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ORIGINAL RESEARCH

Galectin-3, Metabolic Risk, and Incident Heart Failure: The ARIC Study

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BACKGROUND: It is unclear how metabolic syndrome (MetS) and diabetes affect Gal-3 (galectin 3) levels and the resulting implications for heart failure (HF) risk. We assessed relationships of MetS and diabetes with Gal-3, and their joint associations with incident HF.

METHODS AND RESULTS: We included 8445 participants without HF (mean age, 63 years; 59% men; 16% Black race) at ARIC (Atherosclerosis Risk in Communities) study visit 4 (1996–1999). We categorized participants as having MetS only, MetS with diabetes, or neither, and by quartiles of MetS severity *Z* score. We assessed cross-sectional associations of metabolic risk categories with high Gal-3 level (≥75th percentile) using logistic regression. We used Cox regression to evaluate combined associations of metabolic risk categories and Gal-3 quartiles with HF. In cross-sectional analyses, compared with no MetS and no diabetes, MetS only (odds ratio [OR], 1.24 [95% CI, 1.10–1.41]) and MetS with diabetes (OR, 1.59 [95% CI, 1.32–1.92]) were associated with elevated Gal-3. Over a median follow-up of 20.5 years, there were 1749 HF events. Compared with individuals with neither diabetes nor MetS and with Gal-3 in the lowest quartile, the combination of MetS with diabetes and Gal-3 ≥75th percentile was associated with a 4-fold higher HF risk (hazard ratio, 4.35 [95% CI, 3.30–5.73]). Gal-3 provided HF prognostic information above and beyond MetS, NT-proBNP (N-terminal pro-B-type natriuretic peptide), high-sensitivity cardiac troponin T, and CRP (C-reactive protein) (ΔC statistic for models with versus without Gal-3: 0.003; *P*=0.004).

CONCLUSIONS: MetS and diabetes are associated with elevated Gal-3. The HF risk significantly increased with the combination of greater metabolic risk and higher Gal-3.

Key Words: diabetes ■ galectin 3 ■ heart failure ■ metabolic status

Gal-3 (galectin 3), a β-galactoside–binding lectin expressed in various cell types, has been implicated in several functional pathways, including fibrosis and inflammation.[1] Gal-3 is expressed at low levels in healthy cardiac tissue and at much higher levels during cardiac injury.[2] Mechanistic studies have suggested that Gal-3 may play a critical role in the pathogenesis of adverse cardiac remodeling and dysfunction.[3] Several community-based studies have shown a positive association of circulating levels of Gal-3 with left ventricular hypertrophy, left ventricular dysfunction, and incident heart failure (HF).[4–6] Prior studies have not specifically investigated the influence of metabolic syndrome (MetS) and diabetes on Gal-3, as well as related implications for HF risk.

The pathways leading to elevated Gal-3 and subsequent HF remain incompletely understood. Gal-3 can interfere in the signaling pathway involved in collagen synthesis in vascular smooth muscle cells, which is stimulated by high aldosterone levels, thus promoting

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CLINICAL PERSPECTIVE

What Is New?

- The metabolic risk factors of metabolic syndrome and diabetes and the biomarker Gal-3 (galectin 3) are individually associated with the risk of heart failure. It is unclear how interrelationships among these measures affect heart failure risk.
- Metabolic risk factors were associated with elevated Gal-3 (highest quartile).
- Compared with individuals with neither diabetes nor metabolic syndrome and with low Gal-3 (lowest quartile), the combination of metabolic syndrome, diabetes, and elevated Gal-3 was associated with ≈4-fold higher risk of heart failure.

What Are the Clinical Implications?

- Gal-3 can provide heart failure prognostic information above and beyond the presence of metabolic syndrome and traditional cardiac biomarkers.

Nonstandard Abbreviations and Acronyms

Gal-3	galectin 3
MetS	metabolic syndrome

vascular fibrosis and cardiac remodeling.[7] Metabolic traits may also play an important role in the pathways linking Gal-3 and HF. Studies have shown that elevated Gal-3 is associated with impaired glucose regulation, diabetes, obesity, and MetS.[8] Furthermore, MetS[9] and diabetes[10] are established metabolic risk factors for incident HF and are independently associated with adverse cardiac remodeling, marked by evidence of fibrosis, which predisposes to HF. Extant laboratory and clinical data suggest that Gal-3–related myocardial fibrosis is likely more pronounced among individuals with MetS than among those without MetS.[11] Furthermore, it is unclear whether the association of Gal-3 with incident HF differs among subgroups defined by MetS and diabetes (given that diabetes confers cardiovascular disease risk beyond MetS when present), and whether metabolic risk status and Gal-3 provide complementary prognostic information for HF risk.

