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DIABETIC AUTONOMIC NEUROPATHY: INDEPENDENT FACTOR IN LUNG FUNCTION IMPAIRMENT

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ABSTRACT

Objective: Diabetic Autonomic Neuropathy is one of diabetes mellitus complications that might cause respiratory abnormalities and increase the rate of morbidity and mortality. The aim of the present study was to assess pulmonary functions in type 2 diabetic patients with and without diabetic autonomic neuropathy and correlate it with age, disease duration and disease control. ***Materials and methods:*** This study was conducted at Al-Mouassat University Hospital in Damascus during one year (from October 2013 to November 2014). 67 patients with type 2 diabetes mellitus were divided into two groups: with and without diabetic autonomic neuropathy. Diabetics with microangiopathy and macroangiopathy were excluded to evaluate the effect of autonomic neuropathy as an independent factor on lung functions. ***Results:*** Subjects with diabetic autonomic neuropathy showed a significant reduction in forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) compared to their predicted values. Whereas, there was no significant difference in lung function parameters in patients without autonomic neuropathy compared to their predicted values. 45% of patients with autonomic neuropathy had mild degree of restrictive pulmonary disease. There was an inverse, significant correlation between glycosylated hemoglobin A1c, diabetes duration and both FVC and FEV1 values. ***Conclusion:*** *45% of* Patients with type-2 diabetes and autonomic neuropathy had a restrictive respiratory defect. Glycemic levels and duration of disease are probably major determinants of lung pathology.

KEYWORDS: Pulmonary function tests; Diabetic autonomic neuropathy.

INTRODUCTION

Diabetes is one of the most common metabolic diseases. According to The World Health Organization (WHO) in 2014, diabetes affects 9% of adults worldwide, this number is expected to be doubled by 2030. This is a result of inactive lifestyle and other social changes that lead to obesity.[1]

The importance of diabetes not only comes from its wide outbreak but also from its high morbidity and mortality rates. According to 2015 published reports, diabetes was the leading cause to death of 1.6 million. The WHO reported that by 2030, diabetes will be the seventh leading cause of death around the world.[1]

Diabetes complications affect the whole body. They are associated with its duration and degree of control. Several studies suggested that lungs are one target of these complications. This might be explained through several pathologic mechanisms. First, diabetic microangiopathy affects lungs, (the biggest vascular bed in the body). Autopsy studies reported an increase thickness of the alveolo-capillary basement membrane and nodular fibrosis in the alveoli walls.[2,3] Second, diabetes may cause protein non-enzymatic glycosylation. This makes collagen and elastin less responsive to proteolysis, leading to pneumo-sclerosis and decrease elastic recoil which limits the movement of lungs during inhalation and exhalation.[4,5] Third, diabetes increases inflammatory response that play an important role in poor function of endo-alveolocapillary membrane.[6,7] Fourth, insulin resistance in type 2 diabetes plays an important role in poor skeletal muscle function including respiratory muscles.[8] Fifth, some studies have linked the high levels of leptin with poor respiratory function.[9,10] Sixth, autoimmune neuropathy causes disturbance of respiratory neuromuscular function.[11,12]

Diabetic autonomic neuropathy can affect the respiratory system through multiple mechanisms. It causes depressed bronchoconstrictory response whether induced by exposure to cold air or by giving methacoline (Inhaled cholinergic agonist) as a result to decreasing of cholinergic bronchomotor tone following vague parasympathetic neuropathy.[13,14] Central response to hypoxia might be blunted due to impairment of neurotransmitters that reach the brain stem via vague nerve fibers occurring through peripheral chemoreceptors.[15] Also, diabetic autonomic neuropathy causes reduced bronchodilatory response (induced by giving atropin which is an inhaled cholinergic antagonist) as a result of decreasing of adrenergic bronchomotor tone following sympathetic nervous dysfunction.[13,14] This issue has been approved through finding that the lung uptake ratio of inhaled Iodine-123 Metaiodobenzylguanidine (^{123}I-MIBG) was significantly higher than that in the diabetic patients without sympathetic nervous dysfunction, due to decreased clearance of ^{123}I-MIBG from the lung in a way reflects the lack of storage capacity of sympathetic bronchial nervous system.[16] Finally, impaired respiratory neuromuscular function in diabetics leads to respiratory muscles weakness especially during exercise due to the diaphragmatic neuropathy.[17,18]

The aim of this study is to investigate lungs impairment and the role of autonomic neuropathy as an independent factor in Syrians with diabetes mellitus. For this purpose we performed Lung Functions in a sample of diabetics presenting to Al-Mouassat Hospital.

