

## Effect of Phrenic Nerve on Type II Diabetes Mellitus

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### Abstract:

**Background:** Diabetes mellitus, which is one of the leading cause of morbidity, in developing countries. Diabetic neuropathy has emerged as an important complication, with increasing incidence & prevalence. Hence this study is focused to determine the phrenic neuropathy in type II diabetes mellitus patients.

**Aim & objective:** To evaluate the phrenic neuropathy in patients with type 2 diabetes mellitus and also to assess its effect on alteration in pulmonary function tests of these patients.

**Materials and methods:** Around 45 type II diabetic patients (males -15; females -30) attending Diabetology out patient department of Sree Balaji Medical College & Hospitals was recruited. They all belong to 35 – 55 years age. They were divided into three groups based on the duration of diabetes as < 5yrs, 5-10 yrs & >10 yrs. All the patients were subjected to do motor nerve conduction of phrenic nerve using Digital Polyrite & pulmonary function test using Computerized Spirometer. Results were statistically analyzed by Pearson Correlation coefficient test & ANOVA.

**Results:** There was a significant increase in latency ( $p < 0.05$ ) & decrease in nerve conduction velocity ( $p < 0.001$ ) of phrenic nerve. The spirometric variables as FVC, FEV1 & MVV were reduced in all these patients, whereas the FVC/FEV1 ratio was increased. Among the dynamic variables FEF 25% & PEFR was reduced in all the patients of varying duration. Moreover there was a significant negative correlation between MVV, FVC & phrenic nerve latency.

**Conclusion;** We conclude that phrenic neuropathy is the cause for restrictive pattern of lung disorder in type 2 diabetes mellitus patients.

**Key Words:** Diabetes Mellitus, Phrenic Nerve, Spirometric Variables

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### I. Introduction

Type 2 diabetes mellitus (T2DM) is the most common form of diabetes constituting 90% of the diabetic population. The number of patients with diabetes in India is currently around 40.9 million and is expected to rise to 101 million by 2030<sup>1</sup>. Diabetes mellitus is a syndrome of impaired carbohydrate, protein and fat metabolism caused by either lack of insulin secretion or decreased sensitivity of the tissues to insulin<sup>2</sup>.

Diabetes Mellitus comprises a group of common metabolic disorders that share the phenotype of hyperglycemia. The metabolic deregulation associated with diabetes mellitus causes secondary pathophysiologic changes in multiple organ system<sup>3</sup>. The chronic complications of diabetes mellitus include microvascular and macrovascular complications. The overall prevalence of distal peripheral neuropathy in India was 29.2%<sup>4</sup>. Diabetic neuropathy may manifest as polyneuropathy, mononeuropathy and autonomic neuropathy. As with other complications, the development of neuropathy correlates with duration of diabetes and glycemic control<sup>3</sup>.

The association of lung function abnormalities and diabetes mellitus has been described for many years<sup>5</sup>. Pulmonary damage at an early stage in most patients with diabetes mellitus is sub clinical, and rarely present with breathing complaints<sup>6</sup>. Moreover in patients with diabetes, as duration of the disease progress their lung function show a significant decline in all parameters of pulmonary function test.<sup>7</sup>

Various researchers have documented that Detoriation in the pulmonary function tests in diabetic patients is due to microangiopathy changes in lungs. Researchers have also observed that HbA1c is associated with both restrictive and obstructive lung disease. Meo et al., reported that the chest wall compliance, large and small airways are impaired in diabetic patients when compared to the normal subjects<sup>8,9</sup>. This study has been aimed to find out whether there exists any relation between phrenic nerve damage & pulmonary function test.

### II. Materials & Methods

This study was conducted in the physiology department of Sree Balaji Medical College & Hospital. We recruited 45 type II diabetic patients from Diabetology Out Patient Department, out of which 30 were males, 15 were females. They all belong to the age group of 35-55 years. We divided them into 3 groups based on the duration as < 5 years, 5-10 years & > 10 years. The study was approved by the institutional ethical committee. Questionnaire was given to all the subjects who participated in this study and a well informed written consent was obtained.

**Inclusion criteria:**

- a) Type 2 Diabetic patients
- b) Stable patients
- c) Non smokers
- d) Non practicing yoga individuals

**Exclusion criteria:**

The patients suffering from the following diseases were excluded from this study.

- a) Thyroid disorder
- b) Renal failure
- c) Liver diseases
- d) Bronchial asthma
- e) COPD
- f) Smokers
- g) Muscular disorders

**II. 1.Methods**

**Blood parameters:** Around 5ml of venous blood was collected from the patients in order to assess their fasting, post prandial blood sugar level & HbA1c value. The blood parameters were assessed in the central laboratory of Sree Balaji Medical College & hospital.

