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ORIGINAL ARTICLE

Impact of diabetes mellitus and its control on pulmonary functions and cardiopulmonary exercise tests

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Abstract *Background:* Diabetes mellitus (DM) is a leading public health problem with increasing incidence and long term complications. These complications are mainly a consequence of macrovascular and microvascular damages of the target organs. The presence of an extensive microvascular circulation and abundant connective tissue in the lungs, raises the possibility that lung tissue may be a target organ in diabetic patients.

Objectives: To study the impact of DM and its control on pulmonary function and cardiopulmonary exercise tests.

Methodology: This is a cross-sectional study carried out on diabetic mellitus patients (type I or type II $n = 30$) group II divided into two subgroups (group IIA) controlled diabetes (HbA1c $< 7\%$) ($n = 15$) and uncontrolled diabetes (group IIB) (HbA1c $\geqslant 7\%$ ($n = 15$). The control group (group I) was non diabetic healthy ($n = 15$). The following pulmonary function parameters were recorded: Forced Expiratory Volume in the first second (FEV1), Forced Expiratory Volume percent (FEV1/FVC %), Forced Expiratory Flow 25–75% (FEF 25–75%), peak expiratory flow (PEF) and MVV. Also maximum aerobic power (VO_2 max) using cardiopulmonary exercise test was measured.

Results: The mean FEV1, FEV1/FVC%, PEF, FEF 25–75%, MVV and VO_2 max values were low in diabetics (p value < 0.05) compared to non-diabetics. Also, uncontrolled diabetics show a greater decrease in these values than controlled diabetics.

Conclusion: The findings of the present study suggest that, the lung is a target organ for damage in DM and diabetics show a decrease in PFTs and VO_2 max compared to non-diabetics. And this deterioration is exaggerated in uncontrolled diabetics.

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Introduction

Diabetes mellitus describes a metabolic disorder of multiple etiology, characterized by chronic hyperglycemia with disturbances of carbohydrate, protein and fat metabolism, resulting from defects in insulin secretion or insulin action or both [1].

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Diabetes mellitus is a leading public health problem with increasing incidence and long term complications such as diabetic nephropathy, diabetic neuropathy, diabetic retinopathy etc. These complications are mainly a consequence of macrovascular and microvascular damages of the target organs [2].

Deterioration of pulmonary functions in DM is going to be eighty percent of all diabetics from the entire world population [1]. In 2000 the number of people with diabetes was 31.7 million and it is expected that by 2030 this will increase to 79.4 millions [3]. Several factors contributing to this include greater longevity, obesity, unsatisfactory diet, sedentary lifestyle and increasing urbanization. The cause of clinical diabetes is absolute or relative deficiency of insulin. The presence of an extensive microvascular circulation and abundant connective tissue in the lungs raises the possibility that lung tissue may be affected by microangiopathy process and non-enzymatic glycosylation of tissue proteins, induced by chronic hyperglycemia, thereby rendering the lung a "target organ" in diabetic patients. Since normal lung mechanics and gas exchange are influenced by the integrity of pulmonary connective tissue and microvasculature, abnormalities in either of these two structural components of the lung may lead to the development of measurable abnormalities of pulmonary function [4]. In 2004, Wendy et al. observed that a 10% decrease in FEV1 was associated with 12% increase in all-cause mortality [5]. As measures of airflow limitation predict all-cause mortality in diabetes, intensive glycemic management may reduce the risk of death through improved ventilatory function independent of other beneficial effects. So, the assessment of pulmonary function is an important investigation because early detection of functional impairment and its appropriate treatment will help to reduce morbidity and mortality [5].

Cardiopulmonary exercise testing (CPET) is being utilized to investigate cardiac and respiratory function. It can be used to identify an abnormality in patients with exercise intolerance or exercise related symptoms. It is also useful to evaluate patients with cardiovascular disease including cardiac failure and before heart and lung transplantation [6].

