DOI: 10.7860/JCDR/2014/9756.5076

Original Article

Physiology Section

Assessment of Lung Function by Spirometry and Diffusion Study and Effect of Glycemic Control on Pulmonary Function in Type 2 Diabetes Mellitus Patients of the Eastern India

SALIM UZ-ZAMAN[1], JOYASHREE BANERJEE[2], ANILBARAN SINGHAMAHAPATRA[3], PRANAB KUMAR DEY[4], ANINDYA ROY[5], KAUSHIK ROY[6], KAKALI ROY (BASU)[7]

ABSTRACT

Introduction: There are so many complications involving eyes, kidneys, lungs and nerves associated with diabetes. But, pulmonary complications are poorly characterized among eastern Indian diabetic populations.

Aims and Objectives: To assess pulmonary function in patients with type 2 diabetes mellitus. To find out correlation of the pulmonary functions test variables with Glycemic control.

Materials and Methods: Total of 60 type 2 diabetes patient of age between 35-55 y and same number of age and sex matched apparently healthy control individual were included in the present study. All subjects were evaluated for PFT by flow sensitive spirometer (RMS HELIOS-401), the spirometric parameters were measured as a percentage of predicted and DLCO (by single breath technique). HBA1c of all cases were measured and they were grouped according to HBA1c level (Group-a =>7%, Group-b =6%-7%, Group-c =<6%).

Results: Significant differences in the spirometric parameters (FVC, FEV1/FVC) and diffusion capacity (DLCO% and DL/VA%) existed between cases and controls. There was a significant decrease in FVC, DLCO and DL/VA and significant increase in FEV1/FVC in that groups having HBA1c level >7% than the other groups. FEV1, FVC, DLCO, and DL/VA were negatively correlated with HbA1c where as FEV1/FVC has positive association with HbA1c.

Conclusion: Significant deterioration of lung function and diffusing capacity was observed in type 2 diabetes patients with poor glycemic control.

Keywords: Glycemic control, Pulmonary function test, Type-2 diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is a growing public health problem and becoming an epidemic globally and specially in Asian Indian [1]. Diabetes is a systemic disease that causes secondary pathophysiological changes in multiple organ systems and the complications affecting these systems are responsible for the majority of morbidity and mortality associated with the disease [1]. The prevalence of complications such as micro and macro angiopathy involving heart, kidney, eyes, central nervous system (CNS) are also increasing, causing severe economic and social burden. The pathogenesis of diabetic complications are still a matter of debate and are thought to involve both a microangiopathic process and non enzymatic glycosylation of tissue proteins and peptides of extracellular matrix at elevated circulating glucose level [1,2]. Several biochemical processes result in impaired collagen and elastin cross linkage with a reduction in the strength and elasticity of connective tissue and both microvascular and macrovascular complications causing thickening of basement membrane, enothelium and epithelium [1,3,4]. The common microvascular complications or microangiopathy include retinopathy, nephropathy and neuropathy. The presence in the lung of an abundant connective tissues and an extensive microvascular circulations raise the possibility that lung may be a 'target organ' in type2 diabetes (type2DM) [5] in parallel with other systemic complications. Glycemic control depicts the long term glycemic status and degree of hyperglycemia depicts degree of non-enzymatic glycosylation of connective tissue and degree of microangiopathic complications.

Several studies had described the lung function in type2 diabetes mellitus patients for western, northern, and southern regions in India [6-9]. The wide range of geographical and climatic conditions in a large country such as India may be associated with regional differences in lung function. Pulmonary complications are poorly characterized among eastern Indian diabetic populations. On this background this study was conducted on eastern India population for assessment of lung function in type 2 diabetes mellitus.

AIMS AND OBJECTIVES

1. To assess pulmonary function in patients with type 2 diabetes mellitus.
2. To find out correlation of the pulmonary functions test variables with Glycemic control.

