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Determinants of temporal changes in galectin-3 level in the general population: Data of PREVEND☆

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ABSTRACT

Background: High baseline galectin-3 levels are associated with increased risk for adverse cardiovascular outcomes in the general population, but determinants of changes in galectin-3 levels over time have not been established. Therefore, we aimed to identify determinants of (temporal) change in galectin-3 levels.
Methods: Galectin-3 plasma levels were measured in a large community based cohort (PREVEND study) at 3 different time points: at baseline, after ~4 and ~9 years. The association of baseline clinical and biochemical factors and (temporal) changes in galectin-3 level was assessed using multivariable mixed-effects regression modeling.
Results: In 4355 subjects, galectin-3 plasma levels were available at all time points (mean age: 48 ± 12 years; 50% female). Median galectin-3 level at baseline was 10.7 [8.9–12.7] ng/mL which gradually increased to 11.5 [9.4–14.3] ng/mL after ~9 years. Using mixed-effects regression modeling, we first validated as independent determinants of baseline circulating galectin-3: eGFR (chi square (χ^2):210.27, $p < 0.0001$), gender (χ^2:43.85; $p < 0.0001$), BMI (χ^2:19.68, $p = 0.0001$), NT-proBNP (χ^2:18.76, $p = 0.0001$) and serum (total) cholesterol (χ^2:8.63, $p = 0.01$). Furthermore, we identified urinary albumin excretion (χ^2:34.03, p-value: <0.0001) and systolic blood pressure (χ^2:16.81, $p = 0.002$) as independent determinants of *temporal changes* of galectin-3.
Conclusions: In the general population, urinary albumin excretion >30 mg/24 h and systolic blood pressure >170 mmHg were identified as significant determinants of dynamic increases in galectin-3 levels over time. These results implicate that treatment of high blood pressure might be effective to prevent increasing galectin-3 levels and its associated conditions.

1. Introduction

Heart failure (HF) is a lethal disease and surpasses most types of cancer regarding mortality [1]. HF incidence might have shown a slight decline over the past years, primarily because of reduced heart failure with reduced ejection fraction (HFrEF) incidence, but mortality and hospitalization rates remain unchanged [2]. Prior to the diagnosis of HF, patients often experience years of clinically silent cardiac remodeling, slowly progressing to HF [3]. This subclinical disease is common in elderly people and therefore blood-borne biomarkers can be used to identify individuals who are at higher risk for cardiovascular events [4].

Galectin-3 is a marker of cardiac remodeling and is of potential interest to identify patients in the subclinical phase of disease. Galectin-3 is a beta-galactoside binding lectin that is involved in inflammation and fibrosis and is widely studied in cardiovascular disease [5]. Upon cardiac damage, galectin-3 activates fibroblasts into active matrix-secreting myofibroblasts, resulting in cardiac fibrosis [6]. In apparently healthy subjects, elevated baseline galectin-3 levels are associated with increased risk of mortality and new-onset HF [7–9]. Galectin-3 is also predictive in diseased individuals and is especially useful for prediction of short-term outcome (≤1 year) in HF patients [10,11]. Furthermore, galectin-3 levels change over time and these serial measurements add prognostic value [12–14].

These associations have primarily been derived from cross-sectional data and little is known about the temporal change of galectin-3.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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However, evidence of galectin-3 as a prognostic indicator in HF is accumulating, and galectin-3 has been implemented in the 2013 ACC/AHA HF guidelines as a (class of recommendation IIB) prognostic indicator for HF [15]. Since galectin-3 has been recognized as important factor in HF, it now becomes increasingly important to better understand why certain individuals show temporal changes of galectin-3 over time.

However, determinants of temporal change of galectin-3 in ostensibly healthy subjects in the long term are unknown. Identification of these determinants may help us to better understand the underlying causes of disease and provide mechanistic insights [16–19]. Eventually, these determinants may be used to develop new therapeutic targets in order to prevent this "silent" progression to HF and these determinants may also be used to provide lifestyle advice. Therefore, we studied the temporal change of galectin-3 and its determinants in a large, longitudinal, community-based study with repeated measurements of galectin-3.

