Effect of Glucose Improvement on Spirometric Maneuvers in Patients With Type 2 Diabetes: The Sweet Breath Study

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OBJECTIVE

Type 2 diabetes exerts a deleterious effect on lung function. However, it is unknown whether an improvement in glycemic control ameliorates pulmonary function.

RESEARCH DESIGN AND METHODS

Prospective interventional study with 60 patients with type 2 diabetes and forced expiratory volume in 1 s (FEV1) ≤90% of predicted. Spirometric maneuvers were evaluated at baseline and after a 3-month period in which antidiabetic therapy was intensified. Those with an HbA_{1c} reduction of ≥0.5% were considered to be good responders (n = 35).

RESULTS

Good responders exhibited a significant improvement in spirometric values between baseline and the end of the study (forced vital capacity [FVC]: 78.5 ± 12.6% vs. 83.3 ± 14.7%, P = 0.029]; FEV1: 75.6 ± 15.3% vs. 80.9 ± 15.4%, P = 0.010; and peak expiratory flow [PEF]: 80.4 ± 21.6% vs. 89.2 ± 21.0%, P = 0.007). However, no changes were observed in the group of nonresponders when the same parameters were evaluated (P = 0.586, P = 0.987, and P = 0.413, respectively). Similarly, the initial percentage of patients with a nonobstructive ventilatory defect and with an abnormal FEV1 decreased significantly only among good responders. In addition, the absolute change in HbA_{1c} inversely correlated to increases in FEV1 (r = −0.370, P = 0.029) and PEF (r = −0.471, P = 0.004) in the responders group. Finally, stepwise multivariate regression analysis showed that the absolute change in HbA_{1c} independently predicted increased FEV1 (R^2 = 0.175) and PEF (R^2 = 0.323). In contrast, the known duration of type 2 diabetes, but not the amelioration of HbA_{1c}, was related to changes in forced expiratory flow between 25% and 75% of the FVC.

CONCLUSIONS

In type 2 diabetes, spirometric measurements reflecting central airway obstruction and explosive muscle strength exhibit significant amelioration after a short improvement in glycemic control.

The lungs are not conventionally included in the target list of organs that may be affected by type 2 diabetes. However, with its large vascularization and rich amount of collagen and elastin fibers, the lung parenchyma appears to be a potential target of chronic hyperglycemia (1–3). In fact, the same histological and physiologic disturbances that account for complications in other tissues may also be involved in the

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deleterious impact of type 2 diabetes on pulmonary function (3). Therefore, insulin resistance (IR), low-grade systemic inflammation, lung microangiopathy, leptin resistance, autonomic neuropathy, defects in the bronchiolar surfactant layer, and reduced muscle strength have been involved as pathogenic factors (3,4).

Several large epidemiological studies have described how adults with type 2 diabetes have lower forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) values than the healthy population (1,5–8). Moreover, an inverse association has been observed between fasting plasma glucose (FPG), glycosylated hemoglobin (HbA_{1c}), and spirometric values (5,7,8). Longitudinal studies (8,9) have also documented a faster decline of FVC and FEV1 among patients with type 2 diabetes than that observed in their counterparts without diabetes. More importantly, data from the Fremantle Diabetes Study (6) showed that for every 1% increase in the HbA_{1c} level, an FVC decline of 4% predicted value was observed. Although lung damage and respiratory abnormalities were of moderate magnitude and even subclinical, there could be a long-term deleterious impact. In this regard, a 10% decrease in FEV1 was an independent predictor of all-cause mortality in the population with type 2 diabetes (6).

Basic research and epidemiological and clinical data also support the notion that type 2 diabetes has a deleterious effect on sleep breathing and is an independent risk factor for severe nocturnal hypoxemia (10). Moreover, our group demonstrated a significant reversibility of the increased number of nocturnal oxygen desaturation events after only 5 days of intensified glycemic treatment (11). However, it is unknown whether an improvement in glycemic control can also ameliorate lung function parameters in patients with type 2 diabetes. In this setting, weight loss is a major confounding factor that impedes clarification of the real effect of amending metabolic control. Obesity is frequently associated with type 2 diabetes and shows a proportional reduction in FVC and FEV1, suggesting the occurrence of restrictive lung disease (12,13). Moreover, improvements in lung function after weight loss, including FEV1 and FVC, have also been reported in obese patients (14).

