Growth differentiation factor-15 as a biomarker of strength and recovery in survivors of acute respiratory failure

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ABSTRACT

Muscle mitochondrial dysfunction is implicated in intensive care unit-acquired weakness, but there is no serum biomarker of muscle mitochondrial function for critical illness survivors. Higher serum growth differentiation factor-15 (GDF-15) is a biomarker of inherited mitochondrial myopathy disease and is associated with mortality in several age-related diseases. Among 142 older (age ≥65 years) survivors of acute respiratory failure, we found that higher serum GDF-15 measured during the week prior to hospital discharge was cross-sectionally associated with weaker diaphragm, limb and hand-grip strength, and longitudinally associated with lower rates of functional recovery over 6 months, independent of age, sex, pre-existing disability, comorbidity, frailty, Acute Physiology and Chronic Health Evaluation II scores and concurrent interleukin-6 levels.

Survivors of acute respiratory failure often develop skeletal muscle weakness that results in disability.[1] Patients with intensive care unit (ICU)-acquired weakness (ICUAW), defined as a Medical Research Council (MRC) sum score <48,[2] have decreased skeletal muscle mitochondrial content and impaired oxidative phosphorylation,[3 4] but whether skeletal muscle mitochondrial dysfunction affects strength and disability in the larger population of ICU survivors with weakness less severe than ICUAW is unknown. Clinical studies of mitochondrial function in critical illness are often limited to case–control studies with small sample sizes, because the measurement of tissue mitochondrial function requires biopsy and time-intensive and costly laboratory assessments.[3–5]

Serum growth differentiation factor-15 (GDF-15) has been identified as a sensitive biomarker of inherited mitochondrial diseases.[6] GDF-15 is a member of the transforming growth factor-β cytokine family, and identifying its receptors and downstream effects is an area of active investigation. While it is released from many tissues in response to cellular stress or injury, its expression is markedly upregulated in skeletal myocytes of patients with mitochondrial myopathy diseases. Higher serum GDF-15 levels have been associated with older age, higher body mass index (BMI), diabetes; cardiovascular, renal, liver and chronic obstructive pulmonary disease; and some cancers. Independent of these conditions, serum GDF-15 is emerging as a potential marker of skeletal muscle mitochondrial dysfunction in ageing and age-related disorders.[6–8] We hypothesised that higher levels of GDF-15 would be independently associated with worse muscle strength and functional recovery in older survivors of acute respiratory failure.

We examined 142 acute respiratory failure survivors in the Frailty and Outcomes in Critical Illness Survivors (FOCIS) study. Details of the cohort have been published previously.[9] Participants were ≥65 years old, received >24 hours of non-invasive or invasive mechanical ventilation and underwent assessment of the basic activities of daily living (ADLs) at hospital discharge and 1, 3 and 6 months later. We also asked participants or their surrogate about ADL disability and frailty (via the Clinical Frailty Scale)[10] in the month prior to hospitalisation. During the week prior to hospital discharge, while on the general ward, we measured BMI, diaphragmatic strength (via sniff nasal inspiratory pressure according to American Thoracic Society recommendations),[11] limb strength (via manual muscle testing (MRC sum score),[12] dominant-hand grip strength (highest of three measurements with the Jamar Plus+ dynamometer (Patterson Medical, Illinois, USA)) and serum GDF-15 and interleukin-6 (IL-6) concentrations (Quantikine ELISA, R&D Biosystems, Minneapolis, Minnesota). We examined cross-sectional associations between natural log-transformed GDF-15 and the muscle strength measurements using generalised additive linear models with LOESS smoothers, and since there was no evidence for non-linearity, we derived effect estimates from linear models. We examined longitudinal associations between log-transformed GDF-15 and functional recovery using additive Cox models with penalised splines, and since there was no evidence for non-linearity, we estimated recovery rate ratios using competing risk survival regression (*stcrreg* command, Stata V.15.1). We defined recovery as returning to an ADL disability count less than or equal to the prehospitalisation count within 6-month follow-up. We measured time to recovery as the number of days from ICU discharge until the date of the follow-up assessment at which recovery was first achieved (ie, hospital discharge, 1-month, 3-month or 6-month follow-up). Decedents were censored at the time of death if they had not already recovered. We excluded 10 FOCIS pilot cohort participants (7%) who never had disability follow-up and 4 FOCIS main cohort participants (3%) who were lost to follow-up. We adjusted for age, sex, BMI, prehospitalisation ADL disability count and frailty, Acute Physiology and Chronic Health Evaluation (APACHE)-II score, IL-6 and the presence of any diabetes, renal disease, liver disease, prior myocardial infarction, congestive heart failure, chronic pulmonary disease or any cancer, based on Charlson comorbidity

Table 1 Characteristics of older survivors of acute respiratory failure by quartiles of GDF-15

