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Original Article

Nephrotic range proteinuria; does it predict lung involvement in patients with type 2 diabetes☆

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ABSTRACT

Background: Diabetes mellitus is a chronic metabolic disorder that is well known for its long term serious complications. Proteinuria whether micro or macroproteinuria is one of these complications. Many studies has related proteinuria to other complications of diabetes as retinopathy and cardiovascular disease of diabetes, while the lungs of diabetic patients which is the largest organ in the body with a large macro and microvascular bed, has not been related to this complication.
Aim.: The aim of the study was to find out whether proteinuria in diabetic patients can predict lung involvement.
Patients and methods: A comparative cross sectional study in which we compared the lung function of 100 type 2 diabetic patients with proteinuria with that of 100 type 2 diabetic patients without proteinuria. Proteinuria is measured in a random sample by "urine protein/urine creatinine ratio". FEV1 and FVC were measured by spirometer.
Results: The results showed that patients with proteinuria had a high frequency of abnormal PFT (86%), while patients without proteinuria had a low frequency of abnormal PFT (11%).Also diabetic patients with proteinuria had lower FVC (72.9 ± 6.5 vs. 88.2 ± 8.2), than diabetic patients without proteinuria.
Conclusions: We concluded that diabetes mellitus causes a significant impairment in pulmonary function test. This impairment is significantly related with proteinuria.

1. Introduction

Hyperglycemia is one of many problems in patients with diabetes, as it has both direct and indirect effects on the micro and macrovascular tree and in fact it has a detrimental effect on every tissue and each cell in the body. In generally, the complications that occur due to hyperglycemia are divided to macrovascular, microvascular and non vascular complications [1].

The pathophysiology of microvascular complications of diabetes can be summarized to; Increased intracellular glucose, leads to the formation of advanced glycation end products (AGEs). AGEs can change the function and properties of proteins, such as elastin and collagen, which makes the vasculature stiffer and increase the thickness of the basement membrane, in addition to the promotion of inflammation and oxidative stress. Glucose metabolism is increased through the sorbitol pathway, which leads to the accumulation of sorbitol. Sorbitol is osmotically active, leading to increased cellular osmolarity. Hyperglycemia also activates protein kinase C, which leads to changes in the proteins of extracellular matrix of the neurons and endothelial cells [2].

High glucose levels increases the flux through the hexosamine pathway, forming a substrate for (n) and (o) glycosylation of proteins that will ultimately for cytokines which increase tissue damage and sclerosis [3].

The lungs in diabetes is involved in many different ways, as it is considered the 3rd largest internal organ in the body with a large macro and microvasculature in addition to large amounts of collagen and elastin. The normal lung function depends on the wellbeing of the pulmonary parenchyma and microvasculature. Any abnormality in any of these components will lead to abnormal pulmonary function [4]. The alveolar capillary bed in the lung is affected by microangiopathy, as postmortem lungs examination of diabetic patients show thickening of the alveolar epithelium and

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the capillary basal laminae [5]. Diabetes will also affect the elastin and collagen tissue of the lungs leading to loss of elastic recoil [6], which supports the intrathoracic airways and helps to maintain their patency [7]. Also the presence of systemic inflammation that is associated with endothelial dysfunction in patients with diabetes [8], may lead to airflow obstruction, in a manner similar to that in asthma [9]. Other effects of diabetes are; weakness of the skeletal muscle due to protein catabolism, autonomic neuropathy and reduced antioxidant defense, together they will lead to reduced respiratory muscle endurance [10], reduced pulmonary volumes [11] and reduced lung function [5] respectively.

The kidneys are similarly affected by microangiopathy, the postmortem studies of patients with diabetes showed that the thickening of the alveolar epithelium and the capillary basal laminae was of the same magnitude in the lungs as that found in the kidneys [5]. Based on the data that suggest "the presence of a preexisting complication (diabetic retinopathy, diabetic nephropathy, or diabetic neuropathy) contributes to the development of another" [12], this study was designed to determine the effect of diabetes mellitus on lung function, and determine its relation with proteinuria.

2. Patients and Methods

2.1. Selection of the sample

A comparative cross sectional study, comparing the lung function of 100 type 2 diabetic patients with proteinuria with 100 type 2 diabetic patients without proteinuria, (they were age, sex, BMI and duration of diabetes matched), attending Baghdad Teaching Hospital/Iraq, who accepted to take part in this study after fulfilling the inclusion and exclusion criteria.

2.2. Inclusion criteria

1. All patients with type 2 diabetes mellitus.
2. The duration of their diabetes is between 10 and 20 years
3. Patients with normal BMI (18.5–24.9 kg/m^2) to overweight BMI (25.0–29.9 kg/m^2).
4. Type 2 diabetes patients with proteinuria, in the range of $\geq$ 2 g/g creatinine.
5. Type 2 diabetes patients without proteinuria,.

