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A study of pulmonary function abnormalities in patients with Type 2 Diabetes mellitus

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Abstract: *Pulmonary function abnormalities in Type 1 diabetes has been evaluated in various studies but the data regarding this is scanty in Type 2 diabetes. The aim of this study was to assess the presence of pulmonary function abnormalities in Type 2 diabetic patients and to find out the co-existence of this with retinal and renal involvement abnormalities. 32 diabetic patients were taken into the study. They were divided into 2 groups: Group1- patients with retinopathy and or nephropathy and Group2- patients without any complications. An advanced spirometry was done on all patients which included pulmonary diffusion capacity (DLCO) which was done by single breath method. Results: There was a significant reduction in the pulmonary diffusion capacity (DLCO) in patients with evidence of diabetic microangiopathy .A linear relationship was found between the reduction in pulmonary diffusion capacity and the grade of retinopathy and Albuminuria. Conclusions: Reduction in lung diffusion capacity is common in diabetic patients with signs of microangiopathy.The possible pathophysiological mechanism could be a thickening of the alveolar epithelial and pulmonary capillary basal lamina in this group of patients.*

Keywords: *Pulmonary diffusion capacity, Type 2 diabetes, microangiopathy.*

I. Introduction

Diabetes mellitus is a systemic disease that causes secondary pathophysiological changes in multiple organ systems and the complications affecting these systems is responsible for the majority of morbidity and mortality associated with the disease[1].Several theories have been proposed to explain how hyperglycemia leads to end organ damage. These include[2]:

a) Formation of advanced glycosylation end products,
b) Glucose metabolism via sorbitol pathway,
c) Activation of protein kinase C and
d) Increased flux through hexosamine pathway.

These biochemical processes result in impaired collagen and elastin cross linkage with a reduction in the strength and elasticity of connective tissue[1, 3] which can cause both vascular and non-vascular complications. Vascular complications can further be subdivided into microvascular and macrovascular complications. The common microvascular complications include retinopathy, nephropathy and neuropathy. These complications are routinely screened for in all diabetic patients. Diabetes is not associated with any specific pulmonary symptoms and hence periodic screening for lung disease is not done in diabetic patients. However an extensive microvascular circulation and an abundant connective tissue in the lung raise the possibility that the lung may also be a 'target organ' in diabetic patients[4, 5].

There have been several studies which have studied pulmonary function abnormalities in Type1 DM[5, 6], but there are only a few studies which have measured lung function in Type 2 DM.

The global prevalence of diabetes is projected to be highest in Asian Indians by 2025 (57.2 million), hence it is pertinent to study pulmonary function abnormalities in this subgroup[7].

The aim of the present study is to detect lung function abnormalities in patients with Type 2 DM, with lung diffusion capacity for CO (DL_{CO}) as a marker for pulmonary microangiopathy.

II. Objectives

a) To assess the presence of pulmonary function abnormalities in Type 2 DM patients with DL_{CO} as marker of pulmonary microangiopathy.
b) To look for the co-existence of pulmonary angiopathy with retinal and renal abnormalities.

III. Materials

3.1 Design : Prospective non-randomized trial
3**.2 Setting :** M.S. Ramaiah Medical College, Bangalore, Karnataka, India
3.3 Inclusion criteria : All patients above 18yrs diagnosed to be suffering from Type 2 DM according to ADA criteria[17] was included in this study.

3.4 Exclusion criteria : Patients with any underlying pulmonary disease.
Patients with cardiac disease.
Smokers
BMI>30 kg/m2 [11].
3.5 Period of Study : September 2007 to September 2009

IV. Methods

After informed consent was obtained, all patients with proven Type 2 DM were screened for complications (retinopathy, glomerulopathy). Patients included in this study underwent the following investigations. FBS, PPBS, HbA1c, Hemoglobin, Spirometry and DLCO - Pulmonary function test), Chest Radiography, Echocardiography, Ophthalmoscopy, Urine routine examination. Pulmonary function abnormalities in patients with microangiopathic complications were compared with that in patients without complications. Further, the occurrence of pulmonary function abnormalities was correlated with the severity of other target organ involvement.

