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Original Research Paper

Physiology

CORRELATION BETWEEN THE PARAMETERS OF DIFFUSION CAPACITY OF LUNG WITH DIABETIC NEPHROPATHY, A HOSPITAL BASED STUDY IN EASTERN INDIA

Dr. Md. Sadique Mallick — Associate Professor, Dept. of Physiology, N.R.S. Medical College, Kolkata

Dr. Md. Salim Uz Zaman* — Assistant Professor, Dept. of Physiology, Murshidabad Medical College, Berhampore, Murshidabad 742101 *Corresponding Author

ABSTRACT

Background: Diabetes mellitus is a systemic disease with complications involving eyes, kidneys, nerves and vascular system. The presence of an extensive microvasculature and abundant connective tissue raises the possibility that lung may also be a target organ in diabetes.

Aims and Objectives: To compare and correlate diabetic nephropathy with parameters of diffusion capacity of lung.

Methods: A total of 60 T2DM patients with or without complications of age group 35-55years and 60 age and sex matched control were included after inclusion and exclusion criteria. All subjects were evaluated for PFT with Diffusion capacity (DLCO) by single breath technique- INSPIRE HD –PFT) and status of nephropathy by microalbuminuria. DLCO was correlated with diabetic nephropathy. $p<0.05$ was considered as significant.

Results: There was significant ($P<0.05$) changes in diffusion capacity (DLCO% and DL/VA%) in cases compared to controls and significant deterioration of diffusion of lung in Diabetic nephropathy(microalbuminuria) and that was negatively correlated with DLCO% ($r=-o.53$) and DL/VA% ($r=-0.66$) .

Conclusion: There was significant impairment of diffusing capacity of lung in diabetic nephropathy cases compared to controls and also negative correlation found between microalbuminuria with diffusion capacity.

KEYWORDS : Type 2 diabetes mellitus, Diffusion capacity, Diabetic Nephropathy

INTRODUCTION

Diabetes mellitus is a systemic disease that causes secondary metabolic changes in multiple organs and the complications deteriorating these systems are responsible for large morbidity and mortality of the disease [1,2]. The pathophysiologic complications such as micro- and macroangiopathy involving kidney, eyes, nerve, heart and vasculature are also increasing, causing severe social burden. The pathogenesis of diabetic complications are thought to involve in non enzymatic glycosylation of tissue proteins and peptides of extracellular matrix, a microangiopathic process of vasculatures at elevated circulating glucose level[1,2,3] and biochemical processes result in impaired collagen and elastin cross linkage with a reduction in the strength and elasticity [2,3,4,5]. The common microvascular complications include retinopathy, nephropathy and neuropathy. Considering large vascular network and richness of collagen and elastin, the pulmonary system is prone to undergo microvascular damage affecting ventilation and diffusion[3,4,5,6]. It has also been suggested that pulmonary dysfunction is a non metabolic complication in T2DM [6]. Diabetic nephropathy is expressed by Microalbuminuria or macroalbuminuria (albumin/creatinine ratio) and 24 hours urine protein excretion and develops early with uncontrolled T2DM [1,3]. Diabetic nephropathy is due to effects of soluble factors (growth factors, angiotensin II, endothelin, AGEs), hemodynamic alterations in the renal microcirculation (glomerular hyperfiltration, increased glomerular capillary pressure), and structural changes(increased extracellular matrix, basement membrane thickening, mesangial expansion, fibrosis)[1,12]. The wide range of geographical and regional differences of diffusion studies of lung exist in India. As the diffusion studies are poorly characterized in eastern Indian diabetic populations, we intended to assess whether there was any correlation between diffusion capacity of lung with diabetic nephropathy.

AIMS AND OBJECTIVES

1. To compare the diffusion capacity of lung between the cases of type 2 diabetic nephropathy with age and sex specific controls.
2. To find out any correlation between diabetic nephropathy and the parameters of diffusion study of lung..

MATERIALS AND METHODS

After proper ethical clearance, a comparative cross sectional hospital based study was conducted at the Dept. of Physiology, R.G.Kar Medical college & Hospital in collaboration with Dept. of Medicine, Dept. of Biochemistry in the year 2011. Eighty type 2 DM cases, were systematically selected from patients attending Diabetic clinic OPD, R.G.Kar Medical College. Among them 60 patients were included following strict inclusion & exclusion criteria. Age & sex matched 60 healthy controls were included according to inclusion & exclusion criteria. Type 2 diabetes of age group between 35 to 55 years of both sexes with duration not <2 years were included.

