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Relationship between FVC, FEV_1, FEV_1/FVC% and oxidative stress in type 2 diabetes mellitus

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Abstract

Background: Diabetes mellitus causes micro and macrovascular disorder with debilitating effects on many organs including lungs. There is pulmonary impairment in type 2 diabetic patients (T2DM) which is usually characterized by restrictive pattern. Increased oxidative stress is associated with type 2 diabetes which may contribute to microvascular and macrovascular complications.**Objectives:**To assess the relationship between oxidative stress and lung function in patients with type 2 diabetes mellitus. **Methods:** This cross sectional study was carried out in the Department of Physiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka from September'2018 to August'2019. For this study, 35 newly diagnosed type 2 diabetic male patients aged 30-50 years and similar age and BMI 35 apparently healthy subjects were enrolled as control. Forced vital capacity (FVC), Forced expiratory volume in 1st second (FEV_1) and FEV_1/FVC%were assessed by portable spirometer. For evaluation of oxidative stress, plasma malondialdehyde (MDA) and catalase levels were measured by competitive ELISA technique and spectrophotometry. Statistical analysis was done by unpaired 't' test, chi-square test, pearson correlation test and multiple regression analysis as applicable. **Results:** In this study, the mean percentage of predicted value of FVC and FEV_1 were significantly lower ($p<0.001$) in T2DM. In addition restrictive pattern of pulmonary function was found in 65.71% and 14.28% in T2DM and healthy control respectively and the difference was statistically significant. The mean plasma catalase was significantly lower ($p<0.01$) and plasma MDA was

significantly higher ($p<0.001$) in patients. In addition, FVC showed significant negative correlation and significant association with higher MDA level in T2DM. Moreover, FEV_1 also showed significant association with MDA in T2DM. **Conclusion:** The present study reveals that restrictive pattern of pulmonary impairment is related to oxidative stress in T2DM.

Keywords: Newly diagnosed type 2 diabetic patients, FVC, FEV_1, FEV_1/FVC, plasma MDA and catalase.

Introduction

Diabetes mellitus (DM) is the most common of all endocrine diseases which has reached epidemic proportions and it is a leading cause of death and disability in worldwide[1]. Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia due to a defect on insulin production, insulin action or both[2].Biswas et al. reported the overall pooled prevalence is 7.4%in Bangladesh[3]. Diabetic patients are susceptible to a series of complications due to macrovascular and microvascular damages of the target organs[4]. Therefore, lung is also affected in diabetes evidenced by impaired pulmonary function[5]. Previous studies reported restrictive type of pulmonary impairment in T2DM[5-9].But, mixed obstructive - restrictive pattern also has been reported in these patients[4,10.] Moreover, lack of significant difference in pulmonary function test (PFT) parameters between diabetes and controls was also published[11]. An association between decreased FEV_1 and increased all cause mortality has also been reported[12]. In recent decades, oxidative stress has become a major focus of interest in most biomedical disciplines and many types of clinical research. Oxidative stress is one of the important risk factors for onset and progression of diabetes and its associated complications[13].Melondialdehyde (MDA) is a product of lipid peroxidation which is widely used biomarker for oxidative stress in T2DM[14-18]. Catalase (CAT) is regulator of hydrogen peroxide metabolism which is also used as a marker of antioxidant in many studies[13,15,16,19,20]. The lung is one of the most common target organ of oxidative damage because of its direct exposure with oxidants in surrounding air[21]. Though research evidence indicate that oxidative stress may play a key role in the pathogenesis of various obstructive and restrictive lung diseases but there is very little population based data to find out relationship between oxidative stress and pulmonary function impairment. Although several reports from general population and chronic obstructive pulmonary disease (COPD) patients are available but no published data was found to conclude on the relationship between oxidative stress and impaired lung function in T2DM. Therefore, the present study has been designed to assess the relationship between oxidative stress and some aspects of lung functions in type 2 diabetes mellitus.

