TYPE 2 DIABETES MELLITUS AND DYNAMIC PULMONARY FUNCTION TESTS

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CONTENTS

INTRODUCTION

The pulmonary function tests are age old, but time tested parameters for assessing respiratory health of a person. These tests are important for clinical, diagnostic and prognostic values. till now, plenty of work has been done to assess the pulmonary function tests in health as well as in diseases.

There is alarming increase in the incidence and prevalence of Diabetes Mellitus particularly in Asian Indians[1].

In Type1 Diabetes lung function has been investigated in several clinical studies. These studies evidenced reduced elastic recoil[2,3], reduced lung volumes[4,5], diminished respiratory muscle performance[6], decreased in pulmonary diffusion capacity for carbon monoxide[7,8], But there are very few data concerning pulmonary function abnormalities in patients with type 2 diabetes mellitus[9].

Plenty of respiratory alterations have been reported in association with Diabetes Mellitus, including respiratory muscle dysfunctions, and chest wall abnormalities. Further more it is well known that Diabetes Mellitus may damage the autonomic nervous system of virtually all organs. In type2 diabetic populations there is evidence that the expression of neural damage may be more complex due to over lapping hormonal, metabolic and circulatory effects associated with old age.

The autonomic neuropathy of diabetic patients may influence the control of breathing. Parasympathetic regulation of airway calibre may be damaged in diabetes mellitus characterizing a Broncho motor dysautonomy[10].

Diabetes Mellitus is a systemic disease that produces changes in the structure and functions of several tissues particularly connective tissue with complications that affects the eyes, kidneys, capillaries and nervous system. The presence in the lung of an abundant connective tissue and extensive microvascular circulation raises the possibility that lung may be a **Target organ in diabetic patients [9].**

The alveolar capillary network by virtue of its large size is protected against overt respiratory complication at given level of systemic microvascular destruction. Hence lung function could provide useful measure of progression of systemic microangiopathy, and noninvasively quantifies physiological reserve in large microvascular bed[11].

In addition, an improved understanding of the natural history of diabetic lung function is needed in an era, when pulmonary delivery of insulin is actively being pursued as a treatment option[12].

Indeed, its time to add the spirometer to the tools available for monitoring Diabetes Mellitus and its important sequelae[13].

DIABETES MELLITUS
Diabetes mellitus is a clinically and genetically heterogeneous group of disorders characterized by abnormally high levels of glucose in the blood. The hyperglycaemia is due to deficiency of insulin secretion or to resistance of body cells to the action of insulin or to a combination of these. Often there is disturbance in fat, protein and carbohydrate metabolism[14].

It has been centuries since this syndrome was first recognized. The term **DIABETES** which is from the Greek meaning to pass through was first used by ARETAEUS of Cappadocia in the second century AD as a generic description for conditions causing increased urine output. The association of polyuria with a sweet tasting substance in the urine was first reported in Sanskrit literature dating from the 5th and 6th Century AD at the time of two notable physicians, Susruta and Charaka. The urine of certain polyuria patients was described as tasting like honey *madhumeda being sticky to touch and strongly attracting ant.[15]*

CLASSIFICATION OF DIABETES MELLITUS

Etiologic classification of diabetes mellitus[16]

I. **Type1 Diabetes B Cell destruction usually leading to absolute insulin deficiency.**
    a. Immune mediated
    b. Idiopathic

II. **Type2 Diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretary defect with insulin resistance).**

III. **Other specific type.**

 A. **Genetic defect of B cell function**
    a. Chr12 HNF –α (MODY3)
    b. Chr7 glucokinase (MODY2)
    c. Chr20 HNF -4α (MODY1)
    d. Chr13 insulin promoter factor1 (IPF1, MODY4)
    e. Chr17 HNF -1β (MODY5)
    f. Chr2 neuro D, (MODY6)
    g. Mitochondrial DNA
    h. Others

B. **Genetic defect in insulin action**
    a. Type A insulin resistance
    b. Leprechaunism
    c. Rapson Mendenhall syndrome
    d. Lipoatrophic diabetes
    e. Others

