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Role of Duration of Diabetes on Ventilatory Capacities and Expiratory Flow Rates in Type 2 Diabetes Mellitus

Shravya Keerthi G[1*], , Hari Krishna Bandi[2], Suresh M[3], Preetham J K[4], Mallikarjuna Reddy N[1], Sharan B Singh M[1]

1. Dept. of Physiology, Narayana Medical College (NMC), Nellore, Andhra Pradesh, India. E Mail: gsk.respublications@gmail.com
2. Dept. of Physiology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India.
3. Dept. of Physiology, Meenakshi Medical College and Research Institute (MMCH&RI), Kanchipuram, Tamilnadu, India.
4. Dept. of Physiology, All India Institute of Medical Sciences (AIIMS), New Delhi, India.

Abstract
Diabetes mellitus is a chronic debilitating problem with increasing incidence and long term complications such as diabetic nephropathy, diabetic neuropathy, diabetic retinopathy etc. These complications are mainly a consequence of macro vascular and micro vascular damages of the target organs. The magnitude of the complications of diabetes is related to its duration. Less has been known about the after effects of diabetes on lungs. So this work was carried out to know the relation between duration of diabetes and lung volumes and capacities in Type 2 DM patients. The presence of an extensive micro vascular 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, there by rendering the lung a "target organ" in diabetic patients. This is a cross-sectional study, the test group were Type 2 Diabetes Mellitus patients (n=50) with duration of 2-35 years, the control group were staff of Narayana medical college (n=50). Written consent was obtained from them. The following lung function parameters were recorded: Forced Vital Capacity **(FVC),** Forced Expiratory Volume in the first second **(FEV_1),** Forced Expiratory Volume percent **(FEV_1/FVC %),** Peak Expiratory Flow Rate **(PEFR),** Forced Expiratory Flow 25-75% **($FEF_{25-75\%}$),** Maximum Voluntary Ventilation **(MVV).** The mean FVC, FEV_1, PEFR, FEF_{25-75}%, MVV values are low in diabetics compared to controls (p value <0.001) and the parameters showed significant negative correlation with duration of diabetes.
Key words: Chronic hyperglycemia, Diabetes mellitus, Microangiopathy, Micro vascular circulation, Pulmonary function tests

1. Introduction

Diabetes mellitus (DM) is a complex medical syndrome comprising of heterogenous group of diseases resulting from diverse aetiologies predominantly of genetic and environmental origin. It is characterized by chronic hyperglycemia with disturbances of carbohydrate, protein and fat metabolism, resulting from defects in insulin secretion or insulin action or both[1]. According to WHO, the total number of people worldwide with diabetes is projected to rise from 150 million in 2000 to 435 million in 2030 [2, 3]. India is called Diabetic Capital of World as there are going to be 80% of all diabetics from the entire world population, concentrated here [2,3]. Greater longevity, obesity, unsatisfactory diet, sedentary lifestyle and increasing urbanisation are main factors contributing for this. Type 2 or NIDDM, is characterized by insulin resistance and impaired insulin receptors. It is common type of diabetes and usually develops after the age of 40 years. It is associated with normal B cell morphology [4] . Type 2 diabetes comprises 90% of people with diabetes all around the world, and is largely the result of excess body weight and physical inactivity [2, 3]. There is one person in the world dying of diabetes every ten seconds and new diabetic cases being identified every ten seconds [3].

DM is accompanied by widespread biochemical, morphological and functional abnormalities which may precipitate certain complications that may affect neural, Cardiovascular, renal systems and also organs and tissues like skin, liver, collagen and elastic fibers. Thus diabetes is a multisystem disorders that affect many organs of the body [5] . These complications are mainly a consequence of macro vascular and micro vascular damages of the target organs [1] . The micro vascular complications appear early within 5to10 years and macro vascular complications appear within 15 to 20 years from the onset of diabetes. Like other target organs lung is also affected in diabetes[1,5]. The presence of an extensive micro vascular 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, there by rendering the lung a "target organ" in diabetic patients. Hyperglycemia causes thickening of basal lamina in pulmonary capillaries leading to decreased diffusion capacity. The alteration in scleroproteins in turn affect mechanical properties of lungs. In this chronic disease, the susceptibility and severity of systemic inflammation increases which may cause peripheral airway obstruction[1]. Since normal lung mechanics and gas exchange are influenced by the integrity of the pulmonary connective tissue and microvasulature, abnormalities in either of these two structural components of the lung may lead due to the development of measurable abnormalities of pulmonary function [6].