METHODS

Sample: This cross-sectional study was conducted at Al-Mouassat University Hospital in Damascus during one year (from October 2013 to November 2014). Participants were selected from out or in- patients of both genders, who were between 18-75 years old and agreed to participate in the study.

Exclusion criteria included: patients with diabetic microangiopathy (nephropathy and/ or retinopathy) or macroangiopathy (ischemic heart disease, cerebrovascular infarction), current and former smokers, pregnant women, patients with moderate or severe obesity (body mass index $\geq$ 35 kg/m^2), workers in cement, workers in flour or cotton, patients with history of pulmonary diseases (asthma, chronic bronchitis, chronic obstructive pulmonary disease, tuberculosis...etc.) or have taken medicines for these diseases (e.g. inhalation steroids, choline antagonists like ipratropium bromide and beta agonists like albuterol), patients of collagen diseases (rheumatoid diseases, systemic lupus erythematous and scleroderma), patients of neuromuscular diseases (such as myasthenia gravis and Guillain-Barre syndrome), patients with malignant tumors for the possibility of lung metastases, and patients with chest wall or spinal cord abnormalities (pectus excavatum, pectus carinatum and scoliosis) or with previous thoracic, pulmonary, heart, or abdominal surgeries. Ethical approval was obtained according to our university rules. Written informed consent was obtained from the patient for publication of this manuscript.

DATA COLLECTION

Name, gender, age, duration of diabetes and current treatment of diabetes were recorded for each patient. The patient was considered a diabetic depending on the American Diabetes Association standards, if Fasting Blood Glucose (FBG) in two different occasions was ≥ 126 mg/dl or in one occasion ≥ 126 mg/dl plus the diabetic Hemoglobin A1C (HbA1c) was ≥ 6.5% or in case the patient was currently using one of the pharmaceutical groups to treat diabetes.

The height (cm) and weight (kg) of each patient were measured while wearing light clothes without shoes, the BMI was calculated by dividing the weight in kilograms on the square of length in meters.

Autonomic neuropathy was investigated through measuring the pulse (using the Pulsimeter) and the arterial pressure (using the mercurial sphygmomanometer) in both lying and standing positions. The patient was considered suffering from autonomic neuropathy if resting heart rate was ≥100 beats/min, and/or if the pulse differed between supine position and resting position by < 10 pulses/minute (Heart rate monitored by ECG) and in case of systolic pressure drops after two minutes of standing up ≥ 20 mmHg.[17]

Blood samples were taken after 8 hours of fasting. FBG and HbA1c were performed using Hitachi device manufactured in Roche, Mannheim, Germany. The test of HbA1c was performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.[19]

A morning random urine sample was taken from patients who had not previously suffered from diabetic nephropathy. Infection was ruled out by urinalysis and albumin/creatinine ratio in urine (Alb/Cr ratio) was calculated. A diabetic nephropathy was diagnosed when Alb/Cr ratio ≥ 30 mg/g. A funduscopy was performed by the ophthalmologist to investigate the presence of diabetic retinopathy. The patient was considered having microangiopathy in the case of retinopathy and/ or nephropathy. Spirometer (Cosmed model) was used to measure pulmonary function. Forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and FEV1/FVC ratio were measured. FEV1 and FVC were compared with predicted values according to age, gender and height (calculated automatically through spirometer) and were considered normal if ≥ 80%. While FEV1/FVC < 70% was considered as chronic obstructive pulmonary disease.[20,21]

Criteria requested for performing the lung function testing were: absence of current pulmonary infection, absence of abdominal or chest pain for any reason, absence of current face or mouth pain for any reason, avoiding the stressful exercises for 30 minutes before to the test, avoiding wearing tight clothes on chest or abdomen, and avoiding eating a large meal for two hours before the test.[21]