C. **Diseases of the exocrine pancreas**
    a. Pancreatitis
    b. Trauma/ Pancreatectomy
    c. Neoplasia
    d. Cystic fibrosis
    e. Hemochromatosis
    f. Fibro calculous pancreatopathy
    g. Others

D. **Endocrinopathies**
    a. Acromegaly
    b. Cushing's syndrome
    c. Glucagonoma
    d. Pheochromocytoma

    e.   Hyperthyroidism

    f.   Somatostatinoma

    g.   Aldosteronism

    h.   Others

E.   Drugs or chemical induced

    a.   Vacar

    b.   Pentamidine

    c.   Nicotinic acid

    d.   Glucocorticoids

    e.   Thyroid hormones

    f.   Diazoxide

    g. β Adrenergic agonists

    h.   Thiazides

    I.   Dilantin

    j. α-Interferon

    k.   Others

F.   Infections

    a.   Congenital rubella

    b.   Cytomegalovirus

    c.   Others

G.   Uncommon forms of immune mediated diabetes

    a.   Stiff man syndrome

    b.   Anti insulin receptor antibodies

    c.   Others

H.   Other genetic syndromes associated with diabetes

    a.   Down's syndrome

    b.   Klinefelter's syndrome

    c.   Turner's syndrome

    d.   Wolfram's syndrome

    e.   Friedreich's chorea

    f.   Huntington's chorea

    g.   Laurence moon Biedl syndrome

    h.   Myotonic dystrophy

    I.   Porphyria

    j.   Prader Willi syndrome

    k.   Others

IV.   Gestational diabetes mellitus
Epidemiology of diabetes mellitus
Global prevalence
The prevalence of diabetes for all age groups world wide was 2.8% in 2000 and is estimated to reach 4.4% by 2030.The total number of diabetics is projected to rise from 171million in 2000 to 366million in 2030[17].

Prevalence of diabetes in India.
The prevalence of diabetes in India is 2.4% in rural and 4 to 11.6% in urban dwellers. 20% of the current global population resides in South East Asia regions. India comprises 85% of the adult population of South East Asia and therefore the major contribution to diabetic in South East Asia is from India[18].

PATHOGENESIS OF TYPE2 DIABETES.
Type2 diabetes mellitus is characterized by three pathophysiologic abnormalities.

1. Impaired insulin secretion
2. Peripheral insulin resistance
3. Excessive hepatic glucose production

Obesity, particularly visceral or central as evidenced by the waist-hip ratio is very common in Type2 diabetes mellitus. Insulin resistance associated with obesity augments the genetically determined insulin resistance Type2 diabetes mellitus. Adipocytes secrete a number of biologic products (Leptin, tumour necrosis factor A, free fatty acids) that modulate processes such as insulin secretion, insulin action, and body weight may contribute to the insulin resistance.

In the early stages of disorder glucose tolerance remains normal despite insulin resistance, because pancreatic   cells compensate by increasing insulin output. As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets becomes unable to sustain the hyper insulinemic state impaired glucose tolerance marked by elevation in post prandial glucose then develops. A further decline in insulin secretion and increase in hepatic glucose production lead to overt diabetes with fasting hyperglycaemia. Ultimately beta cell failure may ensures[14].

Metabolic abnormalities

A. Insulin resistance

This is caused by the decreased ability of insulin to act effectively on peripheral target tissues (muscle, liver) and is a prominent feature of type2 diabetes. Resistance to action of insulin impairs glucose utilization by insulin sensitive tissues and increases hepatic glucose output both effects contributing to the hyperglycaemia of diabetes.

Increased hepatic glucose output predominantly accounts for increased Fasting Plasma Glucose levels, where as decreased peripheral glucose usage results in post prandial hyperglycaemia.

