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Pulmonary Function Tests in Type 2 Diabetes Mellitus and Their Relationship with Glycemic Control and Duration of the Disease-A Randomized, Double-Blind and Placebo Control Study

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ABSTRACT

Aim: *To evaluate the pulmonary function tests in type 2 Diabetes Mellitus (DM) patients and to determine the co-relation of the HbA1c and duration of the disease with PFTs in type 2 DM patients.* ***Study Design:*** *Randomized, double-blind, and placebo control study.* ***Place and Duration of Study:*** *Department of Medicine, ASCOMS College, and Hospital conducted from 1st November 2019 to 31st October 2020.* ***Methodology:*** *The basic parameters of the subjects like age, sex, weight in kg, and height in cm were recorded. Each subject was instructed to visit the bio-chemistry laboratory with 6 hrs of fasting on a specific date. The FBS and HbA1c were estimated using standardized methods. Spirometry was performed to assess pulmonary functions. The results were analyzed using SPSS version 10.0 software. Using this software, frequencies, range, mean, standard deviation, and 'p' were calculated through Student 't' test, One-way ANOVA, Pearson Correlation, and Chi-square test. The p-value of <0.05 was considered significant.* ***Results:*** *The highest number of patients was recorded in the age group of 61-70 years. The mean age of the cases was 59.38 years while in the control group the mean age was recorded as 55.84 years. Sex distribution of the patients showed males and females were in the ratio of 66:34 while in the control group males were 64% and females were 36%. HbA1c was recorded significantly higher in cases (8.23) as compared to the control group (5.02). Type 2 Diabetes Mellitus (DM) patients had a mean of 67.96 with a range of 48.19-87.73 compared to controls having a mean of 102.24 with a range of 82.13-122.35. Type 2 DM patients had a mean of 109.28 with a range of 93.81-124.75 compared to controls having a mean of 101.70 with a range of 91.56-111.28. Age distribution and HbA1c showed significant association. The highest HbA1c was recorded in the age group of more than 70 years (10.73) which was followed by 51-60 years (7.92) while the lowest HbA1c was recorded in the age group of fewer than 40 years (4.33).* ***Conclusion:*** *FVC and FEV1 were decreased in Type-2 diabetes mellitus compared to controls, whereas the ratio of the two (FEV1/ FVC%) was increased. There was a negative correlation between the duration of diabetes mellitus and pulmonary functions FEV1% Pred, FVC% Pred. A linear relationship exists between increasing duration and FEV1/ FVC%, which is indicative of restrictive disorder of the lung. As the HbA1c level increases, the spirometry values FVC and FEV1 were consistently decreased. Patients with type 2 diabetes mellitus should undergo pulmonary function tests intermittently to detect pulmonary complications.*

Keywords: Type 2 diabetes mellitus, Pulmonary Function Tests (PFTs), Spirometry, Pulmonary complications

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency [1]. This is typically a multi-organ chronic disease and is associated with a ten-year-shorter life expectancy due to its complications. Measurement of glycated haemoglobin (HbA1c) is the standard method for the assessment of long-term glycemic control. HbA1c is a form of haemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods [2].

Pulmonary complications of Diabetes Mellitus (DM) have been poorly characterized with conflicting results. The alveolar-capillary network in the lung is a large micro-vascular unit and may be affected by microangiopathy. There are histopathological changes seen in the lungs of diabetics such as thickened alveolar epithelial and pulmonary capillary basal lamina leading to reduced pulmonary elastic recoil and lung volume. There is impaired diffusion due to reduced pulmonary capillary blood volume and thickening of the basement membrane [3].

Ljubic, et al. in 1998 showed that diabetes could lead to the development of pulmonary complications due to collagen and elastin changes [4].

