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ORIGINAL ARTICLES

Effect of Duration of Disease on Ventilatory Function in an Ethnic Saudi Group of Diabetic Patients

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Abstract

Background:

Diabetes mellitus is a leading cause of illness and death across the world and is responsible for a growing proportion of global health care expenditures. The present study was designed to observe the effect of diabetes mellitus on lung function in patients with diabetes belonging to a specific ethnic group, namely Saudis.

Method:

In this study, a group of 47 apparently healthy volunteer male Saudi patients with diabetes was randomly selected. Their ages ranged from 20 to 70 years. The patients were matched with another group of 50 healthy male control subjects in terms of age, height, weight, ethnicity, and socioeconomic status. Both groups met exclusion criteria as per standard. Spirometry was performed with an electronic spirometer (Schiller AT-2 Plus, Switzerland), and results were compared by a Student's *t* test.

Results:

Subjects with diabetes showed a significant reduction in forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) relative to their matched controls. However, there were no significant differences in the forced expiratory ratio (FEV_1/FVC%) and the middle half of the FVC ($FEF_{25–75\%}$) between the groups. We observed a significantly negative correlation between duration of disease and pulmonary function, as measured by FEV_1 ($r = 0.258$, $p = 0.04$), FVC ($r = 0.282$, $p = 0.28$), and the middle half of the FVC ($FEF_{25–75\%}$) ($r = 0.321$, $p = 0.014$).

Conclusions:

Pulmonary function in a specific ethnic group of patients with diabetes was impaired as evidenced by a decrease in FVC and FEV_1 compared to pulmonary function in matched controls. Stratification of results by years of disease revealed a significant correlation between duration of disease and a decline in pulmonary function.

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Abbreviations: ($FEF_{25–75\%}$) force expiratory flow, (FEV_1) force expiratory volume in 1 second, (FEV_1/FVC) force expiratory ratio, (FVC) force vital capacity

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Introduction

Diabetes mellitus is a leading public health care problem with increasing incidence and long-term complications. In 2003, 194 million people had diabetes mellitus; by 2025 approximately 333 million will develop diabetes mellitus, and almost 1 million people die each year because of diabetes mellitus.[1] Diabetes mellitus is associated with an ongoing malfunction of numerous organs,[2] and its complications are mainly a consequence of macrovascular and microvascular damage.[3] The mechanism by which impaired glycemic control may lead to a reduction in lung function is uncertain, although it has been suggested that the increased systemic inflammation associated with diabetes[4] may result in pulmonary inflammation[5] and hence airway damage.[6] Moreover, hyperglycemia can cause a secondary reduction in antioxidant defense of the lungs and increased susceptibility to environmental oxidative insults, which can result in a subsequent loss of respiratory function.[7]

Immense interest has been focused on the complications of diabetes, including coronary artery disease, diabetic nephropathy, retinopathy, and neuropathy; however, the pulmonary complications of diabetes mellitus have been poorly characterized. Some authors have reported normal pulmonary function,[8] whereas others found abnormal lung function.[9,10] Few studies have been conducted that considered the association between duration of disease and pulmonary function stratified according to such demographic variables as age, height, weight, smoking, ethnic background, and socioeconomic status. Moreover, physicians should be aware of the pulmonary complications in diabetes when they prescribe novel insulin delivery systems, such as inhaled insulin. Therefore, the present study was designed to determine the effect of the disease on respiratory function in patients with diabetes who belong to a specific ethnic group, namely Saudis.

Subjects and Methods

This study was conducted at the Department of Physiology, College of Medicine and Diabetic Center, King Abdul Aziz University Hospital, King Saud University, Riyadh, Saudi Arabia. In this study we obtained institutional approval in compliance with regulation of our institution and with generally accepted guidelines governing such work.