The precise molecular mechanism of insulin resistance in type2 diabetes mellitus has yet to be elucidated. Insulin receptor levels and tyrosine kinase activity in skeletal muscle are reduced, but these alterations are most likely secondary to hyperinsulinemia and are not a primary defects. Therefore post receptor defects are believed to play the predominant role in insulin resistance. A current focus for the pathogenesis of insulin resistance focuses on a PI-3 kinase signalling defect, witch causes reduced translocation of glucose transporter 4 (GLUT4) to the plasma membrane, among other abnormalities.

Another emerging theory proposes that elevated level of free fatty acid, a common feature of obesity may contribute to the pathogenesis of type2 diabetes in several different way free fatty acid can impair glucose utilization in skeletal muscle, promote glucose production by the liver, and impair beta cell function[14].

B. Impaired insulin secretion

Insulin secretion and sensitivity are interrelated in type2 diabetes. Insulin secretion initially increases in response to insulin resistance in order to maintain normal glucose tolerance. Initially insulin secretary defect is mild and selectively involves glucose stimulated insulin secretion.

The reason for the decline in insulin secretary capacity in type 2 diabetes mellitus is unclear. Despite the assumption that a second genetic defect super imposed upon insulin resistance leads to beta cells failure, intense genetic investigation has so far excluded mutation in islet candidate

genes. Islet amyloid polypeptide or amylin is co secreted by beta cells and likely forms the amyloid fibrillar deposit found in the islet of individuals with long standing type 2 diabetes mellitus. Whether such islet amyloid deposits are a primary or secondary event is not known. The metabolic environment may also impact islet function negatively for example chronic hyperglycaemia paradoxically impairs islet function (glucose toxicity) and leads to a worsening of hyperglycaemia, improvement in glycaemic control is often associated with improved islet function, in addition elevation of free fatty acid level (lipotoxicity) also worsen islet function[14].

C. Increased hepatic glucose production

In type2 diabetes mellitus, insulin resistance in the liver arises from the failure of hyperinsulinemia to suppress gluconeogenesis, which results in fasting hyperglycaemia and decreased glucose storage by the liver in the post prandial state. How changes in hepatic glucose flux lead to insulin resistance is not clearly defined.

The mechanisms responsible for the increasing hepatic gluconeogenesis include, Hyperglucagonemia, increased circulating levels of glucogenic precursors (lactate, alanine and glycerol) increased Free Fatty Acid (FFA) oxidation enhanced sensitivity to glucagon and sensitivity to insulin. Although majority of evidence indicates that increased gluconeogenesis is the major cause of hepatic glucose production in type2 diabetes mellitus, it is likely that accelerated glycogenolysis also contribute[14].

Table 2: Major risk factors for type2 diabetes mellitus

1. Family history of diabetes (parents or siblings with diabetes)
2. Overweight (BMI 25kg/m^2)
3. Habitual physical inactivity
4. Race/ ethnicity
5. Previously identified IFG or IGT
6. Hypertension (140/90mmHg in adults)
7. HDL cholesterol <35mg/dl(0.90mmol/L) and are a triglyceride level >250mg/dl (2.83mmol/L)
8. History of GDM or delivery of a baby weight >9lb
9. Polycystic ovary syndrome.

BMI-Basal metabolic rate, IFG-Impaired fasting glucose, IGT-Impaired Glucose Tolerance, GDM-Gestational diabetes mellitus

PATHOGENESIS OF THE COMPLICATION OF DIABETES MELLITUS

The morbidity associated with long standing diabetes of either type result from a number of serious complications namely retinopathy, nephropathy, and neuropathy. Hence the basis of these complications is the subject of a great deal of research. Most of the available experimental and clinical evidence suggests that the complications are a consequence of the metabolic derangements mainly hyperglycaemia. Multicentric clinical trials clearly show delayed progression of microvasculature diabetic complications by strict control of the hyperglycemia[19].

Several respiratory alterations have been reported in association with Diabetes Mellitus, including respiratory muscle dysfunctions, and chest wall abnormalities. Further more it is well known that Diabetes Mellitus may damage the autonomic nervous system of virtually all organs. In type2 diabetic populations there is evidence that the expression of neural damage may be more complex due to over lapping hormonal, metabolic and circulatory effects associated with old age[10].