Using data from the community-based ARIC (Atherosclerosis Risk in Communities) study, we examined the following: (1) the association of metabolic risk status (the presence of MetS with and without diabetes, and levels of MetS severity) with Gal-3 levels and (2) the joint associations of Gal-3 and metabolic risk status with incident HF.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

The ARIC study recruited 15 792 participants from 4 US communities.[12] The first study visit took place in 1987 to 1989, and since then participants have returned for subsequent study visits (7 to date), and have undergone follow-up for cardiovascular disease events by annual telephone interviews and active surveillance of ARIC study community hospitals and review of death certificates.

Of the 11 656 participants who attended ARIC study visit 4 (1996–1998) during which Gal-3 was measured, we excluded individuals with a history of coronary heart disease or HF (n=1375), race other than Black or White (n=69), missing data on Gal-3 or on the *rs4644* variant known to affect the Gal-3 levels[13,14] (n=1166), missing data on MetS components or diabetes status (n=403), and missing data on other covariates, such as estimated glomerular filtration rate (eGFR), smoking status, or alcohol use (n=15). After exclusions, 8628 participants were included in the final analysis.

All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board at each study site.

Gal-3 Assessment

At visit 4, Gal-3 was measured using a chemiluminescent microparticle immunoassay on an Architect i 2000sr instrument (Abbott, Abbott Park, IL) in EDTA-plasma samples collected and stored at –70 °C before measurement. The assay's limit of detection is 1.1 ng/mL; limit of quantitation is 4.0 ng/mL. The interassay coefficients of variation were 5.2%, 3.3%, and 2.3% at mean Gal-3 levels of 8.8, 19.2, and 72.0 ng/mL, respectively.

The *rs4644* variant, a common single-nucleotide polymorphism in the gene encoding Gal-3 (*LGALS3*), lies within the epitope of the binding region for the antibody used to measure Gal-3 in the ARIC study cohort. It can interfere with the plasma Gal-3 assay performance. Similar to the approach used in other investigations using the ARIC study cohort data,[13,14] our analyses adjusted for *rs4644* to account for the variable frequency of this variant across populations. Exome genotyping for common variants was performed using HumanExome BeadChip Array (Illumina, San Diego, CA).[15]

Ascertainment of Diabetes Status and MetS Status

Prevalent diabetes at visit 4 was defined by a physician-reported diagnosis of diabetes, self-reported use of diabetes medications, a nonfasting blood glucose

level ≥200 mg/dL, or a fasting blood glucose level ≥126 mg/dL.

MetS was defined at baseline (visit 4) using the American Heart Association/National Heart, Lung, and Blood Institute criteria guidelines,[16] as the presence of 3 of the 5 following criteria: (1) abdominal obesity (waist circumference ≥102 cm in men or ≥88 cm in women), (2) elevated blood pressure (BP) (systolic BP ≥130 mm Hg, diastolic BP ≥85 mm Hg, or use of antihypertensive medications), (3) impaired fasting glucose (fasting blood glucose level ≥100 mg/dL) without a diagnosis of diabetes, (4) low high-density lipoprotein cholesterol (≤40 mg/dL in men or ≤50 mg/dL in women), and (5) elevated triglycerides (≥150 mg/dL).

We calculated a continuous MetS severity *Z* score at baseline among participants using sex- and race-based formulas.[17] The score was previously derived using a confirmatory factor analysis approach for the 5 traditional MetS components (waist circumference, triglycerides, high-density lipoprotein cholesterol, systolic BP, and fasting blood glucose level) to determine the weighted contribution of each component to a latent MetS factor on a sex- and race- or ethnicity-specific basis. The resulting MetS severity scores are *Z* scores (normally distributed and ranging from theoretical negative to positive infinity with mean=0 and SD=1) of relative MetS severity on a sex- and race- and ethnicity-specific basis.[17]

In the analyses, we considered MetS alone and the combination of MetS and diabetes. This is because MetS is found in most individuals with type 2 diabetes, and when diabetes is present, it confers risk above and beyond that of MetS alone.