4.1 Definitions and cut-offs: Diabetes mellitus was diagnosed according to the American Diabetes Association and WHO criteria[17]. All patients included in this study had a BMI<30 kg/m^2 [11] .

4.2 Pulmonary function test: Chest X-ray was done to exclude the presence of pre-existing pulmonary disease. Ventilatory functions including forced vital capacity (FVC), forced expired volume in one second (FEV1) and peak expiratory flow rate (PEFR) were measured by spirometry according to the American Thoracic Society criteria[18]. DL_{CO} was done by single breath method. The single breath carbon monoxide diffusing capacity (DL_{CO}sb), also called the transfer factor (TLCO), was introduced by Marie and August Krogh in two papers[19]. Physiologically, their measurements showed that sufficient oxygen (by extrapolation from CO) diffused passively from alveolar gas to blood without the need to postulate oxygen secretion, a popular theory at the time. Their DLCOsb technique was neglected until the advent of the infra-red CO meter in the 1950s.
4.3How the test was performed: The subject is asked to breathe into a mouthpiece that is connected to an instrument called spirometer which records flow versus time. For some of the test measurements he can breathe normally and quietly. Other tests require forced inhalation and exhalation after a deep breath. He has to breathe through a tight fitting mouthpiece and with nose clips. Best of three satisfactory readings was taken for analysis. The technique was validated in our laboratory and the prediction equations for normal Indian subjects have been derived and reported previously[26, 27]. Normal values are based upon age, height, ethnicity, and sex. Normal results are expressed as a percentage. A value is usually considered abnormal if it is less than 80% of your predicted value.

4.4 Evaluations for the complications of T2DM:
4.4.1 Diabetic retinopathy: An experienced ophthalmologist performed the direct ophthalmoscopic examination on the patients. Retinopathy was defined as mild to moderate nonproliferative, severe non-proliferative and clinically significant macular edema[28].

4.4.2 Grading of retinopathy(International classification) [28] ICDR
Proposed by American Academy of ophthalmologists
- No DR
- Mild NPDR(microaneurysms only)
- Moderate NPDR(more than microaneurysms only but less than severe NPDR)
- Severe NPDR(any of the following , >20 intraretinal hemorrhages in each of the four quadrants, definite VB in two or more of the quadrants, prominent IRMA in one or more quadrant and no PDR)
- PDR (one or more of retinal neovascularization, vitreous hemorrhage or preretinal hemorrhage)

4.4.4 Diabetic nephropathy*:* Excretion of >150 mg of protein in urine over 24 h was defined as the presence of diabetic nephropathy after excluding urinary tract infection and other causes of renal *disease*[2] .

V. Results

5.1 Sex distribution of patients
32 patients were divided into 2 groups.
Group1: study group-15 patients.
Group2: control group-17 patients.

Table 1. Sex distribution of patients

Sex	Group1	Group2
Males	11	13
females	4	4

In this study, majority of patients were males (75%) and females constituted 25% of the study population.

5.2 Age distribution of the patients

Table 2. Age distribution of patients

Age	Group1	Group2
30-50	4	2
51-65	5	12
66-80	6	3

The majority of patients were aged between 51-65 yrs(53%). Patients were aged from 32yrs to 78yrs.

5.3 PFT parameters:

5.3.1 TLC (Total lung capacity):

Table 3. Total lung capacity

TLC	**Group1**	**Group2**
Normal	13	15
Reduced	2	2
Total	15	17

TLC <80 % of the predicted is reduced TLC.
Out of the 15 patients in group1, 2 (13 %) had reduced TLC . In group2, 2 (11 %) out of 17 patients had reduced TLC. No significant difference was noted between the 2 groups.