MATERIALS AND METHODS

Eighty type 2 DM cases were randomly selected from patients attending Diabetic clinic Out Patient Department (OPD), R.G.Kar Medical College. Among them 60 patients were included following inclusion and exclusion criteria. Age and sex matched 60 healthy controls were included according to inclusion and exclusion criteria. After proper ethical clearance, a comparative cross-sectional study was conducted at the Department of Physiology, R.G.Kar Medical College & Hospital in collaboration with Department of Medicine, Department of Biochemistry from January 2010 to November 2012.

Diagnosis of type 2 DM were done according to the National Diabetes Data Group and World Health Organization diagnostic criteria for DM based on the following premises [1].

Following patients were excluded from the study: Smokers; history of respiratory diseases such as asthma, COPD, tuberculosis,

Parameters	Cases (n= 60) (Mean ± SD)	Control (n=60) (Mean ± SD)	p-value
Age (years)	44.57(±5.678)	44.88 (±5.402)	0.555
Height (cm)	157.58(±8.271)	160.30(±8.737)	0.068
Weight (kg)	60.20(±8.286)	60.13(±4.089)	0.839
BMI (kg/m^2)	24.40(±2.352)	23.579(±1.679)	0.028 *
FBS (mg/dl)	178.71(±57.407)	87.50 (±6.828)	0.0001 *
PPBS (mg/dl)	254.28(±66.103)	119.81 (±7.760)	0.0001 *
HbA1c	7.07 (±1.492)	4.08 (±0.289)	0.0001 *

[Table/Fig-1]: Basic characteristics of study subjects
*= signifant

Lung functions parameters	Cases (Mean ± SD)	Control (Mean + SD)	p-value
FVC Litre (% of predicted)	77.75 (±5.655)	96.50(±9.523)	0.0001*
FEV1 Litre (% of predicted)	81.31(±3.864)	97.50(±9.590)	0.0001*
FEV1/FVC (% of predicted)	102.97(±8.402)	104.25(±5.435)	0.011*
PEFR L/S (% of predicted)	85.31(±5.173)	94.56(±7.770)	0.009*
FEF 25-75 L/S (% of predicted)	82.83(±4.934)	91.76(±6.955)	0.01 *
DLCO (mL/min/ mmHg) (% of predicted)	94.35(±18.635)	108.53(±13.128)	0.002*
DL/VA (mL/min/ mmHg) (% of predicted)	89.47(±12.636)	98.68(±7.890)	0.0001*

[Table/Fig-2]: Comparison of PFT parameters between cases and controls,
*= signifant

ILD; H/O occupational exposure; H/O URTI & LRTI; Hypertension, H/O angina; CVA; Obesity (BMI>30 kg/m^2); known thyroid disorders, autoimmune disease like SLE, RA; known kidney diseases, Hereditary peripheral neuropathy; individuals with unacceptable spirometric technique, due to various causes like obstruction of teeth or tongue, sub-maximal effort, air escape, effort sustained for less than 6 s duration, failure to attain a plateau on volume time curve, recent surgery.

Detailed history and clinical examinations were done and blood sample after overnight fasting was taken for the Fasting plasma glucose and post prandial plasma glucose (by Glucose Oxidase Peroxidase method [10,11], glycated hemoglobin (HbA1C) level as an index of glycemic control (by Ion Exchange Resin method) [12].

Spirometry

Height and weight of each subject was measured. Self-reported smoking history was considered. Pulmonary functions were measured by the electronic spirometer, model-RMS Helios-702 in accordance with the standards of lung function testing of the American Thoracic Society/European Respiratory Society (ATS/ERS) [13]. Pulmonary function report included patient's gender, height, weight, age and smoking status. Standard spirometric measures included, forced vital capacity (FVC), forced expiratory volume in one second FEV1, the ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC), forced expiratory flow rates (FEF25%, FEF50%, FEF75%, and FEF25%-75%) and peak expiratory flow rate (PEFR). Pulmonary function variables were recorded as a percentage of the normal value predicted on reported height and age [14]. Post bronchodilator (reversibility test) testing was performed 10 min after administration of the bronchodilator.

