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CLINICAL RESEARCH

Distinct Pathological Pathways in Patients With Heart Failure and Diabetes

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ABSTRACT

OBJECTIVES The aims of this study were to compare the characteristics of patients with and without diabetes and to use network analyses to compare biomarker profiles and associated pathways in patients with diabetes compared with those without diabetes, which might offer new avenues for potential therapeutic targets.

BACKGROUND Diabetes adversely affects clinical outcomes and complicates treatment in patients with heart failure (HF). A clear understanding of the pathophysiological processes associated with type 2 diabetes in HF is lacking.

METHODS Network and pathway over-representation analyses were performed to identify unique pathological pathways in patients with and without diabetes using 92 biomarkers from different pathophysiological domains measured in plasma samples from 1,572 patients with HF (31% with diabetes) with reduced ejection fraction (left ventricular ejection fraction <40%). The results were validated in an independent cohort of 729 patients (30% with diabetes).

RESULTS Biomarker profiles were first compared between patients with HF with and without diabetes. Patients with diabetes showed higher levels of galectin-4, growth differentiation factor 15, and fatty acid binding protein 4 and lower levels of paraoxonase 3. Network analyses were then performed, revealing that epidermal growth factor receptor and galectin-3 were the most prominent connecting proteins. Translation of these networks to biologic pathways revealed that diabetes was associated with inflammatory response and neutrophil degranulation. Diabetes conferred worse outcomes after correction for an established risk model (hazard ratio: 1.20; 95% confidence interval: 1.01 to 1.42).

CONCLUSIONS Concomitant diabetes in patients with HF with reduced ejection fraction is associated with distinct pathophysiological pathways related to inflammation, protein phosphorylation, and neutrophil degranulation. These data support the evaluation of anti-inflammatory therapeutic approaches, epidermal growth factor receptor in particular, for patients with HF and diabetes. (J Am Coll Cardiol HF 2020;8:234–42)

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Diabetes mellitus (DM) is present in 30% to 40% of patients with heart failure with reduced ejection fraction (HFrEF) (1–3) and increases the risks for mortality and hospitalization for heart failure (HF) (4–6). Patients with DM have an increased risk for developing HF, and patients with HF are at increased risk for developing DM (7,8). Therefore, we need to better understand potential pathophysiological differences between patients with HF with and without diabetes.

Network analyses can identify relevant pathophysiologic mechanisms by enriching empirically found biomarkers within the context of disease pathways (9–12). Therefore, we aimed to: 1) compare the characteristics of patients with and those without DM; and 2) use network analyses to compare biomarker profiles and associated pathways in patients with DM compared with those without DM, which might offer new avenues for potential therapeutic targets.

METHODS

PATIENT POPULATION. We studied patients from the BIOSTAT-CHF (A Systems Biology Study to Tailored Treatment in Chronic Heart Failure) project, which is described elsewhere (13,14). In brief, BIOSTAT-CHF includes 2 cohorts of patients with HF. The main aim of BIOSTAT-CHF was to characterize biologic pathways related to response or no response to guideline-recommended pharmacological therapy for HF. Our index cohort consisted of 2,516 patients with HF from 69 centers in 11 European countries. Inclusion criteria for the index cohort include age >18 years and symptoms of new-onset or worsening HF, confirmed by either a left ventricular ejection fraction of ≤40% or B-type natriuretic peptide (BNP) and/or N-terminal pro-BNP plasma level >400 or >2,000 pg/ml, respectively. All patients were suboptimally treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and/or beta-blockers, with anticipated initiation or up-titration of angiotensin-converting enzyme inhibitors or angiotensin receptor blocker and beta-blockers to European Society of Cardiology-recommended target doses. Patients in both the index and validation cohorts could be enrolled as inpatients or from outpatient clinics (13). Biomarkers were available in 1,572 patients with left ventricular ejection fractions <40% in the index cohort (Online Figure 1) (15). We validated our results in an independent cohort of 1,738 patients from 6 centers in Scotland. In total, 729 patients had left ventricular ejection fractions <40% and biomarker data available. Diabetes was defined as having a medical history of diabetes and/or being on antidiabetic medication.

