Surfactant protein D in chronic obstructive pulmonary disease and type 2 diabetes mellitus

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Objective
The objective of this study was to evaluate the role of serum surfactant protein D (SP-D) in chronic obstructive pulmonary disease (COPD) and type 2 diabetes mellitus (T2DM).

Background
SP-D plays a critical role in innate host defense of the lung. SP-D binds bacterial, fungal, and viral pathogens, enhancing their opsonization and their killing by alveolar macrophages. COPD may be considered as a novel risk factor for T2DM via multiple pathophysiological alterations such as inflammation, oxidative stress, administration of glucocorticoids, insulin resistance, and weight gain. On the other hand, diabetes may act as an independent factor, negatively affecting pulmonary structure and function. Diabetes is associated with an increased risk of pulmonary infections, disease exacerbations, and worsened COPD outcomes.

Patients and methods
This study was carried out on 87 patients classified into the following groups: group I, which included 35 patients with COPD without diabetes mellitus; group II, which included 18 patients with COPD and T2DM; group III, which included 19 patients with T2DM without COPD; and group IV, which included 15 age-matched and sex-matched healthy individuals. All individuals were subjected to full history taking, clinical examination, estimation of BMI, forced expiratory volume in 1 s% (FEV_1%) predicted, forced vital capacity% (FVC%) predicted, and FEV_1/FVC and laboratory investigations including estimation of fasting blood glucose (FBG), glycated hemoglobin (HbA_{1c}), and serum SP-D, which was carried out using the enzyme-linked immunosorbent assay technique.

Results
There was a significant statistical difference regarding serum SP-D between studied groups. The highest level of it was in group I than in group II, more lower in group IV, and the lowest level was in group III. There was a significant positive correlation between SP-D and each of age and smoking index, whereas there was a significant negative correlation between SP-D and each of BMI, FBG, HbA_{1c}, FEV_1% predicted, FVC% predicted, and FEV_1/FVC in studied participants. Age, BMI, and FEV_1% predicted are good predictors of SP-D in studied patient groups. Age and smoking index are risk factors for COPD in group I and for COPD and diabetes mellitus in group II, and they are not risk factors for T2DM (group III).

Conclusion
SP-D was significantly higher in COPD either alone or with T2DM, and it was significantly lower in isolated T2DM. Although SPD did not increase significantly with increasing COPD severity in COPD groups I and II, it correlated negatively with spirometric parameters in all studied participants. There was a positive correlation between SP-D and each of age and smoking index, whereas there was a negative correlation between SP-D and each of BMI, FBG, HbA_{1c}, FEV_1% predicted, FVC% predicted, and FEV_1/FVC. Factors that predicted serum level of SP-D were age, BMI, and FEV_1%. Age and smoking index were risk factors for COPD and they were not risk factors for T2DM.

Keywords:
chronic obstructive pulmonary disease, surfactant protein D, type 2 diabetes mellitus

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Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to severity in individual patients [1]. Type 2 diabetes mellitus (T2DM) has become a global health problem [2]. This type, previously referred to as non-insulin-dependent diabetes mellitus (DM) or adult-onset DM, includes

individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency. Most patients with this type of diabetes are obese, and obesity itself causes some degree of insulin resistance [3]. Diabetic microvascular complications are the major causes of morbidity and premature mortality in T2DM [4].

COPD may be considered as a novel risk factor for T2DM via multiple pathophysiological alterations such as inflammation, oxidative stress, administration of glucocorticosteroids, insulin resistance, and weight gain. On the other hand, diabetes may act as an independent factor, negatively affecting pulmonary structure and function. Diabetes is associated with an increased risk of pulmonary infections, disease exacerbations, and worsened COPD outcomes [5].

Pulmonary surfactant is a complex mixture of lipids (~90%) and proteins (~10%) that constitutes the mobile liquid phase covering the large surface area of the alveolar epithelium. It maintains minimal surface tension within the lungs in order to avoid lung collapse during respiration. Four surfactant proteins (SPs) – SP-A, SP-B, SP-C, and SP-D – are intimately associated with surfactant lipids in the lung [6].