Measurement of DLCO: The DLCO of the subjects of this study were measured by single breath (DLCOsb) method using computerized DLCO measuring machine, - INPIRE- HD–PFT [15]. Best of three satisfactory readings was taken for analysis. The technique was validated in our laboratory and the prediction equations for normal Indian subjects had been derived and reported previously [15,16]. Normal values are based upon age, height, ethnicity, and sex. A value is usually considered abnormal if it is less than 80% of predicted value [15,16].

PFT parameters	HBA1c level Mean ± SD			
	Group-a (HBA1c level >7%)	Group-b (HBA1c level 7%-6%)	Group-c HBA1c level <6%)	p-value
FVC Litre (% of predicted)	75.13±6.555	80.55±2.818	79.54±3.778	0.001*
FEV1 Litre (% of predicted)	80.48±4.649	82±2.427	82.27± 3.523	0.270
FEV1/FVC (% of predicted)	107.93±5.842	97.85±9.371	99.18±3.816	0.0001*
PEFR L/S (% of predicted)	85.06±6.123	85.2±3.833	86.18±4.895	0.830
FEF 25-75 L/S (% of predicted)	82.72±5.999	82.6±3.346	83.54±4.568	0.870
DLCO (mL/min/ mmHg) (% of predicted)	84.76±10.814	97.36±15.867	115.27±20.581	0.0001*
DL/VA (mL/min/ mmHg) (% of predicted)	83.50±9.709	94±11.472	97.90±12.848	0.0001*

[Table/Fig-3]: Comparison of PFT parameters among the groups according to HBA1c level

PFT parameters	Correlation of Lung Functions parameters with HbA1c	
	Cor. Coefficient(r)	p- values
FVC Litre	-0.5	<0.05
FEV1 Litre	-0.3	>0.05
FEV1/FVC	0.5	<0.05
PEFR L/S	0.07	<0.05
FEF 25-75 L/S	-0.01	>0.05
DLCO mL/min/ mmHg	-0.65	<0.05
DL/VA mL/min/ mmHg	-0.62	<0.05

[Table/Fig-4]: Correlation of PFT parameters with glycemic control
*= signifant

STATISTICAL ANALYSIS

Data were analysed in SPSS software- version 17 (IBM, Chicago, Illinois, 2008). p-value of <0.05 was taken as significant with 95% confidence interval.

RESULTS

[Table/Fig-1] demonstrate that cases and control are age matched. The mean BMI, FPG, PPPG, HBA1c were significantly (p<0.05) increased in T2DM patients than the control.

Our study shows that there is a significant (p<0.05) decrease of PFT parameters (FVC, FEV1, PEFR, FEF 25-75) and diffusion capacity (DLCO and DL/VA) whereas FEV1/FVC is significantly increased in cases compared to control [Table/Fig-2].

Applying ANOVA test between three groups according to HBA1c level [Table/Fig-3] shows that there is significant decrease in FVC, DLCO and DL/VA and significant increase in FEV1/FVC in that groups having HBA1c level >7%.

This study shows that [Table/Fig-4] there is negative association between HbA1c level and PFT parameters (FVC, FEV1) but FEV1/FVC is positively correlated with HbA1c level. Regarding diffusion capacity both DLCO and DL/VA are negatively correlated with glycemic status.

Comparison of pulmonary function observed in the present study with the corresponding predicted values published from various regions of India is shown in [Table/Fig-5,6]. When compared to the selected studies our result shows almost similar changes like the most of the studies.