Incident Outcome Assessment

The outcome of interest in prospective analyses was incident HF, defined as the first hospitalization or death related to HF occurring after visit 4, with follow-up through December 31, 2019. Participants were called on a yearly basis to obtain information on hospitalizations, and vital records were examined for all deaths. Hospitalizations and deaths attributable to incident HF were defined by HF discharge codes (*International Classification of Diseases, Ninth Revision* [*ICD-9*], code 428 for hospitalizations early during follow-up and *International Classification of Diseases, Tenth Revision* [*ICD-10*], code I50 for later follow-up).[18]

Covariate Assessment

Information on medical history, medication use, alcohol use, and current smoking was obtained using standardized self-report questionnaires. Systolic and diastolic BP measurements were recorded as the mean of 2 readings. Body mass index was calculated as weight in kilograms divided by the square of height in meters, and obesity was defined as body mass index ≥30 kg/m^2. Serum glucose was measured using the hexokinase method. Plasma glucose was measured using the hexokinase method. Serum, triglycerides, and high-density lipoprotein cholesterol concentrations were measured by using automated enzymatic assays. eGFR was calculated from serum creatinine and cystatin C–based new equation.[19] NT-proBNP (N-terminal pro-B-type natriuretic peptide) was measured using an electrochemiluminescent immunoassay on an automated Cobas e411 analyzer (Roche Diagnostics, Mannheim, Germany), and high-sensitivity cardiac troponin T levels were measured with a highly sensitive assay, Elecsys Troponin T (Roche Diagnostics, Indianapolis, IN) on an automated Cobas e411 analyzer. CRP (C-reactive protein) was measured via immunophelometric assay.

Statistical Analysis

The baseline characteristics of participants were compared across MetS *Z* score quartiles using the ANOVA procedure (for continuous variables) or the χ^2 test (for categorical variables).

In cross-sectional analyses, elevated Gal-3 levels were defined as ≥75th sex-specific percentile. Differences were observed in the distribution of Gal-3 by sex, as described in other studies.[4] Analyses were, therefore, conducted using sex-specific quartiles of Gal-3.

Adjusted logistic regression was used to explore the association of each component of the MetS and of the number of MetS components with elevated Gal-3 levels (≥75th percentile). Associations were also assessed between the severity of MetS, as assessed by the MetS severity *Z* score (modeled as a continuous and categorical [quartile] variables) and elevated Gal-3 levels. Associations were also assessed between 3 metabolic risk categories and elevated Gal-3: no diabetes/MetS (reference); MetS only; and MetS and diabetes. Given the small number of individuals with diabetes without MetS, and that MetS is frequently a precursor to the development of type 2 diabetes, individuals with diabetes without MetS were excluded from this analysis. The logistic regression models were adjusted for age, sex, race/center, alcohol use, cigarette smoking, *rs4644* genotype, and eGFR.

In prospective analyses using visit 4 as the baseline, Cox proportional hazard regression models were used to estimate the adjusted hazard ratios (HRs) and corresponding 95% CIs for associations of cross-categories of quartiles of Gal-3 and quartiles of the MetS severity *Z* score with incident HF, after adjustment for baseline risk factors. The use of cross-categories was meant to inform on the complementary prognostic information provided by Gal-3 and metabolic syndrome severity in

relation to HF risk. We also examined the associations of cross-categories of metabolic risk category and Gal-3 quartiles with incident HF. For all Cox models, we adjusted for age, sex, race/center, alcohol use, cigarette smoking, *rs4644* genotype, eGFR, NT-proBNP, high-sensitivity cardiac troponin T, and CRP. The proportional hazards assumption was tested by inspecting the log-log survival plots.

We assessed the additive predictive value of Gal-3 above and beyond MetS, diabetes, and other risk factors (including all the aforementioned adjustment variables), by evaluating the changes in C-statistic (prediction statistic) associated with the addition of Gal-3 to traditional HF risk factors. The C-statistic was assessed using the Harrell method,[20] and the significance difference in C-statistics was assessed using the likelihood ratio test.

