Liraglutide Improves Forced Vital Capacity in Individuals With Type 2 Diabetes: Data From the Randomized Crossover LIRALUNG Study

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To evaluate the effect of liraglutide, a glucagon-like peptide 1 receptor agonist, on pulmonary function and serum levels of surfactant protein D (SP-D) in type 2 diabetes. A double-blind, randomized, crossover, placebo-controlled clinical trial comprising 76 patients with a baseline forced expiratory volume in 1 s <90% of that predicted. Liraglutide was administered for 7 weeks (2 weeks of titration plus 5 weeks at 1.8 mg daily). This short duration was intentional to minimize weight loss as a potential confounding factor. Serum level of SP-D was used as a biomarker of alveolar-capillary barrier integrity. Liraglutide exerted a positive impact on forced vital capacity (FVC) in comparison with placebo (ΔFVC 5.2% of predicted [from 0.8 to 9.6]; $P = 0.009$). No differences in the other pulmonary variables were observed. Participants under liraglutide treatment also experienced a decrease in serum SP-D ($P = 0.038$). The absolute change in FVC correlated with final serum SP-D in participants receiving liraglutide ($r = -0.313$, $P = 0.036$). Stepwise multivariate regression analysis showed that final serum SP-D independently predicted changes in FVC. In conclusion, liraglutide increased FVC in patients with type 2 diabetes. This effect was associated with a significant decrease of circulating SP-D, thus pointing to a beneficial effect in the alveolar-capillary function.

Cross-sectional studies have shown decreased indices of forced expiration and lung volume and diffusion capacity in subjects with type 2 diabetes in comparison with age-matched healthy populations (1,2). This impairment in pulmonary function mainly been attributed to changes in lung elasticity and decreased muscle strength, which can be mediated by insulin resistance, advanced glycation end products accumulation, and a proinflammatory state (2). In addition, defects in the surfactant layer lining in the wall of the alveoli may also be considered as a contributing factor that impairs airway caliber regulation in type 2 diabetes (3,4). When the alveolar-capillary barrier is damaged,

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surfactant proteins A and D (SP-A and SP-D) leak from the alveolar space into the bloodstream and are useful systemic biomarkers for assessing lung injury (5,6). Notably, experimental studies have shown that glucagon-like peptide 1 (GLP-1) ameliorates lung fibrosis, thus resulting in a decrease in serum SP-D levels (7,8). Our aim was to test the impact of liraglutide, a GLP-1 receptor agonist (GLP-1RA), on pulmonary function and circulating levels of SP-D in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

The liraglutide on lung function (LIRALUNG) study (ClinicalTrials.gov identifier NCT02889510) was approved by the Spanish Agency for Medicines and Health Products. All potential participants gave written informed consent to join the trial, which was conducted according to the Declaration of Helsinki and the Good Clinical Practice guidelines. The reporting has followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines (9). This was a phase II, double-blind, randomized, placebo-controlled, crossover study performed at five hospital sites in Spain. The study flowchart is displayed in Supplementary Fig. 1.

Eligible patients were age ≥18 years, with type 2 diabetes diagnosed for at least 5 years before screening. Other inclusion criteria were antidiabetes therapy for at least 3 months at a stable dose, BMI ≥30 kg/m^2, HbA_{1c} between 7.0% and 10.0% (53.0 and 85.8 mmol/L), a chest X-ray without abnormalities, and not having smoked in the previous 5 years. In addition, to maximize the influence of GLP-1 treatment on pulmonary function, a baseline reduction in forced expiratory volume in 1 s (FEV_1) ≥10% of the predicted value was also considered an inclusion criterion.

Key exclusion criteria included type 1 diabetes, treatment with sodium–glucose cotransporter 2 inhibitors or GLP-1RA, cardiovascular and cerebrovascular diseases, previous bariatric surgery, serum creatinine >1.7 mg/dL, abnormal liver function test, pancreatitis, medullary carcinoma of the thyroid, multiple endocrine neoplasia type 2, pregnancy, or sleep-breathing disorders requiring continuous positive airway pressure therapy. Patients enrolled in the study who initiated any of the following concomitant treatments were also excluded: sodium–glucose cotransporter 2 inhibitors, GLP-1RA, inhaled bronchodilator drugs, continuous positive airway pressure therapy, or oral corticosteroids.

