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Original Article

Galectin-3 and the incidence of abdominal aortic aneurysm: the atherosclerosis risk in communities (ARIC) study

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Abstract: Galectin-3, a β-galactosidase binding lectin, known to be involved in inflammatory processes may be associated with abdominal aortic aneurysm (AAA) incidence. We examined the prospective association between plasma galectin-3 and incident AAA in 9,704 participants of the Atherosclerosis Risk in Communities (ARIC) study cohort. We followed participants from 1996-1998 through 2011 (124,260 person-years) for incident AAA (n=325) defined by ICD codes from hospital records and death certificates. At baseline, participants had a mean (SD) age of 62.8 (5.7) years; 20.9% were blacks and 56.5% females. The median (25^{th}-75^{th} percentile) galectin-3 level was 14.2 (12.0-16.9) ng/mL. Galectin-3 was correlated positively with most cardiovascular risk factors and with several cardiac or inflammatory biomarkers (C-reactive protein, troponin-T, and NT-proBNP). Using Cox proportional hazards regression adjusted for demographic variables and measured AAA risk factors, the hazard ratios for AAA across galectin-3 quintiles were 1 (Referent), 1.54 (1.05-2.26), 1.58 (1.05-2.41), 1.76 (1.15-2.72), and 1.92 (1.22-3.01) (p for trend =0.01). Further adjustment for the cardiac and inflammatory biomarkers largely attenuated the association between galectin-3 and AAA [AAA hazard ratio for galectin-3 $_{\text{Quintile 5}}$ vs. $_{\text{Quintile 1}}$: 1.29 (0.81-2.05); p-trend across quintiles =0.44]. In conclusion, higher concentrations of plasma galectin-3 were associated with greater incidence of AAA though not independent of other cardiac and inflammatory biomarkers. This reinforces that galectin-3, a systemic biomarker reflecting inflammation and probably increased systemic vascular resistance, is elevated early in the pathogenesis of AAA.

Keywords: Abdominal aortic aneurysm, biomarker, epidemiology, galectin-3, inflammation

Introduction

The subtle onset and asymptomatic nature of abdominal aortic aneurysm (AAA) sometimes leads to its late detection and potentially devastating outcomes [1, 2]. In order to reduce the adverse outcomes and mortality associated with undetected AAA, the U.S. Preventive Services Task Force recommends that men who have ever smoked be screened for AAA between the ages of 65-75 years [3, 4]. Despite this and the identification of well-established AAA risk factors such as age, male sex, white race, smoking, family history, and hypertension, AAA remains a public health concern. Although there has been a decline in age-standardized mortality rates in the US [5], the number of deaths attributed to AAAs continues to rise due to population aging and growth [5, 6].

Inflammation plays an important role in the pathogenesis of AAA. First, infiltration of the wall of the aorta by inflammatory cells resulting in degradation of elastin and collagen in the tunica media. Second, smooth muscle cell apoptosis can lead to thinning of the media with the subsequent aneurysmal dilation of the aorta [1]. The identification of pharmacologically modifiable biomarkers or predictors of this pathological pathway may offer avenues to reduce the burden of AAA.

Galectin-3, a beta-galactosidase binding lectin, is expressed and secreted by a number of

inflammatory cells such as activated macrophages, monocytes, mast cells, and eosinophils [7-10]. Galectin-3 has been shown to play regulatory roles in chemotaxis and inflammation [7, 11, 12]. In mouse models, macrophage infiltration of the abdominal aorta was found to be a prominent feature of AAA progression [13]. Currently, the role of anti-inflammatory agents such as cyclosporine A in AAA progression is being explored in clinical trials (NCT02225756) though another has been stopped due to lack of efficacy (NCT02007252). While the association between galectin-3 and other cardiovascular diseases such as coronary heart disease, heart failure, and atrial fibrillation have been explored [14-17], there remains little to no information on the association between galectin-3 and AAA. Therefore, we investigated the association between galectin-3 and AAA in a prospective population-based cohort, while accounting for major AAA risk factors and other biomarkers found to be associated with AAA in this cohort [18].