Methods

This cross sectional study was carried out from September, 2018 to August, 2019 in the Department of Physiology, BSMMU, Dhaka to observe the relationship between oxidative stress and lung function in thirty five newly diagnosed male type 2 diabetic patients aged 30 to 50 years recruited from the Out Patient Department of Endocrinology of BSMMU, Dhaka by purposive sampling. Diagnosis was done by the clinicians of endocrine unit of medicine of BSMMU according to criteria of American Diabetes

Association (ADA)[22]. Thirty five age and BMI matched apparently healthy male were taken as control. The protocol of this study was approved by the Institutional Review Board of BSMMU. Patients with cardiac disease, respiratory disease, renal disease, chronic liver disease and thyroid disorders were excluded from the study. After briefing about the study, informed written consent was taken from each subject. Detail family, medical and dietary history was recorded in a preformed data schedule and thorough physical examination was done. Anthropometric measurement including height and weight were taken and BMI were calculated. Then venous blood was collected under aseptic precaution for estimation of fasting plasma glucose, serum ALT, serum TSH and serum creatinine by autoanalyzer in the laboratory of Department of Biochemistry and Molecular Biology and plasma catalase and plasma MDA in the Department of Physiology by competitive ELISA technique and spectrophotometry. FVC, FEV_1 and FEV_1/FVC% of all subjects were recordedby using a portable spirometer and then data were fed into a computer with software for analysis (PONY FX, cosmed, Italy) in the lung function laboratory in the Department of Physiology. Data were expressed as mean ± SD and percentage. For statistical analysis, independent sample 't' test, chi-square test, pearson's correlation test and multiple regression analysis were applied by using SPSS for windows version 16. In the interpretation of results, p value<0.05 was considered as statistically significant.

Results

General characteristics of all subjects are presented in the Table I.Both groups were comparable in respect of age and BMI. The mean percentage of predicted value of FVC and FEV_1 were significantly lower in T2DM than those of control ($p<0.001$). But the difference in FEV_1/FVC between the groups was not significant (Table II). The frequency of restrictive pattern of pulmonary dysfunction was significantly higher in T2DM than those of control($p<0.001$) (Figure 1). The mean plasma catalase was significantly lower ($p<0.01$) and plasma MDA was significantly higher ($p<0.001$) in T2DM than those of control(Table III). In addition, In the group of type 2 DM, FVC and FEV_1showed negative correlation and FEV_1/FVC showed positive correlation with plasma MDA level but it was statistically significant only for FVC ($p<0.05$) (Figure 2-4). FVC, FEV_1 and FEV_1/FVC showed positive correlation with plasma catalase level but all these were statistically non significant in group A (Table IV). Moreover, significant inverse relationship of FVC and FEV_1 was noted ($p<0.05$) but FEV_1/FVC showed positive relationship with plasma MDA but it was statistically not significant ($p>0.05$) in diabetic patients (Table V-VII).In the group of type 2 DM, FVC, FEV_1 and FEV_1/FVC showed positive relationship with plasma catalase but all these were statistically not significant ($p>0.05$) (Table V-VII).

Table I: General characteristics of participants of two groups (N=70)

Variables	Control (n= 35)	T2DM (n= 35)
Age	36.17±6.33	37.88±6.99
(Year)	(30-50)	(30-50)
BMI	22.92±1.81	23.02±1.76
(Kg/m^2)	(18.15-24.92)	(18.29-24.91)
Pulse rate	75.91±3.76	76.68±3.75
(beats/min)	(72-85)	(72-84)
SBP	115.43±6.57	117.14±7.10
(mmHg)	(110-130)	(110-130)
DBP	75.77±3.78	74.57±4.59
(mmHg)	(70-80)	(70-85)

Data were expressed as mean ± SD. Values in parentheses indicate ranges; Statistical analysis was done by Independent sample 't' test; T2DM-Newly diagnosed type 2 diabetic patients; Control-Apparently healthy subjects; BMI-Body Mass Index; SBP- Systolic Blood pressure; DBP- Diastolic Blood Pressure; ns- non significant ($p>0.05$);N-Number of subjects; n- number of subjects.

