products (AGEs), acting as an AGE receptor, and circulating AGEs are known to contribute to the development of kidney disease.

Our study shows that galectin-3 may be used to risk stratify patients with renal disease across the spectrum severity of renal impairment. Finally, galectin-3 may be not just a marker of disease, like troponin or NT-proBNP, but may be a target for therapy. Recently, the results of phase 2 study, in which patients with CKD stages 3b and 4 were randomized to the galectin-3 inhibitor GCS-100, or 30 mg/m2 of GCS-100a study was conducted with the galectin-3 inhibitor GCS-100, and this treatment led to a statistically significant increase in eGFR compared to placebo (2).

References

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•Graciela Delgado
•Vth Department of Medicine
•Medical Faculty Mannheim
•Heidelberg University
•Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany
•Fon: +49 (0621 383-6562
•Graciela.Delgado@medma.uni-heidelberg.de

Julius-Maximilians-UNIVERSITÄT WÜRZBURG

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URIC LUdwigshafen RIsk and Cardiovascular Health Study

4D

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H) Clinical Nephrology, CKD. H1) Lab methods, progression & risk factors for CKD 1-5, nutrition in CKD, renal diseases (except GNs and cystic diseases).
Graciela Delgado

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