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Insulin-Like Growth Factor–Binding Protein-7 as a Biomarker of Diastolic Dysfunction and Functional Capacity in Heart Failure With Preserved Ejection Fraction

Results From the RELAX Trial

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ABSTRACT

OBJECTIVES This study sought to investigate relationships between insulin-like growth factor–binding protein-7 (IGFBP7) and parameters of diastolic function or functional capacity in patients with heart failure and preserved ejection fraction (HFpEF) who were randomized to receive sildenafil or placebo.

BACKGROUND IGFBP7 was previously found to be associated with diastolic function in heart failure with reduced ejection fraction, but it is unclear whether these associations are present in HFpEF.

METHODS At baseline and 24 weeks, IGFBP7, imaging studies, and peak oxygen consumption (Vo_{2max}) were obtained and compared in 160 patients with HFpEF who were randomized to receive sildenafil or placebo.

RESULTS Patients with supramedian baseline IGFBP7 concentrations were older, had signs of systemic congestion and worse renal function, and had higher concentrations of prognostic heart failure biomarkers including amino-terminal pro-B-type natriuretic peptide ($p < 0.05$). Higher baseline IGFBP7 was modestly correlated with worse diastolic function: higher E velocity (Spearman correlation [ρ] = 0.40), E/E′ ($\rho = 0.40$), left atrial volume index ($\rho = 0.39$), and estimated right ventricular systolic pressure ($\rho = 0.41$; all $p < 0.001$) and weakly correlated with transmitral E/A ($\rho = 0.26$; $p = 0.006$). Notably, change in IGFBP7 was significantly correlated with change in E, E/A, E/E′, and right ventricular systolic pressure. Elevated baseline IGFBP7 was associated with lower baseline Vo_{2max} (13.2 vs. 11.1 ml/min/kg; $p < 0.001$), and change in IGFBP7 was weakly inversely correlated with change in Vo_{2max} ($\rho = -0.19$; $p = 0.01$). Subjects receiving sildenafil had a decrease in IGFBP7 over 24 weeks, in contrast to placebo-treated patients (median change in IGFBP7 −1.5 vs. +13.6 ng/ml; $p < 0.001$).

CONCLUSIONS In patients with HFpEF, IGFBP7 may be a novel biomarker of diastolic function and exercise capacity. (J Am Coll Cardiol HF 2016;4:860–9) © 2016 by the American College of Cardiology Foundation.

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Heart failure (HF) with preserved ejection fraction (EF), abbreviated HFpEF, affects approximately one-half of patients with the clinical syndrome of HF is associated with considerable morbidity and mortality (1,2). A pivotal abnormality in HFpEF is the presence of impaired myocardial diastolic function; echocardiographic parameters to assess such impaired function can be complicated to obtain and interpret accurately (3). This difficulty is further compounded by the fact the clinical diagnosis of HFpEF may be challenging to recognize and manage. Taken together, these issues may be potential reasons that therapeutic trials have been disappointing for this common type of HF.

The use of cardiac biomarkers in HF is a rapidly growing area of interest (4), and it may provide options to assist in the care of patients with HFpEF through better phenotyping of the syndrome. B-type natriuretic peptide (BNP) and its amino-terminal precursor (NT-proBNP) have been examined for both diagnosis and risk stratification in HFpEF (5,6), and the concentrations of these peptides are associated with echocardiographic parameters used to define diastolic dysfunction (7,8). However, because the prime trigger for natriuretic peptide (NP) release is myocardial diastolic wall stress, these peptides may be nonspecific for diastolic function; indeed, many other echocardiographic abnormalities such as left ventricular ejection fraction (LVEF), chamber size, and valvular regurgitation contribute to circulating concentrations of BNP or NT-proBNP (9). Other biomarkers have therefore been explored for profiling of HFpEF (10–13), but they remain nonspecific for the diagnosis, similar to the NPs.

Insulin-like growth factor-binding protein-7 (IGFBP7) was identified as a biomarker associated with cardiac hypertrophy and HF through systematic proteomic candidate searches (14). IGFBP7 concentrations were found to be prognostic for prediction of worsening HF, hospitalization for HF, and cardiovascular death in a well-phenotyped cohort of patients with heart failure and reduced ejection fraction (HFrEF) (15). Although IGFBP7 was not associated with echocardiographic parameters of systolic function or remodeling, it was significantly correlated with multiple parameters of diastolic function (16). Diastolic abnormalities are highly prevalent in patients with HFrEF (9), but it is unclear whether IGFBP7 would demonstrate a similar relationship in a population of patients with HFpEF, in whom diastolic abnormalities are even more important. We therefore sought to examine baseline concentrations and change over time in IGFBP7 in a well-characterized group of patients with HFpEF from the RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in HFpEF) study (17). We also investigated associations between IGFBP7 and peak oxygen consumption (Vo_{2max}), as well as treatment with sildenafil. We hypothesized that baseline IGFBP7 and change in IGFBP7 (ΔIGFBP7) would be significantly associated and correlated with imaging parameters of diastolic dysfunction and Vo_{2max} in patients with HFpEF.

