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Sleep apnea and galectin-3: possible sex-specific relationship

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Abstract

Purpose Sleep apnea is associated with increased risk of cardiovascular disease. Elevated plasma galectin-3 levels, a biomarker associated with myocardial fibrosis, are also associated with adverse cardiovascular events, including heart failure. Our objective was to determine the relationship between severity of sleep apnea and plasma levels of galectin-3 and to determine whether this relationship was modified by sex.

Methods We performed a cross-sectional study of 471 Mexican Americans from Starr County, TX who underwent an overnight, in-home sleep evaluation, and plasma measurement of galectin-3. Severity of sleep apnea was based on apnea hypopnea index (AHI). Multivariable linear regression modeling was used to determine the association between categories of sleep apnea and galectin-3. We also tested for interactions by sex.

Results The mean age was 53 years, and 74% of the cohort was female. The prevalence of moderate to severe sleep apnea (AHI > 15 apnea–hypopnea events per hour) was 36.7%. Moderate to severe sleep apnea was associated with increased levels of galectin-3 in the entire population, but we identified a statistically significant interaction between galectin-3 levels and category of sleep apnea by sex (p for interaction = 0.02). Plasma galectin levels were significantly higher in women with moderate or severe sleep apnea than women with no/mild sleep apnea (multivariable adjusted $p < 0.001$), but not in men ($p = 0.5$).

Conclusions Sleep apnea is associated elevated galectin-3 levels in women but not men. Our findings highlight a possible sex-specific relationship between sleep apnea and galectin-3, a biomarker of potential myocardial fibrosis that has been associated with increased cardiovascular risk.

Keywords Sleep apnea · Galectin-3 · High-sensitivity troponin

Abbreviations

AHI	Apnea hypopnea index
CPAP	Continuous positive airway pressure
ODI	Oxygen desaturation index
T90	Time spent (minutes) below nocturnal oxygen saturation of 90%
hsTnT	High-sensitivity troponin-T
NT-proBNP	N-terminal pro-B-type natriuretic peptide

Introduction

Galectin-3 is a beta-galactoside binding lecithin protein that is expressed in several cell types including inflammatory cells, epithelial cells, and fibroblasts and is involved in important regulatory roles in adhesion, inflammation, immunity, and fibrosis [1, 2]. Galectin-3 functions as a paracrine signal that leads to macrophage and fibroblast proliferation and the development of fibrosis [3]. Elevated plasma levels of galectin-3 are associated with increased risk of total mortality and mortality secondary to cardiovascular disease and incident heart failure in the general population [4–8]. Similarly, sleep apnea is associated with an increased risk of cardiovascular disease, including atrial fibrillation, coronary artery disease, and heart

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failure [9–12]. Although sleep apnea has been associated with increased levels of other biomarkers of cardiac injury and hemodynamic stress [13–16], the relationship between severity of sleep apnea and galectin-3 has not been well studied. We sought to investigate the relationship between sleep apnea and plasma levels of galectin-3 in a Mexican American population, a group with a high prevalence of obstructive sleep apnea [17]. In addition, we investigated whether the relationship between galectin-3 and sleep apnea was modified by sex, as previous studies have suggested potential sex-specific differences in the relationship between sleep apnea and cardiovascular disease [11, 14, 18].

Methods

The cohort for this study included 471 individuals from Starr County, Texas. Starr County is a Texas county located on the border of Mexico, and 96% of residents are Hispanic/Latino in origin [19]. All individuals in this study were classified as Mexican American. The cohort represents a subgroup of 1200 individuals from a recent study exploring the genetic underpinnings of sleep apnea and arterial stiffness [20]. The larger cohort of 1200 individuals was examined with the intent of sampling equal number of individuals with and without type 2 diabetes. We measured galectin-3 in the first 526 individuals that were enrolled in the study. Of these 526 individuals, 471 had sleep evaluations performed, and this group represents the population for our analyses. All aspects of the protocol were approved by the institutional review boards at participating institutions, and informed consent was obtained from all participants.

Examinations in the research center were performed in the morning after an overnight fast. The examination included medical and medication history, anthropometric measurements, glucose, hemoglobin A1c (point of care analyzer, DCA Vantage Analyzer, Siemens, Malvern, PA), and oral glucose tolerance testing in individuals not previously known to have diabetes. Blood pressure was measured three times following a 5-min sitting rest using an automated device (Critikon Dinamap Model 1846SX, Tampa, FL) with the average of the second and third values used as the final measures. Hypertension was defined as a history of hypertension, taking an antihypertensive medication, or a blood pressure > 140/90. Examinations occurred between December 2010 and January 2014.