Patients were randomly allocated with an envelope method in a 1:1 ratio to one of the two treatment groups: 7-week subcutaneous liraglutide treatment (first week, 0.6 mg once daily; second week, 1.2 mg once daily; third week, 1.8 mg once daily until the end of the seventh week) followed by placebo or vice versa, with a 1-month washout period in between. Duration was restricted to 7 weeks to minimize the potential confounding factor of weight loss induced by liraglutide on the parameters of pulmonary function. If a dose of liraglutide was not well tolerated, it was reduced to the minimum tolerated dose.

The primary end point was change in FEV_1. Secondary end points included changes in forced vital capacity (FVC), the other spirometry parameters, and serum levels of SP-D. Forced spirometry measurements were performed with a MasterLab apparatus (MasterLab; Jaeger, Würzburg, Germany), and data were displayed as a percentage of the predicted values (10,11). A nonobstructive ventilatory defect was defined as an FVC <80% of the predicted value, with an FEV_1/FVC ≥70% (10). SP-D was assessed with ELISA (BioVendor R&D, Deltaclon, Barcelona, Spain).

We assumed baseline expected values of FEV_1 for untreated patients with type 2 diabetes of 88.4% ± 19.7%, as previously reported in the Spanish population (12). Therefore, with use of ANOVA to specifically assess the effect in a crossover design and setting the threshold for statistical significance at 5% ($\alpha = 0.05$, one sided), inclusion of 50 patients resulted in 80% statistical power ($\beta = 0.2$) to detect a significant increase, due to the treatment, in FEV_1 levels of at least 20%. For this computation, the within mean square error of the ANOVA for repeated measurements was calculated as $\sqrt{(2 \times 19.7^2)} = 27.8$. However, sample size was increased to a total of 76 patients according to an expected dropout rate of 20% and the lack of data regarding the effect of liraglutide on other lung function parameters and serum levels of SP-D.

Repeated-measures ANOVA was used to first look at the possible existence of period and carryover effects for each variable. If no differences were found, the treatment effect was studied. In the case of differences being found between the period and/or carryover effects, no conclusions were drawn about the effect of the exposure in the measurement being carried out. Efficacy analyzes were performed on the per-protocol population (restricted to participants who completed the study without major protocol deviations), whereas safety analyses were carried out for the safety population (participants who received at least one dose of any study product).

Data and Resource Availability

The data sets generated during or analyzed during the current study are available from the corresponding author upon reasonable request.

RESULTS

There were no differences regarding clinical features, metabolic and pulmonary parameters, or serum SP-D at baseline between groups (Table 1). After the 7-week period, participants treated with liraglutide showed a significant improvement of glycemic control, which was also accompanied by a slight but significant reduction in BMI (Δ −0.5 kg/m^2 [95% CI −0.8 to −0.3]) (Table 2).

Regarding spirometric measurements, no differences were observed in FEV_1 between the liraglutide and placebo groups. However, the evolution of FVC was different: under liraglutide treatment FVC increased by 5.4% (from 78.9% ± 12.9% to 84.3% ± 14.6% of predicted, $P =$

Table 1—Clinical characteristics and metabolic and pulmonary data of all participants randomized at time of recruitment and at baseline visit by group (intention-to-treat population)

	All population at recruitment (*n* = 76)	Liraglutide group at baseline (*n* = 72)	Placebo group at baseline (*n* = 65)	*P*
Age (years)	58.6 ± 7.5			
Women	30 (39.4)			
Caucasian	73 (96.1)			
Never smokers	38 (50)			
BMI (kg/m^2)	34.8 ± 4.1	34.7 ± 4.2	35.0 ± 4.4	0.415
Systolic BP (mmHg)	146.5 ± 19.5	146.9 ± 17.3	145.2 ± 19.8	0.603
Glucose metabolism				
FPG (mmol/L)	10.5 ± 3.8	11.0 ± 3.5	10.9 ± 4.0	0.907
HbA_{1c} (%)	8.1 ± 0.8	8.3 ± 1.1	7.9 ± 0.9	0.077
HbA_{1c} (mmol/mol)	65.7 ± 9.0	67.2 ± 12.1	63.7 ± 10.5	0.077
Lung function				
FEV_1 (%)	77.5 ± 10.8	81.1 ± 12.1	77.8 ± 12.1	0.127
FVC (%)	81.1 ± 17.9	81.9 ± 18.8	79.6 ± 12.6	0.210
$FEF_{25–75}$ (%)	70.2 ± 28.3	79.2 ± 27.2	70.1 ± 28.9	0.075
PEF (%)	74.0 ± 28.0	80.7 ± 27.2	80.7 ± 27.8	0.988
FEV_1/FVC (%)	81.0 (74.9–86.8)	81.6 (77.1–89.0)	82.3 (77.6–90.0)	0.658
Nonobstructive VD	29 (38.1)	27 (37.5)	25 (38.4)	0.455
Serum SP-D (ng/mL)	199.5 (136.0–317.4)	196.5 (128.3–271.5)	184.2 (118.3–287.3)	0.804