Criteria for diagnosis of type 2 DM: The National Diabetes Data Group and World Health Organization have issued diagnostic criteria for DM based on the following premises[2,10].

For T2DM, age, family history, obesity, Basal insulin or C-peptide, CRP (in specific cases), complications at presentation were included.

Following patients were excluded from the study:

Smokers; history of respiratory diseases such as asthma, COPD, tuberculosis, ILD; H/O occupational exposure; H/O URTI & LRTI; Hypertension, H/O angina; CVA; Obesity (BMI>30 kg/m^2); known thyroid disorders, autoimmune disease like SLE, RA; Known kidney diseases, Hereditary peripheral neuropathy; individuals with unacceptable spirometric technique, due to various causes like obstruction of teeth or tongue, sub-maximal effort, air escape, effort, recent surgery.

Detailed history and clinical examinations were done and blood sample after overnight fasting was taken for the Fasting plasma glucose and post prandial plasma glucose (by Glucose Oxidase Peroxidase method using kit developed by Aspen Laboratories Pvt Ltd)[9,10], glycated hemoglobin

(HbA1C) level as an index of glycemic control (by Ion Exchange Resin method)[11]. Complete hemogram with hemoglobin level (as it influences on DLCO), serum urea, creatinine, Creatinine clearanc (by Cockcroft- Gault equation)[1] (in specific conditions), serum TSH, serum ANA, RF (for specific situations)

Special investigation for diabetic nephropathy:

Microalbuminuria estimation: Diabetic nephropathy was evaluated by Microalbuminuria in urine. Microalbuminuria is defined as 30–300 mg/d in a 24-h collection or 30–300 mg/mg creatinine in a spot collection (preferred method)[1,12]. In this study the albumin/creatinine excretion ratio was measured on morning spot urine in each subjects by using micoprotein kit (Pyrogallol Red method)[12].

Special investigation for diffusion of lung: (DLCO)

The Diffusion capacity for Carbon momoxide (DLCO) of the subjects of this study were measured by single breath ($DLCO_{sb}$) method using computerized DLCO measuring machine, - INPIRE- HD–PFT[14]. Best of three satisfactory readings was taken for analysis. The technique was validated in our laboratory and the prediction equations for normal Indian subjects had been derived and reported previously [14,15]. Normal values are based upon age, height, ethnicity, and sex. A value is usually considered abnormal if it is less than 80% of predicted value[14,15].

Statistical analysis: Data were analysed in SPSS software-version 17 (IBM, Chicago, Illinois, 2008)[16] with P value of <0.05 was taken as significant with 95% confidence interval

RESULTS AND ANALYSIS

Table 1: Comparison of Diffusion parameters between cases and controls:

Diffussion parameters of Lung	Cases Mean + SD	Control Mean + SD	P value
DLCO-PP	94.35(+18.635)	108.53(+13.128)	0.002*
DL/VA –PP	89.47(+12.636)	98.68(+7.890)	0.0001*

N.B. PP= Percent predicted *= signifant P value

There was a significant ($p<0.05$) impairment of the parameters of Diffusion capacity (DLCO% and DL/VA%) in cases than controls, DLCO% (P=0.002) and DL/VA% (P=0.0001).

Table 2: Comparison of diabetes indices, nephropathic indices and pulmonary diffusion parameters between diabetic subjects with and without nephropathy.

parameters	Mean	Mean	Valid N	Valid N	P value
	Neph+	Neph-	Neph+	Neph-	
Parameters –diabetic indecies					
FBS	224.5909	152.1579	22	38	**0.0000001**
PPBS	308.9545	222.6316	22	38	**0.0000001**
HbA1c	8.3600	6.3295	22	38	**0.0000001**
Parameters for nephropathy					
MicroAlb	127.6182	10.0105	22	38	**0.000002**
Urea	30.5909	25.7895	22	38	**0.000241**
Cr	0.9923	0.8082	22	38	**0.000874**
Parameters of pulmonary diffusion function					
DLCO_P	79.9545	102.6842	22	38	**0.000001**
DL_VA_P	79.3636	95.3158	22	38	**0.0000001**

