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Growth Differentiation Factor-15 Is Associated With Congestion-Related Anorexia and Weight Loss in Advanced Heart Failure

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ABSTRACT

BACKGROUND Growth differentiation factor (GDF)-15 is a pleiotropic cytokine that is associated with appetite-suppressing effects and weight loss in patients with malignancy.

OBJECTIVES This study aims to investigate the relationships between GDF-15 levels, anorexia, cachexia, and clinical outcomes in patients with advanced heart failure with reduced ejection fraction (HFrEF).

METHODS In this observational, retrospective analysis, a total of 344 patients with advanced HFrEF (age 58 ± 10 years, 85% male, 67% NYHA functional class III), underwent clinical and echocardiographic examination, body composition evaluation by skinfolds and dual-energy x-ray absorptiometry, circulating metabolite assessment, Minnesota Living with Heart Failure Questionnaire, and right heart catheterization.

RESULTS The median GDF-15 level was 1,503 ng/L (Q1-Q3: 955-2,332 ng/L) (reference range: $<1,200$ ng/L). Higher GDF-15 levels were associated with more prevalent anorexia and cachexia. Patients with higher GDF-15 had increased circulating free fatty acids and beta-hydroxybutyrate, lower albumin, cholesterol, and insulin/glucagon ratio, consistent with a catabolic state. Patients with higher GDF-15 had worse congestion and more severe right ventricular dysfunction. In multivariable Cox analysis, elevated GDF-15 was independently associated with risk of the combined endpoint of death, urgent transplantation, or left ventricular assist device implantation, even after adjusting for coexisting anorexia and cachexia (T3 vs T1 HR: 2.31 [95% CI: 1.47-3.66]; $P < 0.001$).

CONCLUSIONS In patients with advanced HFrEF, elevated circulating GDF-15 levels are associated with a higher prevalence of anorexia and cachexia, right ventricular dysfunction, and congestion, as well as an independently increased risk of adverse events. Further studies are warranted to determine whether therapies altering GDF-15 signaling pathways can affect metabolic status and clinical outcomes in advanced HFrEF. (JACC Heart Fail. 2025;■:■-■) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

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**ABBREVIATIONS
AND ACRONYMS****BMI** = body mass index**BW** = body weight**DEXA** = dual-energy x-ray absorptiometry**GDF-15** = growth differentiation factor 15**HF** = heart failure**HFrEF** = heart failure with reduced ejection fraction**LVAD** = left ventricular assist device**MLHFQ** = Minnesota Living With Heart Failure Questionnaire

Growth differentiation factor (GDF)-15 is a pleiotropic cytokine from the transforming growth factor beta superfamily. Under normal conditions, GDF-15 is expressed and secreted at low levels by various cell types.¹ However, its expression increases in response to stressors such as inflammation, senescence, or heightened ambient reactive oxygen species, playing a key role in the cellular stress response program.¹ Blood concentrations of GDF-15 are markedly elevated in chronic diseases such as heart failure (HF), kidney failure, pulmonary diseases, and cancer, and they are predictive of poor survival in these conditions.²⁻⁵ Most of these diseases are also asso-

ciated with body wasting due to enhanced catabolism and diminished caloric intake.⁵⁻⁸

Recent basic science research suggests that GDF-15 could be directly involved in the negative energy balance in chronic diseases due to its appetite-suppressing and catabolic effects. Central anorectic actions of GDF-15 are mediated through interactions with the glial cell line-derived factor-family receptor alpha-like (GFRAL) in the brain.⁹⁻¹¹ In experimental settings, a reduction of GDF-15 signaling using a monoclonal antibody prevented anorexia and weight loss in cancer or multiorgan failure models.^{12,13} It remains unknown whether GDF-15 could play an active role in development of anorexia and cachexia that accompanies HF.

We hypothesized that GDF-15 is associated with anorexia and history of weight loss in HF. We also wanted to examine how GDF-15 links to previously identified risk factors for HF-related anorexia, such as chronic splanchnic congestion or right heart dysfunction.^{14,15} To test these hypothesis, we investigated the relationships between GDF-15 levels, anorexia, and outcomes in a large cohort of thoroughly phenotyped patients with advanced heart failure with reduced ejection fraction (HFrEF) participating in a prospective observational study.

METHODS

STUDY POPULATION. We performed a retrospective analysis of prospectively collected data. The cohort prospectively included consecutive patients with chronic (>6 months) symptomatic HFrEF (left ventricular ejection fraction [LVEF] ≤40%) electively hospitalized for consideration of advanced therapies at the IKEM (Institute for Clinical and Experimental Medicine) in Prague (Czech Republic) from January 2008 to June 2011. To avoid the influence of acute

cardiac and noncardiac conditions potentially influencing GDF-15 values, patients with acute ischemia, uncontrolled cardiac arrhythmia, hemodynamic instability needing inotropes or mechanical circulatory support, active malignancy, endocrine disease, and chronic or acute infection were excluded. Patients with reversible cardiac dysfunction were also excluded. Patients with hypervolemia on admission (based on clinical examination) were enrolled into the study after diuresis and reaching normovolemia (central venous pressure <10 mm Hg), if possible. The local ethics committee approved the protocol. All patients signed informed consent with the procedures and with participation in this research study.

STUDY PROTOCOL. After signing informed consent, all patients (N = 344) underwent history review, physical examination (including body weight measurement), echocardiography, electrocardiogram, and blood sampling with circulating metabolite assessment. Most patients (n = 314) completed the Minnesota Living With Heart Failure Questionnaire (MLHFQ). Some patients also underwent right heart catheterization (n = 172) (as part of the diagnostic work-up) and body composition assessment by dual-energy x-ray absorptiometry (DEXA) (n = 150) and the skinfold method (n = 321) as a part of research study examining substrate metabolism in HF. All investigations were performed in a post-absorptive state following an overnight fasting.

The MLHFQ is a self-administered disease-specific questionnaire for patients with HF¹⁶ comprising 21 items rated on 6-point Likert scales representing different degrees of impact of HF on health-related quality of life (HRQoL) from 0 (none) to 5 (very much). It provides a total score that range from 0 to 105 (best to worst HRQoL). Anorexia severity was graded according to the individual answer to the question 11 of the MLHFQ (MLHFQ-Q11; “Did your HF prevent you from living as you wanted during the past month by making you eat less of the foods you like?”). Model for end-stage liver disease excluding INR (MELD-XI score)¹⁷ was calculated in the subset of patients with available bilirubin concentration (n = 68).

ECHOCARDIOGRAPHY AND INVASIVE MEASURES. The echocardiographic examination was performed on all patients using standard, commercially available ultrasound equipment (Vivid 7, General Electric Medical Systems) with a 2.5-MHz phased-array transducer. Cardiac chambers’ function and dimensions were measured according to contemporary recommendations.¹⁸ Mitral and tricuspid regurgitation was assessed semiquantitatively and expressed in

4 grades (absent/trivial, mild, moderate, and severe). Right ventricular (RV) function was evaluated in the apical 4-chamber view by using tricuspid annular systolic excursion (TAPSE) or tissue Doppler-derived tricuspid lateral annular systolic velocity (S').¹⁹ Right ventricular dysfunction (RVD) was quantified (0 to 3) with the following cutoffs: RVD0 (normal), TAPSE >20 mm, and S' >12 cm/s; RVD1 (mild impairment), TAPSE 16 to 20 mm, and S' 9 to 12 cm/s; RVD2 (moderate impairment), TAPSE 10 to 15 mm, and S' 6 to 8 cm/s; and RVD3 (severe impairment), TAPSE <10 mm, and S' <6 cm/s. In case of disagreement of criteria, qualitative visual estimation of RV motion in apical 4-chamber was also taken into account.

