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Impact of Type 2 Diabetes Mellitus on Pulmonary Function Tests

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Abstract

Diabetes mellitus is a chronic metabolic disorder that may affect different organs including the lungs. Numerous studies have been published on the effects of diabetes mellitus on pulmonary function. A restrictive pattern of lung disorder was reported in some studies, whereas an obstructive pattern was suggested in others. The study aims to determine the impact of type 2 diabetes on pulmonary function tests (PFTs) and the type of respiratory disorder.

This observational study was conducted in Basrah City, Iraq. One hundred and eighty-two participants were enrolled and divided into 2 groups: 100 healthy (group1) and 82 patients with type2 diabetes mellitus (group 2). PFTs were estimated by a medical spirometer and measurments of several hematological tests were done for each individual.

It was found that a significant decline ($p < 0.05$) in forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), peak expiratory flow (PEF), and maximal voluntary ventilation (MVV), and a significant increase in estimated lung age (ELA) in group 2. The restrictive pulmonary disorder percentage was higher (24.39%) than obstructive (10.9%) and combined (2.43%).

Pulmonary function tests were significantly affected by type 2 DM and the percentages of different respiratory disorders were higher among group 2 than in group 1, with an increase in restrictive pattern.

Keywords: Pulmonary function tests, DM2, Restrictive pattern.

تأثير مرض السكري النوع الثاني على وظائف الرئة

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الخلاصة

داء السكري هو اضطراب جهازي يمكن ان يؤثر على أعضاء مختلفة بما في ذلك الرئة. تم نشر دراسات مختلفة حول تأثير مرض السكري على وظائف الرئة. اقترحت بعض الدراسات اضطراب النمط المقيد، بينما اقترح البعض الآخر وجود عائق. الهدف من الدراسة هو تحديد تأثير مرض السكري من النوع ٢ على اختبارات وظائف الرئة ونوع اضطراب الجهاز التنفسي. المادة والطرق: أجريت هذه الدراسة الرصدية في مدينة البصرة، العراق. تم تسجيل مائة وثمانين مشاركًا وتم تقسيمهم إلى مجموعتين: ١٠٠ صحي (المجموعة ١) و٨٢ مريضًا يعانون من داء السكري من النوع ٢ (المجموعة ٢). تم قياس وظائف الرئة بواسطة جهاز السبايروميتر الطبي وكذلك قياس مؤشرات الدم وبعض المؤشرات الالتهابية لكل فرد. النتائج: وقد وجد ان هناك انخفاضًا معنويا في وظائف الرئة وارتفاع معنوي في عمر الرئة الفسيولوجي في المجموعة ٢ وكان الاضطراب الرئوي الاحتقاني أعلى نسبة (٢٤,٣٩٪) من الانسدادي (١٠,٩٪) او مجتمعة (٢,٤٣٪) وأظهرت بعض المتغيرات الدموية، العدلات وكريات الدم البيضاء تغيرات معنويه، اضافه الى التغيرات في بعض المؤشرات الالتهابية. تأثرت اختبارات وظائف الرئة معنويا بالنوع ٢ DM وكانت النسب المئوية لاضطرابات الجهاز التنفسي المختلفة أعلى بين المجموعة ٢ من المجموعة ١، مع زيادة في النمط التقييدي.

الكلمات المفتاحية: اختبارات وظائف الرئة، مرض السكري النوع الثاني، الاضطراب الرئوي الاحتقاني

Introduction

Type 2 diabetes mellitus (DM 2) includes a set of metabolic disorders that affects 12% of the middle-aged population [(1)]. Diabetes leads to different health consequences and affects both large and small vessels, resulting in life-threatening microvascular and macrovascular diseases [(2)]. As a result, it has become one of the most serious risks to public health in the world. The problem becomes much more complicated when considering that up to half of all patients are completely clueless that they have this condition, as blood sugar can be elevated above normal levels in DM2 without noticeable signs [(3)]. Even though the fact that the lungs are not on the usual list of organs that might be impaired by diabetes, their intense vascularity, abundant collagen and elastin fibers place the pulmonary tissues as a possible target for hyperglycemia in the long term [(4)]. Additionally, lung dysfunction develops more frequently in patients with poor glycemic control and who experienced a long period of metabolic illness [(5)].

