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IMPACT OF DIABETES MELLITUS ON PULMONARY FUNCTION TEST IN COPD

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ABSTRACT

Introduction COPD is known to be a multisystemic inflammatory disease that goes beyond lung involvement. The association of decreased lung functions and diabetes mellitus has been studied for many years suggesting that the lung could be a target organ in diabetes mellitus. Objective assessment of pulmonary functions in COPD patients with normoglycemia and with diabetes mellitus, and patients with diabetes mellitus. Patients and Methods The study was conducted in Ain shams university hospitals After the inclusion criteria was met, patients were divided into 3 groups, each group was 20 patients,(group 1): diabetes mellitus patients,(group 2): COPD patients, and (group 3): COPD with diabetes mellitus patients. spirometry was performed and results were analyzed. Results In COPD with diabetes mellitus patients (group 3), the lung functions were the least. Diabetes mellitus was also an independent risk factor for reduced lung functions as was seen in nonsmoking diabetic patients (group 1). Conclusion Pulmonary functions are reduced in DM independent of smoking.

Keywords*: COPD, Diabetes mellitus, normoglycemia*

1. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a disease state characterized by an abnormal inflammatory response of the lungs to noxious particles or gases. The disease is usually progressive, chronic and not fully reversible with treatment. It is often associated with various co-morbidities like diabetes, hypertension, coronary artery disease, malnutrition, endocrine disorders or anxiety. COPD is considered a disease that goes beyond the lung involvement giving it an expression of a multisystem inflammatory disease.

COPD patients have a relatively increased risk of developing diabetes mellitus (DM) and diabetic patients have an increased risk of developing COPD. This side by side development of both diseases is a result of common risk factor like smoking and also synergistic effect of systemic inflammation mediated by common cytokines.

DM affects 1.6 to 16% of subjects with COPD. Metabolic syndrome, insulin resistance and systemic inflammation constitute risk factors for decreased lung function in healthy non smoking subjects which suggest that even in the absence of smoking DM can lead to similar effects on pulmonary function.

The association of reduced lung function and DM has been described for many years suggesting that the lung is a target organ in DM and that glycemic exposure is a strong determinant of reduced pulmonary function in diabetic patients. Hyperglycemia has the potential to impact the respiratory system by inducing oxidative stress, hypoxemia, systemic inflammation, structural changes in the lung tissue and altered gas exchange.1,2 Decrements in the lung function of patients with DM are believed to be the consequence of biochemical alterations in the connective tissue constituents of the lung particularly elastin and collagen as well as micro angiopathy due to the non enzymatic glycosylation of proteins and of the extra cellular matrix or lung parenchyma, thickening of basal lamina, increased susceptibility to infection and a modified sarcolemma with subsequent skeletal muscle weakness which are induced by chronic hypoglycemia. Diabetic micro angiopathy itself alters the alveolar diffusion capacity of the lungs3-9 and autonomic neuropathy may affect phrenic nerves resulting in reduced muscle tone and control of the diaphragm.

In this study, we assessed the pulmonary function in normo glycemic COPD patient, COPD patients with DM and DM patients without a history of COPD.

What Is Diabetes?

Diabetes mellitus is a metabolic disorder characterized by elevated blood glucose levels and disturbances in carbohydrates, fats and protein metabolism. Diabetes occurs either because of a lack of insulin or because of the presence of factors that oppose the action of insulin. The result of the insufficient action of insulin is an increase in blood glucose concentration (hyperglycemias). Many other metabolic abnormalities occur, notably an increase in ketone bodies in the blood when there is a severe lack of insulin [1]. Diabetes mellitus, often simply referred to as diabetes, is a group of metabolic diseases in which a person has high blood glucose, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood glucose produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). Diabetes is a multi-factorial, chronic and progressive metabolic disorder characterized by chronic hyperglycemia due to defects in the metabolism of carbohydrate, fat and protein. Persistent hyperglycemia is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels [1]. Diabetes is a metabolic disorder of carbohydrate, fat and protein, affecting a large number of population in the world [1].

