Growth differentiation factor-15 is a predictor of important disease outcomes in patients with COPD

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In COPD, GDF15 predicts a higher mortality, increased COPD exacerbation rate and a faster decline in FEV1 and FVC http://ow.ly/yDgn307n0SO

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ABSTRACT Increased levels of growth differentiation factor-15 (GDF15) are associated with cachexia, cardiovascular disease and all-cause mortality. The role of GDF15 in chronic obstructive pulmonary disease (COPD) is unknown.

The study included 413 patients with COPD from the Bergen COPD Cohort Study. All patients had a forced expiratory volume in 1 s (FEV_1) <80% predicted, a FEV_1 to forced vital capacity (FVC) ratio <0.7 and a history of smoking. Spirometry, fat free mass index, blood gases and plasma GDF15 were measured at baseline. Patients were followed for 3 years regarding exacerbations and changes in lung function, and 9 years for mortality. Yearly exacerbation rate, survival and yearly change in FEV_1/FVC were evaluated with regression models.

Median plasma GDF15 was 0.86 ng·mL^{-1} (interquartile range 0.64–1.12 ng·mL^{-1}). The distribution was not normal and GDF15 was analysed as a categorical variable. High levels of GDF15 were associated with a higher exacerbation rate (incidence rate ratio 1.39, 95% CI 1.1–1.74, p=0.006, adjusted values). Furthermore, high levels of GDF15 were associated with higher mortality (hazard ratio 2.07, 95% CI 1.4–3.1, p<0.001) and an increased decline in both FEV_1 (4.29% *versus* 3.25%) and FVC (2.63% *versus* 1.44%) in comparison to low levels (p<0.01 for both).

In patients with COPD, high levels of GDF15 were independently associated with a higher yearly rate of exacerbations, higher mortality and increased decline in both FEV_1 and FVC.

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Introduction

Chronic obstructive pulmonary disease (COPD) is among the world's leading causes of disability and death, and has a worldwide prevalence expected to increase for the next decade [1]. COPD is a heterogeneous disease, illustrated by the presence of different phenotypes [2], as well as large variation in morbidity, with patients with end-stage COPD often having frequent exacerbations, cachexia and a high mortality [3].

Growth differentiation factor-15 (GDF15) is a cytokine of the transforming growth factor β-family, also known as macrophage inhibitory cytokine 1 (MIC-1). GDF15 is a 25-kDa protein initially discovered in macrophages but also found in epithelial tissues and plasma in a physiologic state [4–7].

In recent years, GDF15 has emerged as a biomarker for cardiovascular disease [8], diabetes [9], renal failure [10, 11] and several different malignancies [12–14]. Elevated levels of GDF15 are associated with increased disease severity and poor prognosis [15], but the underlying pathophysiology is unknown. GDF15 is also a marker of all-cause mortality [16] and is believed to be a mediator of cachexia both in cancer and chronic disease [17–20].

As a cytokine associated with both inflammation and cachexia, along with increased mortality, GDF15 is of interest in patients with COPD, both as a diagnostic or prognostic biomarker and as a potential treatment target. A few smaller studies have examined GDF15 in COPD, indicating elevated plasma levels of GDF15 in patients with COPD [21, 22], and an additional increase during COPD exacerbations [21, 23, 24]. Nevertheless, the role of GDF15 as a prognostic biomarker in COPD is still unclear.

The aims of our study were to examine the relationship between systemic levels of GDF15 and important COPD characteristics such as lung function, exacerbations, cachexia and mortality, using both cross-sectional and longitudinal data from a large cohort of patients with COPD.

Methods

Study population

The Bergen COPD Cohort Study (BCCS) is a follow-up study from Western Norway started in 2006 that includes 433 patients with COPD and 325 subjects without COPD at baseline. All patients were examined at our study centre in Bergen, with attempts made to follow-up in regular intervals for 3 years. At all visits we took samples to contribute to the study biobank. The BCCS was designed foremost to examine predictors of COPD progression; details regarding study sampling and data collection have previously been described [25–27]. For the current study, we included the 413 patients with COPD who did not use oral steroids at the time of inclusion (n=11) and for whom we had remaining plasma samples in our biobank. All patients were between 41 and 76 years at inclusion, and were former or current smokers. The patients had a clinical diagnosis of COPD, evaluated by a study physician, and a post-bronchodilation forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio <0.7 and FEV_1 <80% of predicted. Cancer within 5 years prior to inclusion, asthma or lung disorders other than COPD, active inflammatory disease other than COPD, or exacerbations in the last 4 weeks were cause for non-inclusion; patients in the latter category could be re-screened later. The Regional Committee for Medical and Health Research Ethics, region west, approved the study (REK-Vest, case number 165.08). Informed written consent was obtained from all participants.