METHODS

PATIENT POPULATION AND STUDY OVERVIEW. The RELAX study evaluated the effect of sildenafil on exercise capacity and clinical status in 216 patients with EF ≥50%, stable HF symptoms with objective evidence of HF (defined as previous HF-related hospitalization, short-term therapy of HF with administration of intravenous diuretic agents, long-term therapy with loop diuretic agents in patients with left atrial enlargement, or invasively documented elevated left ventricular (LV) filling pressures), and Vo_{2max} of ≤60% of age- and sex-predicted value (with respiratory exchange ratio of ≥1.0), as well as either NT-proBNP ≥400 pg/ml or elevated LV filling pressures at the time of NT-proBNP measurement of <400 pg/ml (17). The primary endpoint was change in Vo_{2max} (ΔVo_{2max}) at 24 weeks; secondary endpoints included change in 6-min walk distance, change in clinical status score derived on the basis of time to death, time to cardiovascular or cardiorenal hospitalization, and change in quality of life (for patients who were not hospitalized) at 24 weeks (17). The RELAX trial was funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health and was conducted by the Heart Failure Network. All patients provided written informed consent, and that trial was approved by the Institutional Review Board at each site (17). The current analysis examines IGFBP7 in 160 patients from the RELAX trial who had available blood samples. Echocardiographic measurements, magnetic resonance imaging (MRI) data, and Vo_{2max} were compared at baseline and 24 weeks in patients receiving placebo and sildenafil to characterize the mechanistic links between IGFBP7 and diastology, as well as to evaluate the effects of sildenafil therapy on IGFBP7 in patients with HFpEF.

LABORATORY EVALUATION AND IMAGING STUDIES. Standard biomarker measurements were performed

ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

CPET = cardiopulmonary exercise testing

Δ = change

eGFR = estimated glomerular filtration rate

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

IGFBP7 = insulin-like growth factor–binding protein-7

LV = left ventricular

MRI = magnetic resonance imaging

NP = natriuretic peptide

NT-proBNP = amino-terminal pro-B-type natriuretic peptide

RVSP = right ventricular systolic pressure

Vo_{2max} = peak oxygen consumption

in blinded fashion as previously reported by the Heart Failure Network biomarker core laboratory (University of Vermont, Burlington, Vermont) (18). IGFBP7 was measured using an Elecsys assay (Roche Diagnostics, Penzburg, Germany). The limit of detection for the IGFBP7 assay was 0.01 ng/ml. The interrun and intrarun coefficients of variation were ≤5% and ≤2%, respectively.

Blinded core laboratories assessed data from echocardiography (Mayo Clinic, Rochester, Minnesota), MRI (Duke University, Durham, North Carolina) and cardiopulmonary exercise testing (CPET) (Massachusetts General Hospital, Boston, Massachusetts). Diastolic function parameters assessed included the following: mitral inflow peak early filling velocity (E) and late diastolic filling velocity (A), as well as their ratio (E/A); tissue Doppler early diastolic mitral annular velocity (E′); and estimation of filling pressures using the ratio of E/E′. Additionally, we examined the left atrial volume index and estimated right ventricular systolic pressure (RVSP) and LV hypertrophy because they are considered important echocardiographic measures of diastolic dysfunction (3).

STATISTICAL ANALYSIS. A total of 161 patients were included in the analysis, but 1 subject was missing a baseline IGFBP7 concentration, and another was missing the 24-week IGFBP7 concentration; data are available on 159 patients for ΔIGFBP7. Subjects were initially divided into groups using the median baseline IGFBP7 concentration of 219 ng/ml, and baseline characteristics were compared using the Wilcoxon rank sum test for continuous variables and the chi-square test for categorical variables. Continuous variables are displayed as medians and as 25th and 75th percentiles (interquartile range). IGFBP7 was compared with other established and emerging biomarkers by using bivariate correlations. Baseline imaging parameters were compared between subjects with inframedian IGFBP7 concentrations and compared to those with supramedian concentrations using the Wilcoxon rank sum test.

To investigate the independent predictive value of IGFBP7 further, logistic regression was performed with IGFBP7 as the independent variable and parameters of diastolic dysfunction as the dependent variables, adjusting for age, renal function, and NT-proBNP. Receiver-operating characteristic curves were also constructed for both IGFBP7 and NT-proBNP to identify appropriate cutpoints with parameters of diastolic dysfunction. Relationships between IGFBP7 and imaging parameters are presented as Spearman correlations for both baseline and 24-week change measures. Change was defined as final value minus baseline value for each parameter. Rho (ρ) values, adjusted for baseline variables, are presented for the relationship between the week 24 difference in log-transformed IGFBP7 and the change in imaging variable. Baseline Vo_{2max} and ΔVo_{2max} were examined in a similar fashion; the relationship between ΔVo_{2max} and ΔIGFBP7 is shown with a scatterplot. Analyses of echocardiographic and MRI parameters of diastolic function were repeated using median splits of baseline NT-proBNP and galectin-3, as well as change in NT-proBNP (ΔNT-proBNP) and change in galectin-3 (Δgalectin-3) at 24 weeks.

To evaluate the effects of sildenafil therapy on IGFBP7 concentrations, median baseline IGFBP7, 24-week IGFBP7, and ΔIGFBP7 concentrations were compared between subjects receiving sildenafil and subjects receiving placebo by using the Wilcoxon rank sum test. An adjusted p value for treatment effect comes from a linear regression model that adjusts for log-transformed baseline IGFBP7 concentration.

