RESEARCH ARTICLE

Serum surfactant protein-D as an early marker of pulmonary dysfunction in patients with Type 2 Diabetes

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Abstract

Objective: To investigate the role of surfactant protein D as an early biomarker for diabetic complications.

Method: The cross-sectional study was conducted at the diabetic clinic of Sheikh Zayed Hospital, Lahore, Pakistan, from March 1 to August 31, 2021, and comprised type 2 diabetic patients and non-diabetic controls. Serum surfactant protein D levels were measured using enzyme-linked immunosorbent assay, and pulmonary function was assessed using spirometry. Data analysed was conducted using SPSS 26.

Results: Of the 164 subjects, 82(50%) each were diabetics and controls. In both the groups, there were 49(59.75%) females and 33(40.24%) males. The mean age of diabetics was 51.02±11.98 years, while it was 44.65±15.18 years among the controls (p<0.05). Diabetics had significantly elevated surfactant protein D levels (63.59±26.20ng/mL) compared to non-diabetics (37.41±23.65ng/mL; p<0.05). Pulmonary function was also compromised in diabetics, with lower forced expiratory volume in one second and its ratio with forced vital capacity (p<0.05) despite similar forced vital capacity values (p<0.05).

Conclusion: Increased levels of serum surfactant protein D were found to be linked with pulmonary dysfunction. Surfactant protein D could serve as an early indicator of pulmonary involvement in diabetes.

Keywords: Diabetes mellitus type 2, Surfactant protein D, Pulmonary function tests, Spirometry, Lung diseases, Oxidative stress. (JPMA 76: 872; 2026) **DOI: https://doi.org/10.47391/JPMA.22976**

Introduction

Type 2 diabetes mellitus (T2DM) is a well-known disorder of metabolism in a broad age group, and its complications are widespread involving various organ systems. Worldwide prevalence of diabetes among individuals aged 20-79 years in 2021 was around 10.5% and it is predicted that by the year 2045, it will rise to 12.2%.[1] The International Diabetes Federation (IDF) Diabetes Atlas, 11th edition, assessed that 589 million adults aging between 20–79 years were living with diabetes globally in 2024, representing 11.1% of the worldwide adult population, with predictions reaching 853 million by 2050. Pakistan is one of the 21 states and territories included in the IDF Middle East and North Africa Region and stands with predominantly high burden of diabetes. In 2024, around 34.5 million adults aged 20–79 years were suffering with diabetes in Pakistan, with an age-standardised prevalence of 31.4%. Pakistan has the highest prevalence of diabetes among adults aged 20–79 years and the fourth highest number of adults with diabetes worldwide.[2]

T2DM and low immune status are closely linked to each other.[3,4] Insulin deficiency leads to high blood glucose levels that causes immune malfunction and nerve damage, and decrease blood flow to organs, leading the body susceptible to infections. Hyperglycaemia influences lung function in various ways; it stimulates airway hyper responsiveness, speeds up lung fibrosis, induces chronic inflammatory changes through a myriad of cytokines, creates oxidative stress, and even promotes the growth of cancer cells. Hyperglycaemia stimulates and promotes recurrent pulmonary infections because of raised glucose concentration in airway surface liquid and immune system malfunction that exist together.[5] Diabetics have reduced lung function that is associated with the duration of diabetes, raised fasting plasma glucose and glycated haemoglobin (HbA1c).[6] Obesity is common among diabetics and is commonly measured by body mass index (BMI). The major effect of obesity on lung function is multifactorial, related to mechanical changes causing asthma-like symptoms. Excess adiposity is also associated with amplified production of inflammatory cytokines and immune cells that could also cause disease.[7]

Serum surfactant protein D (SP-D) is one of the components of protein in the surfactant layer, and its detection in serum leads to an idea of its release in blood due to damage in pulmonary epithelium, and its release shows defective pulmonary barrier function possibly due to impaired glucose metabolism.[8] Type 2 diabetics have low forced expiratory volume in one second (FEV1) and

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forced vital capacity (FVC) compared to healthy people. Also, spirometry values have shown an inverse association with fasting plasma glucose and HbA1c levels.[1,9] Pulmonary function tests in diabetic patients having uncontrolled glycaemic status are at lower level than persons having controlled glycaemic status.[9]

The current study was planned to evaluate pulmonary function in type 2 diabetic patients using SP-D as a biomarker, and to determine its association with early pulmonary dysfunction.