All participants underwent an overnight, in-home sleep apnea evaluation. The sleep study was performed using the WatchPat 2000 monitor (Itamar Medical, Caesarea, Israel), an American Academy of Sleep Medicine approved type 3 monitor that provides a validated estimate of the Apnea Hypopnea Index (AHI) using information from digital peripheral arterial tonometry, finger pulse oximetry, and movement [21]. Snoring and body position were also recorded. The severity of sleep apnea was defined by using conventional clinical categories: none (AHI ≤ 5 apnea–hypopnea events per hour), mild (AHI > 5 to ≤ 15 apnea–hypopnea events per hour), moderate (AHI > 15 to ≤ 30 apnea–hypopnea events per hour), and severe (AHI > 30 apnea–hypopnea events per hour). Oxygen desaturation index (ODI) and the total time a person had nocturnal oxygen saturation below 90% (T90) were also recorded. The ODI is the number of oxygen desaturation events (4% minimum desaturation) per estimate hour of sleep.

Biomarkers were measured at the Baylor College of Medicine Atherosclerosis Clinical Research Laboratory. Galectin-3 was measured using a chemiluminescent microparticle immunoassay on an Architect *i* 2000 sr instrument (Abbott, Abbott Park, IL) in EDTA-plasma. 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. Inter-assay coefficients of variation 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.

In addition, we also measured high-sensitivity troponin-T (hsTnT), a biomarker of myocardial injury [22, 23], and N-terminal pro-B-type natriuretic peptide (NT-proBNP), a biomarker of hemodynamic stress and neurohormonal activation [24–26]. High-sensitivity troponin T was measured using a highly sensitive (precommercial) sandwich immunoassay method (Roche Elecsys T, Roche Diagnostic, Indianapolis, IN). The lower limit of blank for the hsTnT is 3.0 ng/L, and the limit of detection is 5.0 ng/L as reported previously (Roche Diagnostics, Indianapolis, IN) [22]. NT-proBNP was measured by using an electrochemiluminescent immunoassay on an automated Cobas e411 analyzer.

Baseline characteristics for the study population were tabulated by grouping individuals into categories of sleep apnea severity. Given the limited sample size in subcategories, sleep apnea was subsequently categorized into two clinically relevant groups: no/mild sleep apnea (AHI $\underline{\leq}$ 15) and moderate/severe sleep apnea (AHI > 15). Continuous variables were presented as means with standard deviations or median with 25th and 75th percentiles. Categorical variables were presented as percentages. Differences in baseline variables were ascertained using chi-square tests for categorical variables and *t* test for continuous variables and Kruskal–Wallis tests for non-normal variables. Correlations between galectin-3 and continuous measures of severity of sleep apnea were performed with Spearman correlation coefficients. Linear regression models were created to determine the relationship between galectin-3 and the categories of sleep apnea. The model was adjusted for age, sex, body mass index (BMI), waist circumference, hypertension status, smoking status, diabetes status, and history of cardiovascular disease. Because of non-normality, galectin-3 was natural log (ln) transformed for model analyses. We tested for sex-galectin interaction by

adding an interaction term into the adjusted linear regression model. Because hs-TnT varies by sex, we used sex-specific cut-points to define elevated hsTnT levels as a categorical variable (≥ 14 ng/L for males and ≥ 8 ng/L for females) [14]. Logistic regression models were used to assess the relationship between elevated hsTnT levels and categories of sleep apnea, as hsTnT could not be transformed into a normal distribution. NT-proBNP levels were ln-transformed for analyses.

Analyses were performed with STATA/IC version 12.1 (StataCorp). All tests were two-tailed with a p value < 0.05 considered as statistically significant.

Results

The analytical sample consisted of a total of 471 participants. The median age was 53 years, and 74% were female. The prevalence of mild, moderate, and severe obstructive sleep apnea was 32.3%, 20.6%, and 16.1%, respectively. Baseline characteristics for the study population by categories of sleep apnea are detailed in Table 1. Individuals with moderate to severe sleep apnea were older, more often male, had a higher BMI, higher waist circumference, higher systolic blood pressure, and a higher prevalence of cardiovascular disease. Diabetes prevalence, hemoglobin A1c, and fasting glucose were higher in those with sleep apnea. The percentage of individuals with detectable hsTnT, median levels of hsTnT, and the proportion of individuals with elevated hsTnT levels increased with increasing severity of sleep apnea. No association was noted amongst severity of sleep apnea and NT-proBNP levels.