We conducted additional analyses accounting for the competing risk of death, because incident death may not be negligible among individuals included in our study given their age. This was done by fitting Fine-Gray proportional subdistribution hazard models. We also conducted sensitivity analyses, in which we excluded the impaired fasting glycemia criterion from the definition of MetS, to assess the extent to which elevated glycemia as a component of MetS influences the estimates of associations with incident HF.

P<0.05 was used to denote statistical significance. *P* values of trends were derived from linear models obtained by regressing the risk estimates on the midpoint of the exposure interval. The trend test was based on the slope of the regression line. All analyses were performed using Stata, version 16.

RESULTS

The study population of 8628 individuals had a mean±SD age of 63.2±5.6 years, with 57.8% women and 16% Black adults. Compared with participants in the lowest quartile of the MetS *Z* score, those in the highest quartile of the MetS *Z* score were older and more likely to have obesity, hypertension, diabetes, and a lower eGFR but were less likely to be current smokers (Table 1).

The proportion of participants with elevated Gal-3 (≥75th percentile) increased with greater MetS severity, with a prevalence of 18.3% among those in the lowest quartile of the MetS *Z* score, and 30.5% among those in the highest quartile of the MetS *Z* score. In cross-sectional analyses, when examining the individual components of the MetS (Table S1), higher Gal-3 levels (≥75th percentile) were significantly associated with an elevated BP (odds ratio [OR], 1.53 [95% CI, 1.35–1.74]), high triglycerides (OR, 1.52 [95% CI, 1.34–1.72]), and elevated waist circumference (OR, 1.19 [95% CI, 1.04–1.36]). The proportion of participants with elevated Gal-3 also differed by metabolic risk categories, from a prevalence of 20.0% among those with no MetS/diabetes, to 27.7% among those with MetS only and 31.7% among those with MetS and diabetes.

In regression analyses, an increasing number of MetS components was strongly linked to elevated Gal-3. The presence of 5 MetS components, relative to no MetS components, was associated with 3-fold higher likelihood of elevated Gal-3 in model 1 (OR, 3.04 [95% CI, 2.27–4.07; Table 2). After additional adjustment for eGFR (model 2), this association remained strong but was attenuated to an OR of 2.04 (95% CI, 1.50–2.78). In the fully adjusted model, the top quartile of the MetS *Z* score was associated with an OR of 1.59 (95% CI, 1.34–1.89) for elevated Gal-3 relative to the bottom quartile (Table S1). The severity of MetS as captured by the score was approximately linearly associated with Gal-3 levels (Figure S1). Compared with people with no diabetes and no MetS, the presence of MetS only (OR, 1.24 [95% CI, 1.10–1.41]) and the presence of MetS with diabetes (OR, 1.59 [95% CI, 1.32–1.92]) were associated with progressively higher odds of having an elevated Gal-3 level (Table 2).

In prospective analyses, over a median follow-up of 20.5 years, there were 1749 incident HF events. There was no significant interaction on the multiplicative scale between the MetS Zscore quartile and Gal-3 on the outcome of incident HF (*P* interaction=0.14). When considering the joint associations of metabolic status and Gal-3 with HF risk, we found that higher Gal-3 was associated with greater absolute HF risk (HF incidence rate) within each quartile of MetS *Z* score (Table 3) and each level of metabolic risk category defined by the presence of MetS, diabetes, or both (Table 4).

Individuals in the highest quartile of MetS *Z* score and highest quartile of Gal-3 had a 3.3-fold higher risk of future HF (HR, 3.27 [95% CI, 2.42–4.41]) than those in the lowest quartiles of both MetS *Z* score and Gal-3 (Table 3). Similarly, compared with individuals with neither diabetes nor MetS and with Gal-3 in the lowest quartile (Table 4), the combination of MetS with diabetes and Gal-3 ≥75th sex-specific percentile was associated with an ≈4-fold higher risk of future HF (HR, 4.35 [95% CI, 3.30–5.73]). There was an increasing trend in the risk of HF associated with Gal-3 modeled continuously within each of the increasing levels of metabolic risk categories (Table S2).

