Review

AN OVERVIEW ON ENDEMIC COPD

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ABSTRACT

COPD, the world's one of the most leading cause for morbidity and mortality and holds 4th position for causing death throughout the world. It has been estimated that, by the year 2020 COPD will become the third biggest cause of death. COPD has been found to causeemptying ofair from the lungs which gets progressively more difficult as it gets associated with cough,mucus production, wheezing and breathlessness.Risk factor include primarily cigarette smoking and other inhaled pollutants such as wood smokebut severalother factors are also responsible.Patientscarryingspecific genetic characters like α1-antitrypsin deficiency are susceptible towards COPD. So due to this factors there is severe inflammation in the respiratory tract which sometimes causes morphological changes such as hypercapnia,loss of elastic recoils of lungs etc. It may results in several co-morbidities which includes different heart disease,diabetes, etc.which adds to the large economic burden associated with this disorder.

KEY WORDS:- COPD, Risk factors; Epidermiology; Genetics; Cigarette smoking; Morphological changes, Hypercapnia,

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INTRODUCTION

The etymology of COPD started with the Greek word emphysema, meaning "to blow into", "air-containing" or"inflated".[1]COPD is a progressive chronic, complex, and incurable condition,which may result in declining pulmonary function, decreasing physical ability and loss of health related quality of life accompanied by symptoms such as anxiety, depression, fear, and fatigue.[2]But GOLD defines COPD as "a preventable and treatable disease with some significant extrapulmonary effects. Its pulmonary component is characterized by airflow limitation that is not fully reversible usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases."[3] COPD was described as "voluminous lungs" by Bonet in 1679 and as "turgid lungs particularly from air" described by Morgagni in 1769[1].

Risk factors for COPD:

•Genes

•Exposure to particles:

1. Tobacco smoke (10 pack Years; 50% smokers develop COPD)

2. Indoor air pollution from heating and cooking with biomass fuel in poorly ventilated homes (at least 25 years of exposures).

3. Occupational dusts, organic and inorganic: (attributable Risk 15% in American population)

a. Automobile-drivers, vehicular mechanics, fertilizer manufacturing, chlorinated organic compounds, dyes, explosives, rubber products, metal etching, plastics, ammonia exposure in refrigeration and petroleum refining, grain dust and funguses in farmers, textile mill manufacturing, leather manufacturing, food products manufacturing and sales, beauty care workers and welders in automotive industries.

b. Exposures to crystalline silica: cement industry, brick manufacturing, pottery and ceramic work, silica sand, granite and diatomaceous earth industries, gold mining, and iron and steel founding.

4. Outdoor air pollution

•Reduced Lung volumes:

1. Lung growth and development

2. Previous Tuberculosis (28-68% cases of post-treated TB; 2.9-6.6 folds increase risk)

3. Early childhood Recurrent Lower Respiratory infections (2-3 fold risk)

4. Poor Nutrition.

•Old Age (physiological obstruction)

•Low-Socioeconomic status(Multi component)[4]

SYMPTOMS ASSOCIATED WITH COPD:

A diagnosis of COPD should be considered in patients over the age of 35 who have a risk factor (generally smoking) and have one or more of the following symptoms:

- exertional breathlessness
- chronic cough
- regular sputum production
- frequent winter 'bronchitis'
- wheezing and decreased breath sounds.
- chest tightness, malaise and fatigue.
- frequent sighing/erratic ventilation at rest.

Patients diagnosed with COPD is considered to experience the following factors:

- weight loss
- effort intolerance
- waking at night
- ankle swelling
- chest pain
- haemoptysis.

NB. These last two symptoms are uncommon in COPD and raise the possibility of alternative diagnoses.[5,6]

COMORBIDITIES ASSOCIATED WITH COPD

- **Cardiovascular**
  1. Coronary artery disease
  2. Congestive heart failure
  3. Ischaemic heart disease
  4. High blood pressure
  5. Left heart failure
  6. Tachyarrhythmia
- **Malignant tumours**
  1. Lung cancer

2. Esophagus cancer
3. Larynx cancer
4. Oral cavity cancer
5. Urinary bladder cancer
6. Pancreas cancer

- **Respiratory**
  1. Pneumonia
  2. Pulmonary embolism
  3. Asthma
  4. Rhinitis
- **Endocrine**
  1. Obesity
  2. Diabetes
  3. Dyslipidaemia
  4. Denutrition
- **Gastroenterology**
  1. Gastric ulcer
  2. Gastro-oesophageal reflux
- **Osteoarticular**
  1. Fractures
  2. Osteoporosis
- **Psychiatric**

