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Original Article

# Correlation of Lung Volumes with HbA1c and Duration of Diabetes, in Type 2 Diabetics, at a Tertiary Care Hospital, Karachi, Pakistan.

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**Abstract:**

**Introduction:** Various studies have detected a link between lung abnormalities and Diabetes Mellitus (DM) but this relationship isn't that well established.

**Objectives**: To document the correlation between pulmonary function tests (PFTs) and glycated hemoglobin (HbA1c) and the duration of DM.

**Methodology**: This single-center study recruited 100 individuals with Diabetes Mellitus, who presented to the medicine Outpatient department (OPD) or admitted in Medical Unit-1/C1 of "Dr. Ruth KM Pfau Civil Hospital Karachi" from 1st November 2019 till 10th October 2020. Data was analyzed using SPSS version 23.0.

**Results**: Of the 100 participants, the majority of them were men (n=57), had DM for the past ≤8 years (n=54), and had moderately controlled DM with an HbA1c in the range 6.5-7.9 (n=37). The spirometry results of over half of the patients (n=57) were normal however, approximately in one third of them (n=35) restrictive lung pattern was detected. Significant inverse correlations were found between HbA1c and FEV1 (r= -0.281, p-value=0.005), HbA1c and FEV1/FVC (r= -0.386, p-value=0.000), duration of DM and FEV1 (r= -0.259, p-value=0.009) and duration of DM and FEV1/FVC (r= -0.381, p-value=0.000).

**Conclusion**: A significant relationship was found between lung function tests (FEV1 and FEV1/FVC ratio) and poor glycemic control and increased duration of DM; therefore, periodic assessment of PFTs and HbA1c is crucial in early screening and management of lung abnormalities in type2 diabetics.

**Keywords:** Type 2 DM, HbA1c, "Forced Vital Capacity (FVC)", "Forced Expiratory Volume in 1second (FEV1)", "Pulmonary Function test (PFT)"

## Introduction:

Diabetes mellitus (DM), a chronic disorder with persistently raised blood glucose levels over several years leading to the development of "micro-vascular and macro-vascular" complications.1 Diabetes Mellitus prevalence is increasing globally, with recent epidemics confirming its increasing incidence in the South Asian region. 2 It is predicted that by the year 2035, one in ten adults will be affected by this metabolic syndrome.3 DM complications, notably retinopathy, nephropathy, neuropathy, coronary artery diseases, and peripheral vascular complications, are well documented. 4 However, the relationship between DM and lung abnormalities is not yet well established. 5. The bidirectional effect of DM on the lung is clinically evident and progressive lung function abnormalities such as "Forced Expiratory Volume in 1 second (FEV1) and Forced Vital Capacity (FVC)" reduction may be clinically significant in individuals with poor control and prolonged duration of DM.6 Suboptimal lung function has

been observed in immune mediated DM patients in association with duration and the control of DM.7 Moreover, Yang Peng et al. 8 describes an association between DM and restrictive lung abnormalities. Clinically DM is associated with progressive decline in FEV1 which consequently leads to bronchial hyper-responsiveness. The development of respiratory complications in DM is considered multi-factorial. It could be due to "decreased elastic recoil, decreased lung volume, reduced performance of respiratory muscles, decreased diffusion capacity for carbon monoxide (DLCO), and autonomic neuropathy of respiratory musculature".9 Hypoglycemic drugs are also postulated in the development of lung complications. 10 Additionally, large lung reserves may be another important etiology of subclinical lung function abnormalities. 11 However, these changes may become clinically evident in diabetic patients when accompanied by acute or chronic respiratory or cardiac disease.12 Therefore, early diagnosis is required to decrease the incidence of microvascular complications of DM.13 Multiple studies have been conducted to detect pulmonary function abnormalities in diabetic patients with variable results. 14,15 Yet, there is a paucity of data pertaining to the association between DM and lung abnormalities in the Pakistani population. This study done to evaluate the correlation of pulmonary function tests (PFTs) and glycated hemoglobin (HbA1c), duration of diabetes, gender and body mass index (BMI) in the hope of guiding us about the patterns of lung abnormalities observed in Pakistani patients having Type 2 Diabetes (T2D). By establishing this association, we hoped to provide information necessary to design strategies, guidelines and recommendations for lung complications in NIDDM.

**Methodology:**

This study was done at the medical department of tertiary care hospital in Karachi, Pakistan, from 1st November 2019 to 10th October 2020, after getting approval from the Institutional Review Board, Ref ID:IRB-1363/DUHS/Approval/2019. PASS 2019 software was used to calculate the sample size by two-sided Z-test using the power of 99%, frequency of 14.9% 16 and alpha of 0.01. The sample size was estimated to be 37 by the above parameters. 20% was further added to reduce the margin of error that increased the sample size to around 45. The sample size was further inflated to 100 to increase the reliability of the research.

