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Original Research Paper

STUDY OF PULMONARY FUNCTION TEST IN TYPE 2 DIABETES MELLITUS WITH SPECIAL REFERENCE TO DURATION OF DIABETES, GLYCEMIC CONTROL AND MICROVASCULAR COMPLICATIONS

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ABSTRACT:

Background: The lung is rich in microvascular circulation and abundant connective tissue, that raises the possibility of pulmonary damage by microangiopathic process and non enzymatic glycosylation of tissue proteins induced by chronic hyperglycemia, rendering the lung a target organ in diabetic patients. This study pertains to corelate the effect of duration of diabetes, glycemic status and association of microvascular complications with PFT **Objectives:** To study the effect of duration of diabetes mellitus and glycemic status on pulmonary function test, and to determine the association of microvascular complications in relation with PFT **Methods:** 100 patients of both genders with type 2 diabetes mellites in the age group of 30 to 65 years with multiple exclusion criteria were subjected for detailed history, examination, and investigations to rule out microvascular complications including HbA1c, microalbuminuria, fundoscopy, nerve conduction velocity study and PFT. **Results:** Among the 100 patients studied, as the duration of the illness progressed, there was a significant reduction in PFT. There was no association between HbA1c and PFT. FVC and FEV1 were reduced in patients with microvascular complications, of which diabetic nephropathy was closely associated with PFT and diabetic retinopathy was the most common microvascular complication. 67% of patients had restrictive pattern and 3% had obstructive pattern of lung impairment **Conclusion:** The PFT parameters were affected more with longer duration of diabetes mellites. Strict glycemic control and regular breathing exercises to strengthen the respiratory muscles may improve the PFT. Spirometry helps in early detection and preventive measures can be advised

Keywords: Hyperglycemia, pulmonary function test, microvascular complications, HbA1c, diabetes mellitus, forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV1)

INTRODUCTION:

Diabetes mellitus is a group of metabolic diseases associated with hyperglycemia due to defects in insulin secretion or insulin action or both. Several pathogenic processes are involved in the development of diabetes, including autoimmune destruction of beta cells of pancreas with consequent insulin deficiency (Type 1 DM), and abnormalities that result in resistance to insulin action (Type 2 DM). Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more point in the pathway of hormone action. There is an alarming increase in the incidence and prevalence of diabetes mellites particularly in Asian Indians. The prevalence has increased two-fold or more within a decade in many countries, especially Nepal, India, and China.[1] Chronic hyperglycemia is the important etiologic factor leading to complications of DM, but the

mechanisms by which it leads to such diverse cellular and organ dysfunction is unknown. An emerging hypothesis is that hyperglycemia leads to epigenetic changes that influence gene expression in affected cells. Other hypotheses are that chronic hyperglycemia leads to formation of advanced glycosylation end products (AGEs; e.g., pentosidine, glucosepane, and carboxymethyl lysine) which bind to specific cell surface receptor and/or the nonenzymatic glycosylation of intra- and extracellular proteins, leading to cross-linking of proteins, accelerated atherosclerosis, glomerular dysfunction, endothelial dysfunction, and altered extracellular matrix composition. Other theories predict that hyperglycemia: (1) increases glucose metabolism via the sorbitol pathway related to the enzyme aldose reductase; (2) increases the formation of diacylglycerol, leading to activation of protein kinase C, which alters the transcription of genes for fibronectin, type IV collagen, contractile proteins, and extracellular matrix proteins in endothelial cells and neurons; and/or (3) increases the flux through the hexosamine pathway, which generates fructose-6phosphate, a substrate for O-linked glycosylation and proteoglycan production, leading to altered function by glycosylation of proteins such as endothelial nitric oxide synthase. Chronic hyperglycemia of diabetes is associated with vascular and non vascular complications. The vascular complications are further subdivided into microvascular complications like retinopathy, neuropathy, nephropathy,and macrovascular complications like cardiovascular disease, peripheral arterial disease, cerebrovascular disease. Non vascular complications include infections, skin changes and hearing loss. The lung is rich in microvascular circulation and abundant connective tissue that raises the possibility of pulmonary damage by microangiopathic process, and non enzymatic glycosylation of tissue proteins induced by chronic hyperglycemia, rendering the lung a target organ in diabetic patients.[2]