Dalquen P, in 1999 suggested that increased non-enzymatic glycation of proteins and peptides of the extracellular matrix at chronic high circulating glucose levels may also have an important role in the pathological changes of the lungs in DM patients [5].The association between reduced lung function and diabetes has been described for many years. Although the clinical significance of this association is not known, it is interesting to think of the lung as another end-organ adversely affected by diabetes. It is also interesting to consider that reduced lung function may be present before the clinical recognition of diabetes or insulin resistance suggesting that the lung may be involved in the pathogenesis of diabetes [6,7].

Diabetes mellitus causes abnormalities in the structural components leading to the development of abnormalities in the pulmonary function such as a reduction in the vital capacity, total lung capacity, lung compliance, reduction of central and peripheral airflows, acceleration of the aging process, alteration in the pulmonary connective tissue by thickening of the alveolar and capillary endothelial basement membranes and modifications of alveolar surfactants altering its function and pulmonary microangiopathy brings about a reduction in diffusing capacity and the muscle endurance [8].

Clear decrements in lung function have been reported in patients with diabetes over the past two decades. However, there are no reports of functional limitations of activities of daily living ascribable to pulmonary disease in patients with diabetes [9].

Aims and Objectives

To evaluate the pulmonary function tests in type 2 diabetes mellitus patients and compare them with the age and gender-matched healthy controls and to determine the co-relation of the HbA1c and duration of the disease with PFTs in type 2 DM patients.

MATERIALS AND METHODS

The study was carried out in collaboration with the Diabetes Outpatient and Inpatient Department of Medicine, ASCOMS College, and Hospital. 50 patients with type 2 DM diagnosed by the treating physician, were randomly selected from the Diabetes Outpatient and Inpatient Department. It was a case-control study with hospital-based computer-generated randomized double-blind, placebo control. The study was conducted from 1st November 2019 to 31st October 2020.

The study protocol was approved by the Institutional Ethics Committee. 50 normal healthy individuals of the same age group from patient′s relatives were selected as a control group. Informed written consent was taken from patients as well as from controls. The controls were thoroughly examined clinically. PFTs of the patients as well as of the controls were performed with-RMS Helios 401 computerized spirometer between 9 am and 3 pm. All the tests were conducted according to the American Thoracic Society/European Respiratory Society (ATS/ERS guidelines) in a quiet room in a sitting position by the trained personnel. The controls and patients performed spirometry three times at the interval of 15 minutes and the best of the three was taken into account. For all these parameters percentage of predicted values for the respective age, height, and weight were taken into consideration. Fasting and postprandial blood glucose levels were measured by the glucose oxidase method to rule out type 2 DM in them. Nearly 2 ml of venous blood was collected in Ethylene Diamine Tetra Acetic Acid (EDTA) bulb in all the diabetic patients with aseptic precautions. HbA1c of all the patients was estimated by the ion exchange resin method by the diagnostic glycosylated haemoglobin kits as per the guidelines provided.

Inclusion criteria included previously diagnosed diabetic patients of more than 1-year duration, non-smokers, with no previous history of any respiratory diseases and clinically ruled out cardiovascular diseases like arterial hypertension, dyslipidemia, etc.

Exclusion criteria included patients having complaints of cough, sputum, or dyspnea, smokers, tobacco chewers, and patients with any cardio-respiratory illnesses or major diseases like cancer, tuberculosis, liver cirrhosis, etc. and patients who underwent chest trauma and chest surgery.

Methodology

The cases and controls were selected as per the inclusion and exclusion criteria. Written consent was taken after explaining the procedure in the language best understood by them. The basic parameters of the subjects like age, sex, weight in kg, and height in cm were recorded. Each subject was instructed to visit the biochemistry laboratory with 6 hrs of fasting on a specific date. The blood samples (2 ml) were drawn for the estimation of FBS and glycated hemoglobin. The FBS and HbA1c were estimated using standardized methods. Spirometry was performed using RMS Helios 401 computerized spirometer to assess pulmonary functions three times for each subject and the best of the three was considered. The objective of the test was to obtain a reproducible flow-volume loop and a volume time curve. The information collected regarding all the selected cases and controls was recorded in a Master Chart. The results were analyzed using SPSS version 10.0 software. Using this software, frequencies, range, mean, standard deviation, and 'p' were calculated through the student 't' test, One-way ANOVA, Pearson Correlation, and Chi-square test. The p-value of <0.05 was considered significant.