Data were analyzed with SAS version 9.4 (SAS Institute, Cary, North Carolina). All p values are 2-sided, with results ≤0.05 considered significant.

RESULTS

BASELINE IGFBP7 CONCENTRATIONS AND BASELINE CHARACTERISTICS. The median IGFBP7 concentration was 219 ng/ml. Online Table 1 compares the baseline characteristics of the subjects included in the current analysis with the characteristics of study subjects who did not have IGFBP7 concentration data available. Compared with the subjects included in the current analysis, those without baseline IGFBP7 concentration data appeared to have characteristics of more advanced HF. **Table 1** shows the baseline characteristics of the subjects in the current analysis divided by the median IGFBP7 concentration. Patients with supramedian IGFBP7 concentrations were older, more likely to have atrial fibrillation or flutter as well as signs of congestion, and more likely to be taking a diuretic. Additionally, these patients had significantly elevated cystatin C, NT-proBNP, pro-collagen type III amino-terminal peptide (PIIINP), highly sensitive troponin I (hsTnI), and galectin-3 concentrations, as well as a reduced estimated glomerular filtration rate (eGFR) when compared with patients with inframedian IGFBP7 concentrations.

Table 2 shows baseline imaging and CPET results. In the current analysis, 159 patients underwent echocardiography, 88 had MRI, and 160 underwent CPET at baseline. Baseline echocardiography revealed modest but significant associations and correlations

TABLE 1 Baseline Characteristics Divided by Median Baseline IGFBP7 Concentration

	N	IGFBP7 <219 ng/ml	N	IGFBP7 >219 ng/ml	p Value
Clinical data					
Age (yrs)	80	67 (60.5–73.0)	80	69 (65–78)	0.02
Male (%)	80	34 (42.5)	80	45 (56.3)	0.08
Self-reported race white (%)	80	76 (95.0)	80	72 (90.0)	0.23
Ischemic heart disease (%)	80	26 (32.5)	80	34 (42.5)	0.19
Hypertension (%)	80	65 (81.3)	80	69 (86.3)	0.39
Presence of atrial fibrillation or flutter (%)	80	30 (37.5)	80	49 (61.3)	0.003
Chronic obstructive pulmonary disease (%)	80	13 (16.3)	80	16 (20.0)	0.54
Diabetes mellitus (%)	80	27 (33.8)	80	38 (47.5)	0.08
Hospitalization for heart failure in last year (%)	80	22 (27.5)	80	29 (36.3)	0.24
Calculated definition of anemia (%)	80	15 (18.8)	80	34 (42.5)	0.001
Physical examination					
Body mass index (kg/m^2)	80	32.8 (29.0–37.7)	80	32.9 (28.1–39.5)	0.85
Systolic blood pressure (mm Hg)	80	126 (113–138)	80	124 (113–135)	0.82
Diastolic blood pressure (mm Hg)	80	70 (64–80)	80	69.5 (61–78)	0.26
Heart rate (beats/min)	80	68.5 (62.0–78.5)	80	68 (60–79)	0.62
Jugular venous pressure ≥8 cm H_2O (%)	77	21 (27.3)	77	42 (54.5)	<0.001
Rales (%)	80	4 (5.0)	80	6 (7.5)	0.51
Peripheral edema (%)	80	10 (12.5)	80	22 (27.5)	0.02
NYHA functional classification >II (%)	80	37 (46.3)	80	46 (57.5)	0.15
Orthopnea (%)	73	42 (57.5)	76	46 (60.5)	0.71
Medications before randomization					
ACE inhibitor or angiotensin receptor blocker (%)	80	58 (72.5)	80	52 (65.0)	0.31
Beta blocker (%)	80	58 (72.5)	80	61 (76.3)	0.59
Aldosterone antagonist (%)	80	7 (8.8)	80	11 (13.8)	0.32
Calcium channel blocker (%)	80	18 (22.5)	80	30 (37.5)	0.04
Statin (%)	80	53 (66.3)	80	50 (62.5)	0.62
Daily diuretic (%)	80	56 (70.0)	80	77 (96.3)	<0.0001
Functional data					
MLWHF total score	78	44 (31–65)	75	42 (26–59)	0.28
MLWHF physical dimension score	80	24 (18.5–30.5)	78	21 (13–29)	0.08
Baseline walk distance (m)	80	357 (288–401)	80	302 (239–359)	0.002
Core laboratory findings					
Creatinine (mg/dl)	80	0.93 (0.75–1.13)	78	1.22 (1.01–1.54)	<0.0001
Cystatin C (mg/l)	80	1.09 (0.91–1.25)	80	1.59 (1.19–1.93)	<0.0001
eGFR (ml/min/1.73 m^2)	80	75.8 (61.1–88.9)	78	55.5 (42.7–68.6)	<0.0001
NT-proBNP (pg/ml)	80	291 (90–620)	79	1,174 (620–1,919)	<0.0001
Pro-collagen III NTP (μg/l)	80	6.78 (5.17–7.99)	80	8.7 (6.5–11.6)	<0.0001
High sensitivity troponin I (pg/ml)	80	5.9 (3.5–11.4)	78	11.2 (7.8–21.9)	<0.0001
Galectin-3 (ng/ml)	80	12.9 (10.3–15.9)	75	15.2 (11.7–20.4)	0.002

Values are n (%) or median (interquartile range).

