



STUDY OF PULMONARY FUNCTION TESTS IN TYPE 2 DIABETIC PATIENTS: CORRELATION WITH GLYCEMIC STATUS

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ABSTRACT

Diabetes is one of the leading causes of death worldwide. As lung is a target organ for diabetes type 1 and 2, in this cross-sectional study, we studied the pulmonary functions of 60 type 2 diabetic patients and 60 matched controls by spirometry. Blood sugar, fasting and post-prandial was measured in all subjects by oxidase-peroxidase method. We found a significant reduction in FVC, FEV1, MVV in diabetics compared to controls. A significant increase in FVC/FEV1% was seen in diabetics compared to controls. Blood sugar, correlated significantly & negatively with FVC, FEV1 and MVV, significantly and positively with FVC/FEV1% in diabetic subjects. Our results showed mainly the restrictive type of lung impairment in type 2 diabetes and significant impairment of lung function with increasing blood sugar levels. It is advisable that diabetic patients should undergo periodic spirometric check up to assess severity of lung function impairment and their glycemetic control should be improved.

KEYWORDS: Type 2 diabetes, Pulmonary functions, Spirometry, Blood sugar, Advanced glycation end products, Restrictive lung impairment.



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INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. Type 2 diabetes or adult-onset diabetes is due to combination of resistance to insulin action and an inadequate insulin secretory response. WHO projects that diabetes will be the 7th leading cause of death in 2030. Complications of diabetes are both acute and chronic¹. Experimental data and histopathological studies support the notion that lung is a target organ for diabetes, both type 1 and type 2². Considering the large vascular network and richness in collagen and elastin of lungs, pulmonary system is prone to undergo micro vascular damage and non-enzymatic glycation in diabetes. Although systemic vascular complications are more common in diabetes, diabetes also affects pulmonary microcirculation^{2,3}. Lung dysfunctions have been more extensively studied in type 1 diabetes than in type 2. Lung dysfunctions also occur in many patients of type 2 diabetes. Many cross-sectional studies have shown reduced FVC, FEV1, DLco i.e. diffusing capacity of lung for carbon monoxide in type 2 diabetic patients compared with their non-diabetic counterparts. Reduced lung function in these patients is inversely related to blood glucose levels, duration of diabetes and its severity and is independent of other variables like age, height, weight, smoking, obesity, etc⁴. Lung dysfunctions in diabetes remain clinically silent for a long time because alveo-capillary system of the lungs is characterized by a great micro vascular reserve. So it compensates for a decline in lung functions. But loss of micro vascular reserves in lungs may become clinically important under stressful conditions like asthma, pneumonia or fluid overload secondary to heart failure⁵. As type 2 diabetes accounts for majority of diabetes cases, so it is important to know whether type 2 diabetes affects lung functions, since this may potentially have an impact on prognosis and disease management. So the present study is undertaken to understand effects of type 2 diabetes on pulmonary functions measured by spirometry and to find a correlation if any between pulmonary function test parameters and glycemic status of diabetic subjects.

MATERIALS AND METHODS

The present study was conducted in 60 cases (30 males and 30 females) and 60 controls (30 males and 30 females) that were age, sex and BMI matched. Apparently healthy individuals having age between 40-60 years, with already diagnosed type 2 diabetes mellitus were included. Controls were selected from healthy relatives accompanying diabetic patients. Subjects having complications of diabetes, history of recent/remote cardiorespiratory diseases, history of tobacco use, smoking, alcohol intake were excluded. Health status of both study cases and controls was determined by thorough clinical examination and history taking. The informed and written consent of all subjects was taken. Approval of the institutional human ethics committee was also obtained.