Data collection

At inclusion, all patients were examined by a study physician, including a clinical interview regarding respiratory symptoms, smoking history, comorbidities and medication. Comorbidities were pooled to calculate the Charlson Comorbidity Score (CCS) [28]. All patients performed spirometry, before and after bronchodilation with 0.4 mg salbutamol, using a VIASYS MasterScope (VIASYS Healthcare GmbH, Hoechberg, Germany). Patients with COPD were categorised according to the 2007 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, the current guidelines at the time of inclusion.

Body composition was assessed with bioelectrical impedance measurements. Cachexia was defined as a fat free mass index (FFMI) <17 $kg \cdot m^{-2}$ in men or <14 $kg \cdot m^{-2}$ in women, which corresponds to the lower 95% confidence limit in a normal population [29]. Obesity was defined as a fat mass index of >9.3 $kg \cdot m^{-2}$ in men or >13.5 $kg \cdot m^{-2}$ in women [29].

The patients were followed for 3 years, with visits and spirometry each 6 months, as well as annual measurement of body composition. The number of exacerbations was assessed *via* regular phone calls by study personnel, combined with an interview and check of hospital journals at each visit [25]. Only COPD exacerbations treated with either antibiotics, peroral steroids or hospital admission were counted, corresponding to moderate or severe exacerbations [30]. Data on mortality, including cause and date of

death, were obtained from the Norwegian Cause of Death Registry, ending registration October 2015. In total, 147 patients died within the follow-up period and 17 had an unknown cause of death.

Laboratory measurements

Peripheral venous blood was drawn into pyrogen-free EDTA collection tubes and centrifuged within 30 min at 2150×*g* for 15 min at 4°C. The plasma was aliquoted and stored in −80°C ultra-freezers until measurements in 2014, meaning that samples were not previously thawed before measurements were taken. Plasma levels of GDF15 were measured in the baseline samples by ELISA (Quantikine, R&D Systems, Inc., Abingdon, UK). All samples were measured in duplicate, and only accepted if intra-assay variance was <10%.

Missing data

18 patients only had spirometry measured at baseline, and 30 patients had only one or no measurements of FFMI. Data from these patients were not included in the longitudinal analysis for each of the two respective outcomes. Further detail is provided in the supplementary material.

Statistical analyses

The distribution of GDF15 was not normal. GDF15 was evaluated as a continuous variable and as a categorical variable, both dichotomised and in quartiles. Evaluating GDF15 as a dichotomised variable (either high or low levels of GDF15), with a cut-off at the median, gave the best discriminative power for our longitudinal outcomes, as it gave the lowest Akaike Information Criterion value, similarly as seen in other studies [31]. Thus, the analyses presented in this paper are with GDF15 as a categorical variable. Cross-sectional associations between COPD disease characteristics and systemic levels of GDF15 were evaluated by logistic regression, with high-*versus*-low GDF15 as the outcome variable. The core regression model included sex, age, smoking and comorbidity. Exacerbation count, body composition (both as a dichotomous cachexia variable and with FFMI in four quartiles), FEV_1 (both as a continuous variable as per cent predicted and as GOLD category) and FVC (as a continuous variable) were added to the core regression model one at a time owing to potential collinearity. Survival analyses were performed with GDF15 as a predictor variable, adjusting for sex, age, body composition, smoking, GOLD stage, CCS and exacerbation count in the 12 months before inclusion, using Cox regression models estimating hazard ratios (HRs) for both all-cause mortality and mortality due to cancer or cardiovascular or respiratory diseases. The incidence rate ratios (IRRs) of yearly exacerbations were estimated using a negative binomial random effects regression model. Yearly changes in FEV_1, FVC and FFMI were analysed using random effects linear regression models. All models adjusted for the same variables as in the survival analysis and Stata 13.1 (StataCorp LP, College Station, TX, USA) was used for the statistical analyses. See the supplementary material for information on missing values.

