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## **Impaired glycemc control as a risk factor for reduced lung function in the Indian diabetic population**

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## **Abstract**

Diabetes mellitus (DM) is a metabolic syndrome associated with chronic hyperglycemia, which results in various acute and chronic complications. DM leads to a state of chronic low-grade inflammation, which can have adverse effects on pulmonary functions. There have been contradictory studies related to the relationship between defects in lung functions in diabetic individuals and their correlation with glycemic control and systemic inflammatory markers. The present study aims to compare pulmonary function in controlled and uncontrolled diabetes in the Indian population while exploring the link between inflammatory markers and lung functions in diabetic patients. This observational, case-control study was conducted in the Department of Biochemistry at Sri Guru Ram Das Institute of Medical Sciences and Research in Amritsar, Punjab, on 116 subjects suffering from DM in the age group of 30-65 years. 58 diabetic patients with poor glycemic control [glycated hemoglobin (HbA1c)>7%] and 58 diabetic patients with good glycemic control served as controls (HbA1c 7%). The duration of the study was two years. Blood samples of each patient were investigated for glycemic control, high-sensitivity C-reactive protein (hsCRP), and serum fibrinogen. Spirometry as a pulmonary function test was undertaken for all participants. The statistical analysis of good and poor glycemic control diabetics showed that the average duration of disease (in years) was  $8\pm 5$  and  $10.2\pm 5.4$ , respectively. A significant positive correlation was found between inflammatory markers (hsCRP and fibrinogen) and HbA1c and fasting blood glucose. A substantial decline in forced vital capacity and normal values of forced expiratory volume in the first second was observed in poor glycemic control diabetics, depicting a restrictive pattern of lung disease. Lung damage is seen to be more prevalent in patients with a longer duration of disease and increased levels of inflammatory markers. Chronic inflammation due to DM can lead to fibrosis and destruction of lung tissue, resulting in the development of diabetic lung disease, which includes a decline in lung function, an increased risk of infection, and an increased risk of respiratory failure. Therefore, it is essential for individuals with DM to have regular pulmonary function tests and to manage their diabetes to minimize the impact on their lung health.

**Key words:** restrictive lung disease, chronic inflammation, pulmonary function tests, uncontrolled diabetes mellitus, diabetic pneumopathy.

## **Introduction**

Diabetes Mellitus is a lifestyle disease and a significant public health problem. Patients of DM suffer from various complications which are majorly categorized as Acute complications – Diabetic ketoacidosis, non-ketotic hyperosmolar state, altered mental status and Chronic Complications such as neuropathy, nephropathy, retinopathy and cardiovascular disease leading to significant morbidity and mortality of disease [1].

Along with other organs, the lungs have recently been stated as one of the target organs of diabetes [2]. DM has been proposed as a risk modifier for respiratory distress, especially acute respiratory distress syndrome (ARDS).

Persistent inadequate glucose control over time may likely alter the regulation of inflammatory pathways that are involved in the impairment of lung function [3]. Oxidative stress, non-enzymatic glycation of proteins, inflammation and the polyol pathway have been recognized to be elaborated in the etiology of diabetic lung injury [4].

Currently, there is a significant focus on the impact of lung dysfunction in individuals with diabetes, highlighting the emerging clinical implications of this issue. Research has shown that young patients with type 1 diabetes, who have never smoked and do not have allergies or preexisting lung disease, exhibit reduced lung elastic recoil and pulmonary vascular changes [5]. Findings suggest that the lung may be susceptible to diabetic microangiopathy, and it has been suggested that individuals with diabetes may be at risk of developing disability due to mechanical dysfunction in their lungs and airways [6].

This study aimed to assess and compare pulmonary function in individuals with controlled and uncontrolled diabetes, along with examining the correlation between inflammatory markers and pulmonary function in diabetic patients.

## **Materials and Methods**

This observational, cross sectional study was conducted after obtaining ethical clearance (Ethical Clearance Number 1063/Tig/2020) from the ethics committee of Sri Guru Ram Das Institute of Medical Sciences and Research, (SGRDIMSR) Sri Amritsar, Punjab, India. 116 subjects of the age group 30-65 years suffering from Diabetes mellitus who visited the Medicine Out Patient Department (OPD) were enrolled in the study. Written informed consent was taken from the study participants. The sample size has been calculated while keeping similar studies in the context of sample size calculation. The sample size was calculated by G Power 3.1 software.