SP-D has an important protective role in the immune system against inhaled microorganisms and allergens. It has a role in protection against viral, bacterial, and fungal infections, as well as apoptotic cells [7]. SP-D, a lung-derived innate immune protein, may be an important effector molecule in the pathogenesis of COPD [8].

Deficiencies in proteins of the innate immune system such as SP-D have been found to be associated with alterations of glucose metabolism. These deficiencies run in parallel with inflammation and impaired insulin action [9].

The aim of this study is to evaluate the role of serum SP-D in COPD and T2DM.

Patients and methods

Patients

This study was carried on 87 patients; there were 30 women and 57 men with age ranging from 51 to 75 years. The patients were attendants of Chest Department and outpatient clinics of Menoufia University Hospitals during the period from April 2014 to January 2015. This study was approved by the ethics committee of Faculty of Medicine, Menoufia University.

They were classified into four groups:

Group I included 35 patients with COPD without DM – seven women and 28 men with a mean age of 62.6 ± 6.5 years; group II included 18 patients with COPD and T2DM – eight women and 10 men with a mean age of 61.2 ± 7.2 years; group III included 19 patients with T2DM without COPD – eight women and 11 men with a mean age of 59.2 ± 4.4 years; and group IV included 15 age-matched and sex-matched healthy individuals – seven women and eight men with a mean age of 59.3 ± 5.4 years.

Inclusion criteria for patients with T2DM were BMI less than 40 kg/m^2, and absence of infection within the previous month and any other systemic diseases.

Exclusion criteria for the studied patient groups were acute exacerbation of COPD in COPD patients, respiratory failure, any other pulmonary diseases, and systemic diseases other than COPD and T2DM.

Methods

All individuals were subjected to full history taking, clinical examination, estimation of BMI, forced expiratory volume in 1 s% (FEV_1%) predicted, forced vital capacity% (FVC%) predicted and FEV_1/FVC and laboratory investigations including estimation of fasting blood glucose (FBG), glycated hemoglobin (HbA_{1c}), and serum SP-D, which was carried out using enzyme-linked immunosorbent assay technique.

Samples collection

Five milliliters of venous blood was taken from each fasting patient (12 h) and divided as follows: 3 ml was put in a plain tube, left to clot for 30 min at room temperature, and then subjected to centrifugation for 10 min at 4000 rpm and the serum obtained was put in plain vacutainer tubes and stored at −20°C until the time of assay of SP-D; 1 ml was put immediately in an EDTA tube for HbA_{1c}; and the remaining 1 ml was transferred into a plain tube for immediate estimation of FBG.

Assay methods

(1) Blood glucose was determined using enzymatic colorimetric method, using Spinreact kit (Spain) [10].

The principle is as follows: glucose is oxidized by glucose oxidase to glucoronic acid and hydrogen peroxide. The formed hydrogen peroxide is detected by a chromogenic oxygen acceptor, phenol aminophenazone, in the presence of peroxidase.

(2) HbA_{1c} was determined using CROMA HbA_{1c} [11] using kits supplied by Boditech Med Inc. (Chuncheon, Gangwondo, Republic of Korea).

The principle is as follows: CROMA HbA_{1c} is based on the fluorescence immunoassay technology, specifically the competition immune-detection method. Whole blood is added to the mixture of hemolysis buffer and detection buffer, which results in hemolysis of red blood cells. The mixture containing HbA_{1c} from the hemolyzed red blood cells and fluorescence-labeled HbA_{1c} peptides from detection buffer is loaded onto the sample well of the cartridge. HbA_{1c} from the blood competes with fluorescence-labeled HbA_{1c} peptides for binding sites on HbA_{1c} antibodies fixed on the nitrocellulose matrix. As a result, the higher concentration of HbA_{1c} produces a lower fluorescence signal from HbA_{1c} peptides. The signal is interpreted and the result displayed on CHROMA Reader in units of percentage.

(3) Human serum SP-D was quantitatively measured according to the manufacturer's protocol using a sandwich enzyme immunoassay technique using the Quantikine kit for Human SP-D Immunoassay [12] (catalog number DSFPD0, USA & Canada; R&D Systems Inc., Minneapolis, MN, USA).