CLINICAL AND BIOMARKER MEASUREMENTS. Medical history, current use of medication, and a physical examination were all recorded at baseline. A large biomarker panel with 92 biomarkers was measured in the index and validation cohort. An overview of biomarkers and their pathophysiological function is presented in Online Table 1. Assay characteristics are presented in Online Table 2. Biomarkers were measured using a high-throughput technique using the Olink Proseek Multiplex CVD III 96 × 96 kit (Olink, Uppsala, Sweden), which measures 92 manually selected cardiovascular-related proteins simultaneously in 1-μl plasma samples. The kit uses proximity extension assay technology, in which 92 oligonucleotide-labeled antibody probe pairs are allowed to bind to their respective targets present in the sample. The proximity extension assay is a homogeneous assay that uses pairs of antibodies equipped with deoxyribonucleic acid reporter molecules. When binding to their correct targets, they give rise to new deoxyribonucleic acid amplicons, each ID-barcoding its respective antigens. The amplicons are subsequently quantified using a Fluidigm BioMark HD real-time polymerase chain reaction platform (Fluidigm, South San Francisco, California). The

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

BNP = B-type natriuretic peptide

CI = confidence interval

DM = diabetes mellitus

EGFR = epidermal growth factor receptor

FABP4 = fatty acid binding protein 4

GDF15 = growth differentiation factor 15

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

PON3 = paraoxonase 3

TNFR = tumor necrosis factor receptor

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platform provides normalized protein expression data wherein a high protein value corresponds to a high protein concentration but not an absolute quantification.

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STATISTICAL ANALYSIS. Differences in clinical characteristics between patients with and those without diabetes were tested using Student's *t*-test, the Mann-Whitney *U* test, or the chi-square test as appropriate. Differences in expression of biomarkers between patients with and those without diabetes was performed using linear models for microarray data analysis (limma version 3.34.9) (16), with a false discovery rate of 0.05 according to the Benjamini-Hochberg method and a $\log_2$ fold-change cutoff of 0.2. In addition, to test the independence of associations, we performed multivariate logistic regression analyses to test the independent associations of biomarkers with diabetes status, correcting for relevant clinical confounders including age, sex, body mass index (BMI), ischemic etiology of HF, history of hypertension, and estimated glomerular filtration rate. Similarly, for both the index and validation cohorts, biomarkers that passed the cutoff values for the false discovery rate-corrected p value and $\log_2$ fold-change cutoff were then used in subsequent network analyses. To provide biologic context to the proteins found, we created a general network of human physical protein-protein interactions, HsapiensPPI, consisting of 17,625 unique nodes with 330,157 interactions among them, on the basis of data from the Biomolecular Interaction Network Database (17), the Biological General Repository for Interaction Datasets (18), the Database of Interacting Proteins (19), the Human Protein Reference Database (20), IntAct (21), and PDZBase (22) (Online Appendix). Context-specific networks were constructed by selecting nodes and interactions that occur only between members from the protein list being investigated (N0 networks, colored orange) and/or by selecting nodes that indirectly interact, 1 neighbor away, with members of the list (N1 networks, colored blue). Physical cohesiveness of context-specific networks was assigned using the physical interaction enrichment procedure, which corrects for biased enrichment, in general protein-protein interaction networks, of proteins that are, for example, often studied (23). Analysis of protein-protein interactions was performed and plotted using Cytoscape version 3.7.0 (24), where the node size corresponds to the betweenness centrality (11,24). The larger the node size, the more connected the node is in the network. Pathway overrepresentation analyses was performed using EnrichR, using Gene Ontology terms (25,26). Survival analyses was performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) using the Survival and Survminer packages (27). Cox regression analyses was used for multivariate survival analyses. Multivariate correction was performed using the BIOSTAT-CHF risk model, which includes age, blood urea nitrogen, N-terminal pro-BNP, hemoglobin, the use of a beta-blocker at the time of inclusion, HF hospitalization in the year before inclusion, peripheral edema, systolic blood pressure, high-density lipoprotein cholesterol, and sodium. All tests were 2 sided, and p values < 0.05 were considered to indicate statistical significance.