2. Methods

2.1. Study population

The Prevention of REnal and Vascular ENd-stage Disease (PREVEND) study is a prospective, observational cohort study, derived from the general population and comprises 8592 participants. This study was designed to monitor long-term development of cardiac, renal and peripheral vascular end-stage disease. More details have been described previously [20,21]. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research review committee. In this study, galectin-3 was measured at 3 time points: at baseline, at 1st follow-up (median: 4.2 years) and at 3rd follow-up (median: 9.3 years). Non-Caucasian subjects were excluded (N = 379) because it is not known whether normal ranges of galectin-3 established in Caucasians can be applied to all ethnicities. Subjects with missing galectin-3 values among these 3 time points were also excluded (N = 3858), and therefore the current study sample comprised 4355 subjects.

2.2. Definitions and measurement of risk factors

Smoking was defined as current smoking or smoking within the last 5 years before baseline visit. Diabetes mellitus was defined as a fasting glucose level of >7.0 mmol L^{-1} (126 mg dL^{-1}) or the use of antidiabetic drugs. History of myocardial infarction (MI) was defined as self-reported hospitalization for at least 3 days as a result of MI. Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg and/or the use of anti-hypertensive medication. Systolic and diastolic blood pressures were calculated as the mean of the last two measurements of ten blood pressure measurements recorded in 10 min, using an automatic Dinamap XL Model 9300 series device. Hypercholesterolemia was defined as having a serum cholesterol level of >6.5 mmol L^{-1} (251 mg dL^{-1}) or the use of lipid-lowering medication. Estimated Glomerular Filtration Rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and cystatin C concentrations [22]. Urinary albumin excretion (UAE) was determined as the average value from two consecutive 24-hour urine collections. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured on an Elecsys™ 2010 analyzer. To be able to clearly define subjects at risk, we decided to categorize our determinants, using 2 cut points and thereby creating normal/high/very high levels. Therefore the following cut points were used to categorize the determinants: BMI: /25/30/; eGFR: /90/60/; CRP: /10/20/; NT-proBNP: /100/300/; heart rate: /90/100/; systolic blood pressure: /140/170/; diastolic blood pressure: /90/100/; triglycerides: /2.0/4.0/; total cholesterol: /5.0/6.5/; LDL: /2.5/4.0/; HDL: /1.7/2.5/; glucose: /7.0/12.0/; cystatin C /1.25/2.0/; creatinine: /100/130/.

2.3. Measurement of galectin-3

Blood was drawn and samples were anticoagulated with EDTA and centrifuged. Plasma was stored at −80 °C until time of analysis. Galectin-3 was measured in plasma using the FDA-cleared BGM Galectin-3 ELISA kit (BG Medicine Inc., Waltham, USA). This assay measures the concentration of human galectin-3 levels and its intra- and inter-assay coefficients are 3.2% and 5.6%, respectively, with a lower limit of detection of 1.13 ng/mL [23]. This assay did not show cross-reactivity with other types of collagens, or with other members of the galectin family. Also, there is no interference with commonly used HF medication. The samples at baseline were measured in duplicate and average values were calculated for our analysis. All samples at the two follow-up visits were measured in singular. To correct for years of storage, a linear correction coefficient for the follow-up galectin-3 measurements was applied, for each age category.

2.4. Statistical analyses

Normally distributed variables are expressed as mean ± standard deviation (SD). Non-normally distributed variables are presented as median [interquartile range (IQR)]. In comparison for normal distributed values across two groups, the two-sample t-test was used. Non-normally distributed values were compared using the Wilcoxon rank-sum test. Comparison of categorical values was performed using the Pearson's chi-squared test. Baseline characteristics across four groups were compared using the ANOVA for continuous, normally distributed values, the Kruskal–Wallis test for continuous, non-normally distributed variables and chi-square test for categorical variables. In an exploratory analysis, the FDA-cleared cut point for galectin-3 of 17.8 ng/mL was used to categorize subjects into high or low level, and increasing (one of the follow-up time points >17.8 ng/mL) or decreasing (one of the follow-up time points <17.8 ng/mL) over time to be able to study differences in baseline variables for these groups. The PREVEND study was designed to overselect subjects with increased UAE (>10 mg/L). Therefore a design-based statistical weighting method was used (pweight) to adjust for this overselection and allowing conclusions to be extended for the general population, as described previously [21]. Measurements of galectin-3 were log-transformed to make them more closely related to a normal distribution. A univariable mixed-effects regression analysis was conducted to screen individual variables for its association with galectin-3. The main effects and the interactions with time were tested using a chi square test and these tests were adjusted for sex and age. We selected variables with $p < 0.05$ for the multivariable analysis. Multivariable mixed-effect regression with a stepwise selection procedure was performed in order to obtain the best-fitted model to estimate galectin-3 levels (over time). Margins of the model were calculated for each determinant in order to obtain the predicted probabilities and were plotted in a marginsplot. Analyses were performed with STATA/MP 13.1 (StataCorp LP, College station, TX, USA).