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The metabolic condition of insulin resistance and insulin insufficiency, which is defined by high blood glucose levels, has a role in the disruption of collagen and elastin cross-linking. Lung elasticity is diminished as a result of this process [(6)].

Hyperinsulinemia promotes the growth and increase in the number of main human airway smooth muscle cells as well as their hyperresponsiveness and contractility, this outcome has been reported to be a possible reason for the link between wheezing and type 1 diabetes [(7)] .Few studies have been done to conclude if subcutaneous insulin treatment is an independent contributor to the decline in lung function designated for DM2.

The most common way to assess lung function is by performing pulmonary function tests (PFTs) that includes three measures : diffusing capacity, lung volumes and spirometry [(8)]. The purpose of PFTs is to identify and characterize disease progressions that results in the decline in lung function. Obstruction of pulmonary airflow, lung volumes restriction, or a combination of both patterns; restrictive and obstructive abnormalities are examples of lung function impairments[(9)]. Although PFTs were created to measure airway function and lung disorders, their use has expanded to include a variety of specializations, and they can now be used as a basis for clinical decision-making in a variety of diseases [(10)]. It is a valuable test for determining lung tissue enrolment in diabetes mellitus disease. The most relevant measurements in this study are the forced vital capacity (FVC), The forced expiratory volume in the first second (FEV1), The ratio of FEV1 to FVC (FEV1/FVC%) which is used as an indicator of obstruction or restriction , peak expiratory flow (PEF), estimated lung age (ELA) and the maximal voluntary ventilation (MVV)[(11)].

We have designed this observational study to reveal the influence of diabetes mellitus type 2 on respiratory function tests as a primary endpoint and to determine the pattern of respiratory impairments.

Patients and Method

Study design

This is a cross-sectional comparative study performed in Basra City, Iraq, from November 2021 to March 2022. It was carried out under the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement's recommendations for reporting observational studies [(12)].

Participants

The study included one hundred and eighty-two participants of both genders between the ages of 33 and 62 years. Participants were categorized into two groups according to their state of health: 100 healthy individuals (52 males and 48 females), within the range (33-57) years of age. The source of these groups was patients' relatives and university employees. This group is the control group (group 1). The other group (group 2) is 82 diabetic patients of (DM2) (38 male and 44 female) with age range of 37-62 years. The patients were on insulin therapy and selected upon certain included and excluded criteria .The source of this group was patients who attended the internal medicine consulting clinic at one of the major hospitals Al-Fayhaa Teaching Hospital, Basrah City, south of Iraq.

To rule out any abnormalities or disorders, all subjects underwent a thorough clinical and physical examination to examine their cardiovascular, pulmonary, neuromuscular, and musculoskeletal systems.

The study procedure was permitted by the University of Basrah's Ethical Committee and Basrah Health Directory.

Included criteria

Patients with DM2 who have been shifted to subcutaneous insulin therapy for at least six months after failure of oral antidiabetic medication to control blood glucose levels were included.

Excluded criteria

Patients with DM2 who are taking oral anti-diabetic medication, newly diagnosed patients who have not started taking oral anti-diabetic medication, patients with cough, sputum, dyspnea, wheezing, and other symptoms; smokers and patients with COPD or restrictive pulmonary condition; patients with cardiovascular disease or major diseases are all excluded [(13)] .

A detailed form of a questionnaire was used to acquire the demographics and features of all patients, including age, gender, height, weight, BMI, co-morbidities, drug intake, and smoking status.

Data sources and measurement

Pulmonary function tests

Spirometry is an old test and most commonly used to assess pulmonary function. PFTs were carried out in agreement with the current recommendations [(14)]. Measurement of PFTs of patients and controls were assessed by a medical spirometer (Medical International Research MIR Spirolab III Diagnostic Spirometer, Rome, Italy). The measurements for all participants were between 9 am and 1 pm.

