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Diabetes Mellitus and Airway Obstruction: Is there an Association?

Lamprini Tina[1], Panagiotis Andriopoulos[2*] and Panagiotis Geogantas[3]

[1]*Respiratory Department, Sparta General Hospital, Sparta, Greece*
[2]*University of Peloponnese, Sparta, Greece*
[3]*Department of Internal Medicine, Sparta General Hospital, Sparta, Greece*

Abstract

Background: The incidence of Diabetes mellitus is increasing rapidly, with type 2 diabetes making up to 90% of the cases. Whether diabetes interferes with lung function is unknown. Aim of this study is to evaluate lung function of diabetic patients.

Materials and Methodology: A cohort of diabetic patients was randomly selected. History and type of diabetes, glycemic control, comorbidities, smoking history was recorded; clinical examination and spirometry was performed.

Results: 62 individuals with type 2 diabetes were enrolled (36 men), aged 64.5 (10.7 Standard Deviation (sd)), Body Mass index 30.1 (6.4 sd), 9.2 years of disease (9.4 sd), HbA1c 7.02% (1.25 sd, 53 mmol/mol, 5.2 sd). 67.7% had arterial hypertension, 14.5% Coronary Heart disease, 54.8% hyperlipidaimia and 16.1% had history of asthmatic symptomatology without any respiratory follow up. 48.3% had smoking history (46.2 pack years) and 20.9% were current smokers. 19.3% had normal spirometry, 30.6% COPD (73.4% mild disease), 6.4% restrictive disorder, 3.2% combined disorder and 40.2% small airway disease (FEF25-75%<60% predicted). In total 74% had obstructive disorder ($p<0.001$). There was no correlation between sex, smoking, years of diabetes, glycemic control, antidiabetic medications or other comorbidities and obstructive pattern in the spirometry. No patient had evaluated lung function before.

Conclusion: These results prompt to the need of a large cohort study to evaluate the state and evolution of respiratory function in patients with diabetes. The existence of obstructive disorder in the majority of our patients may suggest an endothelial inflammatory process that leads to airway obstruction as a complication of type II diabetes

Keywords: Airway obstruction; COPD; Diabetes; Lung function; Small airway disease; Spirometry

Introduction

Diabetes mellitus is a disorder with major microvascular and macrovascular debilitating effects [1]. Well described complications include diabetic retinopathy, nephropathy, cardiovascular disease and neuropathy. These complications are attributed to biochemical and structural changes of basement membrane proteins in different organs. Chronic hyperglycemia of the diabetic state leads to glycosylation of serum and tissue proteins and to the formation of advanced glycosylation products [2]. The disposition of such products within tissues has proinflammatory effects, leading eventually to microangiopathy such as glomerular hypertrophy and nephropathy or proliferation of retinal endothelial cells and retinopathy [3].

Whether the impact of diabetes in microvasculature affects also respiratory function in not very clear yet. Epidemiological studies have found decreased lung function in such patients [4-6]. Several mechanisms have been proposed: 1. Microangiopathy of alveolar capillaries and pulmonary arterioles. 2. Chronic low grade inflammation [6]. 3. Autonomous neuropathy involving respiratory muscles [7]. 4. Loss of elastic recoil due to collagen glycosylation of lung parenchyma [8]. 5. Hypoxia-induced insulin resistance [9]. A recent meta- analysis review linked impaired lung function with insulin resistance but concluded that exact underlying pathophysiological mechanisms remain to be identified [10].

In this pilot study we evaluated the lung function of patients with type 2 diabetes. Aim of the study was to identify any respiratory disorder and to evaluate potential risk factors that may have induced or precipitated such a reduction of lung function.

