Pulmonary Function in Type 2 Diabetes Mellitus: Correlation with Body Mass Index and Glycemic Control

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Abstract

Introduction: The lung with its large surface area and extensive vasculature is postulated to be one of the “target organs” for damage in diabetes mellitus (DM). However, changes in lung function occurring in Type 2 Diabetes Mellitus (Type 2 DM) have not been well-characterized in previous studies.

Purpose: To study the pulmonary function abnormalities in patients with Type 2 DM and to find correlations with duration, body mass index, glycemic control, and nephropathy.

Materials and Methods: This prospective study was conducted among Type 2 DM patients attending the diabetic clinic of a medical college hospital. 124 non-smokers with Type 2 DM, not suffering from respiratory allergies and who did not have any acute or chronic pulmonary diseases were included. Body mass index (BMI) was calculated for all patients. Glycemic control was assessed by measuring glycosylated hemoglobin (serum HBA1c). Spirometry and measurement of diffusing capacity by single-breath method (DLCO-SB) was done in all the patients. The presence of diabetic glomerulopathy was determined by checking urine samples for microalbuminuria in a subset of patients.

Patients were divided into subgroups based on BMI, HBA1c levels, duration of DM and data analyzed using ANOVA and Student’s unpaired t-test. SPSS version 17.0 was used for statistical analysis.

Results: A statistically significant reduction was seen in diffusing capacity with increasing duration of DM (P < 0.05). Statistically insignificant reductions were observed in forced expired volume in 1 s (FEV1), forced vital capacity (FVC), peak expiratory flow rate, (PEFR) forced expiratory flow (FEF 25%-75%) in patients with >20 years of DM in comparison to their counterparts with <10 years of DM; FEV1/FVC was found to be unimpaired in DM.

Conclusions: Type 2 DM is associated with a reduction in diffusing capacity with increasing duration of disease. This reduction was not limited only to patients with microalbuminuria. BMI and level of glycemic control did not affect lung functions in diabetic patients.

Key words: Diffusing capacity, Pulmonary function, Type 2 diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM) is an important universal public health problem. The World Health Organization estimates that about 347 million people worldwide have diabetes with a global average prevalence of approximately 10%.

India is witnessing an epidemic of DM and is referred to as the diabetes capital of the world. It is estimated that by 2025, there will be nearly 70 million people with diabetes in India, meaning, every 5th diabetic in the world would be an Indian.

DM is known to cause widespread metabolic, hormonal and microvascular abnormalities as well as disturbances in the functioning of many organ systems such as the kidneys, retinae, nerves, and the cardiovascular system.
The presence of abundant connective tissue in the lung and an extensive microcirculation raises the possibility that the lung may be an important “target organ” in diabetic patients. However, studies evaluating lung functions in Type 2 DM in the past have observed conflicting results with few reporting only minimal changes and others observing marked (and possibly clinically significant) abnormalities in various lung function parameters.

The underlying mechanism appears to be a microangiopathy brought in by the non-enzymatic glycosylation of various scleroproteins that form the matrix of the lung. There have been several studies putting forth many reasons for the impaired lung function seen in diabetics. One study by Chance et al. revealed that diabetic microangiopathy can involve alveolar tissue and capillaries in the body, leading to restriction of lung volume and alveolar gas transport, as was recorded by the reduced diffusing capacity of the lung for carbon monoxide, as well as its components: membrane diffusing capacity and pulmonary capillary blood volume. Irfan et al. reported in their study that diabetic patients had significant hypertriglyceridemia and concluded that dyslipidemia might have played a role in the pathogenesis of decreased lung functions in diabetic patients.

The present study attempts to assess the lung function in Indian patients with Type 2 DM and to correlate their lung function with duration of DM, glycemic control, body mass index (BMI), and diabetic nephropathy, keeping in mind, the conflicting observations reported from studies carried out in this area earlier.

**MATERIALS AND METHODS**

The study was conducted over a period of 2-months among a total of 124 patients with Type 2 DM attending the diabetic clinic of a medical college hospital using convenient sampling technique. Approval was taken from the Institutional Ethics Committee and was as per the Helsinki Declaration.

Adults with Type 2 DM as diagnosed by the treating physician, having no respiratory symptoms at the time of enrollment and willing to participate were included after taking a written informed consent. Health status was decided by a detailed history followed by a thorough clinical examination. Smokers, patients with respiratory allergies and patients suffering from acute or chronic pulmonary diseases were excluded from the study.

**Anthropometric Measurements**

Height and weight of all subjects were recorded and BMI calculated as weight (kg) divided by height (meters) squared.