Spirometry was performed three times in a standing position at 15-minute intervals, and the best value was used. The recorded Parameters were (FVC) in liters, (FEV1), FEV1/FVC%, (MVV), (PEF) and (ELA), and the absolute values of participants were relied on in this study.

Echocardiogram

All patients went through an echocardiography examination by a cardiologist using GE vivid 7 cardiac ultrasound machine to exclude any cardiac disease that may affect pulmonary function test.

Laboratory measurements

For all participants, almost 5 mL of venous blood sample was collected in a serum separating tube, a sodium citrate, and ethylenediaminetetraacetic acid (EDTA) bulb using aseptic precautions.

A complete blood picture was estimated by SYSMEX XT-2000i, C-reactive protein (CRP) by Tina-quant CRP IV kit / COBAS INTEGRA, and ESR by Westergren method [15].

HbA1c of all the patients was estimated by the diagnostic tina-quant hemoglobin A1c kits of COBAS INTEGRA/ COBAS C SYSTEMS according to the current guidelines [16].

Participant's information was gathered in a collection form and later moved to a Microsoft excel sheet to be analyzed statistically.

Statistical analysis

SPSS version 26 (The Statistical Package for Social Sciences) was used for statistical analysis. Mean and median comparisons, and Skewness, Shapiro–Wilk, and Kolmogorov–Smirnov tests were utilized to determine whether numerical data of normal distribution. For regularly distributed data, an independent sample t-test was utilized, and for the non-normal distribution data, the Mann–Whitney U–test was done. Spearman's rank and Pearson's correlation coefficients were used to determine the strength of the link between the two variables. A P-value of less than 0.05 was defined as a Statistical significance.

Results

For the two study groups (group 1 and 2), there were no significant differences ($p>0.05$) in main features such as age range, gender ratio, BMI, and weight. Furthermore, the two groups showed normal echocardiography. However, the difference was significant in HbA1c between the healthy control group and the diabetic group ($p <0.05$), as illustrated in Table 1.

Table 1. Groups Characteristics

Group Parameters	Group 1 Mean ±SD	Group 2 Mean ±SD	P-value*
Numbers	100	82	
Age range	33-57	37-62	
Gender ratio (Female/male ratio)	48:52	44:38	0.261
Weight (kg)	71.91±14.81	81.89±7.63	0.951
height (cm)	168.77±9.54	170.17±9.42	0.343
BMI (Kg/cm^2)	25.14±4.37	28.51±3..99	0.251
HbA1c	4.67±0.431	8.40±1.16	0.000
Echocardiography	Normal	Normal	

* P-value is considered a significant at a level less than 0.05, mean±SD: mean ± standard deviation

Then again, the comparison between the two groups revealed several variations in hematological parameters as seen in table 2. Both WBC count and neutrophils count were highly increased ($p <0.05$) in group 2 in comparison with cytes count was found ($p>0.05$). Regarding RBC and other indices, there were no significant differences found in each of RBC, MCHC, and HGB ($p >0.05$). Inflammatory markers such as CRP and ESR were significantly increased ($p<0.05$) in group 2 in comparison with group 1.

Table 2. Hematological indices; ESR and CRP in group 1and group 2

Group (Parameters)	Group1 (Mean ±SD)	Group 2 (Mean ±SD)	P-value*
RBC	4.92±0.61	4.85±0.42	0.410
WBC	7.07±1.58	8.01±2.01	0.001
NEUTROPHILS	4.86±1.39	4.18±1.41	0.002
LYMPHOCYTES	2.56±0.78	2.52±0.78	0.727
HCT	42.84±4.18	40.06±4.41	0.000
HGB	13.46±1.54	13.32±1.52	0.765
MCV	88.68±6.69	82.34±5.17	0.000
MCH	30.87±2.89	28.86±1.96	0.000
MCHC	33.93±1.39	34.35±2.04	0.116
ESR	6.06± 2.19	10.37±4.18	0.000
CRP	0.78±0.16	1.70±1.18	0.000

* P-value is considered a significant at a level less than 0.05, RBC: red blood cells; WBC: white blood cells; HGB: hemoglobin; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; and MCHC: mean corpuscular hemoglobin concentration; ESR: erythrocytes sedimentation rate; CRP: C-reactive protein.