The median galectin-3 concentration increased with increasing severity of sleep apnea in the total population (Table 1). Utilizing two clinically relevant categories of sleep apnea, the median galectin-3 concentration was higher in those with moderate/severe sleep apnea (7.63 ng/mL, 25th–75th percentiles 6.10, 8.84) compared to those with no/mild sleep apnea (6.53 ng/mL, 25th–75th percentiles 5.35, 7.57 ng/mL). In multivariable linear regression models for the entire population, moderate/severe sleep apnea was associated with increased levels of ln-galectin-3 in models adjusted for age, body mass index, waist circumference, hypertension, smoking status, diabetes mellitus, and history of cardiovascular disease (ß-coefficient 0.077, $p = 0.015$). When we tested for interaction by sex in full models, we found a statistically significant interaction between sex and categories of sleep apnea (p for interaction = 0.02). Therefore, we subsequently performed sex-specific analyses.

Baseline characteristics by categories of sleep apnea (no/mild sleep apnea and moderate/severe sleep apnea) and sex are shown in Table 2. A total of 351 women were enrolled in the study, and 116 (33%) had moderate to severe sleep apnea. Women with moderate to severe sleep apnea were more likely to be older, have a higher BMI, and have a history of hypertension, diabetes, and cardiovascular disease. Plasma galectin levels were significantly higher in women with moderate or severe sleep apnea (median galectin-3 levels 7.73 ng/mL, 25th–75th percentiles 6.46–9.19 ng/mL) than women with no/mild sleep apnea (median galectin-3 levels 6.29 ng/mL, 25th–75th percentiles 5.45–7.39 ng/mL, $p < 0.001$) (Table 2; Fig. 1). Spearman correlation coefficients for continuous measures of severity of sleep apnea and plasma galectin-3 levels are shown in Table 3.

The relationship between ln-galectin-3 and moderate/severe sleep apnea remained significant after adjusting for age, BMI, waist circumference, hypertension, smoking status, diabetes mellitus, and history of cardiovascular disease (ß-coefficient moderate/severe sleep apnea 0.14, $p < 0.001$). In fully adjusted multivariable model utilizing quartiles of ODI, women with the highest ODI quartile (> 13.9 hypoxic events/h) had increased levels of ln-galectin-3 compared to the lowest quartile (< 1.6 hypoxic events per hour) (ß-coefficient Q4 vs Q1 0.11, $p = 0.03$). The relationship between quartiles of time spent below a nocturnal oxygen saturation less than 90% and ln-galectin-3 levels was not statistically significant in women after adjustments in multivariable models (data not shown).

Women with moderate to severe obstructive sleep apnea also had higher levels of detectable, median hs-TnT, and elevated hs-TnT levels compared to women with mild or no obstructive sleep apnea (Table 2). The relationship between sleep apnea and elevated hsTnT was no longer significant after adjustment for age ($p = 0.22$) or in fully adjusted models ($p = 0.57$). In unadjusted analyses, median NT-proBNP levels were higher in women with moderate to severe sleep apnea compared to women with mild or no sleep apnea ($p = 0.046$), but this was no longer significant after adjustments for age ($p = 0.41$) or fully adjusted models ($p = 0.6$). In exploratory analysis, the relationship between ln-galectin-3 and moderate to severe sleep apnea in women remained statistically significant when NT-proBNP was added to the fully adjusted multivariable model ($p = 0.001$).

