https://doi.org/10.31925/farmacia.2022.6.7 **ORIGINAL ARTICLE**

DISORDERS OF PULMONARY FUNCTION IN TYPE 2 DIABETES MELLITUS PATIENTS WITH DIFFERENT TYPES OF ORAL HYPOGLYCEMIC MEDICATIONS: METFORMIN, METFORMIN PLUS THIAZOLIDINEDIONE AND METFORMIN PLUS SULFONYLUREA

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Abstract

Diabetes mellitus type 2 (DM2) is a chronic condition characterized by elevated blood glucose leading to organ dysfunction including the lung. In this study, we tried to determine the effects of hyperglycemia on lung functions and evaluate the role of certain oral antidiabetic medications in respiratory function changes. Two hundred and sixty individuals of both genders were enrolled in the study: 100 healthy individuals, and an age-matched group of 160 DM2 patients. Patients' groups were further classified into 3 groups: (51) patients on metformin; (56) patients on metformin plus thiazolidinedione and (53) patients on metformin plus sulfonylurea. Clinical examination, electrocardiography, HbA1c, and pulmonary function parameters were estimated for all participants. Pulmonary function parameters significantly diminished ($p < 0.05$) in diabetic patients with increased restrictive disorder. Metformin plus sulfonylurea was more associated with decreased pulmonary function parameters with an odd ratio (OR: 2.999; at 95% confidence interval (CI): 1.006 - 8.937, ($p > 0.05$) than other medications. Pulmonary function parameters may act as a screening method to detect changes in diabetic lungs and manage pulmonary dysfunction, which was mostly restrictive. Assessments of pulmonary function may be useful to prescribe suitable medication, particularly for those with respiratory issues.

Rezumat

Diabetul zaharat de tip 2 (DZ2) este o afecțiune cronică definită prin creșterea glicemiei ce induce disfuncția organelor, inclusiv a plămânilor. În acest studiu, am evaluat efectele hiperglicemiei asupra funcțiilor pulmonare, precum și rolul anumitor medicamente antidiabetice orale în modificările funcției respiratorii. 260 de indivizi de ambe sexe au fost înscriși în studiu: 100 de indivizi sănătoși și un grup de 160 de pacienți cu DZ2. Pacienții au fost împărțiți în 3 grupuri: (51) pacienți tratați cu metformin; (56) pacienți tratați cu metformin plus tiazolidindionă și (53) pacienți tratați cu metformin plus sulfoniluree. S-au efectuat: examenul clinic, electrocardiografia, HbA1c și parametrii funcției pulmonare. Parametrii funcției pulmonare au scăzut semnificativ ($p < 0,05$) la pacienții diabetici. Co-administrarea metformin plus sulfoniluree a fost asociată mai mult cu scăderea parametrilor funcției pulmonare (OR: 2,999; la un interval de încredere (IC): 95%: 1,006 - 8,937, ($p > 0,05$) decât alte medicamente. În urma evaluărilor funcției pulmonare pot fi alese medicamentele adecvate pentru a fi prescrise, în special pentru cei cu probleme respiratorii.

Keywords: pulmonary function parameters, DM2, antidiabetic medications

Introduction

Type 2 Diabetes mellitus (DM2) is a chronic condition characterized by impaired metabolic regulation as well as by the potential for vascular and neuropathic consequences. It comprises a collection of heterogeneous consequences with elevated blood glucose levels as a common diagnostic sign [16]. It is associated with long-term impairment and multi organs dysfunction. Its complications mostly result from macrovascular and microvascular destructions [14, 20].

Although a lot of attention revolved around diabetic complications including cardiovascular; nephropathy; and neuropathy, respiratory complications of DM2 might be clinically unreported. This is primarily because the lung has a considerable physiological reserve, and losing this reserve could have significant clinical consequences [19, 24]. Recently, the concept of the lung as a potential target organ for micro-angiopathy of the disease is getting more attention [25, 42]; and pulmonary function in diabetes has become an interesting topic in the context of evolving research into the lung safety of inhaled insulin [35, 36]. Due to its extensive vascular network and high collagen and elastin content, the pulmonary system is