3. Results

3.1. Study population and baseline characteristics

In total, 4355 subjects had galectin-3 plasma levels available at all time points and baseline characteristics of these subjects are presented in Table 1/Supplemental Table 1. At baseline, mean age (±SD) was 48 ± 11 years, 34% of the participants smoked, mean systolic blood pressure was 127 ± 19 mmHg, mean diastolic blood pressure was 73 ± 10 mmHg, median BMI 25.3 [23.0–27.9] kg m^{-2}, median total cholesterol 5.5 [4.8–6.3] mmol L^{-1}, median glucose 4.7 [4.3–5.1] mmol L^{-1} and median eGFR was 99 [87–108] mL min^{-1}. In the studied population, there was an equal distribution between males and females. Males were slightly older, had more often experienced MI, and more

Table 1
Subject characteristics over time.

Factor	Baseline	4.2-year follow-up	9.3-year follow-up
N[a]	4355	4355	4355
Age (years)	47.9 (11.2)	52.1 (11.2)	57.2 (11.1)
BMI[b] (kg m^{-2})	25.3 [23.0–27.9]	26.0 [23.5–28.7]	25.8 [23.3–28.5]
Systolic blood pressure (mmHg)	124.0 [113.0–137.0]	122.0 [112.0–135.0]	125.0 [114.0–139.0]
Diastolic blood pressure (mmHg)	73.0 [67.0–79.0]	73.0 [67.0–79.0]	74.0 [68.0–80.0]
Heart rate (bpm)	68.0 [62.0–75.0]	67.0 [61.0–74.0]	66.0 [59.0–72.0]
eGFR[c] (mL min^{-1})	98.6 [87.2–108.3]	95.3 [83.8–105.1]	90.7 [78.3–101.0]
Serum creatinine (μmol L^{-1})	82.0 [74.0–91.0]	83.2 [73.9–92.4]	76.0 [66.5–86.0]
Urinary albumin excretion (mg per 24 h)	8.7 [6.1–15.2]	8.4 [6.0–15.0]	9.2 [6.4–16.5]
Total cholesterol (mmol L^{-1})	5.5 [4.8–6.3]	5.3 [4.7–6.1]	5.0 [4.3–5.6]
Glucose (mmol L^{-1})	4.7 [4.3–5.1]	4.8 [4.4–5.3]	5.1 [4.8–5.5]
Galectin-3 (ng/mL)	10.7 [8.9–12.7]	11.3 [8.8–14.0]	11.5 [9.4–14.3]

[a] Number of subjects.
[b] Body Mass Index.
[c] Estimated Glomerular Filtration Rate.

CV risk factors in general, with the exception of hypertension, which was more abundant in females (28.2%), compared to males (26.4%) (Supplemental Table 2).

3.2. Galectin-3 level over time

Galectin-3 plasma level over time increased from 10.7 [8.9–12.7] ng/mL at baseline, to 11.3 [8.8–14.0] after ~4 years and 11.5 [9.4–14.3] after ~9 years (Table 1). Subjects were further categorized based on galectin-3 levels using the FDA-cleared cut point of 17.8 ng/mL (Supplemental Table 3). The vast majority of the study subjects (89%) remained below this cut point during the whole study. Subjects with increasing galectin-3 levels over the established galectin-3 cut point of 17.8 ng/mL (7%) were older, were less likely to smoke, had lower BMI, lower eGFR, higher NT-proBNP and had more cardiovascular risk factors including diabetes mellitus, hypertension, hypercholesterolemia and/or stroke. There were very few subjects with elevated galectin-3 levels at baseline (2%).