A total of 120 men were enrolled in the study. There was no statistical difference in age, hypertension status, or history of cardiovascular disease or diabetes in men with moderate to severe sleep apnea compared to men who had no or mild sleep apnea. Men with moderate to severe sleep apnea had a higher BMI than those with mild or no sleep apnea. In men, the median plasma galectin level was similar between those with moderate/severe sleep apnea (median galectin-3 levels 6.55 ng/mL, 25th–75th percentiles 5.23–8.33 ng/mL) and those with mild/no sleep apnea (median galectin-3 levels 6.62 ng/mL, 25th–75th percentiles 5.11–7.81 ng/mL, $p = 0.86$) (Table 2; Fig. 1). Similarly, in multivariable models, there was no statistically significant relationship between ln-

Table 1 Baseline characteristics for the cohort and by categories of sleep apnea

Baseline characteristics	Entire cohort ($n = 471$)	No sleep apnea ($n = 146$)	Mild sleep apnea ($n = 152$)	Moderate sleep apnea ($n = 97$)	Severe sleep apnea ($n = 76$)	P value
Age (years)	53 ± 11.5	50.0 ± 11.0	54.1 ± 10.7	56.5 ± 10.7	57.9 ± 10.3	< 0.001
Female sex (%)	351 (74.5)	125 (85.6)	110 (72.4)	68 (70.1)	48 (63.2)	0.001
BMI (kg/m^2)	32.1 ± 6.7	29.0 ± 5.1	31.9 ± 5.9	33.8 ± 6.7	36.6 ± 7.6	< 0.001
Waist circumference (cm)	104.4 ± 15.3	95.8 ± 12.0	104.4 ± 13.8	109.2 ± 15.3	114.8 ± 15.2	< 0.001
SBP (mm Hg)	129 ± 21	120 ± 19	131 ± 21	132 ± 22	136 ± 20	< 0.001
Hypertension (%)	278 (59.0)	51 (34.9)	93 (61.2)	75 (77.3)	59 (77.6)	< 0.001
History of CVD (%)	54 (11.5)	9 (6.2)	16 (10.5)	16 (16.5)	13 (17.1)	0.03
Current smoker (%)	66 (14.0)	23 (15.8)	19 (12.5)	12 (12.5)	12 (15.8)	0.08
Diabetes (%)	225 (47.8)	40 (27.4)	76 (50.0)	56 (57.7)	53 (69.7)	< 0.001
HbA1c (%)	6.6 ± 1.8	5.9 ± 1.4	6.7 ± 1.8	7.0 ± 2.0	7.3 ± 2.0	< 0.001
Fasting glucose (mg/dL)	129 ± 54.2	115 ± 47.0	134 ± 54.1	131 ± 56.7	147 ± 58.0	0.0002
Median AHI (25th, 75th)	9.8 (3.8, 20.5)	2.2 (0.7, 3.4)	9.1 (6.9, 11.6)	19.8 (17.4, 23.6)	42.6 (35.5, 53.7)	< 0.001
Median ODI (25th, 75th)	5.3 (1.4, 12.2)	0.8 (0.3, 1.4)	5 (3.1, 6.3)	12 (9.4, 15.5)	31.1 (22.7, 44.6)	< 0.001
Median T90 (min) (25th, 75th)	4.7 (0, 4.7)	0	0.3 (0, 1.2)	4.4 (1.4, 9.8)	21.4 (8.0, 46.7)	< 0.001
Median galectin-3 (ng/mL) (25th, 75th)	6.7 (5.5, 8.0)	6.2 (5.3, 7.3)	6.5 (5.5, 7.7)	7.4 (6.1, 8.8)	7.3 (5.9, 8.8)	< 0.001
Detectable hsTnT (%)	56.7	33.6	59.9	65.0	83.1	< 0.001
Median hsTnT (ng/L)	5 (1, 9)	3 (1, 6)	6 (1, 9)	6 (4, 10)	8 (6, 12.5)	< 0.001
Elevated hsTnT (%)	122 (25.9)	20 (13.7)	40 (26.3)	32 (33.0)	30 (39.5)	< 0.001
Median NT-Pro-BNP, (pg/mL) (25th,75th)	59.2 (34.8, 114)	54.6 (34.8, 83.6)	60.9 (37.5, 131)	63.1 (32.6, 115)	76.2 (32.2, 133)	0.23

Data are presented as mean ± SD, median (25th, 75th percentiles), or percentage

BMI body mass index, *SBP* systolic blood pressure, *CVD* cardiovascular disease, *AHI* apnea hypopnea index, *ODI* oxygen desaturation index, *T90* the total time a person had nocturnal oxygen saturation below 90%, *hsTnT* high-sensitivity troponin T, *NT-proBNP* N-terminal pro-B-type natriuretic peptide

*Elevated hsTnT: ≥ 14 ng/L for men or ≥ 8 ng/L for women

galectin-3 levels and categories of sleep apnea (β-coefficient moderate/severe sleep apnea −0.04, $p = 0.5$). No significant correlations were identified for other continuous measures of severity of sleep apnea and plasma galectin-3 levels in men (Table 3). There was also no significant association between severity of obstructive sleep apnea and median troponin or NT-pro-BNP levels (Table 2).

