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ORIGINAL ARTICLE

Resistin and risks of incident heart failure subtypes and cardiac fibrosis: the Multi-Ethnic Study of Atherosclerosis

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Abstract

Aims Resistin is a circulating inflammatory biomarker that is associated with cardiovascular disease. We investigated the associations of resistin and incident heart failure (HF) and its subtypes, as well as specific measures of subclinical HF (myocardial fibrosis and relevant biomarkers).

Methods We analysed data from 1968 participants in the Multi-Ethnic Study of Atherosclerosis with measurements of plasma resistin levels at clinic visits from 2002 to 2005. Participants were subsequently followed for a median of 10.5 years for HF events. The associations between resistin levels and incident HF, HF with reduced ejection fraction (HFrEF), and HF with preserved ejection fraction (HFpEF) were examined using multivariable Cox proportional hazards models. Linear regression models assessed the associations between resistin levels and myocardial fibrosis from cardiac magnetic resonance imaging, as well as hs-cTnT and NT-proBNP.

Results The mean age of the cohort was 64.7 years, and 50.0% were female. Seventy-four participants (4%) developed incident HF during follow-up. In a Cox proportional hazards model adjusted for age, gender, education level, race/ethnicity, and traditional risk factors, higher resistin levels were significantly associated with incident HF (HR 1.44, CI 1.18–1.75, $P = 0.001$) and HFrEF (HR 1.47, CI 1.07–2.02, $P = 0.016$), but not with HFpEF (HR 1.25, CI 0.89–1.75, $P = 0.195$). Resistin levels showed no significant associations with myocardial fibrosis, NT-proBNP, or hs-cTnT levels.

Conclusions In a multi-ethnic cohort free of cardiovascular disease at baseline, elevated resistin levels were associated with incident HF, more prominently with incident HFrEF than HFpEF, but not with subclinical myocardial fibrosis or biomarkers of HF.

Keywords Cardiac fibrosis; Heart failure; Resistin; Troponin

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Introduction

In the United States from 2013 to 2016, the prevalence of heart failure (HF) has increased from 5.7 million (2009–2012) to 6.2 million.[1] Approximately half of incident hospitalized HF cases are HF with reduced ejection fraction (HFrEF), and the other half are HF with preserved ejection fraction (HFpEF) or HF with mildly reduced ejection fraction (HFmrEF).[2]

Despite the wide acceptance of using traditional risk factors to identify patients at risk for HF,[3] early detection and the prevention of subclinical HF remains challenging. From epidemiologic studies, several biomarkers (e.g. high-sensitivity

troponin and natriuretic peptides) have been shown to correlate with future risk of incident HF.[4] More specifically, and using the Multi-Ethnic Study of Atherosclerosis (MESA) population over a 10-year follow-up period, mildly elevated high-sensitivity cardiac troponin T (hs-cTnT) levels were found to be associated with a higher risk of increased left ventricular (LV) mass and LV dilation, as well as myocardial fibrosis.[5]

Resistin is a circulating peptide hormone released primarily from macrophages.[6,7] Emerging evidence suggests that elevated circulating resistin levels are associated with various cardiovascular diseases (CVD) such as atherosclerosis, acute coronary syndrome, myocardial infarction, ischaemic stroke, hypertrophic cardiomyopathy, and HF.[8–13] In this regard, we have recently demonstrated direct cellular and *in vivo* cardiac effects of resistin, where resistin over-expression in normal rodents induced myocyte injury and cardiac dysfunction, primarily due to increased apoptosis and myocardial fibrosis.[14–16] Furthermore, by using animal models of pressure overload and volume overload, we were able to demonstrate elevated LV resistin levels and increased fibrosis in the pressure overload model of HF, compared with the volume overload model where resistin is minimally elevated.[17] Chronic ischaemic injury in animal models of myocardial infarction also revealed local resistin expression in the infarct area that led to activation of pro-fibrotic pathways and eventually cardiac replacement fibrosis.[17]

Based on these lines of evidence, we hypothesized that resistin levels may be associated with specific HF subtypes and cardiac fibrosis. Therefore, the primary focus of this study was to determine the association of resistin levels with incident HF and its subtypes. In a subset of study participants, we assessed the association of resistin in cardiac fibrosis measured by cardiac magnetic resonance (CMR), as well as the relationships of resistin with hs-cTnT and *N*-terminal pro-brain natriuretic peptide (NT-proBNP).