2.3. Exclusion criteria

1. History of smoking or occupational exposure.
2. Any history of respiratory disease. chest deformity, chest trauma.
3. History of cardiac disease.
5. History of neuromuscular disease.
6. Patients with current febrile illness or urinary tract infections.
7. Patients using angiotensin-converting enzyme inhibitors, angiotensin-receptor blocker and/or Ca^+ channel blockers.

2.4. Measurement of proteinuria

Proteinuria is measured in a random sample by "urine protein/urine creatinine ratio".Proteinuria to creatinine ratio (PCR) in the range of < 2 g/g creatinine indicates a normal urinary. PCR $\geq$ 2 g/g creatinine indicates nephrotic range proteinuria [13].

2.5. Assessment of pulmonary function

Pulmonary function test was done by trained personnel using a master lab. The forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and ratio of FEV1/FVC were measured. The results are given as measured values in liters and were compared to the predicted values of patients themselves, using the European thoracic standardization of spirometry [14].

2.6. Statistical analysis

SPSS 20.0.0 (Statistical Package for Social Sciences) program used to make the statistical analysis, p value considered when appropriate to be significant if less than 0.05. Data were summarized as means ± SD. T test used to analyze the differences in means between patients groups. Binary logistic regression analysis used to calculate the odd ratio (OR) and their 95% confidence intervals, when the outcome can be categorized into 2 binary levels.

3. Results

A total of 100 type 2 diabetic patients with proteinuria compared with 100 type 2 diabetic patients without proteinuria. In patients with proteinuria the age (mean SD 59.5 ± 9.6 years), 52% were males and 48% were females, the duration of diabetes ranges between 10 and 20 years with a mean of (mean SD 17.7 ± 3.9 years), the mean BMI was (mean SD 24.6 ± 5.1), the mean waist circumference was (mean SD 98.2 ± 12.8), the mean systolic blood pressure was (mean SD 145 ± 17.8); and the mean diastolic blood pressure was (mean SD 87 ± 11.2). In patients without proteinuria the age (mean SD 58.7 ± 9.9 years), 51%% were males and 49% were females, the duration of diabetes ranges between 10 and 20 years with a mean of (mean SD 16.8 ± 3.1 years), the mean BMI was (mean SD 23.4 ± 5.5), the mean waist circumference was (mean SD 96.9 ± 13.6), the mean systolic blood pressure was (mean SD 141.3 ± 17.4); and the mean diastolic blood pressure was (mean SD 86.1 ± 11.7), (Table 1).

The frequency of abnormal PFT in diabetic patients with proteinuria was 86%, while the frequency of abnormal PFT in patients without proteinuria was 11%, (Figs. 1 and 2).

There was a strong significant correlation between proteinuria and abnormal PFT (Table 2).

There was an inverse relationship between FVC% and probability of proteinuria, which means that each decrease in FVC increases the probability of proteinuria (since odd ratio is less than 1, indicating the inverse relationship) (Table 3), and (Fig. 3).

4. Discussion

In this study there was a significant correlation between impairment in pulmonary function tests and proteinuria and there was an inverse relationship between FVC% and probability of

Table 1
Demographic data for all patients in this study.

	DM with proteinuria	DM with no proteinuria
Age (mean ± SD)	59.5 ± 9.6	58.7 ± 9.9
Duration of DM (mean ± SD)	17.7 ± 3.9	16.8 ± 3.1
BMI (mean ± SD)	24.6 ± 5.1	23.4 ± 5.5
Male	52%	51%
Female	48%	49%
Waist c. (mean ± SD)	98.2 ± 12.8	96.9 ± 13.6
SBP (mean ± SD)	145 ± 17.8	141.3 ± 17.4
DBP (mean ± SD)	87 ± 11.2	86.1 ± 11.7

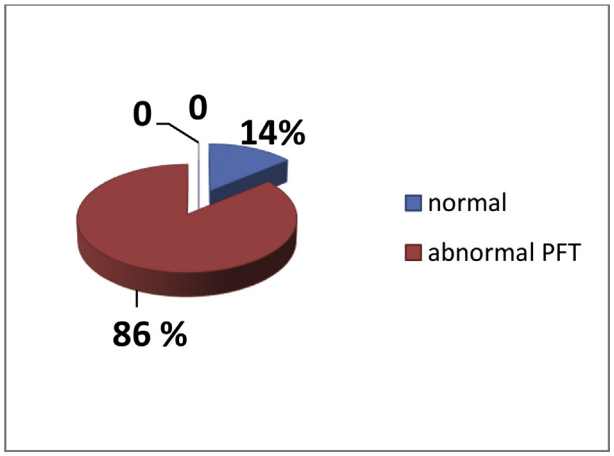

Fig. 1. Frequency of normal and abnormal PFT in patients with proteinuria.

