DOI: JCDR/2012/4107:2084

Original Article

Physiology Section

Respiratory Myopathy in Type II Diabetes Mellitus

NANDHINI R., SYED SAFINA S.S., SAIKUMAR P.

ABSTRACT

Background and Objectives: The incidence of Type II diabetes mellitus is on the rise in developing countries. It is well known that this metabolic disorder leads to a variety of multi-system complications, mainly in the eye, kidney, heart, and the nervous system. Since diabetes affects almost all systems of the body, much importance is given to micro-angiopathy, macro-angiopathy, retinopathy, and nephropathy. The most neglected system in diabetes is the respiratory system. Hence, this study was done to determine the respiratory muscle weakness in Type II diabetes mellitus.

Methods: This study design included 45 type II diabetic patients and 47 healthy non-diabetic volunteers (the sample size was adequate and the sample size calculation was done by our statistician). Pulmonary function tests were done by computerized spirometry (RMS Polyrite). The data which were obtained were analyzed statistically by using the Students 't'-test.

Interpretation and Conclusion: There was a consistent reduction in the spirometry parameters in type II diabetes; this could probably be due to respiratory muscle weakness or phrenic nerve demyelination.

Key Words: Diabetes Mellitus, Lung function, Myopathy, Spirometry

INTRODUCTION

India is witnessing an epidemic of diabetes mellitus [1]. The complication which is caused by diabetes mellitus has become a challenging health problem. Type II diabetes is by far the most common health problem, affecting 90 to 95% of the diabetic population [2]. The prevalence of Type II diabetes in Asian Indians is the highest prevalence in the world [3]. Diabetes is a systemic disease that produces changes in the structure and function of several tissues, particularly of the connective tissues, with complications that affect various systems. The presence of an abundant connective tissue in the lung and an extensive micro vascular circulation raises the possibility that the lung may be a target organ in diabetic patients [4].

The lung parenchyma displays a prominent viscoelastic behaviour [5]. The elastin in the lung parenchyma provides elasticity. The collagen fibres which are arranged loosely become tight only when the parenchyma is distended. Elastin is highly stretchable, while collagen is much stiffer. Collagen maintains the mechanical integrity of the organ. The chest wall and the associated respiratory muscles provide the external distending stress which maintains the lung in the state of inflation. Thus, the mechanical behaviour of the lung depends on the mechanical behaviour of its microstructural element. The microscopic properties of the parenchymal network influence both the elastic and the resistive properties of the lung [6]. Many studies have focussed on the declining pulmonary functions in type I diabetes, but very few have analyzed the pulmonary function in type II diabetics. Studies which have assessed the respiratory muscle weakness have been done, with parameters like maximal expiratory pressure (Pemax) and maximal inspiratory pressure (Pimax) [7,8]. The type I diabetics were found to have a more pronounced declining lung function than the type II diabetics. Pulmonary dysfunction may be one of the earliest measurable non-metabolic alteration in diabetes [4,9]. The major cause for this alteration is protein glycosylation which is responsible for thickening of the basement membrane of various tissues, leading to diffuse micro-angiopathy, demyelination, and chromatolysis of the axons and the Schwann walls [10]. The pathogenesis of the complications of diabetes is still a matter of debate and it is thought to involve both a micro-angiopathic process and the non-enzymatic glycosylation of the tissue proteins. The early enzymatic glycosylation end products are reversible. The advanced enzymatic glycosylation end products accumulate in the vessel wall, which is irreversible. In clinics, the respiratory muscle endurance is generally assessed by using one of the following techniques-Maximal sustainable voluntary ventilation (MSVV) [reported as a fraction of the actually measured MVV (Maximal voluntary ventilation)] and incremental threshold holding [11,12]. The respiratory muscle weakness is classified under restrictive diseases. Along with routine parameters like forced vital capacity (FVC), forced expiratory volume in one second (FEV1), peak expiratory flow rate (PEFR), forced expiratory flow (FEF25-75) and FEV1/FVC, maximum voluntary ventilation (MVV) is also done. Maximum voluntary ventilation (MVV), is the main criterion for the measurement of respiratory muscle strength and it has been interpreted in our study. From our study, it has been hypothesized that there is a strong association between respiratory muscle weakness and type II diabetes mellitus.

MATERIALS AND METHODS

The permission to conduct this study was obtained from the institutional ethical committee. The patients with type II diabetes mellitus, who were taking treatment in the Diabetic Outpatients Department of a hospital in Chennai, India from June 2010 to June 2011, who were without any respiratory illness and complications, were selected for this study. This study included forty five patients

(30 females and 15 males) with type II diabetes mellitus and forty seven healthy non-diabetic volunteers who were age and sex matched [10,13]. Their lung functions were measured by using the Spirometer model, RMS 401with the Helios software [7].