3.3. Covariates over time

Last follow-up visit was at (median of) 9.3 years after baseline visit. During these follow-up visits, BMI and blood pressure remained relatively stable, eGFR decreased from 99 [87–108] to 91 [78–101] mL min^{-1}. Furthermore, total cholesterol decreased over time, and glucose levels were increasing during this time period (Table 1).

3.4. Univariable determinants of galectin-3 level

Mixed-effects regression analysis was used to identify potential determinants of galectin-3 level and herein was adjusted for age and sex, as known confounders for galectin-3 level (Table 2). Using the mixed-effects regression analysis we were able to assess determinants of temporal changes in galectin-3 level, as well as determinants of elevated levels at baseline. At baseline, systolic blood pressure, diastolic blood pressure, UAE, CRP and NT-proBNP significantly predicted temporal changes of galectin-3. Furthermore, BMI, systolic blood pressure, diastolic blood pressure, eGFR, gender, serum creatinine, UAE, triglycerides, cholesterol, LDL, HDL, CRP and NT-proBNP were all determinants of elevated galectin-3 level.

3.5. Independent determinants of galectin-3 level and temporal change of galectin-3

Significant determinants of (temporal change in) galectin-3 level were included in the multivariable mixed-effects regression analysis (Table 3). We used a stepwise elimination approach to establish the best-fitting model. We established that eGFR <90 mL min^{-1}, BMI >25 kg m^{-2}, total cholesterol >5.0 mmol L^{-1}, NT-proBNP >100 pg mL^{-1} and gender were determinants of elevated galectin-3 level cross-sectionally, but they did not predict changes over time

Table 2
Mixed-effects regression of various risk factors and log galectin-3 (over time) during 9.3 years of follow-up, adjusted for age and sex.

Variable		Adjusted for age and sex	
		χ^2	p-Value
Smoking	Smoking	0.53	0.47
	Smoking # time	0.58	0.75
Diabetes mellitus	Diabetes mellitus	2.95	0.09
	Diabetes mellitus # time	3.55	0.17
Myocardial infarction	Myocardial infarction	0.01	0.91
	Myocardial infarction # time	0.50	0.78
Stroke	Stroke	2.22	0.14
	Stroke # time	0.84	0.66
BMI[a]	BMI	19.68	0.0001
	BMI # time	5.18	0.27
Heart rate	Heart rate	3.06	0.22
	Heart rate # time	3.97	0.41
Systolic blood pressure	Systolic BP	7.99	0.02
	Systolic BP # time	16.81	0.002
Diastolic blood pressure	Diastolic BP	10.31	0.006
	Diastolic BP # time	13.54	0.009
eGFR[b]	Renal failure	210.27	<0.0001
	Renal failure # time	4.89	0.30
Serum creatinine	Serum creatinine	49.91	<0.0001
	Serum creatinine # time	6.65	0.16
UAE[c]	UAE	19.91	<0.0001
	UAE # time	34.03	<0.0001
Glucose	Glucose	4.59	0.10
	Glucose # time	3.13	0.54
Triglycerides	Triglycerides	16.13	0.0003
	Triglycerides # time	6.66	0.16
Cholesterol	Cholesterol	8.63	0.01
	Cholesterol # time	4.4	0.35
LDL[d]	LDL	13.24	0.001
	LDL # time	5.95	0.20
HDL[e]	HDL	6.72	0.03
	HDL # time	6.98	0.14
CRP[f]	CRP	7.9	0.02
	CRP # time	12.8	0.01
NT-proBNP[g]	NT-proBNP	18.76	0.0001
	NT-proBNP # time	11.51	0.02

[a] Body Mass Index.
[b] Estimated Glomerular Filtration Rate.
[c] Urinary albumin excretion.
[d] Low-density lipoprotein.
[e] High-density lipoprotein.
[f] C-reactive protein.
[g] N-terminal pro-B-type natriuretic peptide.

Table 3
Multivariable mixed-effects regression analysis of significant risk factors and log galectin-3 (over time) during 9.3 years of follow-up.