The VO_2 max (a measure included in CPET) is the maximum amount of oxygen that the body can use in one minute. VO_2 max (also maximal oxygen consumption, maximal oxygen uptake, peak oxygen uptake or maximal aerobic capacity) is the maximum capacity of an individual's body to transport and use oxygen during incremental exercise, which reflects the physical fitness of the individual. The name is derived from V – volume, O_2 – oxygen, max – maximum. VO_2 max is expressed either as an absolute rate in liters of oxygen per minute (L/min) or as a relative rate in milliliters of oxygen per kilogram of bodyweight per minute (i.e., mL/(kg min)). The latter expression is often used to compare the performance of endurance of sports athletes [7].

Accurately measuring VO_2 max involves a physical effort sufficient in duration and intensity to fully tax the aerobic energy system. In general clinical and athletic testing, this usually involves a graded exercise test (either on a treadmill or on a cycle ergometer) in which exercise intensity is progressively increased while measuring ventilation and oxygen and carbon dioxide concentration of the inhaled and exhaled air. VO_2 max is reached when oxygen consumption remains at a steady state despite an increase in workload [7].

There are several factors that affect VO_2 max, including muscle mass, blood oxygen levels, lung capacity and general fitness level. The maximum VO_2 is the first measurement to be examined because it establishes whether the patient's physiologic responses allow normal maximal aerobic function or not. Other measurements are then used to differentiate the cause of any exercise limitation whether or not the subject reaches his/her predicted maximum VO_2. Tests measuring VO_2 max can be dangerous in individuals who are not considered normal healthy subjects, as any problems with the respiratory and cardiovascular systems will be greatly exacerbated in clinically ill patients. Thus, many protocols for estimating VO_2 max have been developed for those for whom a traditional VO_2 max test would be too risky. These generally are similar to a VO_2 max test, but do not reach the maximum of the respiratory and cardiovascular systems and are called sub-maximal tests [8].

Another estimate of VO_2 max, based on maximum and resting heart rates, was created by a group of researchers from Denmark [9]. It is given by:

$$VO_2\text{max} = 15\frac{HR_{max}}{HR_{rest}}$$

This equation uses maximum heart rate (HR_{max}) and resting heart rate (HR_{rest}) to estimate VO_2 max in mL/(kg·min). "Maximal oxygen uptake (VO_2 max) is widely accepted as the single best measure of cardiovascular fitness and maximal aerobic power. Absolute values of VO_2 max are typically 40–60% higher in men than in women [10]."

Aim

The aim of the present study was to assess the pulmonary function test in patients with DM either controlled or not and also to study the changes that may occur in their VO_2 max.

Materials and methods

The present study (a cross-sectional study) included 30 patients group II; 15 patients with controlled DM (group IIA) and 15 patients with uncontrolled DM (group IIB) admitted to chest and internal medicine departments, Menoufiya University hospitals in the period from February 2013 to August 2013. We also included 15 healthy non diabetic subjects who volunteered as a control group.

Inclusion criteria: patients with DM either type I or II.

Group IIA: included in the study were patients with controlled diabetes which is defined as HbA1c $< 7\%$ and were 15 patients and the other group; group IIB was patients with uncontrolled diabetes which is defined as HbA1c $\geqslant 7\%$ and were 15 patients. The subjects of both genders in the age group between 25 and 60 years are included. 15 healthy non diabetic subjects were studied as a control group; group I.

Exclusion criteria: subjects with a past history of smoking, hypertension (HTN), respiratory diseases (Acute or chronic), chest wall injuries, congestive cardiac failure (CHF), and chest wall deformities were excluded from the study.

The subjects were properly explained about the objectives, methodology, expected outcome and implications of the study and written informed consents were obtained from them.

