CLINICAL RESEARCH STUDY

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Physical Rehabilitation in Older Patients Hospitalized with Acute Heart Failure and Diabetes: Insights from REHAB-HF

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ABSTRACT

BACKGROUND: Prior studies showed an attenuated response to exercise training among patients with heart failure and type 2 diabetes mellitus. We explored the interaction between diabetes status and a novel, transitional, tailored, progressive rehabilitation intervention that improved physical function compared with usual care in the Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) trial.

METHODS: The effect of the intervention on 3-month Short Physical Performance Battery (SPPB) (primary endpoint), 6-minute walk distance (6MWD), modified Fried frailty criteria, and quality-of-life scores (Kansas City Cardiomyopathy Questionnaire [KCCQ] and EuroQoL Visual Analogue Scale [VAS]) was compared between participants with and without diabetes. Differences in 6-month clinical outcomes were also explored.

RESULTS: Of the 349 participants enrolled in REHAB-HF, 186 (53%) had diabetes. The prevalence of diabetes was higher in the intervention group (59% vs 48%). Participants with diabetes had worse baseline physical function by the SPPB and 6MWD, but similar frailty and quality-of-life scores. There was a consistent improvement with the intervention for 3-month SPPB, 6MWD, and VAS regardless of diabetes status (all interaction P value > .6), but participants with diabetes had significantly less improvement for frailty (P = .021) and a trend toward lower improvement in KCCQ (P = .11). There was no significant interaction by diabetes status for 6-month clinical event outcomes (all interaction P value > .3).

CONCLUSIONS: Participants with diabetes had worse baseline physical function but showed similar clinically meaningful improvements from the intervention. There was less benefit for frailty with the intervention in participants with diabetes.

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KEYWORDS: Acute decompensated heart failure; Diabetes mellitus; Heart failure; Physical rehabilitation

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INTRODUCTION

Over 40% of patients hospitalized with acute decompensated heart failure, the leading cause of hospitalization in the United States, have comorbid diabetes mellitus.[1,2] Compared with those without diabetes, these patients have a higher risk of death[3] and hospitalization,[4] and a lower overall quality of life.[5] Prior analysis of ambulatory patients with heart failure with reduced ejection fraction and diabetes undergoing an exercise therapy intervention in the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study[6] showed greater impairment of physical function at baseline compared with those without diabetes. However, the diabetes group still benefited from exercise therapy as demonstrated by significant, although attenuated, improvements in peak oxygen consumption and 6-minute walk distance (6MWD).[7] The interaction of diabetes with physical function in older patients hospitalized with acute decompensated heart failure and responses to rehabilitation therapy are unknown.

The Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) study showed that a novel, transitional, tailored, progressive rehabilitation intervention improved physical function and quality of life in patients recently hospitalized with heart failure.[8] Unlike HF-ACTION, the REHAB-HF study focused on patients hospitalized with heart failure and included those with heart failure with preserved ejection fraction, contributing to a growing body of literature investigating the role of physical rehabilitation in acute decompensated heart failure.[9,10] The intervention targeted fundamental improvements in balance, strength, and mobility in an older, sicker population. The intervention in REHAB-HF led to significant improvement in physical function as measured by the Short Physical Performance Battery (SPPB) and quality of life.[8] Stratification by presence of diabetes showed similar improvements in SPPB, but the effect on individual components of the SPPB score and other functional outcomes has not been reported. Given the potential implications for future studies and patient care, we undertook the current analysis to determine the efficacy of the REHAB-HF intervention in participants with diabetes.

CLINICAL SIGNIFICANCE

- Older patients with diabetes and acute heart failure have worse balance, strength, and endurance, but similar quality of life, frailty, depression, and cognition compared with those without diabetes.
- Physical rehabilitation improves physical function in heart failure patients with and without diabetes, but those with diabetes show less improvement in frailty.
- There is no significant difference in risk of rehospitalization or death due to a physical rehabilitation intervention in patients with diabetes.

METHODS

The study design, intervention fidelity, and primary results have previously been published.[8,9,11] REHAB-HF was a multisite randomized single-blind controlled trial of a novel, transitional, tailored, 1:1 physical rehabilitation intervention for adults ≥60 years old hospitalized with acute decompensated heart failure. The intervention began as soon as possible following hospitalization and continued in the outpatient setting. Participants were independent and ambulatory prior to hospitalization and expected to be discharged home. Key exclusion criteria included end-stage heart failure requiring inotropes or expectation of ventricular-assist device within the next 6 months, chronic kidney disease requiring dialysis, participation in formal, facility-based cardiac rehabilitation, and dementia or other impairment that would prevent participation.