1. Depression
2. Anxiety[7,8,9]

EPIDEMIOLOGY

Chronic obstructive pulmonary disease (COPD) is a major cause of disability[10] worldwide and is the only disease for which the prevalence and mortality rates continue to rise.[11]Globally as of 2010 COPD affected approximately 329 million people (4.8% of the population)as compared to the earlier figure of 64 million COPD affected people and 3 million deaths due to COPD as per the 2004 WHO study.[12]In general, COPD mortality was two to three times higher in men than in women, showing an increasing trend in the elderly. The prevalence and morbidity data greatly underestimate the total burden of COPD because the disease is usually not diagnosed until it is clinically apparent and moderately advanced.[13,14,15]These undiagonised and unrecognized patients leads to significant underreporting and it depends on the level of awareness and understanding of COPD amongthe organization of health care services to cope with the chronic disease and the availability of medication for the treatment of COPD.[3]COPD is common in older population and is highly prevalent in those aged more than 75 yr. The global prevalence of physiologically defined chronic obstructive pulmonary disease (GOLD stage 2 or more) in adults aged ≥40 yr is approximately 9-10 per cent.[16]

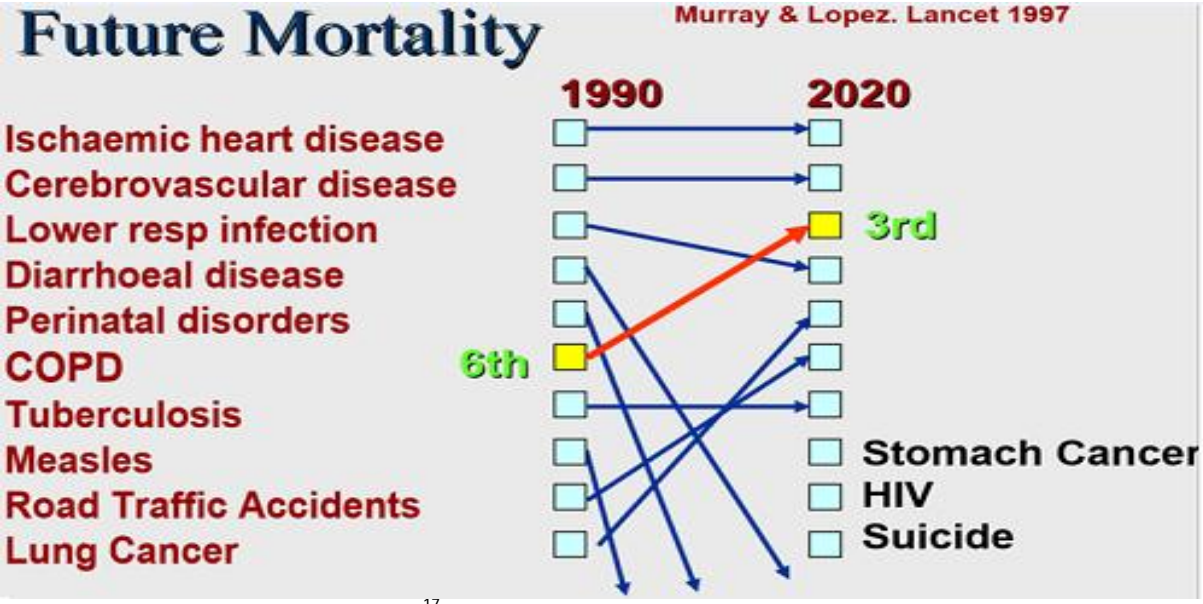


Fig:-Epidermiological overview of COPD.[17]

PATHOGENESIS:-

A. Genetics associated to COPD

Today, the only well established genetic risk factor for COPD is a deficiency in alpha-1-antitrypsin(AAT) gene serpine peptidase inhibitor, clad A, member 1(SERPINA1). Patients lacking this endogenous enzyme are prone to a unopposed proteolyticdestruction of the lung parenchyma predisposing them to development of charecterstics emphysema at an early age. Also installation of proteolytic enzyme directly produces emphysema into the animal lung(without the inhibitor). However,only 1-2% of the patients with emphysema have congential alpha1-deficiency, so scientists are searching for other genetic risk factors that might interact with cigarette smoking to cause COPD .[18,19]So,Sandford et al. have examined gene variants associated with rapid decline in lung function. They had selected 300 continued smokers with the most rapid decline and 300 with the least rapid decline in FEV1 among the approximately 6,000 individuals. They have tested over 50 genes and those with altered risk for decline in FEV1 are presented in the table below.[20]

Significant genetic associations with decline in lung function

Candidate Gene (Gene Symbol)	Polymorphism
α1-antitrypsin (*SERPINA1*)	MZ
MMP-1 (*MMP1*)	-1607 + G
MMP-12 (*MMP12*)	-82A/G
ADAM 33 (*ADAM33*)	F + 1, S_1, etc
microsomal epoxide hydrolase (*EPHX1*)	Tyr113 > His, Arg139 > His
glutathione S-transferase (*GST*)	*GSTP1* Ile105 > Val
heme oxygenase-1 (*HMOX1*)	L-allele (≥33 GT repeats)
glutamate cysteine ligase, catalytic subunit (*GCLC*)	-129C/T
cytochrome P450 3A5 (*CYP3A5*)	*1/*3 vs *3/*3
interleukin-1β (*IL1B*), interleukin-1 receptor antagonist (*IL1RN*)	*IL1B/IL1RN* haplotypes
interleukin-4 receptor α (*IL4RA*)	551RR
interleukin-6 (*IL6*)	-174G/C
β2-adrenergic receptor (*ADRB2*)	Glu27 > Gln

ADAM, a disintegrin and metalloprotease.