Right heart catheterization was performed according to the current recommendation using a 7Fr balloon-tipped triple-lumen Swan-Ganz catheter (Braun Melsungen AG) inserted via the right internal jugular vein.²⁰ Pressure waveforms were recorded and annotated by an invasive hemodynamic module (Mac-Lab, GE Healthcare).

BODY WEIGHT AND BODY COMPOSITION ASSESSMENT.

Body weight (BW) was measured on all patients by using an electronic scale (HBF-510W). Antecedent weight 6 months before the evaluation was carefully ascertained by subjects' historic recollection and by review of available medical records, as done previously.^{15,21} Four-site skinfold thickness (triplicate measurement in nondominant subscapular, bicipital, tricipital, and suprailiac areas) was measured by using Best's caliper with controlled grip strength. Skinfold sum was converted into total body fat by using established age- and sex-specific formulas,²² and then reported as percentage of total body composition by using the Siri equation: body fat percentage = $(4.95/\text{body density}) - 4.50 \times 100$.²³ In a subset of subjects enrolled in the study, body composition was also measured by using DEXA (Lunar prodigy, General Electric Healthcare) to externally validate results. Body fat proportion according to DEXA and the skinfold method showed good agreement ($r = 0.748$; $P < 0.001$). Cardiac cachexia was defined by the presence of significant unintentional loss of edema-free body weight (>5% in the past 6 months).²⁴

GDF-15 AND OTHER LABORATORY ASSAYS. Blood samples were consistently collected from a peripheral vein between 6 and 7 AM, immediately chilled on ice, and centrifuged within 20 minutes at a force of $800 \times g$ at a temperature of 4 °C. Plasma was collected, distributed into aliquots, and frozen at -80 °C. Plasma GDF-15 concentrations were

measured in the Biomarker Research and Clinical Trials Laboratory at Brigham and Women's Hospital in Boston. Patient specimens were diluted 4 times and 50- μ L aliquots were tested in duplicates using the Quantikine Human GDF-15 Immunoassay (R and D Systems Inc; reportable range: 94-6,000 ng/L; reference range <1,200 ng/L; total imprecision: 8.3% at 162 ng/L, 7.6% at 414 ng/L, and 12.0% at 797 ng/L).

The B-type natriuretic peptide (BNP) concentrations were measured using a chemiluminescent immunoassay (Architect BNP, Abbott Laboratories; long-term analytical coefficient of variation [CV] 4.5%). Beta-hydroxybutyrate (beta-OHB; normal value: 0-74 μ mol/L, CV [intra-assay]: 5%) and free fatty acids (FFAs; reference value men: 0.1-0.6 mmol/L; reference value women: 0.1-0.45 mmol/L; CV [intra-assay]: 1.5%) were measured using a commercially available enzymatic assays (Autokit 3-HB and NEFA-HR, Wako Chemicals). The homeostatic model assessment for insulin resistance was calculated using the formula: $[\text{glucose (nmol/L)} \times \text{insulin } (\mu\text{U/mL}) / 22.5]$.¹⁵ Fasting glucose ≥ 126 mg/dL or use of antidiabetic medication defined diabetes mellitus. Insulin concentration was determined using Insulin IRMA kit (Beckman Coulter; normal value: 2.1-22.0 mIU/L; CV [intra-assay]: 4%) and glucagon using Glucagon RIA kit (Millipore; normal value (fasting): 50-150 pg/mL; CV [intra-assay]: 4%-7%). Estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

STATISTICAL ANALYSIS. Data are shown as mean \pm SD or median (Q1-Q3) for continuous variables (according to distribution) and total count (n) with proportion (%) for categorical variables. One-way analysis of variance and Kruskal-Wallis tests were used to compare continuous variables between groups depending on the normality of the distribution, and the chi square test was used for categorical variables. Normality was assessed using the Shapiro-Wilks test. Variables not normally distributed were log-transformed before the analysis. To assess the association of independent variables with continuous (ie, GDF-15), ordinal (ie, MLHFQ question 11), or categorical (ie, cachexia) dependent variables, separate multiple linear, multinomial logistic or binomial logistic regression analyses were conducted, respectively. All regression analyses were age- and sex-adjusted. The assumption of log-linearity for independent continuous variables in binomial and multinomial regression analysis was assessed using restricted cubic splines with 3 knots, according to Harrell's rule.²⁵ Wald test was used to evaluate the

linearity assumptions. The continuous variables were then categorized as needed to satisfy the model's assumptions.

Cox proportional hazards regression, adjusted for potential confounders (age, sex, LVEF, body mass index [BMI], systolic blood pressure, eGFR, hemoglobin concentration, and ischemic HF etiology) was used to analyze the association of GDF-15 concentration with the adverse outcome, defined as a combined endpoint of death, urgent transplantation, or left ventricular assist device (LVAD) implantation without heart transplantation. Because time to nonurgent transplantation reflects donor availability rather than recipient's condition, those patients were censored as having no outcome at the day of transplantation, as previously proposed.¹⁵ Kaplan-Meier curves with the log-rank statistics were used to show the outcome. The two-tailed significance level was set at $P < 0.05$. All analyses were performed using JMP pro 17.0 statistical software (SAS Institute, Inc).

RESULTS

POPULATION CHARACTERISTICS. A total of 344 consecutive HFrEF patients referred to our center for evaluation of advanced HF therapies (cardiac device implantation, heart transplantation, or LVAD implantation) were enrolled in this prospective observational study. Median GDF-15 level was 1,503 ng/L (Q1-Q3: 955-2,332 ng/L). The I-NEED-HELP (inotropes, NYHA functional class, end-organ dysfunction, defibrillator shocks, hospitalizations, low blood pressure, prognostic medication) criteria²⁶ available in our data set, including very low LVEF (mean: 22%; LVEF <20%: 24%), elevated natriuretic peptides (median BNP: 568 ng/L), presence of end-organ dysfunction (eGFR <45 mL/min/m²: 15%), low systolic blood pressure (<100 mm Hg: 17%), advanced NYHA functional class (III/IV: 73%), and the requirement of high doses of diuretic agents (mean daily oral dose of furosemide: 96 ± 81 mg), were consistent with an advanced HF population (Supplemental Table 1). Based on the distribution in the overall population, GDF-15 tertiles were created with cutoffs of the following: 1st tertile (T1): <1,100 ng/L (n = 113); 2nd tertile (T2): 1,100 – 1,900 ng/L (n = 114); and 3rd tertile (T3): >1,900 ng/L (n = 117). Baseline population characteristics according to GDF-15 tertiles are presented in Table 1.

GDF-15 AND ITS CORRELATES. Patients in the higher GDF-15 tertile were older, more likely to be men, had more severe impairment of HRQoL as indicated by higher MLHFQ scores, and were more often diagnosed with ischemic HF etiology (all $P < 0.01$).

Additionally, they exhibited a higher prevalence of comorbidities such as diabetes mellitus, hypertension, atrial fibrillation, and chronic kidney disease (all $P < 0.05$) (Table 1), each of which differently impacted circulating GDF-15 levels (stronger association for eGFR) (Supplemental Table 1). Although patients in the highest tertile did not exhibit significant differences in BMI and BW compared to other tertiles, they had higher scores in the anorexia severity score, greater unintentional body weight lost in the preceding 6 months, and higher prevalence of cachexia, along with a lower percentage of body fat (fat/lean ratio), as measured by both DEXA and the skinfold method (all $P < 0.01$) (Figure 1). No significant differences in baseline characteristics were found between patients who did or did not have DEXA (Supplemental Table 2).