Participants were randomized 1:1 to either the intervention or attention control. The intervention consisted of 1-hour sessions 3 times per week for 12 weeks focusing on strength, balance, mobility, and endurance. Nonintervention days were complemented by home exercise via low-intensity walking and strengthening after a study staff visit to the participant's home to ensure safety. After 12 weeks, participants were transitioned to an independent maintenance phase for months 4-6 with individualized exercise prescriptions and follow-up phone calls every 2 weeks. The control group received telephone calls every 2 weeks through 6 months of follow-up and had in-person visits at months 1 and 3 post discharge.

The primary endpoint at 3 months was the SPPB, a widely used standardized assessment of physical function in older patients that is a strong predictor of clinical outcomes.[12,13] It has 3 components: strength, gait speed, and standing balance, scored on a scale of 0-4. The composite score is out of 12, where lower scores indicate more severe dysfunction. Assessment of outcomes was performed by personnel blinded to treatment assignment. In addition to SPPB, 6MWD, gait speed, and grip strength were also recorded at baseline and 3 months.

Frailty was assessed at baseline and 3 months by the modified Fried frailty criteria. These criteria capture the complex biological syndrome of frailty characterized by decreased physiologic reserve and impaired response to stressors that result in adverse outcomes in older adults.[14-16] There is a significant relationship between the number of criteria met and risk of morbidity/mortality.[17,18] There are 5 areas: 1) unintentional weight loss in the last year; 2) self-reported exhaustion; 3) weakness (grip strength); 4) slowness (gait speed); and 5) low physical activity by the Short Form-12 Physical Composite Score. For this study, the criteria were modified to exclude the weight-loss criterion due to difficulty in ascertaining weight changes because of changes in fluid status.

Additional efficacy parameters measured at baseline and 3 months included quality of life as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) and EuroQoL Visual Analogue Scale (VAS), cognition as measured by Montreal Cognitive Assessment (MoCA), and depression by the Geriatric Depression Scale-15 (GDS-15). All-cause mortality, all-cause rehospitalizations, heart failure hospitalizations, and falls were collected over the 6 months of follow-up.

Diabetes status at admission was prospectively recorded by the clinician-investigator on the basis of available clinical data or medical history of diabetes during the index heart failure hospitalization, including medication use, hemoglobin A1c, and fasting blood glucose levels. Participants were also categorized by insulin and oral diabetes medication use at time of discharge. All participants provided written informed consent and the study was approved by the Institutional Review Board of all the participating sites.

Statistical Methods

Baseline characteristics were reported as mean (SD) or median (interquartile range) for continuous variables and frequency (%) for categorical variables. Differences in characteristics between participants with and without diabetes were compared using *t* tests and chi-squared tests for continuous and categorical variables, respectively. To investigate the potential differences in intervention fidelity between diabetes groups, adherence as measured by percent of 36 sessions attended was compared between participants with and without diabetes using *t* tests. To evaluate the potential moderating effect of baseline diabetes status on the effect of the intervention on 3-month outcomes (SPPB, 6MWD, gait speed, grip strength, KCCQ, Fried criteria, VAS, GDS-15, MoCA), we used general linear models that included indicator variables for intervention, diabetes, and their interaction. All analyses were adjusted for baseline measure, age, sex, ejection fraction category of <45% or ≥45, and clinical site as in other REHAB-HF analyses. We used least square means to estimate the effects of the intervention in diabetes and no diabetes groups, and effect sizes were reported with 95% confidence intervals (CIs).

The moderating effect of baseline diabetes on the effect of the intervention on 6-month clinical outcomes was assessed using Poisson regression for all-cause rehospitalizations, heart failure rehospitalizations, deaths, and all-cause rehospitalization + deaths, negative binomial regression for facility-free days and hospitalized days due to over-dispersion, and logistic regression for proportion of patients with falls. All analyses were adjusted for age, sex, ejection fraction category, and clinical site. All-cause rehospitalization was also adjusted for baseline SPPB score as prespecified. Effect sizes for the diabetes and no diabetes groups were summarized as rate ratio for count-based outcomes and odds ratio for binary outcomes.

A *P*-value of $< .05$ was determined to be statistically significant for overall comparisons. The interaction between diabetes status and the intervention was determined to be significant for $P < .10$. Due to the hypothesis-generating nature of the analysis, there was no correction for multiple comparisons.

RESULTS

Of the 349 participants enrolled in REHAB-HF, 186 (53%) had diabetes. The prevalence of diabetes was higher in the intervention group (59% vs 48%). Baseline characteristics differed between participants by diabetes status (Table 1). Those with diabetes were more likely to be non-white, have an elevated body mass index, hyperlipidemia, chronic kidney disease, and arthritis. They were less likely to have atrial fibrillation or a history of cancer.

Baseline physical function also differed significantly between the 2 groups (Table 2). Those with diabetes scored lower on the baseline composite SPPB assessment as well as the components of balance score and 4-meter walk. The 6MWD was decreased in the group with diabetes and gait speed was slower. There were no significant differences in frailty, quality of life, cognition, or depression scores at baseline. Intervention adherence was similar among patients with diabetes (68%) and without diabetes (66%, $P = .70$).

