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Plasma Galectin 3 and heart failure risk in the Physicians' Health Study

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Introduction

The increase in life expectancy associated with biomedical research and improved living conditions have made older adults a large segment of the US population. Heart failure (HF) is a major comorbidity in older adults and is associated with high healthcare expenditure issue^{1–3}. Despite advances in modern medicine, over 50% of people diagnosed with HF will die within five years of the initial diagnosis^{4–6}, thereby making it imperative to improve primary prevention. Previous studies have demonstrated the importance of cardiac remodeling (including extra cellular matrix remodeling, apoptosis, and fibrosis) in the development of HF^{7–9} after myocardial infarction or due to other diseases. Consequently, recent studies have focused on biomarkers of cardiac remodeling.

Galectin 3 (Gal-3) is a beta-galactoside-binding lectin produced by macrophages and plays a role in tumor growth, inflammation, and fibrosis^{10–12}. Blood Gal-3 concentration has been shown to be elevated in patients with HF and was associated with mortality^{13,14} and adverse outcomes^{11,15–19}. In contrast, other studies found that Gal-3 was not a predictor of total and cardiovascular mortality after adjustment for N-terminal pro-brain natriuretic peptide^{20,21}. While the Framingham Heart Study reported a positive association between Gal-3 and incident HF²², such findings have not been confirmed in other cohorts. As a marker of fibrosis, plasma levels of Gal-3 may be elevated in the presence of hypertension and may play a causal role in the development of HF of non-ischemic etiology. It is unclear whether Gal-3 is causally related to the incidence of HF. Hence, the current project sought to address

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this gap by examining the association between Gal-3 and incident HF among male physicians. We hypothesized that Gal-3 will be positively associated with the risk of HF and such relation would be stronger for HF without antecedent coronary heart disease.

Methods

Study population

We utilized a prospective nested-case control study design for this ancillary study of the Physicians' Health Study (PHS). PHS is a completed randomized trial of the efficacy of low-dose aspirin and beta-carotene for the primary prevention of cardiovascular disease and cancer.²³ For each incident case of HF, we used a risk set technique to randomly select one control among participants who were alive and free of HF at the time of diagnosis of the index HF case. Each control was matched to the index case on age at randomization (within 1 year for >95% of controls), race (white vs. non-white), year of birth (within 2 years), and time of blood collection (within 288 days). We measured Gal-3 on blood samples collected at baseline (1982–83) on 462 pairs. Each participant signed an informed consent and the Institutional review Board at Brigham and Women's Hospital approved the study protocol.

Measurement of plasma galectin 3

Human Gal-3 was measured in plasma using a quantitative enzyme-linked immunosorbent assay (ELISA) from R&D Systems (Minneapolis, MN). Standards, samples, and controls are added to a 96-well microplate pre-coated with monoclonal antibody specific for Gal-3. Gal-3 present in the sample is bound by the immobilized antibody and after unbound substances were removed through washing, an enzyme-linked polyclonal antibody specific for Gal-3 was added. Following another wash to remove unbound antibody-enzyme reagent, a tetramethylbenzidine substrate solution was added to the wells and color develops in proportion to the amount of Gal-3 bound in the initial step. The color development is stopped with sulfuric acid and the intensity of the color is measured using a spectrophotometer (SpectraMax 250, Beckman Coulter) at 450nm. The laboratory inter-assay CV is 6.9%.

Ascertainment of incident HF in the Physicians' Health Study

HF was initially ascertained in this cohort via annual follow-up questionnaires. However, we have previously validated self-reported HF diagnosis in the PHS using the Framingham criteria²⁴ on supplemental questionnaires in a subsample as well as via chart review on limited number of HF²⁵. Overall positive predictive value of self-reported HF was 90% in that subsample.

Other variables

Self-reported baseline weight (kg) was divided by height (meter squared) to compute body mass index. At baseline, each subject provided information on lifestyle factors including exercise [how often do you exercise vigorously enough to work up sweat? Possible answers included rarely/never, 1–3/month, 1/week, 2–4/week, 5–6/week, and daily]; smoking (never, former, and current smoker); and alcohol intake (rarely/never, 1–3 per month, 1 per week, 2–4/week, 5–6/week, daily, and 2+/day). Information on comorbidity including

hypertension, treatment for hypertension, atrial fibrillation, hyperlipidemia, and diabetes was collected through annual follow-up questionnaires. High-sensitive C-reactive protein (hsCRP) was measured using a latex-particle enhanced immunoturbidimetric assay kit (Roche Diagnostics, Indianapolis, IN 46250). The inter-assay CV was 4.5%.