By tertiles of GDF-15, patients did not differ in LVEF or resting cardiac output but displayed worse RV function. Additionally, patients with higher GDF-15 concentrations had more systemic congestion (higher BNP and right atrial pressure [RAP], larger inferior vena cava), increased RAP/pulmonary artery wedge pressure ratio, and more impaired kidney (lower eGFR) and liver (higher MELD-XI score) function (all $P < 0.01$) (Figures 2 and 3A), indicating a close association between GDF-15, RV failure, and splanchnic congestion.

From a metabolic perspective, patients with higher GDF-15 levels were more likely to have diabetes; higher glucagon, lower albumin, and cholesterol levels, along with more marked alterations in humoral regulators of liver ketogenesis (insulin/glucagon ratio) and increased markers of lipolysis (FFA, beta-OHB) (all $P < 0.01$) (Figure 3B).

ASSOCIATION BETWEEN CIRCULATING GDF-15 AND MLHFQ. Patients with higher circulating levels of GDF-15 showed strong positive correlations with more marked signs of congestion (question 1), symptoms of anorexia (question 11), and a higher burden of HF-related hospitalizations (question 14) (all $P < 0.001$). In the psychological domain, increased levels of GDF-15 were associated with higher anxiety (question 19; $P < 0.001$) but did not have a significant link to depression (question 21; $P = 0.528$) (Supplemental Table 3).

DETERMINANTS OF ANOREXIA AND ITS ASSOCIATION WITH GDF-15. Anorexia (score ≥1 at MLHFQ-Q11) was reported by more than two-thirds (n = 220; 70%) of the study population. In the sex- and age-adjusted analysis, higher anorexia severity score was associated with more marked symptoms, increased natriuretic peptides, higher circulating GDF-15, worse

TABLE 1 Baseline Characteristics of the Population According to Circulating GDF-15 Tertiles

	Tertile 1 (n = 113)	Tertile 2 (n = 114)	Tertile 3 (n = 117)	P Value
GDF-15, ng/L	807 (664-953)	1,494 (1,395-1,677)	2,725 (2,295-3,460)	NA
Clinical				
Age, y	53 ± 10	59 ± 10	61 ± 10	<0.001
Male	85 (75)	97 (85)	110 (94)	<0.001
MLHFQ score ^a	43.4 ± 22.7	46.7 ± 21.5	52.6 ± 21.6	0.009
HF ischemic etiology	50 (44)	64 (56)	78 (67)	0.003
HF duration, y	11 (8-15)	11 (7-19)	10 (6-19)	0.831
NYHA functional class				0.016
II	42 (37)	25 (22)	27 (23)	
III-IV	71 (63)	89 (78)	90 (77)	
Diabetes mellitus	14 (12)	38 (33)	59 (50)	<0.001
Hypertension	44 (39)	53 (46)	68 (58)	0.013
Atrial fibrillation	10 (9)	23 (20)	26 (22)	0.015
COPD	11 (10)	13 (11)	20 (17)	0.214
CKD, eGFR <60 mL/min/1.73 m ²	11 (10)	43 (38)	70 (60)	<0.001
Body mass index, kg/m ²	28.2 ± 4.4	27.9 ± 5.2	27.3 ± 4.7	0.302
Body weight, kg	85.7 ± 15.3	85.7 ± 17.9	84.4 ± 16.1	0.788
Body weight change in 6 mo, kg	0 (-2 to 4)	0 (-7 to 2)	-3 (-12 to 2)	<0.001
Cachexia ^b	17 (16)	39 (35)	49 (44)	<0.001
DEXA fat mass, kg ^c	29.8 ± 10.9	25.8 ± 10.8	26.7 ± 11.0	0.178
DEXA lean mass, kg ^c	52.6 ± 11.3	54.6 ± 9.6	55.6 ± 8.6	0.320
DEXA fat/lean mass ratio	0.59 ± 0.24	0.48 ± 0.21	0.47 ± 0.16	0.011
DEXA BMC mass, kg ^c	3.1 ± 0.6	3.1 ± 0.7	3.2 ± 0.6	0.993
Body fat (skinfolds), % ^c	28.2 ± 10.5	24.9 ± 10.2	22.5 ± 8.9	<0.001
Anorexia score ^d	1 (0-3)	2 (0-3)	3 (1-4)	<0.001
MELD-XI score ^c	9.5 ± 3.4	11.0 ± 3.1	16.8 ± 4.2	<0.001
Laboratory values				
Hemoglobin, g/L	142 ± 15	143 ± 16	136 ± 18	0.005
Albumin, g/L	39.5 ± 3.9	38.9 ± 3.8	37.3 ± 4.2	<0.001
eGFR, mL/min/1.73 m ²	84 ± 17	68 ± 18	57 ± 21	<0.001
HbA _{1c} , mmol/mol	42 (39-46)	46 (40-50)	49 (43-58)	<0.001
HOMA-IR index	2.2 (1.3-3.8)	2.4 (1.6-4.3)	2.3 (1.4-3.6)	0.345
Insulin/glucagon ratio	0.13 (0.09-0.19)	0.11 (0.06-0.17)	0.08 (0.05-0.12)	<0.001
Insulin, mIU/L	9.1 (5.6-14.7)	8.9 (6.4-15.0)	8.2 (5.7-13.3)	0.369
Glucagon, pg/mL	76.0 ± 20.7	97.0 ± 43.9	117.3 ± 60.3	<0.001
BNP, ng/L	331 (145-642)	497 (285-990)	1,133 (612-2,060)	<0.001
Triacylglycerols, mmol/L	1.8 ± 0.9	1.7 ± 0.9	1.4 ± 1.2	0.025
Total cholesterol, mmol/L	4.7 ± 0.9	4.4 ± 0.9	3.8 ± 1.1	<0.001
Free fatty acids, mmol/L	0.46 ± 0.22	0.57 ± 0.29	0.62 ± 0.30	<0.001
Beta-hydroxybutyrate, μmol/L	46 (26-98)	65 (36-151)	122 (41-248)	<0.001
Echocardiography^e				
LV end-diastolic diameter, mm	70 ± 9	72 ± 9	70 ± 9	0.198
LV ejection fraction, %	23 ± 5	22 ± 5	22 ± 6	0.234
E/Em ratio	13 ± 5	16 ± 8	17 ± 9	0.012
TAPSE, mm	18 ± 5	16 ± 5	15 ± 4	<0.001
RV dysfunction	74 (76)	79 (88)	88 (91)	0.008
RV dysfunction grade				<0.001
0	38 (34)	22 (19)	12 (10)	
1	33 (29)	30 (27)	23 (20)	
2	33 (29)	42 (36)	56 (48)	
3	9 (8)	20 (18)	26 (22)	
Mitral regurgitation ≥ moderate	38 (35)	47 (42)	34 (29)	0.150
Tricuspid regurgitation ≥ moderate	22 (20)	34 (31)	54 (46)	<0.001
Inferior vena cava, mm	18 ± 5	19 ± 5	22 ± 6	<0.001