RESULTS

Spirometry was done in 50 Type 2 Diabetes mellitus patients and 50 healthy volunteers. The aim was to find out the effect of diabetes mellitus on lung functions. Rearrangements of the master charts were done according to the requirements to find out the relationship of variables like duration of DM, Fasting Blood Sugar (FBS), and HbA1c on the pulmonary functions. Student 't' test was used to analyze the statistical difference of the spirometry values between the 2 groups. Pearson's correlation coefficient test was used to find out the statistical correlation of spirometry values with a duration of DM, FBS, and HbA1c.

In cases, the highest number of patients were recorded in the age group of 61-70 years. The mean age of the cases was 59.38 years while in the control group the mean age was recorded as 55.84 years. The sex distribution of the patients showed non-significant differences between cases and control groups. In cases, males and females were in the ratio of 66:34 while in the control group males were 64% and females were 36%.

A perusal of Table 1 and Figure 1 indicates significant differences between cases and control concerning the Random Blood Sugar (RBS). In cases, the RBS was recorded as 252.20 while in the control group it was observed as 89.14.

Table 1 Group comparison for RBS, HbA1c, PFT, and pattern of PFT

Variables	Mean age ± Standard Deviation		p-value
	Case	Control	
Random Blood Sugar			
RBS	252.20 ± 46.95	89.14 ± 13.97	<0.0001
HbA1c			
HbA1c	8.23 ± 1.21	5.02 ± 0.35	<0.0001
Pulmonary Function Tests			
FEV1% PRED	73.26 ± 19.97	107.14 ± 19.55	<0.0001
FVC% PRED	67.96 ± 19.77	102.24 ± 20.11	<0.0001
FEV1/FVC	109.28 ± 15.47	101.70 ± 10.14	0.004
Pattern of Pulmonary Function Tests			
Obstruction	2 (4.0)	6 (12.0)	
Restriction	40 (80.0)	6 (12.0)	
Normal	8 (16.0)	38 (76.0)	
p-value	<0.0001		

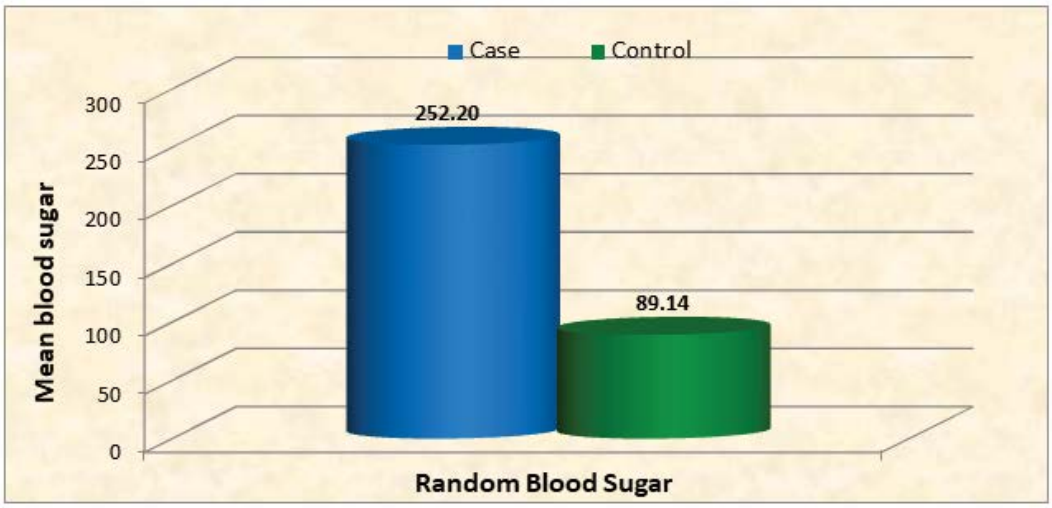

Figure 1 Group comparison for Random Blood Sugar (RBS)

HbA1c was recorded significantly higher in cases (8.23) as compared to the control group (5.02) as shown in Table 1 and Figure 2.