Results

The study population is described in table 1. The median level of GDF15 in 413 patients was 0.86 $ng{\cdot}mL^{-1}$ (interquartile range 0.64–1.12 $ng{\cdot}mL^{-1}$).

Cross-sectional associations between GDF15 and COPD disease characteristics

At baseline, high levels of GDF15 were associated with increasing age, current smoking and increasing comorbidity, shown in table 2. In addition, added to the same model, high levels of GDF15 were independently associated with ⩾2 yearly exacerbations before inclusion and with the presence of cachexia (figure 1), especially in the lowest FFMI quartile. Furthermore, GDF15 was associated with low values of FEV_1, but not FVC.

GDF15 is a predictor of mortality in COPD

Patients with high levels of GDF15 at baseline had a HR of 2.1 (95% CI 1.4–3.1) for all-cause mortality after adjustment for sex, age, body composition, smoking, GOLD stage and CCS (table 3; for all data, see supplementary material, table S1).

Analyses on cause-specific mortality revealed the strongest association between GDF15 and respiratory causes of death. Additional adjustment for heart failure or coronary disease instead of CCS did not significantly change our results (data not shown).

In patients with high GDF15 levels, cachexia was independently associated with higher mortality (HR 2.0, 95% CI 1.2–3.4), whereas in patients with low GDF15 levels, cachexia did not indicate increased mortality (HR 0.9, 95% CI 0.4–2.0). However, there was no statistically significant interaction between cachexia and GDF15 levels (p=0.17) with regards all-cause mortality.

Remarkably, patients with COPD with high levels of GDF15 at baseline continued to have increasingly higher mortality rates for up to 9 years of observation (figure 2).

TABLE 1 Baseline characteristics of the chronic obstructive pulmonary disease study population

Variables	Subjects[#]
Sex	
Male	61.0
Female	39.0
Age years	63.4 (6.9)
Smoking	
Ex-smoker	57.1
Current smoker	42.9
Body composition	
Normal	55.5
Obese	28.3
Cachectic	16.2
FEV_1 % predicted	
50–80%	47.7
30–50%	41.4
<30%	10.9
Charlson Comorbidity Score	
1	56.9
2	24.2
3	11.6
4	7.3
Exacerbations 12 months before inclusion	
0–1	83.5
⩾2	16.5
Plasma level of GDF15 ng·mL^{-1}	0.86 (0.64–1.12)

Data are presented as percentages, mean (SD), or median (interquartile range). FEV_1 : forced expiratory volume in 1 s; GDF15: growth differentiation factor-15. [#]: n=413.

GDF15 is a predictor of increased COPD exacerbation rate

We recorded that 353 patients had one or several exacerbations. A total of 1236 exacerbations were counted, of which 880 were considered moderate and 356 severe. High levels of GDF15 were significantly associated with an increase in the IRR for moderate and/or severe COPD exacerbations in the 3 years of follow-up, both in the unadjusted analysis (IRR 1.64, 95% CI 1.29–2.08) and after adjustment for sex, age, body composition, smoking, GOLD stage and CCS (IRR 1.39, 95% CI 1.10–1.74) (table 4).

GDF15 is a predictor of increased yearly decline in FEV_1 and FVC, but not FFMI

Patients with high GDF15 levels had an additional yearly decline in predicted FEV_1 of 1.04% and in predicted FVC of 1.19% compared to patients with low levels of GDF15 ($p<0.01$ for both) (figure 3). No similar associations were found with yearly decline in FFMI, because levels of baseline GDF15 did not impact the subsequent rate of decline in lean body mass (figure 4). The full analyses of decline in FEV_1 and FVC including coefficients for all co-variables are presented in supplementary tables S2 and S3, and for FFMI in supplementary table S4.

Discussion

Our study showed that plasma levels of GDF15 are associated with several COPD characteristics at baseline, such as smoking, frequent COPD exacerbations before inclusion, cachexia and low levels of FEV_1. Further, during follow-up, our study showed that patients with high levels of GDF15 have a higher mortality, an increased COPD exacerbation rate, and a steeper decline in both FEV_1 and FVC, all after multivariable adjustment. GDF15 had no predictive value on the development of cachexia, measured as a decline in FFMI.