The principle is as follows: this assay uses the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for SP-D has been precoated onto a microplate. Standards and samples are pipetted into the wells and any SP-D present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked monoclonal antibody specific for SP-D is added to the wells. After a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of SP-D bound in the initial step. The color development is stopped and the intensity of the color is measured.

Statistical analysis

The data collected were tabulated and analyzed by statistical package for the social science statistical package, version 20 (Armonk, New York, USA) on IBM-compatible computer.

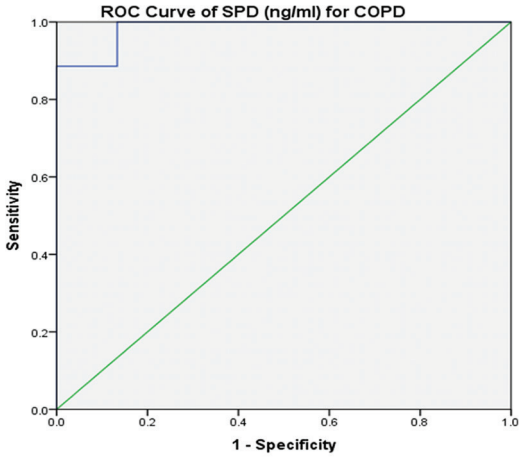
Results

The results of the present study are represented in Tables 1–9 and Figs. 1 and 2.

The results showed no statistically significant difference between the four studied groups as regards age and sex distribution. There was a significant statistical difference between groups I and II, I and III, I and IV, and II and III regarding BMI and between groups I and III, I and IV, II and III, and II and IV regarding smoking. There was a significant statistical difference between studied groups regarding lung function parameters, whereas a nonsignificant statistical difference existed between group I and group II in all lung function parameters and between groups III and IV regarding FEV_1% predicted and FEV_1/FVC (Table 1).

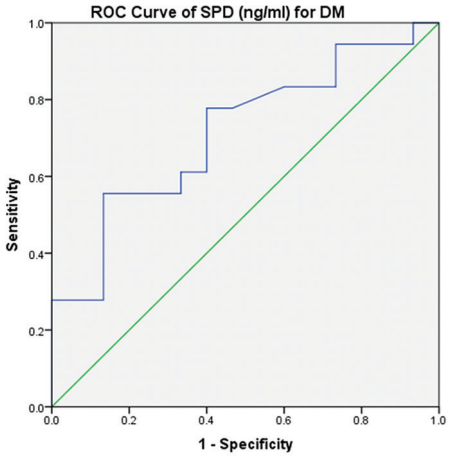
There was a significant statistical difference between studied groups regarding SP-D, FBG, and HbA_{1c}, whereas a nonsignificant statistical difference existed regarding FBG and HbA_{1c} between groups I and IV and II and III (Table 2). Serum SP-D level was significantly higher among smokers than among nonsmokers (Table 3).

Figure 1



Receiver operating characteristic (ROC) curve of surfactant protein D (SP-D) for diagnosis of chronic obstructive pulmonary disease (COPD) patients from controls.

Figure 2



Receiver operating characteristic (ROC) curve of surfactant protein D (SP-D) for diagnosis of patients with type 2 diabetes mellitus (DM) from controls.

Table 1 Sociodemographic characteristics and lung functions parameters of studied groups