Methods

Study population

MESA is a longitudinal study initiated in July 2000 to determine the characteristics and risk factors of subclinical CVD and its procession to clinically overt CVD in a population comprising four racial/ethnic groups (non-Hispanic White, Black, Hispanic American, and Chinese American) from six U.S. field centres.[18,19] Between 2000 and 2002 (Exam 1), the MESA cohort recruited 6814 men, and women aged 45–84 years who had no clinical history of CVD at baseline. Participants were then followed by further clinical evaluation and blood sample collection at Exam 2 (2002–2004), Exam 3 (2004–2005), Exam 4 (2005–2007), and Exam 5 (2010–2011).

Informed consents for participation were obtained from all participants and the MESA study. Associated protocols were approved by the Institutional Review Boards of each participating centre (details available at http://www.mesa-nhlbi.org).

Demographic and clinical characteristics

Demographics, CVD risk factors, and clinical characteristics were obtained as previously reported.[19] Covariates were taken from Exam 2 or 3 to be concomitant to when resistin was measured and included age, gender, race/ethnicity, smoking, diabetes mellitus, height and weight, hypertension, total and LDL levels, and statin use. Diabetes mellitus was defined based on fast plasma glucose ≥126 mg/dL or taking anti-diabetic drugs.[20] Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or taking anti-hypertensive medications.

Biomarker measurements

Blood samples were collected from a random subset of 1968 participants during MESA Exam 2 or 3 (2002–2005) (about one-half at each exam) who were enrolled in an ancillary study utilizing abdominal computed tomography to investigate the associations between abdominal body composition, adiposity, inflammatory biomarkers, and subclinic and incident CVD.[13] Briefly, resistin levels were measured from stored EDTA plasma samples that were processed with Bio-Rad Luminex flow cytometry (Millipore, Billerica, MA) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT). Plasma NT-proBNP and hs-cTnT levels had been previously measured in MESA participants at Exam 3.[5,21]

CMR measurements and myocardial fibrosis study

CMR imaging and myocardial fibrosis study were performed at Exam 5.[22–24] Briefly, mid-LV short-axis T1 maps were acquired before gadolinium administration (native or pre-contrast) and after gadolinium injection (post-contrast) using the modified look-locker imaging (MOLLI) sequence. Myocardial partition coefficient was computed by plotting the 1/T1 times of myocardium against the blood pool and calculating the slope of resultant linear regression line. Extracellular volume fraction (ECV) was derived by multiplying partition coefficient with (1-haematocrit/100).[24] Myocardial scar was defined by sub-endocardial or transmural late gadolinium enhancement areas that match any specific epicardial coronary artery perfusion territory.[25]

Outcomes ascertainment and HF events

At intervals of 9–12 months during the follow-up period, each participant in the MESA cohort or a family member of the participant was contacted by a telephone interviewer regarding all interim hospital admissions, cardiovascular outpatient diagnoses and procedures, and deaths. Additional information was obtained by cohort clinic visits, patient-initiated contact, and medical record data abstraction. Outcomes were adjudicated by a central committee composed of physicians. Myocardial infarction was based on evaluation of symptoms, electrocardiograms, and cardiac biomarker levels. HF and its subtypes were defined with combinations of HF symptoms and one or more imaging criteria, such as pulmonary oedema/congestion on chest X-ray, echocardiography, or radionuclide ventriculogram demonstrating evidence of reduced left ventricular systolic function, or evidence of left ventricular diastolic dysfunction. HFrEF was defined as HF diagnosis with documented left ventricular ejection fraction (LVEF) $<$ 45% and HFpEF with LVEF $\geq$ 45%.[26] The time to incident HF events among participants depended on the time of resistin measurement (Exam 2 or 3). Participants who had HF events before their resistin measurements were excluded. HF incidents that occurred any time after resistin measurement (Exam 2 or 3) were used for further analysis.