RESULTS

BASELINE CHARACTERISTICS AND CLINICAL OUTCOMES. Among 1,572 patients with HFrEF, 493 (31%) had diabetes. Patients with diabetes were slightly older (69 years vs. 67 years; $p = 0.002$), had higher BMI (29 vs. 27 kg/m^2; $p < 0.001$), and had worse signs and symptoms of HF in comparison with patients without diabetes (**Table 1**). Furthermore, patients with diabetes more often had histories of hypertension (72% vs. 53%; $p < 0.001$) compared with patients without diabetes. Among patients with diabetes, 322 (65%), 183 (37%), and 345 (70%) were on oral antidiabetic medications, insulin, and diet control, respectively. Furthermore, patients with diabetes had worse (lower) estimated glomerular filtration rates but similar N-terminal pro-BNP levels compared with patients without diabetes (**Table 1**). Patients in the index cohort were slightly younger and more often in New York Heart Association functional class III or IV compared with the validation cohort but had a similar prevalence of comorbidities as well as signs and symptoms (Online Table 3).

DIFFERENTIAL PROTEIN EXPRESSION, NETWORK, AND PATHWAY ENRICHMENT ANALYSES. In the index cohort, 10 proteins were significantly up-regulated and 1 protein was significantly down-regulated in patients with diabetes compared with those without diabetes (**Figures 1A and 1B**). In the validation cohort, 13 proteins were significantly up-regulated and 3 proteins were significantly down-regulated in patients with diabetes compared with those without diabetes (**Figure 1B**). In both cohorts, 8 proteins were significantly up-regulated. These include chitinase 3-like protein 1, fatty acid binding protein 4 (FABP4), galectin 4, trefoil factor 3, tumor

necrosis factor receptor (TNFR) 1 and 2, TNFR superfamily 14, and growth differentiation factor 15. Paraoxonase 3 (PON3) was down-regulated in both cohorts. After additional correction for age, sex, BMI, ischemic etiology of HF, history of hypertension, and estimated glomerular filtration rate, biomarkers remained differentially expressed in patients with diabetes compared with those without ($p < 0.05$ for all). When investigating the association of these biomarkers with diabetic medication (oral vs. insulin), levels of TNFR2 (odds ratio: 0.76; 95% confidence interval [CI]: 0.59 to 0.99) and TNFR superfamily 14 (odds ratio: 0.75; 95% CI: 0.56 to 0.98) were slightly lower in patients on oral medication compared with those not on oral medication after correcting for age, sex, BMI, ischemic etiology of HF, history of hypertension, and being on insulin or diet control.

Results of network analyses are shown in the **Central Illustration**. The size of the nodes reflects the number of shortest paths running through the node (edge betweenness); the larger the node, the larger the number of shortest paths that run through the node within the network. In other words, a larger node reflects greater connectedness within the network. The color of each node relates to either empirically found proteins (orange) or propagated nodes in the N1 network (blue). In the index cohort, epidermal growth factor receptor (EGFR), galectin 3, and granulin were important nodes (hubs) in the network of patients with diabetes (**Central Illustration**). A summary of the proteins measured and their respective functions can be found in Online Table 1.

We then performed functional classification of our N1 networks (**Central Illustration**) by contrasting the networks against Gene Ontology terms. The top 10 enriched pathways implicated several key pathways involved in the pathophysiology of HF. Pathways relating to positive regulation of intracellular transduction as well as inflammatory response, neutrophil degranulation, and neutrophil-mediated immunity were overrepresented (**Central Illustration**).