	Group I (*n*=35) (mean±SD)	Group II (*n*=18) (mean±SD)	Group III (*n*=19) (mean±SD)	Group IV (*n*=15) (mean±SD)	*F*-test	*P*	*Post-hoc* test
Age (years)	62.6±6.5	61.2±7.2	59.2±4.4	59.3±5.4	1.79	0.15	P_1=0.43 P_2=0.06 P_3=0.08 P_4=0.32 P_5=0.36 P_6=0.98
Sex (*n* (%))					χ^2_1=3.50 χ^2_2=3.00 χ^2_3=3.70 χ^2_4=0.02 χ^2_5=0.02 χ^2_6=0.07		P_1=0.06 P_2=0.08 P_3=0.06 P_4=0.89 P_5=0.89 P_6=0.79
Male	28 (80.0)	10 (55.6)	11 (57.9)	8 (53.3)			
Female	7 (20.0)	8 (44.4)	8 (42.1)	7 (46.7)			
Smoking					χ^2_1=4.02 χ^2_2=29.31 χ^2_3=25.16 χ^2_4=12.55 χ^2_5=10.31		P_1=0.06 P_2<0.001** P_3<0.001** P_4<0.001** P_5=0.001*
Yes	27 (77.1)	9 (50.0)	0 (0.0)	0 (0.0)			
No	8 (22.9)	9 (50.0)	19 (100)	15 (100)			
Smoking index (pack-years)	22.7±18.3	10.2±2.7	–	–	2.26#	0.02*	P_1=0.02*
BMI (kg/m^2)	24.8±4.5	27.9±3.6	31.6±5.4	29.9±2.9	11.6	<0.001**	P_1=0.01* P_2<0.001** P_3<0.001** P_4 0.01* P_5=0.20 P_6=0.26
FEV_1% predicted (%)	45.4±10.4	43.0±7.8	97.0±5.2	98.5±6.8	278.21	<0.001**	P_1=0.34 P_2<0.001** P_3<0.001** P_4<0.001** P_5<0.001** P_6=0.61
FVC% predicted (%)	65.8±6.1	62.8±5.01	73.9±3.8	86.7±3.9	76.97	<0.001**	P_1=0.06 P_2<0.001** P_3<0.001** P_4<0.001** P_5<0.001** P_6<0.001**
FEV_1/FVC	59.6±5.9	59.5±4.5	83.9±3.1	85.5±3.4	192.39	<0.001**	P_1=0.95 P_2<0.001** P_3<0.001** P_4<0.001** P_5<0.001** P_6=0.34

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity. P_1=Group I vs. II. P_2=Group I vs. III. P_3=Group I vs. IV. P_4=Group II vs. III. P_5=Group II vs. IV. P_6=Group III vs. IV. *Significant difference. **Highly significant difference. #Mann–Whitney test.

SP-D increased nonsignificantly with increasing grade of severity of COPD in groups I and II (Table 4). There was a significant positive correlation between SP-D and each of age and smoking index in studied participants, whereas there was a significant negative correlation between SP-D and each of BMI, FBG, HbA_{1c}, FEV_1% predicted, FVC% predicted, and FEV_1/FVC in studied participants (Table 5).

The results showed that factors that predicted serum level of SPD were age, BMI, and FEV_1% (Table 6). Age and smoking index were risk factors for COPD in group I and for COPD and DM in group II and they were not risk factors for T2DM (group III) (Table 7).

The diagnostic accuracy of SP-D in the diagnosis of COPD patients from controls was 94%, with a sensitivity of 97.1%, specificity of 86.7%, positive predictive value of 94.4%, and negative predictive value of 92.9% at a cutoff point of 66.55 ng/ml (Table 8), whereas the diagnostic accuracy of SP-D in the diagnosis of patients with T2DM from controls was 69.7%, with a sensitivity of 77.8%, specificity of 60%, positive predictive value of 70%, and negative predictive value of 69.2% at a cutoff point of 48.85 ng/ml (Table 9).

Table 2 Statistical comparison among studied groups regarding biochemical parameters

	Group I (*n*=35) (mean±SD)	Group II (*n*=18) Mean±SD	Group III (*n*=19) Mean±SD	Group IV (*n*=15) Mean±SD	Kruskal–Wallis test	*P*	*Post-hoc* test
FBG (mg/dl)	90.0±8.8	203.7±48.2	247.7±89.2	88.4±7.2	63.45	<0.001**	P_1<0.001** P_2<0.001** P_3 0.19 P_4=0.36 P_5<0.001** P_6<0.001**
HbA_{1c} (%)	6.0±0.24	8.04±1.36	8.4±0.85	5.8±1.3	11.6#	<0.001**	P_1<0.001** P_2<0.001** P_3=0.68 P_4=0.21 P_5<0.001** P_6<0.001**
SP-D (ng/ml)	87.2±12.0	59.04±14.3	36.5±18.5	48.3±13.1	62.1	<0.001**	P_1<0.001** P_2<0.001** P_3<0.001** P_4=0.001* P_5=0.001* P_6=0.04*

FBG, fasting blood glucose; HbA_{1c}, glycated hemoglobin; SP-D, surfactant protein D. P_1=Group I vs. II. P_2=Group I vs. III. P_3=Group I vs. IV. P_4=Group II vs. III. P_5=Group II vs. IV. P_6=Group III vs. IV. *Significant difference. **Highly significant difference. #*F*-test.