Diabetes mellitus is not a single disorder but it is a group of metabolic disorder characterised by chronic hyperglycemia, resulting from defects in insulin secretion, insulin action, or both. Increased thirst, increased urinary output, ketonemia and ketonuria are the common symptoms of diabetes mellitus, which occur due to the abnormalities in carbohydrate, fat, and protein metabolism. When ketones body is present in the blood or urine, it is called ketoacidosis, hence proper treatment should be taken immediately, else it can leads to other diabetic complications [2]. Diabetes mellitus has caused significant morbidity and mortality due to micro vascular (retinopathy, neuropathy, and nephropathy) and macro vascular (heart attack, stroke and peripheral vascular disease) complications [3]. Diabetes is mainly attributed to the rapid rise in unhealthy life style, urbanization and aging. Hyperglycaemia which is the main symptom of diabetes mellitus generates reactive oxygen species (ROS) which cause lipid peroxidation and membrane damage. ROS plays an important rolein the development of secondary complications in diabetes mellitus such as cataract, neuropathy and nephropathy. Antioxidants protect β-cells from oxidation by inhibiting the peroxidation chain reaction and thus they play an important role in the diabetes. Plants containing natural antioxidants such as tannins, flavonoids, vitamin C and E can preserve β-cell function and prevent diabetes induced ROS formation. Polyphenols, which are classified into many groups such as flavonoids, tannins and stableness, have been known as health-beneficial properties, which include free radical scavenging, inhibition of hydrolytic and oxidative enzymes, anti-inflammatory action and antidiabetogenic potentiality [4]. Aldose reductase as a key enzyme, catalyse the reduction of glucose to sorbitol and is associated in the chronic complications of diabetes such as peripheral neuropathy and retinopathy. Use of aldose reductase inhibitors and α-glucosidase inhibitors has been reported for the treatment of diabetic complications [5]. In people with diabetes, blood sugar levels remain high. This may be due to insulin is not being produced at all, is not made at sufficient levels, or is not as effective as it should be. The most common forms of diabetes are type 1 diabetes (5%), which is an autoimmune disorder, and type 2 diabetes (95%), which is associated with obesity. Gestational diabetes is a form of diabetes that occurs in pregnancy, and other forms of diabetes are very rare and are caused by single gene mutation [6].

Type of Diabetes Mellitus:

Three main types of DM are known type I associated with full insulin deficiency, type II-progressive insulin deficiency15 and gestational DM which is diagnosed in 2nd or 3rd semester of pregnancy. Currently, although type I cannot be prevented, type II is preventable with good health, exercising and healthy diet. Early diagnosis is the key in diabetes management. Nevertheless, type II have affected high population and lead to complications in several body parts, heart, nerves, eyes, kidney and so on16. Diabetes falls into three below general categories [6]:

A) Type 1 diabetes mellitus

It is a chronic autoimmune disease associated with selective destruction of insulin producing pancreatic β cells. When there is transplantation of pancreas from twin donors to chronic diabetic twin recipients in the absence of immune suppression is complicated due to elevated heterogenecity of pancreatic lesions of β-cellswhich are rapidly annihilated, and then there is development of massive insulitis by using infiltrating T lymphocytes which measures an amnestic autoimmune reaction. Type 1 diabetes is often referred to as insulin- dependent (IDDM) or juvenile-onset diabetes [6]. Type 1 diabetes is an autoimmune disease in which the β-cells of the pancreas do not produce sufficient insulin, a hormone which helps use blood sugar (glucose) for energy. The cells become starved of energy and there will be excess of glucose in the blood. This is then followed by life threatening conditions of hypoglycemia, low blood sugar, and hyperglycemia, high blood sugar. When hypoglycemia develops, cells do not get enough glucose and patients suffer of confusion, loss of consciousness, and coma. Even death can results when the brain is deprived of glucose for too long. Hyperglycemia and prolonged absence of insulin may lead to ketoacidosis, which is accumulation of ketones in the blood when the body uses fat for energy instead of glucose. This is because fatty acids cannot be converted into glucose at steady state. Ketones make the blood acidic and slow down all body functions. This also leads to a coma and eventually death. Type I diabetes is as a result of β-cell destruction which customarily provoke complete insulin insufficiency. It was formerly known as insulin-dependent, juvenile or childhood-onset diabetes and it is occasioned by an autoimmune reaction, in which the immune system invaded against the insulin-producing pancreatic beta cells. Type I diabetes is distinguished by deficient insulin production in the body. In such type of DM the patients require daily administration of insulin so as to normalize the glucose level in the blood. Have not taken the insulin, their life is being threatened and can be fatal. The reason of type IDM is not identified yet being presently not preventable. Albeit, the reasons for type I diabetes are still unclear, changes in environmental risk factors and/or viral infections may have an impact on the appearance of DM. Extreme urination and thirst, continuous hunger, weight loss, vision changes and fatigue are the main symptoms of this type of DM. More often than not, the number of people who diagnosed with type I diabetes is escalated [4, 12].