The duration of DM is an important factor affecting the lungs. Chronic hyperglycemia is strongly associated with progressive neurogenic damage. In 2000, Davis et al. observed that some pulmonary functions were decreased in type 2 diabetes and the reduction was directly proportionate to the duration of the disease [1,7]. In 2007, Meo et al. also observed that some spirometric lung function parameters were decreased in type 2 diabetics and the decline was more in patients with longer duration of diabetes [1]. In a Japanese study, the incidence of pulmonary pathology was found to be 50% on autopsy. It has been suggested that pulmonary dysfunction may be one of the earliest measurable non-metabolic alteration in diabetes. If diabetes is detected early and adequate steps are taken, it may be possible to significantly delay the occurrence of complications and there after their progression. Although a lot of research work is being carried out worldwide on the after effects of Diabetes on pulmonary function parameters, the literature pertaining to this is not in abundance in India. Therefore, this study was undertaken to find out the correlation between duration of type 2 diabetes and pulmonary function parameters.

2. Materials and Methods

This was a cross-sectional study undertaken by the Department of Physiology, Narayana medical college (NMC), Nellore, Andhra Pradesh, India. After obtaining approval of Institutional Ethics Committee (IEC), the test group subjects (n=50) type 2 diabetic patients were recruited from Out Patient Departments (OPD) and central laboratory of NMC and hospital. The control group subjects (n=50) were teaching and non-teaching staff of NMC. The subjects in the age group between 30-60 years are included. Subjects with past history of (H/O) smoking, hypertension, respiratory diseases, chest wall injuries, congestive cardiac failure, kyphoscoliosis, and age <30 and >60 years 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. They were instructed to report to Respiratory Physiology Research laboratory of Physiology department at about 9 A.M.

Following 5 minutes sitting rest in the lab, their pulmonary functions were assessed by computerized spirometer (Spiro win Version 2.0 of Genesis Medical systems pvt Ltd) which gives ERS-93 predicted values at BTPS conditions [8]. At the beginning, satisfactory demonstrations were given regarding the equipment and the procedure of the study. During the procedure, the subjects inhaled deeply and then exhaled with maximum effort as much as possible in to the mouth piece. The following parameters were recorded: Forced vital capacity(FVC), Forced expiratory volume in the first second(FEV_1), Forced expiratory volume percent(FEV_1/FVC%), Peak expiratory flow rate(PEFR), Forced expiratory flow 25-75%($FEF_{25-75\%}$) and Maximum voluntary ventilation(MVV).

3. Results

The data were expressed as mean ± SD. The data was analysed by Students 't' test. The p values less than 0.05 was considered significant. In diabetic subjects, there was significant decrease in FVC ($p<0.001$), FEV_1 ($p<0.001$), FEV_1/FVC% ($p<0.01$), PEFR ($p<0.001$), $FEF_{25-75\%}$ ($p<0.001$) and MVV ($p<0.001$) compared to non-diabetic subjects. Relationship of FVC, FEV_1, FEV_1/FVC%, PEFR, $FEF_{25-75\%}$, and MVV with duration of diabetes were observed. The results showed negative correlation with duration of diabetes and were statistically significant (fig.1-6)

4. Discussion

Diabetes mellitus, an incurable lifelong disease, involves multiple systems with wide-ranging and devastating complications, which end up in severe disability and death. 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[9,10]. 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. A study conducted by David. A Kaminsky in 2004 speculates that abnormal lung function may precede the diagnosis of diabetes,

suggesting that lung may contribute to or at least be commonly affected by factors involved in the pathogenesis of diabetes [5].