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VASCULAR ABNORMALITIES IN DIABETES MELLITUS
Mechanism of Vascular abnormalities[20]
1. **Hyperglycaemia**
   Increased diacylglycerol
   Protein kinase C activation
   Increased sorbitol
2. **Hyperinsulinemia**
3. **Oxidative stress**
   Reactive oxygen species
   Carbonyl overload
4. **Advanced glycation end products (AGEs)**
   Activation of nuclear factors kappa B (NF kappa B)

Overproduction of inflammatory cytokines
5. **Dyslipidaemia**
    Small dense LDL
    Low HDL
    Hypertriglyceridemia
6. **Procoagulant antifibrinolytic state**
    Elevated fibrinogen
    Increased plasminogen activator inhibitor (PAI)
    Heightened platelet function
7. **Genetic abnormalities**
    Peroxisomal proliferation activating receptors-gamma mutation

ACTIVATION OF PROTEIN KINASE C IN DIABETES

In diabetes hyperglycaemia can lead to an increased concentration of the metabolite diacylglycerol in the cell. Diacylglycerol is a classic activator of a family of enzymes that performs key regulatory functions by phosphorylating proteins important in metabolic control. This family of enzymes known as protein kinase C has some dozen members. A great deal of recent work has implicated activation of the PKC family in the vascular complication of diabetes. Activation of PKC can inhibit expression of the endothelial forms of nitric oxide synthase and thus promote impaired endothelial vasodilatation function. PKC can also augment cytokine induced tissue factor gene expression and procoagulant activity in human endothelial cell.

Glucose induced activation of PKC can augment the production of extracellular matrices macromolecules that accumulate during atherosclerotic lesion formation

PKC activation can also increase the production of proinflammatory cytokines and the proliferation of vascular wall cell. In vivo evidence support a role of PKC activation in the pathogenesis of various aspects of vascular dysfunction[20].

NON ENZYMATIC GLYCOSYLATION

This refers the process by which glucose chemically attaches to the amino group of protein without the aid of enzymes. Glucose forms chemically reversible glycosylation products with protein (named Schiff bases) that

may rearrange to form more stable Amadori-type early glycosylation products, which are also chemically reversible. The degree of enzymatic glycosylation is directly related to the level of blood glucose.

The early glycosylation products on collagen and other long lived proteins in interstitial tissues & blood vessel walls, rather than dissociating, undergo a slow series of rearrangements to form irreversible advanced glycosylation end products (AGEs) which accumulate over the lifetime of vessel wall. AGEs have a number of chemical and biologic properties that are potentially pathogenic[19].

Chemical and Biologic properties of AGEs
Chemical properties
Cross-link polypeptides of same protein E.g.: Collagen
Trap non glycosylated proteins E.g.: LDL, Ig Complement
Confer resistance to proteolytic digestion
Induce lipid oxidation
Inactivate nitric oxide
Bind nucleic acid

Biological properties
Bind to AGE receptors on monocytes and mesenchymal cells

Induce
Monocyte emigration
Cytokines and growth factor secretion
Increase vascular permeability
Procoagulant activity
Enhanced cellular proliferation
Enhanced extracellular matric production

AGE formation occurs on proteins, lipids, nucleic acids. On proteins such as collagen, they cause cross links between polypeptides of the collagen molecules and also trap non glycosylated plasma or interstitial proteins.

In large vessels, trapping low density lipoproteins (LDL), retard its efflux from the vessel wall and enhances the deposition of cholesterol in the intima thus accelerating atherogenesis. In capillaries including those of

renal glomeruli, plasma proteins such as albumin bind to the glycosylated basement membrane, accounting in part for the increased basement membrane thickening characteristic of diabetic microangiopathy. AGE cross linked proteins are resistant to proteolytic digestion. Thus cross-linking decreases protein removal while enhancing protein deposition. AGE induced cross linking in collagen type IV in basement membrane may also impair the interaction of collagen with other matrix component (laminin, proteoglycan). Resulting in structural and functional defects in the basement membrane.