**Pulmonary Function Tests:** All the patients were subjected to do pulmonary function tests using computerized Spirometer. All the patients were well instructed to inspire air maximally and then breathe out to the maximum using the spirometer mouth piece & were encouraged to do three times. The best of the three values was considered for analysis.

**Nerve conduction study:** The patients were subjected to do phrenic nerve conduction study. They were made to lie supine over the wooden recording table and the recording electrodes were placed over the xiphi sternum & the corresponding side of the costal margin. The stimulation was given behind the posterior border of sternocleidomastoid, using stimulating electrode. The recordings were displayed over the monitor of the digital Polyrite.

**Statistical analysis:** The results were tabulated and all the values have been expressed in mean ± Standard deviation. Tests as ANOVA & Pearson correlation was used for analysis.

**III. Results**

Table 1. Physical characters and Blood Parameters of Diabetic Patients (n=45)

DURATION	< 5 YEARS (n=15)	5-10 YEARS (n=15)	> 10 YEARS (n=15)
AGE ( yrs)	43.6 ± 4.6 **	47.6 ± 6.3**	52 ± 3.7**
HEIGHT ( cm)	154.5 ± 7.5	155.5 ± 7.8	160.1 ± 9.1
WEIGHT (Kg)	60 ± 8	61.8 ± 8.5	65 ± 9.7
BMI (Kg/ m <sup>2</sup> )	25.2 ± 4.4	25.6 ± 4.3	25.2 ± 2.8
FBS (mg/dl)	114.5 ± 21.25*	136.9 ± 35.6*	151.2 ± 49.8*
PPBS (mg/dl)	198.4 ± 48.8	217.6 ± 45.2	219.9 ± 59.7
Hba1c (%)	7.2 ± 0.8	7.29 ± 0.97	7.42± 1.29

FBS - Fasting Blood Sugar; PPBS – Post Prandial Blood Sugar; BMI – Body Mass Index; HbA1c – Glycosylated Hemoglobin.\*\* - Highly Significant (p < 0.001). \* - Significant (p < 0.05)

The physical characters & blood parameters of all the diabetic patients have been displayed in table 1. It is clearly evident from the table that the fasting, post prandial & HbA1c values of the patients is increasing as the duration of the disease progresses.

Table 2. Right side phrenic nerve (motor) conduction study in diabetic patients of varying duration

Duration (n=15)	Latency (ms)	Amplitude (mv)	Conduction Velocity (ms)
< 5 years	10.2 ± 3.9	0.49 ± 57	3.44 ± 1.3 **
5 - 10 years	11.8 ± 2.4	0.45 ± 0.43	2.41 ± 0.73**
> 10 years	12.6 ± 5.6	0.37 ± 0.3	2.30 ± 0.62**

\*\* - Highly Significant (p < 0.001)

\* - Significant (p < 0.05)

Table 3. Left side phrenic nerve (motor) conduction study in diabetic patients of varying duration

Duration (n=15)	Latency (ms)	Amplitude (mv)	Conduction Velocity (ms)
< 5 years	8.94 ± 2.84*	0.51 ± 0.3	3.6 ± 1.6 **
5 - 10 years	9.15 ± 3.3*	0.49 ± 0.56	3.02 ± 0.61**
> 10 years	12.5 ± 4.8*	0.31 ± 0.31	2.84 ± 1.25**

\*\* - Highly Significant (p < 0.001)

\* - Significant (p < 0.05)

Table 2 & 3 shows the results of both sides' phrenic (motor) nerve conduction studies of diabetic patients of varying duration. It's understood from the above tables that as duration of diabetes progresses the latency increases whereas amplitude & nerve conduction velocity reduces significantly.