A non-probability convenience sampling technique was used to recruit participants from the medicine outpatient department (OPD) and admitted to Medical Unit-1/C1 of Dr. R. KM. P. Civil Hospital Karachi, Pakistan. Participants having type 2 diabetes for more than a year, either gender, between 30-68 years of age were included in the study. Participants with a known history of chronic lung diseases like "asthma, chronic bronchitis and bronchiectasis, restrictive airway conditions like scoliosis, pulmonary tumors, respiratory infection (upper and lower respiratory tract infection), active or past tuberculosis, occupational lung diseases", smokers and pregnant women were excluded.

Procedure:

After seeking consent from all the participants, detailed history taken and clinical examination performed. The height and weight of the participants were measured and body mass index (BMI) was calculated. Blood samples for HbA1c were drawn by trained phlebotomists. While trained personnel assessed pulmonary function tests (PFTs) using Spirobank-II according to American thoracic guidelines.18

Operational definitions: For the current study purpose following were the operational definitions.

*Diabetes Mellitus:* As per American Diabetes Association (ADA) criteria17, DM is diagnosed if there is: "A fasting plasma glucose (FPG): 126 mg/dL or higher, or A 2-hour plasma glucose level equal to or greater than 200 mg/dl after giving 75-g oral glucose tolerance test (OGTT), or Random plasma glucose (RPG): 200 mg/dl or more in a patient with classic symptoms of hyperglycemia HbA1c greater than or equal to 6.5%"

*Body Mass Index*: BMI= weight (kilograms) /height2 (meters)

*Restrictive lung defect*: If the ratio of "FEVI/FVC (Forced expiratory volume in 1 second/Forced Vital Capacity)" is greater than 70% and the ratio of obtained FVC to predicted FVC less than 80%.

*Obstructive lung defect*: If FEV1/FVC is < 70%".

Mixed ventilatory defect: If FEV1/FVC is < 70% and the ratio of obtained to predicted FVC is < 80%".

Data analysis:

Data transferred into "Statistical Package for the Social Sciences (SPSS version 23.0)" software from Microsoft Excel for analysis. Frequencies and percentages were taken out for categorical variables, while means and standard deviation were estimated for continuous varia-

bles. An Independent sample t-test assuming equal variance was used to compare the PFTs with the duration of DM. One-way ANOVA was used to compare the PFTs with different categories of HbA1c, denoting how well the DM was controlled. Pearson Correlation used to document the association between PFTs and HbA1c and the duration of DM. Significant P-value set as <0.05.

**Results:**

Hundred participants with type II DM were enrolled in the study. The mean age of the patients was 47.53 ±9.36, while the mean BMI of the patients was 7.60 ±1.95. Of the 100 patients, the majority of them were men (n=57), had DM for the past ≤8 years (n=54), and had moderately controlled DM with an HbA1c in the range 6.5-7.9 (n=37). Table 1. is showing demographic characteristics and biochemical profiles of participants.

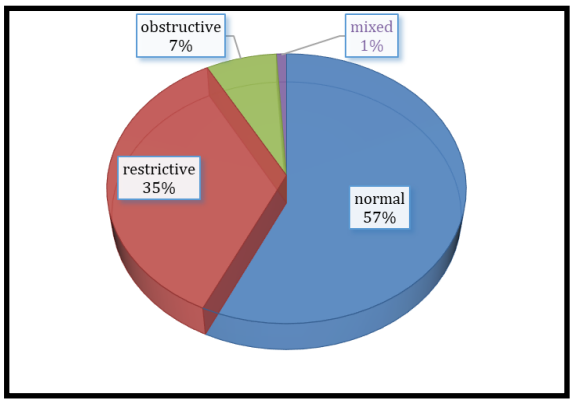
**Table 1: Demographic characteristics and biochemical profiles of the participants.**

| | Total (n=100) |
|---|---|
| Age (years) Mean ± SD | 47.53 ± 9.36 |
| Gender | |
| Male | 57 (57.0%) |
| Female | 43 (43.0%) |
| BMI, Mean ± SD, kg/m2 | 26.82 ± 7.91 |
| Underweight (≤18.4) | 6 (6.0%) |
| Normal (18.5-24.9) | 50 (50.0%) |
| Overweight (25-29.9) | 10 (10.0%) |
| Obese (≥30) | 34 (34.0%) |
| HbA1c, Mean ± SD, % | 7.60 ± 1.95 |
| Good glycemic control (<6.5) | 32 (32.0%) |
| Moderate glycemic control (6.5-7.9) | 37 (37.0%) |
| Poor glycemic control (≥8) | 31 (31.0%) |
| Duration of DM, Mean ± SD, years | 9.25 ± 5.53 |
| ≤8 | 54 (54.0%) |
| >8 | 46 (46.0%) |