Variations in the results of PFTs have been found. Each of FVC and MVV were significantly decreased in group 2 ($p > 0.05$). While ELA was significantly increased in group 2, as illustrated in Table 3.

Table 3. Pulmonary function tests in group 1and group 2

Group (Parameters)	Group 1 (Mean ±SD)	Group 2 (Mean ±SD)	P-value*
FEV1(L)	3.21±0.74	2.71±0.67	0.061
FVC(L)	3.85±0.80	3.18±0.54	0.000
FEV1%(L)	90.86±5.96	84.95±9.91	0.188
PEF(L/S)	6.50±2.01	4.53±1.07	0.082
MVV(L/S)	108.15±16.14	83.69±18.30	0.000
ELA (years)	45.47±17.07	70.98±14.28	0.000

*P-value is considered a significant at a level less than 0.05.

On the other hand, no significant differences were found in each of FEV1, FEV1% and PEF between the two groups. Furthermore, the statistical analysis uncovered that there were variations in the percentage of respiratory disorders (obstructive, restrictive, and combined cases) between group 1 and group 2 .The obstructive diseases percentage in group 1 was (5%) while it was (10.9%) in group 2 . As well as the percentage of restrictive disease in group 2 (24.39%) was higher than that in group 1 (9%). There were no combined cases in group 1 , while it was 2% in group 2. Normal respiratory case percentage in group 1 was higher (86%) than what we found in group 2 (62.19%) (Table 4).

Table 4. Respiratory diagnosis and ELA in group 1 and group 2

Respiratory diagnosis	Group 1 N (%)	Group 1 ELA Mean ± SD	Group 2 N (%)	Group 2 ELA Mean ± SD	*P-value
Obstructive	5(5)	54.27±15.46	9(10.9)	69.10±15.341	0.0021
Restrictive	9 (9)	52.22±12.66	20(24.39)	64.55±10.29	0.0016
Combined	0 (0)		2(2.43)	75.30±13.02	
Normal	86(86)	43.49±15.006	51(62.19)	58.50±9.19	0.000

N: number; ELA: estimated lung age; *P-value is significant at a level less than 0.05

The same table shows that the ELA of the obstructive patients in group 2 was significantly elevated than that of obstructive patients of group 1 ($p < 0.05$). The same finding was reported related to the ELA comparison of the restrictive patients between the two groups. Moreover ELA was also significantly elevated in the normal respiratory cases of the group 2 compared to the normal respiratory cases of group 1 ($p> 0.05$) as shown in table 4. However, the correlations between HbA1c and each of FEV1, FVC, FEV1%, PEF, and MVV were non-significant, ($p> 0.05$). The interesting finding was the significant positive correlation between ELA and HbA1c (r : 0.33, $p > 0.05$), as seen in (Table 5,Figure1).

Table 5. Correlation between PFT and HbA1c in group 2

HbA1c	FVC	FEV1	FEV1%	PEF	ELA	MVV
r value	-0.059	-0.033	-0.274	-0.023	0.33	-0.028
P value	0.210	0.106	0.148	0.978	0.030	0.201