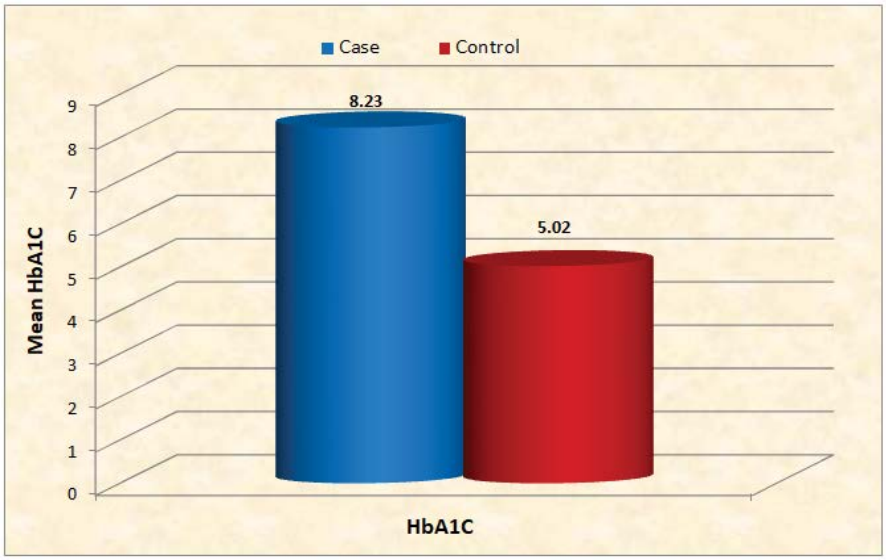

Figure 2 Group comparison for HbA1c

There were significant differences between cases and control groups with regards to the pulmonary function tests. FEV1% PRED (percentage of predicted forced expiratory volume at 1 sec) and FVC% PRED (percentage of predicted forced vital capacity) values were recorded lower in cases group while FEV1/FVC (Forced Expiratory Volume at 1 sec to Forced Vital Capacity) was noticed higher in case group and the decrease in FVC% PRED was more than the decrease in FEV1% PRED. Table 1 and Figure 3 reveal that the FEV1% PRED in Type 2 DM is decreased when compared to the control group. Type 2 DM patients had a mean of 73.26 with a range of 53.29-93.23 compared to controls having a mean of 107.14 off with a range of 87.59-126.69. The results show that the FEV1 in diabetics is decreased. FVC% PRED in Type 2 DM is decreased when compared to the control group. Type 2 DM patients had a mean of 67.96 with a range of 48.19-87.73 compared to controls having a mean of 102.24 with a range of 82.13-122.35. There is little difference in FEV1/FVC in the form of increment when compared to the controls which are of statistical significance. Type 2 DM patients had a mean of 109.28 with a range of 93.81-124.75 compared to controls having a mean of 101.70 with a range of 91.56-111.28.