Fig 1 & 2 . Correlation between FBS & both side phrenic nerve latency

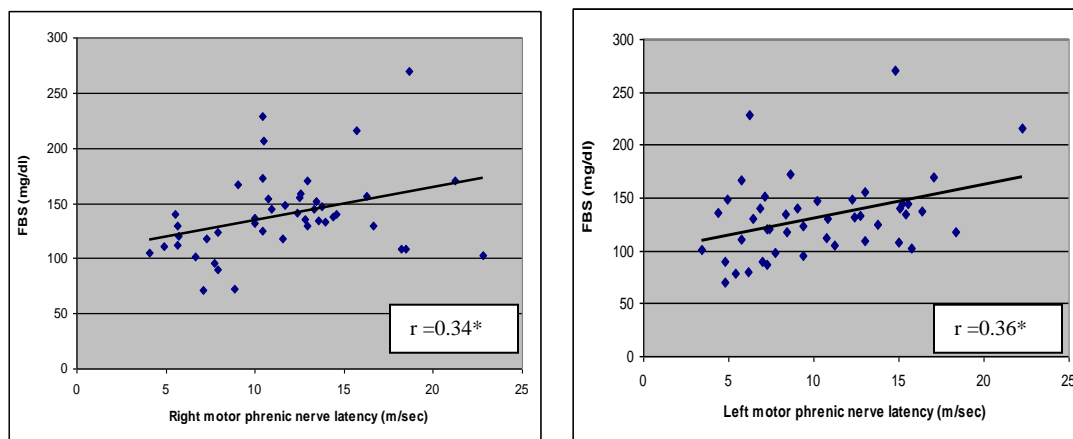


Fig1&2 shows significant positive correlation between fasting blood sugar and both side phrenic nerve latency.

Table 4. Spirometric variables in diabetic patients (n= 45) of varying duration

PARAMETERS	< 5 years (n=15)	5-10yrs (n=15)	>10yrs (n=15)
FVC (%)	54.13 ± 14.68	58.3 ± 16.24	52.74 ± 9.12
FEV1 (%)	49.47 ± 23.82	59.04 ± 20.84	59.82 ± 9.92
FEV1/FVC (%)	92.71 ± 35.8	106.7 ± 28.08	113.81 ± 8.77
MVV (%)	61.1 ± 27.1	62.17 ± 18.32	68.92 ± 11.07

Table 5. Dynamic variables in diabetic patients (n= 45) of varying duration

PARAMETERS	< 5 years (n=15)	5-10 years (n=15)	>10 years (n=15)
FEF25% (%)	46.13 ± 21.7	52.6 ± 18.4	55.8 ± 23.8
FEF50% (%)	76.9 ± 30.7	80.4 ± 21.5	80.8 ± 30.4
FEF75% (%)	100 ± 41	103.3 ± 21.6	114.2 ± 47.3
FEF 50-75% (%)	76.8 ± 31.4	83.4 ± 23.5	89.8 ± 34
PEFR (%)	50.55 ± 16.4	53.06 ± 18.7	58.1 ± 16.3

Table 4&5 shows the spirometric & dynamic variables of pulmonary function test in diabetic patients of varying duration. The FVC, FEV1, MVV values are reduced and moreover the reduction is more as the duration of the disease increased. The FEF 25% & PEFR value is also reduced, but the reduction correlated with

the duration of disease. Whereas the FEV1/FVC ratio and all other dynamic variables namely FEF50%, FEF75% and FEF 50-75% are above normal.

