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ORIGINAL ARTICLE

Lung function measurements in the prediabetes stage: data from the ILERVAS Project

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Abstract

Aims Patients with type 2 diabetes have been considered a susceptible group for pulmonary dysfunction. Our aim was to assess pulmonary function on the prediabetes stage.

Methods Pulmonary function was assessed in 4,459 non-diabetic subjects, aged between 45 and 70 years, without cardiovascular disease or chronic pulmonary obstructive disease from the ongoing study ILERVAS. A "restrictive spirometric pattern", an "abnormal FEV1" and an "obstructive ventilatory defect" were assessed. Prediabetes was defined by glycosylated hemoglobin (HbA1c) between 5.7 and 6.4% according to the American Diabetes Association criteria.

Results Population was composed of 52.1% women, aged 57 [53;63] years, a BMI of 28.6 [25.8;31.8] kg/m^2, and with a prevalence of prediabetes of 29.9% ($n=1392$). Subjects with prediabetes had lower forced vital capacity (FVC: 93 [82;105] vs. 96 [84;106], $p<0.001$) and lower forced expired volume in the first second (FEV1: 94 [82;107] vs. 96 [84;108], $p=0.011$), as well as a higher percentage of the restrictive spirometric pattern (16.5% vs. 13.6%, $p=0.015$) and FEV1 < 80% (20.3% vs. 17.2%, $p=0.017$) compared to non-prediabetes group. In the prediabetes group, HbA1c was negatively correlated with both pulmonary parameters (FVC: $r=-0.113$, $p<0.001$; FEV1: $r=-0.079$, $p=0.003$). The multivariable logistic regression model in the whole population showed that there was a significant and independent association between HbA1c with both restrictive spirometric pattern [OR = 1.42 (1.10–1.83), $p=0.008$] and FEV1 < 80% [OR = 1.50 (1.19–1.90), $p=0.001$].

Conclusions The deleterious effect of type 2 diabetes on pulmonary function appears to be initiated in prediabetes, and it is related to metabolic control.

Trial registration ClinicalTrials.gov NCT03228459.

Keywords Prediabetes · Pulmonary dysfunction · Forced vital capacity · Forced expiratory volume in the first second · Restrictive spirometric pattern

Introduction

Growing evidence indicates that the lung is a new target organ of type 2 diabetes complications, with consequences in both in respiratory function and the sleep breathing [1]. A meta-analysis of 40 studies on lung function in 3182 patients with diabetes and 27,080 healthy controls [2], and a systematic review of 34 studies support the epidemiological evidence that type 2 diabetes is associated with mild, but significant, ventilation abnormalities, more resembling a restrictive pattern [3]. In addition, the reduced lung function in patients with type 2 diabetes is associated with an increase of fasting plasma glucose, glycated hemoglobin (HbA1c) and diabetes duration [4–6].

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The members of the ILERVAS Project Collaborators are listed in Supplementary Appendix.

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Lung alterations in type 2 diabetes involve the alveolar septa and pleura, with the thickening of the basal membrane, as well as hyalinosis, plasmorrhagia, and insudation [1, 7]. Although this involvement appears to be mediated primarily by pathological mechanisms associated with a restrictive pulmonary pattern, also obstructive mechanisms are implicated [1]. The pathogenic role of several factors such as insulin resistance, leptin resistance, low-grade chronic inflammation, microvascular lung damage, autonomic neuropathy, decreased muscle strength and non-enzymatic glycation of lung proteins have been formally recognized [1, 8–10]. It should be noted that the relation between impaired lung function and type 2 diabetes has been described to be present in the newly diagnosed patients [11]. However, little is known regarding the potential pulmonary dysfunction in subjects with prediabetes [4, 12, 13].

Prediabetes, an intermediate metabolic state between type 2 diabetes and normal glucose metabolism, shows an estimated prevalence of 38.0% in the overall 2011–2012 population in United States adults [14]. In addition, not only a higher incidence of cardiovascular disease but also of diabetic microangiopathy has been described in subjects with prediabetes in comparison with those with normal glucose metabolism [15–17]. On this basis, our aim was to assess pulmonary function in a large cross-sectional study of middle-aged subjects without type 2 diabetes according to the presence of prediabetes.