Statistical analysis

Descriptive statistics by incident HF status were presented as mean +/− standard deviations (SD) or frequency (%) and compared using either *t*-tests or chi-squared tests, respectively. Multivariable adjusted Cox proportional hazards models were applied to estimate the associations of resistin level with incident HF, HFrEF, and HFpEF during the period after the resistin measurement (Exam 2 or 3). As we are primarily interested in aetiologic associations, not cumulative incidence, a cause-specific approach was used to accommodate the competing risk of death, and for HF subtypes. Model 1 was adjusted for age, gender, education level, and race/ethnicity. Model 2 was further adjusted for smoking status, diabetes mellitus, body mass index, hypertension, systolic blood pressure, total and LDL cholesterol, and statin use. Model 3 was adjusted based on Model 2 plus an indicator for myocardial infarction prior to HF. Model 4 was adjusted for Model 1 plus ASCVD risk score.

Linear regression models were used to estimate the adjusted associations of resistin with biomarkers and CMR variables of fibrosis. Different subsets of participants were available for these measures depending on when the measurements were made. Cardiac biomarkers hs-cTnT and NT-proBNP were available at Exam 3 and were analysed in relation to the subset of resistin measures that were also taken at Exam 3. Finally, markers of fibrosis were taken from magnetic resonance images at Exam 5. Logistic regression was used to relate resistin to the presence of myocardial scar at Exam 5. For each endpoint, Model 1 included resistin, age, gender, race/ethnicity, and education. Model 2 additionally adjusted for ASCVD risk score. Robust standard errors were used in all models.