Fig 3 & 4. Correlation between FVC & both side phrenic nerve latency

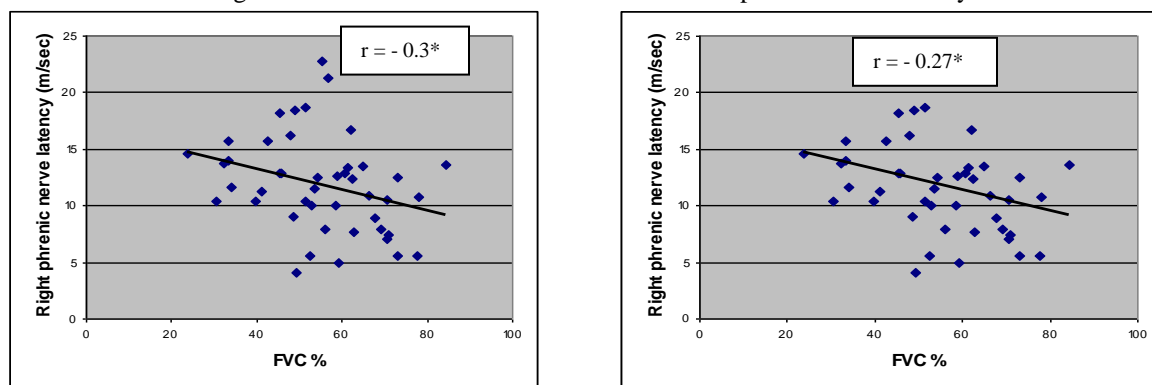


Fig 5 & 6. Correlation between MVV & both side phrenic nerve latency

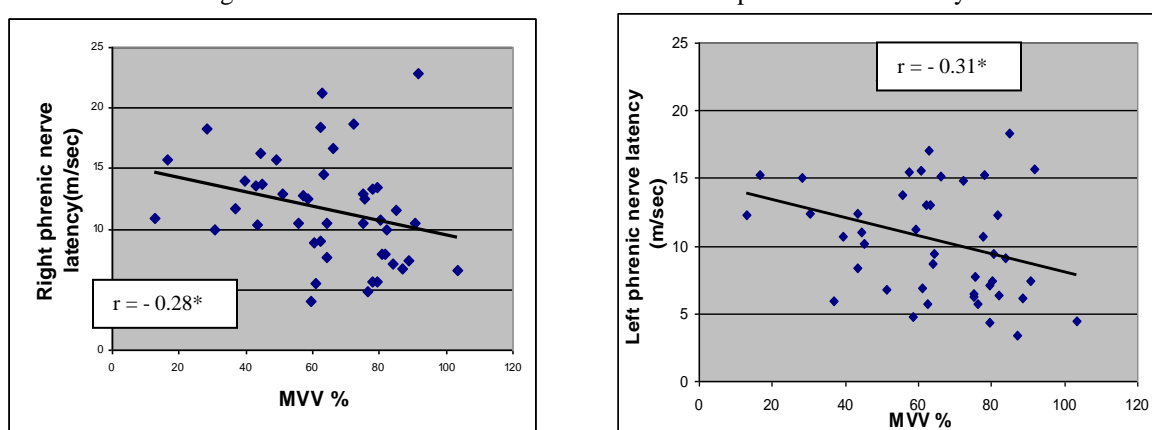


Fig 7 & 8 Correlation between right and left motor phrenic nerve latency with PEFR

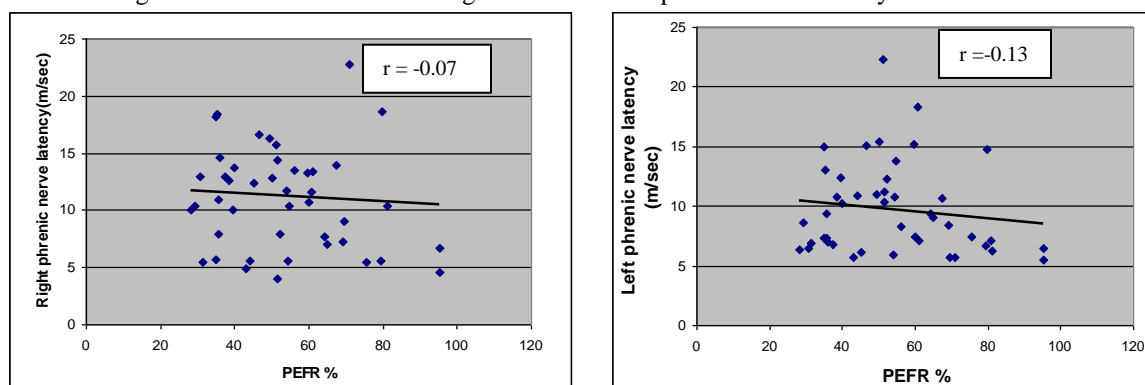


Fig3,4 ,5,6,7 & 8 shows significant negative correlation between FVC, MVV, PEFR and both side phrenic nerve latency. From this it is clearly evident that FVC , MVV & PEFR value as decreases the phrenic nerve conduction latency increases.

#### IV. Discussion

All our patients involved in the study, in spite of having regular medication, were suffering from higher mean values of fasting, post prandial blood sugar level and HbA1c; which was also found to be associated with duration of diabetes (Table 1). This observation was similar to that made by and MD Omar Ali et al.,<sup>10</sup> Sanjeev Sinha et al.,<sup>11</sup> Hence the severity of DSP (diabetic peripheral sensorimotor polyneuropathy) expressed by

electro physiologic criteria was significantly related to glycemic control in patients with type 1 or type 2 diabetes<sup>12</sup>. Prolonged, poorly controlled diabetes were risk factors associated with diabetic neuropathy.<sup>13</sup>

The latency of motor phrenic nerve conduction was increased in all the diabetic patients of varying duration; however the increase was significant in left side (table 2 & 3). The amplitude and the nerve conduction velocity of motor phrenic nerve were inversely proportional to the duration of disease. The increase in nerve conduction velocity was statistically significant. Figure 1 & 2 shows a significant positive correlation between fasting blood sugar and both side motor phrenic nerve latency. This proves that as hyperglycemia of the patients worsen, the latency of the motor phrenic nerve conduction increases. Our study is in par with that of Doaa Hanafy Mahmoud et al.,<sup>14</sup> and Tkac et al.,<sup>12</sup> who had proved that hyperglycemia, can alter the nerve function.