CLINICAL OUTCOMES. Compared with patients without diabetes, those with diabetes were more likely to die or be hospitalized for HF within 2 years (hazard ratio [HR]: 1.32; 95% CI: 1.06 to 1.66) (survival curve as shown in Online Figure 2). A similar increase in risk for death and/or HF hospitalization was found in the validation cohort (HR: 1.63; 95% CI: 1.28 to 2.08; $p < 0.0001$). Among patients who died, patients with DM died equally of cardiovascular causes compared with those without DM in both the index (68% vs. 68%; $p = 0.987$) and validation (68% vs. 65%; $p = 0.77$) cohorts. After correction for the BIOSTAT-CHF risk model, patients with diabetes were at higher risk for the primary composite outcome in the index cohort (HR: 1.20; 95% CI: 1.01 to 1.42). However, this association was attenuated in the validation cohort (HR: 0.92; 95% CI: 0.42 to 1.97). Additional correction for ischemic etiology of HF

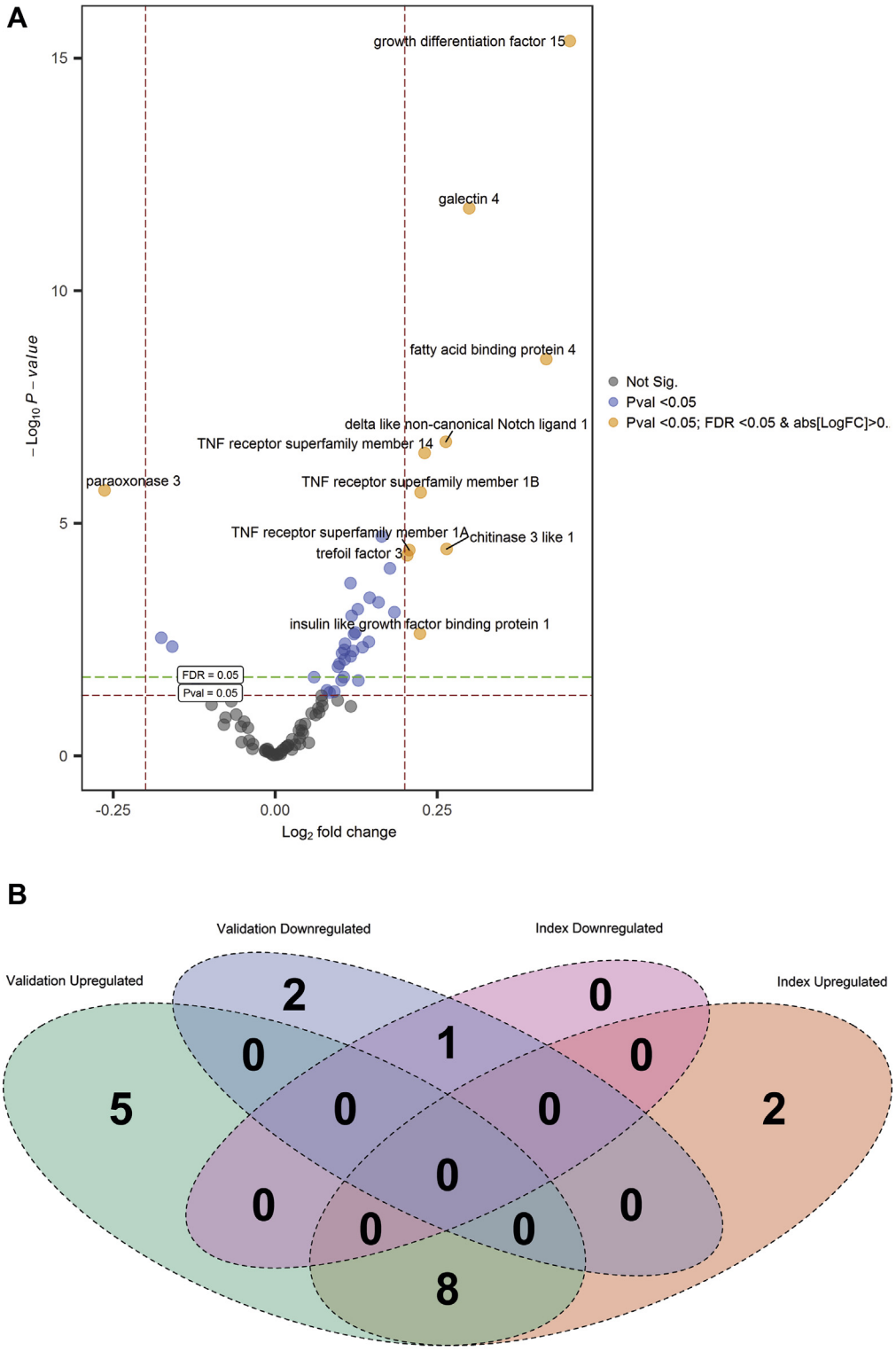
TABLE 1 Baseline Characteristics According to Diabetic Status