4.1. Effect of duration of DM on FEV

There was significant reduction in mean FVC in all diabetic patients and the reduction was more pronounced with increased duration of diabetes. Recent studies conducted by Lange et al. and Asanuma et al indicate that both IDDM and NIDDM patients are associated with slight reduction in FVC and it was because of impaired defense against environmental challenges such as smoking and airway infections in diabetes [11,12]. There was increased cross-linkage formation between polypeptides of collagen in pulmonary connective tissue, which decreases FVC and hence is responsible for restrictive respiratory defects. In a study by Davis A.Wendy et.al., there was a decrease in mean FVC values as the duration of DM increased. In their study the annual rate of fall in FVC was 68 ml [5,7]. In a study by Robert E. Walter et.al., there was a progressive decrease in mean FVC values by 109 ml/year [5]. A study by Timothy M.E Davis, showed there was an average decrease of 9.5% in mean FVC values in diabetics [13].

4.2. Effect of duration of DM on FEV_1

FEV_1 is the volume of air that is exhaled in the first second during FVC manoeuvre. It is useful to detect generalized airway obstruction. The Mean FEV_1 values showed significant negative correlation with duration of diabetes. The values of FVC and FEV_1 in type 2 diabetic patients of different duration were significantly lower than those of non-diabetic subjects. These findings were consistent with findings of Meo et al. and Davis et al [7]. In diabetes, there is a thickening of alveolar epithelium and pulmonary capillary basal lamina leading to pulmonary microangiopathy, reduced pulmonary elastic recoil due to non-enzymatic glycosylation of connective tissue reducing the FEV_1[9,10]. Patients with diabetes for more than 12 years experienced a significant reduction in FVC, FEV1, and FEF25–75% relative to controls [9]. A large Danish cross-sectional population study Lange P (1989) showed a negative association between plasma glucose & both FVC & FEV1 . The negative correlation of FVC & FEV_1 with duration of diabetes indicate that long standing hyperglycemia may intensify the devastating effect of the disease. In a small scale six years study by Ramiriez LC, et al (1991) demonstrated that intensive treatment by subcutaneous insulin infusion improved both FVC & FEV_1 percentage predicted values[13].

4.3. Effect of duration of Type 2 DM on FEV_1 /FVC%

FEV_1/FVC% is the volume of air expired in the first second, expressed as percentage of FVC. It is a more sensitive indicator of airway obstruction, than FVC or FEV_1 alone. The alteration in collagen and elastin ratio is the main factor in the diabetic patients. The decrease in FEV_1/FVC% in diabetic subjects may be related with the poor mechanical properties of the lung, like lung compliance and elastic recoil of lungs. Loss of elastic recoil leads to dynamic collapse of small airways during expiration. In addition, myopathic or neuropathic changes affecting the respiratory muscles further impairs the endurance, efficiency of ventilatory pump. A study conducted by Ali Mo et al. showed similar findings but was not significant [1]. Sreeja et al. reported almost similar type of finding [11].

When FEV1/ FVC% was observed , the actual values were higher than the predicted values by 3.75% and 7.3% which suggest of restrictive pattern in diabetics. In a study by Robert .E. Walter the ratio was increased by 1.5% in diabetics which was statistically significant [5]. This parameter was significantly higher in 10-20 years duration of diabetes than 5-10 years duration and also control group, finding similar to Ali MO et al.[1,10].

4.4. Effect of duration of Type 2 DM on PEFR

PEFR values were observed in all the groups, there was an absolute decrease in the mean values compared to predicted values which was statistically significant ($p<0.001$). In a study by Timothy ME Davis, there was a average decrease in mean value of PEFR by 9.5%[5,13]. As per the study of Sreeja et.al., the decrease in PEFR was 267.65L/sec[11]. The patients with diabetes complicated by autonomic neuropathy have impaired control of bronchomotor tone. Resting vagal tone is depressed which explains the depressed bronchoconstrictory response to both cholinergic stimuli and hyperventilation with cold air [12,14]. Thus, there is a complex alteration of both control of ventilation and bronchomotor tone in diabetic patients with automatic neuropathy[15].