Statistical analyses

We assessed the distribution of Gal-3 in the control series for normal distribution. Given the non-Gaussian distribution of Gal-3, we used log-transformed Gal-3 for analyses. We created quartiles of log-Gal-3 using its distribution in the control series. Continuous and categorical variables were compared between cases and controls using t-test and Chi-square, respectively. We fitted a conditional logistic regression to estimate relative risks of HF across Gal-3 quartiles using sequential models derived using a priori knowledge on confounders. The first model controlled for atrial fibrillation, body mass index, and diabetes; and a second model adjusted for variables in model one plus hypertension and logarithmic transformed high-sensitive C-reactive protein. The final model also controlled for smoking (never, former, current smokers), vigorous physical activity (at least weekly vs. less frequent), and alcohol consumption (rarely/never, <1, 1–6, and 7+ drinks per week). In a subgroup analysis, we repeated above analyses for HF with and without antecedent coronary heart disease (myocardial infarction, coronary angioplasty or revascularization). Alpha level was set at 0.05 and all tests were two-sided using SAS 9.2 for all analyses. To explore the shape of the association, we fitted restricted cubic splines with four knots at the 10th, 36.7th, 63.4th, and 90th, using the 12.5th percentile of Gal-3 as the reference in STATA/MP12. Test for linearity using likelihood ratio test yielded a p value of 0.039 suggesting that a non-linear curve was the best fit for the data. Hence, main results were presented by quartiles of Gal-3.

Results

Of the 462 cases and 462 matched controls, the average age was 58.3±8.1 years at baseline. For cases, the mean age at diagnosis of HF was 75.6 (SD=8.6) years. Median (IQR) log-Gal-3 was slightly higher in cases [1.55 (1.24–1.78) ng/ml] than in controls [1.47 (1.16–1.68) ng/ml] (p=0.06). Characteristics of HF cases and matched controls are shown in Table 1. The highest quartile of log-Gal-3 was associated with a 57% higher risk of HF in a multivariable adjusted model compared with the lowest quartile [OR=1.57 (95% CI: 1.03–2.39), Table 2]. Additional adjustment for interim CHD attenuated the relation of log-Gal-3 with HF [OR: 1.0 (ref), 0.85 (0.54–1.36), 1.08 (0.68–1.70), and 1.51 (0.96–2.36) across consecutive quartiles of log-Gal-3]. Using cubic splines to fit the data, we observed evidence for a positive non-linear relation (p=0.039) of Gal-3 with HF (Fig. 1). In a secondary analysis, we did not observe a difference between HF with and without antecedent CHD: compared to the lowest quartile of Gal-3, odds ratio (95% CI) in the highest quartile was 1.99 (0.92–4.33) for HF with antecedent CHD and 1.63 (0.98–2.69) for HF without antecedent CHD in a conditional regression model adjusting for atrial fibrillation, BMI, diabetes, hypertension, and hsCRP. There was no interaction between CHD and Gal-3 (p=0.39). Plasma Gal-3 was positively correlated with hsCRP (r= 0.23, p<0.0001) and only weakly correlated with age (r=0.10, p =0.04).

Discussion

In this nested case-control study, we demonstrated that higher plasma Gal-3 was associated with a higher risk of HF in male physicians after adjustment for potential confounding factors. In addition, such association was observed for HF with and without antecedent CHD and was attenuated upon additional adjustment for interim CHD. Our findings are consistent with data from the Framingham Heart Study that first demonstrated a 28% higher risk of HF per standard deviation of log-transformed Gal3²². Evidence for a non-linear relation (via splines) in our data precluded estimation of odds ratio per standard deviation for further comparison. Furthermore, our results of no differential relation for HF with and without antecedent CHD are consistent with Framingham data which reported no difference in plasma Gal 3 between participants who developed HF with preserved and those who developed HF with reduced ejection fraction ($p=0.54$)²². Of note is that the Framingham Study²² and the PREVENT study¹³ reported a 14% and 9% higher risk of total mortality, respectively, per standard deviation of log-transformed Gal 3 in multivariable models. Due to the nested case-control design of our study and limited sample size in the control series, we were unable to assess the relation of Gal-3 with mortality in the current study.

Which potential biologic pathways could favor a causal relation between Gal-3 and incident HF? First, a lack of a meaningful correlation between Gal-3 and natriuretic peptide (a marker of hemodynamic strain) suggests that Gal-3 could serve as an early marker of pathologic processes leading to HF at a later time²⁶. Second, attenuation of the results upon additional adjustment for interim CHD suggests that Gal-3 may influence the risk of HF via CHD. Third, Gal-3 expression is associated with proliferation of cardiac fibroblast, generation of collagen, and left ventricular dysfunction^{11,27}. Gal-3 deficient mice are protected against the development of hepatic and renal fibrosis²⁸. In animal models, intrapericardial infusion of Gal-3 led to cardiac dysfunction¹⁰. We lacked data on echocardiogram or left ventricular hemodynamic to further examine physiologic correlates of Gal-3 in the current study.