To shed light on this issue, we performed a prospective and interventional study to determine whether improving type 2 diabetes metabolic control during a 3-month period was accompanied by significant changes in respiratory function. To minimize the impact of weight reduction on the same pulmonary parameters, subjects who experienced a BMI decrease $\geq$2.0 kg/m^2 were excluded from the analysis.

RESEARCH DESIGN AND METHODS

Statement on Ethics

The human ethics committee from the Hospital Universitari Arnau de Vilanova approved the study. Informed written consent was obtained from all participants included in the study, which was conducted according to the ethical guidelines of the Declaration of Helsinki.

Study Design and Description of the Study Population

This prospective interventional study examined the effect of the improvement of glycemic control on respiratory function in subjects with type 2 diabetes without any known pulmonary disease. The study examined a total of 594 consecutive Caucasian subjects with type 2 diabetes at their initial visit to the outpatient Diabetes Clinic from March 2016 to January 2018 (Supplementary Fig. 1). The inclusion criteria were as follows: age between 40 and 70 years, a BMI $<$40 kg/m^2, HbA_{1c} $\geq$7.5% (58 mmol/mol), no medical history of lung disease, and type 2 diabetes with at least 5 years of follow-up. Among the 340 patients who met the inclusion criteria, we excluded 125 for the following reasons: unwillingness to participate in the study (n = 37), hyperglycemia secondary to use of corticosteroids (n = 28), an inability to perform the spirometric maneuvers correctly (n = 25), active malignancy or malignancy diagnosed within the previous 5 years (n = 18), heart failure (n = 11), pregnancy (n = 4), and goiter with compressive symptoms (n = 2). Finally, spirometry was performed in 215 subjects, and only those with a baseline FEV1 $\leq$90% (n = 83) were invited to repeat spirometric maneuvers after a 3-month period, during which antidiabetic therapy was intensified. Four patients failed to perform the final evaluation. In addition, in order to minimize the influence of weight loss on the results, 19 patients who experienced a BMI reduction $>$2.0 kg/m^2 were excluded. Finally, 60 patients were included in the study. Those with a reduction of their HbA_{1c} of $\geq$0.5% (arbitrary set point) were considered to be good responders (n = 35), and the other 25 patients to be nonresponders.

At baseline and at the end of the study, a Clínica Universidad de Navarra-Body Adiposity Estimator (CUN-BAE) (15) and the equation proposed by Bonora et al. (16) were used to estimate total body fat and abdominal fat, respectively.

A control group of 34 healthy subjects, without type 2 diabetes or lung disease, was recruited from January 2017 to January 2018 from among the relatives of patients with diabetes, as well as the employees of our institution.

Measurement of Respiratory Function Data

Forced spirometry was measured using a Datospir Micro C spirometer (Sibelmed, Barcelona, Spain) and carried out under the guidelines proposed by the European Respiratory Society (17). The different spirometric parameters were measured as a percentage of the predicted values, and included FEV1, FVC, peak expiratory flow (PEF), forced expiratory flow between 25% and 75% of the FVC ($FEF_{25–75}$), and the ratio between FEV1 and FVC (FVE1/FVC). Before each assessment, the procedure was demonstrated to the patient, who was asked to make some practice efforts. Subjects were required to perform a minimum of three reproducible measurements, and the output that produced the highest sum of FEV1 and FVC was chosen for analysis.

In accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD), a nonobstructive ventilatory defect was defined by an FVC of $<$80% of the predicted value, with an FEV1/FVC ratio $\geq$70% (18). An abnormal FEV1 was defined as a value $<$80% of that predicted. Similarly, an obstructive ventilatory defect was defined by an FEV1/FVC ratio $<$70% of the predicted value (18).