Variable	Coefficient	[95% CI]	p-Value
eGFR[a]	0.15	[0.13–0.16]	< 0.001
Gender	0.05	[0.03–0.06]	<0.001
NT-proBNP[b]	0.04	[0.02–0.06]	< 0.001
BMI[c]	0.03	[0.01–0.04]	< 0.001
Total cholesterol	0.03	[0.02–0.04]	< 0.001
Urinary albumin excretion # time			
<30 – 4.2 year	0.08	[0.01–0.14]	0.03
<30 – 9.3 year	0.19	[0.12–0.26]	<0.001
30–300 – baseline	0.01	[−0.02–0.04]	0.58
30–300 – 4.2 year	0.03	[−0.04–0.10]	0.46
30–300 – 9.3 year	0.26	[0.19–0.33]	<0.001
>300 – baseline	0.05	[−0.03–0.13]	0.20
>300 – 4.2 year	0.14	[0.03–0.25]	0.01
>300 – 9.3 year	0.28	[0.18–0.39]	<0.001
Systolic blood pressure # time			
<140 – 4.2 year	−0.05	[−0.11–0.02]	0.12
<140 – 9.3 year	−0.13	[−0.19–0.05]	<0.001
140–170 – baseline	0.01	[−0.03–0.02]	0.57
140–170 – 4.2 year	−0.03	[−0.10–0.04]	0.40
140–170 – 9.3 year	−0.10	[−0.18–0.03]	0.01
>170 – baseline	−0.03	[−0.10–0.03]	0.36
>170 – 4.2 year	0	(Omitted)	
>170 – 9.3 year	0	(Omitted)	

[a] Estimated Glomerular Filtration Rate.
[b] N-terminal pro-B-type natriuretic peptide.
[c] Body Mass Index.

(Fig. 2; Supplemental Fig. 1). Our analyses identified that urinary albumin excretion > 30 mg/24 h and systolic blood pressure > 170 mmHg were important determinants of dynamic galectin-3 levels (Fig. 1).

4. Discussion

In this unique, large, community-based cohort with repeated measurements of galectin-3, we report for the first time several determinants of temporal changes of galectin-3. We herein demonstrate that several determinants, especially systolic blood pressure and urinary albumin excretion show interaction with time, and further increments in systolic blood pressure and urinary albumin excretion were associated with incremental changes in galectin-3 over time. This suggests that such factors, when left untreated, are associated with progressive production of galectin-3, which may signify maladaptive structural changes in tissues, including fibrosis. We furthermore show that several factors (eGFR, gender, BMI, cholesterol, and NT-proBNP) that have been linked to elevated galectin-3 levels are associated with elevations at baseline, but also several years later.

Biomarkers could serve as early warning signs that hint towards disease before any clinical manifestation of this disease is present. These biomarkers represent a pathophysiological mechanism that can be triggered by various factors. Galectin-3 is a relatively new prognostic biomarker for HF patients, which is not dependent of cardiac loading conditions [24,25]. In the heart, galectin-3 is primarily involved in immunology and fibrosis. Following cardiac injury, macrophages will release galectin-3, in order to activate quiescent fibroblasts into active matrix-secreting myofibroblasts and to stimulate migration and infiltration of macrophages [5]. We showed before that higher levels of galectin-3 are associated with increased risk for all-cause mortality and new-onset heart failure in the general population [7,14]. This observation has been confirmed by several independent studies [8,9,26]. Therefore, efforts have been made to further elucidate the exact role of galectin-3 in the heart and to establish determinants of human plasma levels.

In this study, we now identify, for the first time, factors that predict increasing galectin-3 levels over time. Using our unique long-term longitudinal study design we have used mixed-effects regression analysis to define predictors of temporal changes of galectin-3 during a ~9-year follow-up. Our results indicate that a (very) high systolic blood pressure (>170 mmHg) is a predictor of increasing galectin-3 level. Moreover, a (modest) urinary albumin excretion (>30 mg/24 h) also results in increasing galectin-3.

Systolic blood pressure and galectin-3 levels have also been linked previously in preclinical studies. In a sensitivity analysis in rats with aldosterone-induced vascular fibrosis was shown that systolic blood pressure was the parameter that was most strongly associated with increased galectin-3 and collagen expression [27]. Furthermore it was observed that patients with LV hypertrophy, which is frequently found in hypertensive patients, had higher levels of galectin-3 [28], also suggesting an association between hypertension and galectin-3 levels.