The patients excluded from the study were known smokers and pregnant females. The study excluded individuals with a body mass index (BMI) greater than 30 kg/m<sup>2</sup>. It also excluded those with a documented history of respiratory allergies or recent acute respiratory infections

within the past 3 months. Patients with prior or current respiratory conditions such as asthma, pleural effusion/empyema, pulmonary tuberculosis, Chronic Obstructive Pulmonary Disease (COPD), bronchiectasis, or lung cancer were not included. Additionally, individuals with acute or chronic pulmonary or connective tissue disorders, congestive heart failure, ischemic heart disease, diastolic dysfunction, rheumatoid arthritis, collagen vascular diseases, recent antibiotic use within the last 4 weeks, or chest deformities affecting spirometric reliability were also excluded from the study.

Five ml of venous blood sample was collected after an overnight fast from the antecubital vein of the subject for plasma blood glucose level (FPG), Glycated Hemoglobin (HbA1c), Highly sensitive C Reactive Protein (hsCRP), serum fibrinogen and renal function tests (serum urea and serum creatinine). Pulmonary function tests (PFT) were performed using Helios 401 spirometer Forced vital capacity (FVC), Forced expiratory volume in 1 second (FEV1), FEV1/FVC, FEV1% (FEV1 as a percentage of FVC) peak expiratory flow rate (PEFR). The Pulmonary Function Test (PFT) predicted values were obtained using American Thoracic Society-European Respiratory Society (ATS-ERS) spirometry guidelines FVC (Forced Vital Capacity), FEV1 (Forced Expiratory Volume in one second) and their ratio are the pivotal spirometric measurements.  $FVC < 80\%$  and  $FEV1/FVC < 0.70$  predict the restrictive pattern of lung disease and the obstructive pattern is depicted by  $FEV1/FVC < 0.70$  and  $FEV1 < 80\%$  [7].

Estimation of Plasma glucose (hexokinase method), Serum urea (urease/glutamate dehydrogenase coupled enzymatic method), Serum creatinine (modified kinetic Jaffe method), HbA1c (Turbidimetric Inhibition Immunoassay), high sensitivity C-reactive protein (Turbidimetrically) was performed on Siemens Auto analyzer. Estimation of serum fibrinogen was done by the ELISA kit method [8-13].

The subjects were divided into two groups. Patients having HbA1c  $\leq 7\%$  were enrolled in group A (good glycemic control) and patients having HbA1c  $>7\%$  (poor glycemic control) were considered in group B. Both groups had 58 diabetic patients.

### ***Statistical analysis***

Patients with controlled and uncontrolled diabetes were compared statistically. SPSS software version 21 was used for statistical analysis. Continuous variables were analyzed using student t-test. The Spirometric data was analyzed using Pearson's correlation coefficient.

### **Results**

The participants in both groups were age and sex-matched. The mean age of participants as expressed in mean  $\pm$  SD (Years) was  $51.7 \pm 9.4$  and  $52.5 \pm 9.0$  years in group of participants

with good glycemic control (group A) and with poor glycemic control (group B) respectively. The average duration of disease (in years) was  $8 \pm 5$  and  $10.2 \pm 5.4$  in the group of participants with good glycemic control (group A) and with poor glycemic control (group B) respectively. There was a statistically significant difference between the mean values of hsCRP, FVC, FEV1 and PEF in the two groups with a significant decline in FVC value and normal FEV1% value in the poor glycemic control group as compared to the good glycemic control group which depicts the presence of a restrictive pattern of Lung disease (Table 1). There was a negative correlation of FVC, FEV1, and PEF with the duration of disease, Inflammatory markers, Glycated hemoglobin & FPG. Hence, higher levels of sugar (HbA1c and FPG) are associated with lower levels of FVC, FEV1 and PEF as shown in Table 2 and Figures 1 and 2.