Type 2 Diabetes Treatment at Baseline and During Glycemic Improvement

At baseline, patients were treated with metformin alone (8.3%), metformin plus other oral agents (26.6%), basal insulin alone (31.6%), or with a basal-bolus

Table 1—Baseline main clinical, metabolic, and pulmonary characteristics of participants in the study according to their response to the intensification of antidiabetic treatment

	All patients (n = 60)	Good responders (n = 35)	Nonresponders (n = 25)	P
Clinical data				
Men	47 (78.3)	28 (80.0)	19 (76.0)	0.711
Age (years)	58.1 ± 6.4	58.3 ± 6.8	57.9 ± 6.0	0.806
BMI (kg/m^2)	32.4 ± 6.1	32.3 ± 6.4	32.5 ± 5.8	0.891
Decrease in BMI (kg/m^2)	−0.18 ± 1.2	−0.2 ± 1.0	0.1 ± 0.7	0.123
Decrease in kg	−0.5 ± 3.7	−1.2 ± 4.5	−0.4 ± 2.0	0.056
Waist circumference (cm)	112.0 ± 14.2	112.1 ± 14.6	111.9 ± 13.9	0.953
Never smokers	43 (71.6)	26 (74.2)	17 (68.0)	0.594
Known type 2 diabetes duration (years)	14.4 ± 8.5	13.4 ± 8.2	15.8 ± 8.9	0.290
Diabetic retinopathy	23 (38.3)	13 (37.1)	10 (40.0)	0.960
Diabetic nephropathy	24 (40.0)	17 (48.5)	7 (28.0)	0.181
Ischemic heart disease	9 (15.0)	7 (20.0)	2 (8.0)	0.281
Metabolic data				
Baseline HbA_{1c} (%)	8.8 ± 1.2	9.1 ± 1.2	8.4 ± 1.1	0.025
Baseline HbA_{1c} (mmol/mol)	67.9 ± 13.7	71.1 ± 14.0	63.4 ± 12.4	0.025
Decrease in HbA_{1c} (%)	−1.0 ± 1.4	−2.0 ± 1.0	0.2 ± 0.7	<0.001
Decrease in HbA_{1c} (mmol/mol)	−12.0 ± 17.0	−22.7 ± 12.2	3.0 ± 9.7	<0.001
FPG (mmol/L)	11.1 ± 3.9	12.4 ± 3.6	9.4 ± 3.6	0.003
Triglycerides (mg/dL)	158.5 (36.0–683.0)	154.0 (36.0–683.0)	170.0 (72.0–331.0)	0.495
LDL cholesterol (mg/dL)	95.7 ± 36.0	99.4 ± 32.9	90.4 ± 39.4	0.338
GFR (mL/min/1.73 m^2)	79.9 ± 16.3	78.9 ± 16.5	81.3 ± 16.3	0.582
Pulmonary function data				
FVC (% of predicted)	77.8 ± 11.3	78.5 ± 12.6	76.9 ± 9.3	0.577
FEV1 (% of predicted)	76.5 ± 13.8	75.6 ± 15.3	77.6 ± 11.6	0.583
PEF (% of predicted)	80.1 ± 21.9	80.4 ± 21.6	80.5 ± 22.5	0.988
$FEF_{25–75}$ (% of predicted)	65.8 ± 25.2	62.0 ± 27.2	71.3 ± 21.3	0.165
FEV1/FVC ratio	85.3 ± 14.0	88.3 ± 16.6	81.2 ± 8.0	0.053

Data are mean ± SD, median (range), or n (%). GFR, glomerular filtration rate using the CKD-EPI (Chronic Kidney Disease-Epidemiology Collaboration) equation.

regimen (25.0%), glucagon-like peptide 1 (GLP-1) receptor agonists (3.3%) plus oral agents, and basal insulin associated with GLP-1 (5.0%). No patient was treated with diet alone.

All subjects underwent treatment intensification to improve glycemic control according to our routine medical practice. At the end of the study, the proportion of patients receiving insulin therapy increased to 66.6%; 23.3% were treated with GLP-1 receptor agonists (10 of the 14 patients receiving GLP-1 in combination with insulin). None of the subjects continued receiving treatment comprising only diet or metformin.