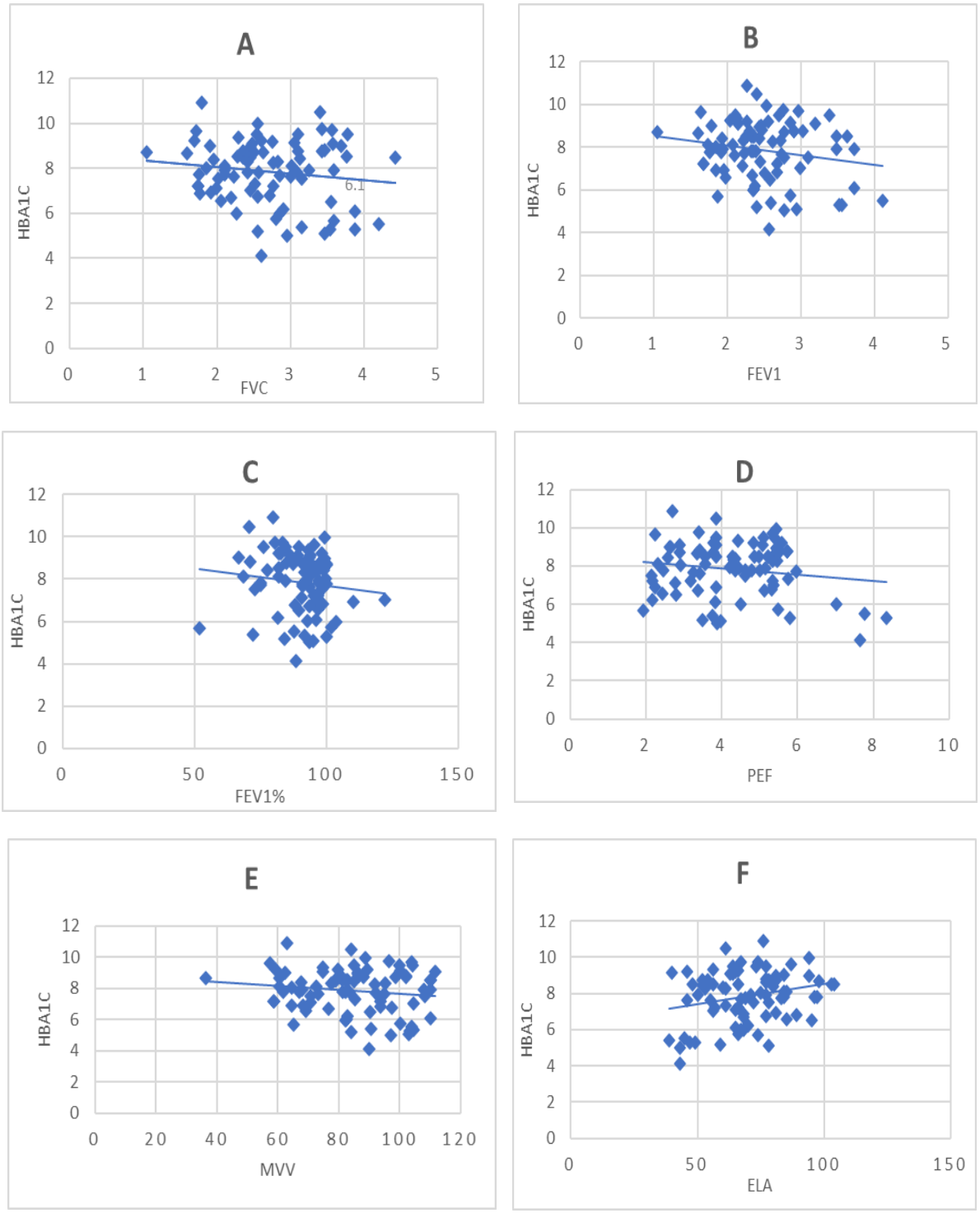

Figure 1. Correlation between HbA1c and PFTs in group 2, A: between HbA1c and FVC, B: between HbA1c and FEV1, C: between HbA1c and FEV1%, D: between HbA1c and PEF, E: between HbA1c and MVV and, F: between HbA1c and ELA.

Discussion

Pulmonary function tests, including FVC, FEV1, FEV1 percent, PEFR, and MVV of patients with DM 2 (group 2) showed a significantly lower values than in healthy controls (group 1). These findings are consistent with prior researches [5,17], which found that diabetes has a negative impact, especially when it is long-term and requires insulin administration. On the other hand, these results are inconsistent with pervious study [18]. More than half of the diabetic patients had normal pulmonary function tests, but a high percentage of patients had asymptomatic evidence of disturbed lung function tests – most commonly was a restrictive pattern, followed by obstructive and mixed pattern. This

outcome was also described by the Fremantle diabetes study [19], which stated that diabetes might be complicated by lower lung volumes and airflow limitation. Thus, the study findings came consistent with those of others, indicating that type 2 diabetes mellitus has an adverse impact on pulmonary functions and that the impairment is predominantly restrictive [4,20]. This finding may be explained by the fact that connective tissues in the lungs undergo glycosylation due to persistent hyperglycemia which may reduce the elastic recoil of the lungs and develop local inflammation in lung tissues, that eventually leads to a restrictive ventilatory changes [13].