An informed written consent was obtained from all the subjects. A detailed history was obtained from both the control and the study groups. They underwent a physical examination, which included fundoscopy also. Their fasting and post-prandial plasma glucose and glycosylated haemoglobin levels were analyzed by a fully automated method (turbidity method-direct method). Pulmonary function testing was done for both the diabetic and the non-diabetic subjects. The pulmonary function test was performed by using computerized spirometry (RMS Polyrite). The performance of the pulmonary function test was demonstrated. The FVC, PEF, FEV1/FVC%, FEF25-75% and MVV were recorded thrice in the sitting posture at 11am everyday and the best of three readings was taken for the statistical analysis. The values were calibrated everyday before the start of the record.

The instrument is designed for lung function screening [14,15]. The Spirometer model RMS HELIOS 401 is an apparatus which measures the volume of air which is inspired and expired by the lungs. It has a precision differential pressure transducer for the measurement of the respiration flow rates.

The master charts of diabetics and non-diabetics were prepared along with the predicted and the percentage predicted values. The statistical analysis was done by the Student's 't'-test, which was used to find the significant difference of pulmonary function parameters between the healthy non-diabetic controls and the type II diabetic cases. The descriptive statistics for the anthropometric, biochemical and the lung function parameters were computed by arithmetic mean and standard deviation. Pearson's correlation co-efficient was used to quantify the extent of the relationship between the PFT parameters and other quantitative variables. SPSS version 15.0 was used for the statistical analysis. All the statistical tests which were used for the analysis were two tailed. A p value of <0.05 was considered as statistically significant.

[Table/Fig-1]: SPIROMETER model RMS HELIOS 401

RESULTS

A total number of 92 subjects were suitable for the analysis. There were 45 diabetics (study group) and 47 non-diabetics (control group). The mean age of the non-diabetic group was 44.04 years, with a range of 35-55 years of age. The mean age of the diabetic group was 47.09, with a range of 31-57 years of age. The subjects were closely comparable in their age distribution within the groups. [Table/Fig-2] The duration of diabetes ranged from 3 months to 22 years, with a mean duration of 6.29 years and an SD of 5.02 years [Table/Fig-3].

Overall, the level of control of the blood sugar among the diabetics appeared to be good, since all of them were on oral hypoglycaemic agents. The mean FBS value was 128.44mg/dl, with an SD of ±46.67mg/dl, which ranged from 68mg/dl to 236mg/dl. The mean PPBS value was 211.89mg/dl, with an SD of ±68.24mg/dl, which ranged from 98mg/dl to 359mg/dl [Table/Fig-4].

The mean Spirometric values were consistently low in diabetics as compared to those in non-diabetics. The differences were statistically significant for all the parameters, which included FVC, FEV1, PEFR, FEF25-75, FEV1/FVC and MVV [Table/Fig-5].

The mean Spirometric values were assessed as the percentage which was predicted to overcome the variations which were caused due to the age, height and weight of the subjects. In the percentage predicted values, the diabetics had lower values as compared to the non-diabetics for FVC, FEV1, PEFR, FEF25-75 and FEV1/FVC. MVV. The significant effect of the diabetes appeared to be on FVC, FEV1, PEFR and FEF25-75. On FEV1/FVC, the differences showed a variable effect [Table/Fig-6].

There was a very rough correlation between the declining Spirometric values and the FBS and the PPBS values. The Pearson's correlation coefficient of the Spirometric values yielded a significance only between HbA1C and the percentage predicted values of FVC and FEV1. Also, the Pearson's correlation coefficient of the Spirometric values yielded a significance between BMI and the

group	Number	Minimum	Maximum	Mean	SD
Nondiabetics	47	35	55	44.04	6.58
Diabetics	45	31	57	47.09	6.68

[Table/Fig-2]: Age

Group	Number	Minimum	Maximum	Mean	SD
Diabetics	45	3months	22years	6.29	5.02

[Table/Fig-3]: Duration of Diabetes

	Number	Minimum	Maximum	Mean	SD
FBS	45	68	236	128.44	46.67
PPBS	45	98	359	211.89	68.24