Continued on the next page

TABLE 1 Continued				
	Tertile 1 (n = 113)	Tertile 2 (n = 114)	Tertile 3 (n = 117)	P Value
Hemodynamics^c				
RAP, mm Hg	7.3 ± 5.4	7.4 ± 4.6	13.3 ± 6.2	<0.001
Mean PA pressure, mm Hg	31.9 ± 12.5	32.3 ± 12.2	37.6 ± 9.8	0.014
PAWP, mm Hg	21.8 ± 9.8	21.3 ± 8.9	25.9 ± 6.9	0.006
RAP/PAWP ratio	0.33 ± 0.25	0.34 ± 0.19	0.51 ± 0.25	<0.001
Cardiac output, L/min	4.1 ± 1.0	3.8 ± 0.7	4.1 ± 1.2	0.327
PVR, WU	2.2 (1.6-3.3)	2.4 (1.8-4.1)	2.6 (1.8-4.1)	0.289
Treatment				
Furosemide	100 (89)	110 (96)	110 (94)	0.317
ACEI or ARB	107 (95)	103 (90)	90 (77)	<0.001
MRA	87 (77)	92 (81)	92 (79)	0.791
Beta-blocker	106 (94)	109 (96)	104 (89)	0.125
Triple therapy (ACEI-ARB/MRA/beta-blocker)	79 (70)	79 (69)	62 (53)	0.010
OAD/insulin	22 (19)/4 (4)	43 (38)/14 (12)	58 (50)/25 (21)	<0.001
Devices				
ICD	61 (54)	65 (57)	70 (60)	0.505
CRT	38 (34)	46 (40)	47 (40)	

Values are HR (95% CI), mean ± SD, and n (%), unless otherwise indicated. ^aRange 0-100; higher scores indicate poorer health related quality of life. Performed in 314 patients. ^bCachexia was defined as an unintentional edema-free weight loss of >5% in the past 6 months. ^cDEXA was performed in 150 patients; the skinfold method was performed in 321 patients; MELD-XI was computable in 68 patients; echocardiography was performed in 344 patients; and right heart catheterization was performed in 172 patients. ^dAnorexia score was quantified by MLHFQ question 11 ("Did your heart failure prevent you from living as you wanted during the past month by making you eat less of the foods you like?") on a scale 0-5.

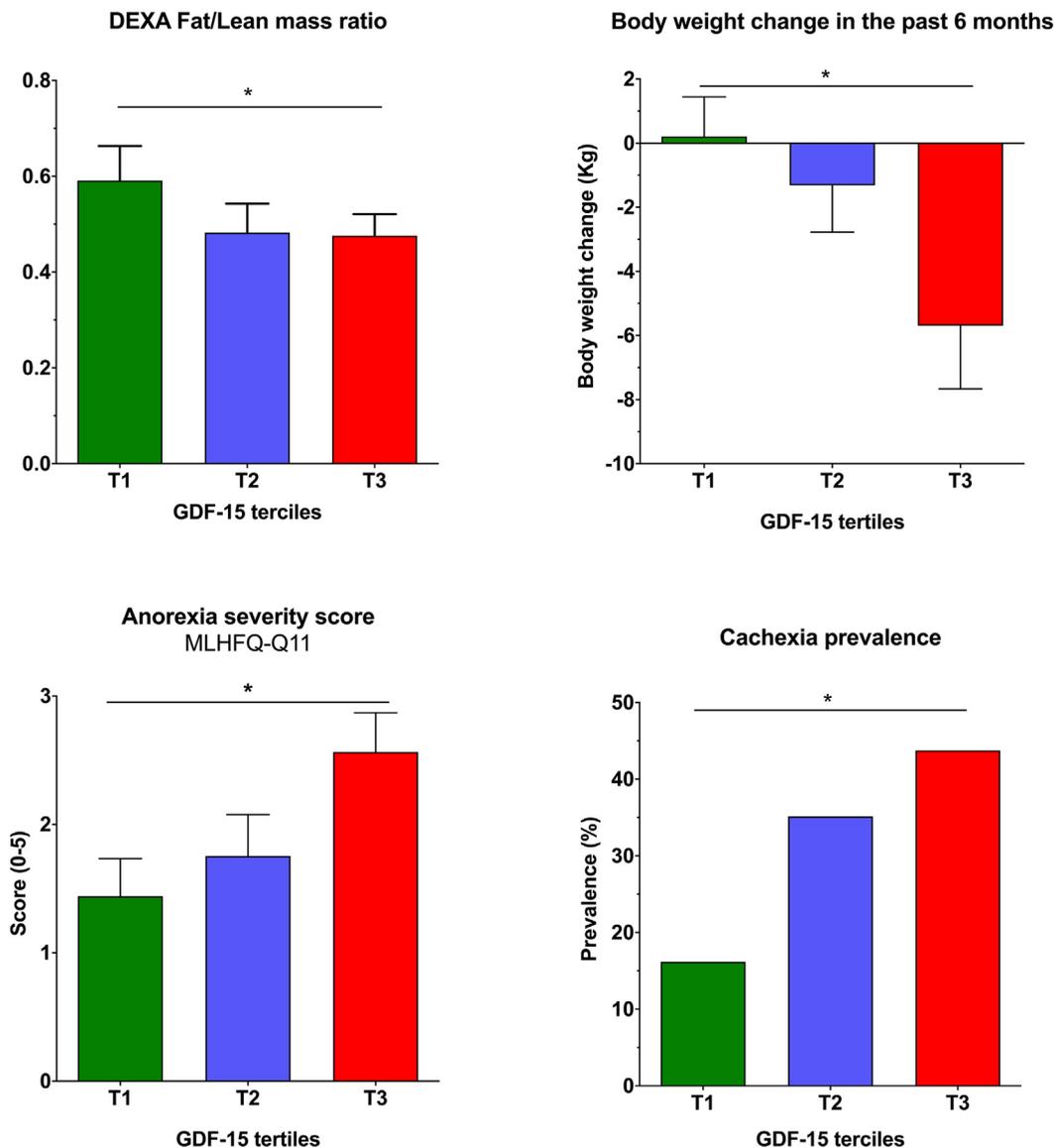
ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMC = bone mineral content; BNP = brain natriuretic peptide; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; DEXA = dual-energy x-ray absorptiometry; eGFR = estimated glomerular filtration rate; GDF = growth differentiation factor; HbA_{1c} = glycated hemoglobin; HF = heart failure; HOMA-IR = homeostasis model assessment of insulin resistance; MLHFQ = Minnesota Living With Heart Failure Questionnaire; ICD = implantable cardioverter-defibrillator; LV = left ventricle; MELD-XI = model for end-stage liver disease excluding INR; MRA = mineralocorticoid receptor antagonist; NA = not applicable; OAD = oral antidiabetic drugs; PA = pulmonary artery; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion.

renal function, and higher prevalence and severity of RV dysfunction (Supplemental Table 4). From a metabolic perspective, more marked symptoms of anorexia were associated with diabetic status and impaired glycemic control, along with increased beta-OHB levels. In the multivariable regression analysis, higher GDF-15 concentrations and the presence of RV dysfunction were identified as the only independent predictors of anorexia severity (Supplemental Table 4).

DETERMINANTS OF CACHEXIA AND ITS ASSOCIATION WITH GDF-15. One third of the study population (n = 105; 32%) experienced unintentional, edema-free BW loss >5% in the past 6 months, compatible with a diagnosis of cardiac cachexia. The presence of cachexia was associated with anorexia severity (MLHFQ-Q11 score ≥3; OR: 2.837 [95% CI: 1.717-4.686]; P < 0.001), along with several metabolic and structural changes indicative of a catabolic state, including lower albumin levels, along with marked reductions in anthropometric parameters (BMI <25 kg/m², BW, and body fat) (Supplemental Table 5). Furthermore, cachexia was strongly associated with an increase in natriuretic peptides

concentration and circulating GDF-15, along with a more severe RV dysfunction. In the multivariable regression analysis, lower BMI and albumin and higher circulating GDF-15 levels were independently associated to an increased probability of having cachexia (Supplemental Table 5). Excluding anthropometric measures typically associated with an unintentional BW loss (BMI, BW, body fat), high circulating GDF-15, albumin levels, and increased severity of RV dysfunction emerged as independent predictors of cachexia (Supplemental Table 5).