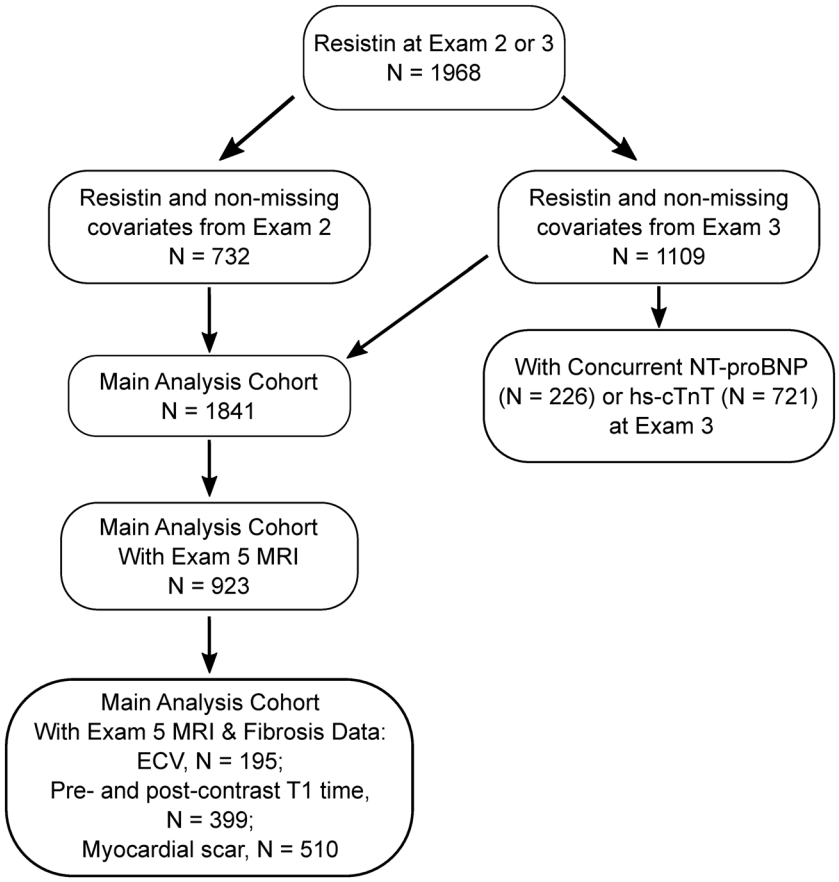
Results

Among the MESA study population at Exams 2 and 3, plasma resistin levels were measured in 1,968 participants (*Figure 1*).[13] After excluding participants with missing covariates, a total of 1841 participants were included in the analysis (732 from Exam 2 and 1109 from Exam 3). CMR was performed in 923 of these participants at Exam 5 with fibrosis measures including ECV available in 195 participants, pre-contrast T1 time and post-contrast 12 min and 25 min T1 time in 399 participants, and myocardial scar in 510 participants. Among 1109 participants with resistin at Exam 3, NT-proBNP and hs-cTnT levels were measured in 226 and 721 participants, respectively.

The baseline demographics characteristics, CV risk factors, and clinical characteristics, stratified by the development of incident HF, are shown in *Table 1*. Over a median follow-up time of 10.5 years, 74 participants out of total 1841 participants developed incident HF, which was significantly associated with elevated resistin levels (19.8 ± 8.8 vs. 16.1 ± 6.7 ng/mL, $P < 0.001$). Participants with incident HF tended to be significantly older and have higher weight and systolic blood pressure, higher 10-year ACVD rate, and a greater prevalence of hypertension and diabetes. There were no significant differences in total or LDL cholesterol, statin use, gender, race, education, smoking history and current smoking status between participants with and without incident HF. Kaplan–Meier failure curves demonstrated divergence of cumulative incidence of developing HF in resistin quartiles,[13] with significance increase in Quartile 4 ($P < 0.001$ based on log-rank test) (*Figure 2*).

Adjusted associations between resistin levels and incident HF and HF subtypes (HFrEF and HFpEF) are shown in *Table 2*. In all four models, elevated resistin levels were consistently associated with incident HF and remained a significant predictor for incident HF after multivariable adjustment (Model 1, HR 1.36, CI 1.14–1.62, $P = 0.001$; Model 2, HR 1.35, CI 1.12–1.63, $P = 0.002$; Model 3, HR 1.44, CI 1.18–1.75, $P = 0.001$; Model 4, HR 1.35, CI 1.13–1.62, $P = 0.001$). Elevated resistin levels were also associated with HFrEF across all models (Model 1, HR 1.34, CI 1.00–1.80, $P = 0.048$; Model 2, HR 1.39, CI 1.02–1.90, $P = 0.039$; Model 3, HR 1.47, CI 1.07–2.02, $P = 0.016$; Model 4, HR 1.34, CI 1.00–1.80, $P = 0.049$). No significant association between resistin level and HFpEF was found after multivariable adjustment in any of the four models.

Figure 1 Study flow chart. The flow chart illustrates the number of MESA participants included in this study based on the availability of resistin levels, non-missing covariates, and other markers.



We examined the association between resistin levels and levels of NT-proBNP and hs-cTnT at Exam 3 (*Table 3*). Resistin was not found to have a significant correlation with either biomarker.

We then examined the association of resistin levels measured at Exam 2 or 3 and CMR analysis at Exam 5 (*Table 3*). Resistin levels were negatively associated with post-contrast T1 time at 12 min (Model 1, β coefficient per SD −7.03, CI −12.06 to −1.99, P = 0.006; Model 2, β coefficient per SD −5.89, CI −10.94 to −0.84, P = 0.022) and 25 min (Model 1, β coefficient per SD −6.65, CI −11.67 to −1.62, P = 0.010; Model 2, β coefficient per SD −5.70, CI −10.71 to −0.70, P = 0.026) after gadolinium administration. Resistin levels did not show significant correlation with native pre-contrast T1 time, ECV, or myocardial scar.

Discussion

Over a median follow-up period of 10.5 years, elevated baseline resistin levels were significant predictors of incident HF and HFrEF in a multi-ethnic population. Conversely, the associations with HFpEF did not reach statistical significance. Elevated resistin levels were associated with shortened post-contrast T1 times at 12 and 25 min on CMR, but did not demonstrate significant associations with other myocardial fibrosis variables including native T1 times, ECV, and myocardial scar.