**Biochemical Investigations**

Glycemic status of subjects was determined by:
1. Fasting blood sugar by glucose oxidase and peroxide method after 12 h of fast
2. Postprandial blood sugar by glucose oxidase and peroxide method after 2 h of meal

In addition, a urine sample was tested for microalbuminuria as a surrogate marker for diabetic nephropathy in a subset of patients ($n = 80$).

**Pulmonary Function Test and Lung Diffusing Capacity (DLCO)**

Pulmonary function parameters recorded included forced vital capacity (FVC), forced expired volume in 1 s (FEV1), peak expiratory flow rate (PEFR), FEV1/FVC ratio and forced expiratory flow (FEF 25-75%) which were measured using the Collins Eagle Spirometer (Ferraris Respiratory, UK). Spirometry was performed using the closed circuit method by first asking the subjects to inhale completely and rapidly with a pause of <1 s at total lung capacity (TLC) followed by a “blast” of exhalation which was continued until the end of test criteria were met. Acceptability and repeatability criteria as laid out in the ATS/ERS document on standardization of lung function testing were strictly followed. The variables were recorded both in absolute volume as well as percent predicted based on regression equations.

DLCO was measured using the single-breath method by the same system using 0.3% CO, 0.3% CH4, 21% O2 and balance N2 by volume.

**Subgroups**

For the purpose of data analysis the BMI, HBA1c, duration of diabetes were divided into the following subgroups:

- **The BMI is stratified into:**
  - <18.5 underweight
  - 18.5-24.9 normal
  - 25-29.9 overweight
  - ≥30 obese

- **HBA1C is subdivided into:**
  - 6-7.5-good control
  - >7.5-poor control

- **Duration of diabetes is further classified as:**
  - <10 years
  - 10-20 years
  - >20 years

**Statistical Analysis**

Results were tabulated using Microsoft Excel 2007 and analyzed using descriptive statistics. Further statistical evaluation of the data was performed using the ANOVA
RESULTS

A total of 124 patients were enrolled in the present study, with the mean age of the study population being 56.57 ± 11.58 years (Range: 20-74 years). The male:female ratio was found to be 61:63. The average duration of DM was found to be 7.69 years. The mean body mass index and HBA1c of the study group were 25.31 ± 3.21 and 8.175 ± 1.6, respectively (Table 1).

Table 2 summarizes the correlation between the lung function parameters and duration of DM. All pulmonary function parameters except FEV1/FVC, that is, FEV1, FVC, PEFR, FEF 25-75%, and DLCO were reduced in patients with duration of diabetes >20 years as compared to diabetics with duration <10 years. However, only one parameter - diffusing capacity shows a statistically significant decline (P = 0.008) with increasing duration of disease. The reduction observed in other pulmonary function parameters was statistically insignificant (P > 0.05).

Table 3 illustrates the lack of correlation between body mass index and pulmonary function parameters observed in the present study.

No correlation was observed between level of glycemic control (HBA1c) and pulmonary function parameters as shown in Table 4.

Microalbuminuria and its relationship with pulmonary function parameters are shown in Table 5. Patients with microalbuminuria (n = 80) did not show any significant deviations when their lung functions were compared against predicted values.

DISCUSSION

Studies analyzing pulmonary function in Type 2 DM patients have observed mixed results, with some studies observing minimal changes and others showing abnormalities in lung volumes, pulmonary mechanics, and diffusing capacity. A meta-analysis of pulmonary function in diabetes by Bram van den Borst et al. concluded that there is a modest but statistically significant restrictive impairment in lung function irrespective of BMI, smoking, diabetes duration, and glycemic control. The Framingham heart study which involved 3254 participants showed that in subjects with diabetes there is a larger reduction in FVC than FEV1 and the larger FEV1/FVC values suggest a restrictive physiology. Reduced lung volumes and airflow limitation, the severity of which relates to glycemic control were the key findings of the Fremantle Diabetes Study, one of the largest community-based prospective study in Western Australia involving Type 2 diabetics. Studies in Asian population have also observed a predominantly restrictive impairment. However, Sinha et al. showed that except DLCO, there were no differences in other pulmonary function parameters like FEV1, FVC, and PEFR in Type 2 diabetic patients as compared to their control group. Benbassat et al. also concluded that lung functions including diffusing capacity are preserved in patients with DM. In the present study, the significant reduction observed in diffusion capacity (DLCO) with reduction in FEV1, FVC, PEF and FEF 25-75% and a
preserved FEV1/FVC ratio (albeit not up to statistically significant levels) in diabetic patients of duration >20 years points to a subclinical restrictive impairment. The likely reason for the lack of a statistically significant reduction in the said parameters could be because we compared the values with predicted values and did not compare the results with a matched control group.