Thus far, studies have shown that age, gender, renal function and NT-proBNP are established determinants of galectin-3 level [7,29–31]. The current data validate these factors as determinants of galectin-3 level at a given time point, and furthermore identify BMI and total cholesterol level as cross sectional determinants of galectin-3 level. We show that a mild impairment of renal function (eGFR: 60–90) results in a significantly elevated level of galectin-3 and that severe impairment of renal function (eGFR < 60) is accompanied with a substantial elevation of galectin-3 level.

Renal function and galectin-3 are closely related to each other [7,32]. It has been shown that galectin-3 levels increased in parallel with progressive renal impairment and that galectin-3 is particularly

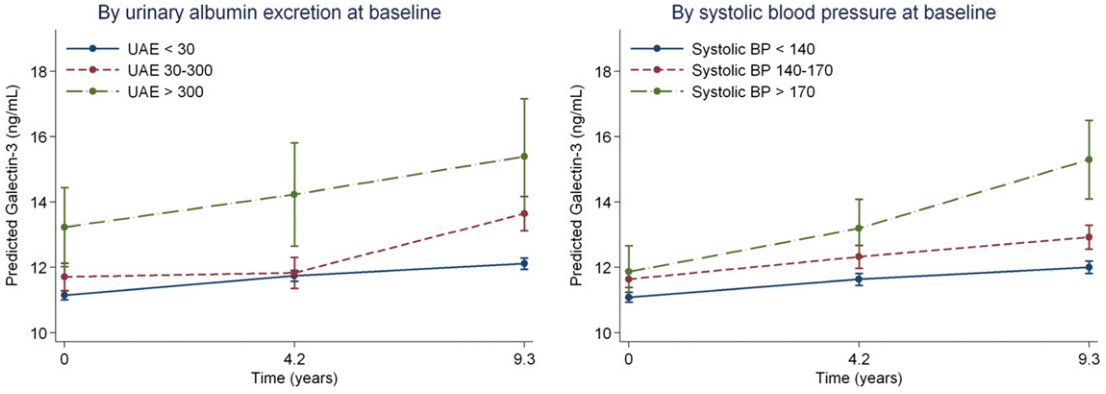

Fig. 1. Determinants of temporal changes of galectin-3. This figure displays that micro-albuminuria at baseline is associated with a mild elevation of galectin-3 levels over time. In subjects with macro-albuminuria, galectin-3 is already elevated and further increases over time. Furthermore, severe hypertension at baseline (>170 mmHg), identifies subjects who develop high galectin-3 levels over time.