Several clinical and epidemiological studies have suggested associations between higher resistin levels and high rates of adverse cardiac events in patients hospitalized for HF or subjects with known CVD.[9,27] In a MESA study[13] with 7 years of follow-up, as well as the Framingham Offspring Study[10] with a mean follow-up time of 6 years, elevated circulating resistin levels were shown to be strongly associated with incident HF. Baseline clinical characteristics stratified by resistin quartiles in the prior MESA study showed that increasing resistin quartiles were associated with significant increases in age, race, and socio-economic status as well as risk factors such as BMI, systolic blood pressure, and the Framingham risk score.[13] We were able to extend these findings by showing associations of baseline resistin levels with incident HF with longer follow-up period of 10.5 years and determine its

Table 1 Demographics by incident CHF

Variable	Incident CHF: No (*N* = 1767)	Incident CHF: Yes (*N* = 74)	*P* value
	Mean ± SD	Mean ± SD	
Age (year)	64.4 ± 9.6	72.3 ± 7.9	<0.001
Height (cm)	166.3 ± 10.0	166.5 ± 10.2	0.841
Weight (lbs)	171.5 ± 37.1	181.9 ± 40.6	0.020
Smoking (pack-years)	11.7 ± 21.4	15.9 ± 23.1	0.100
Systolic BP (mmHg)	123.6 ± 20.8	133.5 ± 22.8	<0.001
Diastolic BP (mmHg)	70 ± 9.8	70.4 ± 12.3	0.711
Total cholesterol (mg/dL)	189.7 ± 34.4	185.1 ± 44.7	0.259
LDL cholesterol (mg/dL)	112.2 ± 30.9	110.6 ± 38.5	0.672
10-year ASCVD rate (%)	.1 ± 0.1	.3 ± 0.2	<0.001
Resistin (ng/mL)	16.1 ± 6.7	19.8 ± 8.7	<0.001
	N (%)	*N* (%)	
Gender			0.098
Female	891 (50.4)	30 (40.5)	
Male	876 (49.6)	44 (59.5)	
Race			0.516
Caucasian	705 (39.9)	33 (44.6)	
Chinese	244 (13.8)	6 (8.1)	
African American	361 (20.4)	14 (18.9)	
Hispanic	457 (25.9)	21 (28.4)	
Education			0.140
<High school	320 (18.1)	20 (27.0)	
High school/some college	803 (45.4)	31 (41.9)	
BS degree	320 (18.1)	15 (20.3)	
Graduate school	324 (18.3)	8 (10.8)	
Current smoker			0.292
No	1574 (89.1)	63 (85.1)	
Yes	193 (10.9)	11 (14.9)	
Diabetes			<0.001
No	1530 (86.6)	52 (70.3)	
Yes	237 (13.4)	22 (29.7)	
Hypertension			<0.001
No	947 (53.6)	19 (25.7)	
Yes	820 (46.4)	55 (74.3)	
On statin therapy			0.213
No	1375 (77.8)	53 (71.6)	
Yes	392 (22.2)	21 (28.4)	

Figure 2 Kaplan–Meier failure curves for incident HF, stratified by resistin quartiles.

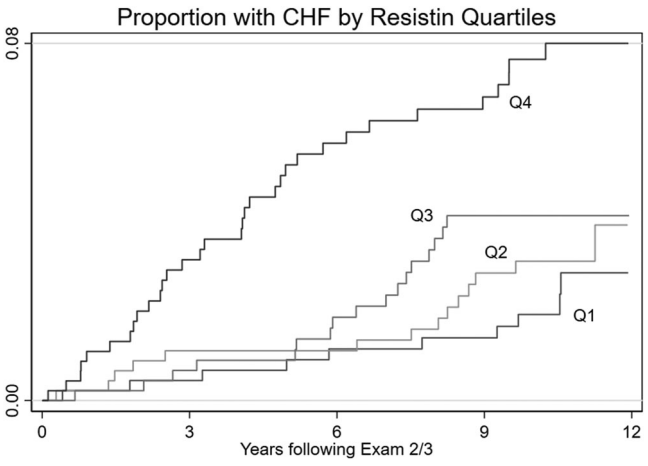


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Table 2 Cox proportional hazards models for incident heart failure (HF), heart failure with reduced ejection fraction (HFrEF), and heart failure with preserved ejection fraction (HFpEF) events