Statistical Analysis

Statistical analyses were performed using SPSS software (Statistics for Windows, version 20.0.; IBM, Armonk, NY). A normal distribution of the variables was established using the Kolmogorov-Smirnov test, and data are expressed as the mean ± SD, median (range), or percentage. A paired Student t test was used to compare the baseline data with those obtained at the end of follow-up, whereas categorical variables were compared using the χ^2 test. The relationship between continuous variables was examined by the Pearson linear correlation test. A stepwise multivariate regression analysis was performed to explore the variables independently related to the absolute change of FEV1, FVC, PEF, and $FEF_{25–75}$. Variables significantly associated with changes in lung function in the bivariate analysis (i.e., age, baseline HbA_{1c}, and the absolute change in HbA_{1c}), together with clinically relevant variables with a potential impact on lung function (i.e., sex, BMI, smoking habit, and type 2 diabetes duration) were included in the analysis. All P values were based on a two-sided test of statistical significance. Significance was accepted at a level of $P < 0.05$.

RESULTS

The main clinical features and metabolic data of the study population are presented in Table 1. After a mean follow-up period of 80.0 ± 8.6 days, 35 patients (58.3%) were classified as good responders. In this group, HbA_{1c} had significantly decreased from 9.1 ± 1.2% to 7.1 ± 0.7% (71.1 ± 14.0 to 48.3 ± 8.0 mmol/mol, $P < 0.001$). On the other hand, 25 patients (41.7%) were classified as nonresponders, with a mean change in HbA_{1c} of 0.2% (95% CI −0.1 to 0.3). Changes in BMI were not significant in either group after this follow-up period (P = 0.103 in good responders, P = 0.398 in nonresponders). Apart from a higher baseline HbA_{1c} (9.1 ± 1.2% vs. 8.4 ± 1.1%, P = 0.025) and FPG (224.1 ± 65.5 vs. 170.4 ± 66.0 mg/dL, P = 0.003) in the responder group, no other differences were observed between both groups. Baseline pulmonary parameters were also similar in either good responders or nonresponders.

Spirometric values (FVC, FEV1, PEF, $FEF_{25–75}$, and FEV1/FVC) did not change between baseline and the end of the study when the group of nonresponders was evaluated (Table 2). However, subjects who exhibited a significant improvement in their metabolic control also revealed a positive and significant impact in their FVC (78.5 ± 12.6 at baseline vs. 83.3 ± 14.7 at the end of study, P = 0.029), FEV1 (75.6 ± 15.3 vs. 80.9 ± 15.4,

Table 2—Evolution of the main pulmonary function parameters according the response to the intensification of the antidiabetic treatment