AGE binds to receptors on many cell types endothelium, monocytes, macrophages, lymphocytes, and mesangial cells. Binding induces a variety of biological activities, including monocyte emigration, release of cytokines and growth factors from macrophages , increased endothelial permeability, increased procoagulant activity on endothelial cells and macrophages and enhanced proliferation of and synthesis of extracellular matrix by fibroblasts and smooth muscle cells. All these effects can potentially contribute to diabetic complications[20].

The presence in the lung of an abundant connective tissue and extensive microvascular circulation raises the possibility that lung may be a **"Target organ in diabetic patients"**

PULMONARY FUNCTION TESTS
There are various pulmonary function tests. These tests provide quantitative and objective assessment of physiological derangement associated with pulmonary diseases. They do not give specific etiological or pathological diagnosis[21,22]. The tests can be divisible into three categories, and are as follows[23].

1. Tests to assess ventilatory function of lungs.
2. Tests to assess the exchange of gases across the lungs.
3. Tests to assess the transport of gases in the body.

A) TESTS TO ASSESS VENTILATORY FUNCTIONS OF LUNGS.
1) Assessment of expansion of lungs and chest wall
   a) Measurement of pressure changes.
       Ex: Intra pulmonary (Intra alveolar) pressure

       Intra pleural (Intra thoracic) pressure
- b) Measurement of compliance
  Ex: compliance of lungs and chest wall
  Compliance of lungs alone.

2) Assessment of restrictive and obstructive ventilatory defects
- a) Measurement of static and dynamic lung volumes and capacities measured by spirometry.
- b) Measurement of airway resistance. This provides a fairly good idea of
  - i) Physical fitness in normal individuals
  - ii) Type & Extent of derangement of lung functions in patients
- B) TESTS TO ASSESS GASEOUS EXCHANGE ACROSS THE LUNGS.
  - a) Measurement of Functional Residual Capacity.
  - b) Measurement of Dead Space and uniformity of Alveolar Ventilation.
  - c) Measurement of Diffusing Capacity of Lungs.
- C) TESTS TO ASSESS THE TRANSPORT OF GASES IN THE BODY.
  - a) Measurement of Gas Tension.
  E.g.: pO_2 pCO_2 in inspired, expired and alveolar air.
  - b) Measurement of gas tension, Acid-Base status of blood.

These pulmonary function tests may show alterations in physiological processes.

The static lung Function tests are: Tidal Volume (VT), Inspiratory Reserve Volume (IRV), Inspiratory Capacity (IC), Functional Residual Capacity (FRC), Vital Capacity (VC) and Total Lung Capacity (TCL).

The dynamic lung function tests are: Forced Expiratory Volume or Timed Vital Capacity (FEV or TVC), Maximum Ventilatory Volume or Maximum Breathing Capacity (MVV or MBC), and Peak Expiratory Flow Rate (PEFR).

The lung volumes and capacities (V_T, IRV, ERV, IC & VC) and also FEV and MVV can be measured by Spirometer. Peak Expiratory Flow Rate can be measured by mini Wright's Peak Flow Meter (WPFM).

FRC cannot be measured by simple Spirometer. It can be measured by Nitrogen wash out or Helium dilution method.

Volumes and Capacities

Definition: Volumes are basic entities while capacities are derived from volumes. Each capacity is the sum of two or more volumes.

LUNG VOLUMES:

a)   **Tidal Volume (V_T)**

It is the volume of air that is inspired or expired during each normal respiratory cycle.

Normal range-350 to 500 ml

b) **Inspiratory Reserve Volume (IRV)**

It is the maximum volume of air that can be forcefully inhaled following a normal inspiration from end inspiratory position.

Normal range- 2500 to 3000 ml.

c) **Expiratory reserve Volume (ERV)**

It is the volume of air that can be forcefully exhaled following a normal expiration from end expiratory position.