Methods

Study population

The Atherosclerosis Risk in Communities (ARIC) study is a population based cohort comprising 45-64 year old predominantly black or white men and women (n=15,792) recruited between 1987 and 1989 from Washington County, MD; the northwestern suburbs of Minneapolis, MN; Jackson, MS (blacks only); and Forsyth County, NC [19]. Participants have been reexamined 5 times since study onset and are also being followed by annual or semiannual telephone interviews and active surveillance of ARIC community hospitals. ARIC was approved by the institutional review board of each participating center, and all participants provided written informed consent. We used visit 4 (1996-1998) as the baseline visit for this analysis, since galectin-3 was measured using stored specimens from this visit. Participants were followed for AAAs through December 31, 2011.

Among 11,656 study participants present at the 1996-1998 visit, we excluded those with a prior history of AAA (n=66), prior AAA surgery at visit 1 (n=2), and those whose follow-up AAA status was uncertain (n=13). This left a total of 11,575 at risk of incident AAA. We further excluded those who were not white or black (n=30) due to small numbers, who were missing galectin-3 measurements (n=927), or who were missing covariates (n=914). This left a total of 9,704 study participants for analysis.

AAA ascertainment

The ARIC investigators identified incident AAAs occurring during the study period (1996-2011) through the use of follow-up calls and review of hospital discharges and death certificates. We also identified missing hospitalizations or outpatient events for those > 65 years of age by linking participant identifiers with fee-for-service Medicare data from the Centers for Medicare and Medicaid Services for 1991 to 2011. We identified clinical AAAs as those with a hospital discharge diagnosis from any source or 2 Medicare outpatient claims that occurred at least 1 week apart. ICD-9-CM codes of 441.3, 441.4; procedure code 38.44 or 39.71; or a listed cause of death coded ICD-9 441.3 or 441.4 or ICD-10 codes of I71.3, or I71.4. AAAs based on procedure codes were required to be verified by diagnosis codes [20]. Asymptomatic and symptomatic AAAs were classified as events, while thoracic, thoracoabdominal, or unspecified aortic aneurysms as nonevents.

Galectin-3 and covariate ascertainment

Galectin-3 was measured using a chemiluminescent microparticle immunoassay on an Architect *i* 2000sr instrument (Abbott, Abbott Park, IL) in EDTA-plasma samples that were collected at visit 4 and stored at -70°C prior to analysis. The measurements were performed July 2015-February 2016. The Architect galectin-3 assay has a limit of detection of 1.1 ng/mL and a limit of quantitation of 4.0 ng/mL. Interassay coefficients of variation (CV) were 5.2%, 3.3%, and 2.3% at mean galectin-3 levels of 8.8 ng/mL, 19.2 ng/mL and 72.0 ng/ml, respectively. At the time of blood processing, 402 participants' plasma specimens were split, masked, and sent to the laboratory to assess galectin-3 laboratory reliability. The reliability coefficient was r=0.92 and CV=7.5%. After removing 7 potentially mislabeled "outlier" samples these respective values were r=0.95 and CV=5.7%. The rs4644 single-nucleotide polymorphism (SNP) genotyping was performed using the HumanExome BeadChip Array [21]. This

SNP has been found to be strongly associated with galectin-3 levels and may explain racial differences in plasma levels [22].