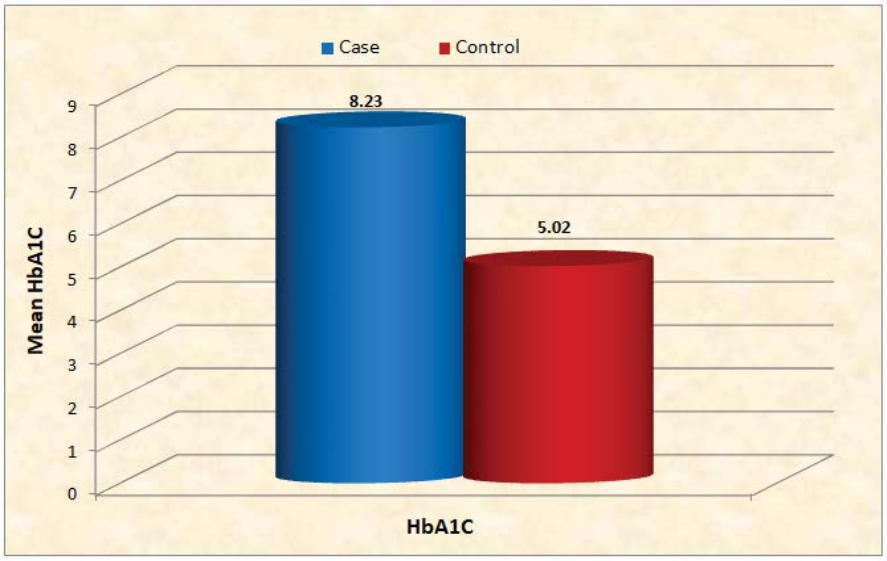

Figure 3 Group comparison for Pulmonary Function Tests (PFTs)

A perusal of Table 1 and Figure 4 revealed that 80% restriction was noticed in cases while in the control group only 12% restriction was observed. The statistical differences were significant. According to our study profile, most of the people with Type 2 diabetes mellitus were having a restrictive type of lung disease. About 80% were having a restrictive pattern and about 4% had an obstructive pattern and about 16% had a normal pattern. The relation between Type 2 diabetes mellitus and restrictive pattern of lung disease is statistically significant.

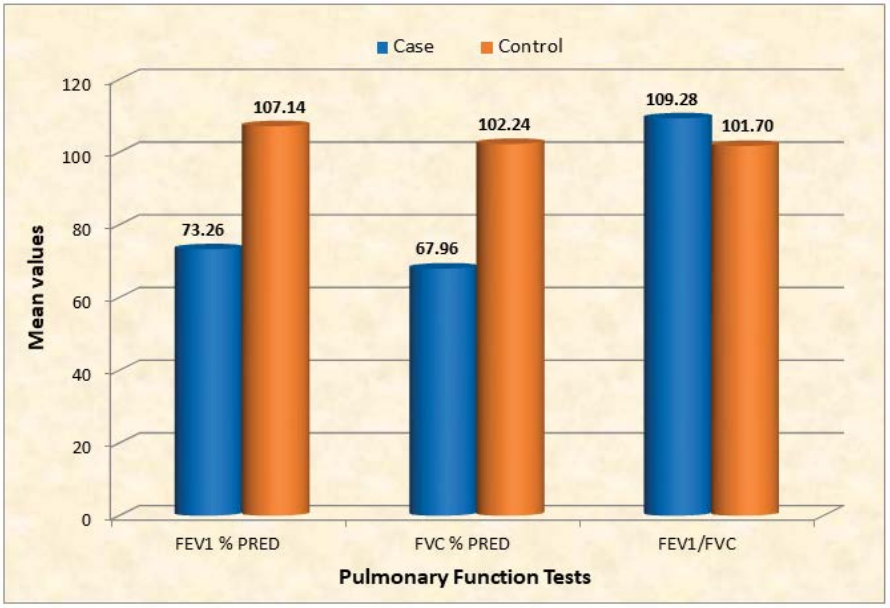

Figure 4 Group comparison for a pattern of pulmonary function tests

About the duration of diabetes, the patients were distributed into five groups. Amongst the five groups, the highest number of patients was recorded in 7-8 years (34%) which was followed by 9-10 years (24%) and 5-6 years (20%) while the lowest number of patients was found in less than 4 years group (10%). The mean duration of the disease was 8.04 years. Age distribution and HbA1c showed significant association. The highest HbA1c was recorded in the age group of more than 70 years (10.73) which was followed by 51-60 years (7.92) while the lowest HbA1c was