METHODS:

The study was a hospital based observational study conducted between 2015 and 2017. After approval from the institutional ethics committee, written informed consent was obtained from all patients. 100 diabetic patients of both genders, in the age group of 35 to 60 years, attending medicine OPD/admitted in RRMCH were screened during this study. Patients with any acute or chronic respiratory diseases, like pneumonia, COPD, TB, known case of cardiac diseases, IHD, patients with physical disabilities that may affect pulmonary functions like spinal deformities, gross ascites, patients who are smokers, obese persons (BMI>30) were excluded from the study. Detailed history was taken. Thorough clinical examination was done, and patients were subjected to investigations, including routines, FBS/PPBS, HbA1c (immunoturbimetric test ERBA-XL 640), microalbuminuria (prietest ROBONIK), spirometry to assess pulmonary function (using MINISPIR S/N T03144), fundoscopy for retinopathy status, and nerve conduction study (Neuropack NIHON KOHDEN) Data collected were analyzed using SPSS V23.0. Descriptive and inferential statistical analysis was done. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in number (%). The following assumptions were made; 1. Dependent variables should be normally distributed, 2. Samples drawn from the population should be random, cases of the samples should be independent. ANOVA has been used to find the significance of study parameters between three or more groups of patients. Student T test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (intergroup analysis) on metric parameters. Levene's test for homogeneity of variance has been performed. The confidence limit for significance was fixed at 95% level with p value < 0.05.

RESULTS:

A total of 100 subjects, of both genders, who consented for the study, fulfilling the inclusion and exclusion criteria,were studied. 56% were males and 44% females. 26 males have duration of diabetes of less than 5 years. 30 males had duration of diabetes more than 5 years. Similarly, 21 females had duration of diabetes less than 5 years and 23 females had duration more than 5 years (Fig 1). The mean duration was 6.9 years. Among the patients studied, 58% had HbA1c more than 7.5%. 36% were in the range of 6.5 to 7.5%, and 6% wereless than 6.5% (Fig 2). Mean HbA1c was 7.86±1.32. Diabetic retinopathy was the commonest microvascular complication present in our study. The pulmonary functions test profile was normal in 30 patients. 67% had restrictive pattern of lung impairment and 3% had obstructive pattern of lung impairment (Fig 3). PFT test

parameters (FVC, FEV1, FEV1/FVC) were not significantly related to age of the patients. The FVC and FEV1 were significantly reduced in both genders (Table 1), whereas FEV1/FVC ratio measured percentage was more than predicted percentage and was not statistically significant. FVC and FEV1 were significantly reduced as the duration of diabetes increases, whereas FEV1/FVC ratio predicted and measured value was not significant (Table 2). PFT profile was not significantly related to HbA1c values of the patients studied (Table 3). FVC and FEV1 were significantly reduced in patients with microvascular complications, of which, diabetic nephropathy was closely associated with PFT. Among the patients studied, the most common microvascular complication was diabetic retinopathy (36%). 33% patients had neuropathy and 27% patients had nephropathy. 26 patients had only one microvascular complication, 14 had two, and 14 had all three microvascular complications each (Table 4).