	Baseline	3 months	Mean difference (95% CI)	*P*
Entire population	(*n* = 60)	(*n* = 60)		
FVC (% predicted)	77.8 ± 11.3	80.8 ± 13.0	3.0 (0.3–5.6)	0.025
FEV1 (% predicted)	76.5 ± 13.8	79.5 ± 13.4	3.0 (0.5–5.5)	0.017
PEF (% predicted)	80.1 ± 21.9	86.4 ± 19.3	6.0 (1.8–10.2)	0.006
$FEF_{25–75}$ (% predicted)	65.8 ± 25.2	66.5 ± 21.8	−0.7 (−4.3 to 5.7)	0.779
FEV1/FVC (% predicted)	85.3 ± 14.0	85.8 ± 12.4	0.5 (−2.5 to 3.6)	0.728
Nonobstructive defect	34 (56.6)	24 (40.0)		0.007
Abnormal FEV1	31 (51.6)	27 (40.0)		<0.001
Obstructive defect	4 (6.6)	4 (6.6)		1.000
HbA_{1c} (%)	8.8 ± 1.2	7.7 ± 1.2	−1.1 (−1.4 to −0.7)	<0.001
HbA_{1c} (mmol/mol)	67.9 ± 13.7	55.9 ± 15.4	−12.0 (−16.4 to −7.6)	<0.001
BMI (kg/m^2)	32.4 ± 6.1	32.2 ± 6.1	−0.1 (−0.4 to 0.1)	0.249
Waist circumference (cm)	112.0 ± 14.2	112.1 ± 14.1	0.1 (−1.0 to 1.1)	0.880
Bonora equation (cm^2)	253.2 ± 85.8	252.6 ± 85.4	−0.5 (−1.6 to 1.0)	0.273
CUN-BAE (%)	36.3 ± 9.0	36.4 ± 9.0	−0.2 (−0.5 to 0.1)	0.275
Good responders	(*n* = 35)	(*n* = 35)		
FVC (% predicted)	78.5 ± 12.6	83.3 ± 14.7	4.7 (0.5–8.9)	0.029
FEV1 (% predicted)	75.6 ± 15.3	80.9 ± 15.4	5.2 (1.3–9.1)	0.010
PEF (% predicted)	80.4 ± 21.6	89.2 ± 21.0	8.8 (2.6–15.0)	0.007
$FEF_{25–75}$ (% predicted)	62.0 ± 27.2	63.6 ± 23.3	1.6 (−6.2 to 9.5)	0.676
FEV1/FVC (% predicted)	88.3 ± 16.6	89.4 ± 14.4	1.1 (−4.1 to 6.3)	0.668
Nonobstructive defect	20 (57.1)	10 (28.5)		0.022
Abnormal FEV1	18 (51.4)	14 (40.0)		<0.001
Obstructive defect	2 (5.7)	3 (8.5)		0.166
HbA_{1c} (%)	9.1 ± 1.2	7.1 ± 0.7	−2.0 (−2.4 to −1.6)	<0.001
HbA_{1c} (mmol/mol)	71.1 ± 14.0	48.3 ± 8.0	−22.7 (−26.9 to −18.5)	<0.001
BMI (kg/m^2)	32.3 ± 6.4	31.9 ± 6.3	−0.4 (−0.8 to 0.0)	0.103
Waist circumference (cm)	112.1 ± 14.6	112.0 ± 14.5	−0.1 (−1.6 to 1.5)	0.941
Bonora equation (cm^2)	254.3 ± 89.0	253.8 ± 88.5	−0.5 (−2.0 to 1.0)	0.502
CUN-BAE (%)	36.2 ± 9.6	35.8 ± 9.5	−0.4 (−0.9 to 0.1)	0.126
Nonresponders	(*n* = 25)	(*n* = 25)		
FVC (% predicted)	76.9 ± 9.3	77.4 ± 9.3	0.5 (−1.5 to 2.6)	0.586
FEV1 (% predicted)	77.6 ± 11.6	77.6 ± 9.8	0.0 (−2.2 to 2.1)	0.978
PEF (% predicted)	80.5 ± 22.5	82.5 ± 16.4	2.0 (−3.0 to 7.1)	0.413
$FEF_{25–75}$ (% predicted)	71.3 ± 21.3	70.7 ± 19.3	−0.6 (−5.9 to 4.6)	0.800
FEV1/FVC (% predicted)	81.2 ± 8.0	80.9 ± 6.5	−0.2 (−2.4 to 1.9)	0.818
Nonobstructive defect	14 (56.0)	14 (56.0)		1.000
Abnormal FEV1	13 (52.0)	13 (52.0)		1.000
Obstructive defect	2 (8.0)	1 (4.0)		0.763
HbA_{1c} (%)	8.4 ± 1.1	8.6 ± 1.5	0.2 (−0.1 to 0.3)	0.159
HbA_{1c} (mmol/mol)	63.4 ± 12.4	66.5 ± 17.0	3.0 (−0.9 to 7.0)	0.159
BMI (kg/m^2)	32.5 ± 5.8	32.6 ± 5.9	0.1 (−0.1 to 0.4)	0.398
Waist circumference (cm)	111.9 ± 13.9	112.2 ± 13.8	0.2 (−1.3 to 1.8)	0.718
Bonora equation (cm^2)	251.6 ± 82.9	250.9 ± 82.7	−0.6 (−1.9 to 0.6)	0.327
CUN-BAE (%)	37.2 ± 8.3	37.3 ± 8.2	0.1 (−0.18 to 0.4)	0.412

Data are mean ± SD or *n* (%) unless otherwise indicated.

P = 0.010), and PEF (80.4 ± 21.6 vs. 89.2 ± 21.0, *P* = 0.007) values. These changes were similar when pulmonary function was assessed in the entire population. In the control group, spirometric values did not change between baseline and after a follow-up period of 84.5 ± 36.3 days, similar to the group of nonresponders (Supplementary Table 1).