Materials and methods

Design of the study and description of the study population

A total of 4,650 subjects were recruited between July 2015 and December 2017 from primary health care centers in the in-progress ILERVAS Project, a randomized intervention study to assess the prevalence of subclinical vascular disease in the province of Lleida, Spain (ClinTrials.gov Identifier: NCT03228459) [18]. Participants fulfilled the following inclusion criteria: men and women aged between 45 and 70 years, without any history of vascular disease, and at least one cardiovascular risk factor (hypertension, dyslipidemia, obesity, smoking or a first-degree family member with premature cardiovascular disease). According to the 1998 "Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—The Evidence Report", obesity was defined as a body mass index ≥ 30 Kg/m^2 [19]. The exclusion criteria were presence of diabetes, chronic kidney disease, active neoplasia, and a life expectancy of less than 18 months. No pregnant women were included. The prescribed antihypertensive, lipid-lowering and antithrombotic medications were assessed from prescription- and pharmacy-invoicing databases provided by the CatSalut (Catalan Health Service), which are yearly incorporated into the Information System for the Development of Research in Primary Care database.

History of smoking habit (non-smoker/current/former smoker) was recorded. Smokers who stopped smoking ≥ 1 year prior to recruitment were considered former smokers. Smoking intensity and participant's exposure to tobacco was assessed as the number of packs of cigarettes smoked per year (pack-years). Finally, 72 subjects with previously unknown type 2 diabetes (HbA1c ≥ 48.0 mmol/mol or $\geq 6.5\%$) and 119 subjects with the previous diagnosis of chronic obstructive pulmonary disease were excluded from the final analysis, which was performed in 4459 participants.

Prediabetes was diagnosed in 29.9% ($n = 1392$) of subjects according to the American Diabetes Association criteria (HbA1c between 39 and 47 mmol/mol or 5.7 to 6.4%) [20]. The HbA1c test was performed using a point-of-care instrument [Cobas B 101® (Roche Diagnostics) system], based on latex agglutination inhibition immunoassay methodology that meet the generally accepted performance criteria for HbA1c [21].

Measurement of respiratory function

Forced spirometry was performed using a portable ultrasonic spirometer (Datospir©, Sibelmed). Pulmonary function tests were performed by trained and certified pulmonary technicians in agreement with the American Thoracic Society and European Respiratory Society Guidelines [22]. Subjects were required to perform at least three reproducible measurements, and the output that produced the highest total of forced vital capacity (FVC) and forced expiratory volume in the first second (FEV1) was selected for analysis. A bronchodilator test was not included in the evaluation of lung function. The spirometric parameters were measured as a percentage of the predicted values, and included FVC, FEV1, and the ratio between them (FEV1/FVC). Predicted values based on the European Respiratory Society (ERS) criteria were used [22].

A "restrictive spirometric pattern" was defined by FVC $< 80\%$ of the predicted value with a FEV1/FVC ratio $\geq 70\%$, with a flow–volume curve showing a convex pattern [23]. An abnormal FEV1 was defined as a value lower than 80% of that predicted. An "obstructive ventilatory defect", a disproportionate reduction of maximal airflow in relation to the maximal volume that can be displaced from the lung, was defined by a FEV1/FVC $< 70\%$ [24]. In addition, FVC and FEV1 values were stratified in the next five groups: $< 5\%$, 5–10%, 10–15%, 15–20% and $\geq 20\%$ decrease of predicted value. As forced spirometry was performed only once, a coefficient of repeatability from

the study population in the normoglycemic and prediabetes stages was not available.

Statistical analysis

The statistical analyses were performed using SSPS statistical package (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA). The normal distribution of the variables was evaluated using the Shapiro–Wilk test. Given its skewed distribution, quantitative data are expressed as the median (interquartile range). Comparisons between the two groups were made using the Mann–Whitney *U* test for quantitative variables, and the Pearson's chi squared for categorical variables. The relationship between continuous variables was assessed by the Spearman correlation test. Two multivariable logistic regression models for the presence of a restrictive spirometric pattern and an abnormal FEV1 (FEV1 < 80% of predicted) for development cohort were done including the following confounding factors in the analysis: age, gender, BMI, HbA1c and tobacco pack-years. Calibration of model was assessed using the chi-squared goodness of fit test. All "*p*" values were based on a two-sided test of statistical significance. Significance was accepted at the level of $p < 0.050$.