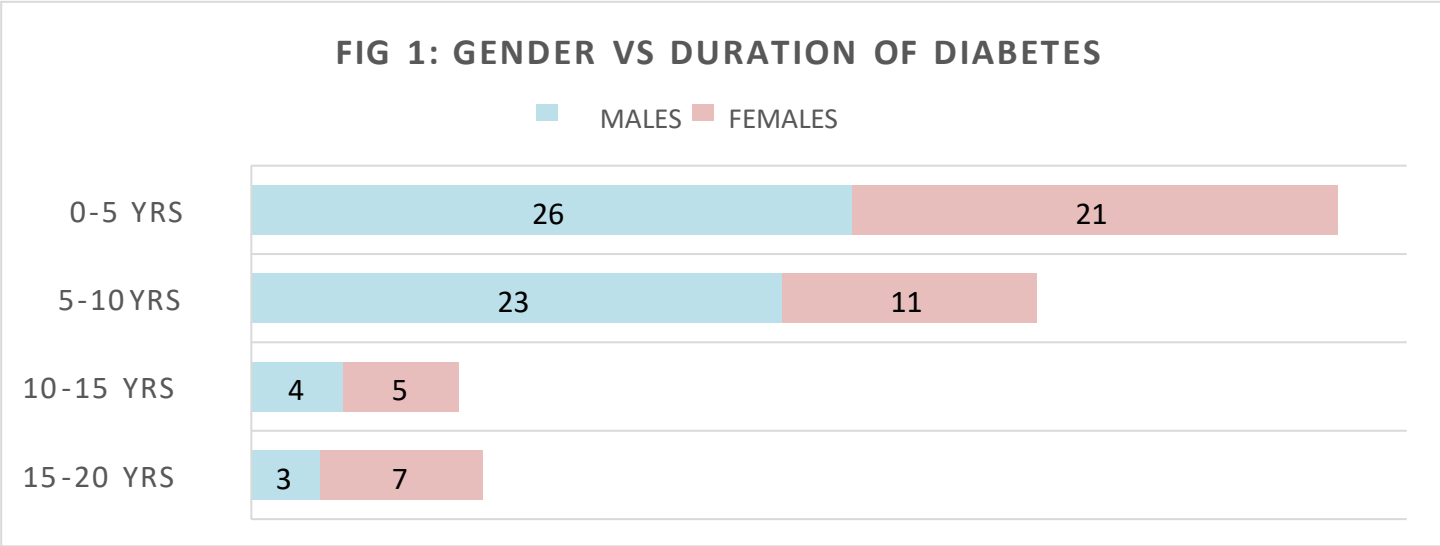


Table 1: PFT based on gender

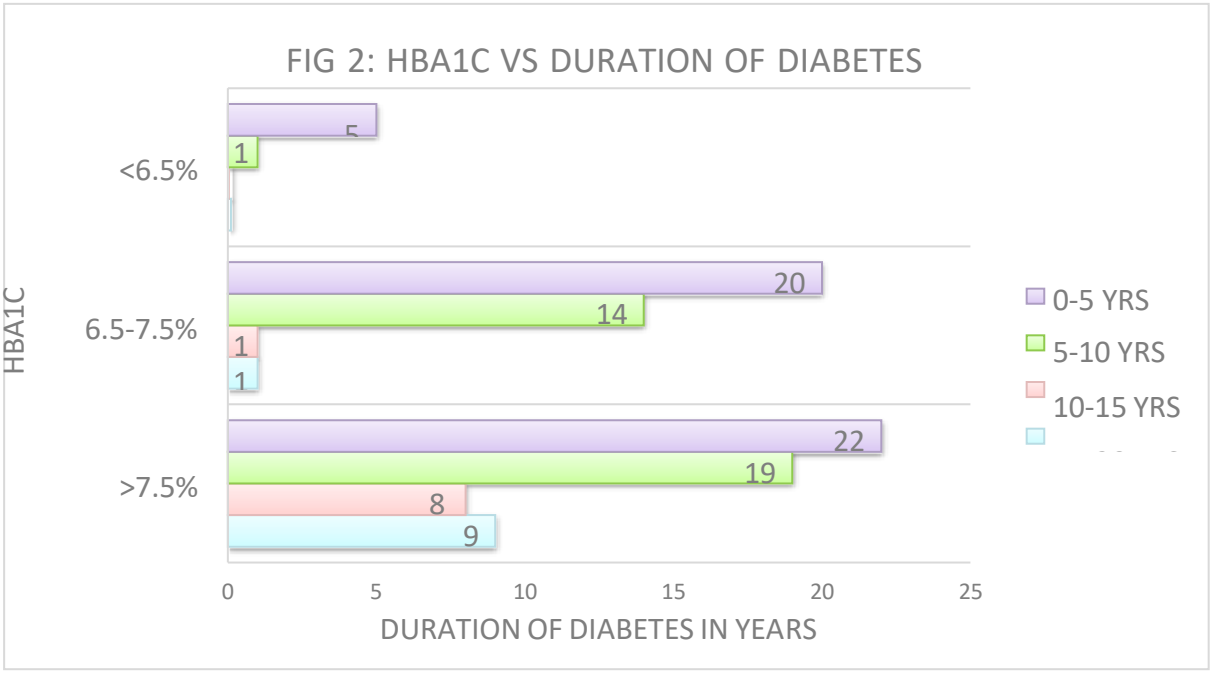
	Gender		Total	P value
	Male	Female		
FVC PRED	3.70±1.08	2.40±0.75	3.13±1.15	<0.001
FVC MEASURED	2.37±0.74	1.88±0.60	2.15±0.72	0.001
FVC PRED%	66.99±22.71	80.18±22.20	72.79±23.32	0.004
FEV1 PRED	2.34±0.63	1.77±0.48	2.09±0.63	<0.001
FEV1 MEASURED	1.83±0.56	1.44±0.50	1.66±0.57	<0.001
FEV1 PRED%	78.7±25.64	82.64±23.61	80.43±24.72	0.431