Subjects

The principal investigator and coinvestigators reviewed 348 medical files of patients with diabetes. Patients were then invited to the diabetic center and interviewed. A detailed clinical history was taken with regard to smoking cigarettes and other tobacco products. After the initial interviews, 47 apparently healthy male patients with diabetes with a mean age of 46.45 ± 2.21 years (mean ± SEM), age range of 20–75 years, and mean duration of disease of 10.60 ± 1.11 years were selected. Their duration of disease ranged from 1 to 30 years. An additional 301 patients were excluded. Of these 47 patients with diabetes, 23 had type 1 and 24 had type 2. Controls were selected in a similar manner to that of the patients with diabetes. We interviewed 180 healthy people and selected 50 apparently healthy male control subjects with a mean age of 45.58 ± 1.74 years and an age range of 23–71 years. Patients with diabetes were individually matched with controls for age, height, and weight. Matching between both groups was within ±3 years for age, ±4 centimeters for height, and ±5 kilograms for weight. Overall, there were no significant differences in anthropometric means in combined or stratified data. Ethnicity, age, and height were given more emphasis for matching, as these three relate better to lung function than weight.[11] Controls were from a similar community with the same socioeconomic status relative to patients with diabetes. All subjects had never smoked. All subjects completed a questionnaire, which included anthropometric data and a consent form. The ethics committee at the College of Medicine approved the study. The present study is a continuation of previous studies[9,10]; however, this work has been updated. New subjects and case controls have been matched and added according to central criteria specified (ethnicity, age, height, weight, smoking, socioeconomic status, etc.).

Exclusion Criteria

Subjects with gross abnormalities of the vertebral column or thoracic cage, known history of acute or chronic respiratory infections, neuromuscular disease, malignancy, cardiopulmonary disease, or a history of major abdominal or chest surgery were excluded from the study. In addition, subjects with current or previous drug or tobacco (smoked or chewed) addictions were excluded. Patients with complications of diabetes such as neuropathy, nephropathy, and retinopathy were also excluded from the study.

Spirometry

Spirometry was performed with an electronic spirometer (Schiller). All pulmonary function tests were carried out at a fixed time of the day (10.00–14.00 hours) to minimize diurnal variation.[12] The apparatus was calibrated daily and operated within the ambient temperature range of 20–25° C. The precise technique in executing various lung function tests for the present study was based on the operating manual of the instrument with reference to the official statement of the American Thoracic Society of Standardization of Spirometry (1987).[13] After the study, subjects provided a detailed history and anthropometric data, were trained about the entire maneuver, and were encouraged to practice this maneuver before doing the pulmonary function tests. The tests were performed (with each subject in the standing position) by using a nose clip. The tests were repeated three times after adequate rest. The parameters that were measured included force vital capacity (FVC), force expiratory volume in 1 second (FEV_1), force expiratory ratio (FEV_1/FVC), and force expiratory flow ($FEF_{25–75\%}$).

Statistical Analysis

Statistical analysis was conducted using a Student's *t* test for independent groups (two tailed), initially on all matched pairs of subjects and then in three subsets of our study subjects, which were divided according to their duration of disease (less than 5 years, 5–12 years, and more than 12 years). The level of significance was taken as $p < 0.05$. Pulmonary function data were correlated against the duration of exposure. Linear regression was applied on this correlation, and the equation $y = mx + c$ was derived with the correlation coefficient (r). The level of significance of correlation was determined by the r value.

Results

Results are presented as both overall and stratified according to the duration of disease in patients with diabetes (less than 5 years, 5–12 years, and more than 12 years). In **Tables 1–4**, the formal statistical comparison of the "matching" variables (age, height, and weight) was thought to be appropriate, as these variables were observed to be similar for the two groups and hence statistical confirmation of this fact is not discussed.