	Incident HF events = 74		Systolic HF (HFrEF) events = 29		Diastolic HF (HFpEF) events = 33	
Resistin per (SD = 6826)	HR[a] (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Model 1[b]	1.36 (1.14,1.62)	0.001	1.34 (1.00,1.80)	0.048	1.21 (0.91,1.62)	0.190
Model 2[c]	1.35 (1.12,1.63)	0.002	1.39 (1.02, 1.90)	0.039	1.18 (0.87,1.61)	0.295
Model 3[d]	1.44 (1.18,1.75)	0.001	1.47 (1.07, 2.02)	0.016	1.25 (0.89,1.75)	0.195
Model 4[e]	1.35 (1.13,1.62)	0.001	1.34 (1.00,1.80)	0.049	1.19 (0.89,1.59)	0.242

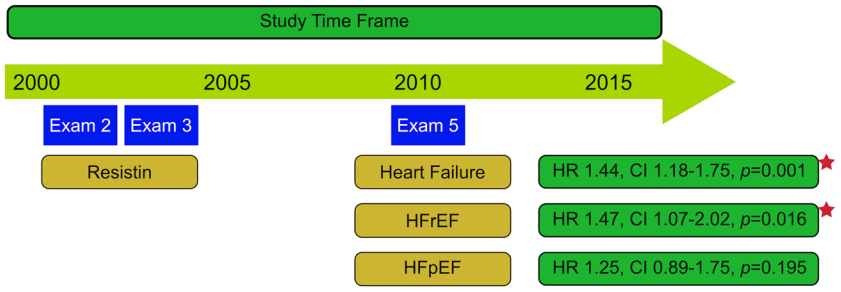
[a]HR is reported as per standard deviation increment in resistin levels.
[b]Model 1: adjusted for age, gender, education level, and race/ethnicity.
[c]Model 2: Model 1 plus smoking (current or not; pack-years over lifetime), diabetes mellitus, body mass index, hypertension, systolic blood pressure, total and LDL level, and statin use.
[d]Model 3: Model 2 plus interval myocardial infarction.
[e]Model 4: Model 1 plus ASCVD risk score.

Table 3 Association of resistin with cardiac biomarkers and fibrosis variables

		Model 1		Model 2	
	N	Resistin coefficient per SD (95% CI)	*P* value	Resistin coefficient per SD (95% CI)	*P* value
Limited to Exam 3 when BNP and hs-cTnT were measured					
NT-proBNP (pg/mL)	226	−11.0 (−32.9, 10.9)	0.322	−11.7 (−33.4, 10.0)	0.289
Hs-cTnT (ng/L)	721	0.49 (−0.13, 1.11)	0.123	0.44 (−0.16, 1.04)	0.154
Limited to Exam 5 when MRI was conducted					
Extracellular volume fraction (%)	195	−0.06 (−0.54, 0.42)	0.815	−0.22 (−0.71, 0.28)	0.390
Pre-contrast T1 time (ms)	399	2.79 (−1.44, 7.02)	0.196	2.04 (−2.30, 6.38)	0.356
12 min post-contrast T1 Time (ms)	399	−7.03 (−12.06, −1.99)	0.006	−5.89 (−10.94, −0.84)	0.022
25 min post-contrast T1 Time (ms)	396	−6.65 (−11.67, −1.62)	0.010	−5.70 (−10.71, −0.70)	0.026
		Odds ratio per SD (95% CI)	*P* value	Odds ratio per SD (95% CI)	*p*-value
Myocardial scar assessment	510	0.92 (0.65, 1.31)	0.649	0.91 (0.63, 1.31)	0.614

hs-cTnT, high-sensitive cardiac troponin T; *NT-proBNP*, amino-terminal B-type natriuretic peptide.
Model 1: adjusted for age, gender, education level, and race/ethnicity.
Model 2: Model 1 covariates plus ASCVD risk score.