Normal range- 900 to 1100 ml.

d) **Residual Volume (RV)**

It is the volume of air that is remaining in the lungs at the end of maximal expiration. Normal range: 100 to 1200 ml

LUNG CAPACITIES:

a)   **Inspiratory Capacity** (IC).It is the maximum of air that can be inspired from resting Inspiratory level. It is about 3500 ml.
IC = VT + IRC

b**) Functional Residual Capacity (FRC)**

It is the volume of air that is remaining in the lungs at resting expiratory level.

It is about 2300 ml.

FRC = ERV + RV

c) **Vital Capacity (VC)**

It is the volume of air that can be forcibly exhaled after maximum inspiration.

It ranges from 3500 to 4000 ml.

VC = V_T + IRV + ERV

d**) Total Lung Capacity (TLC**)

It is the volume of air that can be present in the lungs at the end of maximum inspiration.

It is about 5800 ml.

TLC = VC + RV

DYNAMIC LUNG FUNCTION TESTS

Types of Dynamic Lung Tests[24]

1. Forced Expiratory Volume (Timed Vital Capacity)

It is the fraction of Vital Capacity that is exhaled at the end of first (FEV1), second (FEV2) or third (FEV3) second.

FEV 1% = Volume of air exhaled in the first second x 100

Normal values

FEV1 = 85% (85% of air comes out of the lungs in first second x 100)

FEV2 = 96%

FEV3 = 100%

FEV1 is limited by speed with which gas can be forced through the airways. Is is reduced in Obstructive Lung Diseases. As magnitude of FEV1 is always reduced in parallel with reduction in Forced Vital Capacity (FVC), even in the absence of obstruction, diagnostically FEV1/FVC is useful.

Normally, it is more than 75% (0.75) in healthy people and below 50% (0.5) is encountered in increased airway resistance as seen in case of Asthma.

2. Maximum Ventilatory Volume

It is the largest volume of air that can be moved in or moved out of lungs per minute by maximum voluntary ventilator efforts.

It is about 170 L/ min

3. Peak Expiratory Flow Rate (PEFR)[25].

It is the amount of air that can be blown out of fully inflated lungs as rapidly as possible.

Peak Expiratory Flow Rate achieved is recorded with a Peak Flow Meter. PEFR is the measurement that measures efficiency of lungs by recording maximum flow of air.

Peak Expiratory Flow Rate is dependent upon Age, Sex, Build[26].

It is about 10 L/Sec (6 to 15 l/sec)
In a young adult, it is about 400 L/min
It falls dramatically in cases of Chronic Obstructive Lung Diseases (COPD).

4. Maximum Expiratory Pressure (MEP).

Various respiratory symptoms are associated with respiratory muscle dysfunction. There are reports of progressive weakness of respiratory muscles in patients with multicore myopathy, multiple sclerosis, motor neuron disorder, malnutrition and congestive heart failure.

Measurement of strength of respiratory muscles is useful in order to detect the weakness of respiratory muscles and to quantity its severity. In patients with severe weakness of respiratory muscles. Vital Capacity is reduced, but is a non specific and relatively insensitive measurement. Conveniently, strength of respiratory muscles is evaluated by determining both Maximal Inspiratory Pressure (MIP) and Maximum Expiratory Pressure (MEP), during maximal static manoeuvre against a closed shutter.

However, studies showed that Maximal Expiratory Pressure alone can be used as a measuring tool for strength of respiratory muscles. MEP is useful in determining the ability of a person to cough effectively. This is of relevance to clinician in trying to predict the risk of developing Atelectasis, Pneumonia or gas exchange abnormalities in patients due to inability to cough effectively. A reduced MEP has also been seen to be associated with sensation of dyspnoea.