In this study, 9 patients were with the obstructive pulmonary pattern. Some recent studies suggested an obstructive pathology of the lungs [21]. Theusen BH *et al.* [22] showed in their study that insulin resistance is an important predictor of the occurrence of symptoms that resembles asthma symptoms. While Balducci *et al.* [23] revealed that in DM 2, the strength of respiratory muscle declines corresponding to the metabolic regulation of the disease which may lead to reduced lung volumes. Another study conducted by Fuso L *et al.* [24] showed a distinct relationship between respiratory muscle efficacy and glycemic regulation. It demonstrated that MVV which is a measure of the respiratory muscle performance, lung volume variations, and airway resistance is elevated in patients with good control of blood glycemic levels and reduced in others with poorly controlled glycemia. This finding is consistent with our study that showed a statistically significant decrease in MVV of DM patients compared to their non-diabetic controls. However, MVV can be utilized as a simple means for the assessment of respiratory muscle strength [25] . Furthermore, another interesting finding was the significant elevation in ELA of the diabetic patients (group 2). ELA is the person's real age when respiratory functions are normal [26]. Deterioration of PFTs was inversely linked with ELA, implying that ELA increased as PFTs deteriorated [27] We suggest that significantly affected pulmonary function in DM type 2 on insulin and expressing a restrictive pattern could be explained by several reasons: Though morbid obesity had been excluded (two patients) , yet there are sizable numbers of overweight (33 patient) and obese (27 patient), a factor that might contribute to the restrictive derangement of respiratory function test [28,29]; Long standing DM may cause autonomic neuropathy that may associated with Gastroesophageal Reflux Disease (GERD) which may lead to recurrent aspiration pneumonitis and consequent fibrotic parenchymal lung changes and there is a high incidence of infections among DM patient (such as pulmonary tuberculosis) that may leave marked fibrotic changes in lung [30].

In this study, no relationship was found between HbA1c levels and PFTs results during the time of pulmonary function measurements which came consistent with Mori H *et al.* study [31] and Benbassat CA *et al.* [32] except for ELA that showed highly significant correlation with HbA1c. They attributed these results to the fact that HbA1c measurements indicate glycemic regulation for a short time (3-4 months). However, the absence of a significant relationship between spirometric parameters and glycemic control of patients indicates a more complicated model of lung damage caused by diabetes.

Regarding the hematological indices, group 2 showed a statistically significant increase in total WBC and absolute neutrophil counts in comparison to controls (group 1), which came close to another study by Biadgo B *et al*. [33]. When DM2 patients were compared to the healthy control group, statistically significant increases in MCV, MCH, and HCT were detected. According to Chen LK *et al*., a higher WBC count was significantly related to insulin resistance in elderly middle-aged patients [34]. However, there was no link found between insulin resistance and RBC count. Furthermore, we found that both ESR and CRP were significantly elevated in group 2. They are sensitive blood inflammatory markers might be used to evaluate certain inflammatory processes and infections in DM [35] .It has been reported by Mottaghi *et al.* that their levels were significantly associated with the progress of DM [36].

Conclusion

Pathological process of Diabetes mellitus may extend to include lung physiology, some pulmonary function tests were significantly affected by DM2 which includes FVC, MVV and, ELA while FEV1, PEF and, FEV1% were not significantly affected and the percentages of different respiratory disorders were higher among group 2 than group 1, with an increase of restrictive pattern.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

Ethics Statements

This study was conducted in accordance with the guidelines of the local ethical committee in University of Basrah, College of Pharmacy, and Basrah Health Directory

Author Contribution

we believe this original article research will contribute to knowledge in medicine and Pharmaceutical Sciences. since there are few studies regarding the association between antidiabetic medication and lung function in type 2 diabetic patients. This article may help to encourage physicians to consider the lungs as a target organ for diabetic complications and help to choose the best anti-diabetic medication.

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