Table 2: PFT based on duration of diabetes

	DURATION OF DIABETES				TOTAL	P VALUE
	0-5yrs	5-10yrs	10-15yrs	15-20yrs		
FVC/PRED	3.15±1.10	3.28±1.15	3.53±1.30	2.11±0.79	3.13±1.15	0.020
FVC/MEASURED	2.40±0.71	2.06±0.67	2.15±0.64	1.35±0.30	2.15±0.72	<0.001
FVC/PRED%	80.72±26.32	65.88±17.39	62.94±20.49	67.92±18.10	72.79±23.32	0.013
FEV1/PRED	2.22±0.63	2.12±0.57	1.98±0.27	1.49±0.79	2.09±0.63	0.008
FEV1/MEASURED	1.85±0.59	1.58±0.53	1.57±0.38	1.15±0.23	1.66±0.57	0.002
FEV1/PRED%	84.36±21.19	76.59±24.11	79.97±27.90	75.46±37.97	80.43±24.72	0.497
FEV1/FVC PRED%	80.54±7.09	82.83±13.86	76.75±3.30	90.19±26.40	81.74±12.72	0.098+
FEV1/FVC MEASURED	78.07±11.45	75.69±13.97	74.63±10.62	86.26±8.86	77.77±12.33	0.095+
FEV1/FVC PRED%	98.35±16.69	94.06±12.56	97.75±16.30	103.18±22.7	97.32±18.99	0.559

Table 3: PFT parameters based on HbA1c

	HbA1c			TOTAL	P VALUE
	< 6.5 %	6.5 - 7.5 %	>7.5 %		
FVC PRED	3.07±1.44	2.97±0.95	3.23±1.23	3.13±1.15	0.556
FVC MEASURED	2.34±0.40	2.18±0.76	2.12±0.73	2.15±0.72	0.762
FVC PRED%	87.2±32.07	74.92±19.28	69.98±24.36	72.79±23.32	0.181
FEV1 PRED	1.97±0.48	2.17±0.69	2.05±0.61	2.09±0.63	0.591
FEV1 MEASURED	1.60±0.29	1.74±0.61	1.62±0.56	1.66±0.57	0.553
FEV1 PRED%	83.21±15.05	82.88±21.95	78.63±27.17	80.43±24.72	0.696
FEV1/FVC	78.17±18.13	81.61±10.83	82.18±13.37	81.74±12.72	0.764
FEV1/FVC MEASURED	70.63±12.39	78.60±13.75	78.02±11.32	77.77±12.31	0.311
FEV1/FVC PRED%	93.56±23.63	98.36±20.76	97.07±17.61	97.32±18.99	0.841