ACE = angiotensin converting enzyme; eGFR = estimated glomerular filtration rate; IGFBP7 = insulin-like growth factor-binding protein 7; IQR = interquartile range; MLWHF = Minnesota Living With Heart Failure; NT-proBNP = amino-terminal pro-B-type natriuretic peptide; NTP = amino-terminal peptide; NYHA = New York Heart Association.

between baseline IGFBP7 and transmitral E velocity ($\rho = 0.40$; $p < 0.0001$), E/E′ ($\rho = 0.40$; $p < 0.0001$), left atrial volume index ($\rho = 0.39$; $p < 0.0001$), and estimated RVSP ($\rho = 0.41$; $p < 0.0001$). Baseline echocardiography was also weakly associated and correlated with the transmitral E/A ratio ($\rho = 0.26$; $p = 0.006$). Scatterplots of these correlations are shown in **Figure 1**. These results demonstrated stronger correlations than our previous findings in patients with HFrEF (16). Notably, there were no significant associations or correlations with measures of systolic function including LV end-diastolic volume index ($\rho = 0.19$; $p = 0.10$), LV end-systolic volume index ($\rho = 0.16$; $p = 0.16$), and LVEF ($\rho = -0.13$; $p = 0.09$). LV hypertrophy ($\rho = 0.23$; $p = 0.01$) and LV mass index as assessed by both echocardiography and MRI were significantly associated with IGFBP7 concentrations ($\rho = 0.23$; $p = 0.01$ and $\rho = 0.22$; $p = 0.04$, respectively). MRI estimates at baseline revealed significantly reduced aortic

TABLE 2 Baseline Imaging and Cardiopulmonary Exercise Testing Results, Divided by Median Baseline IGFBP7 Concentration

	N	IGFBP7 <219 ng/ml	IGFBP7 >219 ng/ml	Wilcoxon Rank Sum p Value	Spearman Correlation With Baseline IGFBP7 (ρ)	Spearman Correlation p Value
Baseline echocardiography						
MV inflow: E velocity at leaf tip (m/s)	151	0.9 (0.7–1.1)	1.1 (0.9–1.4)	<0.0001	0.395	<0.0001
MV inflow: A velocity at leaf tip (m/s)	112	0.7 (0.5–0.9)	0.6 (0.4–0.9)	0.30	−0.066	0.49
E/A ratio	112	1.18 (1.00–1.80)	1.80 (1.13–3.25)	0.01	0.258	0.006
LV relaxation septal − E′ (m/s)	146	0.06 (0.05–0.08)	0.06 (0.04–0.07)	0.047	−0.203	0.01
Filling pressure septal (medial) − E/E′ (m/s)	143	13.3 (10.0–18.2)	18.3 (13.3–26.7)	<0.001	0.398	<0.0001
LA volume index (ml/m^2)	113	40.3 (31.7–47.3)	53.9 (39.8–63.1)	<0.001	0.386	<0.0001
RVSP (mm Hg)	103	35.7 (32.0–43.6)	48.4 (36.4–56.0)	<0.001	0.413	<0.0001
LV mass index (g/m^2)	117	65.6 (56.5–83.3)	80 (67–103)	0.006	0.227	0.01
LV hypertrophy	117	22 (37.9)	35 (59.3)	0.021	0.234	0.01
LV end diastolic volume index (ml/m^2)	79	48.8 (42.8–55.0)	55.8 (45.0–65.2)	0.09	0.189	0.10
LV end systolic volume index (ml/m^2)	79	18.4 (15.9–22.5)	23.0 (16.4–30.7)	0.13	0.158	0.16
LVEF (%)	159	60.5 (57.5–68.0)	60 (55–65)	0.24	−0.134	0.09
Baseline cardiac MRI						
LV stroke volume (ml)	l8	67.2 (60.3–82.3)	81.2 (69.2–94.1)	0.05	0.121	0.27
LV mass index (g/m^2)	88	59.7 (49.3–73.0)	63.8 (54.1–85.5)	0.10	0.218	0.04
LV end-diastolic volume index (ml/m^2)	88	50.4 (43.1–58.4)	60.6 (53.9–69.3)	0.004	0.225	0.04
LV end-systolic volume index (ml/m^2)	88	17.3 (14.0–22.1)	22.3 (18.8–27.3)	0.02	0.186	0.08
LVEF (%)	88	67.2 (59.6–72.1)	63.7 (57.3–68.3)	0.20	−0.101	0.35
Cardiac index (l/min/m^2)	87	2.23 (1.82–2.52)	2.4 (2.01–2.77)	0.17	0.106	0.33
Aortic distensibility (10^{-3} mm Hg^{-1})	61	1.22 (0.74–2.05)	0.79 (0.55–1.70)	0.08	−0.301	0.02
CPET						
Baseline Vo_{2max} (ml/min/kg)	160	13.2 (11.1–16.1)	11.1 (9.9–13.4)	<0.0001	−0.339	<0.0001

Values are median (interquartile range) or n (%).