[Table/Fig-4]: Blood glucose levels

Predicted values	Nondiabetic Mean ± ± SD	Diabetic Mean ± ± SD	P value
FVC	2.86 ± ± 0.62	2.57 ± ± 0.52	0.017
FEV1	2.27 ± ± 0.50	1.97 ± ± 0.46	0.005
PEF	7.32 ± ± 1.46	6.59 ± ± 1.37	0.016
FEF25-75	3.07 ± ± 0.69	2.62 ± ± 0.70	0.003
FEV1/FVC	79.38 ± ± 2.17	77.62 ± ± 2.73	0.001
MVV	113.57 ± ± 17.94	101.64 ± ± 17.58	0.002

[Table/Fig-5]: Spirometric results

% Predicted	Nondiabetics	Diabetics	P value
FVC	81.83 ± ± 21.91	60.78 ± ± 19.18	0.000*
FEV1	94.40 ± ± 27.36	67.64 ± ± 21.99	0.000*
PEFR	59.36 ± ± 24.44	47.87 ± ± 21.24	0.018*
FEF25-75	92.66 ± ± 42.98	71.02 ± ± 33.82	0.009*
FEV1/FVC	114.68 ± ± 7.79	112.40 ± ± 16.48	0.403
MVV	42.68 ± ± 18.46	47.87 ± ± 15.22	0.144

[Table/Fig-6]: Spirometric results
Significant P values*

% predicted	Age	Duration of diabetes	BMI	FBS	PPBS	HbA1C
FVC%	0.039	0.158	0.034	0.548	0.335	0.078
FEV1%	0.139	0.168	0.129	0.187	0.151	0.036
PEFR%	0.524	0.027	0.945	0.181	0.159	0.459
FEF25-75%	0.397	0.065	0.781	0.595	0.511	0.844
FEV1/FVC%	0.394	0.823	0.178	0.131	0.309	0.423
MVV%	0.170	0.197	0.646	0.762	0.639	0.306

[Table/Fig-7]: Regression analysis

percentage predicted values of FVC. Regression analysis revealed a significance between the duration of diabetes and the percentage predicted values of PEFR and FEF25-75 [Table/Fig-7].

DISCUSSION

The present study mainly focussed on the assessment of the ventilatory function in type II diabetes mellitus patients and its comparison with age and sex matched healthy non-diabetic controls. As the literature review suggested that the parameter MVV measures the strength of the inspiratory muscles, and as our results showed that there was muscle weakness in type II diabetes mellitus, this study focussed on the parameter MVV to detect the respiratory muscle weakness in the type II diabetes mellitus subjects. This study included more number of females as compared to males. The female preponderance was mainly due to the rejection of many numbers of male diabetics with a history of smoking.

The duration of diabetes in this study ranged from a minimum of three months to a maximum of twenty two years. Since all the patients were on oral hypoglycaemic drugs, their FBS and PPBS levels were all in fair control. Their glycated haemoglobin levels with a mean of 6.88, again showed a fair, long term control of their sugar levels. The BMI of both the diabetics and the non-diabetics with a mean of 26.35 and 24.43 respectively, also did not fall under the obesity category. The mean values of all the Spirometric parameters were all higher in the non-diabetics as compared to the diabetics.

The percentage predicted FVC values were consistently lower in the diabetics as compared to the non-diabetics, with a significant p value of 0.01. The results of this study were in agreement with those of Sanjeev et al and Maurizio et al. study [4,16]. They had demonstrated a consistent FVC reduction in their studies on non-insulin dependent diabetic patients. This reduction can be explained on the basis that in diabetes, thickening of the basal lamina occurs in the alveolar epithelium and the pulmonary capillary. Also, due to the non-enzymatic glycosylation of the connective tissue, the elastic recoil of lung is reduced. This leads to the reduced FVC in diabetics.

The percentage predicted values of FEV1 were again consistently lower in diabetics than in non-diabetics, with a significant P value of 0.01. The findings of this study were in agreement with those of the study of Sanjeev Sinha et al [16], who demonstrated a decrease in the FEV1 values in diabetics as compared to those in non-diabetics. This reduction was due to the thickening of the alveolar epithelium and the pulmonary capillary basal lamina and also due to the reduced recoiling of the lung.

The PEFR values were again reduced in diabetics, with a significant p value of 0.01. The findings of this study were in agreement with those of the study of Wendy A. Davis et al [17] and Vinay Agarwal et al, which showed decreased PEFR values. The possible explanation for this reduction is the reduced force generating capacity of the expiratory muscle and the reduced recoiling of the lungs [17, 18].

The FEF25-75 was again reduced in diabetics, with a significant p value of 0.00. The findings of this study were in agreement with those of the study of Sreeja et al, which showed a significant reduction in the FEF25-75 values in diabetics. The initial part of an FVC curve indicates FEF25-75, which depends on bronchopulmonary factors like neuromuscular factors and the mechanical properties of the lung. Both were altered in diabetics, as was suggested by a literature review [19].