We used the following apparatus

- 1) Electronic computerized portable medspiror spirometer: The instrument fulfils criteria for performance and reproducibility laid down by A.T.S.
- 2) Instruments and chemicals required for estimating blood sugar level by glucose oxidase-peroxidase method.
- 3) Measuring tape, weighing machine, B.P. apparatus, stethoscope

Procedure

1) Measurement of pulmonary function tests

All subjects were first explained in detail about the procedure of performing lung function tests. Initially, relevant data of case number, date, name, age, sex, height, weight, room temperature was entered in the spirometer. The height was measured with help of a measuring tape with the person standing bare foot with feet together. The weight was measured in upright position with very light clothing present, with the help of weighing machine. The demonstration was shown prior to recording and adequate trials were given to the subjects before actually performing the tests. Then, readings were taken in comfortable sitting in an upright position. Activities like doing severe exercise within 30 minutes of testing, wearing clothes which prevent full expansion of chest and abdomen were asked to avoid. Each subject was asked to perform following two manoeuvres,

according to performance criteria laid down by ATS and ERS.

Forced vital capacity (FVC) ^{6,7}

Nose-clip was attached to the subject's nose and then the subject was asked to inhale completely. The inhalation should be rapid but not forced. Then immediately subject was asked to place mouth-piece in his/her mouth, making sure that his/her lips sealed around the mouth-piece and to exhale forcefully and completely. A minimum of three acceptable FVC manoeuvres were performed. FVC manoeuvre to be acceptable should be free from artifacts like cough or glottis closure during the first second of exhalation, early termination or cut-off, variable effort, leak or obstructed mouthpiece.

Maximum voluntary ventilation (MVV) ⁷

Nose-clip was attached to the subject's nose and subject was asked to make an airtight seal around the mouthpiece. Then subject was asked to have three tidal breaths followed by breathing as rapidly and as deeply possible for 12 seconds. The tongue and teeth were positioned so as to not obstruct the airflow. An acceptable MVV manoeuvre performance is one which is performed with maximum effort without evidence of leakage,

hesitation, or measurement artifact. With the help of entered data and standard regression equations in the software of microprocessor, predicted values of pulmonary function parameters were calculated by the instrument and converted to body temperature and pressure by the instrument itself. But as the instrument is made and standardized in Chandigarh and diabetic patients are from Maharashtra, racial differences ⁸ could also affect lung functions. So the predicted values were not taken for the comparison. Each subject performed the tests three times and best of the three readings was taken for analysis. In the present study, observed values of following parameters were considered

- Forced Vital Capacity, FVC (liters)
- Forced Expiratory volume in 1st second, FEV1 (liters)
- FEV1/FVC%
- Forced Expiratory Flow, FEF 25-75% (liters/second)
- Peak Expiratory Flow Rate, PEFR (liters/second)
- Maximum Voluntary Ventilation, MVV (liters/minute)

Spirometer



Figure 1
Medspiror spirometer

Procedure of spirometry



Figure2
Diabetic patient performing pulmonary function test

2) Estimation of blood sugar level by glucose oxidase–peroxidase method⁹

Principle-

Glucose is converted to gluconic acid and hydrogen peroxide (H₂O₂) in the presence of glucose oxidase. Peroxidase acts on H₂O₂ liberating oxygen which then couples with chromogenic substances producing red colored complex, which is maximally absorbed at 505 nm. The intensity of colored complex is directly proportional to glucose concentration in

specimen when compared with standard. Procedure: We collected 2 ml of blood in fluoride bulb and centrifuged it for 2-5 minutes at 2000 rpm. With the help of micropipette, 0.02 ml of plasma was collected from test tube. Following reagents were pipetted into 3 test tubes labeled blank (B), standard (S), and test (T).

Table I
Composition of mass mixture for estimation of blood sugar level

Reagent	B	S	T
Working reagent	3.0 ml	3.0 ml	3.0 ml
Glucose standard	-	0.02 ml	-
Plasma	-	-	0.02 ml

After mixing, we incubated them at 37°C for 10 minutes and read absorbance of standard and test against blank on photo colorimeter with green filter or spectrophotometer at 510 nm.

Calculations

$$\text{Plasma glucose in mg/dl} = \frac{\text{Absorbance of T}}{\text{Absorbance of S}} \times 100$$

Statistical analysis¹⁰

All the data were presented as mean \pm S.D. (Standard Deviation). The significance of difference in parameters between study group and control group was ascertained by a student's unpaired t test. The results were expressed as statistically non significant if $P > 0.05$, as statistically significant if $P < 0.05$, $P < 0.01$ and $P < 0.001$. Correlation analysis was used to determine the strength of association between pulmonary function test parameters

and glycemc status of type 2 diabetic patients.