*S.D= Standard Deviation, HbA1c = glycated hemoglobin, BMI= Body Mass Index, DM = Diabetes Mellitus.*

Spirometry findings of over half of the patients were normal (n=57); however, about a third of the patients displayed patterns of restrictive lung disease (n=35). Spirometry interpretation of the patients (Fig 1)

**Figure 1: Spirometry results interpretation of the patients.**




Relationship between PFTs and glycemic control:

A one-way ANOVA comparing FEV1 values across the different categories of HbA1c revealed an overall significant difference (F (2, 97) = 7.321, p-value = 0.001). A Post-hoc Scheffe test ascertained those participants with poor glycemic control (HbA1c ≥8%) had significantly reduced (p= 0.001) FEV1 values compared to participants with good diabetic control (HbA1c <6.5%). Comparing FEV1/FVC values across the different categories of HbA1c revealed an overall significant difference (F (2, 97) =7.280, p=0.001). A Post-hoc Scheffe test demonstrated that participants with poor glycemic control (HbA1c ≥8%) had significantly reduced (p-value = 0.001) FEV1/FVC values compared to participants with good glycemic control (HbA1c <6.5%).

**Table 2: Relationship between pulmonary function tests and HBA1c.**

| | HbA1c (%) | | | | |
|---|---|---|---|---|---|
| | Total (n=100) | <6.5 (n=32) | 6.5-7.9 (n=37) | ≥8 (n=31) | P-value |
| FVC, L | 2.82 ±0.53 | 2.92 ±0.42 | 2.84 ±0.52 | 2.71 ±0.62 | 0.271 |
| $FEV_1$, L | 2.41 ±0.49 | 2.65 ±0.38 | 2.38 ±0.47 | 2.21 ±0.52 | 0.001 |
| PEF, L | 2.44 ±0.54 | 2.59 ±0.35 | 2.35 ±0.40 | 2.39 ±0.77 | 0.157 |
| $FEV_1$/ FVC, % | 86.61 ±9.82 | 91.08 ±2.26 | 86.46 ±10.75 | 82.18 ±11.53 | 0.001 |

*FVC = Forced Vital Capacity, FEV1= Forced Expiratory Volume in 1 second, PEF = Peak Expiratory Flow, HbA1c = glycated hemoglobin.*

Relationship between PFTs and duration of Type 2 Diabetes:

Compared to patients who had DM for greater than, or equal to eight years, patients with T2D for less than eight years had a significant decrease in FEV1 (t (98) = -2.114, p-value = 0.037) and FEV1/FVC (t (98) = -2.885, p-value = 0.005) as shown in Table 3.

**Table 3: Relationship between pulmonary function tests and diabetes duration.**

| | Duration of DM (years) | | | |
|---|---|---|---|---|
| | Total (n=100) | ≤8 (n=54) | >8 (n=46) | P-value |
| FVC, L | 2.82 ±0.53 | 2.86 ±0.44 | 2.78 ±0.62 | 0.498 |
| $FEV_1$, L | 2.41 ±0.49 | 2.51 ±0.45 | 2.30 ±0.51 | 0.037 |
| PEF, L | 2.44 ±0.54 | 2.47 ±0.47 | 2.41 ±0.61 | 0.603 |
| $FEV_1$/ FVC % | 86.61 ±9.82 | 89.14 ±5.40 | 83.65 ±12.70 | 0.005 |

*"FVC = Forced Vital Capacity", " FEV1= Forced Expiratory Volume in 1 second",*
*PEF = Peak Expiratory Flow, DM = Diabetes Mellitus*

Correlation of PFTs and HbA1c, duration of T2D, and demographics:

Moderately weak statistically significant negative correlation identified between HbA1c and FEV1 (r=-0.281, p=0.005) and HbA1c and FEV1/FVC (r=-0.386, p=0.000).