The addition of Gal-3 to a model including traditional risk factors, MetS *Z* score, NT-proBNP, high-sensitivity cardiac troponin T, and CRP showed that Gal-3 significantly improved risk prediction for HF (C-statistic for model without Gal-3: 0.759 [95% CI, 0.748–0.771] versus C-statistic for model with Gal-3: 0.762 [95% CI, 0.749–0.772]; C-statistic improvement [ΔC statistic]: 0.003; *P* for difference: 0.006). When we

Table 1. Baseline Characteristics of ARIC Study Participants at Visit 4 (1996–1998) by Metabolic Status Categories

Characteristic		MetS *Z* score					
	Total (N=8628)	Quartile 1 (N=2157)	Quartile 2 (N=2157)	Quartile 3 (N=2157)	Quartile 4 (N=2157)	*P* value*	*P*-trend
Age, y	63.2 (5.6)	62.7 (5.7)	63.1 (5.7)	63.4 (5.6)	63.4 (5.6)	<0.001	<0.001
Female sex, N (%)	4990 (57.8)	1372 (63.6)	1207 (56.0)	1134 (52.6)	1277 (59.2)	<0.001	0.001
Race and center, N (%)						<0.001	<0.001
White, Minneapolis, MN	2599 (30.1)	725 (33.6)	678 (31.4)	642 (29.8)	554 (25.7)		
White, Washington County, MD	2193 (25.4)	441 (20.4)	492 (22.8)	590 (27.4)	670 (31.1)		
White, Forsyth County, NC	2098 (24.3)	600 (27.8)	552 (25.6)	519 (24.1)	427 (19.8)		
Black, Forsyth County, NC	184 (2.1)	48 (2.2)	47 (2.2)	49 (2.3)	40 (1.9)		
Black, Jackson, MS	1554 (18.0)	343 (15.9)	388 (18.0)	357 (16.6)	466 (21.6)		
Drinking, N (%)						<0.001	<0.001
Current	4428 (51.3)	1286 (59.6)	1158 (53.7)	1056 (49.0)	928 (43.0)		
Past	2431 (28.2)	513 (23.8)	575 (26.7)	669 (31.0)	674 (31.2)		
Never	1769 (20.5)	358 (16.6)	424 (19.7)	432 (20.0)	555 (25.7)		
Smoking, N (%)						<0.001	0.001
Current	1238 (14.3)	364 (16.9)	339 (15.7)	277 (12.8)	258 (12.0)		
Past	3686 (42.7)	884 (41.0)	902 (41.8)	974 (45.2)	926 (42.9)		
Never	3704 (42.9)	909 (42.1)	916 (42.5)	906 (42.0)	973 (45.1)		
eGFR-Cr-CysC, mL/min per 1.73 m^2	86.4 (16.0)	90.0 (14.5)	87.0 (15.5)	84.5 (15.6)	83.9 (17.4)	<0.001	<0.001
BMI, kg/m^2	28.6 (5.5)	24.3 (3.4)	27.2 (3.7)	29.6 (4.1)	33.1 (6.0)	<0.001	<0.001
Obese (BMI ≥30 kg/m^2), N (%)	2897 (33.6)	113 (5.2)	427 (19.8)	924 (42.8)	1433 (66.4)	<0.001	<0.001
SBP, mm Hg	126.8 (18.6)	119.7 (17.5)	125.2 (17.5)	128.5 (17.9)	133.9 (18.6)	<0.001	<0.001
Hypertension medications, N (%)	3337 (38.7)	508 (23.6)	721 (33.4)	918 (42.6)	1190 (55.2)	<0.001	<0.001
Total cholesterol, mg/dL	201.8 (36.2)	196.0 (33.2)	200.6 (34.8)	204.0 (36.6)	206.8 (39.2)	<0.001	<0.001
HDL cholesterol, mg/dL	50.8 (16.7)	66.4 (17.1)	51.6 (12.6)	44.5 (11.6)	40.7 (11.6)	<0.001	<0.001
Fasting glucose, mg/dL	107.2 (30.7)	93.6 (8.6)	98.1 (8.8)	103.2 (12.2)	133.8 (49.6)	<0.001	<0.001
Diabetes, N (%)	1123 (13.0)	38 (1.8)	53 (2.5)	157 (7.3)	875 (40.6)	<0.001	<0.001
MetS, N (%)	4446 (51.5)	82 (3.8)	690 (32.0)	1631 (75.6)	2043 (94.7)	<0.001	<0.001
rs4644 Variant, N (%)						0.90	0.488
AA	1300 (15.1)	325 (15.1)	322 (14.9)	334 (15.5)	319 (14.8)		
AC	4058 (47.0)	990 (45.9)	1024 (47.5)	1017 (47.1)	1027 (47.6)		
CC	3270 (37.9)	842 (39.0)	811 (37.6)	806 (37.4)	811 (37.6)		
Galectin-3, ng/mL	14.1 (11.9–16.7)	13.7 (11.6–16.0)	14.0 (11.8–16.4)	14.2 (12.0–16.7)	14.7 (12.4–17.5)	<0.001	<0.001
Elevated galectin-3 (≥75th percentile), N (%)	2109 (24.4)	395 (18.3)	493 (22.9)	563 (26.1)	658 (30.5)	<0.001	<0.001