Pearson's Coefficient Correlation for relationships between glucose control (HbA1c & FPG) and inflammatory markers (hsCRP and Fibrinogen) showed a positive correlation (Table 3, Figures 3 and 4). As the values of glucose (as indicated by HbA1c and FPG) rise, there is a notable increase in the levels of inflammatory markers (hsCRP and Fibrinogen).

## **Discussion**

On comparison of pulmonary functions in the diabetic participants of good glycemic control with those with poor glycemic control, the latter showed lower mean values for FVC, FEV1 and PEF. FEV1% values were normal in both groups. This pattern in spirometric values identifies the presence of a restrictive deficit. Glucose level (HbA1c and FPG) showed a negative correlation with FVC, FEV1 and PEF which means if serum HbA1c or FPG value increases the value of these parameters decreases.

This study highlights that elevated levels of glucose in the plasma exacerbate damage to the lungs in individuals. These findings are consistent with the study of Vanidassane et al stating that diabetic subjects with inadequate glucose control have significantly lower values of lung volumes [14]. A study done in Egypt on Type 1 DM children showed impairment of lung functions in these children and this impairment increases with poor glycemic control [15]. In diabetic patients, chronic hyperglycemia can bring about a rise in collagen molecule synthesis and cross-linking via the acceleration of advanced glycation end-products, which can negatively influence lung function [16,17]. The decline in vital capacity as evidenced in FVC, FEV1 and normal FEV1% suggested the restrictive pattern of lung disorder. Certain studies showed contradicting results, where no significant association was found between HbA1c and lung volumes [5,18]. The study of Shah et al. further contradicts our result by stating that abnormal levels of serum HbA1c levels do not intensify the damage to the lungs in patients suffering from diabetes mellitus [19].

It was found in our study, that on comparing hsCRP and fibrinogen in the two groups, hsCRP had a significantly higher mean value in poor glycemic control diabetics. Whereas, for fibrinogen, even though the mean value was higher in this group, the difference was statistically not significant ( $p = 0.543$ ). HbA1c and FPG had a highly significant positive correlation with increased levels of serum hsCRP. Fibrinogen showed a positive and statistically significant correlation with HbA1c ( $r = 0.199$  and  $p = 0.032$ ) whereas with FPG it had an insignificant positive correlation ( $r = 0.180$  and  $p = 0.53$ ).

The positive association of hsCRP and Sugar levels is in accordance with findings from various other studies [14,19,20]

Further in our study, it was found that the serum hsCRP and fibrinogen levels had a negative correlation with pulmonary function tests, thereby reflecting inflammatory response due to damaged lung.

The above data is in agreement with the study by Glaser et al which was done on the general population of about 1466 subjects aged 25 – 85 years. Significantly high values of hsCRP were associated with decreased lung volume [20]. In a few other studies fibrinogen and hsCRP were associated with abnormal FVC and FEV1 values [21-23].

Previous studies have stated the association of inflammation in diabetic individuals is due to  $\beta$  cell dysfunction. In response to inflammation cytokines such as Tumor Necrosis Factor, Interleukin 6 (IL-6) etc are released. CRP secretion is regulated by IL-6 in the liver [24]. During inflammation, it accumulates in adipocytes in excess. Hence, increased levels of CRP can be explained by the presence of small grade inflammation in diabetic patients which might be induced by hyperglycemia. Although the mechanism is not properly understood, environmental factors such as infection, overnutrition and lack of physical activity are found to elevate the levels of CRP in the circulation. IL-6 induces synthesis of, fibrinogen in hepatocytes [25]. Furthermore, the correlation between fibrinogen and glycemic control might be explained due to decreased susceptibility to proteolysis of glycated fibrinogen and due to differential synthesis of proteins due to insulin deficiency in DM. There is a 29% decrease in albumin synthesis and a 50% increase in fibrinogen synthesis [26].

During inflammation, the breakdown of elastic tissue occurs by tipping the balance of proteolytic enzymes and their inhibitors. C-reactive protein (CRP) and interleukin (IL)-6 in a common mechanistic pathway contribute to reduced lung function and increased cardiovascular events. IL-6, the potential component of chronic inflammation that regulates other inflammatory markers or acute phase reactants, is produced by the epithelium of blood vessels, macrophages and other sites of inflammation in response to environmental stress or other factors [21]. The TNF and IL-6 in the circulation stimulate the clotting action, thereby blocking the capillaries. Lungs being a highly vascular structure gets impaired by increased

levels of these markers secreted in response to factors such as insulin resistance (IR), glucose intolerance and obesity [27].