The Patient had to sit on an armchair without wheels. He/she had to take a peak inhalation as much as possible then they had to exhale as strong, quick and long as possible through lips which are fully surrounding the carton. The criteria of accepting the test include the following: A good starting exhalation (a maximum exertion and no hesitation while exhaling), enough duration of test (minimum 6 seconds), no coughing or blocking of epiglottis during the test especially during the first second, absence of leak (blowing) outside the piece of cartoon, and not blocking the carton with patient's tongue.[21]

Spirometry tracing time–volume and flow–volume loops were repeated several times for each participant until three reliable tracings were obtained. The best two tracings for FEV1 and FVC within 5% or 150 mL of each other were examined, and the highest values were retained for the study analysis (American Respiratory Society/European Respiratory Society recommendations).[20,21]

Lung functions were read as follows: The first step is reading FEV1/ FVC%. The normal rate is ≥ 70%, whereas in obstructive pulmonary disease is less than 70%. The rate in restrictive pulmonary disease is often high and sometimes normal. If FEV1/FVC% is less than 70%, FEV1% was read to determine the severity of obstruction. If FEV1/FVC% is normal or high, there are two possibilities, either there is a normal lung function or there is a restrictive pulmonary disease. In this case we read the FVC%. The normal rate is ≥80%, whereas in restrictive pulmonary disease it is less than 80%, FEV1% was read to determine the severity of restriction.[20,21] Table 1 shows values of FEV1% to determine the severity of lung disease (obstructive and restrictive).

STATISTICAL ANALYSIS

SPSS version 18 was used for statistical study. The differences between the variables were examined using the independent t-test (when studying the relationship between two variables only) besides the one-way ANOVA test (when studying the relationship between more than two variables) on the statistical significance level (P-value) $\leq$ 0.05.

RESULTS

67 patients with type 2 diabetes fulfilled inclusion criteria: 40 females (59.7%) and 27 males (40.3%). They were divided into two groups: the first one: 22 patients (32.8%) with isolated autonomic neuropathy. The second: 45 patients (67.2%) with no vascular or neurological complications. Average of participant's age was 52.71 ± 13.47 years, with an average height of 162.68 ± 8.76 cm, and average duration of diabetes of 4.93 ± 4.33 years (Table 2).

A comparison of isolated autonomic neuropathy group lung function with the predicted values according to age, gender and height showed that FEV1/FVC% for patients was higher than expected, FVC and FEV1 values were lower than the expected values; the differences were statistically significant (Table 3).

The lung function values of diabetic patients who did not suffer from autonomic neuropathy did not differ from the expected values according to age, gender and height (Table 4).

After comparing the values of lung function of patients with the expected values according to gender, age, and height (patients versus predicted), the values of patients' lung function were compared among patients themselves (patients versus patients).

Table 5 shows the results of the independent t test that compared the averages of age, height, BMI, duration of DM by years, FBG values and HbA1c between the two groups of the studied samples. There was a statistically significant difference in the age, duration of DM, FBG and HbA1c which their values in the group of patients with no complications were lower than the values of patients with autonomic neuropathy. On the other hand, there was no statistically significant difference in height and BMI among the two groups.

Table 6 shows a comparison of the averages of the pulmonary indexes between the two groups. There was no significant difference in FEV1/FVC% values; whilst, FEV1 and FVC were lower (statistically significant) in patients with autonomic neuropathy.

The study showed that 45.45% of patients with autonomic neuropathy (10 patients out of 22 patients) had restrictive pulmonary disease. The degree of restriction was divided according to FEV1% values into: 80% had FEV1% ≥ 70% (mild restriction), 20% had FEV1% ranged between 60-69% (moderate restriction), whereas no patient had FEV1% <60% and no patient had obstructive pulmonary disease when FEV1/FVC% ≥ 70% for all individuals of the sample (Table 7).

Table. 1 FEV1 to define the severity of lung disease according to ERS/ETS guidelines.