Our study is in accordance with earlier studies which describe GDF15 as a marker of all-cause mortality [16], as we found a clear correlation between increasing GDF15 and risk of death in patients with COPD, for as long as 9 years of follow-up. The novel findings in our study are that high levels of GDF15 at inclusion predict a higher incidence of COPD exacerbation and a steeper decline in lung function, shown for both FEV_1 and FVC.

TABLE 2 Associations between chronic obstructive pulmonary disease characteristics and high levels of growth differentiation factor-15 using bi- and multivariable logistic regression

	Unadjusted		Adjusted	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age				
per 10-year increase	2.48 (1.81–3.40)	<0.001	2.73 (1.93–3.86)	<0.001
Sex				
Female	1		1	
Male	1.14 (0.77–1.70)	0.51	0.90 (0.59–1.39)	0.64
Smoking status				
Ex-smoker	1		1	
Current smoker	1.59 (1.08–2.36)	0.02	2.48 (1.58–3.87)	<0.001
Charlson Comorbidity Score				
1	1		1	
2	1.58 (0.99–2.54)	0.06	1.43 (0.86–2.35)	0.17
3	2.46 (1.29–4.69)	0.006	1.92 (0.97–3.82)	0.06
⩾4	3.15 (1.38–7.17)	0.006	2.52 (1.05–6.02)	0.04
Exacerbations 12 months before inclusion [#]				
0–1	1		1	
⩾2	2.07 (1.21–3.55)	0.008	2.28 (1.27–4.09)	0.006
Body composition[#]				
Normal	1		1	
Cachectic	2.39 (1.51–3.78)	<0.001	1.77 (1.07–2.94)	0.03
Obese	1.30 (0.75–2.24)	0.35	1.05 (0.57–1.92)	0.88
Free fat mass index[#]				
Q1 (highest)	1		1	
Q2	1.06 (0.61–1.83)	0.84	1.07 (0.59–1.96)	0.82
Q3	0.85 (0.49–1.47)	0.56	0.99 (0.49–2.02)	0.99
Q4 (lowest)	2.85 (1.61–5.05)	<0.001	3.25 (1.48–7.15)	0.003
FEV_1 % predicted[#,¶]	0.98 (0.97–0.99)	0.003	0.98 (0.97–1.00)	0.01
GOLD 2007 classification[#]				
FEV_1 50–80%	1		1	
FEV_1 30–50%	1.72 (1.14–2.60)	0.01	1.58 (1.00–2.48)	0.048
FEV_1 <30%	1.84 (0.96–3.55)	0.07	2.03 (0.99–4.15)	0.053
FVC % predicted[#,¶]	0.99 (0.98–1.00)	0.07	0.99 (0.98–1.01)	0.37

FEV_1 : forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FVC: forced vital capacity. [#]: for multivariable regression, variables added one at a time to the model above; [¶]: per % increase.

The main strengths of our study were the large number of participants (n=413), combined with longitudinal follow-up for 3 years for all outcomes but mortality, where registration lasted approximately 9 years. The patients underwent comprehensive evaluation both at inclusion and during follow-up, allowing for detailed multivariable regression analysis with adjustment for important co-variables.

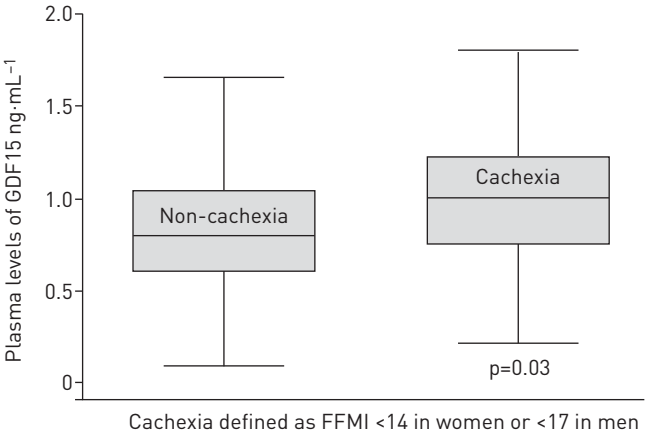

FIGURE 1 Growth differentiation factor-15 (GDF15) levels in non-cachectic *versus* cachectic patients. p=0.03 after multivariable adjustment for sex, age, smoking, Global Initiative for Chronic Obstructive Lung Disease stage, Charlson Comorbidity Score and exacerbation count 12 months before inclusion. Outliers are not shown. FFMI: fat free mass index.