Patients and Methods

The descriptive, analytical, cross-sectional study was conducted at the diabetic clinic of Sheikh Zayed Hospital, Lahore, Pakistan, from March 1 to August 31, 2021. After approval from the institutional ethics review board, the sample size was calculated using Fisher's Z-transformation-based method for correlation studies, with 95% confidence level, 90% statistical power, and an expected correlation of 0.265 between serum SP-D levels and FEV.[10] The sample size was inflated by >5% to account for potential variability and ensure adequate representation. The sample was raised using convenience sampling technique, and written, informed consent was obtained from all the participants who had been enrolled from among diabetic patients and non-diabetic relatives of the patients visiting the hospital. Those included were T2DM patients and non-diabetic controls of either gender aged 18-80 years. The sample was unmatched, but an equal number of males and females were enrolled in the two groups for a balanced comparison. Individuals having heart failure, chronic renal failure, chemotherapy, hormone replacement therapy, malignancy, pregnancy and type 1 diabetes were excluded.

Demographic data was noted along with patient history, followed by general physical examination and systemic examination. The BMI of each subject was estimated by taking height and weight with the help of a measuring tape and a digital weighing machine. Waist circumference (WC) was also recorded with the help of the measuring tape.

Spirometry was performed for the estimation of pulmonary functions by using a Spirolab III diagnostic spirometer. Average of three acceptable values of FVC, FEV1 and FEV1/FVC was obtained using repeatability criteria. The two groups were further stratified into three groups each, based on FEV1/FVC ratio (normal, decreased and increased ratio). Normal FEV1/FVC ratio was taken as 0.7-0.85 (70-85%) normal. Ratio <0.7 was considered to indicate obstructive lung dysfunction, and >85% was taken as restrictive lung dysfunction.[11]

Blood samples were taken by routine venipuncture under aseptic conditions. Blood (3ml) was drawn from each subject, and transferred to non-coated gel containing vacutainers at room temperature. After clotting, the sample was centrifuged at 3,000 revolutions per minutes (rpm) for 5 minutes. The samples were transferred in properly labelled eppendorf-tubes, and stored at 20 degrees Celsius till analysis for the estimation of SP-D levels, FBG, HbA1c on a semi-automated analyser at National Health Research Council (NHRC) and Federal Postgraduate Medical Institute (FPGMI), Lahore.

Data was analysed using SPSS 26. Continuous variables were presented as mean +/- standard deviation or median with interquartile range (IQR). Categorical variables were expressed as frequencies and percentages. Data normality was checked using the Shapiro-Wilk's test. Data for age, WC and FEV1 were normally distributed, while SP-D and FVC were not normally distributed. Independent sample t-test was used for comparing normally distributed variables (age, WC, FEV1). Mann-Whitney U test was used for non-normally distributed continuous variables (HbA1c, fasting blood glucose [FBG], BMI, FVC, FEV1/FVC ratio, SP-D). Chi-square test was used to compare categorical variables. Spearman's correlation was applied to find correlations among non-normally distributed variables. For >2 groups, Kruskal-Wallis test was used instead of one-way analysis of variance (ANOVA), since the data did not follow normal distribution. P≤0.05 was considered significant.

Results

Table-1: Comparison of data between type 2 diabetic and non-diabetic subjects (n=164).

Study variables	Type 2 Diabetic subjects (n=82) Mean±SD/Median (IQR)	Non-diabetic subjects (n=82) Mean±SD/Median (IQR)	*p*-value	Test Used
Age (years)	51.02±11.97	44.65±15.18	0.002*	Independent t-test
Waist circumference	99.41±12.28	95.99±14.37	0.070 NS	Independent t-test
Glycated haemoglobin (HbA1c)	7.61±1.38/7.20 (1.10)	5.67±0.57/5.50 (1.10)	<0.001**	Mann-Whitney U
Fasting blood glucose (FBG)	180.39±54.02/168.50 (67.00)	97.11±10.09/94.00 (13.00)	<0.001**	Mann-Whitney U
Body mass index (BMI)	26.68±4.00/26.05 (17.00)	27.31±5.51/25.80 (8.50)	0.970 NS	Mann-Whitney U
Forced expiratory volume in one second (FEV1%)	82.37±14.90	87.39±13.31	0.029*	Independent t-test
Forced vital capacity (FVC%)	86.38±19.69/89.00 (37.00)	86.62±21.88/95.00 (37.00)	0.583 NS	Mann-Whitney U
FEV1/FVC Ratio	71.07±14.19/70.00 (2.00)	79.63±14.40/83.00 (23.00)	<0.001**	Mann-Whitney U

SD: Standard deviation, IQR: Interquartile range.