vulnerable to microvascular injury and nonenzymatic glycation in diabetes [8, 33]. Despite, the fact that many researchers have investigated the pulmonary functions and diffusion capacity of diabetic patients, the results have consistently been inconsistent [23]. Pathological studies in diabetic patients have depicted alterations in the basal lamina of the alveolar walls and pulmonary capillaries [21] and obstructive or restrictive disorders may arise as a result [7]. Some histopathological evidence indicated the involvement of lungs in patients with DM2 demonstrating that alveolar walls and pulmonary capillary walls were thickened due to collagen and elastin changes and microangiopathy. These changes might be the cause of pulmonary complications [6]. In this context, many researchers tried to investigate the association between antidiabetic medications and pulmonary impairment in DM2. Previous studies suggested that metformin might play a role in respiratory diseases independently from the antidiabetic role, and it might be of therapeutic effect in lung diseases and clinical uses [26, 37]. While other studies indicated that Pioglitazone (a thiazolidinedione) had a favorable impact on lung fibrosis, indicating that it may act as an anti-fibrotic agent [3]. On the other hand, glibenclamide (sulfonylurea) has been represented to play a protective role in the development of asthma through the relaxation of respiratory airway muscles in mice [11]. Therefore, this study was conducted to assess the effects of chronic hyperglycemia on lung functions, focusing on spirometric parameters which determine the mechanism of lung function the precise volume or flow of air inhaled and exhaled in one maneuver, as well as to discover the role of certain oral antidiabetic medications (metformin, metformin plus thiazolidine-dione and metformin plus sulfonylurea) in respiratory function changes.

Materials and Methods

Study design

This observational cross-sectional study was carried out in Basra City, Iraq, from November 2021 to April 2022. It has been performed according to the guide-lines of STROBE (Strengthening the Reporting of Observational Studies in Epidemiology), the statement's recommendations for reporting observational studies [13]. The protocol was approved by the local Ethical Committee of the University of Basrah, College of Pharmacy, Iraq.

Participants

A total of two hundred and sixty participants of both sexes were enrolled in the present study. The participants were divided into two major groups: 100 healthy individuals in (group 1), (48% females and 52% males), were within the age range of (40 - 62) years, and had a mean of 51.49 ± 10.99. The other participants were 160 patients with diabetes mellitus type 2 (DM2), divided into 3 groups based on the type of antidiabetic medication: (51) patients on metformin as group 2. This group included (24 females and 27 males), with a mean age of 55.48 ± 7.62. The other group (group 3) on metformin plus thiazolidinedione was 56 (27 females and 29 males) patients with a mean age of 53.78 ± 7.25 and (group 4) included 53 (25 females plus 28 males) patients on metformin plus sulfonylurea with a mean age of 54.52 ± 8.55. Characteristics of each group are illustrated in Table I.

Participants were randomly selected according to several inclusion and exclusion criteria applied in this study. All patients were selected from the internal medicine consulting clinic at one of the Teaching hospitals in Basrah City, Iraq, while participants of healthy group 1 were university employees and patients' relatives. However, the participants were physically and clinically examined by a specialized physician to assess their health status including the cardiovascular system, respiratory system; neuromuscular functions to exclude inadequate patients.

Inclusion and exclusion criteria. Patients with DM2 who had been on oral hypoglycemic medicines for at least a year were eligible, while patients with a chest infection, chronic respiratory diseases, cardiovascular problems, smoking, and morbid obesity (BMI $\geq$ 40) were excluded from the study.

Demographics and characteristics of all individuals such as age, sex, height, weight, body mass index (BMI), diseases/drug history and smoking status were collected via a questionnaire.

Measurements

Measurement of HbA1c of all participants was done by the diagnostic tina-quant hemoglobin A1c kits of COBAS INTEGRA/COBAS C SYSTEMS according to the current guidelines [46]. Patients were previously diagnosed with diabetes mellitus type 2 based on symptoms of diabetes plus clinical measurements; random blood sugar (200 mg/dL), Fasting blood glucose level (126 mg/dL) or glycated Hemoglobin A1c $\geq$ 6.5% [18].

Pulmonary function parameters

Measuring the parameters of pulmonary functions was done by a medical and diagnostic spirometer (MIR Spirol III Diagnostic Spirometer, Ltd. England). The procedure was performed for all participants, in standing position between (9:00 am - 12:00 pm), by one trained expert technician, following the American Thoracic Society (ATS) guide [17]. The individual's characteristics (age, gender, weight, height and race) were all recorded and the participant was instructed to inhale and exhale the air forcefully and continuously in the mouthpiece of the instrument.