Table 3 95% confidence interval for the mean of serum log surfactant protein D according to smoking status

	Smokers (*n*=36) (mean±SD)	Nonsmokers (*n*=51) (mean±SD)	Mann–Whitney test	*P*	95% confidence interval	
					Lower limit	Upper limit
					77.2	89.1
SP-D (ng/ml)	83.2±17.6	47.6±20.2	6.36	<0.001**	41.9	53.3

SP-D, surfactant protein D. **Highly significant difference.

Table 4 Statistical comparison among grades of chronic obstructive pulmonary disease severity of groups I and II regarding surfactant protein D

	Grade 2 (*n*=15) (mean±SD)	Grade 3 (*n*=33) (mean±SD)	Grade 4 (*n*=5) (mean±SD)	*F*-test	*P*
SP-D (ng/ml)	76.6±21.2	76.9±17.1	85.1±21.3	0.45	0.64

SP-D, surfactant protein D.

Table 5 Correlation coefficient between surfactant protein D serum levels and all parameters among studied groups

	Serum level of SPD (ng/ml)	
	r	*P*
Age (years)	0.610	<0.001**
Smoking index (pack-years)	0.673	<0.001**
BMI (kg/m^2)	−0.620	<0.001**
FBG (mg/dl)	−0.364	0.001*
HbA_{1c} (%)	−0.282	0.008*
FEV_1% predicted (%)	−0.654	<0.001**
FVC% predicted (%)	−0.495	<0.001**
FEV_1/FVC	−0.583	<0.001**

FBG, fasting blood glucose; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HbA_{1c}, glycated hemoglobin; SP-D, surfactant protein D. *Significant difference. **Highly significant difference.

Discussion

SP-D is an important regulatory protein that may aid in controlling chronic inflammation, reducing oxidative radical formation, facilitating phagocytosis and agglutination, reducing cell death, and enhancing apoptotic and necrotic cell clearance [13].

SP-D is produced predominantly by type II pneumocytes; its expression is correlated with pulmonary function and is increased in stable COPD, with higher levels observed during acute exacerbation. Changes in SP-D level are associated with the improvement of COPD symptoms [14].

A reduced ability to sense and eradicate pathogens could thus cause frequent respiratory tract infections, reduced vital capacity, and chronic inflammation resulting in insulin resistance and T2DM [15].

This study assesses serum SP-D in COPD and T2DM.

In the present study, neither age nor sex was significantly different between patients and controls. This was in agreement with the studies of Makarevich *et al.* [16], Wang *et al.* [17], Jeon *et al.* [18], and Zahran *et al.* [19].

In the present study, there was a significant statistical difference between group I and controls regarding FEV_1% predicted, FVC% predicted, and FEV_1/FVC.

These results were in agreement with those of Pride and Soriano [20] and Donaldson *et al.* [21], who found significantly lower values of FEV_1 and FEV_1% predicted in smokers with COPD than in controls.

In the present study, there was a significant statistical difference between group III and controls regarding FVC% predicted. This was in agreement with the study of Uz-Zaman *et al.* [22], Anandhalakshmi *et al.* [23], and Aparna [24], who found that FVC and FEV_1 were significantly reduced in T2DM.

In the current study, there was a significant statistical difference between groups I and IV regarding SP-D.

Table 6 Univariate regression analysis to predict circulating surfactant protein D in patients groups

Model	β	t	P	95% CI	
				Lower	Upper
Age (years)	0.23	2.99	0.004*	0.19	0.94
Smoking index (pack-years)	0.16	1.94	0.06	−0.01	0.52
BMI (kg/m²)	−0.23	−2.97	0.004*	−1.93	−0.38
FBG (mg/dl)	−0.07	−0.59	0.55	−0.09	0.05
HbA_{1c} (%)	−0.12	−1.09	0.23	−5.53	1.61
FEV_1% predicted (%)	−0.54	−2.87	0.005*	−0.86	−0.16
FVC% predicted (%)	−0.03	−0.23	0.82	−0.74	0.59
FEV_1/FVC	0.19	1.07	0.29	−0.33	1.09

CI, confidence interval; FBG, fasting blood glucose; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HbA_{1c}, glycated hemoglobin. *Significant difference.