Fig:-Genes associated with decline in lung function[20]

Among all these genes, EPHX1 and ADRB2 have noticeable importance. Microsomal epoxide hydroxylase (EPHX1) is an important enzyme which involves in the detoxification of harmful epoxides from smoking, chemicals and drugs, which is strongly expressed in bronchial epithelium. Enzyme activity varies widely in the population and two common coding polymorphisms confer fast and slow enzyme activity, Tyr113His and His139Arg, respectively.[21]β_2-adrenergic receptor or ADRB2 is of importance because β_2-receptor agonists are widely used for the treatment of obstructive lung disease. Two coding polymorphisms of functional significance have been extensively studied from a pharmacogenetic perspective (OMIM:109690), but only one previous study has assessed its role in the susceptibility of COPD.[22]

B. Cytokines, intracellular signaling and immunology

The innate immune response of cigarette smokers and subjects exposed to other environmental pollutants.[23]And these interleukin-8 (IL-8), IL-1β, tumor necrosis factor-α (TNF-α), granulocyte–macrophage colony-stimulating factor, and intercellular adhesion molecule-1, could be a potent stimulator of an innate immune reaction.[24]The presence of inflammatory cells in airways in COPD would suggest that proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin-6, and C-reactive protein are active and have helped drive

chemotaxis of these cells. In addition, an increased levels of important neutrophill chemotactic factors such as interleukin-8 (IL-8), tumor necrosis factor (TNF), C- X-C motif ligand 1 (CXCL1), and monocyte chemo attractant protein (MCP)-1 are found in sputum of a COPD patient.[25,26]It has been also found that increased B-cell follicles in more advanced COPD emphasized the possible importance of an autoimmune component in COPD pathology. Autoimmune diseases are characterized by circulating antinuclear antibodies (ANA) and these are found at greater levels in the serum of 25-30% of COPD patients. Initial reports also described that auto-antibodies against elastin have not been consistently reproduced although autoantibodies against other matrix components of the airway such as collagen V have been reported.[23] In addition to the potential direct effects of nicotine on leukocyte responses,[27,28] it might influence the immune system through the central nervous system (CNS). An intimate relationship exists between the neuroendocrine and immune systems, and a large body of evidence indicates that there is a bidirectional communication between the CNS and the immune system.[29]The brain modulates the immune system through two known pathways: the production of glucocorticoids through activation of the hypothalamus–pituitary–adrenal (HPA) axis and the activation of the autonomic nervous system. Nicotine is a potent neuroactive compound, and our results show that the in vivo immunosuppressive effects of nicotine might be mediated through the CNS, as well as in the periphery.[30,28]