	No Diabetes (n = 1,079)	Diabetes (n = 493)	p Value
Demographics			
Age (yrs)	66.7 ± 12.6	68.8 ± 10.6	0.002
Women	269 (24.9)	103 (20.9)	0.081
BMI (kg/m^2)	26.9 ± 4.9	29.1 ± 5.8	<0.001
Ischemic etiology	425 (40.2)	293 (60.5)	<0.001
LVEF (%)	27.0 (21.0–32.0)	30.0 (25.0–35.0)	0.006
NYHA functional class			0.079
I	94 (8.7)	28 (5.7)	0.073
II	497 (46.1)	250 (50.7)	
III	316 (29.3)	134 (27.2)	
IV	32 (3.0)	22 (4.5)	
Not available	140 (13.0)	59 (12.0)	
Systolic BP (mm Hg)	122.3 ± 21.8	124.2 ± 19.5	0.096
Diastolic BP (mm Hg)	75.3 ± 12.9	74.4 ± 11.7	0.17
Heart rate (beats/min)	80.6 ± 19.8	78.8 ± 16.7	0.072
Signs and symptoms			
Elevated JVP	217 (28.4)	116 (33.0)	0.14
Hepatomegaly	149 (13.8)	84 (17.1)	0.096
Orthopnea	319 (29.6)	186 (37.7)	0.001
Edema	453 (51.9)	257 (61.8)	0.001
Medical history			
Anemia	289 (28.1)	203 (42.0)	<0.001
Atrial fibrillation	447 (41.4)	219 (44.4)	0.26
COPD	171 (15.8)	99 (20.1)	0.039
Hypertension	569 (52.7)	357 (72.4)	<0.001
Peripheral arterial disease	76 (7.0)	76 (15.4)	<0.001
Stroke	86 (8.0)	56 (11.4)	0.030
Medication			
Oral antidiabetics	0 (0.0)	322 (65.3)	NA
Insulin use	0 (0.0)	183 (37.1)	NA
Diet controlled	0 (0.0)	345 (70)	NA
Loop diuretics	1,075 (99.6)	490 (99.4)	0.51
Aldosterone antagonist	599 (55.5)	273 (55.4)	0.96
ACE inhibitor/ARB	806 (74.7)	359 (72.8)	0.4
Beta-blocker	913 (84.6)	411 (83.4)	0.438
Laboratory			
Hemoglobin (g/dl)	13.6 ± 1.8	13.0 ± 1.8	<0.001
Sodium (mmol/l)	140.0 (137.0–142.0)	139.8 (137.0–142.0)	0.21
Potassium (mmol/l)	4.3 (3.9–4.6)	4.2 (3.9–4.6)	0.91
HbA_{1c} (%)	5.9 (5.5–6.3)	7.2 (6.5–8.2)	<0.001
NT-proBNP (ng/l)	4,440.0 (2,360.0–8,330.0)	3,993.0 (2,136.0–8,648.0)	0.58
Troponin I (μg/l)	0.0 (0.0–0.1)	0.1 (0.0–0.2)	0.001
Glucose (mmol/l)	5.8 (5.2–6.6)	7.8 (6.3–10.1)	<0.001
eGFR (ml/min1.73 m^2)	63.8 (48.0–80.5)	55.6 (42.7–74.4)	<0.001

Values are mean ± SD, n (%), or median (interquartile range).