At the end of follow-up, 30 subjects were receiving insulin treatment (50.0%), 4 subjects were receiving GLP-1 receptor agonist treatment (6.6%), and 10 subjects were receiving treatment with insulin plus GLP-1 receptor agonist (16.6%). The spirometric measurements at baseline and after the metabolic improvement period in these three groups did not experience significant changes (Supplementary Table 2).

According to the GOLD criteria, almost one of every two patients at baseline showed a nonobstructive ventilatory defect, which decreased significantly at the end of the intensification period (56.6% vs. 40.0%, *P* = 0.007). When these data were evaluated according to the response to antidiabetic treatment intensification, the improvement was only significant among good responders (57.1% vs. 28.5%, *P* = 0.022) (Table 2). Similarly, the percentage of subjects with an abnormal FEV1 value only decreased significantly among good responders (51.4% vs. 40.0%, *P* < 0.001).

Table 3—Correlations of the absolute changes in HbA_{1c} with changes in spirometric values obtained in the univariate analyses

	Entire population		Good responders		Nonresponders	
	r	*P*	*r*	*P*	*r*	*P*
Δ FVC (% predicted)	−0.127	0.335	0.061	0.728	0.189	0.376
Δ FEV1 (% predicted)	−0.402	0.001	−0.370	0.029	0.243	0.264
Δ PEF (% predicted)	−0.348	0.006	−0.471	0.004	0.292	0.167
Δ $FEF_{25–75}$ (% predicted)	−0.188	0.151	−0.335	0.049	0.274	0.196
Δ FEV1/FVC	−0.165	0.208	−0.409	0.015	0.135	0.539

Δ, absolute change.

Univariate analysis showed that the absolute decrease in HbA_{1c} was correlated to increases in FEV1 ($r = -0.402$, $P = 0.001$ in the entire population; $r = -0.370$, $P = 0.029$ in the responder group) and PEF ($r = -0.348$, $P = 0.006$ in the entire population; $r = -0.471$, $P = 0.004$ in the responder group) (Table 3). In addition, a similar correlation was observed between the absolute decrease in HbA_{1c} and increments in $FEF_{25–75}$ in the responder group ($r = -0.335$, $P = 0.049$). The rest of the correlations observed in the univariate analysis are displayed in Supplementary Table 3.

Finally, stepwise multivariate regression analysis showed that the absolute change in HbA_{1c} (but not age, sex, known years with type 2 diabetes, smoking status, absolute change in the BMI, and the baseline FEV1) independently predicted increased FEV1 ($R^2 = 0.174$) (Table 4). In addition, the absolute change in HbA_{1c}, together with baseline PEF, independently predicted changes in PEF ($R^2 = 0.309$). However, the known duration of type 2 diabetes, but not the amelioration of HbA_{1c}, was related to changes in $FEF_{25–75}$.

CONCLUSIONS

To the best of our knowledge, this is the first study to provide evidence that spirometric maneuvers in patients with type 2 diabetes exhibit significant amelioration after a short improvement in glycemic control. The favorable change in the spirometric parameters was present only in the group of patients who achieved a final reduction of their HbA_{1c} >0.5%, reinforcing the idea that the lungs should be considered as an end target of chronic hyperglycemia. Interestingly, the most sensitive spirometric parameters for this rapid amelioration of metabolic control were associated with intrapulmonary airway caliber and neuromuscular integrity (19,20). Our data, obtained from patients without known pulmonary disease, also suggest that the duration of type 2 diabetes is related with a more irreversible impact in distal obstruction (21). It should be noted that in our study, the group of "good responders" experienced a 6.4% increase in their FEV1 after the 3-month period of metabolic improvement. In the Fremantle Diabetes Study (6), a 10% decrease in FEV1 was associated with a 12% increase in all-cause mortality. Therefore, it seems reasonable to postulate that the impact of the improvement of glycemic control on pulmonary function could have positive clinical consequences. However, larger studies and with longer follow-up are needed to examine this crucial point.