Table II: FVC, FEV_1 and FEV_1/FVC (% of predicted value) in two groups (N=70)

Variables	Control (n=35)	T2DM (n=35)
FVC	86.88±8.37 (69-105)	74.25±9.24*** (58-93)
FEV_1	84.82±8.39 (67-103)	73.60±9.40*** (51-87)
FEV_1/FVC%	101.74±6.64 (89-111)	102.57±8.15 (71-114)

Data were expressed as mean ± SD. Values in parentheses indicate ranges; Statistical analysis was done by independent sample 't' test; T2DM-Newly diagnosed type 2 diabetic patients; Control-Apparently healthy subjects; FVC-Forced vital capacity; FEV_1-Forced expiratory volume in 1st second; ns- non significant ($p > 0.05$); ***$p < 0.001$; N-Number of subjects; n = number of subjects.

Table III: Plasma catalase and MDA in two groups (N=70)

Variables	Control (n= 35)	T2DM (n= 35)
Plasma catalase (U/ml)	276.06± 108.16 (116-463)	212.89± 82.73** (67-432)
Plasma MDA (ng/ml)	179.76± 88.58 (100.20-439.11)	368.03± 173.88*** (156.60-699.26)

Data were expressed as mean±SD. Values in parentheses indicate ranges; Statistical analysis was done by Independent sample t-test; MDA-Malondialdehyde; T2DM-Newly diagnosed type 2 diabetic patients; Control-Apparently healthy subjects; ** $p < 0.01$; *** $p < 0.001$; N-Number of subjects; n-number of subjects.

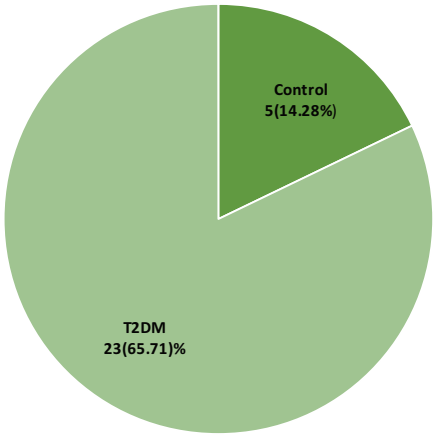

Figure 1: Frequency distribution of restrictive pattern of pulmonary dysfunction in two groups (N=70). Data were expressed as number and percentage.

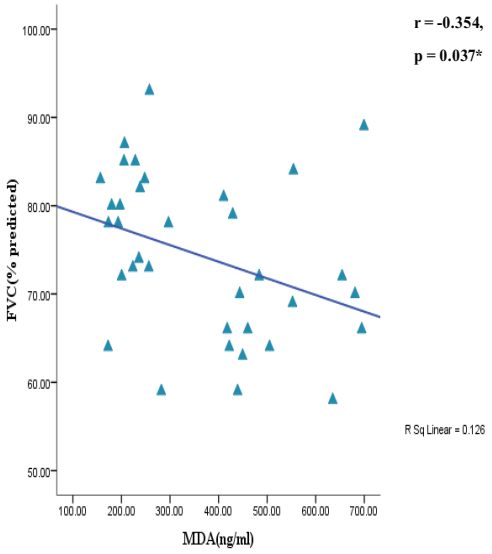

Figure 2: Correlations of FVC (% predicted) with plasma MDA levels (ng/ml) in Newly diagnosed type 2 diabetic patients; FVC-Forced vital capacity; MDA-Malondialdehyde; *$p<0.05$.

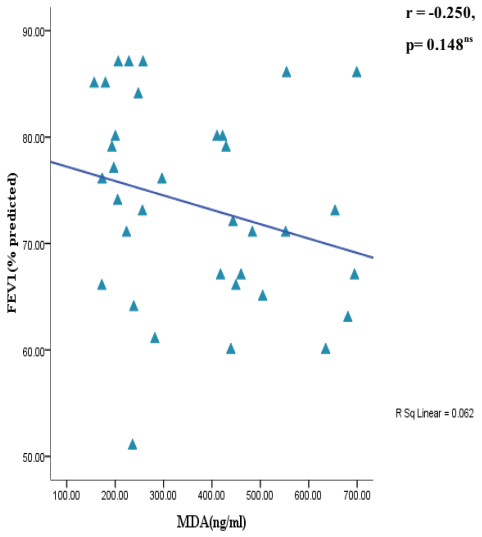

Figure 3: Correlations of FEV_1 (% predicted) with plasma MDA levels (ng/ml) Newly diagnosed type 2 diabetic patients; FEV_1 - Forced expiratory volume in 1st second; MDA- Malondialdehyde; ns- statistically nonsignificant.