The strength of respiratory muscles is assessed by measuring Maximal Expiratory Pressure (MEP) by using a Modified Black's apparatus[27]. The apparatus consisting of a small cylinder of dimension specified by Black. The cylinder is connected to an aneroid pressure gauge. A three way connector connects the cylinder and pressure gauge to a Mercury Manometer. This allows the calibration check in the instrument. Maximal Expiratory Pressure is measured near Total Lung Capacity (TLC) after a maximal inspiration in sitting position. The pressure measured is maintained for at least one second. Three maximal expiratory efforts are to be done by each subject with rest period of one minute between each effort. The highest reading is accepted for statistical analysis[28].
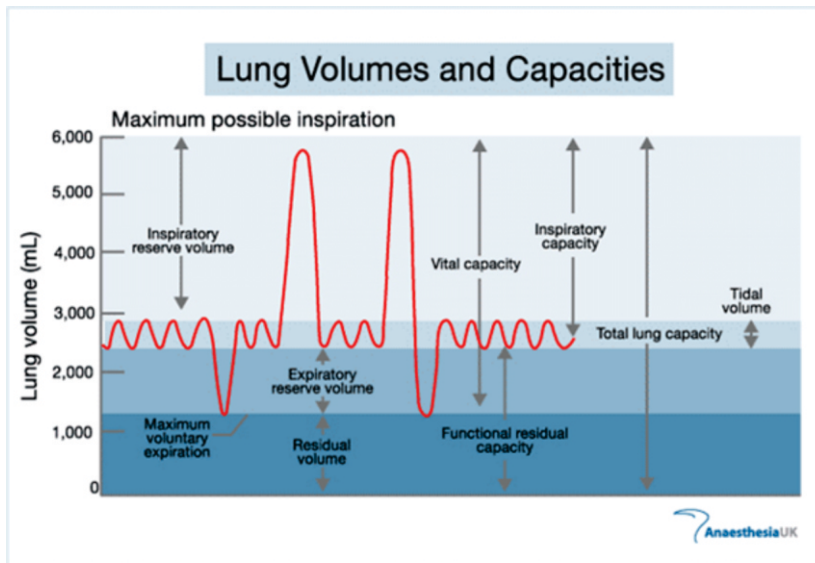

Figure: 1. Diagram showing different lung volumes and capacities.

REVIEW OF LITERATURE

Hippocrates (460-377 B.C.) and Galen believed that breathing is for cooling of the heart. Galen (130-211 A.D) gave idea that respiratory act depends upon the diaphragmatic contraction and chest wall movements.

Robert Boyles (1627-91) noted that air contains vital constituents required for life. In 1680 , G.A. Borllely[35] for the first time measured the inspiratory volumes and he also mentioned Residual volume (as quoted by Fenn 1976).

J. Black (1728-1799) discovered CO_2. Then, in 1800, Sir Humphery Davy measured the lung volumes by using Hydrogen. In 1846, John Hutchinson[35] measured vital capacity and made the subdivisions of lung volumes. The Functional Residual Capacity was measured by N. Grehent in 1880. Hermansen[35] in1933, introduced Maximum Breathing Capacity. At 1950 the unanimously agreed nomenclature was given by "United State respiratory Physiologists committee". In 1951 Tiffeneau and Pinelli and also Gaensler developed the technique for measuring timed volumes and the procedure. The procedure was referred to "Forced Vital Capacity manoeuvre" which quantifies the air volume dynamics and shows the rates of air flow along the respiratory tree and useful for obtaining pulmonary function tests. (Fenn 1965)[36].

Several respiratory alterations have been reported in association with Diabetes Mellitus including, respiratory muscle dysfunctions and chest wall abnormalities. Further more it is well known that Diabetes Mellitus may damage the autonomic nervous system of virtually all organs. The autonomic neuropathy of diabetic patients may influence the control of breathing[9].

It seems astonishing that the literature dealing with the effects of Diabetes Mellitus on human lungs is scanty, though the lung is equipped with an extended & extremely dense capillary system[37].