The measurement was repeated three times, reaching the accepted degree of patient cooperation to get the most suitable record of pulmonary function parameters and diagnosis. The recorded parameters included forced

vital capacity (FVC), forced expiratory volume in 1 second (FEV1), FEV1/FVC in percentage (%), estimated lung age (ELA), maximal voluntary ventilation (MVV) and peak expiratory flow rate (PEFR). Normal pulmonary function is when the values of FVC and FEV1 are normal. A decrease in one parameter or more refers to pulmonary disorder.

Echocardiogram test

To rule out any heart conditions that can alter the results of the lung function test, all patients underwent an echocardiography evaluation by a cardiologist using a (GE vivid 7 U.S.A.) cardiac ultrasound machine. The necessary information was gathered on a collection form and then moved to an Excel sheet. The data collecting form was checked to adjust any discrepant values. Then, the required data were statistically evaluated and compared.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS version 26) program was used to analyze the data. For comparisons, the data were given as Mean plus standard deviation. To check whether numerical data had a normal distribution, the Shapiro-Wilk and Kolmogorov-Smirnov tests were used. An independent sample t-test was used for data with a regular distribution, while the Mann-Whitney U-test was used for data with a non-normal distribution. The strength of the association between two variables was assessed using Spearman's rank and Pearson's correlation coefficients, while the binary logistic regression analysis was used to determine the odd ratio (OR) and confidence interval (CI) for DM2 patients. Statistical significance was considered as a p value of less than 0.05.

Results and Discussion

Table I illustrates the demographics of the healthy controls (group 1) and other groups of diabetic patients with different medications (groups 2, 3 and 4). These groups were matching in age, height, weight, BMI, as well as gender distribution (females/males' ratio), when statistically analyzed it revealed no significant difference ($p > 0.05$), while HbA1c revealed significant differences between healthy (group 1) and each of diabetic patient's groups (groups 2, 3 and 4) with $p < 0.05$. All participants were free of any other disease including hypertension or other serious disease.

Table I

Groups Characteristics

Group parameters	Group 1 (N = 100) Mean ± SD	Group 2 (N = 51) Mean ± SD	Group 3 (N = 56) Mean ± SD	Group 4 (N = 53) Mean ± SD	*p value
Age (years)	51.49 ± 10.99	55.48 ± 7.62	53.78 ± 7.25	54.52 ± 8.55	0.632
Gender ratio Female/male ratio)	48:52 (48%, 52%)	24:27 (48%,52%)	27:29 (48%, 52%)	25:28 (48%, 52%)	
Weight (kg)	71.91 ± 14.81	82.00 ± 7.79	81.98 ± 13.56	80.84 ± 6.96	0.734
height (cm)	168.77 ± 9.54	169.46 ± 9.88	168.78 ± 10.74	169.90 ± 10.48	0.920
BMI (Kg/cm^2)	28.54 ± 4.24	28.77 ± 3.86	29.06 ± 5.88	28.22 ± 3.59	0.545
HbA1c	4.67 ± 0.43	8.93 ± 1.61	8.38 ± 1.59	8.23 ± 1.39	0.001
Echocardiography	Normal	normal	Normal	normal	
Hypertension	No	No	No	No	

*A significant difference is when $p < 0.05$; N: number; Mean ± SD is the mean value + standard deviation

In this study, we compared healthy individuals (group 1) and all DM2 patients regardless of the type of medication and it revealed that pulmonary function parameters (FVC, FEV1, PEF, MVV and ELA) were significantly lower in DM2 patients (2.88 ± 0.72; 2.96 ± 0.79; 4.91 ± 2.07; 59.03 ± 18.53 and 66.17 ± 13.11) than healthy (group1) (3.45 ± 0.80; 3.21 ± 0.74; 6.50 ± 2.01; 108.15 ± 16.14 and 45.47 ± 17.07) ($p < 0.05$) except for FEV1/FVC% which showed a non-significant difference ($p > 0.05$) between healthy and DM2 patients in general (90.86 ± 5.96 *vs*. 89.61 ± 8.68), as illustrated in Table II.