All covariates except pack-years of smoking were measured at visit 4 (1996-1998). During visit 1 (1987-1989), participants reported the average number of cigarettes smoked per day. Pack-years of smoking were calculated as the average number of cigarettes smoked per day multiplied by the years of smoking divided by 20 (the number of cigarettes in a standard packet). At visit 4, participants reported demographic information, use of antihypertensive and cholesterol lowering medications within the previous 2 weeks, and smoking status. Blood pressure was measured with the use of a random-zero sphygmomanometer. Two readings were taken after the participant had rested for 5 minutes and these readings were averaged. Height and weight were measured. Diabetes mellitus was defined as fasting glucose ≥126 mg/dL (7.0 mmol/L), nonfasting glucose ≥200 mg/dL (11.1 mmol/L), treatment for diabetes mellitus, or self-reported physician diagnosis of diabetes mellitus. Plasma total cholesterol was measured by enzymatic methods [23] while HDL cholesterol (HDL-C) was measured after dextran-magnesium precipitation of non-HDL lipoproteins. Cardiac troponin T (cTnT) was measured on a Cobas e411 analyzer using the Elecys Troponin T, a high sensitivity assay (Roche Diagnostics, Indianapolis, IN) [24]. The reliability coefficient for blinded replicate measurements of cTnT was 0.98 (n=418 pairs). Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured on a Cobas e411 analyzer using the Elecys proBNP II immunoassay (Roche Diagnostics, Indianapolis, IN) [25]. The reliability coefficient for blinded replicate measurements of NT-proBNP was 0.99 (n=418 pairs). High-sensitivity C-reactive protein (CRP) was measured by the immunoturbidimetric assay using the Siemens (Dade Behring) BNII analyzer (Dade Behring, Deerfield, Ill) [26]. The reliability coefficient for blinded replicate measurements of CRP was 0.99 (n=421 pairs).

Statistical analysis

Baseline characteristics of participants are described by galectin-3 quintiles. Categorical variables are presented as counts and percentages. Normally distributed continuous variables are presented as means and standard deviations (SD). Non-normally distributed variables are presented as medians with their 25th to 75th percentiles. Restricted cubic splines adjusted for age, sex, and race were used to characterize the galectin-3 AAA association. The median value of galectin-3 was used as the referent and knots were placed at the 5th, 27.5th, 50th, 72.5th and 95th percentiles. Multivariable Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and 95% confidence interval (CI) for the association between galectin-3 quintiles and incident AAA using the lowest quintile as the reference group as well as per 1 standard deviation increment in natural log-transformed galectin-3. We ensured that the proportional hazards assumption was not violated by testing the interaction between galectin-3 and log follow-up time in an unadjusted model. We also tested whether the association between galectin-3 quintiles and incident AAA differed by age, sex, or race by modeling interaction terms with galectin-3. Model 1 of our Cox regression was unadjusted. Model 2 was adjusted for demographic variables-age (years), sex (male, female), and race (black, white). Model 3, our main model, additionally adjusted for several AAA risk factors that may be confounding variables-smoking status (current, former, never), pack-years of cigarettes smoked, height (meters), weight (kilograms), systolic blood pressure (mmHg), antihypertensive medication use (yes, no), diabetes mellitus (yes, no), total cholesterol (mg/dL), HDL-C (mg/dL), use of cholesterol lowering medication (yes, no), and rs4644 SNP genotype (AA, AC, CC). A fourth model further adjusted for several biomarkers measured at our baseline visit (1996-1998) that have been found to be associated with AAA in this cohort and may be mediators of the association between galectin-3 and AAA [18]-ln cTnT (ln ng/L), ln NT-proBNP (ln pg/mL), and ln CRP (ln mg/L). These cardiac or inflammatory biomarkers were adjusted for to determine whether the galectin-3 association with AAA was unique, versus a general phenomenon that could be explained by other biomarkers. We tested for linear trends in HRs across galectin-3 quintiles by using the quintile number for each category in the Cox models.

All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC) and STATA, version 12 (Stata, College Station, TX).

Table 1. Baseline characteristics of participants stratified by galectin-3 quintiles, ARIC, 1996-1998