In the present study, the relationship between the duration of disease and pulmonary function tests showed a negative correlation with all the parameters of spirometric values. Our data showed that pulmonary functions are significantly reduced in patients who have suffered from the disease for more than 10 years. Our study was supported by a study done Talpur AS et al, 2021. The research indicated that individuals with elevated glycated Hemoglobin for a longer duration experience a more pronounced decline in lung function, due to more glycosylation of the proteins in the respiratory tree and the thickening of the basal lamina [28]. Our result was opposed by the study of Shah et al. which found no significant association between duration of illness and FVC and FEV1 values [19].

Limited research is available regarding the relation of lung functions in diabetes ( charted in Table 4). Metabolic disorders, especially diabetes are generally manifested with obesity and are associated with a substantial loss of pulmonary function in a restrictive pattern. Many hypotheses have emerged to elucidate the pathogenesis of diabetic lung injury, and characteristic “diabetic lung”. Oxidative stress, non-enzymatic glycation of proteins, and the polyol pathway have been recognized to be elaborated in the etiology of diabetic lung injury [27]. We speculate that glycemic control linked with collagen and elastin changes can lead to significant structural changes in the respiratory system.

Lung is an organ having great vascularization and abundant collagen and elastin fibers. Understanding the pathophysiology of reduced lung function is an ongoing area of study, particularly regarding the intricate relationship between normal lung mechanics and gas exchange and the integrity of pulmonary connective tissue and microvasculature. In diabetic patients due to the condition of hyperglycemia, proteolysis of collagen is inhibited due to non-enzymatic glycosylation of proteins in the lungs and chest wall. This leads to the accumulation of collagen in lung connective tissue, which further increases the stiffness of parenchymal cells of the chest wall and lungs. This condition is enhanced by poor glycemic control. The whole process explains the restrictive pattern of lung disease. The reduction of the elastic recoil capacity of the lung leads to a dynamic collapse of small airways during exhalation. Another hypothesis promotes that chronic hyperglycemia induces abnormal regulation of inflammatory mechanisms. This abnormal action of inflammatory response in the lung results in diminished lung function. Hyperglycemia leads to the overproduction of reactive oxygen species (ROS), changes various signalling pathways and inhibits the endogenous vascular protective mechanism, thereby causing various complications in all organs with large vascular network systems which includes the lungs [29]. Hyperglycemia exacerbates airway hyperresponsiveness through the Rho-associated protein kinase (ROCK) pathway and accelerates



lung fibrosis. Additionally, it promotes chronic inflammation, the release of inflammatory cytokines, and oxidative stress by activating pathways such as nuclear factor kappa-light-chain-enhancer of activated B-cells (NFκB), NADPH oxidase (NOX), and the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). This systemic chronic inflammation, in conjunction with oxidative stress and reduced antioxidant capacity, can lead to lung endothelial dysfunction and interstitial thickening in diabetic patients. This thickening of the lung interstitium exacerbates restrictive lung disease.

The lung houses a vast capillary network with a significant microvascular reserve, serving as the primary protective mechanism against diabetes-induced pulmonary complications. Due to this substantial pulmonary reserve, micro- and macrovascular dysfunctions related to diabetes typically arise later in the lung compared to other organs. Consequently, patients with a longer duration of the disease often experience more severe impairment of lung functions [30].

Therefore, impaired glucose control and longer disease duration contribute to the development of restrictive lung disease in individuals with diabetes.

## **Conclusions**

Through meticulous examination and analysis of pertinent data, a compelling correlation emerges, highlighting the alarming propensity of uncontrolled diabetes to contribute to the manifestation and progression of restrictive lung conditions. The findings highlight that prolonged exposure to elevated glucose levels and the associated metabolic imbalances can detrimentally impact lung function, leading to a gradual decline in lung capacity and compliance. The close link between diabetes and lung disease calls for a combined approach in managing these conditions. The study focuses that diabetes and lung diseases should not be approached in silo but in combination. The insights gained from this research not only underscore the imperative of vigilant glycemic management in individuals with diabetes but also stress the necessity of incorporating regular pulmonary assessments into their comprehensive care regimen.