Value of FEV1%	Degree of severity
%70 ≤	Mild
60-69%	Moderate
50-59%	Moderate to severe
35-49%	Severe
%35 >	Very severe

FEV1: Forced Expiratory Volume in one second

Table. 2: Patients characteristics.

	Mean	Standard deviation SD
Age (Years)	52.71	13.47
Height (cm)	162.68	8.76
BMI (kg/m^2)	26.92	4
DM Duration (Years)	4.93	4.33
FBG (mg/dl)	208.57	63.72
HbA1c (%)	8.73	1.58

BMI: Body Mass Index; DM: Diabetes Mellitus; FBG: Fasting Blood Glucose; HbA1c: Hemoglobin A1c

Table. 3: Comparing the values of patients (isolated neuropathy) with the standard predicted values.

Lung index	Mean in diabetics with isolated neuropathy	SD	P value
FEV1 patients	2.3605	.82107	.001
FEV1 predicted	2.6950	.75385	
FVC patients	2.8014	.92698	.001
FVC predicted	3.3509	.84066	
FEV1/FVC% patients	83.4318	6.13191	.001
FEV1/FVC% predicted	79.0373	2.43973	

Lung functions showed restrictive pattern in patients with neuropathy

Table. 4: Comparing values of patients with no vascular or neuropathy with the standard predicted values.

Lung index	Mean in diabetics with no neuropathy	SD	P value
FEV1 patients	2.9813	.68314	.812
FEV1 predicted	2.9711	.64205	
FVC patients	3.5851	.80843	.855
FVC predicted	3.5813	.80900	
FEV1/FVC% patients	84.1622	6.59691	.886
FEV1/FVC% predicted	83.7713	5.45740	

Diabetics with non-vascular or neuropathy have normal lung functions

Table. 5: Comparing the averages of age, height, BMI, duration of DM in years, FBG, and HbA1c among the studied groups.

Variable	Group	Number	Mean	SD	P value
Age (Years)	Autonomic Neuropathy	22	52.14	12.673	0.001
	No Autonomic Neuropathy	45	44.29	14.478	
Height (cm)	Autonomic Neuropathy	22	161.9545	9.42882	0.612
	No Autonomic Neuropathy	45	163.5111	7.55472	
BMI (kg/m^2)	Autonomic Neuropathy	22	27.2818	3.73027	0.283
	No Autonomic Neuropathy	45	26.0689	4.56408	
Duration of DM (Years)	Autonomic Neuropathy	22	5.3636	2.85433	0.001
	No Autonomic Neuropathy	45	2.2426	2.75383	
FBG (mg/dl)	Autonomic Neuropathy	22	208.5455	66.17777	0.007
	No Autonomic Neuropathy	45	199.0222	64.77671	
HbA1c (%)	Autonomic Neuropathy	22	8.9048	1.96462	0.007
	No Autonomic Neuropathy	45	8.2215	1.33481	

Diabetics with normal PFT are younger, have shorter duration of DM, better sugar control compared with diabetics with abnormal PFT.

BMI: Body Mass Index, FBG: Fasting Blood Glucose, HbA1c: Hemoglobin A1c, PFT: Pulmonary Function Test

Table. 6: Comparing of the averages of lung indexes among the two studied groups.

Index	Group	Number	Mean	SD	P value
FEV1 Patients	Autonomic Neuropathy	22	2.3605	.82107	0.001
	No Autonomic Neuropathy	45	2.9813	.68314	
FVC Patients	Autonomic Neuropathy	22	2.8014	.92698	0.001
	No Autonomic Neuropathy	45	3.5851	.80843	
FEV1/ FVC%	Autonomic Neuropathy	22	83.4318	6.13191	0.052
	No Autonomic Neuropathy	45	84.1622	6.59691	

Diabetic autonomic neuropathy is significantly associated with lower FEV1 and FVC compared to diabetics with no neuropathy.

Table 7 type of Lung Function Impairment in Individuals with Diabetes with autonomic neuropathy.