Results

The main clinical characteristics of the subjects with or without prediabetes are shown in Table 1. Apart from a higher HbA1c, subjects with prediabetes presented a higher proportion of women and were older and with higher BMI than normoglycemic patients. In addition, they presented a higher prevalence of cardiovascular risk factors and were more often treated with antihypertensive, lipid-lowering and antithrombotic medications. No significant differences were observed when spirometric measurements were assessed according beta-blocker treatment (data not shown).

Subjects with prediabetes displayed significantly lower FVC (93 [82;105] vs. 96 [84;106] %, $p < 0.001$) and FEV1 (94 [82;107] vs. 96 [84;108] %, $p = 0.009$) than control participants. In addition, a higher percentage of subjects with

Table 1 Main clinical characteristics, comorbidities, pulmonary function and breathing pattern of the study population according to the presence of prediabetes

	Prediabetes	Non-prediabetes	*p*
n	1392	3067	–
Women, *n* (%)	802 (57.5)	1528 (49.8)	< 0.001
Age (years)	59 [54;64]	57 [52;62]	< 0.001
BMI (Kg/m^2)	29.7 [26.9;33.3]	28.1 [25.2;31.2]	< 0.001
Obesity[a], *n* (%)	509 (36.6)	798 (26.0)	< 0.001
Hypertension, *n* (%)	668 (48.0)	1,139 (37.1)	< 0.001
Dyslipidemia, *n* (%)	781 (56.1)	1,522 (49.6)	< 0.001
Antihypertensives[b], *n* (%)	570 (40.9)	912 (29.7)	< 0.001
Beta-blockers, *n* (%)	122 (8.8)	152 (5.0)	< 0.001
Lipid-lowering agents[c], *n* (%)	314 (22.6)	469 (15.3)	< 0.001
Antithrombotics[d], *n* (%)	56 (4.0)	69 (2.2)	0.001
Current smoker, *n* (%)	307 (22.1)	940 (30.6)	< 0.001
Tobacco pack-years	20 [10;34]	21 [10;32]	0.776
HbA1c (%)	5.8 [5.7;6.0]	5.4 [5.2;5.5]	< 0.001
HbA1c (mmol/mol)	40 [39;42]	36 [33;37]	0.000
FVC (% predicted)	93 [82;105]	96 [84;106]	< 0.001
FEV1 (% predicted)	94 [82;107]	96 [84;108]	0.009
FEV1/FVC	79 [74;83]	78 [74;82]	0.206
Restrictive spirometric pattern, *n* (%)	229 (16.5)	414 (13.5)	0.011
Obstructive ventilatory defect, *n* (%)	170 (12.2)	366 (11.9)	0.804

Data are expressed as a median [interquartile range] or *n* (percentage)

BMI body mass index, *HbA1c* glycosylated hemoglobin, *FVC* forced vital capacity, *FEV1* forced expired volume in the first second

[a]Obesity was defined as a BMI ≥ 30 Kg/m^2

[b]Antihypertensive treatment agents included ACE inhibitors, diuretics, ARA II, beta-blockers, calcium antagonists and other antihypertensives

[c]Lipid-lowering drugs included statins, fibrates, ezetimibe and omega-3 fatty acids

[d]Antithrombotic treatment comprised the use of anticoagulant or antiplatelet agents

restrictive spirometric pattern (16.5% vs. 13.7%, $p=0.013$) and FEV1 < 80% (20.3% vs. 17.3%, p = 0.017) were found among subjects with prediabetes. However, no differences in FEV1/FVC ratio or the prevalence of an obstructive ventilatory pattern were observed between groups. Participants with prediabetes also exhibited significantly higher rates of FVC and FEV1 reductions ≥ 15% (Table 2).

A positive correlation between HbA1c and age ($r=0.167$, $p<0.001$) and BMI ($r=0.209$, $p<0.001$) was found in the bivariate analysis. In addition, in the prediabetes group, a significant but negative correlation between HbA1c and pulmonary parameters (FVC: $r=-0.113$, $p<0.001$; FEV1: $r=-0.079$, $p=0.003$) (Fig. 1) was observed. However, this relationship was not detected among participants without prediabetes.

When the whole population was assessed, the multivariable logistic regression model showed that there was a significant and independent association between HbA1c (together with older age, male gender and obesity) with both restrictive spirometric pattern [OR = 1.42 (1.10–1.83), $p=0.008$] and FEV1 < 80% [OR = 1.50 (1.19–1.90), $p=0.001$] (Table 3). Similar to the bivariate analysis, the significant association between HbA1c and pulmonary disease persisted among patients with prediabetes but disappeared when participants without prediabetes were analyzed alone (Tables S1 and S2).