## ***Limitations of the study***

- Since this study is cross-sectional, only one reading of HbA1c is used in determining the glucose levels. Hence, long term changes of hyperglycemia were not available
- Larger studies with prospective endpoints are needed to investigate the natural cause of Restrictive Lung Disease
- Only spirometric tests were analyzed for evaluation of pulmonary function

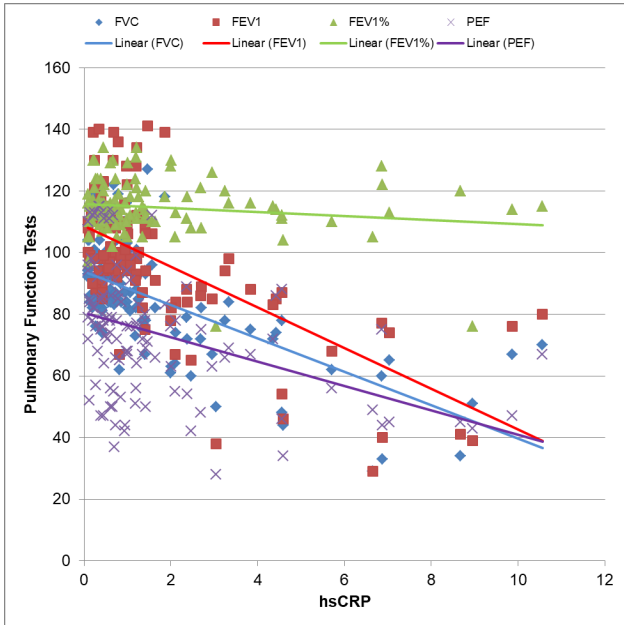
- Passive smoking has not been studied, despite its known adverse effects on exercise capacity and pulmonary functions.

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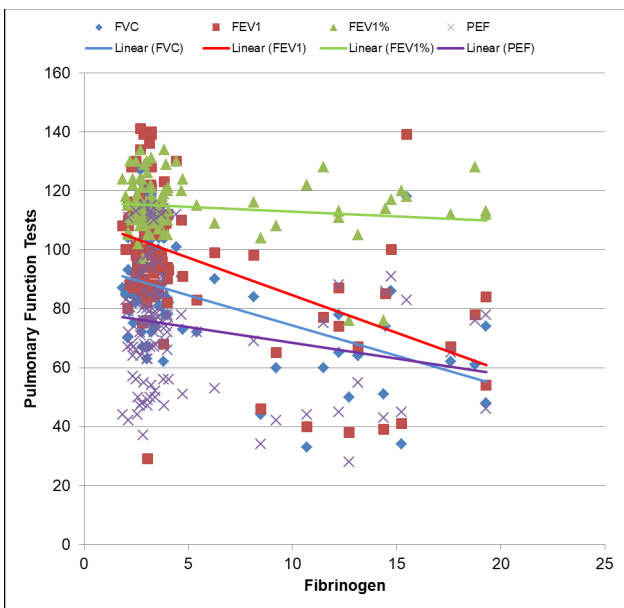
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**Figure 1. Correlation of hsCRP with Pulmonary Function Tests - Force Vital Capacity (FVC), Force Expiratory Volume(FEV), , Force Expiratory Volume 1% (FEV1 %), Peak Expiratory Flow (PEF).**



**Figure 2. Correlation of Fibrinogen with Pulmonary Function Tests- Force Vital Capacity (FVC), Force Expiratory Volume(FEV), Force Expiratory Volume 1% (FEV1 %), Peak Expiratory Flow (PEF).**