DISCUSSION

Renal, retinal and other manifestations of diabetic microangiopathy have frequently been studied but pulmonary complications of Type

Study		FVC Litre (% predicted) Mean ± SD	FEV1 Litre (% predicted) Mean ± SD	FEVI/FVC (% predicted) Mean ± SD	FEF25-75 (L/s) (%predicted) Mean ± SD	PEFR (L/s) (% predicted) Mean ± SD
Present study (Eastern India)		77.75 ±5.655	81.31±3.864	102.97±8.402	82.83±4.934	85.31±5.173
Shah et al.,[8] (Western India)		77.97±12.99	78.98±14.09	112.83±9.35	67.00±15.08	59.16±99.35
Agarwal et al.,[7] (western India)	with microangiopathy	80.0±9.34	80.2±13.26	-	79.4±18.06	81.4±18.0
	without microangiopathy	83.13±7.36	83.0 ± 8.0	-	87.67±9.37	86.6±13.09
Sinha et al.,[6] (North India)	with complications	80.4±10.7	81.0±9.4	-	-	83.3±18.2
	without complications	80.7±15.8	80.1±16.2	-	-	84.1±25.3
Murthy et al.,[9] (South India)	Male	2.66±0.56 (absolute)	2.01±0.41 (absolute)	75.56±9.35 (absolute	-	337.92±98.48 (absolute)
	female	1.89±0.45 (absolute)	1.53±0.41 (absolute)	80.72±14.83 (absolute)		231.75±82.59 (absolute)

[Table/Fig-5]: Variation of spirometric parameters in type 2 diabetes mellitus patients in different regions of India *= signifant

Study		DLCO(mL/min/ mmHg) (% predicted) Mean ± SD	DL/VA (mL/min/ mmHg) (% predicted) Mean ± SD
Present study (Eastern India)		94.35±18.635	89.47±12.636
Shah et al.,[8] (Western India)	with complications	15.8±3.1(absolute)	-
	without complications	17.5±2.1 (absolute)	-
Agarwal et al.,[7] (Western India)	with microangiopathy	72.33±16.0	76.4±10.22
	without microangiopathy	82.67±14.88	88.22±5.21
Anandhalakshmi S, [17] et al., (South India)		15.07 ±3.7(absolute)	3.7 ± 1.4(absolute)

[Table/Fig-6]: Variation of diffusion study in type 2 diabetes mellitus patients in different regions of India

2 Diabetes have been poorly characterized specially in the eastern Indian regions. In this study fasting and post meal blood glucose levels and HbA1c% were found to be significantly more in type 2 diabetics than the controls pointing to the fact that there was poor glycemic control. This may be because of irregular drug intake, inappropriate drugs, sub-dosing, overeating, lack of diabetic life style discipline, etc practiced by the patients [18]. HbA1c% is an indicator of diabetes control. Higher the level of HbA1c%, poor is the diabetic control i.e. higher level of circulating glucose. If circulating glucose is constantly at a higher level for 3 month (as measured by HbA1c%), it can lead to more and more nonenzymatic glycosylation of tissue proteins. If respiratory system is a target, this will be reflected in the PFT parameters analysed.

Our study found that FVC, FEV1 were significantly reduced in type 2 diabetics whereas FEV1/FVC was significantly increased in cases compared to control. This signifies that restrictive lung pathology occurs in diabetes. Similar findings were observed by other authors [6,19].

In type 2 diabetics FEF 25- 75% is significantly reduced compared to controls. FEF 25-75% is an indicator of force of expiration of gases during middle 50% of forced expiration. Forced expiration is supported by muscular and recoil forces of the respiratory system. Thus decrease in muscular and recoiling forces of the respiratory system because of increased glycosylation is responsible for significant decrease in FEF 25-75%. Similar findings were observed in other studies [18,20]. The flow can also be decreased due to obstruction.

PEFR is the gas exhaled in 1/10th of a second during forced expiratory manoeuvre when recoiling forces of the lungs and contractile forces of respiratory muscles are functioning maximally and supporting the expiration to the maximal. Due to glycosylation of the connective tissues of the respiratory apparatus, the recoiling forces of the lungs and the contractile forces of the respiratory muscles might be decreased, leading to a significant reduction in PEFR [21,22]. Our study also shows the similar finding and extended the observations of previous researchers.