Table 2 Prevalence of participants with predetermined FVC and FEV1 declines according to the presence of prediabetes

	Prediabetes	Non-prediabetes	*p*
Decline in FVC value			
5.0–9.9%, *n* (%)	163 (11.7)	342 (11.2)	0.079
10.0–14.9%, *n* (%)	169 (12.2)	328 (10.7)	0.012
15.0–19.9%, *n* (%)	133 (9.6)	272 (8.9)	0.067
≥ 20%, *n* (%)	285 (20.5)	500 (16.4)	< 0.001
Decline in FEV1 value			
5.0–9.9%, *n* (%)	151 (10.9)	351 (11.5)	0.845
10.0–14.9%, *n* (%)	126 (9.1)	291 (9.5)	0.813
15.0–19.9%, n (%)	135 (9.7)	242 (7.9)	0.016
≥ 20%, *n* (%)	280 (20.2)	525 (17.2)	0.006

FVC forced vital capacity, *FEV1* forced expired volume in the first second

Discussion

In the present study, we provide first evidence in Caucasian population that in the prediabetes stage the lung function is already impaired. We have found in both genders that not only FVC but also ventilatory patterns and abnormal FEV1 occur in prediabetic population. Overall, our data reinforce the idea that pulmonary dysfunction is a progressive defect across glucose abnormalities, appearing in the prediabetes stage and increasing when type 2 diabetes appears. In this regard, it should be noted that HbA1c was negatively and independently related to pulmonary parameters in the group of patients with prediabetes.

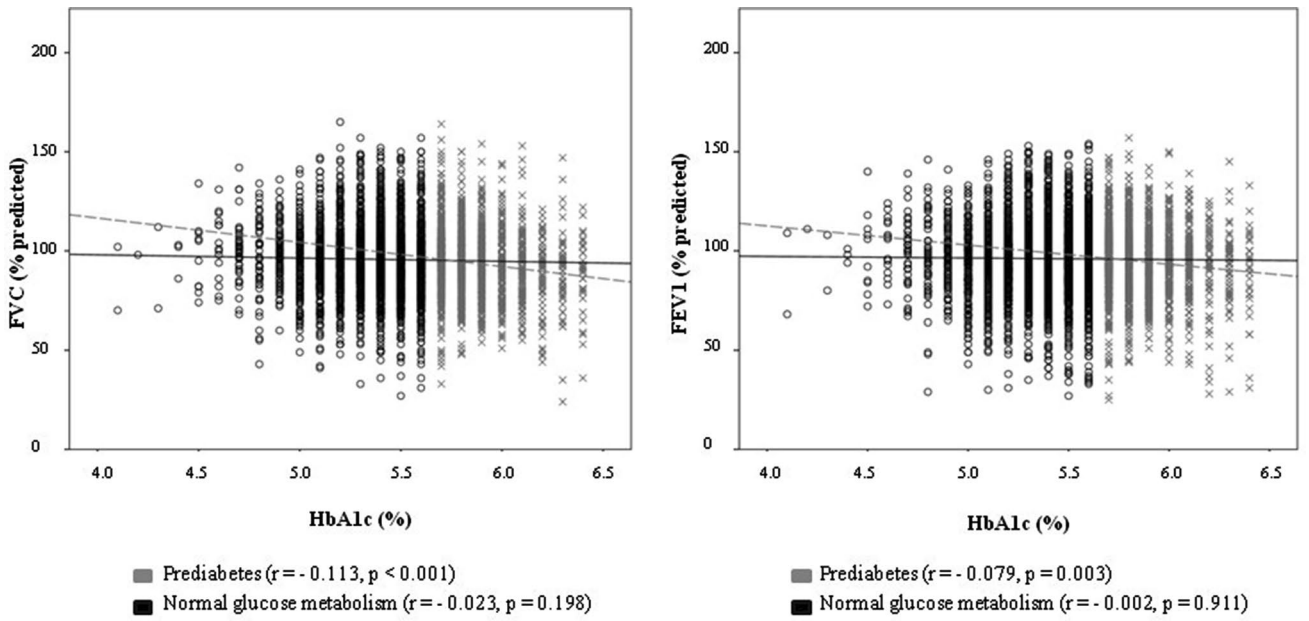

Fig. 1 Scatter plot showing the linear correlation between pulmonary parameters and glycosylated hemoglobin according to glucose abnormalities