Figure 3 Resistin and risk of heart failure. In a multi-ethnic cohort free of cardiovascular disease at baseline, elevated resistin levels measured at Exam 2 or 3 were significantly associated with incident HF and HFrEF that had occurred over a median 10.5-year follow-up after resistin measurement until the completion of Exam 5 in 2011. HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.



association with HF subtypes. The associations of resistin levels with incident HF and HFrEF remained statistically significant even after comprehensive multivariable adjustment models (*Table 2*).

Baseline hs-cTnT level has been proposed to be strongly associated with adverse ventricular remodelling in response to chronic subclinical cardiac injury in adults without clinical overt CVD.[4,5] We found that resistin levels at baseline were not associated with hs-cTnT levels or NT-proBNP. As a circulating peptide hormone, resistin levels at baseline perhaps reflect a systemic response to cardiovascular risk factors such as hypertension, diabetes, and vascular inflammation,[28] not limited to subclinical cardiomyocyte injury detected by mildly elevated hs-cTnT levels.

ECV is calculated from pre- and post-contrast myocardial T1 imaging, which gives relative quantification of the

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extracellular matrix component that is often affected by reactive fibrosis.[29] Despite post-contrast myocardial T1 times appeared to be significantly shortened with higher resistin levels, resistin levels did not demonstrate a significant association with ECV and native T1 times, which are considered to be more reliable MRI variables for myocardial fibrosis.[24] It should be noted that the models in *Table 3* were performed among all participants with both baseline resistin level and CMR data at Exam 5 available, not limited to participants who had developed incident HF. Therefore, the association between resistin and myocardial fibrosis in HF patients could be diminished due to the small number of HF incident cases in the current study. Further investigation is warranted to determine the association of resistin with cardiac function and myocardial fibrosis in a larger patient population of HF.

Despite diastolic dysfunction and myocardial fibrosis being detected in both HFrEF and HFpEF, there are significant differences at the molecular and cellular levels accounting for the pathophysiological progression between HFrEF and HFpEF.[30,31] Our epidemiologic study shows resistin may potentially serve as an early biochemical signature associated with HF and HFrEF. Clinical application of resistin measurement certainly requires further validation in larger patient cohorts.[32] Animal experiments have also provided insights into the relationships among resistin levels, HF and myocardial fibrosis, and modulation of resistin in alleviating HF at the molecular and cellular levels.[14–16,33] Therefore, resistin could also become a potential therapeutic target to alleviate cardiac remodelling and improve systolic function in patients with HF.

Limitations

Because the MESA study involves a large and ethnically diverse population from six communities with longitudinal follow-ups in the USA, there might be residual confounding. CMR and cardiac fibrosis data were restricted to a limited number of participants due to data availability, and some of the fibrosis variables were only examined once. Limitations also include the asynchronous nature of cross-sectional analyses in the present study with resistin measured at Exam 2 or 3, NT-proBNP and hs-cTnT at Exam 3, and CMR analysis at Exam 5 as well as the limited number of participants with measurements available for resistin, NT-proBNP, and hs-cTnT.

Conclusions

We have shown that in a multi-ethnic adult population without evidence of clinically overt cardiovascular disease, elevated baseline resistin levels are significantly associated with incident HF and HFrEF over a median 10.5-year follow-up (*Figure 3*), whereas the association between resistin levels and incident HFpEF was not statistically significant. Moreover, elevated resistin levels were not associated with CMR-derived myocardial fibrosis variables or biomarkers of HF. Future studies to investigate the relationship between resistin and cardiac remodelling CMR variables in a large population of HF patients are needed to determine the clinical significance and investigate the potential application of resistin as a novel biomarker and therapeutic target in HF patients.

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Conflict of interest

The authors report no relevant financial disclosures.

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