Diffusion capacity of the type-2 diabetic patients also deteriorated in our study. Asanuma et al., [23] reported a significantly lower forced vital capacity in diabetics along with a decreased diffusing capacity. Sinha et al., [6] also concluded that impairment of DLCO was common in type2DM Asian Indian having pulmonary capillary endothelial dysfunction and it could be related to insulin resistance and dyslipidaemia. In contrast to the above findings, Bulbou et al.,[24] did not find any correlation between reduced diffusion capacity in diabetics with diabetic complications and others [25] have reported no significant difference in diffusing capacity between healthy subjects and diabetics.

Study of Agarwal et al.,[7] showed the relation of lung function parameters with glycemic control(HBA1c). There was a decrease in FVC%, FEV1%, PEFR%, FEF25-75%, DLCO%, DL/VA% and an increase in FEV1/FVC% with increase in HBA1c level. Another Study by Sinha et al., [6] also showed that lung function parameters were decreasing with deterioration of glycemic control and there was a negative correlation between DLCO and HBA1c level($r=0.62$, $p<0.05$). They found no difference in other pulmonary function only correlations were observed between DLCO and HbA1C ($r=0.62$, $p<0.05$). Other studies [6,7] have observed only correlation between diffusing capacity but spirometric values did not differ in type-2 diabetes patients.

A small sample size and non-measurement of TLC, cross-sectional study with no follow-up are the limitations of the present study. Further, histological studies on pulmonary microvasculature and compliance measurements of the lung would be useful to investigate reasons for reduced DLCO values.

CONCLUSION

Our study shows significant changes of FVC%, FEV1/FVC%, DLCO% and DL/VA% in Type-2 diabetes patients and it has been correlated with poor glycemic control. The above pattern of changes are possibly due to hyperglycemia induced non enzymatic glycosylation of tissue proteins and chronic diabetic microangiopathy causing basement membrane thickening (capillaries and endothelium) leading to reduction in strength and elasticity of connective tissues and reduced pulmonary blood volume with V/Q mismatch impairing the diffusion capacity.

REFERENCES

[1] Fauci AS, Kasper DL, Longo DL, Braunwald E, Hauser SL, Jameson JL,et al. Diabetes Mellitus. Harrisons principals of Internal Medicine 17th edition: 2008(II) 2286-90.

[2] Marvisi M, Lino BL, Del BP, Brianti M, Marrani G, Guariglia A, et al. Pulmonary Function in non-insulin-dependent diabetes mellitus. *Respiration.* 2001;68:268-72.

[3] Ljubic S, Metelko Z, Car N, Roglic G, Drazic Z. Reduction of diffusion capacity for carbon monoxide in diabetic patients. *Chest.* 1998;114:1033-35.

[4] Weynand B, Jonckheere A, Frans A, Rahier J. Diabetes mellitus induces thickening of the pulmonary basal lamina. *Respiration.* 1999;66:14-9.

[5] Sandler Malcom. Is the lung a target organ in diabetes mellitus? *Arch Intern Med.* 1990; 150:1385- 88.

[6] Sinha S, Guleria R, Misra A, Pandey RM, Yadav R, Tiwari S, et al. Pulmonary functions in patients with type 2 diabetes mellitus & correlation with anthropometry

