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Original Article

Decline of the lung function and quality of glycemic control in type 2 diabetes mellitus

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ABSTRACT

Objective: The aim of this study was to verify to which extent in type 2 diabetes mellitus respiratory function and respiratory muscle efficiency decline over time in relation to the quality of glycemic control (GC).
Methods: Forty-five non-smoker diabetic patients without pulmonary diseases performed a complete respiratory function assessment at baseline and after a follow-up of 4.9 ± 0.6 years. The respiratory muscle efficiency was assessed by maximal inspiratory pressure (MIP) and maximum voluntary ventilation (MVV). Patients with an average yearly value of glycosylated hemoglobin ≥ 7.5% at least in two years during follow-up were considered to have a poor GC.
Results: Residual volume and pulmonary diffusing capacity significantly declined over time in the whole sample of patients ($p = 0.049$ and 0.025, respectively), but without difference between patients with poor (n. 12) and good (n. 33) GC. MIP declined in patients with poor GC (from 83.75 ± 32.42 to 71.16 ± 30.43% pred), and increased in those with good GC (from 76.22 ± 26.00 to 82.42 ± 30.34% pred), but the difference between groups was not significant ($p = 0.091$). Finally, MVV significantly declined in patients with poor GC (from 70.60 ± 25.49 to 68.10 ± 18.82% pred) and increased in those with good GC (from 66.40 ± 20.39 to 84.00 ± 23.09% pred) with a significant difference between the two groups ($p = 0.003$).
Conclusion: These results show that, in type 2 diabetic patients, respiratory muscle efficiency, but not lung volumes and diffusing capacity, might suffer from a poor GC over time.

1. Introduction

An association between diabetes mellitus and impaired lung function has been frequently observed and various respiratory functional disorders have been described in patients with either type 1 or type 2 diabetes mellitus [1]. Mechanisms potentially explaining the association between lung impairment and diabetes are microangiopathy of the alveolar capillaries and pulmonary arterioles, chronic inflammation, autonomic neuropathy involving the respiratory muscles, loss of elastic recoil secondary to collagen glycosylation of lung parenchyma, hypoxia-induced insulin resistance and low birth weight [2].

A significant time-related effect of lung injury caused by diabetes mellitus has also been detected in some longitudinal studies, showing an accelerated decline in lung function in patients with diabetes [3,4]. However, in two other longitudinal studies, the Copenhagen City Heart Study [5] and the Normative Aging Study [6], lung function declined comparably in non-diabetic and diabetic subjects.

In all these studies only some functional parameters have been monitored during the follow-up, particularly dynamic lung volumes, whereas the pulmonary diffusing capacity for carbon monoxide (DLCO) and the static lung volumes, such as residual volume (RV) and total lung capacity (TLC) have not. Similarly, the respiratory muscle efficiency has been rarely studied in patients with diabetes mellitus. The respiratory muscle strength has been found reduced both in type 1 [7,8] and in type 2 diabetic patients [9] and this impairment might to some extent explain the restrictive functional pattern typically observed in patients with diabetes mellitus [10].

Further complicating the issue is the existence of conflicting data about the relationship between poor glycemic control and reduction in dynamic lung volumes [11–13]. A recent metaanalysis found that the glycemic state did not appear to influence the association between reduced lung function and diabetes mellitus [10].

This longitudinal study was designed to verify in patients with type 2 diabetes mellitus to which respective extent lung volumes, pulmonary

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; DLCO, pulmonary diffusing capacity for carbon monoxide; FVC, forced vital capacity; GC, glycemic control; HbA1c, glycosylated hemoglobin; KCO, coefficient of diffusion; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; MVV, maximum voluntary ventilation; PASE, physical activity scale for the elderly; RV, residual volume; TLC, total lung capacity.

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diffusing capacity and respiratory muscle efficiency decline over time and whether the decline of the lung function is related or not to the quality of the glycemic control. Since respiratory and skeletal muscle weakness are strictly related [14], general physical activity has also been assessed in all the patients and related to glycemic control and muscle efficiency.

2. Materials and methods

2.1. Patients and study design

We studied 45 patients (28 males and 17 females) with type 2 diabetes mellitus, diagnosed according to standardized criteria [15]. We had the opportunity of following up patients previously enrolled in another study on the respiratory effects of diabetes [9] and 45 of them agreed to be recalled in order to control their respiratory function. Criteria of exclusion from the study were current history of smoking and history or functional-radiological evidence of lung disease.

The study was in accordance with the recommendations of the Helsinki Declaration. All subjects gave informed consent to participate in the study. Considering that neither interventions nor invasive procedures had to be performed on patients, the local Ethical Committee judged that the study protocol conformed to the Institution policy and did not need a formal discussion.