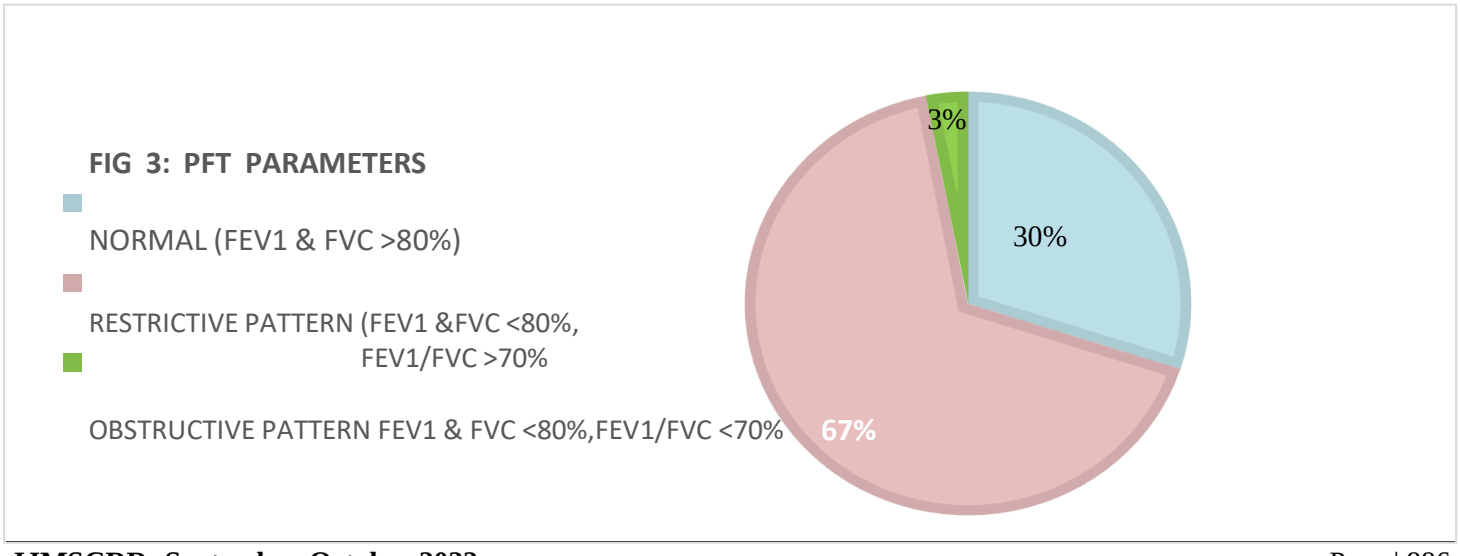


Table: 4 Complications

Complications	No. of patients
Diabetic nephropathy	27
Diabetic retinopathy	36
Diabetic neuropathy	33

Number of complications	Number of patients
No complication	46
One complication	26
Two complications	14
Three complications	14

DISCUSSION:

Type 2 Diabetes mellitus is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency.[3] This is typically a multi-organ chronic disease and is associated with a ten-year-shorter life expectancy due to its complications.[4] More than 20.9 million live births were affected by diabetes during pregnancy in 2015 - 1 in 7 births.[5] The countries with the largest number of people with diabetes are, and will be in the year 2025, India, China, and the US.[6] There is an alarming increase in the incidence and prevalence of diabetes mellitus (DM) in Asian Indians. Diabetes causes micro-vascular and macro-vascular complications with debilitating effects on many organs. The alveolar capillary network in the lung is a large micro-vascular unit and may be affected by microangiopathy.[7] However, because of its large reserve, substantial loss of the micro-vascular bed can be tolerated without developing dyspnea. As a result, pulmonary diabetic micro-angiopathy usually remains under-recognized clinically. As the duration of the illness progressed, there is a significant decline noted in the pulmonary function tests. In thepresent study, significant decline was observed in FVC and FEV1 as the duration of illness increased. Davis et al.[8] supported this concept as he found that there was a clear decline in PFT with an increase in the duration of DM. The same findings were consistent with the results met by Sinhs et al.[9] as they found a reduced ventilatory functionin diabetics and they related this observation to the chronic inflammatory process, the severity of which would increase with a longer duration of diabetes. In a study done by Mohammed Irfan et al.[10] demonstrated that diabetic patients had significant reduction in FVC and FEV1 relative to their non diabetic controls. They concluded that reduced lung function is a chronic complication of diabetes mellitus. There was no relation found between HbA1c levels and pulmonary function tests. The association was statisticallyinsignificant in our present study. Benbassat CA et al.[11] showed there is no correlation between HbA1c and PFT in their study. Microvascular complications had significant involvement in deteriorating lung functions. FVC and FEV1 was found to be reduced in patients with microvascular complications, of which diabetic nephropathy was closely associated with PFT variables compared to diabetic retinopathy and neuropathy. In the study by Weynand et al. [13] it was found that alveolar epithelium, endothelium capillary, and basal laminaes were thickened in the lungs on electron microscopy, when compared with the controls, and the thickening of basal laminae was of the same magnitude in lung and kidney. Moreover, reduced pulmonary capillary blood volume was found, favoring the evidence of microangiopathy. This could result in well ventilated areas to become under perfused. In a study conducted by Kornum JB et al.[14] concluded pulmonary dysfunction should be regarded as a specific derangementinduced by DM. The impairment in PFTs can lower the threshold for clinical manifestations of acute or chronic lung disease. Patients with DM admitted with pneumonia have increased risk of complications and mortality. In our present study, 67% of patients have restrictive pattern of lung impairment, 3% had obstructive pattern of lung involvement and 30% patients had normal pulmonary function test. FVC and FEVI significantly reduced and FEV1/FVC ratio increased signifies restrictive pattern of lung impairment and was statistically significant in our study. In a study conducted by P Zimmet et al.[15] it was found that persistent inadequate blood glucose control overtime may alter the regulation of inflammatory pathways that are involved in pulmonary function impairment; this impairment is mainly restrictive with obvious reduction in diffusing capacity to carbon monoxide. In a study conducted by Sanjeev Sinha et al.[16] he explained that the restrictive ventilatory dysfunction in diabetic patients include the involvement of the neuromuscular respiratory muscles due to diabetic neuropathy of the thoracic nerves that