& microvascular complications. Department of Medicine, Biostatistics and Cardiology AIIMS, New Delhi. *Indian Med Res.* 2004;119:66-71.
[7] Agarwal AS, Fuladi AB, Mishra G, Tayade BO, et al. Spirometry and Diffusion Studies in Patients with Type-2 Diabetes Mellitus and Their Association with MicrovascularComplications. *Indian J Chest Dis Allied Sci.* 2010;52:213-16.
[8] Shah SH, Sonawane P, Nahar P, Vaidya S, Salvi S, et al. Pulmonary function tests in type 2 diabetes mellitus and their association with glycemic control and duration of the disease. *Lung India.* 2013;30(2):108-12.
[9] Murthy M, et al. Changes in lung function tests in type-2diabetes mellitus. *International Journal of Basic Medical Science.* 2012;3(2): 54-61
[10] Longmore M,Wilkinson I, Turmezei T, Cheung CK. *Oxford Handbook of Clinical Medicine* 7th ed. 2007;190-91.
[11] Trinder, P. Deter mination of glucase in blood using grocase oxidose with an alternative oxygen acceptor. *Ann Clin Biochem.* 1969;6:24-27.
[12] Nathan DM. A1c-Derived Average Glucose Study Group. Translating the A1c assay into estimated average glucose values. *Diabetes Care*. 2008;31(8):1473–78. [PMID: 18540046].
[13] American Thoracic Society – Standardization of spirometry 1995 update. *Am J respire Crit Care Med.* 1995;152:1107-36.
[14] Miller MR, Hankinson J, Brusasco V, et al. Standardization of spirometry. *Eur Respir J*. 2005;25:319-38.
[15] R. Pellegrino, G. Viegi, V. Brusasco, R.O. Crapo, et al. Interpretative strategies for lung function tests. *Eur Respir J.* 2005; 26: 948–68.
[16] MacIntyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CPM, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J*. 2005;26:720-35.
[17] Anandhalakshmi S, Manikandan S, Ganeshkumar P, Ramachandran c, et al. Alveolar gas exchange and pulmonary functions in patients with Type II Diabetes Mellitus. *Journal of Clinical and Diagnostic Research*. 2013;7(9):1874-77.
[18] AJMS Ramirez LC, Nogare AD, Hsia C and Arauz C. Relationship between diabetes control and pulmonary function in IDDM. *The American Journal of Medicine.* 1991; 91:371-76.
[19] Davis WA, Knuiman M, Kendall P, Grange V, Davis TM. Glycemic exposure is associated with reduced pulmonary function in type 2 diabetes: the Fremantle Diabetes Study. *Diabetes Care.* 2004;27:752–57.
[20] Sreeja CK, Samuel E, Kesavachandran C and Shashidhar S. Pulmonary function in patients with diabetes mellitus. *Indian J Physiol Pharmacol.* 2003;47(1):87-93.
[21] Gajbhiye R.N., Tambe A.S., et al. Pulmonary function test in type 1 diabetics. *Al Ameen J Med Sci.* 2013; 6(3) :285-89.
[22] Meo SA, Al-Drees AM, Shah SF, Arif M, Al- Rubean K. Lung function in type 1 Saudi diabetic patients. *Saudi Med J.* 2005;26:1728-33.
[23] Asanuma Y, Fujiya S, Ide H, Agishi Y. Characteristics of pulmonary function in patients with diabetes mellitus. *Diabetes Res Clin Pract.* 1985;1:95-101.
[24] Boulbou MS, Gourgoulianis KI, Klisiaris VK, Tsikrikas TS,Stathakis NE, Molyvdas PA. Diabetes mellitus and lung function. *Med Princ Pract.* 2003;12:87-91.
[25] Maccioni FJ, Colebatch HJ. Lung volume and distensibility in insulin-dependent diabetes mellitus. *Am Rev Respir Dis.* 1991;143:1253-56.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Physiology, Murshidabad Medical College, Berhampore, India.
2. Assistant Professor, Department of Physiology, RGKar Medical College, Kolkata, India.
3. Professor and Head, Department of Physiology, RGKar Medical College, Kolkata, India.
4. Assistant Professor, Department of Paediatrics Midnapur Medical College, Midnapur, India.
5. Assistant Professor, Department of Physiology, RGKar Medical College, Kolkata, India.
6. Junior Resident, Department of Physiology, RGKar Medical College, Kolkata, India.
7. Professor and Head, Department of Physiology, Malda Medical College, Malda, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Joyashree Banerjee,
Flat No B-6,Govt Housing Estate, 82-Belgachia Road, Kolkata-37, India.
Phone : 9433121826, E-mail : banerjeedrjoyashree@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Apr 24, 2014**
Date of Peer Review: **Jun 25, 2014**
Date of Acceptance: **Jul 19, 2014**
Date of Publishing: **Nov 20, 2014**