The bronchiolar surfactant layer is involved in maintaining airway stability and caliber, and, when damaged, surfactant proteins migrate into the bloodstream from the alveolar space (22). In this way, the underlying deficit in GLP-1 in type 2 diabetes could be involved in the impairment of airway caliber. The GLP-1 receptor is abundant in the lungs, and it has played a role in the stimulation of pulmonary surfactant production by type II alveolar cells in experimental studies (23,24). In fact, in a rat model with streptozotocin-induced diabetes, the reduced level of surfactant proteins was restored after the administration of liraglutide, a GLP-1 receptor agonist (25). López-Cano et al. (4) have recently communicated how serum concentrations of surfactant protein D are independently associated with an abnormal FEV1 level in obese subjects with type 2 diabetes, suggesting its measurement for identifying patients requiring a pulmonary function examination. Therefore, the potential pulmonary benefit of incretin-based therapies seems particularly relevant, and a clinical trial aimed at answering this question is ongoing (clinical trial reg. no. NCT02889510, ClinicalTrials.gov). However, in our study, antidiabetic therapy with GLP-1 receptor agonist was added only in nine patients, and no conclusion could be obtained.

The role of other antidiabetic drugs in lung function remains unclear, since most studies are cross-sectional, which precludes the establishment of any causal links. In the Copenhagen City Heart Study, which comprised 323 subjects with type 2 diabetes and 68 patients with type 1 diabetes, lung injury was slightly more pronounced in those subjects treated with insulin in comparison with those treated with oral agents or diet (26). Although this finding might suggest a deleterious effect of insulin, it is more reasonable to attribute this relationship to the severity and duration of diabetes rather than to the insulin itself. In fact, type II alveolar cells also express insulin receptors that favor surfactant synthesis (27). In our study, the number of years since the time of type 2 diabetes diagnosis was independently related to changes in $FEF_{25–75}$ in the multivariate analysis.

The contribution of IR in initiating lung abnormalities also deserves attention. First, lung function measures were inversely associated with IR in the British Women's Heart and Health Study (28). In addition, IR was recognized as an independent predictor of altered airway resistance in morbidly obese women without diabetes (29). In a cross-sectional study investigating 196 patients, Vargas et al. (30) evaluated pulmonary function among those receiving metformin or secretagogues. After adjustment for metabolic control and the duration of the disease, the metformin group showed significantly lower differences from the expected values of FVC compared with those treated with secretagogues. In addition, the beneficial effect of metformin on sleep breathing disorders through its capacity to reduce the IR has also been documented. In nonobese rats, metformin administration not only prevented but also reversed the development of apnea episodes (31). In our study, the role of insulin-sensitizer therapies on the respiratory parameters

Table 4—Variables independently related to changes in sprirometric measurements in the multiple regression analysis (stepwise method)

	β	Beta 95% CI	*P*
Δ FVC			
Age (years)	0.336	0.485 (0.125–0.844)	<0.001
Δ BMI (kg/m^2)	−0.185		0.141
Baseline FVC (% predicted)	−0.113		0.382
Known type 2 diabetes duration (years)	−0.105		0.414
Sex	−0.079		0.535
Δ HbA_{1c} (%)	−0.059		0.680
Smoking status*	0.051		0.695
Baseline HbA_{1c} (%)	0.005		0.971
Constant		−25.890 (−47.021 to −4.760)	0.017
R^2 = 0.113			
Δ FEV1			
Δ HbA_{1c} (%)	−0.418	−2.172 (−3.424 to −0.858)	0.001
Baseline FEV1 (% predicted)	−0.218		0.071
Baseline HbA_{1c} (%)	0.199		0.180
Δ BMI (kg/m^2)	−0.156		0.201
Sex	−0.080		0.514
Smoking status*	−0.083		0.595
Age (years)	−0.064		0.597
Known type 2 diabetes duration (years)	0.013		0.914
Constant		−0.178 (−2.392 to 2.036)	0.873
R^2 = 0.175			
Δ PEF			
Baseline PEF (% predicted)	−0.451	−0.287 (−0.430 to −0.145)	<0.001
Δ HbA_{1c} (%)	−0.308	−3.264 (−5.441 to −1.088)	0.004
Baseline HbA_{1c} (%)	0.199		0.148
Smoking status*	0.123		
Sex	0.105		0.349
Known type 2 diabetes duration (years)	0.085		0.449
Δ BMI (kg/m^2)	−0.082		0.468
Age (years)	−0.045		0.687
Constant		24.592 (12.289–36.893)	<0.001
R^2 = 0.323			
Δ$FEF_{25–75}$			
Baseline $FEF_{25–75}$ (% predicted)	−0.510	−0.371 (−0.531 to −0.210)	<0.001
Age (years)	−0.327	−0.934 (−1.555 to −0.313)	0.004
Known type 2 diabetes duration (years)	0.273	0.564 (0.109–1.020)	0.016
Δ HbA_{1c} (%)	−0.166		0.118
Δ BMI (kg/m^2)	−0.172		0.120
Baseline HbA_{1c} (%)	0.133		0.214
Smoking status*	−0.059		0.594
Sex	−0.050		0.647
Constant		70.843 (35.251–106.435)	<0.001
R^2 = 0.403			