TABLE 3 The unadjusted and adjusted hazard ratios for death among patients with chronic obstructive pulmonary disease with high levels of growth differentiation factor-15 at baseline

Cause of death	Subjects n	Unadjusted HR (95% CI)	p-value	Adjusted[#] HR (95% CI)	p-value
All-cause	147	3.00 (2.10–4.27)	<0.001	2.07 (1.40–3.05)	<0.001
Cancer	27	1.82 (0.85–3.94)	0.13	1.60 (0.70–3.65)	0.27
Cardiovascular	20	3.73 (1.36–10.3)	0.01	1.72 (0.56–5.30)	0.34
Respiratory	70	3.63 (2.12–6.21)	<0.001	2.38 (1.31–4.31)	0.004
Other/unknown	30	2.76 (1.29–5.91)	0.009	2.39 (1.04–5.49)	0.04

HR: hazard ratio. [#]: adjusted for sex, age, body composition, smoking, Global Initiative for Chronic Obstructive Lung Disease stage, Charlson Comorbidity Score and exacerbation count before inclusion.

Some limitations of our study should be mentioned. First, this study is not a randomised controlled study, thus the predictive value of GDF15 cannot be interpreted regarding causality. Second, the selection of patients with COPD was not a random sampling from a general population, but instead a sampling of COPD patients from previous patient studies or outpatient clinics [26]. In addition, GOLD stage 1 patients were not included by design. Our study sample is representative of a population with more advanced COPD, in that half the patients were GOLD stage 3 or 4. Thus, we would not be able to demonstrate an effect of GDF15 on a decline in FFMI if the effect was exclusively present in early stages of disease. Third, a replication cohort for validation of our findings would strengthen our study. Fourth, there is a lack of longitudinal follow-up for some of the patients, especially among patients with an apparently poor prognosis at inclusion and also with a high mortality, thus our findings in this patient category may be less robust (see supplementary material for details). Finally, although increased systemic levels of GDF15 are associated with both COPD [21] and lung injury [11], GDF15 is not lung specific, and we cannot tell whether the source of GDF15 is from lung tissue or other organ systems.

The mechanisms behind both GDF15 secretion as well as its action on target receptors in the airways are incompletely understood. However, studies by Wu *et al.* indicated GDF15 induction in airway epithelium after exposure to cigarette smoke [32, 33]. These authors described activation of both the phosphoinositide 3-kinase and the Smad1 pathways *via* GDF15, where the activing receptor-like kinase-1 was a possible GDF15 receptor. Wu *et al.* further found an association between increased airway GDF15 levels and several cellular senescence markers, as well as a potential role for GDF15 in mucin induction. These findings may help explain our findings of increased exacerbation count and a faster lung function decline in patients with high levels of GDF15.

Several studies have linked elevated circulating levels of GDF15 to cardiovascular disease, particularly heart failure [8], but also coronary disease [34] and pulmonary hypertension [35]. These conditions frequently coexist with COPD, and are also associated with adverse outcomes in patients with COPD [36, 37]. Even though high levels of GDF15 have been seen in patients with heart disease, it has been shown that GDF15 is secreted from cardiomyocytes after oxidative stress, and GDF15 has been proposed to have a beneficial anti-inflammatory effect in protecting against myocardial damage [38]; however, the role of GDF15 in cardiovascular disease is not fully understood. Several of our patients with COPD had coexisting cardiovascular disease that could have affected their plasma GDF15 levels. Although adjustment for