Participants with diabetes had a similar intervention effect size in SPPB at 3 months compared with the AC group (Table 3). After adjusting for the prespecified covariates, there was no significant interaction between diabetes status and the primary outcome of SPPB score or any of its individual components. Despite worse baseline functional status, participants with diabetes in the intervention group showed a similar effect size from the intervention for SPPB composite score, balance score, gait speed score, and chair stand score compared with the group without diabetes. The absolute magnitude of the effect size of the intervention in SPPB was 1.5 points in both participants with diabetes and those without diabetes. The intervention effect size on gait speed and 6MWD also showed no interaction by diabetes status.

There was a significant interaction between diabetes and the intervention for frailty; participants without diabetes had a significant decrease in modified Fried frailty score with the intervention (−0.6 points, $P = .001$), while participants with diabetes had significantly less benefit (0.0 points, $P = .99$, p for interaction = 0.021). For KCCQ, although the interaction ($P = .11$) did not quite meet the prespecified level of significance, the effect size for participants with diabetes (3.8 points) appeared smaller and was not significant ($P = .30$), whereas the effect size for participants without diabetes was larger (12.2 points) and significant ($P = .002$). There was no significant interaction between diabetes status and VAS, MoCA, or GDS-15.

As was the case in the primary analysis, there was no significant effect of the intervention on 6-month clinical events in participants with or without diabetes (Table 4). Rates of all-cause rehospitalization, the prespecified key