GDF-15 (pg/mL), range	Quartile 1 (614–2060)	Quartile 2 (2065–3193)	Quartile 3 (3240–4771)	Quartile 4 (4821–27 000)
No. of participants	**n=36**	**n=35**	**n=36**	**n=35**
Age, mean (SD)	73 (8.0)	73 (9.5)	76 (7.5)	73 (6.8)
Male, n (%)	19 (53)	13 (37)	17 (47)	15 (43)
BMI, mean (SD)	27 (7.7)	30 (8.5)	27 (6.4)	27 (5.9)
Prehospitalisation ADL disability count,* median (IQR)	0 (0–0)	1 (0–4.5)	0 (0–1)	0 (0–1)
Comorbidities†				
Diabetes, n (%)	7 (19)	13 (37)	16 (44)	15 (43)
Renal disease, n (%)	0 (0)	1 (2.9)	8 (22)	13 (37)
Liver disease, n (%)	2 (5.6)	0 (0)	2 (5.6)	5 (14)
Prior myocardial infarction, n (%)	4 (11)	6 (17)	5 (14)	8 (23)
Congestive heart failure, n (%)	10 (28)	16 (46)	13 (36)	12 (34)
Chronic pulmonary disease, n (%)	18 (50)	15 (43)	7 (20)	7 (20)
Any cancer, n (%)	2 (5.6)	5 (14)	9 (25)	8 (23)
APACHE II score, mean (SD)	28 (8.2)	28 (6.5)	32 (8.3)	31 (7.5)
Type of respiratory support, n (%)				
Non-invasive positive pressure ventilation or high flow nasal cannula only	7 (20)	10 (29)	5 (14)	4 (11)
Mechanical ventilation	29 (80)	25 (71)	30 (86)	32 (89)
ICU length of stay, median (IQR)	4 (2–6)	4 (3–7)	6 (3–14)	8 (5–11)
Sniff nasal inspiratory pressure (cm H_2O), median (IQR)	52 (35-69)	34 (28-45)	21 (18-32)	36 (28-43)
MRC sum score, median (IQR)	60 (59-60)	58 (56-60)	58 (54-59)	58 (53-60)
Grip strength, women (kg), mean (SD)	17 (4.6)	13 (6.4)	11 (6.4)	12 (6.6)
Grip strength, men (kg), mean (SD)	28 (9.3)	22 (8.8)	19 (5.3)	20 (7.9)
ADL disability count at hospital discharge,* median (IQR)	1 (0–2)	5 (2–6)	5 (3–5)	5 (2–6)
Discharge location, n (%)				
Home	27 (75)	21 (60)	11 (31)	17 (49)
Skilled care facility	9 (25)	14 (40)	24 (69)	19 (53)
Mortality, n (%)	2 (5.6)	3 (8.6)	7 (20)	9 (26)

* Activities of daily living (ADLs) (eating, toileting, bathing, dressing,walking and transferring).
†Presence of comorbidities are based on Charlson comorbidity criteria.[13]
APACHE-II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; GDF-15, growth differentiation factor-15; ICU, intensive care unit; MRC, Medical Research Council.

index criteria.[7 13] We confirmed the proportional hazards assumption of the Cox models using the Schoenfeld residuals test.

The mean (SD) age of participants was 74 (8) years, median (IQR) prehospitalisation ADL disability count was 0 (0–1), mean (SD) APACHE II score was 29 (8), median (IQR) hospital discharge ADL disability count was 4 (1–5), with 21 (15%) dying within six months and 91 (64%) recovering in a median (IQR) 45 (7–113) days. The median (IQR) GDF-15 level was 3216 (2060–4771) pg/mL. Those in higher GDF-15 quartiles tended to have more comorbidities, higher APACHE II scores, invasive mechanical ventilation, longer ICU length of stay, discharge to a skilled-care facility and death within 6 months (table 1). GDF-15 had statistically significant and linear inverse cross-sectional associations with measures of muscle strength (figure 1A–D). For 1 SD decrease in sniff force (20 cm H_20), GDF-15 increased 17% (95% CI 5.1% to 27%); for 1 SD decrease in MRC score (5.7), GDF-15 increased 14% (95% CI 3.4% to 23%); and for 1 SD decrease in hand-grip strength (8.7 kg), GDF-15 increased 13% (95% CI 1.9% to 23%). GDF-15 had a statistically significant and linear association with the ADL recovery rate (figure 1D). For every one natural log increase in GDF-15, the rate of ADL recovery decreased 57% (95% CI 31% to 74%).

In older acute respiratory failure survivors, we demonstrated that higher serum GDF-15 levels were independently associated with weaker diaphragm, limb and hand grip strength during the week prior to hospital discharge and lower rates of ADL recovery over 6-month follow-up. Prior studies have reported that GDF-15 improves in-hospital mortality prediction when added to the APACHE-III for Acute Respiratory Distress Syndrome patients,[14] and that serum GDF-15 and muscle GDF-15 mRNA are elevated in cardiothoracic ICU patients with ICUAW compared with elective cardiac surgery controls.[15 16] Our findings suggest that GDF-15 has potential as a biomarker to risk stratify ICU survivors for functional recovery during the post-ICU period on the general ward when postacute care is being considered.