OUTCOMES. During a median follow-up of 1,163 days (Q1-Q3: 384-2,945 days), there were 247 composite events including 165 deaths, 33 LVAD implantations, and 49 urgent cardiac transplantations. Nonurgent cardiac transplantation was not included in the composite and occurred in 20 cases (6%). Patients in the highest tertile of GDF-15 showed a heightened risk of adverse clinical events compared to those in the lower tertile (T3 vs T1: HR: 3.79 [95% CI: 2.71-5.31]; P < 0.001) in univariate Cox regression analysis (Figure 4). Increased anorexia score severity and cachexia were also linked to poorer survival outcomes in univariate Cox regression analysis. Patients

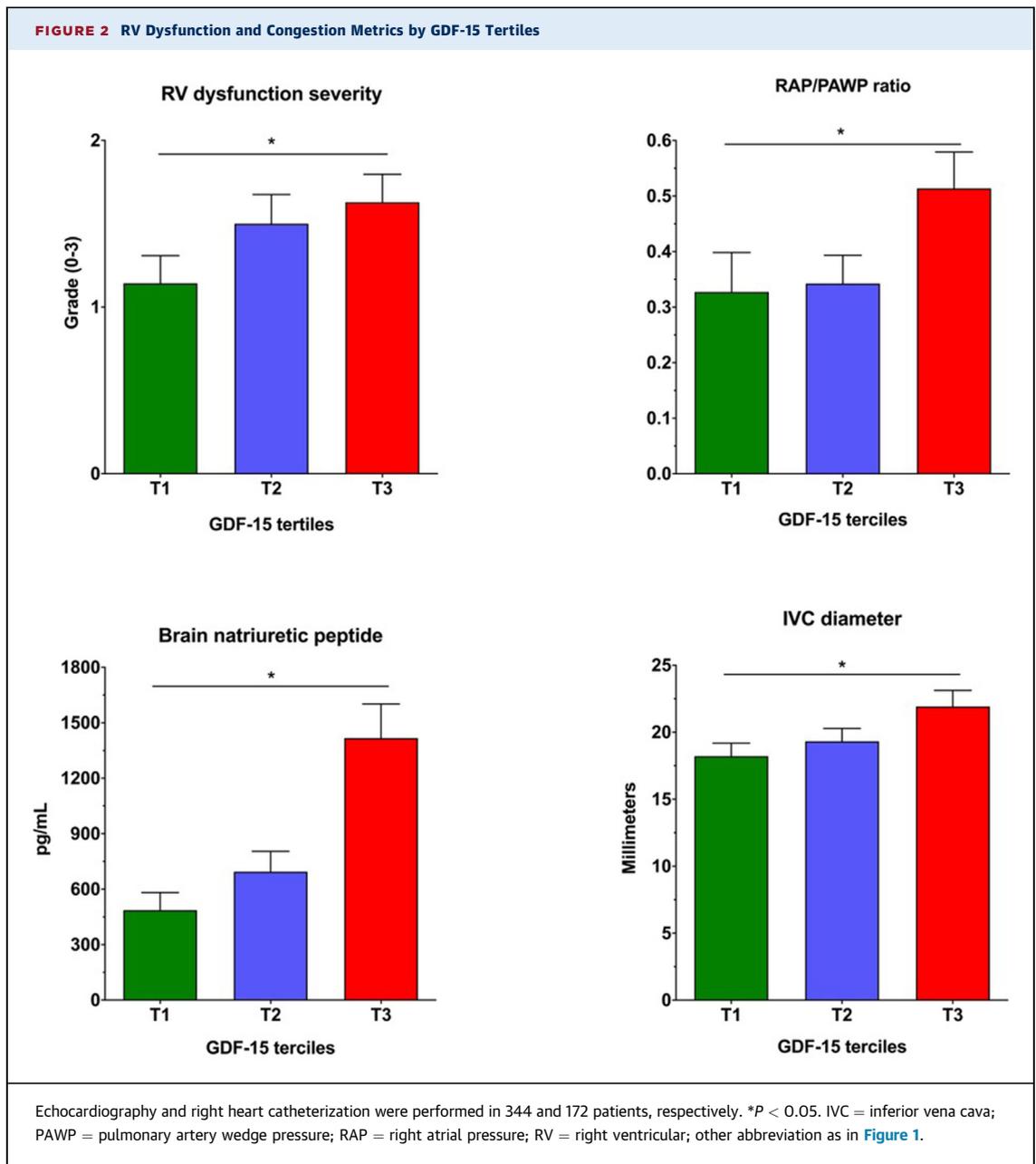
FIGURE 1 Fat/Lean Mass Ratio, Body Weight Change, Anorexia Severity, and Cachexia Prevalence by GDF-15 Tertiles

Minnesota Living With Heart Failure Questionnaire (MLHFQ) and dual-energy x-ray absorptiometry (DEXA) scans were performed in 314 and 150 patients, respectively. * $P < 0.05$. GDF-15 = growth differentiation factor-15; Q11 = question 11.

with more pronounced anorexia symptoms according to MLHFQ question 11 score (none = 0; low = 1-3; high = 4-5) exhibited an increased risk of adverse clinical events compared to those reporting no anorexia symptoms (HR: 1.78 [95% CI: 1.29-2.47]; $P < 0.001$) (Supplemental Figure 1A). Similarly, patients diagnosed with cachexia had a worse prognosis than those without (HR: 1.41 [95% CI: 1.08-1.85]; $P = 0.010$) (Supplemental Figure 1B). Sensitivity

analysis using as endpoint a composite of death or urgent cardiac transplantation (ie, excluding LVAD implantation to avoid potential referral bias to our tertiary center) showed similar results (GDF-15, T3 vs T1 HR: 4.32 [95% CI: 2.98-6.26]; $P < 0.001$; anorexia HR: 1.39 [95% CI: 1.02-1.90]; $P = 0.038$; cachexia HR: 1.43 [95% CI: 1.08-1.91]; $P = 0.013$).