At baseline the patients underwent a complete respiratory function assessment which was repeated at the end of the follow-up. Patients had to be in stable metabolic condition, as reflected by normal glycemic 6-point profile and absence of glycosuria, in the week prior to each assessment. The physical activity scale for the elderly (PASE) was assessed at the end of the follow-up as a measure of the physical activity [16]. During the follow-up, the patients were monitored every 3 months by a clinical visit and measurements of glycosylated hemoglobin (HbA1c) were performed to evaluate the quality of the metabolic control. Patients with an average yearly value of HbA1c $\geq$7.5% at least in two years during the follow-up were considered to have a poor glycemic control. We remind that the HbA1c value of 7.5% is associated with the lowest hazard for all-cause mortality [17] and, then, can be considered a reasonable cut off for categorizing the quality of glycemic control. All patients were treated with oral antidiabetic agents and 9 of them also with insulin for all the follow-up period. Lifestyle interventions, such as diet and physical activity, were strengthened in all patients during the follow-up and the dosage of the antidiabetic drugs was eventually adjusted.

2.2. Respiratory function assessment

The respiratory function assessment was performed by using a computerized system (Sensor Medics Vmax 229; SensorMedics Corporation, Yorba Linda, CA, USA). Lung volumes and flows had to meet the American Thoracic Society criteria of acceptability and reproducibility of curves [18], whereas DLCO was measured by the single-breath method [19]. The coefficient of diffusion (KCO), derived from DLCO divided by lung volume, was considered as a measure of diffusion per unit of alveolar volume. All values were expressed as percentage of a normal reference population.

The respiratory muscle strength and functioning was evaluated by the same computerized system measuring maximal inspiratory and expiratory pressures (MIP, MEP) and maximum voluntary ventilation (MVV).

While comfortably sitting and wearing a nose clip, the patient had to seal the lips firmly around a rubber mouthpiece with flanges. An occlusion valve, distal to the pneumotachograph, could be occluded at the beginning of the manoeuvre. A small hole contained in the valve allowed an air leak and this prevented the patient from generating pressure by using the cheek muscles. To measure MIP, the patient was instructed to exhale slowly and completely up to RV and then to pull in as hard as possible against the occluded valve. The inspiratory pressure had to be maintained for at least 1.5 sec, and the largest negative pressure sustained for at least 1 sec was recorded. The maximum MIP value of at least three different manoeuvres that varied by less than 10% was reported. For MEP measurement, the patient had to inhale completely up to TLC and then to push (or blow) as hard as possible against the occluded valve. The expiratory pressure had to be maintained for at least 1.5 sec, and the largest positive pressure sustained for at least 1 sec was recorded. The maximum MEP value of at least three different manoeuvres that varied by less than 10% was reported.

In order to measure MVV, the patient was instructed to make at least three resting tidal breaths and then to breathe as deeply and rapidly as possible over a 12-sec period with a tidal volume greater than the own resting tidal volume. The breathing frequency had to be about 90 breaths/min.

2.3. Statistical analysis

Unpaired t-test or chi-square test, as appropriate, were used to evaluate differences between groups. Paired t-test was used to assess differences in respiratory function indexes measured at baseline and at the end of follow-up. Differences between groups in changes of recorded variables from baseline to follow-up were assessed by the analysis of variance (ANOVA) for repeated measures having the group membership as the grouping factor. A p-value <0.05 was assumed as significant.

3. Results

The follow-up lasted (mean $\pm$ SD) 4.9 $\pm$ 0.6 years. The main characteristics of the patients are reported in Table 1. The patients were, on average, overweight at the beginning of the study and their body mass index (BMI) remained substantially unchanged at the end of follow-up. Also hemoglobin did not change during the follow-up. On the contrary, the number of patients with diabetic complications increased, particularly those with cardiovascular comorbidity. However, no patients had signs and symptoms of an overt heart failure such to decrease the cardiac output at the end of follow-up.

Changes over time in the respiratory function are reported in Table 2. Both dynamic (forced vital capacity: FVC) and static (RV and TLC) lung volumes were normal at baseline. Only RV significantly declined during the follow-up. Similarly, DLCO was normal at baseline and significantly decreased at the end of follow-up. Also KCO, a measure of diffusion per unit of alveolar volume, significantly decreased during the follow-up, thus showing that the decline of DLCO did not simply reflect a change in lung volume. Both respiratory muscle strength and functioning were slightly reduced at baseline, being less than 80% of predicted values. MIP and MEP did not significantly change during the follow-up whereas MVV surprisingly improved at the end of follow-up.

The HbA1c level was on average reduced during the follow-up, from 7.18% in the first year, to 6.65% in the last year. According to the criteria mentioned above, the quality of the glycemic control during the follow-

Table 1
Patient characteristics at the beginning of the study (baseline) and at the end of the follow-up.

	At baseline	After follow-up
N.	45	
Gender, M/F	28/17	
Age, years	63.81 $\pm$ 6.36	68.79 $\pm$ 8.35
BMI, kg/m^2	29.46 $\pm$ 4.99	29.20 $\pm$ 5.08
Hemoglobin, g/dL	13.49 $\pm$ 1.28	13.57 $\pm$ 1.46
Duration of disease, years	15.88 $\pm$ 7.94	21.19 $\pm$ 11.58
Neuropathy, n.	3	8
Nephropathy, n.	3	6
Rethinopathy, n.	4	6
Cardiovascular disease, n.	7	19
PASE score		116.26 $\pm$ 55.41

Values are expressed as mean $\pm$ SD.
BMI: body mass index; PASE: physical activity score for the elderly.