Table 1 Baseline Characteristics of Patients with and Without Diabetes Mellitus

Characteristics	Diabetes Mellitus			No Diabetes Mellitus			*P* Value
	All (n = 186)	Rehabilitation Intervention (n = 103)	Attention Control (n = 83)	All (n = 163)	Rehabilitation Intervention (n = 72)	Attention Control (n = 91)	
Age, years	72.0 (7.7)	72.9 (8.1)	70.9 (7.1)	73.4 (8.5)	73.3 (9.0)	73.5 (8.0)	.11
Women	96 (51.6%)	48 (46.6%)	48 (57.8%)	87 (53.4%)	37 (51.4%)	50 (54.9%)	.74
Non-White	101 (54.3%)	50 (48.5%)	51 (61.4%)	71 (43.6%)	31 (43.1%)	40 (44.0%)	.045
Ejection fraction ≥45%	106 (57%)	63 (61.2%)	43 (51.8%)	79 (48.5%)	30 (41.7%)	49 (53.8%)	.11
NYHA Class							.21
I-II	32 (17.2%)	18 (17.5%)	14 (16.9%)	35 (21.5%)	16 (22.2%)	19 (20.9%)	
III	98 (52.7%)	57 (55.3%)	41 (49.4%)	92 (56.4%)	43 (59.7%)	49 (53.8%)	
IV	56 (30.1%)	28 (27.2%)	28 (33.7%)	36 (22.1%)	13 (18.1%)	23 (25.3%)	
BMI, kg/m^2	34.5 (8.4)	34.3 (8.1)	34.7 (8.8)	31.1 (8.4)	30.8 (8.0)	31.4 (8.7)	< .001
B-type natriuretic peptide, pg/mL (n = 113), median (IQR)	522 (290-884)	583 (345-872)	473 (246-985)	682 (332-1399)	759 (408-1443)	673 (278-1381)	.078
N-terminal proBNP, pg/mL (n = 56), median (IQR)	2625 (1607-6204)	2717 (1492-6983)	2488 (2095-4828)	3459 (1425-6507)	4722 (2324-9650)	2970 (1274-5174)	.80
Prior hospitalization in last 6 months	82 (44.1%)	46 (44.7%)	36 (43.4%)	74 (45.4%)	30 (41.7%)	44 (48.4%)	.81
Hypertension	174 (93.5%)	94 (91.3%)	80 (96.4%)	147 (90.2%)	65 (90.3%)	82 (90.1%)	.25
History of myocardial infarction	31 (16.7%)	18 (17.5%)	13 (15.7%)	32 (19.6%)	13 (18.1%)	19 (20.9%)	.47
History of coronary revascularization	60 (32.3%)	39 (37.9%)	21 (25.3%)	42 (25.8%)	16 (22.2%)	26 (28.6%)	.18
Atrial fibrillation	83 (44.6%)	50 (48.5%)	33 (39.8%)	93 (57.1%)	39 (54.2%)	54 (59.3%)	.021
Hyperlipidemia	132 (71%)	68 (66.0%)	64 (77.1%)	98 (60.1%)	42 (58.3%)	56 (61.5%)	.033
Chronic obstructive pulmonary disease	46 (24.7%)	30 (29.1%)	16 (19.3%)	52 (31.9%)	24 (33.3%)	28 (30.8%)	.14
Chronic kidney disease	72 (38.7%)	40 (38.8%)	32 (38.6%)	45 (27.6%)	19 (26.4%)	26 (28.6%)	.028
History of stroke	29 (15.6%)	14 (13.6%)	15 (18.1%)	23 (14.1%)	12 (16.7%)	11 (12.1%)	.70
Peripheral vascular disease	24 (12.9%)	21 (20.4%)	3 (3.6%)	16 (9.8%)	6 (8.3%)	10 (11.0%)	.37
Arthritis, muscle/joint pain, or connective tissue disease	94 (50.5%)	55 (53.4%)	39 (47.0%)	60 (36.8%)	29 (40.3%)	31 (34.1%)	.010
Liver disease	11 (5.9%)	5 (4.9%)	6 (7.2%)	3 (1.8%)	1 (1.4%)	2 (2.2%)	.060
History of cancer	30 (16.1%)	21 (20.4%)	9 (10.8%)	45 (27.6%)	21 (29.2%)	24 (26.4%)	.009
Sleep apnea	74 (39.8%)	44 (42.7%)	30 (36.1%)	51 (31.3%)	24 (33.3%)	27 (29.7%)	.099
Depression	35 (18.8%)	20 (19.4%)	15 (18.1%)	27 (16.6%)	9 (12.5%)	18 (19.8%)	.58
Dementia or cognitive impairment	6 (3.2%)	6 (5.8%)	0 (0.0%)	4 (2.5%)	0 (0.0%)	4 (4.4%)	.67
Baseline frailty							1.00
Non-frail	6 (3.2%)	4 (3.9%)	2 (2.4%)	6 (3.7%)	2 (2.8%)	4 (4.4%)	
Pre-frail	77 (41.4%)	45 (43.7%)	32 (38.6%)	68 (41.7%)	32 (44.4%)	36 (39.6%)	
Frail	103 (55.4%)	54 (52.4%)	49 (59.0%)	89 (54.6%)	38 (52.8%)	51 (56.0%)	
Urinary incontinence*	137 (83.5%)	75 (85.2%)	62 (81.6%)	109 (89.3%)	50 (89.3%)	59 (89.4%)	.16
Patients with falls in last 3 months†	30 (18%)	17 (18.9%)	13 (16.9%)	14 (11.5%)	7 (12.5%)	7 (10.6%)	.13
Medical Therapies at Discharge							
Loop diuretic	176 (94.6%)	96 (93.2%)	80 (96.4%)	150 (92.6%)	66 (91.7%)	84 (93.3%)	.51
Beta-blocker	150 (80.6%)	83 (80.6%)	67 (80.7%)	126 (77.8%)	55 (76.4%)	71 (78.9%)	.51
Angiotensin-converting enzyme inhibitor	65 (34.9%)	31 (30.1%)	34 (41.0%)	66 (40.7%)	34 (47.2%)	32 (35.6%)	.27
Angiotensin II receptor blocker	41 (22%)	24 (23.3%)	17 (20.5%)	34 (21%)	14 (19.4%)	20 (22.2%)	.81
Aldosterone antagonist	33 (17.7%)	19 (18.4%)	14 (16.9%)	30 (18.5%)	10 (13.9%)	20 (22.2%)	.85
Digoxin	12 (6.5%)	6 (5.8%)	6 (7.2%)	7 (4.3%)	2 (2.8%)	5 (5.6%)	.38
Insulin	99 (53.2%)	54 (52.4%)	45 (54.2%)	0 (0%)			
Oral diabetes medication	85 (45.7%)	51 (49.5%)	34 (41.0%)	0 (0%)			

BMI = body mass index; BNP = B-type natriuretic peptide; HF = heart failure; NYHA = New York Heart Association.
Presented as n (%), mean (SD), or median (interquartile range [IQR]).
*Data collection in Attention Control (AC) = 76, Rehabilitation Intervention (RI) = 78.
†Data collection in AC = 77, RI = 79. *P* Value for difference between diabetes mellitus (DM) and non-DM groups.

secondary outcome, showed a similar nonsignificant trend toward benefit in both the diabetes and no diabetes groups. All-cause death at 6 months, which was nominally higher among the intervention group than the control group in the primary analysis,[8] showed no difference between those with diabetes and those without diabetes.