Values are mean (SD) or median (interquartile range) for continuous variables and number (percentage) for categorical variables. The *rs4644* variant is included because of its effects on galectin-3 levels. ARIC indicates Atherosclerosis Risk in Communities; BMI, body mass index; eGFR-Cr-CysC, estimated glomerular filtration rate using creatinine and cystatin C; HDL, high-density lipoprotein; MetS, metabolic syndrome; and SBP, systolic blood pressure.

**P* values for continuous variables are based on ANOVA or Kruskal-Wallis tests, depending on distribution. *P* values for categorical variables are based on χ^2 tests.

used metabolic risk category (no diabetes/MetS, MetS only, or MetS and diabetes) instead of MetS *Z* score in the models, Gal-3 similarly improved risk prediction for HF (C-statistic for model without Gal-3: 0.759 [95% CI, 0.750–0.773] versus C-statistic for model with Gal-3: 0.762 [95% CI, 0.750–0.773]; C-statistic improvement [ΔC statistic]: 0.003; *P* for difference: 0.004).

In additional analyses that account for the competing risk of death, we obtained approximately similar results for the joints associations of metabolic risk status and Gal-3 with HF (Tables S3 and S4). In these competing risk analyses, although there was a slight attenuation of the magnitude of the estimates, risk associations remained significant (Tables S3 and S4).

Table 2. ORs (95% CIs) for the Associations of MetS and Diabetes Status With Elevated Gal-3 (Top 25%) at Baseline (Visit 4, 1996–1998), the ARIC Study

Metabolic status	OR (95% CI)	
	Model 1	Model 2
No metabolic syndrome and no diabetes	1 (Reference)	1 (Reference)
Metabolic syndrome only (no diabetes)	1.57 (1.39–1.77)*	1.24 (1.10–1.41)*
Metabolic syndrome and diabetes	1.68 (1.41–2.00)*	1.59 (1.32–1.92)*
P value for trend	<0.001	0.001

Model 1 adjusts for age, sex, race and center, smoking, alcohol, and *rs4644*. Model 2 adjusts for model 1 variables+estimated glomerular filtration rate (linear spline at 60 mL/min per 1.73 m^2). The *rs644* genotype was adjusted for because it influences Gal-3 levels. Individuals with diabetes without MetS excluded because of small numbers. ARIC indicates Atherosclerosis Risk in Communities; Gal-3, galectin 3; MetS, metabolic syndrome; and OR, odds ratio.

*$P<0.05$.

In additional sensitivity analyses, the exclusion of fasting glucose measurement from the MetS definition resulted in a notable attenuation of the magnitude of our estimates (Tables S5 and S6). Further analyses examining the risk of HF in relation to Gal-3 and metabolic risk over the first 5 years (short-term) and beyond 5 years (long-term) showed no significant difference in the risk over the 2 periods (Tables S7 and S8).

DISCUSSION

In a large community-based cohort of Black and White adults free of cardiovascular disease, metabolic dysregulation was associated with a higher odds of elevated Gal-3, a biomarker of inflammation and fibrosis. More important, even after adjustment for covariates in prospective analyses, an adverse metabolic profile and elevated Gal-3 provided complementary prognostic information about HF risk. Similarly, the concomitance of severe MetS and elevated Gal-3 was associated with a 4-fold higher HF risk compared with the lowest level of MetS severity and low Gal-3. Moreover, the combination of MetS/diabetes and elevated Gal-3 was associated with ≈6-fold higher risk. These findings have significant clinical implications, as MetS commonly precedes and coexists with type 2 diabetes,[21] with most individuals with type 2 diabetes having MetS (>70%).[22,23] Furthermore, MetS, diabetes, and Gal-3 are each independently associated with an increased risk of incident HF.