Characteristics*	Galectin-3 Quintiles (ng/mL)				
	Q1 (4.4-11.4)	Q2 (11.5-13.3)	Q3 (13.4-15.1)	Q4 (15.2-17.6)	Q5 (17.7-114.0)
N	1909	1983	1904	1985	1923
Age (years)	61.5 (5.4)	62.1 (5.6)	62.7 (5.6)	63.2 (5.6)	64.5 (5.7)
Sex (% female)	38.5	49.0	56.8	65.0	73.1
Race (% black)	15.9	17.7	20.2	23.6	27.1
Diabetes	13.8	13.9	15.7	17.1	22.1
Height (m)	1.71 (0.09)	1.69 (0.09)	1.68 (0.09)	1.67 (0.09)	1.65 (0.09)
Weight (kg)	81.6 (16.2)	80.8 (17.1)	80.3 (17.2)	81.2 (17.6)	81.7 (18.7)
Systolic BP (mmHg)	125 (18)	126 (19)	127 (19)	128 (19)	130 (20)
Antihypertensive medication	32.7	37.1	38.0	47.3	62.3
Total chol (mg/dL)	196.8 (34.6)	199.2 (35.3)	201.8 (37.3)	201.7 (36.1)	203.5 (38.7)
HDL-C (mg/dL)	48.8 (16.0)	49.9 (16.5)	50.2 (16.5)	50.9 (16.8)	50.2 (16.9)
Chol lowering medication	12.1	13.7	14.5	14.6	17.6
Current smoker	14.2	15.0	14.3	13.8	14.1
Former smoker	47.2	45.0	43.2	42.5	38.3
Pack-years of smoking†,‡	21.0 (9.0-36.0)	22.0 (10.0-35.0)	22.1 (10.5-36.0)	20.5 (8.8-35.0)	24.0 (10.5-38.0)
CRP (mg/L)†	1.6 (0.8-3.6)	2.0 (1.0-4.4)	2.3 (1.1-5.1)	3.0 (1.3-6.1)	4.0 (1.7-8.1)
Troponin T (ng/L)†	5.0 (3.0-7.0)	5.0 (3.0-8.0)	5.0 (3.0-8.0)	5.0 (3.0-8.0)	6.0 (3.0-10.0)
NT-proBNP (pg/mL)†	54.5 (26.5-108.1)	62.9 (30.2-121.0)	66.5 (33.5-123.7)	69.5 (36.2-136.2)	96.6 (47.4-186.3)

BP = blood pressure; Chol = cholesterol; CRP = C-reactive protein; HDL-C = high density lipoprotein cholesterol; NT-proBNP = N-terminal pro-B-type natriuretic peptide. *Values are mean (standard deviation) for continuous variables and percentages for categorical variables unless otherwise specified. †Data are expressed as median (25^{th}-75^{th} percentile). ‡Measured at ARIC visit 1 (1987-1989).

Results

Baseline characteristics

Among the 9,704 study participants, the median (25^{th}-75^{th} percentile) galectin-3 concentration was 14.2 (12.0-16.9) ng/mL. As shown in **Table 1**, higher plasma galectin-3 concentrations were associated with higher mean age, systolic blood pressure, total cholesterol, and HDL-C and shorter height. Participants in the highest quintile of galectin-3 were more likely to be female, black, have diabetes, and be on antihypertensive or cholesterol lowering medications. cTnT, NT-proBNP, and CRP were all significantly and positively correlated with galectin-3 concentrations, with Pearson correlations of 0.35, 0.32, and 0.20 respectively (all $p < 0.0001$). There was no overall association of galectin-3 quintiles with weight, current smoking status, or pack-years of cigarettes smoked.