5.3.2 FEV_1 % (Forced Expiratory Volume 1st sec):

Table 4. Forced Expiratory Volume 1st sec %

FEV1 %	**Group1**	**Group2**
Normal	14	16
Reduced	1	1
Total	15	17

*FEV1 % <80 % of the predicted is reduced FEV1.
Out of 15 patients in group1, 1 (7 %) had reduced FEV1 %. In group2, 1 (6 %) out of 17 patients had reduced FEV1 %.
No significant difference was noted between the 2 groups.

5.3.3 FVC (Forced Vital Capacity):

Table 5. Forced Vital capacity

FVC	**Group1**	**Group2**
Normal	13	16
Reduced	2	1
Total	15	17

FVC<80 % of the predicted is reduced FVC.
Out of the 15 patients in group1, 2 (13 %) had reduced FVC. In group2, 1 (6 %) out of 17 patients had reduced FVC.
No significant difference was noted between 2 groups.

5.3.4 RV (Residual Volume):

Table 6. Residual Volume

RV	**Group1**	**Group2**
Normal	14	16
Reduced	1	1
Total	15	17

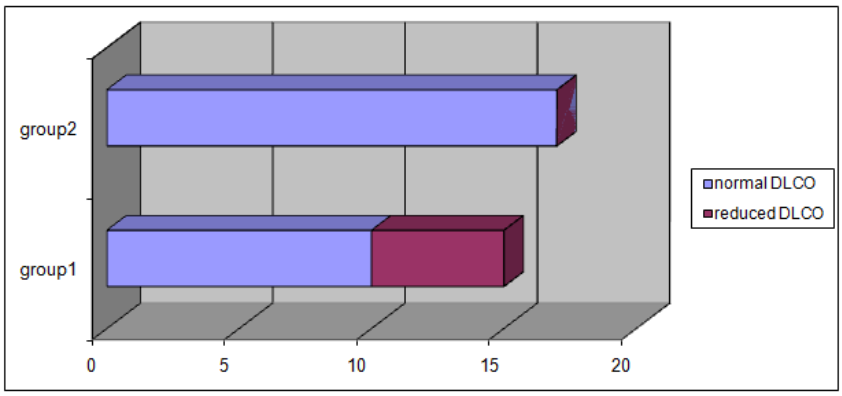
Out of the 15 patients in group1, 1 (7 %) had reduction in Residual volume. In group2, 1 (6 %) out of 17 patients had reduction in RV.
No significant difference was noted between 2 groups.

5.4 (Diffusing capacity of lung for CO) DL_{CO}

Table 7. DL_{CO}

DL_{CO}	Group1	Group2
Normal	10	17
Reduced	5	0
Total	15	17

Figure1. DL_{CO}



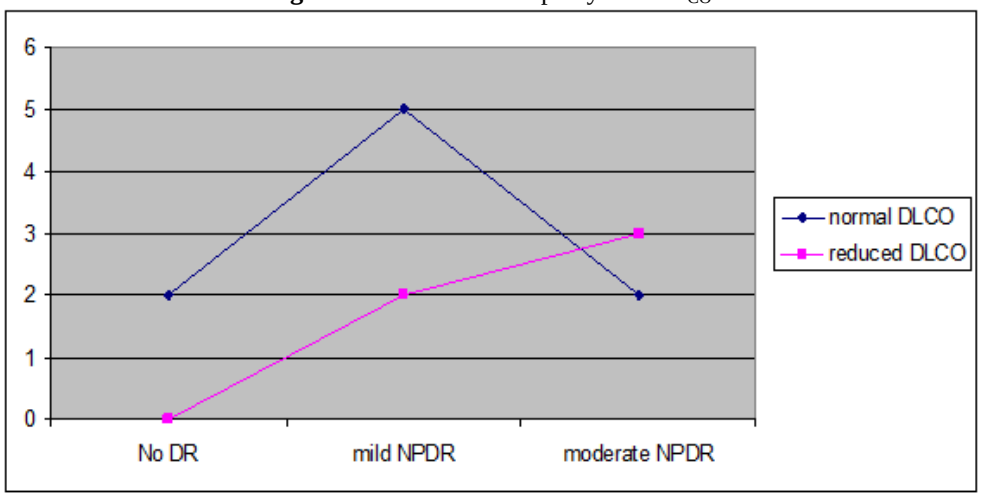
DL_{CO} < 80 % of the predicted is reduced DL_{CO}.
Out of the 15 patients in group1, 5 (33 %) had reduction in DL_{CO}. In group2,(0 %) none of the patients had reduction in DL_{CO}.
There is a significant difference between the 2 groups in the reduction of diffusing capacity with a 'p' value of 0.007.