B) Type 2 diabetes mellitus

Type 2 diabetes mellitus is also known as adult-onset diabetes. The progressive insulin secretary defect on the background of insulin resistance. People with this type of diabetes frequently are resistant to the action of insulin. Globally, it affects 5-7% of the world's population.

The disease is usually controlled through dietary therapy, exercise and hypoglycemic agents. This is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, older age, obesity and lack of exercise [6]. Type II diabetes which earlier termed non-insulin-dependent or adult-onset diabetes, assumed to be a result from a continuousinsulin secretory defect on the background of insulin resistance on account of the body's inefficient use of insulin. Type II diabetes is the most typical DM. In this type, the body is capable of producing insulin but becomes so resistant that the insulin is ineffective. By the time, insulin levels could subsequently turned out insufficient. The cause of high blood glucose levels are both the insulin resistance and deficiency. Given that the symptoms (coincidental to type I diabetes symptoms) are generally less noticeable or absent, the illness could be dismissed and be undiagnosed for numerous years, and not until complications have already ascended [7]. For various years, type IIDM was observed only in adults, nowadays it has started to be seen also in children. Until present the exact causes for the development of type II diabetes are unknown, some significant risk factors being pointed out. The most significant ones include: excess body weight, physical Inactivity and poor nutrition. Other factors which impacted are ethnicity, family history of DM, past history of gestational diabetes and advancing age [4].

C) Gestational diabetes mellitus

Gestational diabetes mellitus (GDM) is a type of DM determined in the second or third trimester of pregnancy that is not clearly overt diabetes. GDM is a provisional disorder that happens in pregnancy and brings enduring danger of type II diabetes. Pregnant women often develop diabetes. During pregnancy large quantities of hormones are produced, these hormones may reduce insulin action in the mother's body, causing insulin resistance. Women that develop diabetes mellitus during pregnancy and women with undiagnosed asymptomatic type 2 diabetes mellitus that is discovered during pregnancy are classified with gestational diabetes mellitus [4, 5]. Clinical importance of GDM lies in the fact that it is associated with significant maternal and fetal morbidity [6]. Women with slightly elevated blood glucose levels are diagnosed as having gestational diabetes, whilst women with substantially elevated blood glucose levels are classified as having diabetes mellitus in pregnancy. GDM tends to arise from the 24th week of pregnancy. Screening by means of an oral glucose tolerance test is therefore recommended and must be conducted early in pregnancy for high risk women, and between the 24th and 28th week of pregnancy in all other women. Women with hyperglycemia diagnosed during pregnancy are at greater risk of adverse pregnancy outcomes such as: very high blood pressure and foetal macrosomia, with the vaginal birth being difficult and risky. In some cases, clinicians prescribe insulin or oral medication in order to control the blood glucose levels. Notwithstanding, gestational diabetes normally disappears after delivery but women who have been previously diagnosed are in danger of presenting GDM in subsequent pregnancies and type IIDM later in their life. In addition, infants beared by mothers with GDM also have a higher risk of developing type II diabetes during adolescence or early adulthood [7,11].

D) Other types of diabetes

a) Diabetes LADA

Latent Autoimmune Diabetes of the adults is autoimmune diabetes defined by adult-onset, presence of diabetes associated autoantibodies, and no insulin treatment requirement for a period after diagnosis [6]. It is becoming evident that a proportion of adults may have a slowly evolving kind of Type 1 diabetes, which is characterized by the presence of autoantibodies. Some people diagnosed with type 2 diabetes soon find themselves dependent on insulin; these people may have a slowly progressive form of type 1 diabetes or LADA [13].