(1) Full history taking and complete clinical examination.
(2) Routine laboratory investigations including complete liver and kidney functions, complete blood count

(CBC), erythrocytic sedimentation rate (ESR), and lipid profile.
(3) Fasting and post-prandial blood glucose levels.
(4) Urine glucose and acetone.
(5) Electrocardiogram (ECG) and echocardiography, if needed.
(6) Chest X-ray (postero-anterior and lateral views if needed).
(7) *Pulmonary function tests:* Pulmonary function tests were done for all studied patients. The following parameters in PFTs were measured [11]:
(a) Forced Expiratory Volume in the first second (FEV1).
(b) FEV1/FVC ratio.
(c) Peak expiratory flow (PEF).
(d) Forced mid-expiratory flow (FEF 25–75%).
(e) Maximal voluntary ventilation (MVV).
(8) Cardiopulmonary exercise test was used to measure VO_2 max:

Cardiopulmonary exercise protocol [12]

The goal of CPET protocols is to stress the organ systems involved in the exercise response in a controlled manner. In our research (using Treadmill exercise testing), incremental exercise testing protocol was used as a modification of Balk's protocol [13]. The test duration is 12 min divided into: 3 min warming up, 3 min rest, and 6 min exercise. The speed starts by 3 Km/h during warming up stage, then the speed decreases gradually until it stops in resting stage, then the speed increases gradually to reach 3 Km/h during exercise and the subject increases the speed manually until he can tolerate.

Statistical methodology

The data collected were tabulated & analyzed by SPSS (statistical package for the social science software) statistical package version 11 on IBM compatible computer. Quantitative data were expressed as mean & standard deviation (X ± SD) and analyzed by applying Student's *t*-test for comparison of two groups of normally distributed variables. Qualitative data were expressed as number and percentage (No & %) and analyzed by applying chi-square test (χ^2). Whenever the expected values in one or more of the cells in 2×2 tables were less than 5, fisher's exact test was used instead.

Results

Data are mean ± SD age and anthropometric values are not statistically significant ($p > 0.05$) (Fig. 1).

In Table 1 group I was compared with group II, there was a significant decrease in FEV1, FEV1/FVC% and FEF 25–75% between both groups. While there was a non-significant difference regarding MVV.

Table 2 shows that there was a statistically significant difference between groups I and IIA regarding FEV1, FEV_1/FVC, FEF 25–75% and PEF but there was no significant difference between them regarding FEF_{25-75} and MVV.

Table 3 shows that there was a statistically significant difference between groups I and IIB regarding FEV_1, FEV_1/FVC, PEF, FEF_{25-75} and MVV.

Table 4 shows that there was a statistically significant difference between groups IIA and IIB regarding FEV_1, FEV_1/FVC, FEF_{25-75} and MVV.

Table 5 and Fig. 2 show that there was a statistically significant difference between groups I, IIA and IIB regarding VO_2 max/kg (ml/min/kg) and also all parameters in pulmonary function.