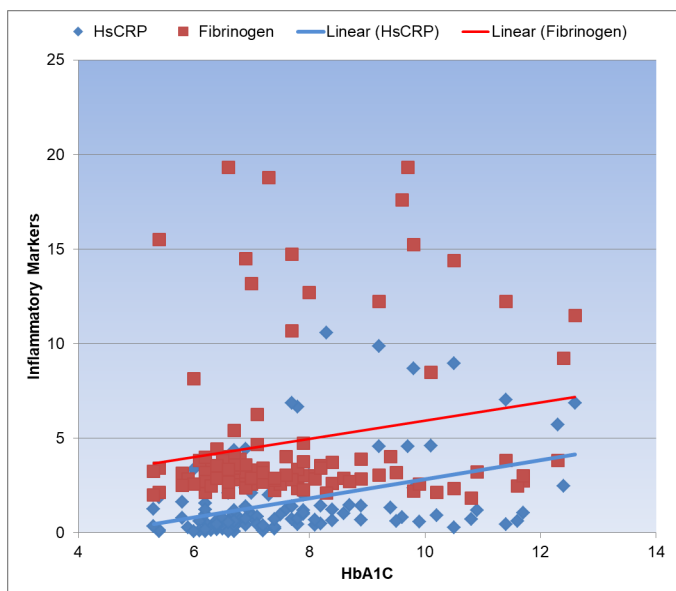


Figure 3. Correlation of inflammatory markers with Glycated Hemoglobin(HbA1c).

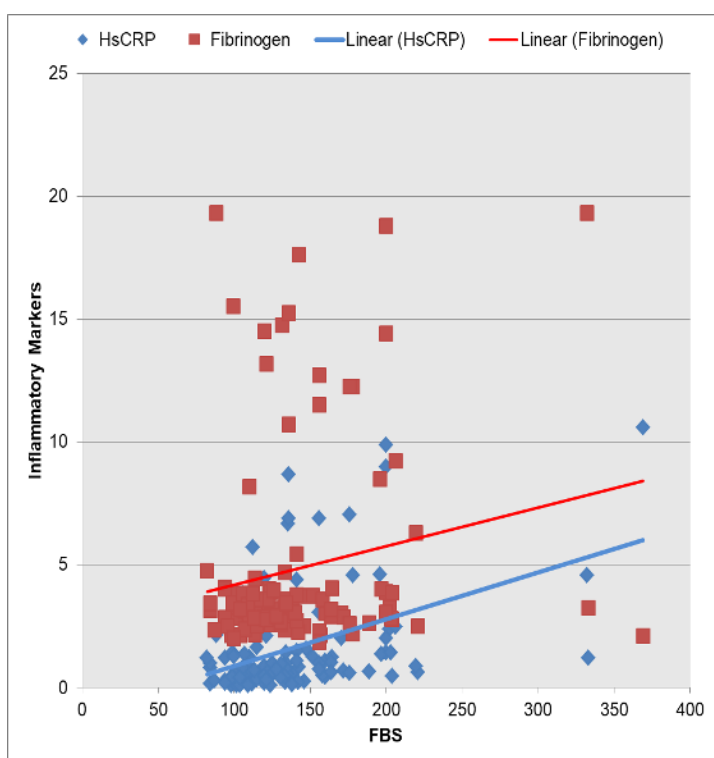


Figure 4. Correlation of inflammatory markers with Fasting Plasma Glucose (FPG).

**Table 1. Comparison of inflammatory markers and spirometric values in good and poor glycemic control participants.**

	Group A (Good glycemic control participants)			Group B (Poor glycemic control participants)			't' value	p value
	Range (%)	Mean	SD	Range(%)	Mean	SD		
hsCRP	0.09-4.42	1.006	1.077	0.12-0.56	2.290	2.706	3.358	0.001**
Fibrinogen	2.00-9.30	4.171	3.318	1.84-9.30	5.459	4.754	1.693	0.093; NS
FVC	64-119	89.91	12.697	29-127	80.02	20.693	3.105	0.002**
FEV1	67-140	102.76	15.566	29-141	92.69	25.960	2.533	0.013**
FEV1%	97-134	114.09	6.137	76-134	115.17	10.754	0.668	0.505; NS
PEF	54-115	85.16	17.093	28-99	62.78	17.294	7.009	< 0.001**

FVC, forced vital capacity; FEV, forced expiratory volume; PEF, peak expiratory flow; \*p<0.05 significant; \*\*p<0.01 highly significant.