**Table 4: Correlation between pulmonary function tests and HBA1c, duration of diabetes, and age.**

| | | HbA1c (%) | Duration of DM (years) | Age (years) |
|---|---|---|---|---|
| FVC, L | R | -0.080 | -0.066 | 0.010 |
| | p= | 0.428 | 0.516 | 0.918 |
| FEV1, L | R | -0.281 | -0.259 | 0.043 |
| | p= | 0.005 | 0.009 | 0.674 |
| PEF, L/s | R | -0.101 | -0.119 | 0.172 |
| | p= | 0.319 | 0.237 | 0.086 |
| FEV1/ FVC, % | R | -0.386 | -0.381 | -0.046 |
| | p= | 0.000 | 0.000 | 0.651 |

**Table 5: Correlation between pulmonary function tests with gender and BMI.**

| | | Gender | BMI (kg/m2) |
|---|---|---|---|
| FVC, L | R | -0.165 | 0.337 |
| | p= | 0.101 | 0.001 |
| FEV1, L | R | 0.017 | 0.356 |
| | p= | 0.865 | 0.000 |
| PEF, L/s | R | 0.081 | 0.404 |
| | p= | 0.424 | 0.000 |
| FEV1/ FVC, % | R | 0.145 | 0.013 |
| | p= | 0.150 | 0.897 |

*FVC = Forced Vital Capacity, FEV1= Forced Expiratory Volume in 1 second, PEF = Peak Expiratory Flow, R = Pearson's coefficient, DM = Diabetes Mellitus, BMI= Body Mass Index.*

Moreover, moderately weak statistically significant negative correlation was identified between duration of DM and FEV1 (r=-0.259, p=0.009) and duration of DM and FEV1/FVC (r=-0.381, p=0.000). However, moderately weak positive correlation was observed between BMI and FVC (r= 0.337, p=0.001), FEV1 (r= 0.356, p=0.000) and PEF (r= 0.404, p=0.000) as displayed in Table 4 and 5.

**Discussion:**

Diabetes Mellitus (DM) is a multisystem disorder that affects 79% of the adults residing in developing countries and getting more and more prevalent in developed countries now a days. With a prevalence of 9.3% (463 million), which is expected to rise to 10.9% (700 million) by the year 2045, DM has become one of the challenging pandemics as 50.1% (232 million) of diabetics are oblivious to suffering from the disease.19 Moreover, coronavirus disease (COVID-19) is often more severe in diabetics which further exacerbates the economic burden on countries.20 Diabetic microangiopathy, a consequence of hyperglycemia and increased duration of the disease, affects various organs, among which the lung is one of them. However, due to the subclinical nature of the impairment, it often goes unnoticed by both the patients and the practitioners. 11 Our results demonstrated pulmonary function impairment in association with NIDDM independent of smoking and other chronic lung diseases. This is in occurrence with a meta-analysis that demonstrated a

relationship between impaired pulmonary function and T2DM. 21 In our study, all the PFTs including FVC, FEV1, PEF and FEV1/FVC %, were reduced in participants with poor glucose control. However, a significant reduction in the FEV1 (p=0.001) and FEV1/FVC % (p=0.001) was noted in participants with poorly controlled diabetes (HbA1c ≥8) in comparison to those with good diabetic control (HbA1c <6.5). This finding is similar to other studies [22, 23]. Stringent glycemic control is suggested to improve respiratory muscle mass, strength and physiology and thereby reduce microangiopathy-associated complications [24].

Sonoda et al. [25] reported a 2.4 times higher risk of pulmonary function deterioration in diabetic patients with HbA1c equal to or higher than 8.0% than those with HbA1c less than 6.9%. Moreover, a significant decline in the FEV1 (p=0.037) and FEV1/FVC % (p=0.005) was noted in our participants with a duration of more than or equal to eight years of DM compared to those with duration of DM less than eight years. An inverse correlation was also found in our study between all the PFTs and HbA1c and the duration of the disease, which is comparable to the findings of Tai et al. [26] and Asanuma [27]. Spirometry results of our patients indicated restrictive ventilatory defects in over one third of the participants (n=35) while obstructive ventilatory defects were found in only 7% of the participants. This is emphasizing the findings of Meo et al. [28] and Davis et al. [29], who reported both restrictive and obstructive ventilatory defects in diabetics; however, found the restrictive lung disease to be more prevalent. The association of DM with restrictive lung disease could be explained by the fibrotic histopathological changes observed in autopsied lungs from DM patients [30].

Our study has quite a few limitations. Firstly, we didn't take a healthy control group against whom PFTs of diabetic patients could be compared; therefore, an accurate cause and effect relationship of DM and lung impairments can't be determined. Secondly, decreased diffusing capacity for carbon monoxide (DLCO), which is observed to be impaired in DM patients despite normal spirometry results, was not measured. Thirdly, this was not a longitudinal study; therefore, accurate conclusions pertaining to the duration of DM and its association with lung function impairments cannot be drawn.

**Conclusion:**

Apparently, patients having type 2 diabetes are venerable for lung parenchymal changes and therefore, periodic assessment of PFTs and HbA1c is crucial in early screening and management of lung abnormalities brought about by diabetic microangiopathy.

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