Overall Group Results

Lung function data for diabetic patients and their matched controls are shown in **Table 1**. Patients with diabetes had statistically significant reductions in FVC and FEV_1. The means for FEV_1/FVC%, $FEF_{25–75\%}$, and $FEF_{75–85\%}$ were not significantly different between the two groups. The mean duration of disease for patients with diabetes was 10.60 ± 1.11 years (mean ± SEM), with a range of 1 to 30 years.

Table 1.
Anthropometric and Lung Function Data for Total Diabetic Patients Compared with Their Matched Controls

Parameter	Diabetic patients (mean ± SEM) (n = 47)	Control subjects (mean ± SEM) (n = 50)	Percentage change (%)	p value
Age (years)	46.45 ± 2.21	45.58 ± 1.74	-1.90	NS[a]
Height (cm)	168.27 ± 1.13	169.30 ± 1.08	+0.60	NS
Weight (kg)	79.48 ± 1.79	84.30 ± 1.76	+5.71	NS
FVC (liters)	3.33 ± 0.13	3.74 ± 0.66	+10.96	0.012
FEV_1 (liters)	2.79 ± 0.12	3.13 ± 0.07	+10.86	0.016
FEV_1/FVC%	84.13 ± 1.55	84.25 ± 0.83	+0.14	NS
$FEF_{25–75\%}$ (liters/s)	3.34 ± 0.21	3.76 ± 0.16	+11.17	NS
$FEF_{75–85\%}$ (liters/s)	1.30 ± 0.11	1.50 ± 0.13	+13.33	NS

[a]Nonsignificant.

Table 2.
Anthropometric and Lung Function Data for Diabetic Patients with Duration of Disease Less Than 5 Years Compared with Their Matched Controls

Parameter	Diabetic patients (mean ± SEM) (n = 17)	Control subjects (mean ± SEM) (n = 50)	Percentage change (%)	p value
Age (years)	38.65 ± 3.56	45.58 ± 1.74	+15.20	NS[a]
Height (cm)	170.00 ± 2.47	169.30 ± 1.08	-0.41	NS
Weight (kg)	78.82 ± 3.54	84.30 ± 1.76	+6.50	NS
FVC (liters)	3.68 ± 0.20	3.74 ± 0.66	+1.60	NS
FEV_1 (liters)	3.12 ± 0.18	3.13 ± 0.07	+0.31	NS
FEV_1/FVC%	85.14 ± 1.82	84.25 ± 0.83	-1.05	NS
$FEF_{25–75\%}$ (liters/s)	3.80 ± 0.41	3.76 ± 0.16	-1.06	NS
$FEF_{75–85\%}$ (liters/s)	1.44 ± 0.22	1.50 ± 0.13	+4.00	NS

[a]Nonsignificant.

Table 3.
Anthropometric and Lung Function Data for Diabetic Patients with Duration of Disease 5–12 Years Compared with Their Matched Controls

Parameter	Diabetic patients (mean ± SEM) (*n* = 11)	Control subjects (mean ± SEM) (*n* = 50)	Percentage change (%)	*p* value
Age (years)	49.73 ± 4.19	45.58 ± 1.74	-9.10	NS[a]
Height (cm)	166.18 ± 2.28	169.30 ± 1.08	+1.84	NS
Weight (kg)	79.54 ± 2.95	84.30 ± 1.76	+5.64	NS
FVC (liters)	3.16 ± 0.29	3.74 ± 0.66	+15.50	0.021
FEV_1 (liters)	2.74 ± 0.26	3.13 ± 0.07	+12.46	NS
FEV_1/FVC%	86.69 ± 3.04	84.25 ± 0.83	-2.89	NS
$FEF_{25–75\%}$ (liters/s)	3.68 ± 0.41	3.76 ± 0.16	+2.12	NS
$FEF_{75–85\%}$ (liters/s)	1.25 ± 0.23	1.50 ± 0.13	+16.66	NS

[a]Nonsignificant.