5.4.1 DLCO and Diabetic Retinopathy:

Table 8. Diabetic retinopathy

Diabetic retinopathy	Number(Group1) (n=15)	%
NO DR	2	13.3
MILD DR	5	33.3
MODERATE DR	7	46.7
SEVERE DR	1	6.7

Figure 2. Diabetic retinopathy and DL_{CO}



5 patients with diabetes had reduction in DL_{CO}. All had retinopathic changes. 3 had moderate NPDR and 2 had mild NPDR.

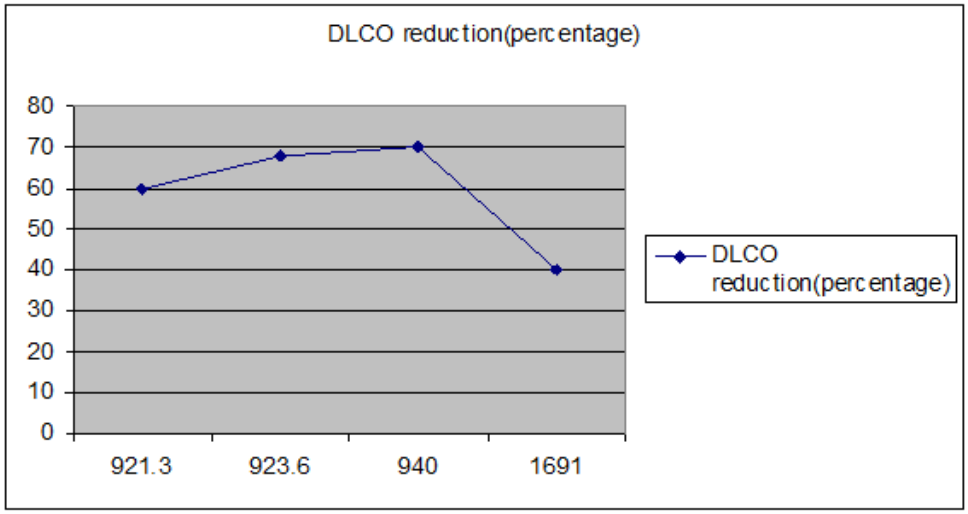
5.4.2 DLCO and Diabetic nephropathy:

Out of 5 patients with reduction in DL_{CO}, 4 had nephropathic changes.

Table 9. Diabetic nephropathy

24 hrs urine protein	Reduction in DL_{CO} (percentage)
921.3 mg/24 hrs	60 %
923.6 mg/24 hrs	68%
940 mg/ 24hrs	70 %
1.6g/ 24hrs	40 %
100.4mg/24hrs	78%