More than a quarter century ago, M Schuyler, Newoehner D, Inklay S(1976) investigated lung functions in 11 Young (21-28 years old) patients with type 1 diabetes and age matched normal control subjects. This classic study was the first to report measurement of nearly all the available tests of the lung functions, including lung elasticity, capacity to transfer carbon monoxide, absolute thoracic gas volumes, air flow resistance and maximal forced spirometric pulmonary function tests (PFTs). This was the first suggestion in the literature that the lung may be a target organ in Diabetes Mellitus.[3]

Bell & Colleagues (1988) observed proportional reductions in FEV_1 & FVC in 28 young individuals with diabetes compared with age & height matched control subjects. These changes were more pronounced among those with diabetes who smoked tobacco[38].

The cardiovascular health study((1993) in determining reference standards for a healthy population, found diabetes to be significantly associated with decreased FEV_1[39].

Innocenti & Colleagus (1994) demonstrated nearly equal reduction in FEV_1 & FVC in 24 insulin dependent non –smokers compared with control subjects[40].

Schnack & Colleagues (1996) compared 31 individuals with type 1 Diabetes who were never smokers were compared to healthy control subjects. There was significant reduction in lung function among those with diabetes, especially among those with microalbuminuria. This relationship was stronger for FEV_1 than for FVC[41].

In the Framingham heart study in 3254 members of Framingham offspring cohort, Robert E Walter (2003), have demonstrated an association between glycaemic state and reduced lung function with a difference of approximately 85 ml in residual FEV_1 & 94 ml in residual FVC from highest to lowest quartile of fasting blood glucose[42].

P. Lange (2002) in their longitudinal analysis of ventilatory capacity in diabetic and nondiabetic adults in the 17,506 adult participants of the Copenhagen City Heart study, which included 266 individuals with diabetes found that in both sexes, FEV_1 & FVC were consistently lower in diabetic individuals compared with healthy individuals with an average reduction of nearly 8% of the predicted value[12].

Devis (2000) found reduced spirometric pulmonary function (in comparison with normal population) in patient with type 2 diabetes, obesity, vascular disease, and duration of diabetes also contributed significantly to a reduction in the lung function[43].

In one recent Fremantle study (2004), reduced lung volumes and airflow are complications of type 2 diabetes. According to the results of a prospective trail, from community based cohort-495 patients of European origin with type 2 diabetes had baseline spirometry between 1993-1994, repeat spirometry was performed in 125 patients at a mean follow up of a 7 years. Mean percentage predicted values of each spirometric measures were decreased more than 10% in the whole cohort at baseline and absolute measures continued to decline at a annual rate of 68, 71, 84 ml / year & 17 ltr / min for FVC, FEV_1, VC & PEFR respectively in the 125 prospectively studied patients. Declining lung functions measures were consistently predicted by poor glycaemic control in the form of a higher updated mean glycosylated haemoglobin or follow up fasting plasma glucose[44].

Sanjeev Sinha, R. Guleria (2004) in their study concluded that, impairment of pulmonary diffusion capacity for carbon monoxide (CO) was common in type 2 diabetes Asian Indian patients having microangiopathy. Pathophysiologically it could be related to glycemic control or dyslipidaemia[45].

Engstrom reported association between lower values of spirometric PFTs and the incidence of diabetes in middle aged men[46].

In one study Davis Timothy M E(2000) et al, demonstrated that diabetes is associated with 9.5% reduced PEFR compared to age, gender, height matched non diabetic controls[43].

Type 2 Diabetes Mellitus and Dynamic Pulmonary Function Tests

In one Wisconsin Epidemiologic study Barbara E K et al (2001), demonstrated significant relationship between peak expiratory flow rate and glycaemia[47].

In one study Sanjeev Sinha et al, demonstrated statistically comparable decrease in MEP in Type2 diabetes patients compare to control group. They suggest that hyperglycaemia and dyslipidaemia might have a contributory role in its pathogenesis[45].

It is obvious from the literature that, most studies based on pulmonary functions in type 1 Diabetes Mellitus patients. However only a few studies have been based on pulmonary functions in type 2 Diabetes patients.

Possible mechanism of reduced lung function in type2 diabetes mellitus may be due to respiratory muscle weakness, because of glycosylation of proteins such as collagen in the chest wall and pulmonary tree.

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