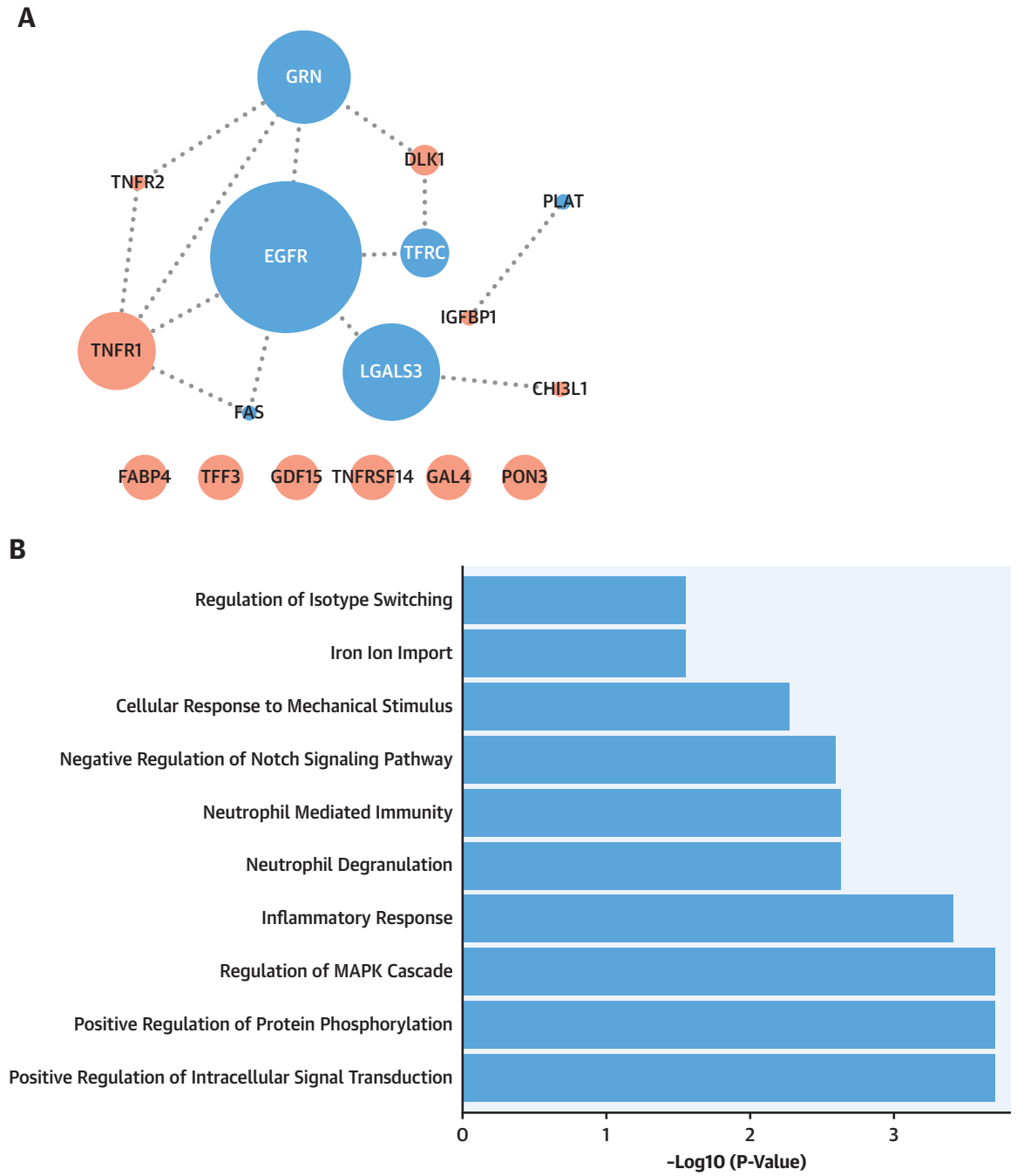
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycated hemoglobin; JVP = jugular venous pressure; LVEF = left ventricular ejection fraction; NA = not applicable; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

FIGURE 1 Differentially Regulated Proteins in Patients With Diabetes Versus Those Without



(A) Volcano plot depicting differentially expressed proteins at a log2 fold change (FC) of >0.2 and a p value <0.05, with a false discovery rate (FDR) of <0.05 in the index cohort. A greater log2 of the FC and −log10 of the p value signifies a greater increase in the mean level or a more significant difference, respectively, of each individual biomarker. **(B)** Venn diagram showing the overlap of proteins up- and down-regulated in patients with heart failure (HF) and diabetes in the index and validation cohort of BIOSTAT-CHF (A Systems Biology Study to Tailored Treatment in Chronic Heart Failure). TNF = tumor necrosis factor.