Table-2: Comparison of serum surfactant protein D (SP-D) between type 2 diabetics and non-diabetics.

Group	FEV1/FVC Ratio <70	FEV1/FVC Ratio 70-85	FEV1/FVC Ratio >85	*p*-value (Kruskal-Wallis)
	Mean ± SD	Mean±SD	Mean±SD	
Type 2 Diabetics (n=82)	90.24±5.78	93.36±0.008	94.46±0.06	<0.001
Non- Diabetics (n=82)	94.48±2.63	93.35±3.70	91.49±5.10	0.049

FEV1/FVC: Ratio between forced expiratory volume in one second and forced vital capacity.

Table-3: Spearman's correlation among biochemical variables in diabetic subjects (n=82).

Variables		FEV1%	FVC%	FEV1/ FVC	SP-D
FEV1%	Correlation Coefficient	1.000	0.679	0.609	-0.711
	p-value	.	<0.001**	<0.001**	<0.001**
FVC%	Correlation Coefficient	0.679	1.000	0.531	-0.721
	p-value	<0.001**		<0.001**	<0.001**
FEV1/FVC Ratio	Correlation Coefficient	0.609	0.531	1.000	-0.717
	p-value	<0.001**	<0.001**		<0.001**
SP-D	Correlation Coefficient	-0.711	-0.721	-0.717	1.000
	p-value	<0.001**	<0.001**	<0.001**	

FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, FEV1/FVC: Ratio between FEV1 and FVC, SP-D: Surfactant protein D.

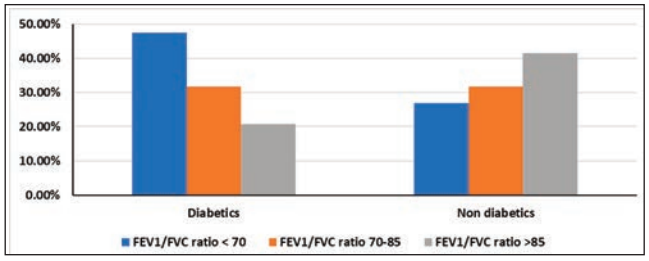

Figure: FEV1/FVC ratio between type 2 diabetics and non-diabetics.

Of the 164 subjects, 82(50%) each were diabetics and controls. In both the groups, there were 49(59.75%) females and 33(40.24%) males. The mean age of diabetics was 51.02±11.98 years, while it was 44.65±15.18 years among the controls (p<0.05). Mean BMI and WC values were not significantly different between the groups (p>0.05), while HbA1c and FBG values were significantly different (p<0.05). Pulmonary function was compromised in diabetics, with lower FEV1 and its ratio with FVC (p<0.05) despite non-significantly different FVC values (p>0.05) (Table 1).

Mean serum surfactant protein D (SP-D) levels were significantly higher in diabetics (63.59±26.20ng/mL) compared to non-diabetics (37.41±23.65ng/mL; p<0.05). When stratified according to FEV1/FVC ratio, SP-D levels showed significant differences across pulmonary function categories in both groups, with higher levels observed in subjects with abnormal lung function, particularly among diabetics (Table 2).

Correlation analysis revealed a significant negative correlation between serum SP-D levels and pulmonary function parameters, including FEV1, FVC, and FEV1/FVC ratio, in diabetic subjects (p<0.001), indicating that higher SP-D levels were associated with greater impairment in lung function (Table 3).

The Figure illustrates a significantly lower FEV1/FVC ratio among diabetic subjects compared to non-diabetic controls, further demonstrating compromised pulmonary function in the diabetic group.

Discussion

The current study explores the potential of SP-D as an early marker for lung function decline in diabetes, correlating serum SP-D levels with pulmonary function tests. The results suggest that SP-D could serve as a biomarker for lung injury and lung function decline related to the long-term effects of diabetes on the pulmonary parenchyma.