Table 4.
Anthropometric and Lung Function Data for Diabetic Patients with Duration of Disease Greater Than 12 Years Compared with Their Matched Controls

Parameter	Diabetic patients (mean ± SEM) (*n* = 19)	Control subjects (mean ± SEM) (*n* = 50)	Percentage change (%)	*p* value
Age (years)	51.53 ± 3.24	45.58 ± 1.74	-13.05	NS[a]
Height (cm)	167.94 ± 1.14	169.30 ± 1.08	+0.80	NS
Weight (kg)	80.05 ± 2.73	84.30 ± 1.76	+5.04	NS
FVC (liters)	3.11 ± 0.20	3.74 ± 0.66	+16.84	0.002
FEV_1 (liters)	2.53 ± 0.18	3.13 ± 0.07	+19.16	0.0001
FEV_1/FVC%	81.75 ± 2.99	84.25 ± 0.83	+2.96	NS
$FEF_{25–75\%}$ (liters/s)	2.75 ± 0.27	3.76 ± 0.16	+26.86	0.002
$FEF_{75–85\%}$ (liters/s)	1.20 ± 0.14	1.50 ± 0.13	+20.00	NS

[a]Nonsignificant.

Duration of Disease Less Than 5 Years

Table 2 summarizes the comparison of lung function parameters between patients with diabetes and their matched control group. There was no significant difference between the means of any lung function data between the groups. The mean duration of disease for patients with diabetes was 2.82 ± 0.23 years (mean ± SEM), with a range of 1 to 4 years.

Duration of Disease 5–12 Years

There were no significant differences among the means of FEV_1, FEV_1/FVC%, $FEF_{25–75\%}$, and $FEF_{75–85\%}$ for patients with diabetes on the basis of duration of disease 5–12 years compared with their matched controls (**Table 3**). However, patients with diabetes did show a significant reduction in FVC. The mean duration of disease in patients with diabetes was 8.45 ± 0.82 years (mean ± SEM), with a range of 5 to 12 years.

Duration of Disease More Than 12 Years

Patients with diabetes with duration of disease more than 12 years showed a significant reduction in FVC, FEV_1, and $FEF_{25–75\%}$ relative to their matched controls (**Table 4**). Similarly, the percentage change in diabetic patient's data relative to controls was also decreased for FVC, FEV_1, and $FEF_{25–75\%}$. However, there was no significant difference in FEV_1/FVC% and $FEF_{75–85\%}$ data relative to controls. The mean duration of disease in this group was 18.79 ± 0.80 years (mean ± SEM), with a range of 15–30 years.

Regression Analysis

Regression analyses were performed on pulmonary function data against duration of disease. Significant positive correlations for *r* values were found for FVC (r = 0.25, $p < 0.04$), FEV_1 ($r = 0.28$, $p < 0.02$), and $FEF_{25–75\%}$ (r = 0.32, $p < 0.01$); this information is shown in **Figures 1–3**, respectively.

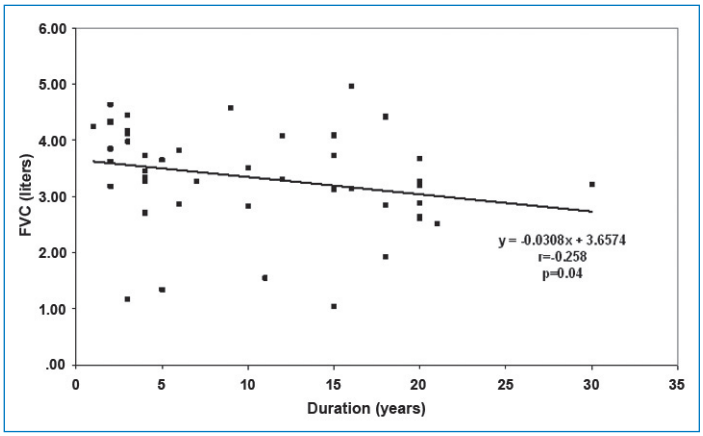

Figure 1. Regression analysis for forced vital capacity against duration of disease in diabetic patients. A significant negative correlation was found, indicating that increased duration of disease decreased the FVC.