4.5. Effect of duration of diabetes on $FEF_{25–75\%}$

$FEF_{25-75\%}$ is the average flow rate during middle 50% of FVC. It indicates patency of the small airways. $FEF_{25-75\%}$ depends on non-bronchopulmonary factors like, neuromuscular factors and mechanical equipment factors of inertial distortion of lungs[15]. The thickening of alveolar wall due to the increased amounts of collagen and elastin

in basal lamina results in microangiopathy. Chronic hyperglycemia causes fibrous tissue formation in the chest wall and bronchial tree protein by non-enzymatic glycation. This may cause reduced compliance of lung and chronic airflow obstruction [14,15,17].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 [14]. As per the study of Sreeja et. al., there was decrease in $FEF_{25-75\%}$ by 2.45 ± 0.55[5,11]. So our results coincide with the same.

4.6. Effect of duration of diabetes on MVV

MVV is the maximum breathing capacity which is decreased in poor respiratory muscle strength, emphysema etc. There was a significant reduction in MVV values in diabetics compared to controls, shows poor skeletal muscle strength due to increased protein catabolism and diabetic autonomic neuropathy. A study conducted by Park SW et al. and Meo SA et al. showed similar results. Thus, respiratory muscle endurance decreases in diabetes mellitus[9,11].

Hyperglycemia causes over production of mitochordrial superoxides and reduction in anti-oxidant defence of the lungs [17]. The glycation of proteins can lead to oxidative stress by direct release of O_2 and H_2O_2, and activation of phagocytes through a specialized receptor for advanced glycosylation end products (AGEs). Oxidants include reactive oxygen species (ROS), reactive nitrogen species (RNS), sulphur centered radicals and others. Phagocytic cells generate large amounts of NO and ROS. In diabetes there are alterations in antioxidant enzymes, impaired glutathione metabolism, and decreased ascorbic acid levels. Nitric oxide is produced by nitric oxide synthase (NOS). Three different forms of NOS expressed in lungs are neuronal (n NOS), endothelial (e NOS), and inducible (i NOS). Excessive NO produced by i NOS and its potent oxidative derivative peroxynitrate via oxidation, hydroxylation, and nitration is involved in acute lung injury [16,17]].

The alvelolar capillary network is the largest microvascular organ (Surface area 140 m^2) and receives entire cardiac output[18] . As the pulmonary reserves are larger, the symptoms and disability from diabetes develop earlier in other organs than in the lungs.

The correlation graphs reflect a relation between the duration of diabetes on FVC, FEV_1, FEV_1/FVC%, PEF, $FEF_{25-75\%}$ and MVV. The correlation graphs show a negative correlation between duration of diabetes and lung function parameter values in diabetics. FEV_1/FVC% showed a positive correlation with duration of diabetes. Similar findings were observed by Ali MO et al. and Meo et al.[1,9].

5. Conclusion

The correlation graphs in our study, reflect a relation between the effect of duration of diabetes on lung function parameters i.e; the reduction is directly proportionate to the duration of the disease. Even though Type2 diabetic patients did not have any respiratory symptoms, they did have underlying subclinical restrictive patterns of lung functions. As the duration of diabetes increases the restrictive profile is more prominent. The findings of present study suggest that, lung is a target organ for damage in diabetes and the glycemic exposure is a strong determinant of reduced pulmonary function in type 2 diabetics. As measures of airflow limitation predict all-cause mortality in type 2 diabetes, intensive glycemic management may reduce the risk of death through improved ventilatory function independent of other beneficial effects. The lower lung function, particularly reduced vital capacity, not only precedes the onset of diabetes but also continues, at an accelerated pace with the onset of the disease. As pulmonary dysfunction may be one of the earliest and easily measurable non-metabolic alteration in diabetes, the patients with diabetes are suggested to undergo pulmonary function testing along with other investigations. Additional research is required to identify pathophysiologic mechanisms and to determine clinical significance of this association. Hence, it is an alarming signal to clinicians to pay heightened attention to pulmonary function in their patients with type 2 diabetes.

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Result fig 1-6.