Data are mean ± SD, median (interquartile range), or *n* (%). BP, blood pressure; $FEF_{25–75}$, maximum midexpiratory flow; PEF, peak expiratory flow; VD, ventilatory defect; SP, surfactant protein. Student *t* test, Mann-Whitney *U* test, and χ^2 test were used to compare the baseline data between groups.

0.002), whereas there were no changes in those participants on placebo (from 79.1% ± 9.3% to 79.4% ± 13.3%, $P = 0.854$). Therefore, the treatment effect in the LIRALUNG study, with an increase of 5.2% of predicted in FVC (95% CI 0.8–9.6), was statistically significant ($P = 0.009$) (Fig. 1). In addition, the prevalence of a nonobstructive ventilatory defect among participants receiving liraglutide decreased from 40.0% to 21.7% ($P = 0.013$).

The 7 weeks of liraglutide treatment decreased the serum SP-D concentration: 196.4 ng/mL (128.2–271.4) at baseline vs. 169.6 ng/mL (108.1–233.6) at 7 weeks; $P = 0.038$ (Supplementary Fig. 2). However, no changes were observed in serum SP-D under placebo (207.8 ng/mL [136.6–313.2] at baseline vs. 201.5 ng/mL [115.3 to 284.7] at 7 weeks; $P = 0.718$).

Univariate analysis showed that under liraglutide treatment the absolute change in FVC negatively correlated with the final serum concentration of SP-D ($r = -0.313$, $P = 0.036$) (Supplementary Fig. 3). However, no correlations between the absolute change in FVC and variations in fasting plasma glucose (FPG), HbA_{1c} or BMI were observed in participants receiving liraglutide (respectively, $r = 0.122$, $P = 0.400$; $r = -0.007$, $P = 0.963$; and $r = -0.142$, $P = 0.321$).

Finally, stepwise multivariate regression analysis showed that the final serum concentration of SP-D (but not sex, age, or absolute change in BMI, FPG, HbA_{1c}, and SP-D concentration) predicted changes in FVC in participants under liraglutide treatment ($\beta = -0.322$, $P = 0.037$, $R^2 = 0.104$) (Table 3). A total of 51 adverse events (30 under liraglutide and 21 under placebo treatment) occurred during the study. The more frequent under liraglutide treatment (66.6%) were related to gastrointestinal disorders.

DISCUSSION

Although no significant changes were observed in FEV_1 (the primary end point), the results of the LIRALUNG study provide the first clinical evidence that treatment with a GLP-1RA has a positive impact on pulmonary function in patients with type 2 diabetes. This effect was restricted to FVC and appears to be independent of weight loss and an improvement in glycemic control. In addition, it was associated with changes in serum levels of SP-D, thus reflecting a beneficial effect on the alveolar-capillary barrier. It should be noted that these results were obtained from patients with a basal FEV_1 <90% of that predicted and, therefore, point to liraglutide as an antidiabetes agent particularly useful for those patients with associated lung dysfunction.

The effect of liraglutide on FVC could be relevant to clinical practice. In this regard, it should be noted that subjects with intermediate coronary hearth risk with FVC ≤85% had an almost threefold greater risk of mortality than those with FVC ≥95% of that predicted (13). Therefore, the impact of liraglutide on FVC may be one more factor implicated in the reported low rates of cardiovascular mortality in patients with type 2 diabetes receiving this drug (14).