contribute to the dysfunction. A study conducted on Indian Diabetes Kanya Kumari et al.[17] showed that FVC, FEV1, FEV1/FVC, PEFR, and FEF 25-75% were reduced when compared with predicted values. She also demonstrated that T2DM was associated with restrictive pattern of respiratory abnormality. As the duration of diabetes increases, the restrictive profile becomes more prominent. Diabetic patients are found to have significant reduction in the pulmonary function tests as the disease progresses. In the present study, there is a significant decline in both FVC and FEV1 suggestive of restrictive pattern of lung impairment as the duration of diabetes increases, but has no relation to glycemic status, and nephropathy is the most closely associated with these parameters.

SUMMARY & CONCLUSION:

Our study included 100 patients of both gender and the study was conducted in Rajarajeswari Medical College and Hospital over a period of 2 years. There were 100 patients studied in total and out of that there were 56 males and 44 females. The mean age of the study population was 53.6±8.28 The duration of diabetes mellitus is found to have significant relation with the impairment of lung functions. As the duration of the illness is progressed there is a significant decline noted in the pulmonary function tests. The mean duration of illness of the patients studied was 6.9+4.74 Significant reduction in spirometry values such as FVC and FEV1 are seen in almost 80% of the patients. FVC and FEV1 was significantly reduced in both males and females compared with the predicted values of the same. The results were statistically significant. There was no association between pulmonary function test profile values (FVC, FEVI, FEV1/FVC) and HbA1c. Both predicted and measured values were not significantly correlated in the patients studied. Microvascular complications had significant involvement in deteriorating lung functions. FVC and FEV1 was found to be reduced in patients with microvascular complications, of which diabetic nephropathy was closely associated with PFT variables compared to diabetic retinopathy and neuropathy. Diabetic retinopathy was the commonest microvascular complication present in our study which accounts for 36%of the total population studied. 33% of patients had diabetic neuropathy and 27% of patients had diabetic nephropathy respectively. 26 % of patients had only one microvascular complication. 14% of patients had two microvascular complications and 14% of patients had all the three microvascular complications. Restrictive pattern of lung impairment is most common in type 2 diabetes mellitus. In the present study 67% of the total patients studied had restrictive pattern of lung impairment. FEV1/FVC ratio was significantly increased in those patients.3% of patients had obstructive pattern of lung impairment. 30% of the study population had normal pulmonary function tests. Long standing uncontrolled type 2 diabetes causes various microvascular and macrovascular complications. In the present study reduced lung function tests (FVC & FEV1) and increase in the ratio of FEV1/FVC suggests restrictive type of pulmonary disease. The PFT parameters were affected more with longer duration of diabetes mellitus. In diabetic patients' strict glycemic control, regular breathing exercises to strengthen the respiratory muscles may improve the pulmonary function tests. Spirometry is a simple reliable noninvasive diagnostic tool and its regular use helps in early detection and to take easy preventive measures in diabetes.

DECALARATION:

I declare that this study is an original report of my research, has been written by me and has not been submitted for any previous degree. The collaborative contributions have been indicated clearly and acknowledged.

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