Galectin-3 and incident AAA

We identified 325 incident cases of AAA during 124,260 person-years of follow-up. The incidence rates per 1,000 person-years increased across galectin-3 quintiles from 1.98 in quintile 1, to 3.13 in quintile 5 (**Table 2**). The association between galectin-3 quintiles and incident AAA did not differ by age ($p_{interaction}$ =0.74), race ($p_{interaction}$ =0.64), or sex ($p_{interaction}$ =0.65). In our minimally adjusted model, which included demographic variables, there was a positive association between galectin-3 and AAA incidence, with hazard ratios (HRs) and 95% confidence intervals (CI) of AAA across galectin-3 quintiles of 1 (referent), 1.46 (1.01-2.09), 1.48 (1.02-2.15), 1.64 (1.13-2.37), and 2.03 (1.39-2.95) respectively (p for trend =0.0004). Similarly, **Figure 1** shows the HR (95% CI) of incident AAA using restricted cubic splines adjusted for demographic variables. In model 3, our main model, the association remained strong and significant after additional adjustment for AAA risk factors and the rs4644 SNP [HR of AAA for galectin-3 $_{Quintile\ 5\ vs.\ Quintile\ 1}$: 1.92 (1.22-3.01); p-trend across quintiles =0.01]. Further adjustment for ln cTnT, ln CRP, and ln NT-proBNP in model 4, eliminated all significant associations [HR of AAA for galectin-3 $_{Quintile\ 5\ vs.\ Quintile\ 1}$: 1.29 (0.81-2.05); p-trend =0.44]. The HRs (95% CI) per 1 SD increment in ln galectin-3 were 1.15 (1.03-1.29), 1.26 (1.12-1.41), 1.23 (1.08-1.41), and 1.06 (0.92-1.21) for models 1-4 respectively. When ln CRP, ln NT-proBNP and ln cTnT were independently added to model 3, all resulted in attenuation of the HRs [HR (95% CI) per 1 SD increment in ln

Table 2. Incidence rates (95% CI) and hazard ratios (HRs) (95% CI) of abdominal aortic aneurysm in relation to galectin-3 quintiles, ARIC, 1996-2011

	Galectin-3 Quintiles (ng/mL)					P for trend	Per 1 SD increment in ln galectin-3
	Q1 (4.4-11.4)	Q2 (11.5-13.3)	Q3 (13.4-15.1)	Q4 (15.2-17.6)	Q5 (17.7-114.0)		
AAA, n	50	71	64	68	72	-	-
Person-years	25201	25913	24798	25359	22990	-	-
Incidence rate*	1.98 (1.50-2.62)	2.74 (2.17-3.46)	2.58 (2.02-3.30)	2.68 (2.11-3.40)	3.13 (2.49-3.95)	-	-
Hazard ratios							
Model 1	1 (Referent)	1.38 (0.96-1.98)	1.30 (0.90-1.89)	1.36 (0.94-1.96)	1.61 (1.12-2.30)	0.03	1.15 (1.03-1.29)
Model 2	1 (Referent)	1.46 (1.01-2.09)	1.48 (1.02-2.15)	1.64 (1.13-2.37)	2.03 (1.39-2.95)	0.0004	1.26 (1.12-1.41)
Model 3	1 (Referent)	1.54 (1.05-2.26)	1.58 (1.05-2.41)	1.76 (1.15-2.72)	1.92 (1.22-3.01)	0.01	1.23 (1.08-1.41)
Model 4	1 (Referent)	1.37 (0.94-2.00)	1.30 (0.85-1.96)	1.40 (0.90-2.16)	1.29 (0.81-2.05)	0.44	1.06 (0.92-1.21)

AAA = abdominal aortic aneurysm. SD ln galectin-3=0.27 (ln ng/mL). *Incidence rate is unadjusted and per 1000 person-years. Model 1: unadjusted model. Model 2: adjusted for age (continuous), sex (female, male), and race (white, black). Model 3: Model 1 plus smoking status (current, former, never), pack-years of cigarettes smoked (continuous, from 1987-1989), height (continuous), weight (continuous), systolic blood pressure (continuous), antihypertensive medication use (yes, no), diabetes mellitus (yes, no), total cholesterol (continuous), HDL-C (continuous), use of cholesterol lowering medication (yes, no), and rs4644 SNP genotype (AA, AC, CC). Model 4: Model 2 plus ln cTnT (ln ng/L), ln NT-proBNP (ln pg/mL), and ln CRP (ln mg/L).