Discussion

Our study showed all the pulmonary parameters, that is, there was a significant decrease in pulmonary function tests among diabetic patients (FEV1, FEV1/FVC%, PEF, FEF 25–75% and MVV) compared with healthy controls. Also in diabetic subjects (uncontrolled), there was a significant reduction in FEV1, FEV1/FVC%, PEF, FEF 25–75% and MVV) as compared with the controlled diabetic patients. This is in accordance with previous studies [14–16]. Meta-analysis by van den Borst et al. showed that DM is associated with statistically significant, impaired pulmonary function in a restrictive pattern. Moreover, these results were irrespective of body mass index (BMI), smoking, diabetes duration, and HbA1c levels [17]. Uchida, et al. found that there was a decreased pulmonary diffusing capacity in patients with diabetes with perfusion defect on ventilation perfusion scintigrams [18]. It was not possible for us to analyze the pulmonary diffusing capacity because of practical difficulties. Davis et al. conducted a study in Western Australia in a large number of patients of type 2 DM. They found that VC, FVC, FEV_1, and PEFR decreased at an average of between 1.1% and 3.1% of predicted values/year in DM patients [5]. Ehrlich et al. [19] showed that patients with type DM were at increased risk of several pulmonary conditions like – asthma, Chronic Obstructive Pulmonary Disease (COPD), fibrosis, and pneumonia. Normal lung mechanics and gas exchange are influenced by the integrity of the pulmonary connective tissue and microvaculature. Acceleration of aging process in connective tissue cross links and the presence of nonenzymatic glycosylation and modification of alveolar surfactant action cause reduction in PFTs [20]. There have been reports of histopathological changes in the diabetic patients. In the study by Weynand et al. [21], it was found that alveolar epithelium, endothelium capillary, and basal laminaes were thickened in the lungs on electron microscopy, when compared with the controls. Diabetic microangiopathy might be existing in the pulmonary vascular bed. Moreover, reduced pulmonary capillary blood volume was found, favoring the evidence of microangiopathy. This could lead to redistribution of the pulmonary circulation, resulting in well ventilated areas to become under-perfused [22]. There are certain studies showing no correlationship between HbA1c and PFTs [23,24]. They argued that HbA1c levels are indicators of glycemic control for a short period of 1–2 months, it was not adequate to conclude that the plasma glucose level was not related to decreased PFTs. The thickening of the alveolar wall due to the increased amounts of collagen and elastin in basal lamina results in microangiopathy. There was a significant reduction in FEF 25–75% among diabetics compared to controls, shows a lower airway caliber and higher airway resistance and this finding was similar to Ashapherwani et al. and Malcom Sandler et al. [20]. The role of strict glycemic control on pulmonary function in diabetic patients is another interesting aspect and

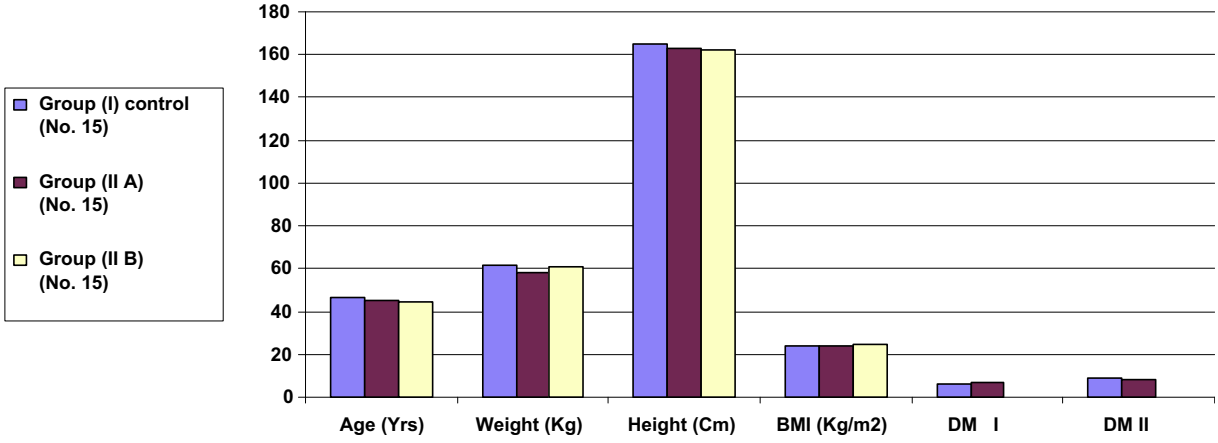

Figure 1 Domographic parameters among the studied groups.

Table 1 Comparison of groups I and II regarding pulmonary functions.

	Group (I) control (No. 15) Mean ± SD	Group (II) (No. 30) Mean ± SD	*t* Test	*p* Value
FEV1	89.86 ± 8.36	79.30 ± 9.30	3.71	0.001**
FEV1/FVC	96.56 ± 6.38	84.11 ± 9.57	4.55	0.001**
PEF	90.00 ± 5.95	82.94 ± 7.09	3.3	0.002**
FEF_{25-75}	96.74 ± 1.96	94.59 ± 3.01	2.50	0.02*
MVV	98.95 ± 1.98	96.65 ± 5.49	1.57	0.12

Table 2 Comparison of groups I and IIA regarding pulmonary functions.