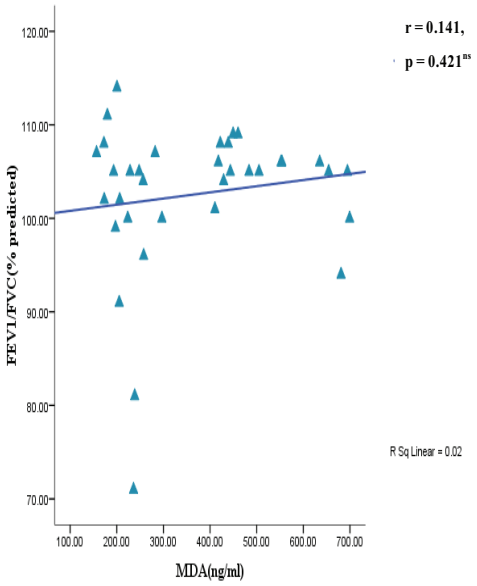

Figure 4: Correlations of FEV_1/FVC ratio with plasma MDA levels (ng/ml) Newly diagnosed type 2 diabetic patients; MDA- Malondialdehyde; ns- statistically nonsignificant.

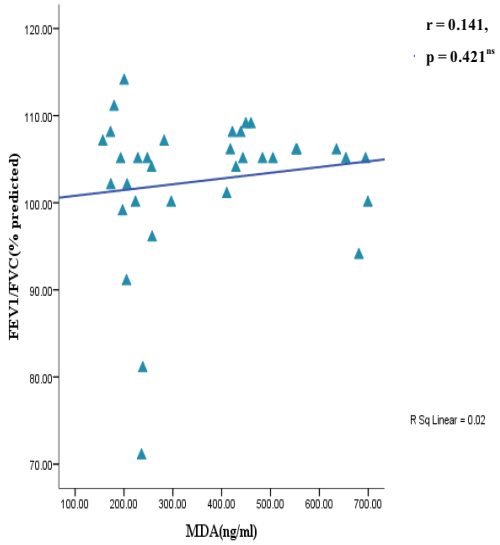

Figure 4: Correlations of FEV_1/FVC ratio with plasma MDA levels (ng/ml) Newly diagnosed type 2 diabetic patients; MDA- Malondialdehyde; ns- statistically nonsignificant.

Table IV: Correlations of FVC, FEV_1 and FEV_1/FVC(% of predicted value)with plasma catalase level inT2DM (n= 35)

Variables	T2DM	
	r value	p value
FVC	0.048	0.784
FEV_1	0.169	0.332
FEV_1/FVC	0.063	0.720

Statistical analysis was done by pearson correlation test. T2DM-Newly diagnosed type 2 diabetic patients; FVC-Forced vital capacity; FEV_1-Forced expiratory volume in 1st second n-number of subjects.

Table V: Multiple regression analysis of FVC (dependent variable) with plasma catalase and MDA levels (independent variable) in T2DM (n= 35)

FVC	Coefficients		95% CI		p
	B	β	Lower limit	Upper limit	value
Constant	77.653	-	68.503	86.802	0.000
Plasma Catalase(U/ml)	0.024	0.218	-0.015	0.064	0.221
Plasma MDA(ng/ml)	-0.023	-0.439	-0.042	-0.004	0.017*

T2DM-Newly diagnosed type 2 diabetic patients; FVC-Forced vital capacity; MDA-Malondialdehyde; *p<0.05; n-number of subjects.