RESULTS

- (i) Anthropometric parameters: The differences in all anthropometric parameters (age, height, weight and BMI) between diabetic subjects and controls are not significant.
 (ii) Pulmonary function test parameters

Table II
Pulmonary function test parameters of diabetic subjects vs. controls

Parameter	Diabetics (n=60)	Controls (n=60)	t value	Level of significance P value
	Mean \pm SD	Mean \pm SD		
FVC (L)	1.96 \pm 0.57	2.37 \pm 0.55	4.0095	$P < 0.001$
FEV1 (L)	1.67 \pm 0.41	1.94 \pm 0.42	3.5632	$P < 0.001$
FEV1/FVC%	86.40 \pm 4.43	82.11 \pm 2.63	6.4501	$P < 0.001$
PEFR (L/s)	5.50 \pm 1.29	5.80 \pm 1.28	1.2787	$P > 0.05$
FEF25-75% (L/s)	2.75 \pm 0.67	2.95 \pm 0.71	1.5869	$P > 0.05$
MVV (L/min)	69.18 \pm 18.33	101.34 \pm 21.32	8.86	$P < 0.001$

L: liter(s), s: second, min: minute

FVC, FEV1 & MVV show significant reduction in diabetic subjects compared to controls. FEV1/FVC% shows significant increase in diabetic subjects compared to controls

significant increase in diabetic subjects compared to the controls.

(iii) Blood sugar measurements

Fasting and post-prandial blood sugar shows

- (iv) Correlation between pulmonary function test parameters and blood sugar in diabetic subjects

Table III
Correlation between pulmonary function test parameters and blood sugar

Parameters	Correlation coefficient (r)	Level of significance P value
FBS vs. FVC	$r = -0.7109$	$P < 0.001$
FBS vs. FEV1	$r = -0.7127$	$P < 0.001$
FBS vs. FEV1/FVC%	$r = 0.6402$	$P < 0.001$
FBS vs. MVV	$r = -0.7163$	$P < 0.001$
PPBS vs. FVC	$r = -0.7543$	$P < 0.001$
PPBS vs. FEV1	$r = -0.7551$	$P < 0.001$
PPBS vs. FEV1/FVC%	$r = 0.6936$	$P < 0.001$
PPBS vs. MVV	$r = -0.7613$	$P < 0.001$

FBS: Fasting blood sugar, PPBS: Post-prandial blood sugar, vs: Versus

FVC, FEV1, MVV correlated significantly & negatively while FEV1% correlated significantly & positively with both fasting and post-prandial blood sugar in diabetics.

DISCUSSION

Our study shows a highly significant decrease in FVC in diabetic patients compared to matched controls. Our results are in agreement with studies by Lange P et al¹¹, Walter RE et al¹², Davis WA et al¹³, Chance WA et al¹⁴, Yeh HC et al¹⁵, Agarwal V et al¹⁶, Dennis RJ et al¹⁷, Nandhini R et al¹⁸, Keerthi SG et al¹⁹, Aparna A²⁰. Our study shows a significant decrease in FEV1 in diabetics compared to controls. Our results are in agreement with studies by Lange P et al¹¹, Davis WA et al¹³, Yeh HC et al¹⁵, Agarwal V et al¹⁶, Dennis RJ et al¹⁷, Dharwadkar AR et al²¹, Nandhini R et al¹⁸, Keerthi SG et al¹⁹, Aparna A.²⁰ Our study shows a highly significant increase in FEV1/FVC% in diabetic patients compared to matched controls. Our results are in agreement with studies by Walter RE et al¹², Chance WA et al¹⁴, Yeh HC et al¹⁵, Dennis RJ et al¹⁷, Aparna A²⁰. Thus, our study is suggestive of a predominant restrictive pattern of lung impairment. There have been different mechanisms explained for decreased spirometric indexes in type 2 diabetes. The reduced spirometric indexes in type 2 diabetes do not identify a specific underlying pathology but there are histopathological reports²² of basal lamina thickening of pulmonary capillaries and alveoli in humans and there are also reports of an association of pulmonary fibrosis with type 2 diabetes²³.