Additional limitations of our study include a single measurement of plasma Gal-3 with 20+ years of follow up. We could not account for change of plasma Gal-3 concentration over time. We had limited statistical power to detect small effects or evaluate effect modification by age, body mass, etc. Since all our participants were whites, we cannot generalize our findings to other ethnic groups and gender. However, since our data are consistent with the reports from the Framingham Study, this may not be a major concern. This study is limited by the lack of echocardiographic evaluation or left ventricular hemodynamic studies to further examine physiologic correlates of Gal-3. Furthermore, we did not have information on brain natriuretic peptide or echocardiography on PHS participants. Hence, it is possible that we may have missed mild HF cases or erroneously classified other conditions (i.e., lung disease) as HF. However, since blood collection to measure Gal-3 occurred at baseline prior to HF diagnosis, above misclassification is more likely to be non-differential and would have biased the results towards no association. Given the case-control design, we cannot eliminate survival bias introduced by early death of subjects with elevated Gal-3 prior to the development of HF. Lastly, we did not have data on creatinine, cystatin C, or other measures of kidney function for further adjustment. On the other hand, the focus on a novel biomarker

of myocardial fibrosis, relatively large sample size, use of matched risk set to minimize confounding, and good validation of self-reported HF are major strengths of this study. Future studies are needed to evaluate Gal-3 in context with other novel biomarkers associated with cardiac remodeling and strain and evaluate whether Gal-3 is causally related to HF development and assess the incremental value of Gal-3 among prevailing HF biomarkers.

In conclusion, our data showed a higher risk of HF in the highest quartile of plasma Gal-3 in apparently healthy male subjects. Such association was apparent for HF with and without antecedent CAD.

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Figure 1.

Cubic splines showing association of galectin 3 with HF in the Physicians' Health Study. Solid dark line represents the odds ratio and dotted lines represent 95% confidence intervals. The top and bottom 1% of study participants were excluded to obtain stable estimates. The 12.5th percentile was used as the reference and we fitted restricted cubic splines with four knots at the 10th, 36.7th, 63.4th, and 90th percentile in a conditional logistic regression model adjusted for body mass index, atrial fibrillation, diabetes, hsCRP, and blood pressure. P for linear association = 0.039.

Table 1

Baseline characteristics of the 924 participants in the Physicians' Health Study

Characteristics	Cases	Controls	P value
N	462	462	
Age at baseline (y)	58.2 ± 8.1	58.2 ± 8.1	1.00
BMI (kg/m ²)	25.7 ± 3.2	24.6 ± 2.3	<0.0001
Smoking status			0.04
Never	40.7	47.6	
Past	46.3	42.9	
Current	13.0	9.1	
Alcohol consumption			0.34
Rarely/Never	15.8	15.6	
1–3x/month	12.6	8.9	
1–6x/week	44.8	45.0	
1 or more/day	26.4	30.3	
Atrial fibrillation	5.4	2.4	0.02
Exercise	71.7	73.6	0.53
Diabetes	6.9	3.5	0.02
Hypertension	37.5	23.6	<0.0001
hsCRP (mg/L)	2.7 ± 4.6	2.2 ± 4.7	0.10

* Data are presented as means±SD or percentages

Table 2

Odds ratio (95% CI) for heart failure by quartile of log-galectin 3

Quartiles of log Galectin 3 Median (range)	Cases	Odds ratio (95% CI)		
		Model 1 [*]	Model 2 [†]	Model 3 [‡]
0.88 (−0.72, 1.16) Low	94	1.00	1.00	1.00
1.34 (1.16, 1.46)	94	0.92 (0.61–1.39)	0.91 (0.60–1.39)	0.89 (0.58–1.38)
1.57 (1.47, 1.68)	117	1.19 (0.78–1.80)	1.15 (0.76–1.76)	1.08 (0.71–1.67)
1.85 (1.68, 2.79) High	157	1.60 (1.07–2.40)	1.63 (1.08–2.46)	1.57 (1.03–2.39)

^{*} Model 1 adjusted for atrial fibrillation, BMI, and diabetes

[†] Model 2 adjusted for atrial fibrillation, BMI, diabetes, hypertension, and log(hsCRP)

[‡] Model 3 adjusted for atrial fibrillation, BMI, diabetes, hypertension, log(hsCRP), alcohol, exercise, and smoking