Table 4 describes the spirometric variables of all the diabetic patients of varying duration. The forced vital capacity (FVC) of the patients decreases whereas FEV1/FVC increases as duration of disease progressed. These results prove that as duration of disease progresses patients suffer from restrictive pattern of lung disease. Moreover figure 3 & 4 shows significant negative correlation between latency of right and left motor phrenic nerve and FVC; which means that the decrease in FVC is due to increase in the latency of phrenic nerve.

It has been proved that restrictive pattern of lung disease in diabetics is due to chronic hyperglycemia that leads to fibrous tissue formation in chest wall and bronchial tree protein (collagen) by non enzymatic glycation which causes reduction in lung compliance<sup>15,10</sup>. But our study proves that along with the above mentioned causes the major reason for decrease in FVC is the phrenic nerve damage.

In this study MVV was found to be reduced, < 80% however the value increased along with the duration of the disease (table 8). Our study results are not in par with that of Theodar Wanke et al.,<sup>16</sup> who stated that MVV did not correlate with the duration of diabetes. Thus this increase in MVV as duration progressed may be due to training effect on increased work of breathing. Marks J et al.,<sup>17</sup> has concluded in his study that above normal inspiratory muscle strength in asthmatics result from training effect of increased work of breathing. Thus the diabetic patients get acclimatized to their breathing pattern by increasing their work of breathing. Hence this might be the reason for the increase in respiratory muscle endurance as the duration of disease progressed and also the patients being asymptomatic.

Moreover figure 5 & 6 showed significant negative correlation between MVV and motor phrenic nerve conduction. As the latency of motor phrenic nerve increased the MVV value decreased. This once again proves that respiratory muscle weakness in our patients is due to phrenic nerve damage.

The mean values of FEF 25% were reduced than normal, but as duration of the disease progressed the values also increased (table 5). This indicates that all the diabetic patients in our study might suffer from small airway obstruction. The reason for this obstruction may be due to hyperglycemia which causes NO dependent endothelial dysfunction and decreased production of NO which ultimately lead to bronchoconstriction<sup>18,19</sup>

The mean values of both FEF 50% and FEF 25-75% were reduced only among patients <5 years duration (table 5) this was in par with the study done by MD Omar Ali et al.,<sup>10</sup>. In our study the mean values of both FEF 50% and FEF 25-75% was above normal in patients belonging to 5-10 years duration & >10 years duration. The reason might be that the patients suffer from obstructive pattern of lung disease during the initial stage of their illness and as duration of illness progresses they get shifted towards restrictive pattern. This can be clearly evidenced from the parameter PEFr.

Though the mean values of PEFr were very much reduced than normal (table 13). Figure 7 & 8 shows negative correlation between right and left phrenic nerve latency and PEFr. This proves that the decrease in PEFr diabetic patients in is due to reduced respiratory muscle strength which in turn is due to phrenic nerve damage.

The respiratory muscles perform the crucial function of sustaining ventilation<sup>20</sup>. The central muscle of respiration, diaphragm is innervated by the phrenic nerve which is the sole motor innervation to the diaphragm<sup>21</sup>. Though peripheral polyneuropathy is one of the commonest complications of diabetes mellitus, the attention towards the phrenic nerve is very negligible.

Earlier through various researches the reasons which were given for the reduction in lung volumes in diabetic patients are changes occurring in connective tissue, especially collagen and elastin, as well as microangiopathy due to a non-enzymatic glycosylation of proteins. In our study, we would say that the reduction in FVC, MVV & PEFr seen in our patients were due to reduced respiratory muscle weakness, which in turn was due to phrenic nerve damage. Our study is in par with that of Song SH et al.,<sup>24</sup> who had concluded that the diabetic patients with decreased pulmonary function might be related to phrenic neuropathy.

White JE et al.,<sup>23</sup> and Thomas H Brannagan et al.,<sup>24</sup> had reported that diabetic patient who had presented with symptoms of dyspnoea and ventilatory failure: on evaluation showed bilateral diaphragmatic paralysis due to phrenic neuropathy. Diabetes causes lower motor neuron type of paralysis<sup>21</sup>. Unilateral paralysis might not present clinically, but bilateral paralysis causes respiratory failure and might end in mortality.

Phrenic neuropathy should be considered as an important complication of diabetes. Phrenic nerve conduction should be assessed routinely like other peripheral nerves in order to prevent morbidity and mortality.

## V. Conclusion

We conclude that the reduction in lung volumes as FVC, MVV and PEFR in type 2 diabetic patients might be due to phrenic neuropathy. Phrenic neuropathy is the reason for restrictive pattern of lung disease in type 2 diabetes mellitus.

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## Limitation

Difference in nerve conduction velocity among patients taking oral hypoglycemic drugs and insulin was not done.

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