Figure 3 . Diabetic nephropathy and DL_{CO}

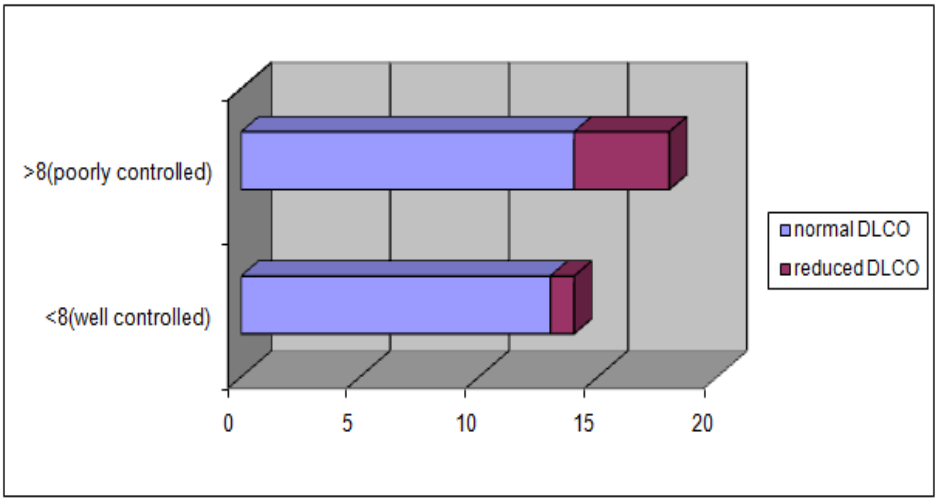


5.4.3 DLCO and Glycemic control:

Table 10. Glycemic control

	Group1		Group2	
HbA1C	**<8(well controlled)**	**>8(poorly controlled)**	**<8(well controlled)**	**>8(poorly controlled)**
Normal DL_{CO}	5	5	9	8
Reduced DL_{CO}	1	4	0	0
Total	6	9	9	8

Figure 4.Glycemic control and DL_{CO}



Out of the 14 patients in the well controlled group, 1(7 %) had reduction in DL_{CO}. In poorly controlled group, 4 (23 %) out of 18 patients had reduction in DL_{CO}. ($p = 0.06$, $r = 0.32$).

5.4.4 DLCO and BMI:

Table 11. Body mass index

	BMI(18-24)	BMI(>24)
Normal DL_{CO}	23	6
Reduced DL_{CO}	4	1
Total	27	7

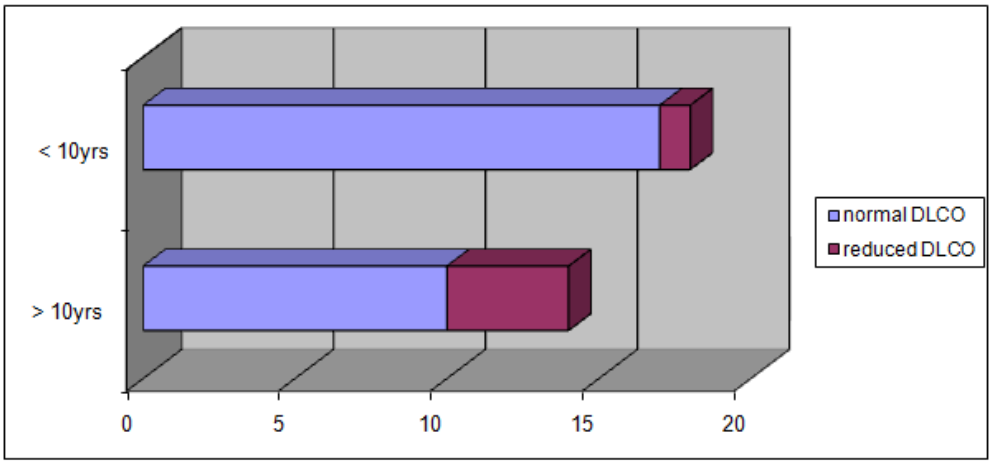
Out of the 27 patients in the BMI(18-24)group, 4 (15 %) had reduction in DL_{CO}. In BMI(>24)group, 1(14 %) out of 7 patients had reduction in DL_{CO}.
No significant difference between the 2 groups.