b) Diabetes MODY

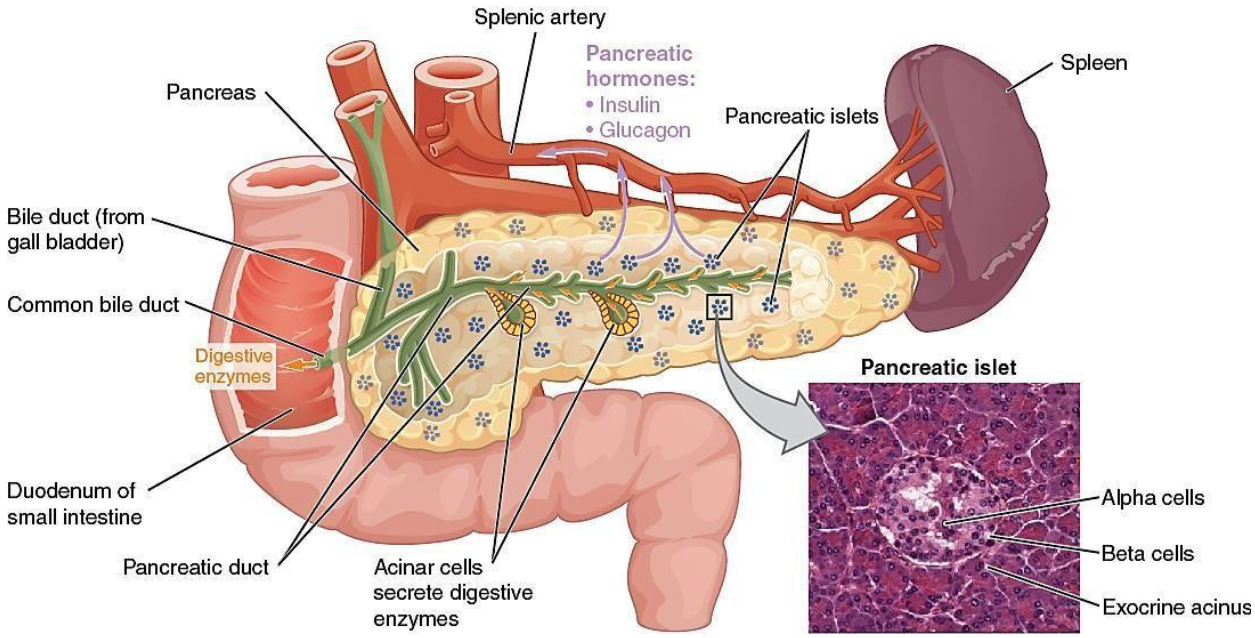
Maturity onset diabetes of the young is an autosomal dominantly inherited type of diabetes that results from heterozygous mutations in various transcription factors acting in the development and maturation of pancreatic β-cells [6]. Characteristics features of MODY are autosomal inheritance, early onset of diabetes, no signs related to the autoimmune process or insulin resistance, and preservation of endogenous insulin secretion [14].

2. ANATOMY OF THE PANCREAS

The pancreas is located in the abdomen behind the stomach and has both exocrine and endocrine functions. The endocrine functions include the production of hormones, which include insulin and glucagon; the exocrine functions include the production of digestive enzymes, such as amylase, lipase and proteases. The pancreas also contains a group of cells known as the islets of Langerhans, which are responsible for theproduction of four types of cells [11]:

- Alpha cells – production of glucagon. Beta cells – production of insulin.
- Delta cells – production of somatostatin.
- Pancreatic polypeptide (PP) cells – production of pancreatic polypeptide.

The secretion of these hormones is regulated through sympathetic and parasympathetic stimulation, which prevents the development of endocrine disorders. Alpha cells, beta cells and delta cells have a primary role in the management of blood glucose levels, known as glucose homeostasis. In hyperglycaemia, the beta cellssecrete insulin to reduce the blood glucose level; conversely, in hypoglycaemia (reduced glucose levels inthe blood), the alpha cells secrete glucagon, which promotes glycogenolysis (breakdown of glycogen into glucose to provide immediate energy) by the liver. Somatostatin, which is produced by the delta cells, inhibits insulin and glucagon [7, 11].



What Is COPD?

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disease that causes obstructed airflow from the lungs. Symptoms include breathing difficulty, cough, mucus (sputum) production and wheezing. It's typically caused by long-term exposure to irritating gases or particulate matter, most often from cigarette smoke. People with COPD are at increased risk of developing heart disease, lung cancer and a variety of other conditions.

Emphysema and chronic bronchitis are the two most common conditions that contribute to COPD. Thesetwo conditions usually occur together and can vary in severity among individuals with COPD.

Chronic bronchitis is inflammation of the lining of the bronchial tubes, which carry air to and from the air sacs (alveoli) of the lungs. It's characterized by daily cough and mucus (sputum) production.

Emphysema is a condition in which the alveoli at the end of the smallest air passages (bronchioles) of the lungs are destroyed as a result of damaging exposure to cigarette smoke and other irritating gases and particulate matter.