Methods

A cohort of patients from the diabetes clinic of our hospital was randomly selected. 62 individuals with type 2 diabetes were enrolled. The diagnosis of diabetes was made before the entrance to the study according to ADA criteria [11]. A detailed medical history had been recorded in the diabetes clinic, including years of the disease, levels of glycated hemoglobin (HbA1c), body mass index (BMI), treatment, comorbidities such as arterial hypertension, coronary heart disease, heart failure, hyperlipidaimia and stroke. During the examination a detailed smoking history and any history of obstructive lung disease (asthma or chronic obstructive pulmonary disease (COPD)) was recorded. Clinical examination and spirometry for evaluation of lung function was performed, according to American Thoracic Society criteria [12] in all patients using computerized spirometer (Zan100 nSpiring Health Inc) of the respiratory department. No patient had ever before evaluated lung function with spirometry.

All tests were conducted in standing posture before and after reversibility test with inhalation of 400 mcg of salbutamol. Parameters used in the study were Forced Expiratory Volume in 1 second (FEV1),

***Corresponding author:** Panagiotis Andriopoulos, Orthias Artemidos & Plataion, Sparta 23100, Greece, Tel: 30697339814; E-mail: andriopa@otenet.gr

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Forced Vital Capacity (FVC), Forced expiratory volume percentage (FEV1/FVC) and Forced Expiratory Flow between 25%-75% (FEV 25-75) and were evaluated according to ECCS reference values.

Patients with COPD were classified according to the severity of airflow limitation using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [13,14]: All patients with FEV1/FVC <70% were classified as 1. Mild COPD : FEV1 >80% of predicted. 2. Moderate COPD: 50%<FEV1<80%. 3. Severe COPD: 30%<FEV1<50%. 4. Very Severe COPD: FEV1<30%.

Patients were classified as having a restrictive disorder when both FEV1 and FVC were reduced with FVC<80% of predicted and normal FEV1/FVC ratio. Combined disorder was considered when patients reduced FEV1, FVC<80% and FEV1/FVC ratio <70% in spirometry. Finally patients were classified as having small airway disease when reduction of forced expiratory flow at 25-75% (FEF25-75%) was <60% of the predicted and FEV1/FVC ratio in the low to normal range [15]. Stratified analysis was performed between the different groups of patients with obstruction and normal spirometry, in two steps. First the between the three different categories of patients (normal spirometry, COPD and small airway disease) and then between patients with normal spirometry and obstruction. The number of patients with restrictive or combined disorder was too small to be included in the stratified analysis.

Data are presented as mean ± SD unless stated otherwise. All analyses were performed with SPSS software version 22. $p<0.05$ was considered statistically significant in the analyses. Analysis of variance and Pearson's chi square test were used.

Written informed consent was obtained by all patients and the study was approved by the Sparta General Hospital ethics committee.

Results

Sixty two patients (36 men) with type 2 diabetes were enrolled in the study. Table 1 summarizes baseline data and medical history of the patients. Patients had obesity (mean BMI 30.1), arterial hypertension (67.7%) and hyperlipidemia (54.8%). Thirty patients had a smoking history (46.2 pack years) and 13 of them were still smoking (20.9%). 16.1% reported symptoms that may have been caused by bronchial asthma sometime in the past, without any regular treatment or respiratory follow up. Details on the diabetes status of the cohort are shown in Table 2 Patients had a borderline acceptable HbA1c in their last measurement (7.02%), 6 patients (9.6%) had mild renal failure (glomerular filtration rate (GFR) 60-89 ml/min/1.73 m^2) and 4 (6.4%) diabetic retinopathy. The majority of the patients controlled their diabetes with oral medications (metformin and other agents).

Patient Data	
Number of Patients	62 (36 male)
Age	64.5 (10.7)
Body Mass Index (BMI)	30.1 (6.4)
Arterial Hypertension	67.7%
Coronary Heart Disease	14.5%
Hyperlipidaemia	54.8%
Reported History of Respiratory Symptoms	16.1%
Use of Neuroleptic Agents	6.4%
Smoking Status	20.9% current smokers
Smoking History	48.3%
Pack Years of Past and Present Smokers	46.2 years (34.02)

Table 1: Summarizes patient data, comorbidities and any reported smoking history. Data are presented as mean (standard deviation) and percentages. Half of the cohort had a smoking history.