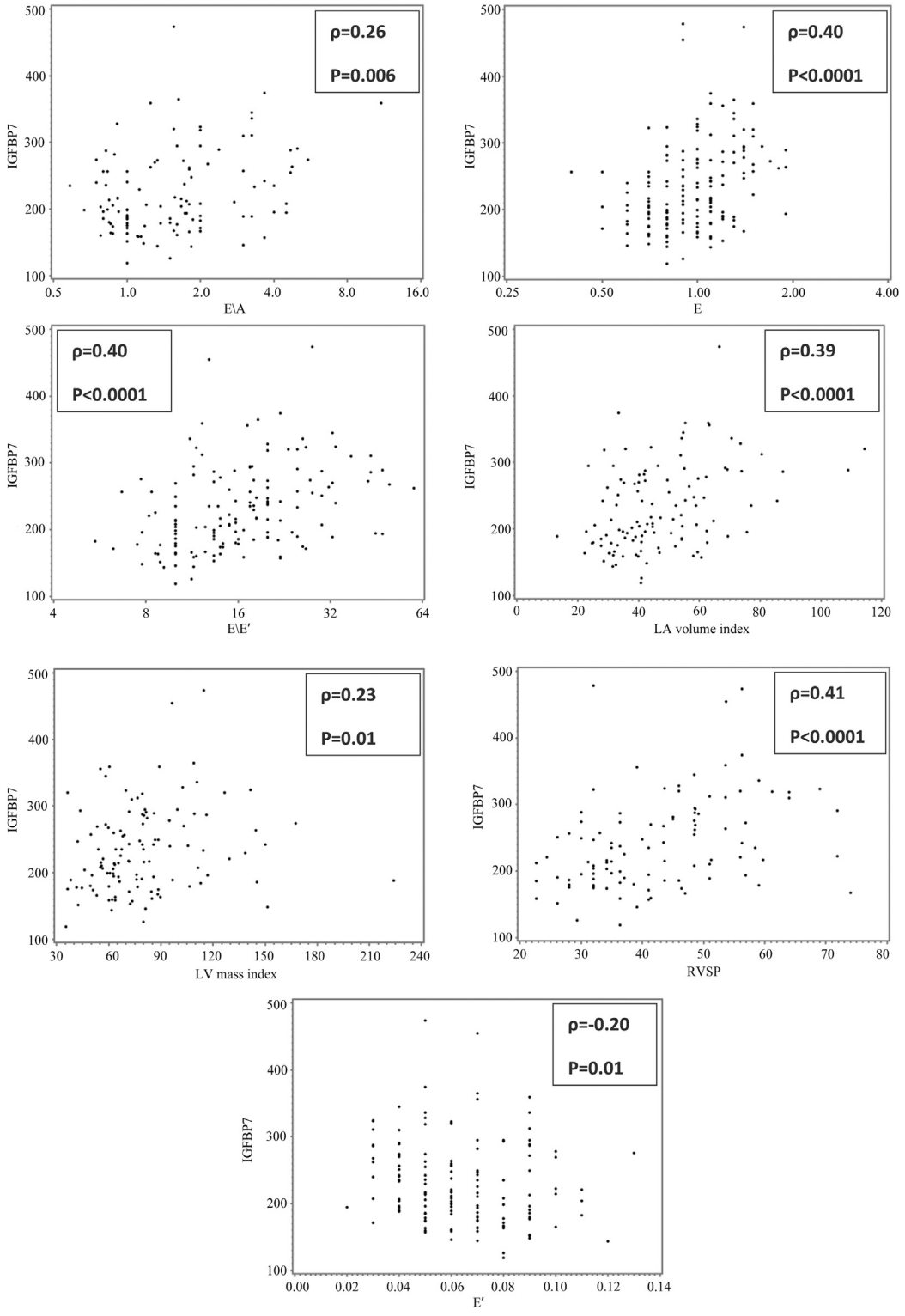
CPET = cardiopulmonary exercise testing; LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MV = mitral valve; RVSP = estimated right ventricular systolic pressure; Vo_{2max} = peak oxygen consumption; other abbreviations as in Table 1.

distensibility in patients with supramedian IGFBP7 concentrations (ρ = −0.30; p = 0.02); however, there were no significant relationships between IGFBP7 and MRI measures of systolic function. Baseline CPET demonstrated that patients with supramedian IGFBP7 concentrations had a significantly reduced Vo_{2max}. Similarly, patients with inframedian Vo_{2max} (≤11.7 ml/kg/min) had significantly higher baseline IGFBP7 concentrations (243 vs. 197 pg/ml; p < 0.0001).

COMPARISON BETWEEN BASELINE IGFBP7 AND OTHER BIOMARKERS AND CLINICAL FACTORS. Correlations between IGFBP7 and other established and emerging biomarkers were performed, as shown in Table 3. Many of these correlations were significant, with IGFBP7 most strongly correlated with cystatin C (ρ = 0.64; p < 0.0001) and the carboxy-terminal telopeptide of collagen type 1 (ρ = 0.65; p < 0.0001). IGFBP7 was also strongly correlated with NT-proBNP (ρ = 0.59; p < 0.0001). Given the significant correlations with parameters of renal function, we further investigated the relationship between IGFBP7 and eGFR. Baseline eGFR was not significantly associated with ΔIGFBP7. However, eGFR at 24 weeks and change in eGFR (ΔeGFR) were significantly associated with ΔIGFBP7 (β = −0.001; 95% confidence interval: −0.002, −0.0001; p = 0.02; and β = −0.003; 95% confidence interval: −0.004, −0.0009; p = 0.003, respectively).