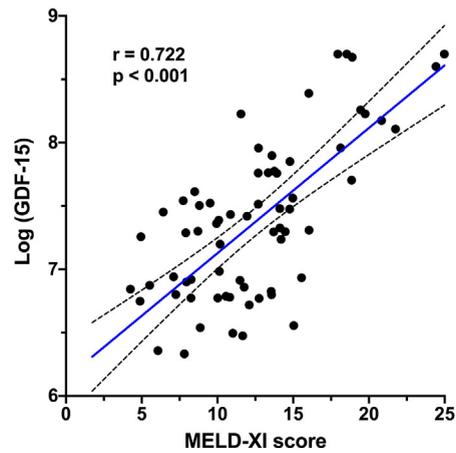
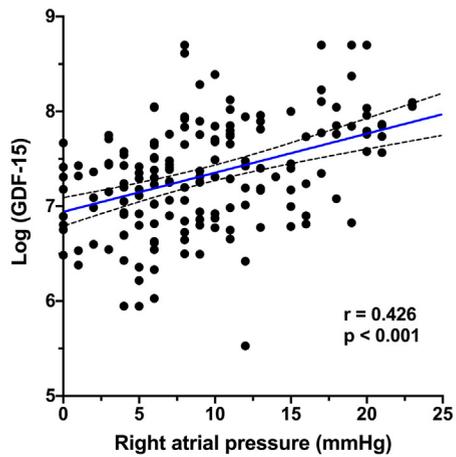
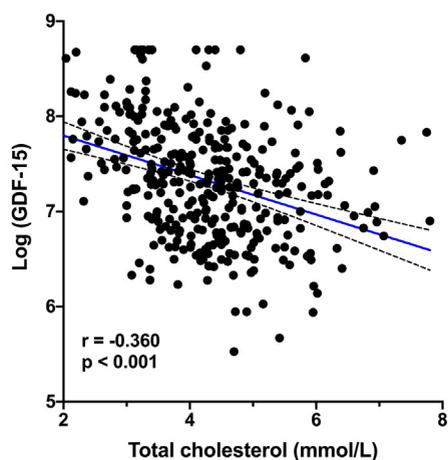
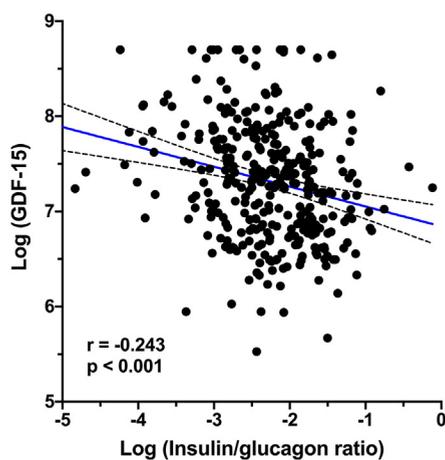
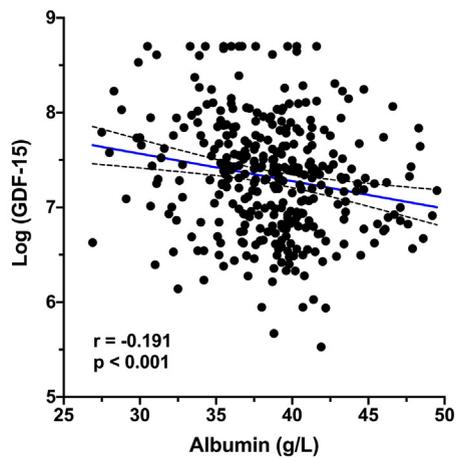
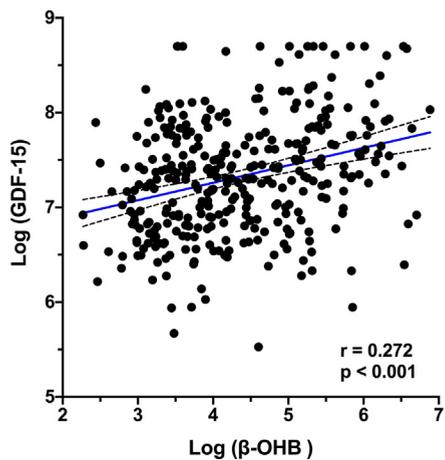
In multivariable Cox analysis, elevated GDF-15 was independently associated with increased risk for



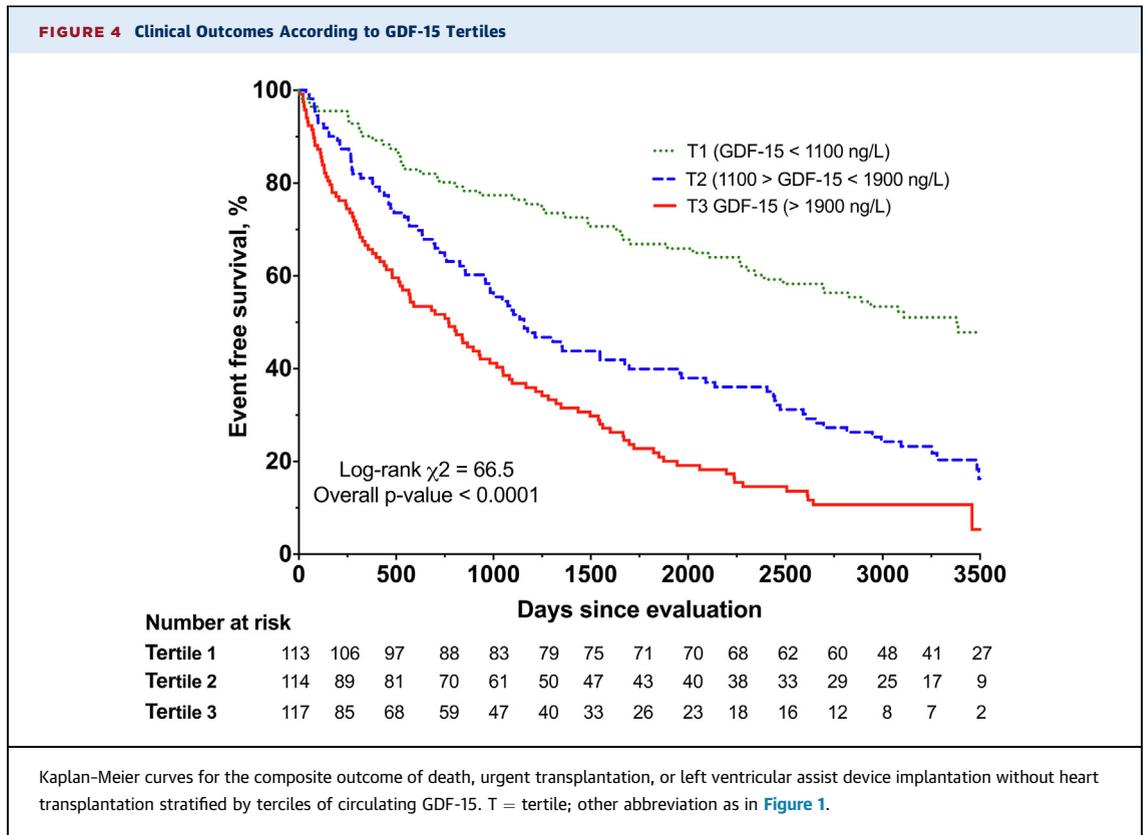
adverse outcomes, even after adjusting for coexisting anorexia and cachexia (T3 vs T1 HR: 2.31 [95% CI: 1.47-3.66]; $P < 0.001$). When RV dysfunction, a well-known determinant of anorexia-cachexia syndrome¹⁴ and a strong driver of adverse outcomes,¹⁵ is included in the model, both the presence of RV dysfunction (HR: 1.86 [95% CI: 1.11-3.13]; $P = 0.019$) and increased circulating GDF-15 (T3 vs T1 HR: 2.20 [95% CI: 1.34-3.62]; $P = 0.002$) were retained as independent predictors of adverse outcome.

DISCUSSION

In this study, we observed that elevated circulating levels of GDF-15 were associated with increased severity of anorexia and a higher prevalence of cachexia in patients with advanced HFREF. RV dysfunction and systemic congestion were associated with GDF-15 levels and were significantly related to anorexia and cachexia (Central Illustration), suggesting that there are 2 possible mechanistic

FIGURE 3 Correlation of GDF-15**A****B**

(A) RAP and liver dysfunction. (B) Metabolic parameters. RAP and MELD-XI were available in 170 and 68 patients, respectively. MELD-XI = model for end-stage liver disease excluding INR; other abbreviations as in [Figures 1 and 2](#).