Spirometry results are shown in Table 3 19.3% (12 patients) had normal spirometry, 30.6% (19 patients) had COPD, 6.4% (4 patients) restrictive disorder, 3.2% (2 patients) combined disorder and 40.3% (25 patients) had small airway disease. In total 74% (46 patients) had some kind of obstructive disorder ($p<0.001$), which was diagnosed for the first time during the study, although we cannot be certain when the disorder had begun. Stratified analysis for comorbidities and diabetes status, history and complications was performed. No statistically significant correlation between COPD or small airway disease in the spirometry results and smoking status and history, BMI, years of diabetes, glycemic control, antidiabetic medications and comorbidities was recorded. Patients with normal spirometry were younger than those with COPD or small airway disease (mean age 58.1(8.8 sd) *vs* 67.1(11.2 sd) for COPD patients and 64.8 (11.5 sd) for small airway disease, p=003). All analysis were performed in two steps. First we compared the three groups, (patients with normal spirometry, patients with COPD and patients with small airway disease (Table 4) and then patients with normal spirometry *vs* all patients with obstructive pattern with similar results.

Discussion

Our study differentiates from what other studies have shown so far about patients with diabetes and pulmonary function tests. Previous cross-sectional studies have also showed that adults with diabetes have decreased FEV1 and FVC compared with adults without diabetes,

History of Diabetes	
Years of Diabetes	9.2 (9.4)
HbA1c	7.02% (1.25 sd)
Renal Impairment	9.6%
Diabetic Retinopathy	6.4%
Diabetic Foot	1.6%
Medication for diabetes 1. Metformin 2. Metformin+DPP4 inhibitors 3. Metformin+GLP1 agonists 4. Metformin+Sulfonylurea 5. DPP4 inhibitors 6. Insulin+oral agents 7. Insulin combinations	 17% 27% 3.2% 11.2% 6.4% 29% 6.2%

Table 2: Presents the status of diabetes in the patient cohort. The most recent HbA1c measurement was used. 9.6% of the patients had mild renal failure (GFR: 60-89 ml/min/1.73 m^2). Inhibitors of dipeptidyl peptidase 4 (DPP4 inhibitors) were saxagliptin vildagliptin sitagliptin. Glucagon like peptide-1 (GLP1) agonists were exenatide and liraglutide. Sulfonylureas used were gliclazide and glimepyride. Patients used basal insulin (detemir and glargline) with oral agents in various combinations. Insulin combinations stand for basal and bolus regiments and mixed combinations of nph or protamine and regular or fast acting insulin.

Spirometry Results	
Normal Spirometry	19.3% (12)
COPD 1. Mild 2. Moderate 3. Severe 4. Very Severe	30.6% (19) 73.6% (14) 2 patients 2 patients 1 patient
Restrictive Disorder	6.4% (4)
Combined Disorder	3.2% (2)
Small Airway Disease	40.3% (25)

Table 3: Shows the post reversibility spirometry results of the patients. Data are presented as percentages (sd).

Spirometry Results and Patients Characteristics				
	Normal spirometry 12 patients	COPD 19 patients	Small airway disease 25 patients	
Age	58.1 (8.8)	67.1 (11.2)	64.8 (11.5)	***p=003***
Body Mass index (BMI)	33.04 (6.3)	29.3 (66.3)	27.4 (3.2)	p=0.32
Arterial Hypertension	9/12	15/19	13/25	p=0.26
Coronary Heart Disease	1/12	5/19	2/25	p=0.37
Hyperlipidaemia	5/12	11/19	14/25	p=0.62
Reported History of Asthmatic Aymptoms	3/12	4/19	3/25	p=0.64
Use Oof Neuroleptic Agents	1/12	2/19	0/25	p=0.067
Current Smokers	3/12	5/19	3/25	p=0.37
Past Smokers	6/12	10/19	11/25	p=0.5
Pack Years of Past and Present Smokers	40 (23.6)	59.3(37.7)	40.4 (39.9)	p=0.54
Years of Diabetes	5.8 (5.5)	12.7 (7.8)	10.7 (11.03)	p=0.29
Hba1c	6.78 (0.9)	6.8 (0.9)	7.2 (1.5)	p=0.84
Renal Impairment	0/12	2/19	2/15	p=0.067
Diabetic Retinopathyt	0/12	1/19	2/25	p=0.47
Diabetic Foot	0/12	1/19	0/25	p=0.68