recorded in the age group of fewer than 40 years (4.33). FVC has a moderate negative correlation and FVC% have a strong negative correlation with HbA1c levels i.e. FVC and FVC% decreases as the HbA1c increases. FEV1 has a weak negative correlation than FEV1% which has a strong negative correlation i.e. FEV1 and FEV1% decreases as HbA1c value increases. FEV1/FVC has a weak negative correlation and FEV1/FVC% has no significant relationship concerning the HbA1c values. A perusal of Table 2 and Figure 5 indicates that the association between HbA1c with FEV1 and FVC was negative but statistically significant while it showed positive and significant association with FEV1/FVC which indicates that an increase in HbA1c i.e. poor glycemic control is associated with a decrease in Pulmonary Functions.

Table 2 Co-relation of the HbA1c and PFT

HbA1c Correlation Coefficient		p-value
Association of HbA1c and FEV1% PRED, FVC% pred, FEV1/FVC		
FEV1	-0.689	<0.0001
FVC	-0.842	<0.0001
FEV1/FVC	0.380	0.007
Association of the duration of diabetes and FEV1% PRED, FVC% PRED, FEV1/FVC		
FEV1	-0.46	0.001
FVC	-0.453	0.001
FEV1/FVC	0.300	0.034

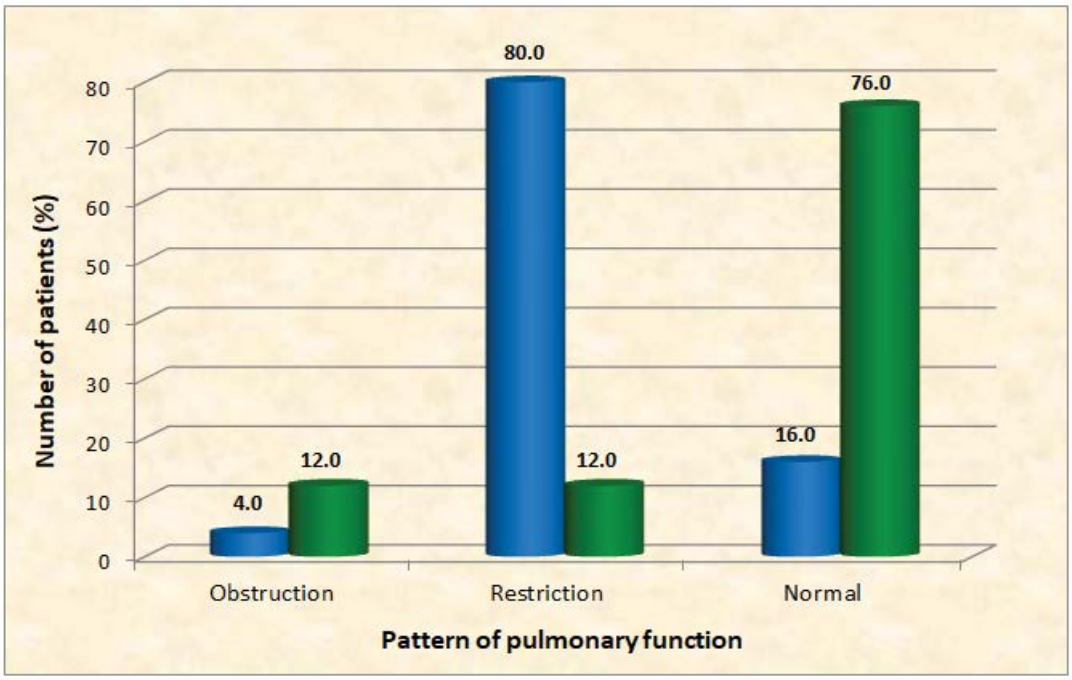

Figure 5 Co-relation of the HbA1c and PFT; association of HbA1c and FEV1% PRED, FVC% PRED, FEV1/FVC

Data presented in Table 2 and Figure 6 indicates that the association between the duration of diabetes with FEV1 and FVC was negative but statistically significant while it showed a positive and significant association with FEV1/FVC. FVC% PRED has a negative correlation concerning the duration of diabetes i.e. FVC decreases with increasing duration of diabetes. FEV1% PRED also has a negative correlation concerning the duration of diabetes i.e. FEV1 decreases with increasing duration of diabetes.