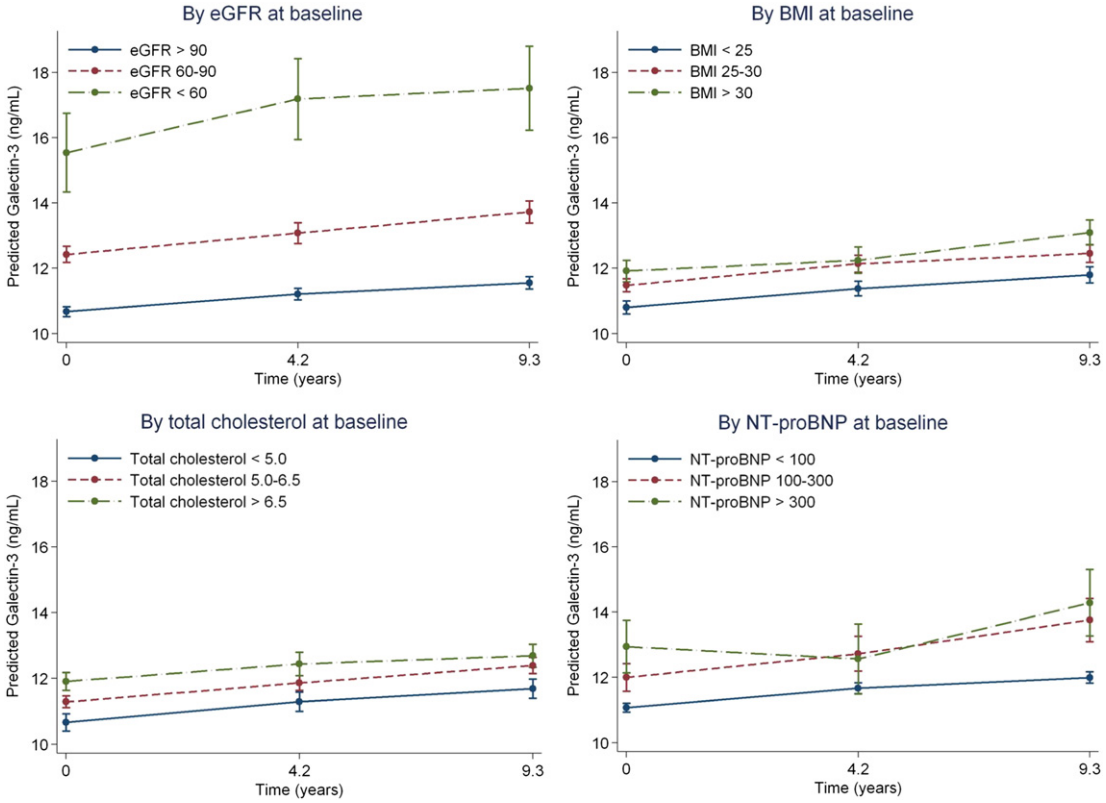

Fig. 2. Determinants of galectin-3 level, stratified by pre-specified cut points. This figure displays that impaired renal function is the major determinant of (already) elevated galectin-3 level, but not for progressive increase.

associated with outcome in patients with impaired renal function, and to a lesser extent in subjects with normal kidney function [29]. Possibly, galectin-3 is cleared by the kidney and therefore impaired renal filtration results in elevated levels, mainly because fractional galectin-3 clearance is reduced [33]. Our study cannot be conclusive in what develops first: renal dysfunction or elevated eGFR. However we observe that galectin-3 levels are already elevated with reduced eGFR. Furthermore, data from the Framingham cohort suggest that elevated levels of plasma galectin-3 precede the development of de novo chronic kidney disease [34].

Obesity and systolic blood pressure are also closely related — obese patients show higher blood pressure and therefore could experience higher galectin-3 levels [35]. However, in our analysis, BMI remained an independent predictor of galectin-3 level suggesting there might be an additional pathway. Previous work suggested that systemic galectin-3 is elevated in obesity, possibly via the increased contribution of visceral fat leading to activation of systemic inflammation [36]. Determinants of increasing NT-proBNP levels have also been established previously, which include incident myocardial infarction, new beta-blocker medication and increased cardiac parameters, indicating that galectin-3 and NT-proBNP levels represent different pathophysiological pathways.

Our findings are supportive of the assumption that an unhealthy lifestyle is associated with elevated galectin-3 levels. Specifically, we found that common risk factors in cardiovascular disease, like blood pressure, renal function, blood pressure, gender, obesity, cholesterol and NT-proBNP are important in predicting galectin-3 level. As most important driving force, systolic blood pressure and renal function were identified, which may be regarded as two signs from a common disease. Based on the findings in our studies we speculate that treatment of high blood pressure could be beneficial in the prevention of increasing galectin-3 levels. However, further prospective studies are needed to elucidate whether modification of these risk factors, possibly guided by galectin-3 increases, is more effective than current CV risk management.

4.1. Study limitations

The strength of this study is the large, community-based cohort with almost 10-year follow-up and galectin-3 measurements at three time points. This large sample size allows us to draw adequate conclusions. Intrinsic to studying biomarker changes over time, survival bias can be present. Because changes in galectin-3 level over time were studied, patients with missing galectin-3 values were excluded, including patients that died during follow-up. Finally, this was a post hoc analysis of observational data, so there might be a risk for residual confounding.

5. Conclusions

In the general population, baseline systolic blood pressure >170 mmHg and urinary albumin excretion >30 mg L^{-1} were identified as important predictors for increasing galectin-3 levels over a period of ~9 years. Furthermore, we validate baseline eGFR <60 mL min^{-1} as a strong determinant and BMI, total cholesterol and NT-proBNP as moderate determinants of cross sectional galectin-3 level. We speculate that treatment of high blood pressure can prevent increasing galectin-3 levels, but further prospective studies are needed to determine whether modifying these factors would prevent increasing galectin-3 levels, and its associated diseases.

Potential conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2016.07.241.

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