5.4.5 Duration of Diabetes and DLCO:

Table 12. Duration of Diabetes

	Duration of Diabetes	
	> 10 yrs	< 10 yrs
Normal DL_{CO}	10	17
Reduced DL_{CO}	4	1
Total	14	18

Figure 5. Duration of Diabetes and DL_{CO}



Out of the 14 patients in the >10 yrs duration group, 4 (26 %) had reduction in DL_{CO}. In the < 10 yrs duration group, 1 (5 %) out of 18 had reduction in DL_{CO}. (p value=0.053, r value=0.4).

5.5 Comparison of study characteristics in two groups of patients

Study characteristics	Group I	Group II	P value
Age in years	59.60±10.36	58.33±11.57	0.755
Duration of disease	9.80±5.87	7.07±4.73	0.053*
BMI (kg/m^2)	23.05±1.66	22.88±1.99	0.797
FBS (mg/dl)	139.93±46.08	141.13±57.21	0.950
PPBS (mg/dl)	201.07±61.56	212.47±73.08	0.648
Haemoglobin gram%	12.11±2.28	13.41±1.17	0.159
HbA1c %	8.79±2.25	8.11±2.18	0.062*
DL_{CO}	82.39±19.82	96.81±9.41	0.007*
TLC	85.47±9.61	88.58±9.72	0.386
FEV1%	98.56±9.68	92.48±12.42	0.148
FVC%	91.70±11.5	93.52±12.84	0.685

***** statistically significant

VI. Discussion

Diabetes mellitus (DM) is a metabolic disease characterized by absolute or relative insulin deficiency[32].Hyperglycemia and microvascular complications of retinopathy, nephropathy, and neuropathy are shared by type 1 and type 2 diabetes. Diabetes mellitus may involve the lung apart from kidneys, eyes and nerves since the pulmonary microvascular circulation is extensive and has abundant connective tissue[1.] Renal and retinal manifestations of diabetic microangiopathy have frequently been studied[33-38] and there are also several studies on diabetic microangiopathy in other organ systems[42-44] but pulmonary complications of diabetes

mellitus have been poorly characterized. Although some authors have reported normal pulmonary function, others found abnormalities in lung volumes, pulmonary mechanics, and diffusing capacity[42].

Many authors described a thickening of alveolar epithelial and pulmonary capillary basal lamina in human subjects with IDDM; others found ultrastructural changes in pneumocytes, bronchiolar epithelium and connective tissue proteins in rats with streptozotocin-induced diabetes[43]. The first physiopathologic change in microangiopathic complications is thickening of the basement membrane. Alveolar capillary membrane begins to thicken with longer diabetes duration, and this reflects itself both on ventilation functions and ventilation perfusion parameters[44].

The study of Weynand et al[45] shows basal lamina thickening of capillaries and epithelia in lungs and kidneys in a couple of diabetic patients. However, whereas basal lamina thickening of renal capillaries correlated well with the duration of diabetes, the pulmonary lesions did not. Weynand et al did not discuss the discrepancy of their results in detail. The discrepancy can be explained by functional differences or by differences in vascular pressure between the kidney and the lung.

The second study of Minette et al [46] on a small cohort of life-long non-smoking insulin-dependent diabetic patients could not demonstrate any differences in gas exchange compared to a carefully matched control group. One possible explanation is the huge reserve capacity of the lung which may compensate losses of even large amounts of functioning tissue. In view of the pathogenetic mechanisms, one may assume that in the lung diabetic lesions only develop if the capillary pressure rises. Since diabetic patients nearly regularly suffer from coronary heart disease, left heart failure is the most frequent cause of raised pressure in their pulmonary capillaries. Left heart failure, however, develops only late and not necessarily in each patient[47].