There was a rough decrease in the value of FEV1/FVC in diabetics as compared to that in non-diabetics, though it didn't reach a statistical significance. This result agreed with the results of the study of Vinay Agarwal et al, which showed decreased FEV1/FVC values in both males and females, thus suggesting a restrictive pattern of the disease.

The absolute MVV values were lower in diabetics, with a significant p value of 0.01. But the percentage predicted MVV showed a rise in the MVV values in diabetics, as compared to those in non-diabetics due to the descriptive variables such as age, height and weight [14]. This finding was in agreement with the findings of Sultan Ayoub Meo et al [20] and Vinay Agarwal et al [18], which showed reduced MVV values, thus reflecting the reduced strength of the respiratory muscles and the reduced compliance of the thorax-lung complex.

Overall, the literature review suggests that pulmonary dysfunction may be one of the earliest measurable non metabolic alterations in diabetes [18]. The major cause for this alteration is protein glycosylation, which is responsible for thickening of the basement membranes of various tissues, leading to diffuse microangiopathy, demyelination, and chromatolysis of the axons and the Schwann walls [21]. Since the phrenic nerve is the principal nerve supply of the respiratory muscles including the diaphragm, the observation of the reduced FEF25-75, PEFR and MVV values might be due to the phrenic nerve involvement and its alteration due to diabetes.

On comparison of the duration of diabetes with all the Spirometric parameters, a significant reduction was observed in the PEFR values though other parameters were also reduced with an increasing duration of diabetes, this but did not reach a statistical significance.

On comparison of the FBS and the PPBS values with the Spirometric variables, no statistical significance was found to be reached but a rough correlation was observed.

On comparison of HbA1C with the Spirometric values, a significant correlation was observed with FVC and FEV1. The poor lung function values were associated with a poor sugar control. A significant association was observed between HbA1C and the declining FVC and FEV1 values. This finding was in agreement with that of the Fremantile Diabetes Study which was done by Wendy

A.Davis et al, which indicated a poor lung function which was associated with a poor glycaemic control.

In our study, we found a predominant restrictive pattern of the disease, with a significant FVC and FEV1/FVC reduction, that was < 80% of that which was predicted. A reduced PEFR value indicated the reduced capacity of the expiratory muscles. Significant FEF25-75 values indicated reduced bronchopulmonary factors like the mechanical properties of the lung and also neuromuscular properties. The reduced MVV values indicated the reduced endurance of the respiratory muscles.

As the force generating capacity was predominantly observed to be reduced in diabetics, it indicated respiratory muscle weakness in the diabetics as compared to that in the non-diabetics. Since respiratory muscle weakness is classified under restrictive lung diseases, our study supported other researches, thus suggesting the weakness of the respiratory muscle in type II diabetes.

CONCLUSION

According to our study, there was a predominant restrictive pattern of the disease in type II diabetes mellitus, with a significant reduction of FVC and FEV1/FVC. A reduced PEFR value indicated the reduced capacity of the expiratory muscles. A significant decrease in the FEF25-75% values indicated the reduced mechanical and the neuromuscular properties of the lung. The reduced MVV indicated the reduced endurance of the respiratory muscles, thus indicating respiratory muscle weakness in diabetics.

In diabetes mellitus, thickening of the basement membrane of various tissues including the phrenic nerve tissue leads to demyelination and chromatolysis of the axons and Schwann cells, which would be the reason for the reduced respiratory muscle strength. The reduction in the respiratory muscle strength in type II diabetics in this study was indicated by reduced MVV, PEFR and FEF25-75 values. Thickening of the alveolar epithelium and the pulmonary capillary basal lamina and the reduced recoiling of the lung could be the reasons for the reduced spirometric parameters. Hence, an early detection of the reduced pulmonary function and the respiratory myopathy through simple spirometry as a routine test is essential for preventing the respiratory complication outcome which is caused by diabetes mellitus. In future, the same study can be extended by including parameters like respiratory pressures, diffusion capacity and non-volitional tests to assess the respiratory muscle strength in a larger sample group.