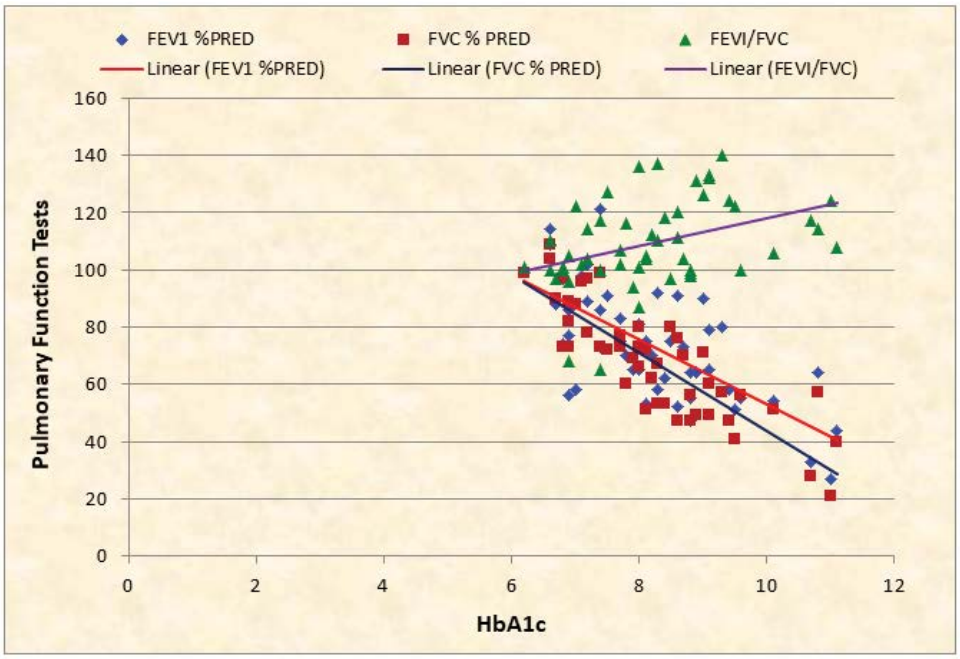

Figure 6 Co-relation of the duration of diabetes and PFT; association of duration of diabetes and FEV1% PRED, FVC% PRED, FEV1/FVC

DISCUSSION

This study was done to find out the impact of diabetes or pulmonary functions. Two Groups namely the study and control groups were assigned with the fulfillment of inclusion and exclusion criteria already mentioned. 100 participants were studied of which 50 had Type 2 diabetes mellitus (cases) and 50 without diabetes mellitus (controls) and the males were 65 and females were 35 in number. The age distribution in our study was mostly between 45-70 years. Pulmonary function tests were conducted in all the persons. The FEV1 and FVC both are reduced in type 2 diabetic patients and the FEV1/FVC is increased. The p-value for FEV1 in type 2 diabetics was <0.0001 and for FVC was <0.0001. The pattern of lung disease was mostly restrictive in patients having type 2 diabetes mellitus. Only 2 persons with diabetes had the obstructive type of disease and the p-value was <0.0001. A statistically significant value in the correlation between HbA1c and pulmonary function test results was noted and the p-value was <0.0001.

In a study done by Robert E. Walter, et al. it was found that there was a progressive decrease in the mean forced vital capacity value of 109 ml/year. The FEV1/FVC% has increased in type 2 diabetics as compared to that in the controls and the increase was statistically significant. The increased FEV1/FVC% suggested that the impairment of pulmonary functions in type 2 diabetics was primarily restrictive [10].