This result shows that diabetes mellitus gradually affects the lungs among other body organs and systems with multisystemic complications [10]. Pulmonary complications of diabetes and the exact etiology of pulmonary complications are not fully established yet.

As seen in Table II, analysis displayed a significant decline in values of most pulmonary function parameters including FVC, FEV1, PEF and MVV ($p < 0.05$) when comparing DM2 patients in general to healthy controls (group 1), whereas, the mean value of (FEV1/FVC%) showed a non-significant difference between group 1 and DM2 patients in general, ($p > 0.05$). This finding might rule out the obstructive pattern disorder among DM2 patients involved in the study. It is well established that FEV1/FVC ratio is used to determine if a person is with a restrictive or an obstructive lung pattern. When FVC is declined and FEV1/FVC ratio is normal, this indicates a restrictive pattern. A restrictive disorder occurs when an individual can't breathe in deeply and forcefully as normal. It is linked to damage of lung tissues [32].

Table II

Comparison between pulmonary function test for all patients and control

Group / Pulmonary function parameters	Group 1 (N = 100) Mean ± SD	DM2 Patients (N = 160) Mean ± SD	*p value
FVC (L)	3.45±0.80	2.88±0.72	0.001
FEV1(L)	3.21±0.74	2.96±0.79	0.001
FEV1%	90.86±5.96	89.61±8.68	0.225
PEF(L/s)	6.50±2.01	4.91±2.07	0.001
MVV(L/s)	108.15±16.14	59.03±18.53	0.000
ELA (years)	45.47±17.07	66.17±13.11	0.000

*p value is significant when it > 0.05; N: number; Mean ± SD is the mean value + standard deviation; DM2: diabetes mellitus type 2; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; FEV1%: is the FEV1/FVC ratio; MVV: maximal voluntary ventilation; PEF: peak expiratory flow; ELA: estimated lung age

Regarding the respiratory patterns, the percentages of normal spirometry were as the following: 86% in group 1 and a lesser percentage in the different medication groups of diabetic patients (84%, 75% and 64% in groups 2, 3 and 4, respectively). The groups also showed a significant variation in the percentage of spirometry disorders. The percentage of the restrictive pattern was 9% in group 1, while it was (14%, 24% and 30% in groups 2, 3 and 4, respectively). The obstructive pattern was also found, but in a lesser percentage (5% in group 1) and (2%, 4% and 8% in groups 2, 3 and 4, respectively), (Table III, Figure 1).

Table III

Respiratory diagnosis

Respiratory diagnosis	Group 1 (N = 100)	Group 2 (N = 51)	Group 3 (N = 56)	Group 4 (N = 53)	*p value
Obstructive N(%)	5 (5%)	1 (2%)	2 (4%)	4 (8%)	0.31
Restrictive N(%)	9 (9%)	7 (14%)	12 (24%)	15 (30%)	0.001
Combined N(%)	0 (0)	0	0	0	
Normal N(%)	86 (86%)	43 (84%)	42 (75%)	34 (64%)	0.001