Baseline concentrations of NT-proBNP and galectin-3 were also examined in relation to echocardiographic and MRI parameters, divided by the respective median concentrations, as shown in Online Table 2. As anticipated, baseline NT-proBNP showed similar correlations to echocardiographic parameters of diastolic function when compared with IGFBP7; however, baseline NT-proBNP also demonstrated significant correlations with measures of systolic function including LV stroke volume and cardiac index, whereas IGFBP7 did not. Furthermore, NT-proBNP was not significantly correlated with LV hypertrophy, whereas IGFBP7 was weakly but significantly correlated. NT-proBNP also did not demonstrate significant inverse correlation with aortic distensibility (ρ = −0.23; p = 0.07). Baseline galectin-3 did not show significantly consistent correlation with any of these measures.

FIGURE 1 **Correlation Between Baseline IGFBP7 and Baseline Parameters of Diastolic Dysfunction**



There were significant correlations between insulin-like growth factor–binding protein-7 (IGFBP7) and E/A, E/E′, left ventricular (LV) mass index, E′, left atrial (LA) volume index, and estimated right ventricular systolic pressure (RVSP).

TABLE 3 Bivariate Correlations of Other Biomarkers With IGFBP7

	Spearman Correlation With IGFBP7 (ρ)	Spearman Correlation p Value
Creatinine (mg/dl)	0.494	<0.0001
eGFR (ml/min/1.73 m^2)	−0.471	<0.0001
Uric acid (mg/dl)	0.356	<0.0001
Aldosterone (pg/ml)	0.114	0.15
Cystatin C (mg/l)	0.637	<0.0001
NT-pro BNP (pg/ml)	0.589	<0.0001
Pro-collagen III amino-terminal peptide (μg/l)	0.442	<0.0001
High sensitivity troponin I (pg/ml)	0.438	<0.0001
Endothelin-1 (pg/ml)	0.571	<0.0001
High-sensitivity C-reactive protein (mg/l)	0.046	0.56
Carboxy-terminal telopeptide of collagen type I (μg/l)	0.651	<0.0001
Galectin-3 (ng/ml)	0.350	<0.0001

Values are Spearman correlations and p values, as shown
Abbreviations as in Table 1.

IGFBP7 was not independently predictive of measures of diastolic dysfunction such as E/A >1.5, E/E′ >15, E′ ≤ 0.08 m/s, and LV mass index after adjustment for NT-proBNP, age, and eGFR; however, NT-proBNP retained independent value in each model except LV mass index. To investigate the relationship between IGFBP7 and NT-proBNP further, we identified the optimal cutpoint using receiver-operating characteristic curves for each marker with respect to the diastolic function parameters of E/A >1.5 and E/E′ >15. The area under the curve for IGFBP7 was 0.68 for E/A >1.5 and 0.71 for E/E′ >15; for NT-proBNP the values were 0.74 and 0.67, respectively. Most patients with E/A >1.5 and E/E′ >15 had elevated concentrations of both markers (74% and 78% for each parameter, respectively). Notably, fewer patients with abnormal diastolic function had either elevated IGFBP7 concentrations without elevated NT-proBNP concentrations (44% for E/A >1.5 and 25% for E/E′ >15) or elevated NT-proBNP without elevated IGFBP7 concentrations (64% for E/A >1.5 and 54% for E/E′ >15).

TABLE 4 Change in IGFBP7 and Imaging Parameters Over 24 Weeks

Diastolic Function Measure	N	Spearman Correlation With Change in IGFBP7 (ρ)	Spearman Correlation p Value	Adjusted p Value
Echocardiography change from baseline to week 24				
MV inflow: E velocity at leaf tip (m/s)	144	0.114	0.17	0.006
MV inflow: A velocity at leaf tip (m/s)	102	−0.141	0.16	0.14
E/A ratio	102	0.225	0.02	0.02
LV relaxation septal (medial) − E′ (m/s)	135	−0.096	0.27	0.06
Filling pressure septal (medial) − E/E′ (m/s)	133	0.174	0.05	0.001
LA volume index	99	0.024	0.81	0.52
RVSP (mm Hg)	88	0.282	0.008	0.03
Cardiac MRI change from baseline to week 24				
LV stroke volume	78	−0.674	0.56	0.75
Cardiac index	77	−0.139	0.23	0.25
Aortic distensibility	46	0.067	0.66	0.90

Values are Spearman correlations and p values, as shown.
Abbreviations as in Tables 1 and 2.

CHANGE IN IGFBP7, IMAGING, AND FUNCTIONAL CAPACITY OVER 24 WEEKS. The relationship between ΔIGFBP7 and imaging parameters is shown in Table 4. As seen with baseline measurements, significant but weak correlations were found between ΔIGFBP7 and change in echocardiographic measures of diastolic function including change in transmitral E velocity (ρ = 0.11; p = 0.006), E/A ratio (ρ = 0.22; p = 0.02), E/E′ (ρ = 0.17; p = 0.002), and estimated RVSP (ρ = 0.28; p = 0.04). When examining the relationship between IGFBP7 and Vo_{2max} at 24 weeks, patients with supramedian Vo_{2max} (>11.9 ml/kg/min) had a significantly lower median IGFBP7 concentration of 206 ng/ml versus 244 ng/ml in patients with inframedian Vo_{2max} (p = 0.004). Similarly, patients with supramedian 24-week IGFBP7 concentrations (>228 ng/ml) had a numerical trend toward lower peak Vo_{2max} compared with patients with inframedian concentrations (11.4 vs. 12.8 ml/min/kg; p = 0.10). Spearman correlation (adjusted for baseline Vo_{2max} and IGFBP7) revealed a weak but significant inverse relationship between ΔIGFBP7 and ΔVo_{2max} over the 24-week study period (ρ= −0.19; p = 0.013), as shown in Figure 2.