One significant observation in the present study was an impairment of DLCO, which was more prominent with increasing duration of diabetes in patients with Type 2 DM. This observation is in agreement with findings of a previous study by Mori et al. who reported that pulmonary diffusing capacity correlated negatively with the duration of diabetes. However, the present study did not show a statistically significant correlation between the reduction in DLCO and renal microangiopathy as assessed by microalbuminuria. Agarwal et al. reported a significant reduction in diffusing capacity in patients with Type 2 DM with microangiopathy - microalbuminuria and/or retinopathy. No difference was observed in the other spirometric values. Another study by Sinha et al. showed a significant reduction in pulmonary diffusing capacity in Type 2 DM Asian Indian patients with any or a combination of microangiopathy(ies) (retinopathy, nephropathy, and peripheral neuropathy). Our findings are in agreement with previous studies by Benbassat et al. and Pinar Celik et al. which did not find any correlation between reduced diffusion capacities in diabetics with other chronic complications. Fusó et al. and Ozmen et al. taking note of these conflicting observations regarding the effect of DM on diffusing capacity opined that the usual clinical method of measuring DLCO, i.e., the Single-breath method may not be sensitive enough to detect pulmonary vascular angiopathy and have proposed measuring the CO transfer capacity in both seated and supine positions, i.e., measurement of posture related variation in DLCO to increase the sensitivity and diagnostic utility of the test.

The pathophysiological mechanism responsible for the reduction in diffusion capacity is believed to be multifactorial. Chronic hyperglycemia, as reflected by elevated HBA1c seen in 53.23% of our patients, leads to non-enzymatic glycosylation of collagen and elastin present in the extracellular matrix of the lung. The structural result of these biochemical alterations is a thickening of the basement membrane and decrease alveolar microvascular perfusion. Other postulated mechanisms include changes in surfactant and its actions and decreased affinity of HbA1c to carbon monoxide.
The present study failed to show any correlation between glycemic level and pulmonary function parameters. The average duration of disease in our patients was 7.69 years, whereas HBA1C is more predictive of short-term glycemic control. Previous studies by Mori et al.\(^{23}\) and Pinar Celik et al.\(^{29}\) have also reported a similar lack of association between this index of diabetes control and lung function. Since HbA1C reflects the glycemic control over the previous 3-4 months, it improper to conclude that control of blood glucose level in diabetics has no bearing on pulmonary functions on the basis of this result alone. Davis et al.\(^{5}\) Dennis et al.\(^{25}\) and McKeever et al.\(^{26}\) in their studies have reported that diabetics with inadequate glucose control have a lower pulmonary function as compared to those with adequate control.

The present study had a few limitations. First, the spirometry values in our patients were compared against predicted pulmonary function determined from age, gender and body habitus instead of using a control group without DM. Second, we were unable to include static lung volume measurements such as residual volume (RV), total lung capacity (TLC), and functional residual capacity (FRC) in the present study since we lacked equipment to record the said parameters. Reduction in measured volumes would have helped to further confirm our observation of subclinical restriction seen in long-standing diabetics. Third, although we had a good number of patients, yet our results cannot be extrapolated to a vast country like India with different ethnic groups. Probably a multicentric prospective study including population representation from different parts of the country and a longer follow-up period would address this issue. Fourth, we used microalbuminuria as a marker of nephropathy since the test is easily done on outpatient basis. However, for microalbuminuria to signify diabetic nephropathy it needs to be persistent. Probably, a better marker would be a 24 h urine albumin excretion which is, however, difficult to use in an outpatient setting. Moreover, a large number of our patients were already on angiotensin converting enzyme (ACE) inhibitors causing microalbuminuria levels to be less than expected. Studies using 24 h protein excretion and taking ACE-inhibitors use into consideration needs to be done to correlate lung function and renal damage more accurately in diabetic patients.

CONCLUSION

The present study hints at the possibility of a restriction in lung function in patients with long-standing Type 2 DM. However, this impairment was not manifest as clinical symptoms in these patients and did not correlate with body habitus or degree of glycemic control. The observed reduction in diffusing capacity (DLCO) was not restricted only to patients with microalbuminuria. Further studies using a non-diabetic control population and recording static lung volume measurements (RV, TLC, FRC) would be needed to confirm our observation.

REFERENCES


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