N: number

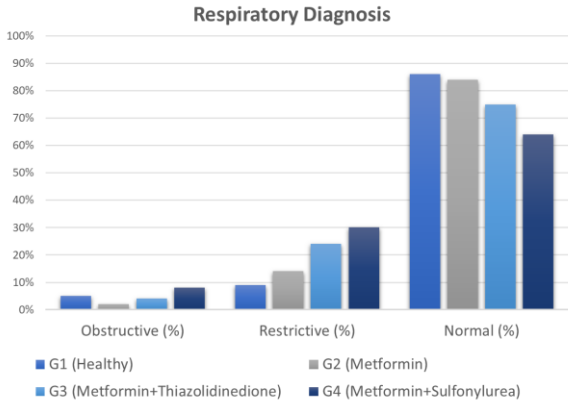

Figure 1.
Respiratory diagnosis

We found that the percentage of restrictive patterns was higher among DM2 patients, particularly patients on metformin plus sulfonylurea combination (group 4) than the restrictive percentage among healthy individuals (group 1). A prior study by Mandal A *et al*. has concluded the presence of a restrictive pattern of lung function impairment in patients suffering from diabetes of both sexes [27]. As well as a study by Mittal S *et al*. [30] has demonstrated that pulmonary function parameters declined and a restrictive pattern of pulmonary dysfunction was observed in patients with type 2 diabetes mellitus when compared with healthy individuals suggesting the lungs may be considered a primary target organ of DM complication beside other micro and macrovascular consequences. On the other hand, a study by Talpur AS *et al*. [41] confirmed that restrictive lung disease is significantly associated with type 2 Diabetes mellitus patients, especially those with complicated longstanding diabetes who were found to have restrictive lung disease and severe dyspnea. The researchers Shah SH *et al*. [39] explained the cause of the restrictive pulmonary disorder in DM2 suggesting that diabetes mellitus may target the glycosylation of connective tissues resulting in a reduction of tissue elasticity in the lung, or creating marked inflammatory changes in the lungs.

Furthermore, the obstructive pulmonary disorder was also reported in this study among DM2 patients with different medications, but in a small percentage 2%, 4% and 8% in groups 2, 3 and 4 which were not significantly different from group 1 (5%), (Table III). However, the presence of obstructive cases was reported in a few previous studies one of them done by Theusen BH *et al.* [43] who suggested an obstructive pattern of the lung pathology and showed that insulin resistance is an important predictor of the occurrence of symptoms that resembles asthma symptoms. While Balducci *et al*. revealed the strength of the respiratory muscle in DM 2 declines corresponding to the metabolic regulation of the disease which may

lead to reduced lung volumes [5]. Another prior study by Fuso L *et al*. [15] showed a distinct relationship between respiratory muscle efficacy and glycemic regulation. It demonstrated that MVV, a simple mean for measurement of respiratory muscle performance and strength is increased in patients with good control of blood glycemic levels and reduced in others with uncontrolled glycaemia. This finding was consistent with our study that showed a statistically significant decrease in MVV of DM patients compared to healthy (group 1). On the other hand, a prior study by Mishra GP *et al*. reported the presence of restrictive lung patterns in DM patients with asthma and obstructive pattern (combined pattern) [29]. However, there were no combined cases among DM2 patients in the present study. Another interesting finding reported by this study is the significant increase in ELA of DM2 patients in general, but no significant changes were reported among patients of the three groups of medications (groups 2, 3 and 4). The parameter ELA refers to the physiological lung age. It is the real age of the individual when respiratory functions are normal [2]. Deterioration of PFTs was inversely linked with ELA, implying that ELA increased as PFTs deteriorated [4, 22].

No significant correlation between diabetic control index (HbA1c) and pulmonary function parameters were found in this study $p > 0.05$ (Table IV).

Table IV

Correlation between PFT and HbA1c for all patients

HbA1c	FVC	FEV1	FEV1%	PEF	ELA	MVV
r value	0.027	-0.077	-0.033	-0.021	0.077	-0.108
p value	0.741	0.346	0.689	0.796	0.350	0.187

HbA1c: Glycosylated Hemoglobin Type A1C; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; FEV1%: is the FEV1/FVC ratio; MVV: maximal voluntary ventilation; PEF: peak expiratory flow; ELA: estimated lung age

Previous studies by Acharya PR *et al*. [1], Chidri SV *et al*. [9] and Shah SH *et al*. [39] have also reported a lack of relation between this index of diabetes control and lung function. Because the HbA1C is predictive of short-term glycemic control over the last 3 - 4 months, concluding that blood glucose control has no influence on pulmonary functioning in diabetics based on this finding alone is inaccurate. Several studies by Vanidassane I *et al*. [44], Tai H *et al*. [40] and Dennis RJ *et al*. [12] have stated that diabetics with uncontrolled glucose levels have decreased pulmonary function parameters compared to those with good control.

Comparison of pulmonary function parameters among the study groups revealed that group 1 differed significantly from DM2 groups (2, 3 and 4), as clarified by Table V. The mean values of FEV1, FVC, PEF and MVV were significantly higher in group 1 compared to other groups ($p < 0.05$). While the mean value of ELA was significantly elevated in each DM2 patient's group of different medications (groups 2, 3 and 4), ($p < 0.05$). On the other hand, there were no significant changes in FEV1/FVC% in the DM2 patients' groups (2, 3 and 4) compared to healthy group 1. Moreover, the results revealed that there was no significant variation when comparing every two groups of DM2 patients' groups of different medication, *e.g.*, between groups 2 and 3, or between 3 and 4, ($p > 0.05$), (Table V).