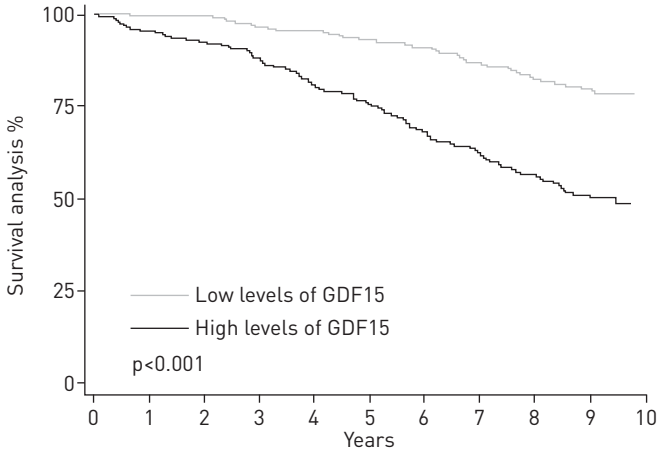

FIGURE 2 Survival analysis, high *versus* low levels of growth differentiation factor-15 (GDF15). p<0.001 after multivariable adjustment in a Cox regression model for sex, age, body composition, smoking, Global Initiative for Chronic Obstructive Lung Disease stage, Charlson Comorbidity Score and exacerbation count 12 months before inclusion.

TABLE 4 Multivariable models of the yearly incidence rate ratio of moderate or severe chronic obstructive pulmonary disease exacerbations, estimated by a random effects negative binomial model

Baseline explanatory variables	IRR (95% CI)	p-value
Sex		
Men	1	
Women	1.35 (1.08–1.69)	0.01
Age		
per 10-year increase	1.10 (0.92–1.32)	0.28
Body composition		
Normal	1	
Cachectic	1.01 (0.77–1.31)	0.96
Obese	1.18 (0.87–1.61)	0.28
Smoking		
Ex-smoker	1	
Current smoker	0.98 (0.77–1.24)	0.84
Exacerbations 12 months before inclusion		
0–1	1	
⩾2	2.03 (1.55–2.66)	<0.001
GOLD 2010 classification		
FEV_1 50–80%	1	
FEV_1 30–50%	1.59 (1.26–2.01)	<0.001
FEV_1 <30%	3.09 (2.15–4.43)	<0.001
Charlson Comorbidity Score		
1	1	
2	0.94 (0.72–1.23)	0.66
3	1.00 (0.70–1.44)	0.98
⩾4	1.07 (0.69–1.66)	0.77
GDF15		
Low levels[#]	1	
High levels	1.39 (1.10–1.74)	0.006

IRR: incidence rate ratio; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 s; GDF15: growth differentiation factor-15. [#]: cut-off median.

comorbidities including known cardiovascular disease did not change our results, we cannot exclude the impact from these conditions on either measured GDF15 levels or on adverse outcomes in our patients.

Cachexia is another condition frequently seen in COPD. It is associated with increased disease burden and mortality but its causes are multifactorial and it remains difficult to treat [39]. Several studies have described cachexia as being closely related to elevated levels of GDF15, especially in cachexia related to cancer [18–20], and cachexia has also recently been described in COPD [22]. It has been suggested that GDF15 has a suppressive effect on body weight both *via* appetite control on the hypothalamus and *via* peripheral regulation of energy metabolism [18, 40]. In our study, high levels of GDF15 were a strong independent predictor for increased mortality regardless of the patient's nutritional status. Interestingly, cachexia was not associated with increased mortality in patients with low GDF15 levels, indicating an upstream role for GDF15 in cachexia development. However, although we found a clear relationship between GDF15 and cachexia at inclusion, having high levels of GDF15 did not predict increased decline of FFMI in the longitudinal analysis.

The search for biomarkers in COPD is important for several reasons. There exists no useful biomarker for the diagnosis of COPD, or for a COPD exacerbation. Further, it is important to identify patients with increased risk for adverse outcomes in order to intensify observation and treatment in these patients. Although GDF15 lacks the combined sensitivity and specificity of an ideal biomarker in COPD, it could give prognostic information in addition to other easily accessible clinical parameters. Finally, the investigation of GDF15 and other biomarkers could provide valuable insight into the pathophysiology behind the disease, and the markers could themselves be targets for pharmacologic treatment. In murine models, treatment with antibodies targeting GDF15 has shown reversal of cancer-related cachexia after only a single injection [17, 41]. The association between elevated GDF15 and several adverse outcomes in patients with COPD makes GDF15 a potential treatment target of high interest.