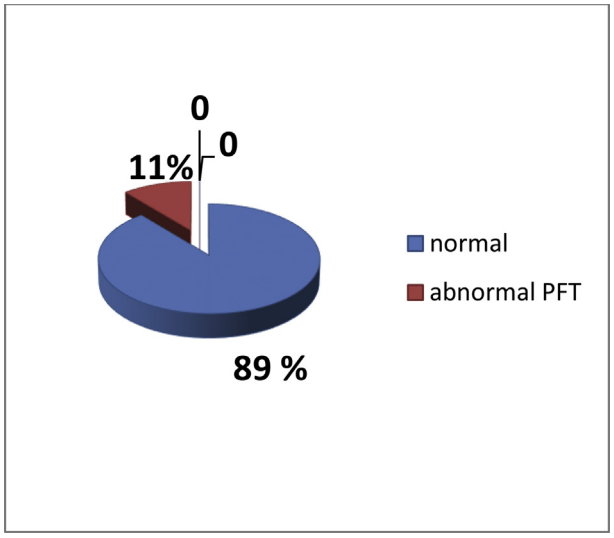

Fig. 2. Frequency of normal and abnormal PFT in patients without proteinuria.

Table 2
Relationship between proteinuria and abnormal PFT.

FVC%	No proteinuria	Proteinuria	OR	95%CI	P value
≥80%	89 (89.0%)	14 (14.0%)	49.70	21.38 to 115.53	<0.001
<80%	11 (11.0%)	86 (86.0%)			

Table 3
Relationship between FVC% and proteinuria.

	Proteinuria	Without Proteinuria	OR	95%CI	P value
FVC%	72.9 ± 6.5	88.2 ± 8.2	0.711	0.621–0.815	<0.001

proteinuria. Shegokar et al., in 2015 [15], conducted a cross-sectional study of 70 patients with type 2 diabetes in India. They found that 48.6% of patients had abnormal PFT and 91.1% of those patients with abnormal PFT had other microvascular complications. Klein et al., in 2016 [16], conducted a prospective study of 2959 patients with type 2 diabetes and 11496 healthy adults from Latino or Hispanic descend. They found that diabetic patients had a significant lower predicted FEV1 and FVC and higher dyspneic score

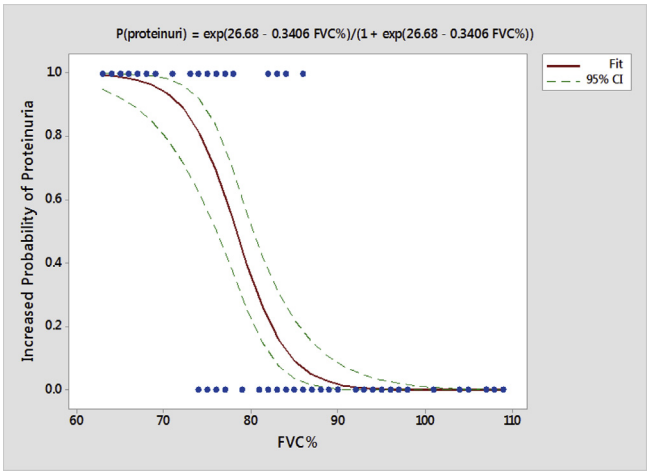

Fig. 3. Relationship between FVC% and proteinuria.

than those without diabetes. They also found that diabetic patients with albuminuria had 10% lower FVC, 6% lower FEV1 and 2.5 folds higher dyspneic score than diabetics without albuminuria. The results of these two studies agree with this study in that patients with diabetes are at high risk of pulmonary dysfunction and that there is a significant relation with other microvascular complications. The correlation of reduced lung function in type 2 diabetes mellitus, support the concept that the lung is a target organ involved by diabetes complications and this involvement can be predicted or coincide with other complications of diabetes. All of the patients, who had abnormal pulmonary function test in this study, had a restrictive pulmonary dysfunction which is considered in many reviews and studies as the most common type of lung impairment in diabetic patients. The following studies "Zainab et al. [17], Pawar et al. [18], Jamatia et al. [19], Muhammad et al. [20], and Adeyeye et al. [21]" also agreed that restrictive pattern is the predominant pattern, although other patterns of involvement may occur but to lesser extent.

5. Conclusion

Diabetes mellitus cause a significant impairment in pulmonary function test. This impairment is significantly related with proteinuria.

Author(s) agreement/declaration

We certify that all authors have seen and approved the final version of the manuscript being submitted. They warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

Conflicts of interest

The author(s) declared no conflict of interest with respect to the research, authorship, and/or publication of this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2018.11.031.

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