Other possible contributory factors include

- Glycation of chest wall and bronchial tree proteins²⁴
- Autonomic and/or phrenic neuropathy causing alterations in bronchial reactivity and respiratory muscle function.^{25, 26}
- Chronic inflammation¹⁷
- Oxidative stress²⁷
- Increased propensity to, and severity of, respiratory infections²⁸.

Chronic hyperglycemia in type 2 diabetes, by inducing increased oxidative activity, intracellular NF- κ B inflammatory mediator expression, can bring about a rise in collagen molecule synthesis and their cross-linking, via increasing formation of advanced glycation end

products (AGEs)²⁹. Cross-linked collagen being susceptible to proteolysis and being less soluble by acid and pepsin and more stable to heat induced denaturation, accumulates in both lung and chest wall resulting in increased stiffness of lung and chest wall. So lung compliance is decreased due to increase in interstitial tissue (collagen) of the lung. This leads to restrictive lung impairment causing decrease in forced vital capacity (FVC), seen in our study^{25, 30, 31}. Due to weakness of expiratory muscles or stiffness of chest wall (increase in recoil of the chest wall) in diabetes, the force generated by the expiratory muscles to overcome the outward recoil of the chest wall is reduced. This leads to decrease in expiratory flow and decrease in FEV1^{25, 30, 32}. In our study, decrease in FVC is proportionately more than decrease in FEV1. So FEV1/FVC% is significantly higher in diabetic patients which is suggestive of restrictive type of lung impairment. Our study shows significant decrease in MVV in diabetic patients compared to matched controls. Our results are in agreement with studies by Agarwal V et al¹³², Keerthi SG et al¹⁴⁴. Significant reduction in MVV in diabetic patients reflects the reduced strength of respiratory muscles like diaphragm and intercostal muscles and reduced compliance of the thorax-lung system³². Cascade of protein glycation due to hyperglycemia may lead to demyelination or axonal atrophy in the peripheral nerves causing peripheral neuropathy³³. Since phrenic nerve is the principal nerve supplying the respiratory muscles including the diaphragm, the observation of reduced MVV might be due to phrenic neuropathy²⁶ or due to myopathic processes³⁴ in diabetes. Correlation between pulmonary functions and glycemic status in diabetic patients: Our results show that glycemic status may play a key role in association of type 2 diabetes and reduced pulmonary functions. Our study is in agreement with studies performed by Walter RE et al¹¹⁹, Davis WA et al¹²⁴, Yeh HC et al¹³⁰, Dharwadkar AR et al¹³⁸. Hyperglycemia promotes the production of AGEs which cause increased production and altered properties of matrix proteins like collagen and elastin. The

process of collagen glycation in lung and chest wall, which cause increased stiffness, is more pronounced in patients with poor glycemic control²⁵. AGEs also alter expression of inflammatory mediators like IL-1, IL-6, TNF- α by endothelial cells via activation of nuclear transcription factor kB³⁵. Also receptors for AGEs are seen in lung parenchymal tissue and respiratory epithelium²⁴. So, if diabetes mellitus and hyperglycemia are themselves pro-inflammatory, then impaired glycemic control may cause pulmonary inflammation and ventilatory impairment. So a good glycemic control could positively influence lung function parameters.

CONCLUSION

The findings of the present study are in agreement with findings of many other studies which strongly suggest that type 2 diabetes

mellitus adversely affects lung functions and impairment of lung function is primarily restrictive, although patients did not have any respiratory symptoms. Findings in our study suggest that lung is a target organ for type 2 diabetes and glycemic exposure is a strong determinant of reduced pulmonary functions in type 2 diabetes. So an improved glycemic control will help to improve the ventilatory functions in diabetic patients. It is advisable therefore that, diabetic patients should undergo periodic spirometric tests to assess the severity of lung function impairment as pulmonary dysfunction may be one of the earliest and easily measurable non-metabolic alteration in diabetes. These measures will help to prevent lung damage in initial stages and thus will contribute to reduction in morbidity and mortality associated with type 2 diabetes. Limitations of the present study are that, we have not measured DLco in our patients.

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