Table V

Pulmonary function parameters in the study groups

Group parameters	Group 1 N = 100 Mean ± SD	Group 2 N = 51 Mean ± SD	Group 3 N = 56 Mean ± SD	Group 4 N = 53 Mean ± SD	p value 1 vs 2	p value 1 vs 3	p value 1 vs 4	p value 2 *vs* 3	p value 2 *vs* 4	p value 3 *vs* 4
FEV1	3.45 ± 0.80	2.58 ± 0.52	2.47 ± 0.56	2.65 ± 0.65	0.001*	0.001*	0.001*	0.178	0.366	0.617
FVC	3.21 ± 0.74	2.64 ± 0.54	2.66 ± 0.72	2.42 ± 0.54	0.001*	0.001*	0.006*	0.067	0.063	0.973
FEV1%	90.86 ± 5.96	89.73 ± 8.84	87.52 ± 6.91	85.84 ± 14.21	0.297	0.128	0.888	0.608	0.923	0.707
PEF	6.50 ± 2.01	4.27 ± 1.22	3.80 ± 1.05	3.81 ± 1.18	0.001*	0.001*	0.001*	0.967	0.079	0.065
MVV	108.15 ± 16.14	87.47 ± 17.1	88.56 ± 14.91	90.78 ± 19.86	0.001*	0.001*	0.001*	0.260	0.193	0.275
ELA	45.47 ± 17.07	60.56 ± 12.15	64.98 ± 14.51	66.98 ± 12.49	0.001*	0.001*	0.001*	0.940	0.166	0.129

*A significant difference is when $p < 0.05$; N: number; Mean ±SD is the mean value + standard deviation; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; FEV1%: is the FEV1/FVC ratio; MVV: maximal voluntary ventilation; PEF: peak expiratory flow; ELA: estimated lung age

The results of statistical binary logistic regression analysis in our study show the combination of metformin plus sulfonylurea (in group 4) is more likely to be associated with the changed pulmonary function parameters and lung dysfunction with an odd ratio (OR: 2.999; at 95% confidence interval (CI): 1.006 - 8.937, $p > 0.05$), whereas metformin and metformin plus thiazolidinedione drug combination showed a non-significant association and less OR (1.061 and 1.986), $p > 0.05$). Sulfonylurea glibenclamide has been demonstrated to have impacts on the attenuation of eosinophil-mediated airway inflammation and hyperresponsiveness in an animal model in a previous study [11]. However, no previous studies

have been published about its effect on human respiratory function yet. On the other hand, other medications metformin and metformin plus thiazolidinedione did not reveal such association with impairment of pulmonary function parameters. A previous study found that exposure to thiazolidinediones was related to a significant decline in the exacerbation of obstructive disorder among diabetic patients [34].

Regarding metformin, a prior study reported that metformin might be a promising anti-fibrotic modality for the treatment of pulmonary fibrosis [37] as well as the relationship between metformin and reduction of respiratory exacerbations which improved quality of life in bronchospastic diseases was reported by another study [26]. It has been found by a prospective study of the significant effects of six months of metformin medication in COPD, improvement in respiratory signs and inspiratory muscle function [38].

According to prior studies, it is more likely that diabetic lungs express a restrictive disorder due to the disease itself regardless of the medication [28, 31]. Long-standing DM2 results in autonomic neuropathy that may be associated with gastroesophageal reflux disease leading to recurrent aspiration pneumonitis and consequent fibrotic parenchymal lung changes. On the other hand, there is a high incidence of infections among DM2 patients, such as pulmonary tuberculosis, that may leave marked fibrotic changes in the lungs [45]. Further studies are required involving a large number of patients instead of a limited number which may be considered a study limitation. However, the inclusion of healthy individuals as a control group for comparison as well as a commitment to a wide range of exclusion criteria considered a positive aspect of accurate investigation.

Conclusions

Pulmonary functions were significantly affected by DM2. Assessment of pulmonary function parameters can be used as a screening method to detect early changes in lung parameters in persons suffering from DM2, to manage pulmonary dysfunction, which was mostly a restrictive pattern. Additionally, assessments of diabetic patients' pulmonary function characteristics may be used to help prescribe suitable medication, particularly for those with specific respiratory issues.

Conflict of interest

The authors declare no conflict of interest.

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