Table 2 showing significant ($P<0.05$) comparison of diabetic indices(FBS,PPBS, HBA1c, microalbumin), nephropathic indices and lung diffusion parameters between T2DM patients with and without nephropathy. The DLCO% (P=0.00001) with DL/VA%(P=0.000001) maximally and significantly decreased in T2DM cases with nephropathy

Table 3: Correlation of lung diffusion parameters of T2DM patients with nephropathy (microalbuminuria):

Diffussion Parameters	r value	P value
DLCO% pred	-0.539	0.0001
DL/VA% pred	-0.662	0.0001

Diagram 1: Scatter diagram showing correlation of DLCO%, DL/VA% with microalbuminuria

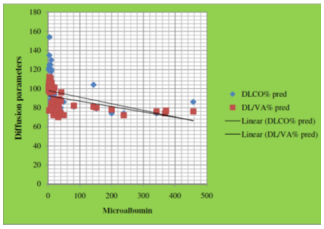

Table 3 & Diagram 1 showing correlation DLCO% pred.(r=-o.539,P=0.0001) and DL/VA%pred.(r=-0.662,P=0.0001) with microalbuminuria and negatively correlated with microalbuminuria.

DISCUSSION

Diabetic microangiopathy in kidneys, nerves, eyes have frequently been studied but pulmonary complications of diabetes have been poorly evaluated . As the prevalence of diabetes is increasing ,the potential implication of diabetic patients with overt pulmonary disease demand further attention.

From this study, we could say that lung diffusion capacity impaired significantly in T2DM with nephropathy and DLCO% and DL/VA% significantly correlated with microalbuminuria.

The findings of this study were not almost same to previous studies[2,3,7,18]. But larger population-based studies had been more consistent, demonstrating reduced pulmonary functions in patients of uncontrolled DM[19]. An Indian study[7] reported that the mean value of absolute uncorrected DLCO was significantly lower in patients with type-2 DM with microangiopathy as compared to those without microangiopathy and healthy controls. Ljubic *et al* [3] has demonstrated the relationship between pulmonary functions and chronic complications in diabetes with proteinuria as the significant independent predictor of DL/VA. Other studies[3,7,18] have observed only correlation between diffusing capacity and microalbuminuria. and spirometric values did not differ in the diseased and healthy controls. Asanuma *et al*[20], reported a significantly lower FVC in diabetics and a decreased diffusing capacity. In contrary, Bulbou *et al*[21] did not find any correlation between reduced diffusion capacity in diabetes with complications and also some other studies[22] have reported no significant difference in diffusing capacity between healthy subjects and diabetics.

The main pathophysiological mechanisms have been proposed as underlying impaired lung diffusion in diabetes.

- Non enzymatic glycosylation of connective tissue, especially collagen and elastin, which might be responsible for end organ damage causing structural alterations including lung tissue (thickened alveolar epithelial and pulmonary capillary basal lamina).
- Pulmonary diffusion capacity for carbon monoxide (DLCO) estimates the transfer of oxygen from alveolar gas to red blood cells and is determined by area of alveolar capillary membrane, thickness of the membrane and driving pressure of oxygen (Po_2). A combination of increased thickness of respiratory membrane and basal lamina, reduced pulmonary blood volume (V/Q mismatch), modification of surfactant activity and altered

affinity of HBA1c to carbon monoxide may impair the diffusion capacity in diabetes[3,5].

It has been suggested that the increased systemic inflammation associated with diabetes may result in pulmonary inflammation, and hence, airway damage[23]. Alternatively, a reduction in antioxidant defenses resulting from increased oxidative activity in diabetes may lead to a secondary reduction in the antioxidant defenses of the lung, and hence, resulting in loss of lung function[23].

A small sample size and non-measurement of TLC, cross-sectional study with no follow-up are the limitations of the present study. Further, histological studies on pulmonary microvasculature and compliance measurements of the lung would be useful to investigate for reduced DLCO values.

In conclusion, our study had shown an impairment of diffusion capacity of lung in diabetic nephropathy which was negatively correlated with the parameters of diffusion capacity.

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