CENTRAL ILLUSTRATION **Results of Network Analyses and Pathway Over-Representation Analyses in Patients With Diabetes Compared to Those Without Diabetes**



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(A) Network of protein biomarkers in patients with diabetes. **Red** nodes reflect experimentally found biomarkers. **Blue** nodes are propagated within the network. The size of each node corresponds to the edge betweenness. **(B)** Overrepresented pathways of protein biomarkers in diabetes. CHI3L1 = chitinase 3-like protein 1; DLK1 = Delta Like Non-Canonical Notch Ligand 1; EGFR = epidermal growth factor receptor; FABP4 = fatty acid binding protein 4; FAS = Fas cell surface death receptor; GAL4 = galectin 4; GDF15 = growth differentiation factor 15; GRN = granulin; IGFBP1 = Insulin-like growth factor-binding protein 1; LGALS3 = Galectin 3; MAPK = mitogen-activated protein kinase; PLAT = Tissue plasminogen activator; PON3 = paraoxonase 3; TFF3 = trefoil factor 3; TFRC = transferrin receptor; TNFR1 = tumor necrosis factor receptor 1; TNFR2 = tumor necrosis factor receptor 2; TNFRSF14 = tumor necrosis factor receptor superfamily 14.

TABLE 2 Summary of Novel Findings

	Finding
Biomarker levels	↑ Galectin 4, GDF15, and FABP4 ↓ PON3
Network analyses	EGFR and galectin 3 identified as central hubs in the network, signifying possible biological importance
Pathways	↑ Positive regulation of intracellular transduction ↑ Neutrophil degranulation ↑ Neutrophil mediated immunity ↑ Inflammatory response

EGFR = epidermal growth factor receptor; FABP4 = fatty acid binding protein 4; GDF15 = growth differentiation factor 15; PON3 = paraoxonase 3.

attenuated the association in the index cohort (HR: 1.15; 95% CI: 0.96 to 1.36). Of the 10 differentially expression biomarkers, only GDF15 was independently associated with the primary combined outcome after correction for the BIOSTAT-CHF risk model (Online Table 4). Correcting for GDF15 in addition to the clinical risk model attenuated the association of DM with higher rates of the composite primary outcome ($p = 0.07$).

DISCUSSION

This is the first study using comprehensive network analyses to distinguish pathophysiological pathways in patients with HF with and without diabetes. In 2 independent cohorts, we found that patients with diabetes had higher levels of galectin 4, GDF15, and FABP4 and lower levels of PON3. Furthermore, network analyses showed that EGFR, galectin 3, and granulin are important hubs in patients with HF with diabetes. Last, we found that specific pathophysiologic processes in diabetes are associated with inflammation and neutrophil degranulation (**Table 2**).

In a previous study, network analyses were used to compare biomarker profiles between patients with HFrEF and HF with preserved ejection fraction (28), where patients with HF with preserved ejection fraction had increased inflammation compared with those with HFrEF. In the present study, patients with diabetes and HFrEF had up-regulation of inflammatory pathways, suggesting that inflammation might also play an important role in patients with HFrEF and diabetes. In the BIOSTAT-CHF study, patients with diabetes and HFrEF were more likely to die or be hospitalized for HF within the first 2 years compared with patients with HFrEF without diabetes. These findings are in line with earlier results from the CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity) study, which produced similar results (6).