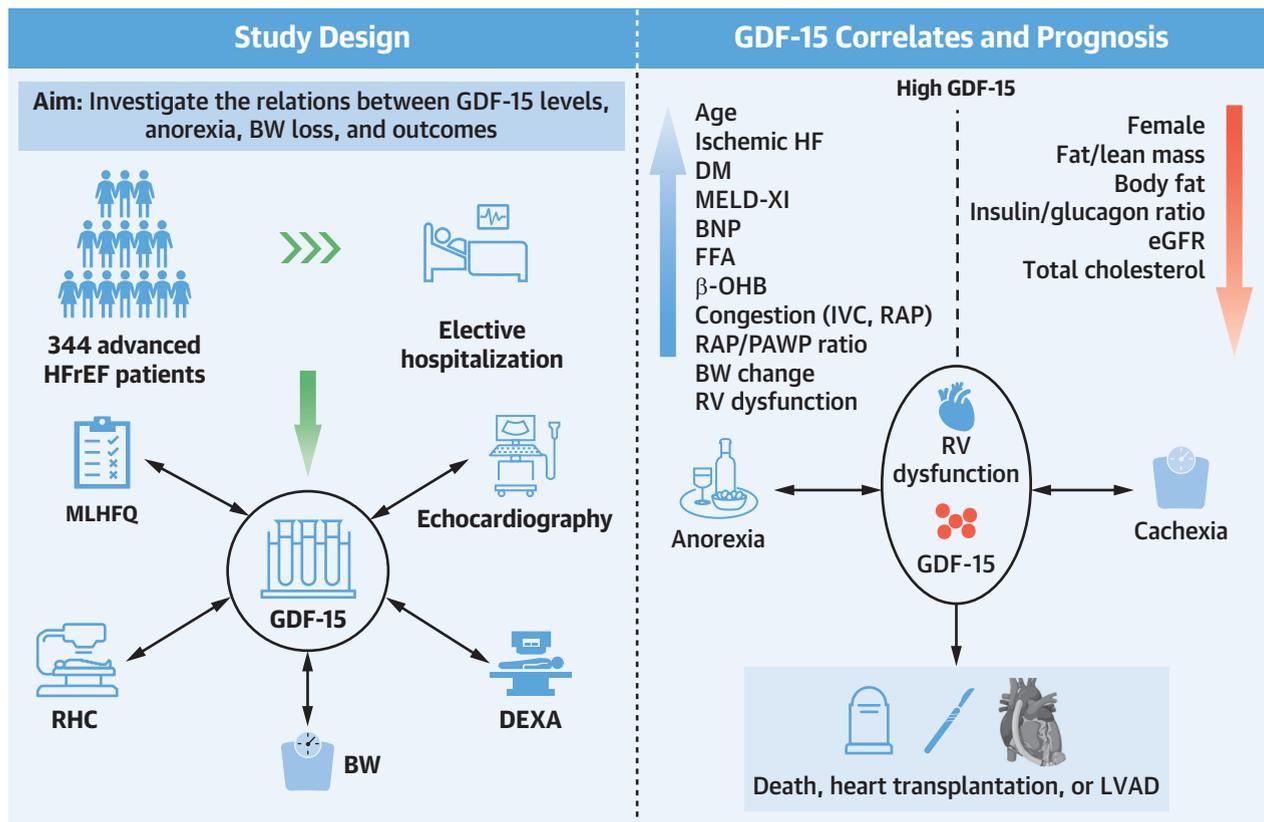


pathways—1 direct hemodynamic and another indirect neurohumoral, mediated by GDF-15—that may link systemic congestion to anorexia in advanced HF (Supplemental Figure 2). Our data support the concept that pharmacologic interference with GDF-15 signaling can improve nutritional status in advanced HF and prevent the progression of cardiac cachexia.

Although anorexia and cachexia are 2 well-recognized findings in cancer,²⁷ they can also complicate other chronic diseases, including HF.²⁸ In patients with advanced HF, the prevalence of anorexia and cachexia is high, with a strong negative impact on the quality of life and survival, as again confirmed in this study.^{29,30} To emphasize the clinical importance of wasting in HF patients, it was recently proposed to modify the acronym summarizing indications for advanced therapies referral (I-NEED-HELP) to include a C for cachexia, resulting in C-I-NEED-HELP.³¹ The mechanisms through which HF may lead to malnutrition are complex, involving a combination of neurohormonal, metabolic, and

immunological factors, all contributing to an imbalance between anabolic and catabolic processes.³²

Experimental and human data suggest that GDF-15 plays a crucial role in the development of cancer-related anorexia and weight loss^{33,34} and is associated with poor survival.⁵ Moreover, GDF-15 has recently been shown to play a pivotal role in the nausea associated with pregnancy.³⁵ GDF-15 impacts energy metabolism by binding to its receptor GFRAL, which is selectively expressed in the brain neurons of the area postrema and the nucleus of the solitary tract, which are important brainstem regions involved in appetite and weight regulation.⁹ Through this interaction, GDF-15 activate neuronal pathways that are perceived as aversive,³⁶ thereby suppressing food intake and mediating the central anorectic effect.³⁷ Experimental data have shown that the administration of recombinant GDF-15 can trigger conditioned taste aversion in mice.³⁸ Additionally, the GDF-15/GFRAL signaling pathway also induces the expression of genes involved in lipid metabolism and activates the peripheral sympathetic axis.¹³

CENTRAL ILLUSTRATION Design and Key Findings

Monzo L, et al. JACC Heart Fail. 2025;■(■):■-■.

In the right panel, double-headed arrows show that circulating growth differentiation factor (GDF)-15 and right ventricular (RV) dysfunction are independently associated with anorexia and cachexia. Variables listed next to the upward or downward arrow are positively or negatively associated with higher GDF-15 levels, respectively. Parts of the figure were created using Biorender.com. BNP = brain natriuretic peptide; β -OHB = beta-hydroxybutyrate; BW = body weight; DEXA = dual-energy x-ray absorptiometry; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; FFA = free fatty acids; HF = heart failure; HFREF = heart failure with reduced ejection fraction; IVC = inferior vena cava; LVAD = left ventricular assist device; MELD-XI = model for end-stage liver disease excluding INR; MLHFQ = Minnesota Living With Heart Failure Questionnaire; PAWP = pulmonary artery wedge pressure; RAP = right atrial pressure; RHC = right heart catheterization.

These mechanisms elicit a lipolytic overdrive in adipose tissue, resulting in BW reduction independent of anorexia.^{9,13}

In our study, GDF-15 had a stronger association with fat mass than with lean mass. This finding may reflect recent cachexia, where fat tissue catabolism, likely accelerated by lipolytic activity of highly increased natriuretic peptides,³⁹ precedes the breakdown of lean tissue. This hypothesis is supported by previous evidence indicating that the loss of fat mass, along with appendicular muscle mass, is closely associated with adverse outcomes and may serve as an early indicator for detecting cardiac cachexia.^{15,40,41}

Our data suggest that the effects of GDF-15 in HF may be similar to those observed in patients with malignancies.²⁷ In particular, we propose that the combination of a strong central anorectic effects of GDF-15, along with nutrient malabsorption due to RV failure and consequent bowel congestion, could lead together to malnutrition and wasting syndrome in patients with advanced HF. Circulating GDF-15 is elevated in patients with HF⁴² and correlates with disease severity and prognosis.⁴³ We found that elevated circulating levels of GDF-15 were associated with more severe RVD and worse congestion as evidenced by elevated BNP levels, more pronounced edema severity (MLHFQ question 1), enlarged inferior

vena cava dimension, raised central venous pressure, and more impaired function of liver and kidneys. These findings suggest that RV failure and the ensuing congestion could be key factors in driving the development of HF-related anorexia/cachexia, potentially triggering an increase in circulating GDF-15 levels, which then acts centrally to reduce appetite. In other studies in patients with chronic HF, GDF-15 was also associated with increased severity of congestion.⁴⁴ Similarly, GDF-15 levels were markedly increased in acute HF patients, and rapidly declined with decongestion, supporting the enhancing effect of hypervolemia on GDF-15 levels.⁴⁵ Likewise, mechanical left ventricular (LV) unloading and improved LV end-organ perfusion from LVAD implantation in end-stage HF also significantly rapidly reduced plasma GDF-15 levels, along with improvements in kidney and liver function. This study also showed that peripheral tissues, rather than the heart itself, are the primary source of GDF-15 in HF patients.⁴⁶