REFERENCES

[1] Wild S, Roglie G, et al. *Global Prevalence of Diabetes*: estimation for 2000 and projection for 2030. Diabetes Care 27(5): 1047-53.
[2] Ahmed AM. History of Diabetes Mellitus. Saudi Med J 2002 Apr;23(4): 373-78 [Pubmed].*Respiration* 2001;68:268-72.
[3] Albert RE KH, Herman NH. Global burden of diabetes, 1995-2025: Prevalence, Numerical Estimates and Projection. *Diabetes Care* 1998; 21: 1414-31.
[4] Marvisi M, Bartolini L, del Borrello P, Brianti M, Marani G, Guariglia A, et al. Pulmonary function in non-insulin dependent diabetes mellitus. *Respiration* 2001;68:268-72.
[5] Joshi AR, Singh R, Joshi AR. Correlation of the pulmonary function tests with the body fat percentage in young individuals. *Indian J Physiol Pharmacol* 2008; 52(4):383-88.
[6] Chandran CK, Nair RH, Shashidhar S. Respiratory functions in Kalaripayattu practitioners. *Indian J Physiol Physiol Pharmacol* 2004; 48(2): 235-40.
[7] Hamnegard CH, Wragg S, Kyroussis D, Aquilina R, Moxham J, Green M. Portable measurement of the maximum mouth pressures. *Eur Respir J* 1994; 7: 398-401.
[8] Nedel, et al. Reference values for the lung function tests. II. Maximal respiratory pressure and voluntary ventilation. Braz *J. Med Biol Res* 32(6)1999.
[9] Cavalheri V, et al. Effects of arm bracing on the respiratory muscle strength and the pulmonary function in patients with chronic obstructive pulmonary disease. *Rev Port Pneumol* 2010;16(6)887-91.
[10] Saxena Y, Saxena V, Dvivedi J, Sharma RK. Evaluation of dynamic function tests in normal obese individuals. *Indian J Physiol Pharmacol* 2008; 52(4): 375-82.
[11] Chadha AS, Pal P, Amudharaj D, Pal GK. Effect of gender in the assessment of pulmonary functions in pre-hypertensive and hypertensive subjects. *Biomedicine* 2009;29(4): 345-48.
[12] Bagavad GM, Rao M, Subhashini AS. Study of breath holding in young adults. *Biomedicine* 2010; 30(2): 216-21.
[13] Saxena Y, Sidhwani G, Upmanyu R. Abdominal obesity and pulmonary functions in young Indian adults: A prospective study. *Indian J Physiol Pharmacol* 2009; 53(4): 318-26.
[14] Evans JA, Whitelaw WA. The assessment of maximal respiratory mouth pressures in adults. *Respiratory care*. October 2009; 54 (10).
[15] Hogben K. Lung function testing equipment: What's in the future for spirometry and other tests? *A manufacturer's unbiased viewpoint*.
[16] Sinha S, Guleria R, Misra A, Pandey RM, Yadav R, Tiwari S. Pulmonary functions in patients with type 2 diabetes mellitus and their correlation with anthropometry and microvascular complications. *Indian J MedRes*, February 2004; 119: 66-71
[17] Davis WA, Knuiman M, Kendell P, Grange V, Davis TME. Glycaemic exposure is associated with reduced pulmonary function in type 2 diabetes.*The Fremantile Diabetes Study.* Diabetes Care 2004;27:752-57.
[18] Agarwal V, Gupta B, Dev P, Kumar Y, Ahmad N, Gupta KK. Deterioration of the lung functions in type II diabetic subjects from northern India. *Indian J Physiol Pharmacol* 2009; 53(2) 189-91.
[19] Sodhi C, Singh S, Dandona PK. A study of the effect of yoga trainingon the pulmonary functions in patients with bronchial asthma. *Indian J Physiol Pharmacol* 2009; 53(2): 169-74.
[20] Meo SA, Al-Drees AM, Ahmed Shah MAF, Al-Rubean K. *Assessment of endurance of the respiratory muscles in Saudi diabetic patients*.
[21] Subramaniam S. Textbook of Human Physiology. Chapter "*Physiological anatomy and respiratory movements*."

AUTHOR(S):

1. Dr. Nandhini R.
2. Dr. Syed Safina S.S.
3. Dr. Saikumar P.

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Physiology, Sree Balaji Medical College & Hospital, Chennai, Tamil Nadu, India.
2. Final year PG, Department of Physiology, Sree Balaji Medical College & Hospital, Chennai, Tamil Nadu, India.
3. Prof&HOD, Department of Physiology, Sree Balaji Medical College & Hospital, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. R. Nandhini, Associate Professor
T-2, Sindur Palace, 10 Thirumurthy Street, T. Nagar, Chennai-17
Phone: 9150716371
E-mail: nandhinisrikanth@yahoo.com.

FINANCIAL OR OTHER COMPETING INTERESTS:

None.

Date of Submission: **Feb 05, 2012**
Date of peer review: **Feb 27, 2012**
Date of acceptance: **Mar 22, 2012**
Date of Publishing: **May 01, 2012**