Table 4: Shows patients' characteristics according to spirometry results and any possible correlations. Data are shown as means (sd) for continuous variables and presence of comorbidities or diabetic complications/total patients. Statistically significant differences were considered for p<0.05.

however FVC decrement was more consistent than FEV1, suggesting a restrictive pattern that was not associated with obesity or elevated BMI [16-18]. Other studies showed that patients with diabetes have decreased FEV1, FVC, peak expiratory flow (PEF) and vital capacity (VC) than the predicted values in various patterns other obstructive and other restrictive [19,20]. Thus the impairment of pulmonary function test in diabetic patients is not yet clarified.

Diffusion capacity of the lung for carbon monoxide (DLCO) and its components (membrane diffusing capacity and capillary blood volume) in diabetic patients (obese and non-obese) and healthy individuals at rest and exercise has also been studied. DLCO was reduced in both diabetic groups at peak exercise but after adjustment for pulmonary blood flow this finding persisted only in obese participants [21]. Another study showed reduced alveolar diffusion in patients with poor glycemic control of their diabetes (HbA1C>7%) independently of the duration of their disease [22].

In Fremantle Diabetes study [23], the decline of FEV1, FVC, Peak Expiratory Flow (PEF) and Vital Capacity (VC) was predicted by poor glycemic control. 1% increase of HbA1c was associated with 4% decline of FEV1 (p<0.004) and 6% decline of FVC (p<0.001). In the Atherosclerosis in Communities study [24] the FVC decline was inversely associated with the years of diabetes at baseline. In the Normative Aging Study decline of lung function over time was similar between participants with diabetes and participants without diabetes [25]. Although the study did not show greater decline of lung function in the two groups over time, some of the participants who developed diabetes during the study had decreased lung function than predicted before the disease onset [26]. Is decreased lung function a risk factor for diabetes? The pathophysiological basis for such a correlation is not clear. Experimental studies have shown hypoxia – mediated insulin resistance but these results have not been reproduced in humans [27,28].

Can systemic inflammation of diabetes explain the altered lung function? In our cohort 74% had some kind of obstructive disorder (p<0.001), which was diagnosed for the first time and was associated only with older age. Several recent studies point to that direction. First a recent cohort study verified again a temporal relationship between poor lung function and diabetes risk that was not associated with glycemic control [29]. Also the lung seems to be a target organ for diabetic patients both DLCO and spirometry results [30,31]. Recent reports [31,32] have linked inflammatory markers with airway obstruction and moreover a large cohort study [33] associated lung function and airway obstruction with incident heart failure and circulating markers of cardiac function. Thus the mechanisms that link inflammation, lung function and diabetes remain to be elucidated.

Several limitations are present in our study. First patients with type 2 diabetes were included so the results may not be applicable to other patients with diabetes (type 1 diabetes or latent autoimmune diabetes of adults). Second the patients had well controlled diabetes without serious micro and macro vascular complications. Lung function in such patients has not been evaluated. Third the antidiabetic medications used varied between the patients so any correlation may have remained unidentified. Finally our cohort was a small group and results need to be validated in larger studies.

Conclusions

In our study we found significant obstruction in lung function of patients with type II diabetes that was not associated with smoking history, years of diabetes, glycemic control, antidiabetic medications or other comorbidities, only with older age. No patient had prior to the study evaluated lung function. These results prompt to a large cohort study that will evaluate and follow up lung function of different groups of diabetic patients and will assess the need to implement a non-invasive tool as spirometry in the monitoring of diabetes.

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Lamprini Tina participated in the study design, gathered the data and drafted the manuscript. Panagiotis Andriopoulos participated in the study design, performed the statistical analysis and drafted the manuscript. Panagiotis Georgantas participated in the gathering the data. All authors read and approved the manuscript.

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