Table 7 Multivariate regression analysis to predict risk factors of each studied group

Risk factors for COPD	β	Odds ratio	P	95% CI	
				Lower	Upper
Age (years)	0.10	1.11	0.01*	1.02	1.21
Smoking index (pack-years)	0.06	1.06	0.02*	1.01	1.11
BMI (kg/m²)	0.003	0.89	0.98	−0.78	1.29
Risk factors for DM					
Age (years)	−0.04	0.96	0.28	−0.89	1.04
Smoking index (pack-years)	0.11	0.74	0.15	−0.23	1.38
BMI (kg/m²)	0.08	0.88	0.29	−0.93	1.27
Risk factors for COPD and DM					
Age (years)	0.12	1.13	0.01*	1.02	1.26
Smoking index (pack-years)	0.11	1.11	0.04*	1.002	1.23
BMI (kg/m²)	−0.40	0.96	0.81	−0.69	1.32

CI, confidence interval; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus. *Significant difference.

This was in agreement with the study of Lomas *et al.* [7] and Winkler *et al.* [25]. Alveolar damage in COPD causes leakage of SP-D from the pulmonary compartment into the systemic circulation, resulting in lowered broncoalveolar lavage fluid but higher serum SP-D levels [8].

In the current study, in group I and II there was a nonsignificant increase in serum SP-D level with an increase in the grade of severity of COPD. This was in agreement with the studies of Lomas *et al.* [7], Liu *et al.* [14], Winkler *et al.* [25], and Ozyurek *et al.* [26]. Liu *et al.* [14] stated that the serum SPD levels were not associated with COPD disease severity according to the GOLD guidelines.

In contrast to these findings, El-Deek *et al.* [27], Ju *et al.* [28], and Sin *et al.* [29] found that SP-D levels increased significantly and correlated with the degree of airway obstruction and grade of severity of COPD.

In the present study, serum SP-D level was significantly higher among smokers than among nonsmokers. This was in agreement with the study of Lomas *et al.* [7], Fernández-Real *et al.* [30], and also Winkler *et al.* [25], who stated that cigarette smoke is capable of disrupting SP-D's quaternary structure, which might play a role in an impaired immunological function and an increased translocation of SP-D from the lung into the circulation.

In the current study, there was a statistically significant difference between groups II and IV regarding FBG, HbA_{1c}, and SP-D. This was in agreement with the study by Mishra *et al.* [31], who found a significant difference in FBG and HbA_{1c} between controls and patients complaining of COPD and T2DM.

In the current study, there was a statistically significant difference between groups III and IV regarding FBG, HbA_{1c}, and SP-D. This was in agreement with the studies of Pueyo *et al.* [32] and Fernández-Real *et al.* [30], who found that circulating SP-D concentrations were significantly decreased in T2DM when compared with nondiabetic individuals in both nonobese and obese individuals. There is a relationship

Table 8 Cutoff value of surfactant protein D (ng/ml) in diagnosis of chronic obstructive pulmonary disease patients from controls

	AUC	Cutoff point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
SP-D (ng/ml)	0.985	66.55	97.1	86.7	94.4	92.9	94

AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; SP-D, surfactant protein D.

Table 9 Cutoff value of surfactant protein D (ng/ml) in diagnosis of patients with type 2 diabetes mellitus from controls

	AUC	Cutoff point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
SP-D (ng/ml)	0.715	48.85	77.8	60	70	69.2	69.7

AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; SP-D, surfactant protein D.

between plasma insulinase activity and serum SP-D. SP-D is inactivated by neutrophil serine proteinases. Insulinase activity has been shown to be increased 14.5-fold in neutrophils from diabetic patients; a number of different peptides have been described to be degraded by insulinase, including insulin, insulin-like growth factor-I, and insulin-like growth factor-II. It is unknown whether SP-D could be cleaved by insulinase. In addition, some molecules with insulinase activity (protein disulfide isomerase) seem to control insulin degradation and the inflammatory process simultaneously [30].