Discussion

In this community-based cohort of Mexican Americans from Starr County, Texas, we demonstrate a relationship between moderate/severe sleep apnea and elevated galectin-3 levels. Elevated plasma levels of galectin-3, a beta-galactoside-binding lecithin, have been associated with increased risk of heart failure and mortality in multiple epidemiologic studies in the general population [4–8]. Galectin-3 functions as a paracrine signal that is secreted in the bloodstream and directly in the extracellular matrix and leads to macrophage and fibroblast proliferation and the development of fibrosis. Galectin-3 has been shown to be a mediator of aldosterone-induced vascular fibrosis [27]. In a heart failure-prone rat model, upregulation of myocardial galectin-3 is seen early in the development of left ventricular hypertrophy and is increased in rats developing heart failure [3]. A potential causal role of galectin-3 is further supported by animal studies where administration of galectin-3 results in myocardial fibrosis and heart failure [3], while pharmacologic or genetic disruption of galectin-3 attenuates myocardial fibrosis and alleviates cardiac dysfunction [28, 29].

Sleep apnea is associated with an increased risk of arterial hypertension, atrial fibrillation, coronary artery disease, and heart failure [9–12, 30]. Similarly, sleep apnea has been associated with cardiac structural changes including left atrial enlargement and abnormalities of diastolic function that may predispose to development of atrial fibrillation and heart failure [31, 32]. Mechanisms behind sleep apnea-associated cardiovascular disease are thought to be related to intermittent hypoxia, increased sympathetic activity, increased ventricular afterload, inflammation, oxidative stress, and endothelial dysfunction [12, 33, 34]. Our study implicates a potential role of galectin-3 and myocardial fibrosis in the cardiovascular dysfunction associated with obstructive sleep apnea. These findings are consistent with animal studies that have demonstrated that intermittent hypoxia is associated with myocardial fibrosis [35, 36].

Importantly, we demonstrate a possible novel sex-specific association between galectin-3 and sleep apnea, with the relationship between moderate to severe sleep apnea and galectin-

Table 2 Baseline characteristics by sex and category of sleep apnea

Baseline characteristics	Female ($n = 351$)			Male ($n = 120$)		
	No/mild sleep apnea ($n = 235$)	Mod/severe sleep apnea ($n = 116$)	p value	No/mild sleep apnea ($n = 63$)	Mod/severe sleep apnea ($n = 57$)	p value
Age (years)	49.6 ± 10.9	57.2 ± 10.9	< 0.001	54.3 ± 12.5	56.8 ± 9.9	0.24
BMI (kg/m^2)	30.7 ± 6.0	36.0 ± 7.4	< 0.001	29.7 ± 4.5	33.1 ± 6.5	0.001
Waist circumference (cm)	99.1 ± 13.7	111.8 ± 16.1	< 0.001	104.5 ± 12.6	111.4 ± 14.3	0.006
SBP (mm Hg)	122 ± 19	133 ± 23	< 0.001	138 ± 22	137 ± 18	0.81
Hypertension (%)	102 (43.4)	91 (78.5)	< 0.001	42 (66.7)	43 (75.4)	0.29
History of CVD (%)	14 (6.0)	16 (13.8)	0.01	11 (17.5)	13 (22.8)	0.47
Current smoker (%)	30 (12.8)	8 (6.9)	0.25	12 (19.1)	16 (28.6)	0.21
Diabetes (%)	75 (31.9)	73 (62.9)	< 0.001	41 (65.1)	36 (63.2)	0.97
HbA1c (%)	6.1 ± 1.5	7.3 ± 2.1	< 0.001	7.1 ± 2.0	6.8 ± 1.7	0.29
Fasting glucose (mg/dL)	116 ± 44.5	140 ± 59.9	< 0.001	154 ± 63.8	135 ± 53.2	0.08
Median AHI (25th, 75th)	4.3 (1.7, 8.7)	24.9 (18.8, 40.1)	< 0.001	7.3 (3.8, 10.9)	29.1 (18.1, 40)	< 0.001
Median ODI (25th, 75th)	1.7 (0.7, 4.6)	16.4 (11.1, 28.6)	< 0.001	3.1 (1.5, 5.6)	19.8 (11.2, 32.4)	< 0.001
Median T90 (min) (25th,75th)	0 (0, 0.3)	8.7 (2.2, 19.3)	< 0.001	0.1 (0, 0.6)	8.1 (2.5, 26.5)	< 0.001
Median galectin-3 (ng/mL) (25th, 75th)	6.29 (5.45, 7.39)	7.73 (6.46, 9.19)	< 0.001	6.62 (5.11, 7.81)	6.55 (5.23, 8.33)	0.86
Detectable hsTnT (%)	96 (40.9)	78 (67.3)	< 0.001	44 (69.8)	49 (86.0)	0.04
Median hsTnT (ng/L)	4 (1, 7)	6 (4, 9.5)	< 0.001	8 (4. 12)	9 (6, 15)	0.13
Elevated hsTnT*	46 (19.6)	44 (37.9)	< 0.001	14 (22.2)	18 (31.6)	0.25
Median NT-Pro-BNP (pg/mL) (25th, 75th)	58.8 (38.3, 91.7)	78.5 (38.8, 126)	0.046	44.5 (27.5, 132)	47.8 (19.4, 127)	0.33