	Group (I) control (No. 15) Mean ± SD	Group (IIA) (No. 15) Mean ± SD	*t* Test	*p* Value
FEV1	89.86 ± 8.36	82.08 ± 12.40	2.015	0.04*
FEV1/FVC	96.56 ± 6.38	89.24 ± 11.30	2.185	0.03*
PEF	90.00 ± 5.95	84.36 ± 8.56	2.096	0.04*
FEF_{25-75}	96.74 ± 1.96	95.82 ± 2.99	0.995	0.33
MVV	98.95 ± 1.98	98.46 ± 2.44	0.608	0.55

* *p* Value is significant if <0.05. SD, standard deviation.

Table 3 Comparison of groups I and IIB regarding pulmonary functions.

	Group (I) control (No. 15) Mean ± SD	Group (IIB) (No. 15) Mean ± SD	*t* Test	*p* Value
FEv1	89.86 ± 8.36	76.53 ± 3.01	5.814	0.01*
FEv1.FVC	96.56 ± 6.38	78.97 ± 2.34	10.024	0.01
PEF	90.00 ± 5.95	81.53 ± 5.16	4.166	0.02*
FEF_{25-75}	96.74 ± 1.96	93.37 ± 2.57	4.040	0.04*
MVV	98.95 ± 1.98	94.84 ± 7.03	2.180	0.038*

* *p* Value is significant if <0.05.

Table 4 Comparison of groups IIA and IIB regarding pulmonary functions.

	Group (IIA) (No. 15) Mean ± SD	Group (IIB) (No. 15) Mean ± SD	*t* Test	*p* Value
FEv1	82.08 ± 12.40	76.53 ± 3.01	1.7	0.05*
FEv1.FVC	89.24 ± 11.30	78.97 ± 2.34	3.4	0.002**
PEF	84.36 ± 8.56	81.53 ± 5.16	1.1	0.2
FEF_{25-75}	95.82 ± 2.99	93.37 ± 2.57	2.4	0.02*
MVV	98.46 ± 2.44	94.84 ± 7.03	1.88	0.05*

* *p* Value is significant if <0.05.

Table 5 Comparison of the three groups regarding pulmonary function and VO_2 max/kg (ml/min/kg).

	Group (I) control (No. 15) Mean ± SD	Group (IIA) (No. 15) Mean ± SD	Group (IIB) (No. 15) Mean ± SD	*t* Test	*p* Value
FEv1	89.86 ± 8.36	82.08 ± 12.40	76.53 ± 3.01	8.7	0.01**
FEv1.FVC	96.56 ± 6.38	89.24 ± 11.30	78.97 ± 2.34	20.2	0.001**
PEF	90.00 ± 5.95	84.36 ± 8.56	81.53 ± 5.16	6.2	0.001**
FEF_{25-75}	96.74 ± 1.96	95.82 ± 2.99	93.37 ± 2.57	7.04	0.01*
MVV	98.95 ± 1.98	98.46 ± 2.44	94.84 ± 7.03	3.8	0.003**
VO_2 max/kg (ml/min/kg)	94.8 ± 3.4	91.8 ± 4.03	88.88 ± 7.08	5.08	0.001**