Venous congestion could also directly impact on the development of cardiac cachexia in HF.^{15,47} RV failure results in splanchnic congestion, visceral organs edema with increased bowel wall thickness, and, ultimately, malabsorption.¹⁴ Intestinal congestion can also induce appetite loss and postprandial satiety,¹⁴ further worsening the reduction in food intake. Mesenteric venous congestion can facilitate the development of cardiac cachexia by promoting increased bowel permeability, leading to bacterial translocation and subsequent release of endotoxins into the bloodstream,⁴⁸ stimulating immune activation and the production of proinflammatory cytokines.⁴⁹ Although the precise mechanisms linking hemodynamic congestion to elevated GDF-15 remain unclear, GDF-15 production in this context may serve as a protective mechanism by increasing intestinal mucin secretion, thereby counteracting alterations in the bowel barrier and preventing bacterial translocation.⁵⁰ Liver distress due to splanchnic congestion may also be as a primary source of GDF-15 in HF patients,⁵¹ as supported by the strong positive correlation between GDF-15 levels and MELD-XI scores (Supplemental Figure 2).

Inhibition of the GDF-15/GFRAL signaling in brainstem neurons holds promising therapeutic potential to mitigate the occurrence of appetite and weight loss in patients with HF. Building on previous cancer research where preclinical studies showed that antibody-mediated inhibition of GDF-15/GFRAL pathway effectively mitigated tumor-induced weight loss,^{13,52,53} similar experimental studies were conducted in HF models. In a rat model of monocrotaline-induced RV dysfunction,

neutralization of GDF-15 with a selective monoclonal antibody prevented experimentally induced anorexia and weight loss, and preserved lean and fat mass.¹²

This study contributes human data to the existing experimental evidence, providing biological plausibility for testing novel therapies aimed at antagonizing GDF-15 pathways in chronic HFREF. Our findings indicate that GDF-15 levels were not significantly associated with static anthropometric measures such as BMI but were instead correlated with changes in BW over time. Consequently, the potential selection of patients for GDF-15-lowering therapies should focus on the history of weight loss, rather than on BMI or absolute weight. Future studies in advanced HF might include GDF-15 as a core variable. This approach could enhance our understanding of GDF-15 role in HF, especially when combined with data on downstream effects such as anorexia, appetite, and energetic balance, and possibly guide the development of more effective treatments.

Some treatments that improve outcomes in chronic HF, such as valsartan and sacubitril-valsartan,^{54,55} do not significantly alter circulating levels of GDF-15, even though they enhance cardiovascular outcomes. In contrast, ivabradine has been shown to reduce GDF-15 concentrations,⁵⁶ whereas metabolic drugs such as empagliflozin have been found to increase these levels in ambulatory HF patients.⁵⁷ This may suggest that the GDF-15 response to guideline-directed medical therapy is not uniform and may reflect diverse mechanisms how these drugs work. Future studies on GDF-15 modulation might benefit from focusing on patients with advanced HF for whom the association between GDF-15 levels and clinical events is likely to be most pronounced.⁵⁸

Recently, a novel monoclonal antibody therapy (ponsegromab), designed to selectively bind and inactivate GDF-15, was shown to increase weight gain, enhance physical activity, and reduce anorexia, cachexia symptoms, and nausea in a dose-dependent manner among cancer patients with elevated GDF-15 levels,⁵⁹ confirming its key role in the development of anorexia and cachexia. Ponsegromab is currently being evaluated in a clinical trial (GARDEN-TIMI 74; [NCT05492500](https://clinicaltrials.gov/ct2/show/study/NCT05492500)) to assess its potential to improve HrQOL and 6-minute walk distance in patients with advanced HF. Our findings suggest that antianorexic and anticatabolic effects of GDF-15 antagonism may be beneficial beyond traditional neurohormonal and cardiorenal mechanisms in advanced HFREF with wasting.

STUDY LIMITATIONS. The observational design of this study limits its ability to make inferences toward

causality. We did not collect information on dietary intake, leaving us unable to determine whether patients with anorexia/cachexia experienced deficiencies in energy or protein intake. Potential unmeasured confounders, such as dietary habits,⁶⁰ physical activity levels,⁶¹ proinflammatory states,⁶² and genetic predispositions,⁶³ may also have influenced the observed relationship between GDF-15 levels and anorexia. There are more specific instruments for the evaluation of anorexia than those we used,^{64,65} and more detailed nutritional surveys in advanced HF patients are warranted in the future. Our data set lacked the granularity to precisely assess all the I-NEED-HELP markers of advanced HF.²⁶ Nevertheless, the available I-NEED-HELP criteria and other common parameters used to estimate HF severity (eg, high events rate, severe LV remodeling) were consistent with the advanced stage of the HF patients studied. Our population mainly comprises middle-age, White males with advanced HF_{rEF}. This imbalance was likely caused by both HF demographics in the explored age strata (ie, <65 years of age) and selection bias (patients referred or enrolled in a single tertiary center). We did not identify significant interaction effects between sex and the association of GDF-15 with anorexia, cachexia, and clinical outcomes (all $P > 0.10$); however, additional data are needed to confirm these findings. Additionally, caution is advised when extending these results to patients with different types of HF, including HF with preserved ejection fraction (HF_{pEF}). HF_{pEF} is more commonly associated with an obesity phenotype, which contrasts sharply with the cachexia often observed in advanced HF_{rEF}. BW data were not consistently collected throughout the follow-up period of the study, limiting our ability to analyze the impact of GDF-15 levels on prospective weight changes. Finally, we do not have specific DEXA data on the regional distribution of body composition, preventing us from analyzing changes in appendicular muscle mass in the limbs, which has been associated with adverse outcomes in patients with HF.^{15,40,41}

CONCLUSIONS

In patients with advanced HF_{rEF}, elevated circulating GDF-15 levels were associated with a higher prevalence of anorexia and cachexia along with increased risk for adverse events. The central and peripheral effects of GDF-15 on energy metabolism, potentially mediated by RV failure and congestion,

could play a crucial role in the development of HF-related anorexia and cachexia. These findings support future study of novel interventions targeting of GDF-15 as a strategy to prevent anorexia and weight loss in patients with chronic advanced HF_{rEF}.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Increased circulating levels of GDF-15 were associated with more severe anorexia and a higher incidence of cachexia in patients with advanced HF_{rEF}, as well as an increased risk of adverse events. The impact of GDF-15 levels on energy metabolism, possibly influenced by RV failure and fluid overload, suggests a connection between systemic congestion and the onset of cardiac anorexia and cachexia in advanced stages of HF.

TRANSLATIONAL OUTLOOK: Our findings provide biological plausibility for testing novel therapies that target the inhibition of GDF-15/GFRAL signaling in brainstem neurons, aiming to mitigate appetite loss and weight reduction in advanced HF_{rEF}.

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APPENDIX For supplemental figures and tables, please see the online version of this paper.