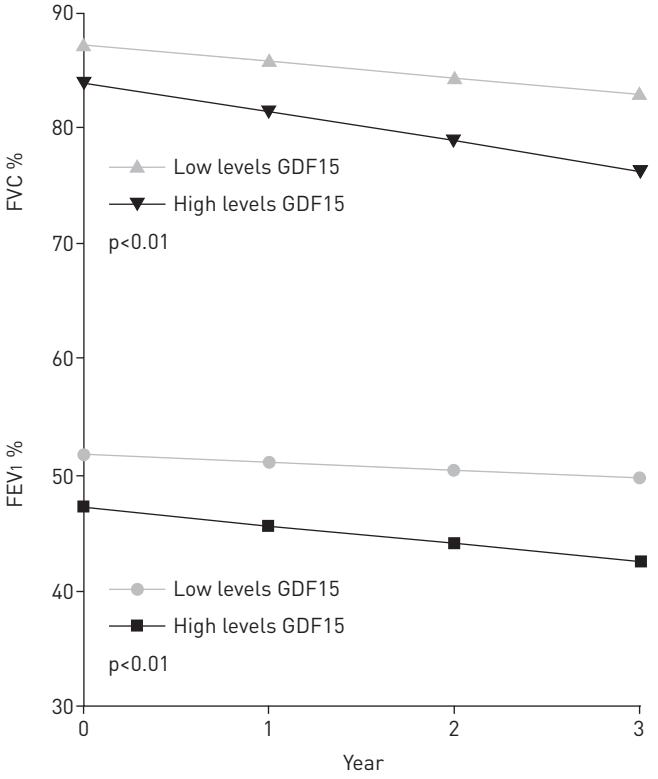

FIGURE 3 Modelled decline in forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) in patients with high *versus* low levels of growth differentiation factor-15 (GDF15) using a random effects linear regression model. p<0.01 after multivariable adjustment for sex, age, body composition, smoking, Global Initiative for Chronic Obstructive Lung Disease stage, Charlson Comorbidity Score and exacerbation count 12 months before inclusion.

Although its biological mechanisms remain incompletely understood, GDF15 emerges as a central biomarker in a variety of conditions. We show that elevated GDF15 levels can predict several adverse outcomes in COPD. To our knowledge, these have not been described in earlier studies. The existence of inhibitory antibodies and their therapeutic potential makes GDF15 even more intriguing. Nevertheless,

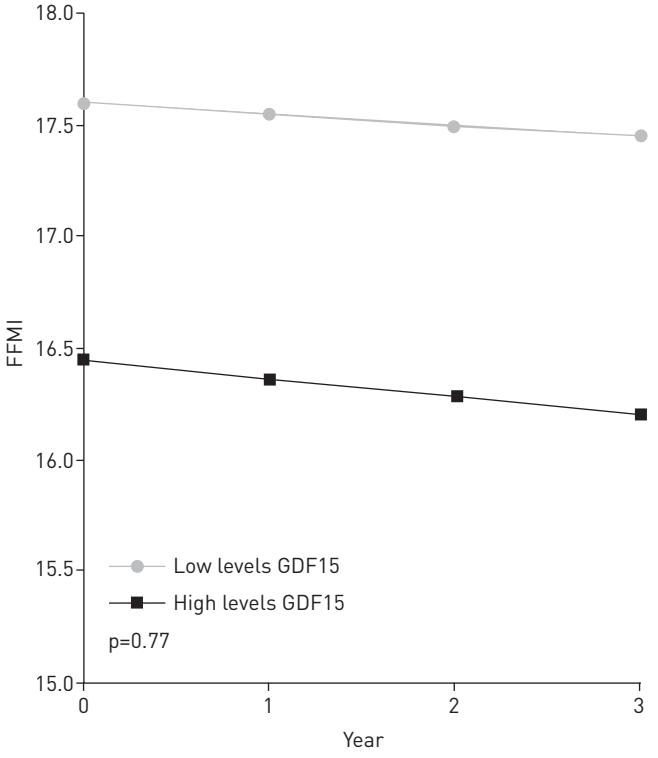

FIGURE 4 Modelled decline in fat free mass index (FFMI) in patients with high *versus* low levels of growth differentiation factor-15 (GDF15) using a random effects linear regression model. p=0.77 after multivariable adjustment for sex, age, body composition, smoking, Global Initiative for Chronic Obstructive Lung Disease stage, Charlson Comorbidity Score and exacerbation count 12 months before inclusion.

more research on GDF15 and its biochemical properties is needed to understand its role in COPD especially, as well as in general pathophysiology.

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