Although COPD is a progressive disease that gets worse over time, COPD is treatable. With proper management, most people with COPD can achieve good symptom control and quality of life, as well as reduced risk of other associated conditions.

Symptoms:

COPD symptoms often don't appear until significant lung damage has occurred, and they usually worsen over time, particularly if smoking exposure continues.

Signs and symptoms of COPD may include:

- Shortness of breath, especially during physical activities
- Wheezing
- Chest tightness
- A chronic cough that may produce mucus (sputum) that may be clear, white, yellow or greenish
- Frequent respiratory infections
- Lack of energy
- Unintended weight loss (in later stages)
- Swelling in ankles, feet or legs

People with COPD are also likely to experience episodes called exacerbations, during which their symptoms become worse than the usual day-to-day variation and persist for at least several days.

3. CAUSES

The main cause of COPD in developed countries is tobacco smoking. In the developing world, COPD often occurs in people exposed to fumes from burning fuel for cooking and heating in poorly ventilated homes.

Only some chronic smokers develop clinically apparent COPD, although many smokers with long smoking histories may develop reduced lung function. Some smokers develop less common lung conditions. They may be misdiagnosed as having COPD until a more thorough evaluation is performed.

4. MATERIAL AND METHODS

The study was conducted in Jubilee Mission Medical College and Research Centre Thrissur. It was a case control study over a period of 5 months from March 2016 to August 2016. A detailed case history proforma was filled out during the recruitment of patients. Twenty normoglycemic COPD patients, 20 patients with COPD and DM and 20 diabetic patients were included in the study.

Inclusion Criteria:

Patients already on treatment for COPD by a chest physician or newly diagnosed COPD patients based on post bronchodilator FEV1/FVC < 0.7 on spirometry with or without DM. Patients with DM already on treatment or newly detected patients with FBS ≥126 mg/dl without a history of COPD.

Exclusion Criteria:

Patients aged more than 80 years, those having a history of bronchial asthma, interstitial lung disease, concomitant lung cancer, present or past history of tuberculosis, decompensated cardiac disease and patients not willing to participate in the study were excluded from the trial. 1Professor & Head of the Department, Department of Pulmonary Medicine, Jubilee Mission Medical College & Research Institute, 2Head of the Department, Department of Pharmacy Practice, Nehru College of Pharmacy, Thrissur, 3M Pharm Student, 4Research Coordinator, Jubilee Centre for Medical Research, JMMC & RI, Thrissur, Kerala, India

5. RESULTS

The study included 60 patients who were categorized into 3 groups.

1. Group 1-COPD patients
2. Group II-COPD with DM
3. Group III-DM patients

Maximum patients were in the age group of 61-70 years showing that COPD commonly affects the elderly population. The COPD severity distribution in the three groups is shown in figure 1. According to the GOLD(Global Initiative for Chronic Obstructive Lung Disease) grading system for COPD based on post bronchodilator FEV1, lung functions were found to be normal or near normal in 75% of DM patients (group II). Very severe and severe COPD patients were seen in group II that is COPD with DM. Though, the first group was suffering from COPD, patients with severe disease were seen in a few patients clearly indicating that DM has a detrimental effect on the lung functions.

Parameter	COPD (Mean±SD)	COPD with DM (Mean±SD)	DM (Mean±SD)	*P* value
RBS(mg/dl)	-	233.1±49.52713	230.73±36.87521	0.014
FBS(mg/dl)	-	124.65±13.6122	122.9286±16.07418	0.037
HbA1C	5.7±0.56	7.9±1.89	7.64±1.55	0.001

Table-1: Glycemic status in 3 groups

Table 1 shows that group II patients (COPD with DM) had relatively higher sugars and HbA1C levels are compared to group III (that is DM) alone indicating that systematic inflammation, metabolic syndrome and corticosteroid therapy quite often used in COPD patients could induct a diabetic state in such patients. Table 2 shows that lung functions were reduced in group II patients (COPD with DM) as compared to group I and group III patients. It could be interpreted that presence of DM worsens the lung functions including FVC, FEV1, FEV 25- 75 and PEF and pushes the COPD patients to the next severity stage. COPD and DM act as double edged sword in reducing the lung functions as is seen in table 3 proving that lung is a target organ for damage patients with DM. Group 2 patients had lowest lung functions followed by group 1 and lastly by group 3.