Regarding previously published data[4, 48-50] it is of paramount importance, in order to assess the influence of DM on transfer factor, to select life-long nonsmoking patients as it has been shown that both DL_{CO} and transfer factor were decreased even in asymptomatic smokers as compared to well-matched nonsmokers probably because of a mild degree of asymptomatic emphysema [51].Sandler, Bunn, and Stewart (1987) mentioned the decrease in DL_{CO}, which became more apparent with the increase in duration of Type 1 diabetes[4]. Mori et al. found out a decrease in DL_{CO}, and they mentioned that this decrease was independent of smoking and related with microangiopathy and seen especially in patients who had nephropathy and used insulin[52].

The significant observation in our study was impairment of DL_{CO} in T2DM patients with microangiopathy (ies). Ljubic et al[3] suggested a relationship between diabetic complications, particularly microangiopathy with collagen and elastin changes in lungs. In another study, on a larger number of patients with T2DM (n=80) a reduction of DL_{CO} in patients with diabetic microangiopathy was observed[47].DL_{CO} was reported to be significantly lower in patients with proliferative retinopathy vs patients with background retinopathy[15]. Isotani et al [15] carefully excluded patients with other risk factors, which could affect pulmonary flow volume curves. In our study, we found that patients with severe NPDR had greater reduction in DL_{CO} compared to patients with mild NPDR.

A significant correlation between reduction of DL_{CO} and the grade of albuminuria demonstrated a relationship of diffusion capacity derangement with other diabetic microangiopathic complications as well[1, 11]. In our study we arrived at similar findings. Absence of correlation between pulmonary function tests and the presence of microangiopathy or glycemic control has also been reported[52].Guazzi, Oreglia, and Guazzi noted that DL_{CO} improved with insulin infusion, but there were no variations in FEV and vital capacity. Gu¨vener et al found out a decrease in DL_{CO} in diabetic patients. However, Weir et al and C elik et al mentioned that they did not detect any difference in DL_{CO} in Type 1 and 2 diabetics[53-55].Fuso et al.[14] demonstrated, measuring postural variation of DL_{CO} and capillary blood volume, that in IDDM patients there is no significant increase in DL_{CO} in supine position.

It is also reasonable to expect that a decrease in DL_{CO} may occur with the increasing duration of diabetes[47], when prevalence of microangiopathic complications also increases.Gu¨vener et al (2003) have reported a negative correlation between the DL_{CO} and diabetes duration[56] . Our study observed a positive correlation between DL_{CO} and diabetes duration.Mousa et al. (2000) reported that the patients with poor glycemic control had abnormal 99mTc-DTPA[57] .We found that patients with poor glycemic control had greater reduction in DL_{CO} compared to patients with good glycemic control.

It might be possible hat further histological studies on pulmonary microvasculature and compliance measurements of the lung would give more informations about the reasons for reduced DL_{CO} values. At this point the following questions still need to be addressed. What is the significance of subclinical pulmonary dysfunctions in terms of the development of pulmonary disease? Can this mild reduction in diffusion capacity at rest impair exercise tolerance.

VII. Conclusion

- A significant reduction in DL_{CO} was observed in diabetic patients with nephropathy and retinopathy.
- A linear relationship was found between the grade of retinopathy and Albuminuria with reduction in DL_{CO}.

- There was a significant correlation between DL_{CO}, duration of diabetes and HbA1C.

VIII. Summary

The microvascular complications of diabetes mellitus mainly affect the renal, retinal and nervous systems. Recent studies show that it may affect the respiratory system, since the lung has got an extensive microvascular circulation. The aim of this study was to assess the presence of pulmonary complications inpatients with Type 2 DM the possible correlations between diabetic renal microangiopathy, retinopathy, age and diabetic control.Our study included 32 diabetic patients and the study was conducted over a period of 2 years. Out of these patients , 5 of them had reduction in the lung diffusing capacity. All 5 had microangiopathy. 4 of them had both retinal and renal involvement and 1 had only retinal involvement. This study shows that the impairment of pulmonary diffusion capacity for carbon monoxide was common in Type 2 DM patients having microangiopathy.

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