Table 3 A multivariable logistic regression model for the presence of restrictive spirometric pattern and FEV1 < 80% predicted for development cohort in the whole population

Restrictive spirometric pattern	OR (95% CI)	*p* value
Age (years)	1.04 (1.02–1.06)	< 0.001
Gender		
Women	Reference	
Men	1.79 (1.39–2.31)	< 0.001
BMI (Kg/m^2)		
< 25	Reference	
25–30	1.19 (0.84–1.68)	0.322
≥ 30	2.22 (1.59–3.10)	< 0.001
HbA1c (%)	1.45 (1.05–2.01)	0.026
Tobacco pack-years	1.00 (0.99–1.01)	0.318
Hosmer–Lemeshow test of fit	–	0.188
Area under the ROC curve	0.65 (0.62–0.68)	< 0.001
FEV1 < 80%		
Age (years)	1.03 (1.01–1.04)	0.005
Gender		
Women	Reference	
Men	1.43 (1.15–1.77)	0.001
BMI (Kg/m^2)		
< 25	Reference	
25–30	0.88 (0.67–1.15)	0.336
≥ 30	1.27 (0.97–1.66)	0.087
HbA1c (%)	1.46 (1.09–1.94)	0.011
Tobacco pack-years	1.03 (1.02–1.03)	< 0.001
Hosmer–Lemeshow test of fit	–	0.863
Area under the ROC curve	0.66 (0.64–0.69)	< 0.001

OR odds ratio, *CI* confidence interval, *BMI* body mass index, *HbA1c* glycosylated hemoglobin, *FEV1* forced expired volume in the first second

The lung dysfunction in type 2 diabetes is a relatively usual but generally under-recognized complication [1–3]. As bronchial circulation transitioned to a dense network of pulmonary capillaries at the level of the alveolar ducts, and the pulmonary parenchyma is rich in collagen and elastin fibers, it has been suggested that the histological disorders promoted by hyperglycaemia may induce ventilatory dysfunction [1, 2]. In fact, physio-pathological mechanisms present in prediabetes (i.e. insulin resistance, inflammation, leptin resistance, microangiopathy, and increased advanced glycation end-products) have been recognized to mediate the negative impact on lung function in type 2 diabetes [1, 15, 25–27].

It could be argued that the slight decrease in pulmonary parameters observed in subjects with prediabetes, although statistically significant, could be clinically irrelevant. However, it should be emphasized that not only in general population FEV1 was a statistically significant predictor for all-cause mortality after 29 years of follow-up, but also that in subjects with type 2 diabetes a 10% decrease in FEV1 has also been described as an independent predictor of all-cause mortality [28, 29]. Similarly, in another lung disease as idiopathic pulmonary fibrosis, a percent-predicted FVC decline of 5–10% conferred a more than twofold increase in the risk of mortality over the subsequent year [30]. Therefore, cost-effectiveness studies addressed to determine the potential usefulness of the assessment of respiratory parameters in the routine visits of individuals with prediabetes are needed. The planned 10-year follow-up of the ILERVAS Project will give us more data about the deleterious relation of prediabetes, lung function impairment and the incidence of cardiovascular events [18].

The potential deleterious effect of insulin resistance (IR) in pulmonary measurements deserves attention. Using indirect measures of IR, the *Normative Aging Study* showed that fasting insulin was negatively associated with FVC and FEV1 in nondiabetic males after adjusting for BMI, age, smoking, and physical activity [31]. The *British Women's Heart and Health Study* also showed a linear opposite association between IR and pulmonary function measurements such as FEV1 and FVC in non-diabetic women [32]. Similarly, our group provided evidence that IR, measured through the homeostasis model assessment was an independent determinant of pulmonary function in non-diabetic morbidly obese women, suggesting that the metabolic pathways linked to IR are crucial in initiating pulmonary abnormalities before the development of the overt type 2 diabetes [33]. One of the advocated mechanisms to explain the lung function impairment in subjects with IR is the weakening of skeletal muscle strength due to mitochondrial impairment [34]. In this regard, when the skeletal muscle strength was measured with a handgrip dynamometry in 655 men from the *Normative Aging Study*, a negative association with fasting insulin levels was observed [35]. Two other explanations accounting for the negative impact of IR on the lung may be related to systemic inflammation and direct effects on lung structure and function. Data from 9581 nonsmoking healthy Korean male subjects showed that the lowest FVC and FEV1 (% predicted) quartiles were independently associated with abdominal obesity, higher levels of high-sensitive C-reactive protein and IR [36]. In addition, insulin increases the proliferation of primary human airway smooth muscle cells, and its contractility and hyperresponsiveness upon insulin exposure [37, 38]. In fact, baseline IR has been associated with an increased risk of developing wheezing and asthma-like symptoms after a 5-year follow-up period [39]. Finally, insulin receptors in type II alveolar epithelial cells mediate the cellular uptake of glucose, which is a major substrate for the biosynthesis of surfactant phospholipids [40]. In this regard, López-Cano et al. [41] have recently described how the measurement of circulating levels of surfactant protein