DISCUSSION

In this preplanned subgroup analysis of participants with diabetes in the REHAB-HF trial, a novel, transitional, tailored, progressive multidomain physical rehabilitation intervention in older adults with acute decompensated heart failure was found to provide similarly large and significant

Table 2 Baseline Functional Performance Stratified by Presence of Diabetes Mellitus

Characteristics	Diabetes Mellitus			No Diabetes Mellitus			*P* Value
	All (n = 186)	Rehabilitation Intervention (n = 103)	Attention Control (n = 83)	All (n = 163)	Rehabilitation Intervention (n = 72)	Attention Control (n = 91)	
SPPB score	5.7 (2.7)	5.7 (2.9)	5.7 (2.4)	6.4 (2.7)	6.4 (2.6)	6.5 (2.7)	.013
Balance score	2.5 (1.3)	2.4 (1.4)	2.6 (1.2)	2.8 (1.3)	2.8 (1.3)	2.7 (1.3)	.023
4-meter walk score	2.2 (1.0)	2.2 (1.1)	2.1 (0.9)	2.4 (1.0)	2.4 (1.0)	2.5 (1.1)	.032
Chair rise score	1.1 (1.1)	1.1 (1.1)	1.1 (1.1)	1.2 (1.3)	1.2 (1.3)	1.3 (1.3)	.19
6-minute walk distance (m)	180.8 (102.2)	183.0 (105.5)	178.0 (98.7)	207.5 (107.2)	209.2 (99.6)	206.2 (113.3)	.019
Gait speed (m/s)	0.58 (0.22)	0.59 (0.24)	0.58 (0.19)	0.63 (0.22)	0.62 (0.21)	0.64 (0.24)	.041
Male grip strength (kg)	29.3 (9.3)	28.2 (8.1)	31.0 (10.8)	31.8 (10.8)	33.7 (10.8)	30.2 (10.7)	.12
Female grip strength (kg)	20.9 (6.6)	21.1 (6.6)	20.6 (6.7)	19.2 (7.2)	20.1 (8.0)	18.6 (6.5)	.12
Modified Fried frailty score	2.4 (1.1)	2.3 (1.2)	2.6 (1.0)	2.3 (1.1)	2.3 (1.0)	2.2 (1.1)	.20
KCCQ overall	40.5 (20.3)	40.1 (19.8)	41.0 (20.9)	41.2 (21.0)	40.3 (21.7)	42.0 (20.5)	.74
EQ5D VAS	58.0 (21.9)	57.5 (22.3)	58.8 (21.5)	58.4 (21.5)	59.5 (22.7)	57.5 (20.6)	.87
Cognition (MoCA Score)	21.8 (4.2)	21.7 (4.4)	22.0 (4.0)	21.9 (4.6)	22.3 (3.9)	21.5 (5.1)	.89
Depression (GDS-15 Score)	4.8 (3.4)	4.8 (3.3)	4.7 (3.5)	4.5 (3.4)	4.4 (3.4)	4.7 (3.4)	.50

EQ5D VAS = EuroQol visual analogue scale; GDS-15 = Geriatric Depression Scale-15; KCCQ = Kansas City Cardiomyopathy Questionnaire; MoCA = Montreal Cognitive Assessment.; SPPB = Short Physical Performance Battery.

Presented as mean (SD). KCCQ scores range 0-100, with higher score meaning better health status. MoCA score ranges 0-30, with higher score meaning better cognitive function. GDS-15 score ranges 0-15, with higher score meaning worse depressive symptoms. *P* value for difference between diabetes mellitus (DM) and non-DM groups.

improvements in physical function for participants both with and without diabetes (Figure). Those with diabetes had significantly worse baseline functional impairment but similar frailty, quality of life, cognition, and depression. The magnitude of the intervention-related improvements among both the diabetes and no diabetes (1.5 points) groups for SPPB significantly exceeded the reported minimal clinically important difference (0.5 points).[13,19] Changes in endurance by 6MWD were not significantly different between groups ($P = .67$), and the improvements (28.8 m in diabetes and 38.7 m in no diabetes) were also similar to what is considered clinically meaningful.[20] The effect of the intervention on quality of life as measured by KCCQ was numerically threefold larger in the no diabetes group (12.2 points vs 3.8), although this interaction narrowly missed the prespecified significance threshold ($P = .11$). In contrast to participants without diabetes, those with diabetes showed significantly less improvement in frailty.

Diabetes and heart failure synergistically contribute to severely decreased physical function through skeletal muscle atrophy, inflammation, and metabolic dysfunction.[21] Levels of cardiac dysfunction may correlate poorly with symptoms,[22,23] and exercise training, although associated with improved physical function,[6] has relatively little effect on cardiac function in heart failure.[24,25] The benefits of physical rehabilitation and exercise are thought to be primarily through peripheral mechanisms such as improved skeletal muscle, mitochondrial, and microvascular function.[25-27]

Patients with diabetes and heart failure experience greater functional limitations than those with heart failure alone. Muscle strength among heart failure patients with diabetes is impaired compared with patients without diabetes,[28] potentially as a result of mitochondrial dysfunction, reactive oxygen species generation, insulin resistance, lipotoxicity, and inflammation.[21] Other complications of diabetes can lead to significant impairments in mobility and physical function. Patients with diabetes often have concurrent peripheral neuropathy, which can impair balance and proprioception, leading to reduced functional performance and stability.[29,30] Furthermore, adverse conditions common in patients with diabetes, such as amputation,[31] peripheral vascular disease, and episodes of hypoglycemia, can lead to impaired function and quality of life as well.[32] In the REHAB-HF population, rates of peripheral vascular disease were not significantly different between the diabetes and no diabetes groups, and the presence of neuropathy or hypoglycemic episodes were not measured. Nevertheless, participants with diabetes had significantly worse baseline performance in the SPPB combined score, as well as 4-meter walk, balance, 6MWD, and gait speed, reinforcing the evidence of impaired skeletal muscle function in patients with diabetes and heart failure.