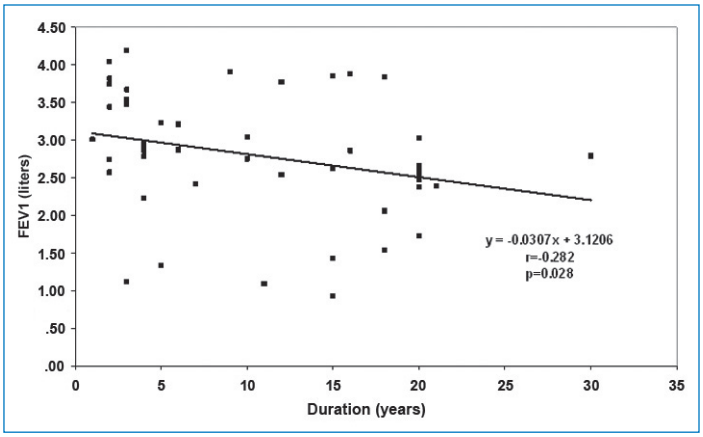

Figure 2. Regression analysis for forced expiratory volume in 1 second against duration of disease in diabetic patients. A significant negative correlation was found, indicating that increased duration of disease decreased the FEV_1.

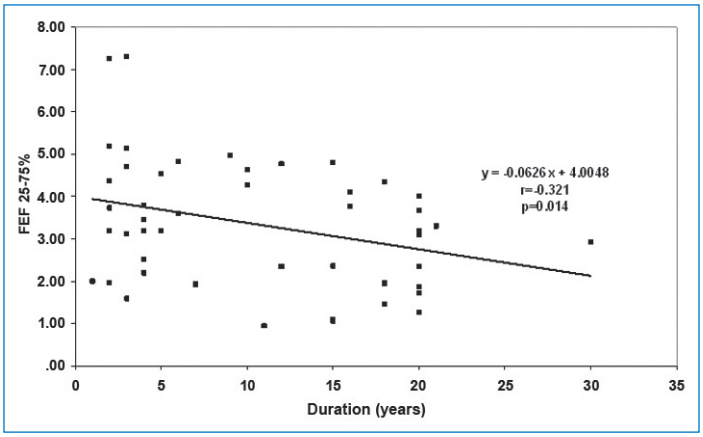

Figure 3. Regression analysis for forced expiratory flow against duration of disease in diabetic patients. A significant negative correlation was found, indicating that increased duration of disease decreased the $FEF_{25–75\%}$.

Discussion

Diabetes mellitus, an incurable lifelong disease, involves multiple systems with wide-ranging and devastating complications, which end up in severe disability and death.[2] Despite effective interventions directed at the complications of diabetes mellitus, including coronary artery disease, diabetic nephropathy, retinopathy, and neuropathy, the pulmonary complications of diabetes mellitus have been poorly characterized. Furthermore, there have been very little data reported on whether there is an association between years of disease and pulmonary function, and there are very few reports of pulmonary function in patients with diabetes that control for such demographic factors as age, height, weight, smoking, ethnicity, and socioeconomic status. Therefore, the present study was designed to determine the effect of diabetes in a specific Saudi ethnic group of diabetic patients by considering potential factors such as age, height, weight, smoking, or economic status. The present study showed a correlation between duration of disease and decreased pulmonary function. This association is explained by age, height, weight, ethnic matching, and smoking. Patients with diabetes for more than 12 years experienced a significant reduction in FVC, FEV_1, and $FEF_{25–75\%}$ relative to controls.