** Highly significance difference.

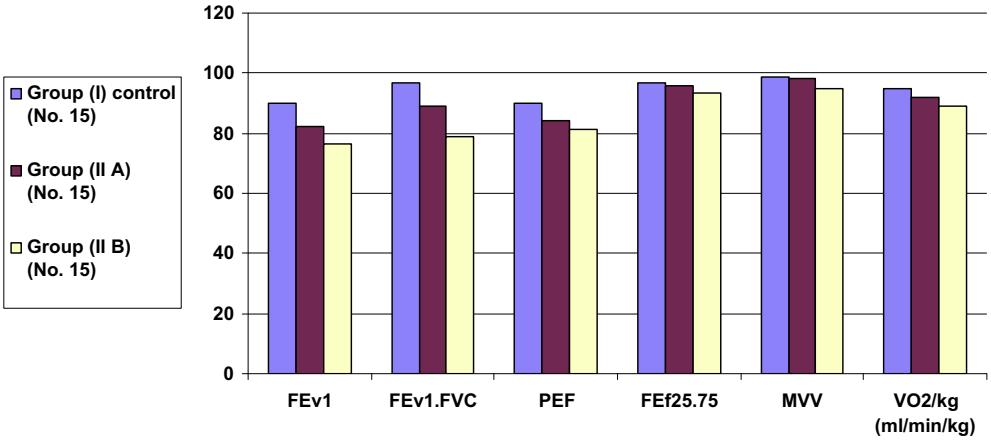

Figure 2 Comparison of the three groups regarding VO_2/kg (ml/min/kg).

needs further studies. The impairment in PFTs can lower the threshold for clinical manifestations of acute or chronic lung disease. There was a parallel association between poor control of DM and reduction in pulmonary function tests.

The present study prospectively determined that VO_2 max was greater in healthy subjects versus diabetic patients. Also VO_2 max was greater in diabetes with good versus poor glycemic control. Similar results were published in subjects when Niranjen et al. [25], randomly assigned patients with type I diabetes into groups that maintained "normoglycemia" (HbA_{1c} = 5.6) or hyperglycemia (HbA_{1c} = 8.8) for 6 years. After their intervention, which included no exercise training, peak workload, VO_{2max} were reduced in the hyperglycemic but not in the normoglycemic group. In this context, our findings and those of Niranjen et al. [25] confirm a relationship between aerobic fitness and glycemic control and suggest that careful glycemic control improves aerobic capacity in trained and untrained subjects. In contrast, it is unclear whether aerobic training improves glycemic control.

The mechanism through which poor glycemic control influenced cardiac and pulmonary responses to maximal exercise is an interesting area for further study. Autonomic dysfunction may have influenced the hemodynamic exercise response in the high-HbA_{1c} group. Neurological impairment in subjects with diabetes is strongly linked with glycemic control [26].

Pulmonary function is similarly affected by hyperglycemia. Approximately 75% of young, nonsmoking individuals with type I diabetes exhibit abnormal lung function [27]. These diabetes-specific limitations are most likely associated with decreased pulmonary elasticity and loss of alveolar microvascular volume caused by protein glycosylation in the lung parenchyma and vascular endothelium [28,29]. These physical restrictions manifest as decreased FVC, FEV_1, and FEF_{50}, which mimic our findings in the high-HbA_{1c} group during peak exercise. Our finding that cardiac and pulmonary capacities were impaired in the high-versus the low-HbA_{1c} group, combined with the previous finding that 6 year of normoglycemia improves aerobic capacity without any exercise training [25]. highlights the potential importance of chronic glycemic control for athletes with type I diabetes.

The low-HbA_{1c} group had an average HbA_{1c} of 6.5%, which is widely considered "good" glycemic control in this population [29]. Although better glycemic control may have further improved the cardiopulmonary response to exercise in the low-HbA_{1c} group, potential gains should be balanced by the increased risk of exercise hypoglycemia when blood glucose levels are maintained too low.

Conclusion

Our study concludes that diabetic subjects show a decrease in PFT values and VO_2 max compared to non-diabetic subjects. Also, uncontrolled diabetics are more prone to respiratory dysfunction than controlled diabetics. Intensive glycemic management may reduce the risk of death through improved

ventilatory function independent of other beneficial effects. The patients with diabetes are suggested to undergo pulmonary function testing along with other investigations.

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