Participants with diabetes and heart failure in REHAB-HF had a lower baseline 6MWD, but similar improvements with the intervention as those without diabetes. In an analysis of ambulatory heart failure with reduced ejection fraction patients in HF-ACTION, those with diabetes were also found to have decreased 6MWD at baseline, which improved with exercise therapy, with no interaction between presence of diabetes and improvement.[7] However, the magnitude of benefit for patients with diabetes was also smaller in HF-ACTION (11.6 m vs 28.8 m in REHAB-HF). Even though the cohort of acute decompensated heart failure patients with diabetes in REHAB-HF had considerably more severe physical limitations at baseline, they had a

Table 3 Physical Function Outcomes at 3 Months Stratified by Diabetes Status with Adjustment for Baseline Covariates*

3-Month Outcome	Diabetes Mellitus: Rehabilitation Intervention (n = 103)	Diabetes Mellitus: Attention Control (n = 83)	Diabetes Mellitus: Difference (95% CI)	Diabetes Mellitus: *P* for Difference	No Diabetes Mellitus: Rehabilitation Intervention (n = 72)	No Diabetes Mellitus: Attention Control (n = 91)	No Diabetes Mellitus: Difference (95% CI)	No Diabetes Mellitus: *P* for Difference	*P* for Interaction
SPPB score	7.8 (0.3)	6.2 (0.3)	1.5 (0.5-2.6)	< .001	8.3 (0.3)	6.8 (0.3)	1.5 (0.4-2.6)	< .001	.99
Balance score	3.0 (0.1)	2.5 (0.1)	0.5 (0.1-1.0)	.004	3.3 (0.2)	3.0 (0.1)	0.3 (-0.2-0.8)	.18	.32
4-meter walk score	2.8 (0.1)	2.3 (0.1)	0.4 (0.0-0.8)	.006	3.1 (0.1)	2.6 (0.1)	0.6 (0.1-1.0)	.001	.62
Chair rise score	1.9 (0.1)	1.4 (0.1)	0.6 (0.1-1.0)	.001	2.0 (0.2)	1.3 (0.1)	0.7 (0.2-1.2)	< .001	.69
6-minute walk distance (m)	281.3 (11.8)	252.5 (13.3)	28.8 (−13.1-70.7)	.076	286.7 (13.9)	248.0 (12.8)	38.7 (−3.8-81.2)	.019	.67
Gait speed (m/s)	0.8 (0.0)	0.7 (0.0)	0.1 (0.0-0.2)	.004	0.8 (0.0)	0.7 (0.0)	0.1 (0.1-0.2)	< .001	.22
Male grip strength (kg)	28.9 (1.0)	30.5 (1.3)	−1.6 (−5.6-2.5)	.32	32.2 (1.3)	30.9 (1.1)	1.4 (−2.6-5.4)	.37	.19
Female grip strength (kg)	20.9 (1.0)	21.9 (1.0)	−1.0 (−3.9-1.9)	.39	22.0 (0.9)	21.2 (0.9)	0.8 (−2.3-3.8)	.52	.29
Modified Fried frailty score	1.7 (0.1)	1.7 (0.2)	−0.0 (−0.5-0.5)	.99	1.2 (0.1)	1.8 (0.1)	−0.6 (−1.1, −0.1)	.001	.021
KCCQ overall	63.8 (2.6)	60.0 (2.9)	3.8 (−5.6-13.2)	.30	74.3 (3.1)	62.0 (2.8)	12.2 (2.3-22.1)	.002	.11
EQ5D VAS	69.4 (2.4)	62.2 (2.7)	7.2 (−1.5-15.8)	.033	72.2 (2.8)	64.8 (2.6)	7.4 (−1.8-16.6)	.038	.97
Cognition (MoCA Score)	22.4 (0.4)	22.4 (0.5)	−0.0 (−1.6-1.5)	.93	22.4 (0.5)	22.8 (0.4)	−0.4 (−2.0-1.2)	.52	.69
Depression (GDS-15 Score)	3.6 (0.3)	4.4 (0.3)	−0.8 (−2.0-0.3)	.050	3.4 (0.4)	4.1 (0.3)	−0.7 (−1.8-0.5)	.15	.77

Presented as mean (SE).

*Adjusted for baseline measure, age, sex, clinical site, and EF category (< vs. ≥45%).