McKeever and colleagues[14] reported that an increase in mean HbA1c is associated with a decrease in lung function parameters FVC and FEV_1. They hypothesized that impaired glucose autoregulation is associated with impaired lung function. These investigators speculated that the decrease in pulmonary function, which is associated with chronic postprandial hyperglycemia, may be mediated by systemic inflammation, intracellular oxidative stress, or accumulation of advanced glycosylation end products, any of which could adversely influence lung function.

Asanuma *et al.*,[15] Lange *et al.*,[16] and Boulbou *et al.*[3] reported that FVC and FEV_1 were reduced in subjects with diabetes compared to control subjects. Similarly, Cazzato *et al.*[17] conducted a cross-sectional study to assess pulmonary function in children with type 1 diabetes and reported that FVC and FEV_1 were significantly lower in diabetics than in controls. Our results for FVC and FEV_1 confirm the results observed by Asanuma *et al.*,[15] Lange *et al.*,[16] Boulbou *et al.*,[3] and Cazzato *et al.*[17]

However, Benbassat and co-workers[8] showed that FVC, FEV_1, and $FEF_{25–75\%}$ were within the predicted values in both type 1 and type 2 diabetes populations. In addition, comparison by diabetes type showed nonsignificant differences in FEV_1 and $FEF_{25–75\%}$. The most probable reason for this contradiction is that Benbassat *et al.*[8] studied the pulmonary function within a group of patients with diabetes, but did not compare their results with the matched control group.

Our results are in partial agreement with those of Primhak *et al.*,[18] Innocenti *et al.*,[19] Makkar *et al.*,[20] and Boulbou *et al.*[3] They performed spirometry on patients with type 1 diabetes and reported that these patients had reduced FVC, FEV_1, and $FEF_{25–75\%}$ compared to their matched controls. Our present study, which is reported in this article, describes 47 patients with diabetes, 23 of whom had type 1 diabetes and 24 of whom had type 2 diabetes.

Matsubara and Hara[21] studied pulmonary function and microscopic changes in the lungs of diabetic patients as compared to those without diabetes and reported that the forced vital capacity, total lung capacity, residual

volume, and maximal expiratory flow rate were decreased significantly in the group with diabetes compared to the control group.

Rosenecker *et al.*[22] reported that in patients with diabetes, FVC and FEV_1 declined significantly over the 5-year study period. Patients without diabetes did not experience a significant decline in these measurements during the study period.

In addition, Bell and colleagues[23] measured lung volumes in 28 young adult men with long-standing type 1 diabetes and compared the results with 16 age- and height-matched adult men without diabetes. Their results showed reduced values for both the forced expiratory volume at 1 second and the vital capacity for type 1 patients compared to the control subjects. Results are consistent with reduced lung volumes in type 1 patients and relate to duration of diabetes. Our results based on the duration of the disease are in agreement with those of Bell *et al.*[23]

However, Maccioni and Colebatch[24] studied the effect of type 1 diabetes on pulmonary function in 22 nonsmokers and showed that for both subjects with diabetes and controls, mean values for VC, FEV_1, and total lung capacity were similar to predicted values. Their findings demonstrated that type 2 diabetes does not affect pulmonary function. The most probable reason for the lack of demonstrated risk in this study is that Maccioni and Colebatch[24] studied pulmonary function in 22 diabetic nonsmoker patients, but did not consider the age-, height-, weight-, and sex-matched control group; additionally, the number of diabetic patients was small. Therefore, our results are in contradiction with results observed by Maccioni and Colebatch.[24]

The present study strongly suggests that diabetes mellitus adversely affects the pulmonary function, and results are in line with other previously conducted studies. Stratification of data demonstrated a correlation between the number of years of disease and the decline in lung function. It is advisable, therefore, that physicians should think about the lungs as potential targets for end-organ damage in diabetes, just as other organs may be targets. We recommend that patients with diabetes undergo periodic spirometry tests to assess their extent of impaired pulmonary function. These measures will help prevent early stages of pulmonary decompensation, which over time contributes to the morbidity and mortality of diabetes.

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