β, standardized coefficient; Beta, nonstandardized coefficient; Δ, absolute change. *Never smokers vs. former and past smokers.

seem negligible because neither metformin nor thiazolidinediones were added to treatment during follow-up. The double effect of weight loss on the amelioration of lung function and IR is an important confounding factor when evaluating the effect of treatment intensification in patients with type 2 diabetes. We have tried to avoid this by excluding patients who experienced a BMI reduction ≥2.0 kg/m^2 during the study follow-up. In addition, in the multivariate regression analysis, the absolute change in HbA_{1c} independently predicted increased FEV1. Therefore, our data support the independent and deleterious impact of type 2 diabetes in lung function tests.

In addition, data from the current study reinforce the theory that diabetes not only influence airway caliber, as also the nonobstructive pattern was highly prevalent in the study population and significantly decreased with the improvement of metabolic control. Although measurements of the FEV1 and PEF are similar, the interpretation may differ, either in repeatability or in the interpretation of what is being measured, and their values cannot be interchanged with certainty (19). The PEF represents a direct measurement of airway obstruction, but it is also an index of explosive abdominal and intercostal muscle strength as well as reflecting the elastic recoil of the lung and chest wall (19,20). In this way, the lungs are rich in collagen and elastin fibers, which are crucial proteins of the extracellular matrix, and might be involved in the development of a nonobstructive pulmonary defect. Thus, it has been suggested that nonenzymatic glycosylation of these proteins may contribute to lung damage in chronic hyperglycemia. Previous data evaluated the potential association between advanced glycation end products (AGEs) and lung function in patients with chronic obstructive pulmonary disease, in which higher skin AGE deposition and plasma AGE concentration had been reported (32). Recently, this relation also has been assessed in 1,924 Caucasian subjects without pulmonary disease according to the presence of glucose abnormalities (33). This cross-sectional study demonstrated that skin autofluorescence, a surrogate measurement of AGE, was related to a significant decrease in FVC and FEV1 values, which was aggravated among subjects with type 2 diabetes (33).

There are some potential limitations that should be considered in evaluating the results of our study. First, we evaluated a relatively small number of patients with type 2 diabetes, those willing to participate and those with low baseline pulmonary function, which means that no conclusive clinical consequences can be inferred to the general population of patients with type 2 diabetes. However, the patients included in the study were carefully selected, with confounding factors associated with lung function, such as weight changes, being avoided, and a control group of nonresponders being introduced. Therefore, it could not be argued that after a first experience with spirometric evaluation, subjects became better at performing

the second spirometric assessment. Second, we did not have specific measurements of the physical exercise performed during follow-up, and, therefore, a potential bias related to the improvement of lung function due to increased cardiorespiratory fitness cannot be ruled out. However, the general information on lifestyle measures given to the subjects with diabetes were the same in "responders" and "nonresponders," so that it is unlikely to have had any influence in the results. Third, our study provides evidence only of the beneficial effect of short-term glycemic improvement on functional long parameters, and long-term studies to confirm our findings seem warranted.

In conclusion, a short-term improvement in glycemic control was accompanied by positive changes in spirometric maneuvers in patients with type 2 diabetes. In addition, the improvement of metabolic control was mainly associated with central airway caliber and explosive muscle strength measurements. Although the mechanisms are not yet fully understood, our results draw attention to the need for strategies for identifying patients with type 2 diabetes who are more vulnerable for pulmonary involvement. Additional studies with a wide range of patients with type 2 diabetes and a longer intervention period are needed to confirm the amelioration of lung function after glycemic optimization.

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