Davis Timothy M, et al. in 2000 found that pulmonary function is reduced in type 2 DM and diabetes duration has more influence on pulmonary function than glycemic control [11].

Davis, et al. in 2004 conducted a study and detected that almost all the parameters like forced vital capacity, forced expiratory volume at 1st second are decreased so that the ratio is increased almost most of the patients with uncontrolled diabetes mellitus [12]. Miller MR, et al. in 2002 cleared that type 2 diabetes mellitus to affect the lung and lung may be the target organ for damage and the pattern of disease is restrictive [13].

Although the underlying mechanisms which relate type 2 diabetes to reduced lung functions remain unclear, previous studies have suggested several possible explanations, which include glycosylation of chest wall and bronchial tree proteins and increased cross-linkage formation between polypeptides of collagen in pulmonary connective tissue, which decreases Forced vital capacity, basal lamina thickening, and increased susceptibility to respiratory infections.

Mario Cazzola, et al. in 2012 found that human isolated bronchi elucidated the obstructive nature of pulmonary

pathology in diabetes at a molecular level [14]. Thus, hyperglycemia may contribute to obstruction of airways. The lungs are affected by diabetic microangiopathy concluded in a study by Engstrom G, et al. in 2002 [15]. This was evidenced autopsy findings in human diabetic subjects which showed pulmonary microangiopathy, thickening of alveolar epithelia, pulmonary capillary basal lamina thickening, centrilobular emphysema, and thickening of alveolar epithelia. Type 2 Diabetes mellitus can cause the development of pulmonary complications due to collagen and elastin changes as well as microangiopathy in a study conducted by Viberti GC, et al. in 2003 and Boulbou MS, et al. in 2003 [16,17].

A study conducted by Walter E. Robert, et al. in 2003 on the association between glycemic state and lung function concluded that higher levels of FBS were associated with lower pulmonary function [10].

SK Rajan, et al. in 2002 conducted a study on spirometry evaluation of type 1 DM and the study shows normal findings in 10 patients (33%) and abnormal findings in 20 patients (67%). Among these 20 patients (67%) with abnormal findings, the obstructive pattern was present in 12 patients (60%), the restrictive pattern was present in 6 patients (30%) and a mixed pattern was observed in 2 patients (10%) [18].

Muhammad Irfan, et al. in 2011 concluded in their study that diabetic patients showed impaired lung function independent of smoking. This reduced lung function is likely to be a chronic complication of diabetes mellitus [19].

Limitation

The maneuver is highly dependent on patient cooperation and effort and is normally repeated at least three times to ensure reproducibility. Since results are dependent on patient cooperation, FVC can only be underestimated, never overestimated in a study done by Simon, et al. in 2010 [20]. Moreover, there are some regional limitations to conducting spirometry tests due to several barriers to access health care, limited health care facilities, physician shortages [21].

CONCLUSION

Spirometry is a useful test to know the prevalence of restriction patterns in lung functions. In the diabetic group, spirometry parameters like FVC, FEV1 were decreased in Type 2 diabetes mellitus compared to controls, whereas the ratio of the two (FEV1/FVC%) was increased. These results can be attributed to the non-enzymatic glycosylation of connective tissue resulting in the non-enzymatic glycosylation of connective in diabetic patients. The present study concluded that there was a negative correlation between the duration of diabetes mellitus and pulmonary functions and a linear relationship exists between increasing duration and FEV1/FVC%, which is indicative of restrictive disorder of the lung due to poor glycemic control in diabetics. The present study adds to the literature insisting on the prevalence of restriction patterns of lung function in diabetics and hence suggests more extensive works on this field. The present study concluded that patients with type 2 diabetes mellitus should undergo pulmonary function tests intermittently to assess and detect the pulmonary complications in the earlier stages.

DECLARATIONS

Acknowledgment

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Conflicts of Interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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