Prior studies had shown an association between diabetes or MetS and Gal-3, as well as between Gal-3 and HF.[4,6,24,25] Indeed, Gal-3 has been associated with a variety of metabolic abnormalities, including insulin resistance, impaired glucose tolerance/diabetes, and obesity.[8,26–29] This is corroborated by our findings of associations of MetS and its various components with elevated Gal-3 levels. Similarly, several studies have shown an association of Gal-3 with incident HF[4,6,24,25] and adverse HF prognosis.[30–32] However, to date, most community-based studies have lacked racial and ethnic diversity, have not examined the severity of MetS in relation to Gal-3, and have also not investigated the combined associations of metabolic risk status (and its severity) and Gal-3 with the risk of HF (including prior analyses of the ARIC study data[6,33]). A single prior study found that Gal-3 was associated with stage B HF among individuals with metabolic abnormalities compared with those without a metabolic abnormality,[34] which is congruent with the results in our study.

Our findings extend prior research by showing the additional prognostic implications of both metabolic dysregulation (including its severity) and elevated Gal-3 levels for incident HF risk. The practical implication of our findings is that the combined use of Gal-3, MetS, and diabetes can enhance HF risk stratification, possibly allowing a better selection of candidates for more intensive HF prevention. Gal-3 could help stratify high-risk individuals (eg, individuals with the combination of diabetes and MetS) who might benefit the most from lifestyle- or pharmacologic-based preventive therapy for HF, including cardioprotective therapies, such as sodium-glucose cotransporter-2 inhibitors,[35,36] and glucagon-like peptide receptors antagonists.[37] Gal-3 levels could also help guide the specific use of mineralocorticoid receptor antagonists for HF prevention, which, in combination to Gal-3 blockade, have been shown to reverse isoproterenol-induced left ventricular systolic dysfunction and prevent the development of myocardial fibrosis.[7,38]

In animal models, Gal-3 was shown to affect glycemic regulation and adiposity.[11] In these models, Gal-3 increases adipocyte differentiation by activating peroxisome proliferator-activated receptor-γ[39]; consequently, Gal-3–deficient mice have a higher frequency of diet-induced obesity and glucose dysregulation.[40,41] Gal-3 expression in adipocytes can be induced by proinflammatory signals, such as circulating free fatty acids and interleukin-6.[42] Gal-3 upregulation plays a crucial role in the initial phases of tissue repair; however, sustained overexpression results in myocardial fibrosis.[3,43] The latter phenomenon may be more pronounced in the

Table 3. Incidence Rates and Adjusted HRs (95% CIs) for the Associations of MetS *Z*-Score Quartiles and Gal-3 Quartiles With Risk of Incident HF

Variable	Gal-3 quartiles			
MetS *Z* score	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Incidence rate-per 1000 person-years (95% CI)				
Quartile 1	5.7 (4.5–7.1)	6.5 (5.2–8.2)	7.1 (5.5–9.0)	11.6 (9.2–14.6)
Quartile 2	7.0 (5.6–8.8)	9.6 (7.9–11.8)	9.7 (8.0–11.9)	13.7 (11.4–16.5)
Quartile 3	8.6 (6.9–10.7)	10.0 (8.2–12.3)	10.7 (8.8–13.0)	16.4 (14.0–19.3)
Quartile 4	16.4 (13.8–19.6)	15.1 (12.7–18.0)	19.1 (16.4–22.2)	26.1 (23.0–29.6)
Adjusted HR* (95% CI)				
Quartile 1	1.00 (Reference)	1.04 (0.74–1.45)	1.12 (0.79–1.58)	1.40 (0.99–1.98)
Quartile 2	1.19 (0.86–1.66)	1.42 (1.04–1.94)*	1.38 (1.00–1.91)*	1.60 (1.16–2.22)*
Quartile 3	1.48 (1.07–2.05)*	1.53 (1.11–2.10)*	1.49 (1.08–2.04)*	1.97 (1.44–2.69)*
Quartile 4	2.61 (1.94–3.53)*	2.40 (1.77–3.25)*	2.90 (2.16–3.90)*	3.27 (2.42–4.41)*

Model includes age, sex, race and center, alcohol use, cigarette smoking, estimated glomerular filtration rate, *rs4644* genotype, NT-proBNP (N-terminal pro-B-type natriuretic peptide), high-sensitivity cardiac troponin T, and CRP (C-reactive protein). The *rs644* genotype was adjusted for because it influences Gal-3 levels. Gal-3 indicates galectin 3; HF, heart failure; HR, hazard ratio; and MetS, metabolic syndrome.