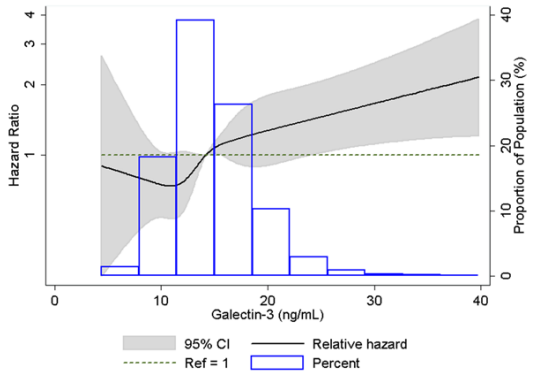

Figure 1. Restricted cubic spline showing the association of galectin-3 with abdominal aortic aneurysm incidence in ARIC 1996-2011. High extreme values of galectin-3 (> 40 ng/ml) were excluded (n=21) from the spline analysis to enhance interpretability of estimates. The median value (14.2 ng/ml) was used as reference in a Cox proportional hazards model adjusted for age, sex, and race. The knots were placed at the 5th, 27.5th, 50th, 72.5th and 95th percentile.

galectin-3: ln cTnT-1.16 (1.01-1.32); ln CRP-1.18 (1.03-1.36); ln NT-proBNP-1.14 (0.99-1.30)].

Discussion

In this large population-based cohort, we found plasma galectin-3 concentrations to be associated positively and moderately strongly with the incidence of AAA. This association did not vary by age, race, or sex and was independent of demographic characteristics and several AAA risk factors. The association was not independent of other measured cardiac and inflammatory biomarkers.

A role of inflammation in the pathogenesis of AAA is well established [1]. Infiltration of the wall of the aorta by inflammatory cells contributes to the degradation of elastin and collagen in the tunica media leading to the thinning of the media with the subsequent aneurysmal dilation of the aorta [1]. In mouse models, macrophage infiltration of the abdominal aorta is a feature of AAA progression [13]. The increased risk of AAA seen at higher galectin-3 levels may therefore be reflecting the recruitment of inflammatory cells including activated macrophages in the arterial system and subsequent secretion of galectin-3. Our findings indicate that in the general population systemic galectin-3 concentrations are elevated years before the identification of incident AAA. Future research could also be useful to determine whether galectin-3 levels might predict the progression or rupture of AAA.

The association between galectin-3 and incident AAA was not independent of the three other biomarkers, particularly NT-proBNP. This is consistent with the general role of inflammation in the development of AAA [1] and suggests no unique etiological role for galectin-3. The attenuation of the galectin-3 AAA association by NT-proBNP adjustment may also indicate the influence of increased systemic vascular resistance in galectin-3 elevation and AAA pathogenesis [18]. Whether galectin-3 might be pharmacologically modifiable and whether this might reduce the burden of AAA is, of course, unknown.

Our study is the first to characterize the prospective association between galectin-3 and

incident AAA, but several limitations should be considered. First, we used ICD codes to ascertain the diagnosis of AAA from hospital records and death certificates. We may have missed some cases who were asymptomatic and did not present to the hospital. This would result in an underestimation of incident AAA, reduction in statistical power, and possible attenuation of the association. Second, we used a single measure of galectin-3 obtained at study baseline which may not be reflective of plasma levels prior to AAA incidence as levels may have changed. We were unable to capture this in our present study. Third, galectin-3 was measured from stored samples. This may have resulted in sample degradation and subsequent reduction in the power of our analyses resulting in further weakening of our associations. In the Cardiovascular Health Study, galectin-3 levels were found to remain stable for a minimum of 2 years when samples were stored at -70°C [27]. Finally, galectin-3 is associated positively with numerous other conditions, including the incidence of heart failure and all-cause mortality [28-30], and involved in the pathogenesis of cancer [31], diabetes [7], and fibrotic processes [32-34]. Thus, galectin-3 may be a nonspecific marker or other conditions might residually confound the association between galectin-3 and AAA risk. Yet, we attempted to reduce such residual confounding by adjusting for many variables known to be associated with galectin-3 levels and AAA, such as diabetes status.

Conclusion

Higher concentrations of plasma galectin-3 were associated with increased incidence of AAA in this large population-based cohort study. This association was not independent of CRP, cTnT, and NT-proBNP, suggesting that galectin-3 reflects the general role of inflammation and increased systemic vascular resistance in AAA pathogenesis.

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Disclosure of conflict of interest

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