6. DISCUSSION

In this study, we tried to associate the lung function in COPD with DM patients. Our study shows that lung functions were much affected in group II than group and III. Irfan *et.al*, studied PFT in diabetics and showed that there was a significant

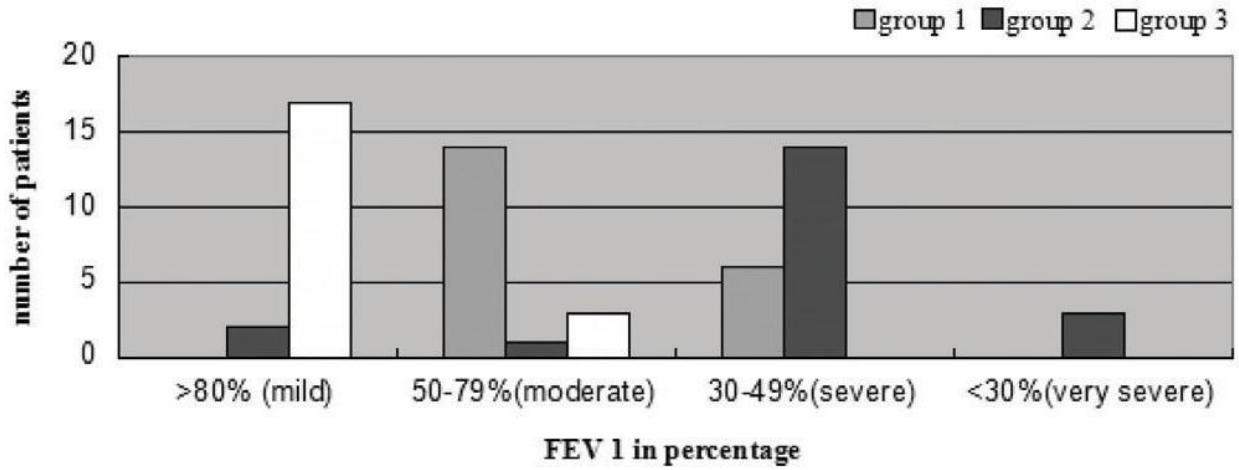


Figure-1: COPD severity distribution in 3 groups

Reduction in FVC, FEV1.7 They also stated that impaired lung function was independent of smoking and is likely to be a complication of DM itself. Davis et.al also showed that reduced lung volumes are the result of chronic complications of DM and is related to glycemic exposure.10 Kaminsky has opined that lung function is an important marker of increased mortality in diabetic patients.11

Path physiology of reduced lung function is still an interesting research issue. Normal lung mechanics and gas exchange are influenced by the integrity of pulmonary vasculature and connective tissue. In a study by Mahmoud,9 it was found that the alveolar epithelium, capillary endotheluim and basal laminae were thickened on election microscopy when compared with the controls. In addition, thickening of the basal laminae was of the same magnitude in lung and kidney favouring that diabetic microangiopathy existed inthe pulmonary vascular bed. The origins of pulmonary function impairment in DM are thought to derive from four primary sources: non enzymatic glycosylation of lung collagen and elastin by advanced glycosylation end products (AGES) generated by disrupted glycemic control resulting in reduced elasticityof the lung. Pulmonary microcragropathy reducing the diffusion capacity and autonomic neuropathy affecting the phrenic nerves and the diaphragm have also been observed. Finally hyperglycemia resulting in frequent infective exacerbations also is associated with poor outcome.

This study showed that lung function in terms of FEV1, FVC, FEV1/FVC, FEF 25-75 were the least in COPD with DM group than DM group. This study has certain limitations though. The study size was small and we cannot analyze the result in different ethnic group. The PFTs were not repeated to access the changesof pulmonary function among the same subjects over a period of time.

It has been shown that DM is associated with continuing damage, dysfunction and failure of various organs including the lungs. Indeed it seems prudent to add the spirometry to the tools available for monitoring DM and important sequelae.

7. CONCLUSION

We conclude that COPD with DM patients showed a decrease in PFT values compared to the other two groups. The findings of the study proved that lung is a target organ for damage in DM and that the glycemic exposure is a strong determinant of reduced pulmonary function in type 2. Pulmonary functions are reduced in DM independent of smoking as was seen in the female non smokers. As pulmonary dysfunction may be one of the

earliest and early measurable non metabolic alterations in DM, patients with DM are suggested to undergo PFT along with other investigations. It is advisable therefore, that diabetic patients must undergo periodic spirometry tests to assess the severity of lung function impairment. These measures will help in preventing lung damage in initial stage and thus contribute to reduction in morbidity and mortality of these patients.

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