Correlations between ΔNT-proBNP and Δgalectin-3 with change in measures of diastolic function from echocardiography and MRI were also examined, as shown in Online Table 3. ΔNT-proBNP again demonstrated correlation with change in echocardiographic diastolic function parameters. Similar to baseline measurements, Δgalectin-3 did not demonstrate any significant correlations with change in imaging parameters.

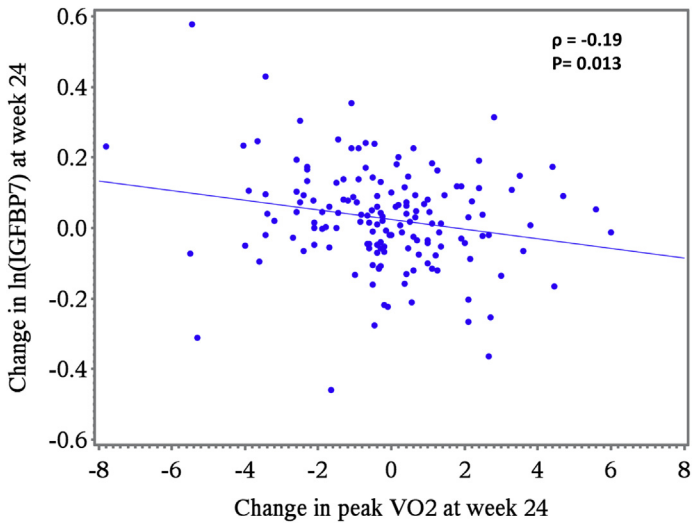
RELATIONSHIP BETWEEN SILDENAFIL AND IGFBP7. Baseline and 6-month IGFBP7 concentrations were similar in study subjects randomized to sildenafil compared with subjects receiving placebo (240 vs. 215 ng/ml; p = 0.17), as shown in Online Table 4. However, when examining ΔIGFBP7 over 24 weeks, subjects receiving sildenafil had significantly lower concentrations of IGFBP7, whereas those receiving placebo showed a significant increase in IGFBP7 concentration (−1.5 ng/ml vs. +13.6 ng/ml; p = 0.001).

DISCUSSION

In our analysis of the relationship between IGFBP7 and indices of diastolic function and functional capacity in patients with HFpEF, we have identified several interesting findings. First, patients with supramedian IGFBP7 concentrations were more likely to show a higher risk profile, with older age, more atrial arrhythmia, greater signs of congestion on history or physical examination, and more elevated concentrations of other established biomarkers. Second, we confirm our hypothesis that both baseline IGFBP7 and ΔIGFBP7 concentrations were modestly but significantly associated with echocardiographic parameters of diastolic function such as transmitral E velocity, E/E′, and estimated RVSP and weakly correlated with E/A ratio. Third, as hypothesized, supramedian IGFBP7 concentrations were also significantly associated with lower Vo_{2max} at baseline; furthermore, ΔIGFBP7 was weakly inversely correlated with ΔVo_{2max} over 24 weeks. Fourth, subjects receiving sildenafil had a significant reduction in IGFBP7 concentrations over the study period when compared with subjects receiving placebo. Our analysis investigated IGFBP7 relative to imaging parameters, functional capacity, and sildenafil therapy in patients with HFpEF.

IGFBP7 is a biomarker that is associated with the G_1 phase cell cycle arrest (19) part of the cellular senescence-associated secretome. Higher levels of IGFBP7 may therefore accelerate cellular senescence, thus potentially contributing to aging of the myocardium (20). IGFBP7 has been localized to the Weibel-Palade bodies (storage organelles) of endothelial cells (21). Furthermore, IGFBP7 has also been associated with collagen deposition (22), and it may therefore also be linked to myocardial fibrosis. The syndrome of HFpEF has been proposed to be a proinflammatory state with production of reactive oxygen species by endothelial cells that subsequently results in concentric LV remodeling, stiffening of cardiomyocytes, and increased collagen deposition, which all ultimately lead to diastolic dysfunction (23). Given the association of IGFBP7, senescence, and collagen deposition, as well as the localization of IGFBP7 to endothelial cells, IGFBP7 may be linked to later stages of this proinflammatory cascade. Such an association could elucidate the relationship of IGFBP7 with echocardiographic parameters of diastolic dysfunction and functional capacity. IGFBP7 is less likely to be a direct marker of inflammation, however, because it was not correlated with C-reactive protein. Finally, another potential mechanism of elevated IGFBP7 concentrations in patients with HFpEF could be through the cardiorenal axis, given that IGFBP7 has been studied as a marker of acute kidney injury and the strongest of the correlations with other biomarkers is with the renal marker cystatin C (19).