Our work is preliminary. The observed associations are subject to unmeasured and residual confounding. Future studies in ICU survivors should correlate serum GDF-15 levels with direct measures of muscle mitochondrial function and muscle GDF-15 expression as serum GDF-15 could also be elevated due to other tissue or organ injury in ICU survivors. Our results need to be externally validated in a cohort that also includes younger adult ICU survivors. Future work should examine the predictive utility of GDF-15 from the onset of critical illness through the early posthospitalisation

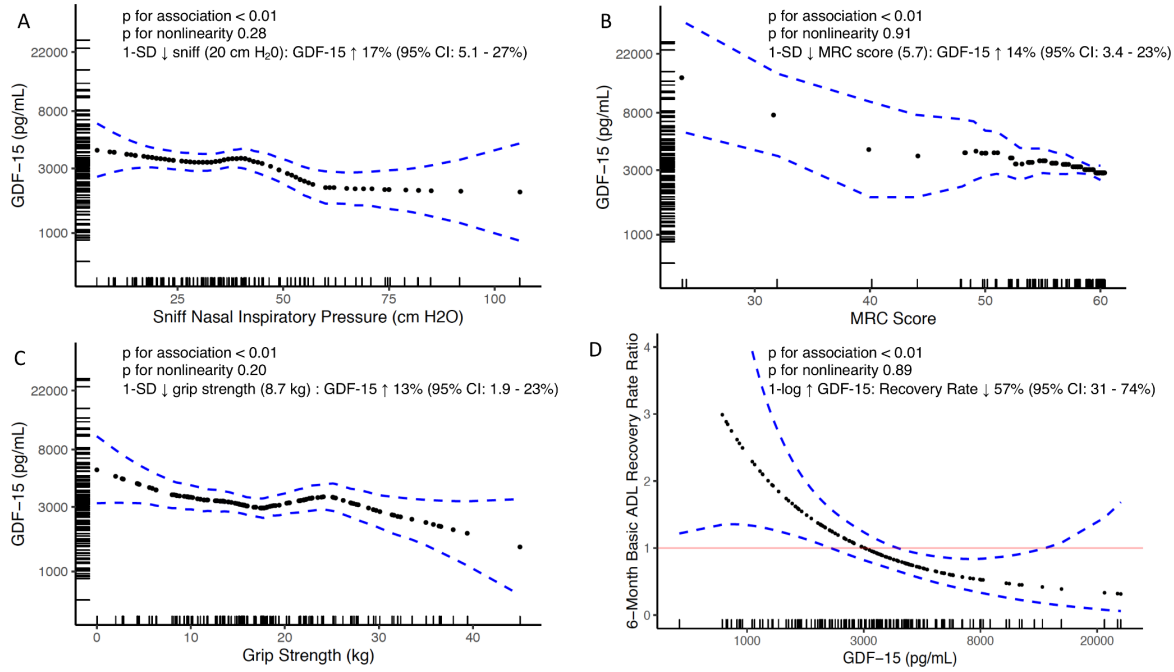

Figure 1 Continuous associations of serum GDF-15 with (A) sniff inspiratory pressure, (B) Medical Research Council (MRC) sum score from manual muscle testing and (C) hand grip strength using generalised additive models with LOESS smoothers for strength measurements. (D) Continuous association of serum GDF-15 with the 6-month ADL recovery rate ratio from an additive Cox model with a penalised spline for natural log-transformed GDF-15. Dotted black lines are predicted values. Blue dashed lines are 95% CIs. Hash marks along the x-axis indicate individual study participants. Since there is no evidence of non-linearity, effect estimates are derived from linear models (A–C) and a competing risk survival regression model (D). Models were adjusted for age, sex, body mass index, prehospitalisation basic ADL disability count and clinical frailty scale score, APACHE-II scores, interleukin-6 levels and presence of diabetes, renal, liver, cardiovascular or chronic pulmonary disease and cancer. ADL, activities of daily living; APACHE-II, Acute Physiology and Chronic Health Evaluation II; GDF-15, growth differentiation factor-15.

period. Despite these limitations, our findings support further study of GDF-15 as a potential serum biomarker of skeletal muscle mitochondrial function in ICU survivors that may be valuable as a predictive or prognostic enrichment tool in early phase trials of post-ICU rehabilitation or novel therapies aimed at improving post-ICU disability.

Contributors Study design and concept: MRB and MH; acquisition, analysis or interpretation of data: BJR, DJL, MRB, EC and DMN; drafting of the manuscript: BJR and MRB; critical revision of the manuscript: all authors. Statistical analysis: BJR, MRB, EC and DJL. Study supervision: MRB. Dr Rosenberg and Dr Baldwin had full access to all of the data in the study and take responsibility of the integrity of the data and accuracy of the data analysis.

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