Data are presented as mean ± SD, median (25th, 75th percentile), or percentage

BMI body mass index, *SBP* systolic blood pressure, *CVD* cardiovascular disease, *AHI* apnea hypopnea index, *ODI* oxygen desaturation index, *T90* the total time a person had nocturnal oxygen saturation below 90, *hsTnT* high-sensitivity troponin T, *NT-proBNP* N-terminal pro-B-type natriuretic peptide

*Elevated hsTnT: ≥ 14 ng/L for men or ≥ 8 ng/L for women

3 being present in women, but not in men. While multiple epidemiologic studies have demonstrated that sleep apnea is associated with abnormalities of cardiac structure and increased risk of cardiovascular disease, including coronary

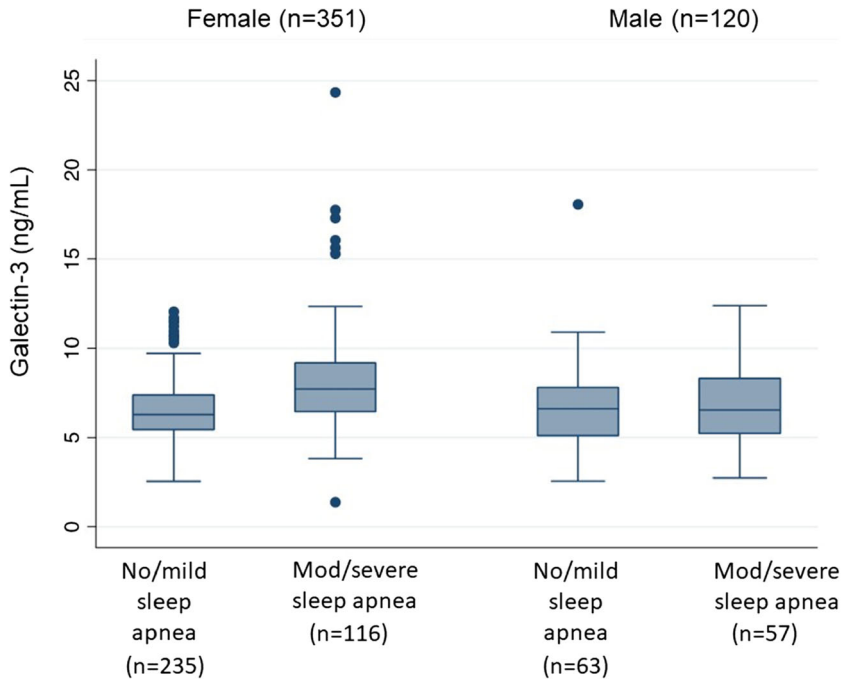

Fig. 1 Plasma galectin-3 levels by sleep apnea categories. Data are median (interquartile range)

Table 3 Spearman correlation coefficients between plasma galectin-3 and select measures of severity of sleep apnea by sex

	Females ($n = 351$)		Men ($n = 120$)	
	Correlation coefficient	p value	Correlation coefficient	p value
AHI	0.29	< 0.001	0.06	0.48
ODI	0.31	< 0.001	0.07	0.47
Mean oxygen saturation	− 0.28	< 0.001	− 0.16	0.08
T90	0.31	< 0.001	0.13	0.16