Table 2—Evolution from baseline to 7 weeks of clinical characteristics and metabolic and pulmonary data of participants according to received treatment, together with analysis of treatment effect

Clinical characteristics	Basal	7 weeks	Mean difference (95% CI)	*P*
BMI (kg/m^2)				
Liraglutide	34.8 ± 4.4	34.2 ± 4.5	−0.5 (−0.8 to −0.3)	<0.001
Placebo	34.3 ± 4.0	34.3 ± 4.3	−0.0 (−0.2 to −0.1)	0.684
Δ	—	—	0.5 (−0.8 to −0.2)	<0.001
FPG (mg/dL)				
Liraglutide	183.4 ± 64.9	160.2 ± 59.5	−23.1 (−34.7 to −11.6)	<0.001
Placebo	215.7 ± 83.5	208.5 ± 79.1	7.1 (−6.6 to 20.9)	0.302
Δ	—	—	−30.3 (−48.2 to −12.4)	0.001
HbA_{1c} (%)				
Liraglutide	8.3 ± 1.1	7.4 ± 1.0	−0.9 (−1.1 to −0.7)	<0.001
Placebo	7.9 ± 0.9	8.2 ± 1.2	0.2 (0.0–0.5)	0.013
Δ	—	—	−1.2 (−1.5 to −0.9)	<0.001
HbA_{1c} (mmol/mol)				
Liraglutide	67.7 ± 12.6	57.3 ± 11.7	−10.3 (−12.5 to −8.0)	<0.001
Placebo	63.7 ± 10.7	67.0 ± 13.2	3.3 (−0.7 to −5.8)	0.011
Δ	—	—	−13.6 (−17.0 to −10.2)	<0.001
FEV_1 (%)				
Liraglutide	81.0 ± 13.0	85.2 ± 18.0	4.1 (0.0–8.3)	0.046
Placebo	78.2 ± 10.5	82.6 ± 14.8	4.3 (0.1–8.5)	0.043
Δ	—	—	−0.1 (−5.9 to 5.6)	0.954
FVC (%)				
Liraglutide	78.9 ± 12.9	84.3 ± 14.6	5.4 (2.1–8.7)	0.002
Placebo	79.1 ± 9.3	79.4 ± 13.3	0.2 (−2.5 to 3.1)	0.854
Δ	—	—	5.2 (0.8–9.6)	0.019
FEV_1/FVC (%)				
Liraglutide	86.6 ± 14.1	84.5 ± 13.6	−2.1 (−5.1 to 0.9)	0.166
Placebo	85.9 ± 13.7	87.6 ± 13.7	1.7 (−0.8 to 4.2)	0.190
Δ	—	—	−3.8 (−7.7 to 0.1)	0.056
Nonobstructive VD				
Liraglutide	24 (40.0)	13 (21.7)	—	0.013
Placebo	25 (41.0)	23 (37.7)	—	0.754

Data are mean ± SD or *n* (%) unless otherwise indicated. VD, ventilatory defect. Significant differences in the carryover and period effects preclude the analysis of the treatment effect for maximum midexpiratory flow and peak expiratory flow. A paired Student *t* test and Wilcoxon test were used to compare the baseline data with those obtained at the end of follow-up, while categorical variables were compared using the McNemar test.

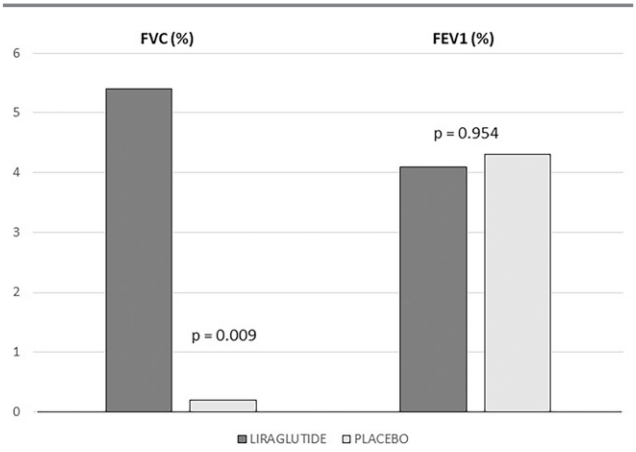

Figure 1—Treatment effect (liraglutide vs. placebo) on spirometric values from baseline to 7 weeks in the LIRALUNG study. A paired Student *t* test was used to compare the baseline data with those obtained at the end of follow-up.