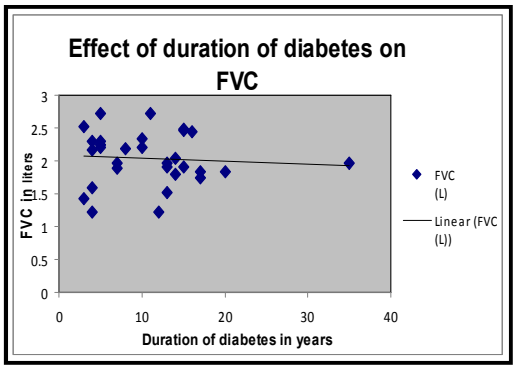

Fig.1: A significant negative correlation was found, indicating that increased duration of disease decreased the FVC.

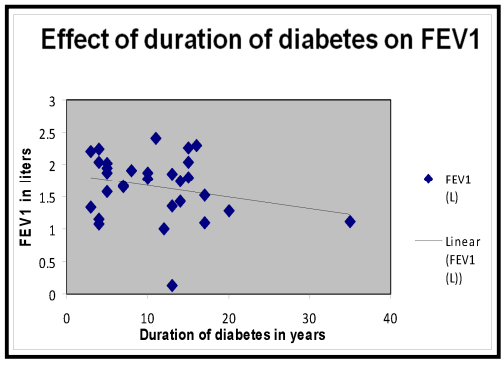

Fig.2: Regression analysis for forced expiratory volume in 1 second against duration of disease in diabetic patients. A significant negative correlation was found, indicating that increased duration of disease decreased the FEV_1.

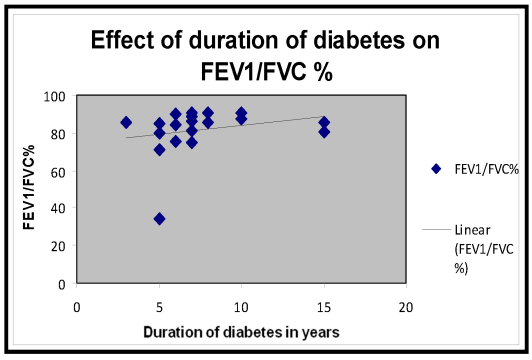

Fig.3: A significant negative correlation was found, indicating that increased duration of disease decreased the $FEV_1/FVC\%$.

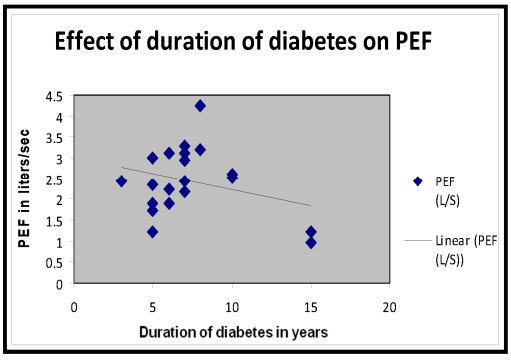

Fig.4: There is slight negative correlation between duration of diabetes and PEFR values.

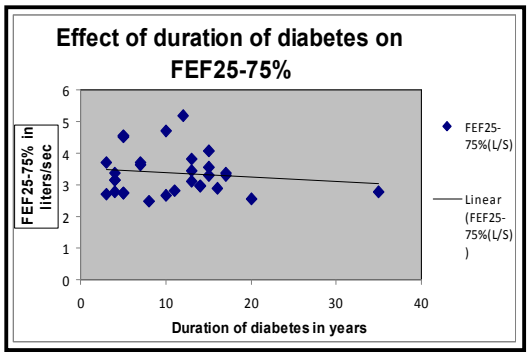

Fig.5:A significant negative correlation was found, indicating that increased duration of disease decreased the $FEF_{25-75\%}$.

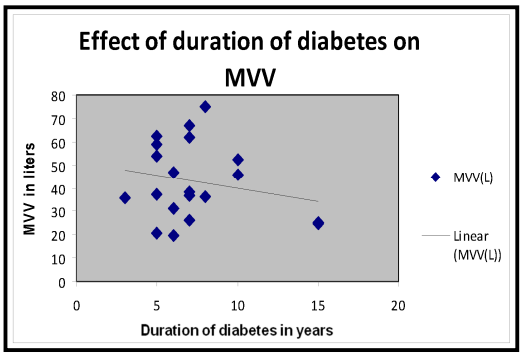

Fig.6: Graph shows a significant negative correlation of MVV values with duration of diabetes.