In the present study, there was a significant positive correlation between SP-D and each of age and smoking index in studied participants, whereas there was a significant negative correlation between SP-D and each of BMI, FBG, HbA_{1c}, FEV_1% predicted, FVC% predicted, and FEV_1/FVC in studied participants.

This was in agreement with the studies of Shakoori *et al.* [8] and Sorensen *et al.* [33], who found a significant positive correlation between SP-D and age. Ozyurek *et al.* [26], El-Deek *et al.* [27], and Sorensen *et al.* [33] found a significant positive correlation between SP-D and smoking index, whereas Shakoori *et al.* [8], Sorensen *et al.* [33], and Zhao *et al.* [34] found a significant negative correlation between SP-D and BMI. Fernández-Real *et al.* [30] and Pueyo *et al.* [32] found a significant negative correlation between SP-D and each of FBG and HbA_{1c}, whereas Ozyurek *et al.* [26], Ju *et al.* [28], El-Deek *et al.* [27], and Sin *et al.* [29] found a significant negative correlation between SP-D and FEV_1% predicted; in contrast to this, Liu *et al.* [14] found that the serum or sputum SP-D levels did not significantly correlate with pulmonary function FEV_1% predicted and FEV_1/FVC.

In the current study, we found that age and smoking index are risk factors for COPD. The link between aging and the pathogenesis of COPD is strongly supported by numerous studies such as the study by Karrasch *et al.* [35], who reported that during aging pulmonary function progressively deteriorates and pulmonary inflammation increases, accompanied by structural changes, which are described as senile emphysema.

Environmental gases, such as cigarette smoke or other pollutants, may accelerate the aging of lung or worsen aging-related events in lung by defective resolution of inflammation – for example, by reducing antiaging molecules, such as histone deacetylases, and this consequently induces accelerated progression of COPD [36].

In addition, Lindberg *et al.* [37] found a high cumulative incidence of COPD after 10 years of smoking. This emphasizes the importance of early smoking cessation in the reduction of incidence of COPD. In contrast to this, the study of Shakoori *et al.* [8] did not show significant correlations of smoking with either serum SP-D levels or risk of COPD.

In the present study, we found that age, smoking index, and BMI are not risk factors for DM. In contrast to this, Hu *et al.* [38] found in a cross-sectional study that age, obesity, total cholesterol, triglycerides, living in rural areas, and diabetes family history are all risk factors for prediabetes and diabetes. In addition, they were surprised to see that smoking appeared to be a protecting factor against diabetes.

In the present study, the diagnostic accuracy of SP-D in diagnosis of COPD patients from controls was 94%, with a sensitivity of 97.1% and a specificity of 86.7% at a cutoff point of 66.55 ng/ml. These results come in line with those of Sin *et al.* [29], Ozyurek *et al.* [26], and Moreno *et al.* [13].

Sin *et al.* [29] reported that elevated serum SP-D is a good marker of reduced lung function, worsening health status (especially dyspnea), and other poor outcomes in patients with lung disease. Thus, serum SP-D is a promising biomarker for tracking disease progression and predicting clinical outcomes in COPD.

In the present work, the diagnostic accuracy of SP-D in diagnosis of patients with T2DM from controls was 69.7%, with a sensitivity of 77.8% and a specificity of 60% at a cutoff point of 48.85 ng/ml, so the diagnostic accuracy of SP-D was higher in diagnosis of COPD than in T2DM. These results are in agreement with those of Fernández-Real *et al.* [30].

Conclusion

SP-D was significantly higher in COPD either alone or with T2DM, and it was significantly lower in isolated T2DM. SP-D increased nonsignificantly with increasing grade of severity of COPD. There was a significant positive correlation between SP-D and each of age and smoking index, whereas there was a significant negative correlation between SP-D and each of BMI, FBG, HbA_{1c}, FEV_1% predicted, FVC% predicted, and FEV_1/FVC. Age and smoking index were risk factors for COPD, and they were not risk factors for T2DM. The diagnostic accuracy of SP-D was higher in diagnosis of COPD than in T2DM.

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Conflicts of interest
There are no conflicts of interest.

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