Table VI: Multiple regression analysis of FEV_1(dependent variable) with plasma catalase and MDA levels (independent variable) in T2DM (n= 35)

FEV_1	Coefficients		95% CI		p value
	B	β	Lower limit	Upper limit	
Constant	73.415	-	63.994	82.836	0.000
Plasma Catalase(U/ml)	0.036	0.313	-0.005	0.077	0.087
Plasma MDA(ng/ml)	-0.020	-0.371	-0.040	0.000	0.044*

T2DM-Newly diagnosed type 2 diabetic patients; FEV_1 - Forced expiratory volume in 1st second; MDA-Malondialdehyde; *p<0.05; ns- non significant (p >0.05); n-number of subjects.

Table VII: Multiple regression analysis of FEV_1/FVC (dependent variable) with plasma catalase and MDA levels (independent variable) in T2DM(n= 35)

FEV_1/FVC	Coefficients		95% CI		p value
	B	β	Lower limit	Upper limit	
Constant	100.008	-	91.261	108.756	0.000
Plasma Catalase(U/ml)	0.001	0.010	-0.037	0.039	0.477
Plasma MDA(ng/ml)	0.006	0.137	-0.012	0.025	0.959

Group A-Newly diagnosed type 2 diabetic patients; FVC-Forced vital capacity; FEV_1 - Forced expiratory volume in 1st second; MDA-Malondialdehyde; ns- non significant (p >0.05); n-number of subjects.

Discussion

In this study the results of significant lower values of all lung function parameters except FEV_1/FVC ratio strongly suggests impaired lung function in T2DM which agrees reports of some previous studies[4-10].In addition, the non significant difference of FEV_1/FVC ratio between groups and absence of abnormal values of FEV_1/FVC in any subject of both groups in the present study also suggests lack of obstructive dysfunction but hinted towards restrictive pattern of pulmonary dysfunction in T2DM patients[7]. It has been supported by the evidence of high frequency distribution of restrictive pattern in

diabetic patient compared to control participated in the study. To explore the oxidative stress among the study participants, the lower plasma catalase level in T2DM patients agrees to other previous investigators suggesting the lower antioxidant status in these diabetic patients[13,19-20].Moreover, significantly higher plasma MDA was found in T2DM patients than those of control group. Similar results of higher plasma MDA in T2DM was reported by some previous investigators[13-18].These results suggest that there is oxidative stress in T2DM. In diabetic patients of this study, significant positive correlation of PEFR with plasma catalase level suggests airflow is well correlated to antioxidant status. In addition, significant negative correlation of FVC with plasma MDA level in T2DM patients indicates their reduced lung function was related to their increased level of oxidants i.e. higher oxidative stress. Similar observation was reported in general population[23-24]. In these studies FVC and FEV_1 was found to have significant correlation with MDA. In diabetic patients, on regression analysis significant positive association of PEFR was noted with plasma catalase after adjustment with plasma MDA. This feature suggests low antioxidant status in T2DM patients is attributed to their reduced ventilatory function. In this study, significant inverse relationship of FVC and FEV_1 was noted with plasma MDA after adjustment with plasma catalase in T2DM. Similar negative association of FVC and FEV_1 with MDA level was also cited by other researchers in both COPD patients and general population[23-25]. These findings provide evidence for impaired lung function was significantly associated with increased oxidative stress. Oxidative stress can directly damage lung tissue and stimulates expression of pro-inflammatory cytokines such as tumour necrosis factor-*á*, interleukin-1, interleukin-12, cell adhesion molecules and inducible nitric oxide synthase, plasminogen activator inhibitor-1 and pro-fibrotic cytokines such as transforming growth factor-*â*, connective tissue growth factor and fibroblast growth factor, resulting in enhanced inflammatory response, fibroblast proliferation, collagen accumulation and extracellular matrix deposition. All these pathogenic changes would cause lung fibrosis and eventually affect lung ventilation[21,24,26,2l]. From the analysis of results of this study it may summarize that there is pulmonary impairment in the present series of T2DM patients and most of which is characterized by restrictive pattern. In addition, there is oxidative stress in T2DM patients in this study. Moreover, impaired lung function in current series of diabetic patients is associated with their oxidative stress.

Conclusion

From the results of this study it is concluded that restrictive pattern of pulmonary dysfunction is related to higher oxidative stress in T2DM.

Conflict of interest The authors have no conflict of interest

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