A better understanding of the pathophysiology of diabetes in HFrEF is a prerequisite for identifying novel treatment targets and effectively treating diabetes in patients with HFrEF. In the first step of our analyses, we compared biomarker levels between patients with and those without diabetes. Our study found that GDF15, galectin 4, and FABP4 were considerably higher in patients with diabetes, while levels of PON3 were lower. Of note, none of the biomarkers identified as hubs within the present study identified patient endotype membership in our previous publication (15), which is also in line with the observation that the prevalence of diabetes did not strongly differ between endotypes. Furthermore, levels of GDF15 are increased in HFrEF and might predict new-onset HF in patients with diabetes (10,29-31). Galectin 4 is involved in inflammation, but no data are available on the role of galectin 4 in patients with concomitant diabetes and HF (32). FABP4 independently predicts left ventricular hypertrophy and dysfunction as well as incident HF in nondiabetic populations (33,34). PON3 is potentially cardioprotective and attenuates atherogenesis in mice (35). There is evidence that paraoxonases prevent the development of HF and have anti-inflammatory properties, but they are often reduced in the presence of atherosclerosis.

To provide biological context, we performed network analyses using biomarkers that were differentially expressed between patients with and those without diabetes to identify protein-protein interactions in patients with diabetes compared with those without. An earlier study in patients with acute HF from the PROTECT (Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) trial revealed that among patients with DM, levels of inflammatory markers (TNFR-1a, periostin) and angiogenesis (vascular endothelial growth factor receptor, angiogenin) were significantly increased (9). In addition, network analysis in this study suggested that inflammation and cardiac fibrosis are potentially increased in patients with DM (9). The present study extends on these previous findings by: 1) providing more comprehensive analysis using more biomarkers in a larger number of patients; and 2) providing independent validation of our findings. Network analyses revealed that EGFR and galectin 3 were important hubs. Galectin 3 is associated with both new-onset diabetes and the severity of HF (36,37). In HF, galectin 3 is increased and associated with cardiac fibrosis,

left ventricular dysfunction, and higher mortality (37). EGFR is a transmembrane protein serving as a receptor for epidermal growth factor. Aberrant EGFR signaling is strongly implicated in diabetic nephropathy and HF in experimental studies (38,39). EGFR inhibition with gefitinib had a protective effect on cardiac remodeling, decreased collagen deposition, and improved levels of BNP and troponin I in a diabetic mouse model (40). In humans, EGFR inhibitors such as cetuximab, panitumumab, and erlotinib are currently used to treat several forms of cancer, including breast, colon, lung, and pancreatic cancer (41). Taken together, our results suggest that EGFR inhibition in patients with DM and HF might warrant further study.

In the following step of our analyses, we used pathway enrichment analyses to identify biologic pathways up-regulated in patients with diabetes. We found that enriched biologic pathways in patients with diabetes were associated with inflammatory response and neutrophil degranulation. This is in line with earlier suggestions by Paulus et al. (42), who suggested that this excess inflammation might be mediated by advanced glycation end product deposition (42–46). Our results highlight the importance of pathways related to inflammation and EGFR in patients with HFrEF and diabetes, which might warrant future studies into patient-specific drug programs involving these pathways.

STUDY LIMITATIONS. BIOSTAT-CHF is primarily a Caucasian cohort, and the validity of extrapolation of results to other ethnicities is unclear. Despite rigorous attempts to identify all patients with diabetes, the diagnosis might have been missed in some patients. However, the fact that no patients without diabetes were on antidiabetic medications (and even not on diet control) makes this unlikely. Glycated hemoglobin was available in only a limited number of patients. Last, no information is available on the duration of diabetes, which might have influenced results. Our biomarker panel of 92 proteins is limited. Future studies with a more comprehensive set of proteins or genes would likely provide more pathophysiological differences between patients with HFrEF with and those without diabetes.

CONCLUSIONS

In the present study, we show that concomitant diabetes in patients with HFrEF is associated with distinct pathophysiological pathways, related to inflammation, protein phosphorylation, and neutrophil degranulation. These data support the evaluation of anti-inflammatory therapeutic approaches, EGFR in particular, for patients with HFrEF and diabetes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Diabetes in patients with HF is associated with unique pathophysiological pathways related to inflammation, protein phosphorylation, and neutrophil degranulation, supporting divergent drug development programs for these patients.

TRANSLATIONAL OUTLOOK: EGFR and pathways related to inflammation are possible important treatment targets in patients with HF and diabetes, which deserves further study.

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APPENDIX For a list of general protein-protein interaction data resources as well as supplemental tables and figures, please see the online version of this paper.