AHI apnea hypopnea index, *ODI* oxygen desaturation index, *T90* the total time a person had nocturnal oxygen saturation below 90%

artery disease, atrial fibrillation, and heart failure, some studies have suggested that the adverse cardiovascular consequences of sleep apnea may be particularly relevant to women [13, 18]. For example, in a community-based cohort of 1645 individuals, obstructive sleep apnea was associated with higher levels of hsTnT in women, but not in men [14]. Furthermore, in the same community-based sample, obstructive sleep apnea was associated with left ventricular hypertrophy and incident heart failure in women but not men [14]. Despite these studies, not all studies have been consistent, as others have demonstrated stronger associations with mortality [37] and incident HF [11] in men with sleep apnea compared to women. In our study, hsTnT levels were increased in women with moderate to severe sleep apnea compared to those with no or mild sleep apnea, but this relationship did not persist after adjustments for baseline characteristics, which may be related to our smaller sample size or differences in baseline characteristics between studies. Future work is needed to confirm our findings and to understand the mechanisms contributing to potential sex differences in the relationship between sleep apnea and cardiovascular disease. Studies have suggested that women with sleep apnea may have more endothelial dysfunction [38], potential microvascular abnormalities [39], and abnormalities of autonomic function [40]. Whether these or other pathways could contribute to increased markers of fibrosis remains unclear and deserves further work. A recent trial reported that treatment with continuous positive airway pressure did not lower the risk of serious cardiovascular outcomes in 2717 non-sleepy patients with previously established moderate to severe obstructive sleep apnea [41]. There was no difference in the efficacy of continuous positive airway pressure (CPAP) to reduce the primary cardiovascular outcome in women compared to men, but only 20% of the participants in the study were females [41]. As moderate to severe sleep apnea in women appears to be associated with markers of adverse cardiovascular outcomes, studies with larger numbers of women are needed to determine if CPAP treatment would have potential sex-specific salutary effects.

Our study also highlights the high prevalence of unrecognized sleep apnea in the Hispanic American population. Over 30% of our study population was found to have moderate to severe sleep apnea. It is important to note that our sample was selected from a larger cohort that was examined with the intent of sampling an equal number of individuals in the community with and without type 2 diabetes. Therefore, our cohort had higher rates of diabetes and obesity, risks factors that have been shown to be strongly associated with sleep apnea [42]. Nonetheless, data from the Hispanic Community Health Study/Study of Latinos demonstrates that sleep apnea is highly prevalent in the Hispanic community, and, despite the high prevalence of sleep apnea, only 1.3% had previously received a diagnosis of sleep apnea [17]. The high prevalence in this population without a previous diagnosis, coupled with increased levels of adverse cardiovascular biomarkers, suggests a large population that may be at risk for adverse cardiovascular events.

There are several limitations to our present study. As described, our cohort was a Mexican American population, and future studies are necessary to examine the relationship between galectin-3 and sleep apnea in other populations. Nonetheless, our finding in this population is important, as previous studies of sleep apnea and cardiovascular biomarkers, such as troponin, have been limited to predominantly non-Hispanic populations [13]. Similarly, the number of men included in our study was smaller than women, and future studies with larger sample sizes of men should be performed to confirm our findings and exclude any potential selection bias of our study as the result of the relatively small sample of men. While we adjusted for potential confounders, residual confounding may still be present. For example, we did not have measures of baseline renal function, which may attenuate the relationship between galectin-3 and incident heart failure [5]. The cross-sectional design precluded assessment of the temporal association between changes in biomarkers and sleep apnea. While sleep apnea assessment was determined using a reliable and validated home sleep apnea test, it did not record information on electro-encephalography (EEG) needed to additionally assess the role of EEG arousals or changes in sleep architecture with our study outcomes.

In conclusion, we demonstrate a relationship between severity of sleep apnea and plasma levels of galectin-3, a biomarker of myocardial fibrosis that has been associated with increased cardiovascular risk. In addition, our finding that the galectin-3 relationship is present in women with moderate/severe sleep apnea and not in men adds to a small, but growing body of literature of potential sex-specific associations between sleep apnea and cardiovascular risk and the potential for women with sleep apnea to be at increased risk for heart failure. Finally, our study highlights the high prevalence of sleep apnea in this cohort of Mexican American and the need for further efforts to raise awareness, screening, and treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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