D can be contemplated as a serum biomarker of lung impairment in patients with type 2 diabetes.

Our results add new information to the growing evidence of pulmonary dysfunction in prediabetes. In a cross-sectional study of 1237 asymptomatic healthy adults who underwent annual medical checkups, prediabetes was significantly associated with a FVC < 80% of predicted, even after adjustment for relevant confounding factors [13]. More recently, Kopf et al. [42] have communicated a significantly increased restrictive lung disease in 68 patients with prediabetes in comparison with 48 normoglycemic subjects from Germany. By contrast, in a cohort of 55 subjects from Mexico City, no differences in FVC or FEV1 were detected between normoglycemic subjects and patients with prediabetes [43].

In addition, lung dysfunction may be also a contributing risk factor for glucose abnormalities. Thus, FVC has been associated with an increased risk for the development of prediabetes in 560 Japanese males [12]. Similarly, restrictive, but not obstructive ventilatory pattern was independently associated with the progression from normal fasting glucose to prediabetes and preceded the development of type 2 diabetes among 9461 Koreans [44]. Also, in the *COPD Genetic Epidemiology* (COPDGene) study, over 21,519 person-years of follow-up, a cluster of pulmonary indicators was associated with incident type 2 diabetes [45].

Focusing on the 29,9% prevalence of prediabetes in our population, our results differs from the Di@bet.es study, that reported a global prevalence of prediabetes in Spanish population older than 18 years of 14.8% (3.4% for impaired fasting glycemia, 9.2% for impaired glucose tolerance, and 2.2% with combined impaired fasting glycemia and impaired glucose tolerance), increasing to 21.9% in men and 18.7% in women aged 61–75 years [46]. Discordances in prevalence must be explained by the characteristics of the evaluated populations, including age range and obesity degree, and because previous studies did not use HbA1c to diagnose prediabetes.

This study has some limitations that need to be considered. Certainly, the cross-sectional nature of the study does not allow us to establish causality. However, our results support the idea that lung function impairment is already detected in very early stages when IR rather that an overt diabetes is the predominant underlying mechanism. Second, we have no data about the duration of prediabetes in our population, a factor that would help us to better interpret our results. Third, and similar to the diagnosis of pulmonary patterns, three definitions for the diagnosis of prediabetes are accepted by the American Diabetes Association [20]: (1) fasting plasma glucose between 100 and 125 mg/dl (impaired fasting glucose), (2) 2-h plasma glucose between 140 and 199 mg/dl (impaired glucose tolerance), and (3) HbA1c between 5.6 and 6.4%. Although not all tests necessarily detect prediabetes in the same subject, our study has been able to identify 2 well-defined populations in which to compare spirometric results. Finally, we cannot estimate pulmonary function based on post-bronchodilator spirometry in our population as this test was not included in the ILERVAS project.

In summary, lung function in prediabetes is modestly decreased and related with metabolic control. So, the present work offers a better understanding of the prodromal stage underlying ventilatory dysfunction in type 2 diabetes. Additional studies to identify those subjects with prediabetes that are more vulnerable to involve the lung function, and factors that accelerate its progression to more severe respiratory patterns, are needed.

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Compliance with ethical standards

Conflict of interest All author(s) declare that they have no conflict of interest.

Ethical approval The protocol was approved by the Arnau de Vilanova University Hospital ethics committee (CEIC-1410). Additionally, the study was conducted according to the ethical guidelines of the Helsinki Declaration and Spanish legislation regarding the protection of personal information was also followed.

Informed consent Informed consent was obtained from all individual participants included in the study.

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