BMI = body mass index; GDS-15 = Geriatric Depression Scale-15; GDS-15 = Geriatric Depression Scale-15; KCCQ = Kansas City Cardiomyopathy Questionnaire; EQ5D VAS = EuroQol visual analogue scale; MoCA = Montreal Cognitive Assessment; SPPB = Short Physical Performance Battery.

Table 4 Clinical Outcomes at 6 Months Stratified by Presence of Diabetes Mellitus

Outcome	Diabetes Mellitus: Rehabilitation Intervention (n = 103)	Diabetes Mellitus: Attention Control (n = 83)	Diabetes Mellitus: RR or OR (CI)	Diabetes Mellitus: *P* for Difference	No Diabetes Mellitus: Rehabilitation Intervention (n = 72)	No Diabetes Mellitus: Attention Control (n = 91)	No Diabetes Mellitus: RR or OR (CI)	No Diabetes Mellitus: *P* for Difference	*P* for Interaction
All-cause rehospitalizations	124 (1.29)	115 (1.46)	0.91 (0.71-1.18)	.49	70 (1.03)	98 (1.12)	0.88 (0.65-1.20)	.43	.87
Deaths	13 (0.14)	8 (0.10)	1.14 (0.47-2.78)	.77	8 (0.12)	8 (0.09)	1.17 (0.43-3.16)	.75	.97
All-cause rehospitalization and death	137 (1.43)	123 (1.56)	0.91 (0.71-1.17)	.46	78 (1.15)	106 (1.21)	0.93 (0.69-1.25)	.62	.93
Heart failure rehospitalizations	57 (0.59)	62 (0.79)	0.81 (0.56-1.16)	.25	37 (0.55)	48 (0.55)	0.90 (0.58-1.39)	.63	.71
Facility-free days	158.85 (170.23)	158.78 (167.40)	1.01 (0.99-1.04)	.23	164.04 (174.22)	167.95 (174.58)	1.00 (0.98-1.02)	.93	.37
Hospitalized days	7.32 (8.63)	9.39 (10.31)	0.87 (0.49-1.55)	.64	7.24 (8.05)	6.11 (7.35)	1.11 (0.60-2.06)	.75	.58
Falls	31 (0.30)	33 (0.40)	0.59 (0.31-1.10)	.097	17 (0.24)	29 (0.32)	0.70 (0.34-1.42)	.32	.72

6-Month clinical event data presented as count (6-month rate) for rehospitalization, deaths, rehospitalizations + deaths, and heart failure rehospitalizations. Presented as mean (6-month rate) for facility-free days and hospitalized days. Presented as count (proportion) for falls. Adjusted for clinical site, age, sex, EF category (<45% vs ≥45%,) and BMI. All-cause rehospitalization at 6 months also adjusted for baseline SPPB score. Effect sizes shown with 95% CIs. For clinical outcomes based on counts and means, effect sizes shown as rate ratios. For clinical outcomes based on proportions (falls), effect sizes shown as odds ratio.

BMI = body mass index; CI = confidence interval; EF = ejection fraction; OR = odds ratio; RR = rate ratio.