**Table 2. Correlation of various factors with Pulmonary Function Tests**

	FVC	FEV1	FEV1%	PEF
<b>Duration of disease</b>				
Pearson correlation	-0.456	-0.455	-0.120	-0.252
P value	<0.001**	< 0.001**	0.199; NS	0.006**
<b>HbA1C</b>				
Pearson correlation	-0.341	-0.309	0.003	-0.501
P value	< 0.001**	0.001**	0.973; NS	< 0.001**
<b>FPG</b>				
Pearson correlation	-0.276	-0.241	0.012	-0.304
P value	0.003**	0.009**	0.894; NS	0.001**
<b>hsCRP</b>				
Pearson correlation	-0.656	-0.647	-0.159	-0.415
P value	<0.001**	<0.001**	0.089; NS	< 0.001**
<b>Fibrinogen</b>				
Pearson correlation	-0.477	-0.480	-0.156	-0.215
P value	< 0.001**	< 0.001**	0.095; NS	0.021*

FPG, fasting plasma glucose; HbA1C, glycated hemoglobin; FVC, forced vital capacity; FEV, forced expiratory volume; PEF- peak expiratory flow; \*p<0.05 significant; \*\*p<0.01 highly significant.



**Table 3. Correlation of Sugar levels with inflammatory markers.**

	Inflammatory markers	Pearson correlation	P value
HbA1C	hsCRP	0.402	< 0.001**
	Fibrinogen	0.199	0.032*
FPG	hsCRP	0.422	< 0.001**
	Fibrinogen	0.180	0.053; NS

HbA1C, glycated hemoglobin; \*p<0.05 significant; \*\*p<0.01 highly significant.

**Table 4. Various studies related to association of diabetes and lung functions.**

S No	Previous studies	Study design	Outcome
1	Irfan M et al <sup>2</sup>	Case control study	Study done in Pakistan showed Pulmonary function impairment in diabetic patients. Diabetics showed a significant reduction in Forced Vital Capacity (FVC), Forced Expiratory Volume in one second (FEV1), and Slow Vital Capacity (SVC) relative to their matched controls.
2	Dennis RJ et al <sup>3</sup>	Cross-sectional study	495 Diabetic subjects were studied out of which 352 had inadequate glucose control. The subjects with inadequate glucose control had lower pulmonary function than those with adequate control. The subjects with inadequate control also had significantly higher levels of inflammatory markers (TNF- $\alpha$ , Ferritin, Fibrinogen, and C-RP), suggesting a potential association of inflammation and reduced Pulmonary functions in Diabetic subjects.
3	Vanidassane I et al <sup>14</sup>	Cohort study	Study showed that Pulmonary functions were decreased and inflammatory markers like hsCRP, fibrinogen, and ferritin significantly increased in uncontrolled diabetics. A potential association was seen between higher values of inflammatory markers like hsCRP and fibrinogen and decrease in lung function.
4	Mohamad IL et al <sup>15</sup>	Case control study	Study done in Type 1 Diabetes Mellitus children showed impairment of lung functions in these children and this impairment increases with poor glycemic control.
5	Kuziemski K, et al <sup>29</sup>	Case control study	The study compared the functional exercise capacity and pulmonary functions in patients with diabetes and in healthy persons concluding that there is impaired exercise capacity in subjects with diabetes, though the mechanism is unknown
6	Talpur et al <sup>28</sup>	Cross sectional study	Research indicated that individuals with elevated HbA1c may experience a more pronounced decline in lung function, due to excessive protein glycosylation of the respiratory tree, leading to thickening of basal lamina.
7	Shah SH et al <sup>19</sup>	Case control study	Study was done in male diabetics and healthy controls. It was found that DM being a systemic disease, affects lungs causing restrictive type of ventilatory changes probably because of glycosylation of connective tissues, reduced pulmonary elastic recoil and inflammatory changes in lungs. Further it was found that glycemic levels and duration of disease are probably not the major determinants of lung pathology.
8	Khan M A et al <sup>17</sup>	Cross sectional study	A cross sectional study conducted on diabetics showed that spirometric variables FEV1, FVC, FEV1/FVC and FEF 25-75% were not different between diabetic subjects who were not having respiratory complaints and healthy controls. Also, duration of diabetes, diabetic control and presence of other diabetes related complications do not affect the lung function among diabetics. So, unlike eye and kidney, there is no need for screening for lung function abnormality among diabetics with no respiratory complaints.