Pulmonary involvement has been related to metabolic control. In the Sweet Breath Study a reduction in HbA_{1c} >0.5% in a 3-month period enhanced FEV_1 and FVC by 5.3% and 4.8% of predicted, respectively (15). Whether an extended treatment with liraglutide could lead also to a significant improvement in FEV_1 values needs to be assessed. Another important issue to be explored is whether the reduction of glycemic variability plays a role in the improvement of lung function parameters.

The mechanisms underlying the improvement of FVC induced by liraglutide should be elucidated. The reported antifibrotic and anti-inflammatory actions of GLP-1RA could be involved (15–17). In this regard, Fandiño et al. (8) have recently shown a myriad of mechanisms accounting for the beneficial effects of liraglutide in ameliorating experimental lung fibrosis induced by bleomycin. In addition, it should be noted that FVC improvement, obtained after only 5 weeks of treatment at the maximum dose of liraglutide, was similar to that obtained after 6 months of

Table 3—Variables independently related to the absolute change in FVC under liraglutide treatment in the multiple regression analysis (stepwise method)

	β	Beta (95% CI)	*P*
Final serum SP-D (ng/mL)	−0.337	−0.041 (−0.078 to −0.004)	0.031
ΔFPG (mmol/L)	0.246		0.113
ΔSerum SP-D (ng/mL)	0.177		0.281
ΔHbA_{1c} (%)	0.116		0.471
Age (years)	0.107		0.485
ΔBMI (kg/m^2)	−0.092		0.555
Sex	−0.090		0.576
Constant	—	11.972 (4.194–19.750)	0.003
R^2 = 0.114			

β, standardized coefficient; Beta, nonstandardized coefficient. A stepwise multivariate regression analysis was performed. Variables significantly associated with changes in lung function in the bivariate analysis (i.e., the final serum concentration of SP-D), together with clinically relevant variables with potential impact on lung function (i.e., sex, age, and absolute change in BMI, FPG, HbA_{1c}, and serum surfactant protein D [SP-D]), were included in the analysis.

treatment with nintedanid, a drug approved for treating idiopathic pulmonary fibrosis (18,19). However, the short period of treatment argues against the antifibrotic action as the primary effect of FVC improvement mediated by liraglutide. Therefore, other mechanisms such as the improvement of cardiac function, the reduction of insulin resistance, the anti-inflammatory effects, and the improvement of the alveolar-capillary unit could be involved (15–17,20).

Experimental studies have shown that GLP-1(7-36) and GLP-1(7-37) amides stimulates surfactant production by human type II pneumocytes (8,21). In the LIRALUNG study, SP-D circulating levels have been used as a biomarker of alveolar-capillary barrier integrity. Thus, the reduction of circulation levels of SP-D observed after liraglutide treatment indicates a positive effect of this drug on the alveolar-capillary barrier function, which could be associated with the retention of surfactant within alveoli. However, in the absence of direct measurements of pulmonary surfactant status, the latter assumption remains speculative.

There are a few potential constraints that should be considered in weighing the results of our study. First, we assessed a relatively low number of patients with type 2 diabetes with low baseline FEV_1, which means that no irrefutable clinical consequences can be inferred regarding the general population. However, the careful selection of participants, the presence of a placebo group, and the crossover design of the LIRALUNG study reduced the influence of confounding covariates, reinforcing the value of our findings. Second, the short period of treatment, conditioned by the attempt to minimize the confusion caused by weight loss, may not have shown the full real effect of liraglutide on lung function and surfactant layer. Therefore, studies with a longer follow-up are needed to confirm not only the positive but also the durable effect of liraglutide on lung function. Third, a slight but significant decrease of 0.5 kg/m^2 in BMI of participants treated with liraglutide was observed. However, in the multiple regression analysis this was not an independent variable associated with changes in FVC. Nevertheless, future studies measuring the impact of body composition rather than merely BMI seem warranted. Finally, the influence of cardiac function on FVC and the reported beneficial effects of liraglutide on the heart do not permit us to rule out the improvement of cardiac function as a factor involved in the enhancement of FVC (21,22). However, the independent negative relationship between FVC and SP-D point to lung as a significant player in this finding.

In conclusion, the results of the LIRALUNG study demonstrate that short-term administration of liraglutide produces a significant increase of FVC. Long-term studies with more patients are warranted to confirm our initial results and for understanding the underlying mechanisms.

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