Lung index	Range of values of lung indexes	Numbers of Patients	%
FEV1 /FVC%	≥ 70%	22	100%
	< 70%	0	0%
FVC %	≥ 80%	12	54.55%
	< 80%	10	45.45%
FEV1%	≥ 70%	8/10	80%
	60-69%	2/10	20%
	50-59%	0	0%
	35-49%	0	0%
	< 35%	0	0%

Diabetics with autonomic neuropathy have abnormal PFT, restrictive pattern, mild to moderate grade.

DISCUSSION

Neuropathy is one of the most important complications of diabetes, due to the delay in diagnosing because of its insidious development affecting all parts of the body. Its presence increases the risk of silent myocardial infarction, amputations and sudden death.[12,17] This study is considered one of the clinical studies which aimed to investigate the respiratory system as a target for the effects of diabetic autonomic neuropathy. The relationship between diabetes and lung functions was carefully studied after excluding all factors that might affect lung functions (especially smoking, pulmonary or occupational diseases, and medicines). These, gave the results strength and credibility. This study showed a statistically significant decrease in lung spirometric values (FEV1, FVC) in patients with autonomic neuropathy comparing with predicted values. This result reflected the role of autonomic neuropathy in impairment of lung function. This was confirmed by noticing that there is no significant difference in the values of lung functions in diabetics who haven't this complication. It was difficult to control the whole factors that could affect the lung functions. We found a statistically significant difference between the average of age, duration of diagnosing diabetes, FBG and HbA1c among the two groups, which confirms that these variables played an important role in lung functions impairment in diabetics.

Two mechanisms might explain results of this study

Firstly, microangiopathy, which affects the lungs (the biggest vascular bed in the body) causing an increase thickness of the basement alveolo-capillary membrane and nodular fibrosis in the alveoli walls. Secondly, by the fact that the autonomic neuropathy affects skeletal muscles including respiratory muscles, causing reduced muscles endurance and performance. The mechanical load on the respiratory muscles increases if those muscles are weak, leading to restriction in the lungs volume during breathing. This was confirmed through assessing the respiratory muscle strength by measuring the maximum static inspiratory pressure (PImax) and the maximum static expiratory pressure (PEmax) using a special type of spirometer to measure the pressure with cm of water unit (cmH2O). The (PImax) values in patients with diabetic autonomic neuropathy were lower than the (PImax) for those without diabetic autonomic neuropathy with a significant difference reached to 22%, whereas there was no significant difference in (PEmax) values.[17] The diaphragmatic muscle power was also valued by measuring twitch trans diaphragmatic pressure (TwPdi), It was measured indirectly through measuring both twitch esophageal pressure (TwPes) and twitch gastric pressure (TwPga). TwPes and TwPga values were recorded during bilateral anterior magnet Phrenic Nerve stimulation. In conclusion, TwPdi values in diabetic patients with moderate to severe neuropathy were lower than the values of patients without neuropathy or with mild neuropathy. This difference was statistically significant.[18]

The results of this study confirmed the results of previous studies that approved the role of neuropathy in causing impairment in lung function in individuals with diabetes.[17,18] These results are also similar to the results of many studies that mentioned the role of diabetes as disease in causing lung function impairment.[22,24]

Study Strength and gaps

1. The study was conducted as a comparison between patients' values and the predicted values; it was not conducted as a case-control study, which is statistically stronger.[25]
2. It was difficult to evaluate the effects of some factors separately on lung functions (controlling other variables) because of small sample size.

RECOMMENDATIONS

1- Diabetes mellitus should be controlled, to lower the risk of neuropathy and consequently, lung functions impairment. As well to prevent further decrease in lung functions and give references if possible.

2- We suggest measuring the lung functions routinely for all patients with diabetes. It is scientifically logical to measure lung function for all diabetics although there isn’t any recommendation yet. It is a simple, non-invasive and accurate test and contributes in diagnosing pulmonary disease early.

3- Providing more care for diabetics with pulmonary diseases like asthma and chronic obstructive pulmonary disease because diabetes increases the risk of hospitalization, severe crises, and death.

4- Conducting further studies to examine the relationship between lung functions and diabetes and assessing other factors that may affect the lungs, such as proteins non enzymatic glycosylation of lungs and chest wall, resistance to insulin, and leptin.

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