*$P<0.05$.

setting of metabolic dysregulation, which could be associated with myocardial injury, leading to tissue repair. Indeed, a few studies have suggested that Gal-3 mediates cardiac remodeling caused by impaired glucose and lipid metabolism,[44] or by obesity.[45]

There are limitations to our study. First, the diagnosis of incident HF was based on hospital discharge and death certificate codes, which may have resulted in some misclassification. Second, our analysis does not account for the potential impact of medical therapies, especially therapies that may have mitigated metabolic risk during the follow-up period. In addition, cardiac imaging data were not available to assess the subtypes of HF (HF with reduced ejection fraction and HF with preserved ejection fraction), as the observed associations may vary across HF subtypes. Third, we also did not incorporate repeated assessments of MetS, diabetes status, or Gal-3; thus, we did not examine their change in relation to HF risk. Fourth, we only used 1 of the 4 proposed definitions of MetS; hence, the results could be different if other criteria were used (eg, the International Diabetes Federation criteria). Finally, we did not specifically account for dietary intake and drugs, such as mineralocorticoid receptor antagonists, which can affect the aldosterone-related Gal-3 pathway.

The strengths of our study include the community-based design, the large sample with a significant representation of Black and White adults, as well as male and female individuals in middle and older age, long-term follow-up for incident HF events, and the rigorous measurement of potential confounding factors, including the *rs4644* genotype, which likely improved the accuracy of the results.

Table 4. Incidence Rates and Adjusted HRs for the Associations of Cross-Categories of Metabolic Risk Group and Gal-3 Quartiles With Risk of Incident HF

Metabolic status	Gal-3 quartiles			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Incidence rate-per 1000 person-years (95% CI)				
No diabetes and no MetS	6.2 (5.2–7.3)	7.4 (6.3–8.7)	8.0 (6.8–9.5)	12.0 (10.3–14.0)
MetS only	10.8 (9.2–12.6)	11.2 (9.6–13.0)	12.8 (11.1–14.7)	17.4 (15.4–19.6)
Diabetes and MetS	17.7 (13.8–22.7)	19.3 (15.1–24.7)	24.1 (19.6–29.7)	39.4 (33.4–46.5)
Adjusted HR* (95% CI) for cross-category diabetes, MetS, and Gal-3 comparisons				
No diabetes–no MetS	1 (Reference)	1.07 (0.84–1.35)	1.14 (0.89–1.46)	1.35 (1.04–1.74)*
No diabetes–MetS only	1.58 (1.25–2.00)*	1.50 (1.18–1.90)*	1.64 (1.29–2.08)*	1.89 (1.48–2.40)*
Diabetes and MetS	2.62 (1.91–3.58)*	2.68 (1.97–3.66)*	2.98 (2.24–3.98)*	4.35 (3.30–5.73)*

Model includes age, sex, race and center, alcohol use, cigarette smoking, estimated glomerular filtration rate, *rs4644* genotype, NT-proBNP (N-terminal pro-B-type natriuretic peptide), high-sensitivity cardiac troponin T, and CRP (C-reactive protein). The *rs644* genotype was adjusted for because it influences Gal-3 levels. Gal-3 indicates galectin 3; HF, heart failure; HR, hazard ratio; and MetS, metabolic syndrome.

*$P<0.05$.

CONCLUSIONS

Our study showed that greater severity of metabolic risk is independently associated with elevated Gal-3, a marker of inflammation and fibrosis. Furthermore, the combination of adverse metabolic risk and elevated Gal-3 identifies a subgroup at particularly high risk of future HF. This subpopulation could benefit in particular from aggressive pharmacologic and lifestyle measures to prevent HF.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S8.
Figure S1.

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