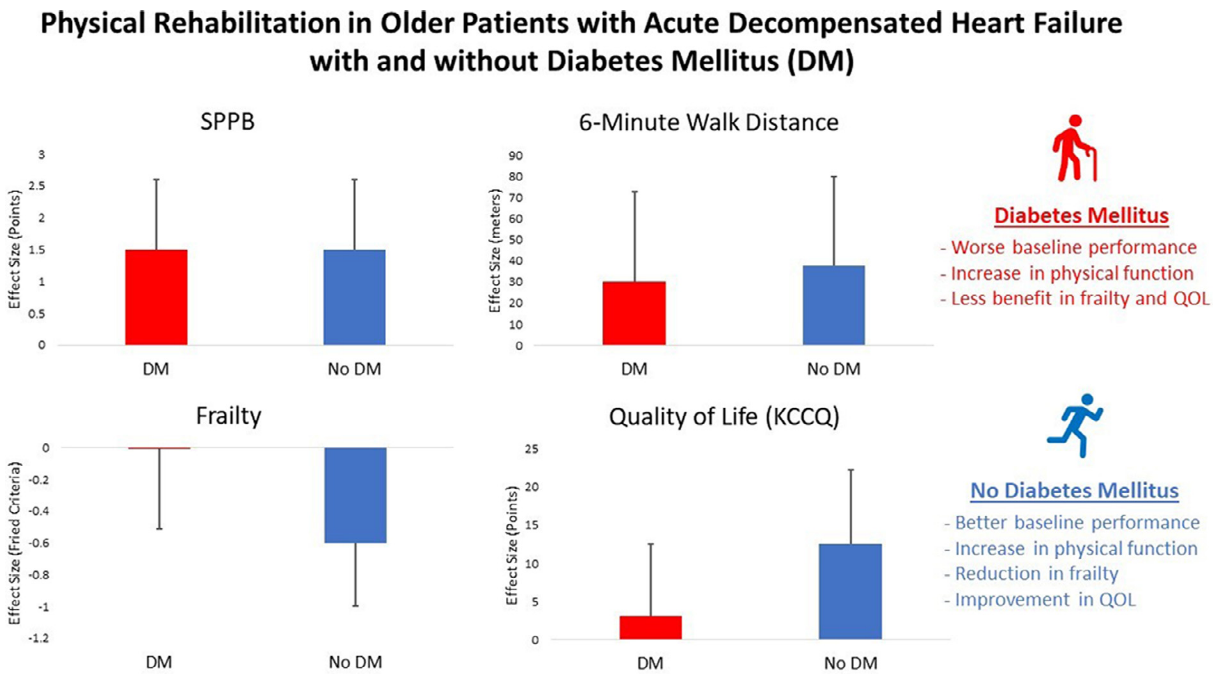

Figure Effect of the novel REHAB-HF intervention in patients with acute decompensated heart failure on outcomes at 3 months in participants with diabetes mellitus (shown in red) and without (shown in blue). SPPB = Short Physical Performance Battery; DM = diabetes mellitus; QOL = quality of life; KCCQ = Kansas City Cardiomyopathy Questionnaire.

greater magnitude of improvement from the intervention. These results further extend prior work by incorporating older, sicker patients with either reduced or preserved ejection fraction previously thought to be too high risk for exercise therapy.

Prior studies of exercise and physical rehabilitation in older patients with diabetes have shown improvements in functional status, balance, and strength, along with a reduced risk for falls.[33,34] However, few studies have adequately addressed clinical events such as rehospitalization or death. Among participants with diabetes, the REHAB-HF intervention appeared safe regarding clinical events at 6 months, with no significant differences in hospitalizations or deaths between treatment groups and no effect modification by diabetes status during this period. The safety and tolerability of this intervention will need to be confirmed by future, larger studies powered to detect differences in clinical outcomes.

This study suggested there may be differences in changes in quality of life as measured by KCCQ for participants with diabetes. Although the interaction term just missed the prespecified significance threshold, participants with diabetes in the intervention arm did not show significantly improved KCCQ scores, while those without diabetes did. Furthermore, the effect size of the intervention was 3 times larger in the no diabetes group, indicating that the differences in quality-of-life changes are substantial. Previous studies have found that heart failure patients with diabetes tend to have a worse health-related quality of life.[5,35,36] Together, this evidence suggests that patients with diabetes and heart failure may have significant lasting impairments in quality of life due to complications of diabetes that are resistant to change with physical rehabilitation.

There was also a significant difference in the effect of the intervention on frailty, as measured by the Fried criteria, depending on participant's diabetes status. Participants without diabetes showed a significant improvement by a reduction of 0.6 points, while those with diabetes showed less improvement in frailty with physical rehabilitation. With regard to the clinical significance, one study used a distribution-based approach to calculate the minimal clinically important difference in Fried frailty score, finding that changes of 0.249 and 0.623 points corresponded with small and large clinically meaningful changes, respectively.[37] Therefore, the improvement seen in the participants without diabetes may represent a large and clinically meaningful change.

Despite the significant improvements in functional status, frailty appears to be resistant to change in patients with heart failure and diabetes undergoing physical rehabilitation. Frailty is a complex condition characterized by chronic inflammation, metabolic impairment, and insulin resistance in patients with heart failure.[38,39] As diabetes and heart failure are also inflammatory conditions, the synergy between these 2 comorbidities may contribute to a persistent proinflammatory state that leads to functional impairment and a decrease in physiological reserve, resulting in the frailty phenotype. Multimodal approaches involving prevention of complications of diabetes, hypoglycemic medication de-escalation, and nutritional therapy, in addition to physical rehabilitation, may be necessary to adequately address frailty in this population.[40,41]

Limitations

This is a hypothesis-generating subgroup analysis and causation cannot be inferred by any associations present. Randomization was not stratified by diabetes, and there was an imbalance in rates of diabetes between the treatment and intervention groups. Despite having knowledge of insulin use, we did not have information about whether participants had type 1 or type 2 diabetes. We did not specifically measure certain complications of diabetes such as peripheral neuropathy, which may explain some of the differences in physical function. Stratifying the 349 participants into 4 groups (diabetes or no diabetes and intervention or control) reduced statistical power. There was no correction for multiple comparisons due to the hypothesis-generating analysis.

CONCLUSIONS

The progressive multidomain physical rehabilitation intervention in REHAB-HF led to improved functional performance in participants with and without diabetes, despite worse baseline performance among the diabetes group. Those with diabetes had less improvement in frailty. There were no differences in clinical event outcomes by diabetes status.

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