FIGURE 2 Correlation Between ΔIGFBP7 and ΔVo_{2max} Over 24 Weeks



There was a significant inverse correlation over the study period. The p value comes from a linear regression model that adjusts for baseline insulin-like growth factor–binding protein 7 (IGFBP7) and peak oxygen consumption (Vo_{2max}). Δ = change.

The syndrome of HFpEF remains a clinical conundrum. Biomarkers may provide further insight into the complexities of HFpEF, potentially lead to better understanding of this condition, and supplement what is ascertained by echocardiography and physical examination. The NPs have previously been associated with diastolic dysfunction (7,8), and they may imply a propensity for treatment response in patients with HFpEF (24), although other biomarkers may add to information provided by BNP or NT-proBNP. In the current study, both NT-proBNP and IGFBP7 had similar correlations with parameters of diastolic dysfunction, they had a similar area under the curve with regard to the diastolic function parameters of E/A and E/E′, and they were strongly correlated with each other. However, NT-proBNP and IGFBP7 may reflect different aspects of diastolic dysfunction given that NT-proBNP also demonstrated correlation with cardiac structure and function beyond diastolic abnormalities, whereas IGFBP7 did not. This specificity of IGFBP7 may result in improved phenotyping of patients with HFpEF beyond what has been achieved with the NPs. Furthermore, most patients with significant diastolic dysfunction had elevations in both IGFBP7 and

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NT-proBNP, whereas fewer had elevations in only 1 of the biomarkers, thus raising the possibility that the combination of these markers may be superior to either in isolation for identifying diastolic dysfunction. Future investigation of IGFBP7 as a tool to phenotype patients with HFpEF more accurately is needed to explore the hypothesis that elevation of the biomarker identifies a therapeutic imperative. Notably, patients receiving sildenafil therapy had a reduction in IGFBP7 concentrations compared with patients receiving placebo, whereas in the original study, patients receiving sildenafil had increase in NT-proBNP (17). Whether this observation may identify a subgroup of patients who would benefit from sildenafil therapy is unclear.

Moreover, IGFBP7 showed a significant inverse correlation with Vo_{2max} at baseline, and ΔIGFBP7 was correlative with ΔVo_{2max}. Given that worse diastolic function is inversely linked to exercise capacity, it is tempting to speculate that the correlation between IGFBP7 values and functional capacity may reflect changes in diastolic function; invasive analyses exploring this hypothesis are planned. Serial data with biomarkers, echocardiography, and functional capacity are not often readily available in HF trials, hence our study is important, by lending comprehensive analyses with both baseline and change in each of these parameters.

STUDY LIMITATIONS. First, our study is retrospective, and thus our findings can be regarded only as hypothesis generating. Our study is also limited by a small sample size, missing data for some parameters, and a short follow-up of 24 weeks. However, even with these shortcomings, we confirmed our hypothesis of a modest but significant correlation between IGFBP7 and parameters of diastolic function and functional capacity. Second, given the limited sample size, we could not investigate outcomes as a function of IGFBP7 because our primary focus was mechanistic, but we previously demonstrated the prognostic value of IGFBP7 in another cohort of patients with HFpEF (25). Third, supramedian IGFBP7 concentrations were associated with other established biomarkers, thus raising the concern that IGFBP7 provides redundant biological information, particularly with regard to NT-proBNP. However, IGFBP7 was much less strongly correlated with systolic parameters, a finding suggesting that IGFBP7 and NT-proBNP likely reflect different aspects of diastolic function. Our goal was to pursue characterization of a marker more specific to the molecular processes leading to echocardiographic parameters of diastolic dysfunction, to assist with further understanding of the pathophysiology and mechanism of HFpEF, with the ultimate possibility of objectively phenotyping this heterogeneous population of patients. Although it is speculative, given the paucity of treatments for HFpEF (whose efficacy was tested largely on a clinical picture of HF with an LVEF >50%). It is possible that a combination of clinical data, echocardiographic imaging, and molecular phenotyping may more effectively inform responses to therapy. Finally, given the relationship between IGFBP7 and sildenafil therapy, there may be an association between IGFBP7 and cyclic guanosine monophosphate, but these data were not available in the current study.

CONCLUSIONS

IGFBP7 may be a novel biomarker of diastolic dysfunction in patients with HFpEF. Furthermore, IGFBP7 also appears to be modestly related to functional capacity, itself an important component of the syndrome of HFpEF. A better understanding of the link or links between IGFBP7 and diastolic function would be of value as the search continues for further clarity with regard to diagnosis and treatment of patients with HFpEF. More studies are needed to elucidate the optimal diagnostic and treatment strategies for patients with this complex condition.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The syndrome of HFpEF remains a clinical challenge, given its complicated diagnosis and the lack of viable therapeutic options. The current study examines the biomarker IGFBP7 and demonstrates its weak to modest correlation with diastolic function and functional capacity in patients with HFpEF.

TRANSLATIONAL OUTLOOK: Biomarkers such as IGFBP7 can provide insight into the complex pathophysiology of HFpEF. Given the weak to modest relationship of IGFBP7 with diastolic function and functional capacity, as well as the potential interaction between IGFBP7 and therapy, it is conceivable that, in the future, IGFBP7 may play a role in personalizing the care of patients with HF.

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KEY WORDS biomarkers, diastolic function, heart failure with preserved ejection fraction, insulin-like growth factor–binding protein 7

APPENDIX For supplemental tables, please see the online version of this article.