In this study, 164 participants were recruited from a tertiary care hospital in Lahore, evenly split between diabetics and non-diabetics. This balanced sample size builds on prior international research and contrasts with an international study which used unequal group sizes.[12] A Karachi-based study had a smaller sample, but did not include spirometry.[13] These factors make the current findings a more reliable indicator of diabetes and respiratory function.

In this study, the overall mean WC of the subjects was 97.70±13.44cm, which was higher than the 88cm reported earlier by a study conducted in Pakistan.[13] An international study by Hou et al. also showed a WC mean of 87.9cm.[14] WC is a good indicator of abdominal obesity, and the higher value found in this study shows the rising prevalence of obesity in Pakistan.

Values of HbA1c showed a higher HbA1c level among diabetics 7.61±1.38 compared to non-diabetics 5.67±0.57, which was consistent with a previous research on optimal HbA1c values.[15] This higher HbA1c indicates poor disease control, likely affecting lung function. FBG levels averaged 180.39±54.02 for diabetics and 97.11±10.09 for the non-diabetics, aligning with the IDF's diagnostic criteria.[16] These elevated levels suggest under-treatment among diabetic patients. Mean BMI was 26.86±4 in diabetics and 27.31±5.51 in non-diabetics. The slight decrease among diabetics was potentially due to diabetes management, which was similar to earlier findings.[1]

The current study found that diabetic patients have a significantly lower mean predicted FEV1 and FVC compared to non-diabetics. The FEV1/FVC ratio was significantly lower in diabetics compared to non-diabetics, showing a strong association. Lower FEV1/FVC ratios were more common in participants with lung disease, indicating larger decline in lung function and suggesting an

obstructive lung dysfunction pattern, especially prominent among diabetics. Similar findings were reported by like López-Cano et al.[1] Additionally, diabetics face a higher risk of pulmonary infections, which may contribute to an obstructive lung defect over time. Two studies suggested restrictive lung disease in diabetics, which may have been due to small sample sizes.[17,18] Overall, the current study supports an obstructive lung disease pattern in diabetics, with some restrictive cases.

The current study found significant differences in FEV1% and FVC% between diabetics and non-diabetics, with the combined FEV1/FVC ratio significantly lower in diabetics. Both diabetic and non-diabetic groups with lung disease showed lower FEV1/FVC ratios compared to those without lung disease. These results align with previous studies.[19,20] Pulmonary function declines may be due to prolonged diabetes, leading to lung damage from inflammation and oxidative stress.[21] The current study suggests that these issues may relate to surfactant dysfunction and inflammation, though it did not analyse the duration of diabetes, which is a limitation.

The current study found significantly higher serum SP-D levels in diabetics, particularly those with lung disease, compared to non-diabetics Elevated. SP-D levels in diabetics may reflect early pulmonary barrier dysfunction, even without spirometric abnormalities, suggesting SP-D as a potential marker for early lung damage in diabetes. These findings align with different studies though contrasting with other researchers[1,12] probably because they did not measure key lung function parameters, such as FEV1%, FVC% and the FEV1/FVC ratio. Akasaka et al. did not find any significant association between serum SP-D with diabetes mellitus.[22] Future research is recommended, and it has been suggested that SP-D may be validated as an early screening marker for diabetic pulmonary complications.[23]

The current study suggests that SP-D could be a general biomarker for lung dysfunction, regardless of diabetes status. This novel insight highlights SP-D's potential to indicate lung injury across various health conditions, offering a valuable contribution to the field. It may aid in early disease detection, monitoring progression, and guiding personalised therapies.

The current study has certain limitations. It was conducted at a single, localised centre due to limited resources and time, which may affect the generalisability of the results. A large-scale study with a more diverse sample is recommended to validate and expand upon the current findings. Additionally, the cross-sectional design of the study restricts the ability to establish a causal relationship among T2DM, pulmonary dysfunction and serum biomarkers. Furthermore, the results are based on univariate analyses, and are not adjusted for potential confounders. Further longitudinal studies with larger sample sizes are required to confirm the current findings.

Conclusion

SP-D levels in serum were elevated in T2DM patients, and they were associated with early pulmonary dysfunction. SP-D may serve as an early indicator of lung involvement in diabetes, depicting early damage of the pulmonary epithelium before progressive spirometric deterioration becomes evident.

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Author Contribution:
HZ & SZ: Concept, design, data acquisition, analysis, interpretation, drafting, revision, final approval and agreement to be accountable for all aspects of the work.