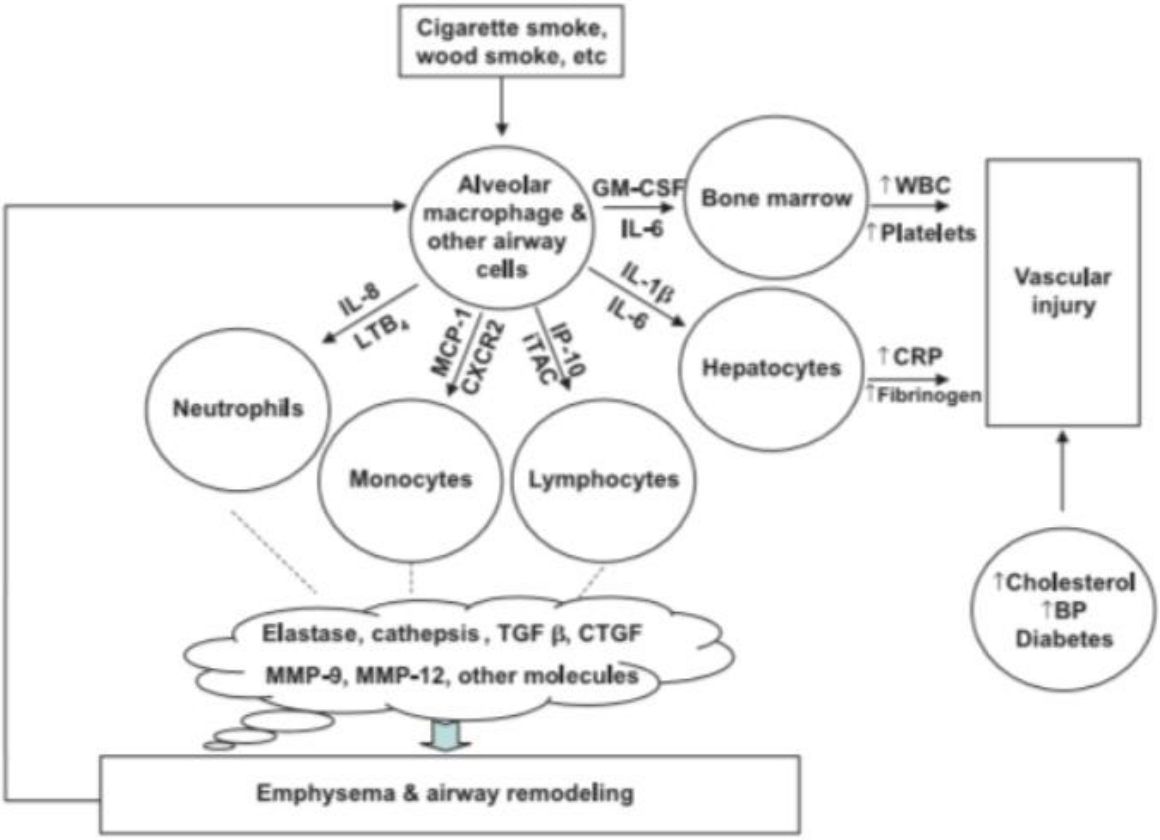
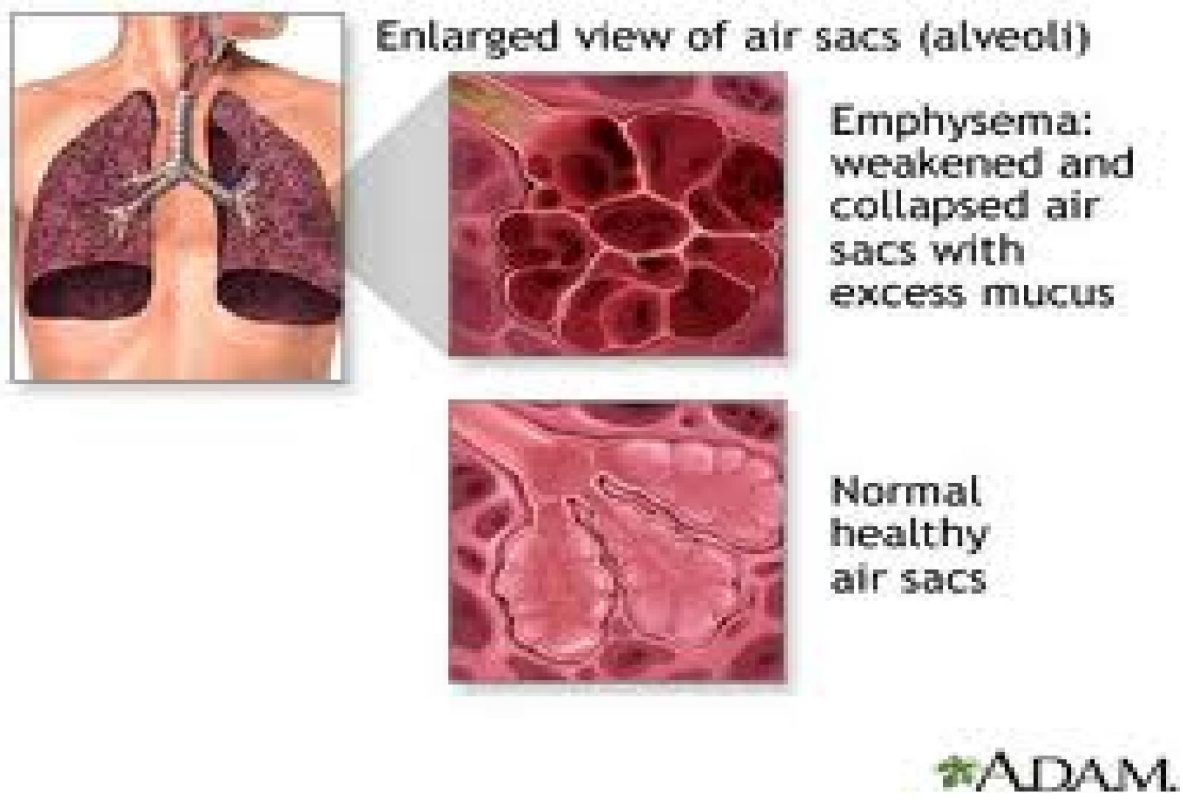


Fig:-Intracellular signaling pathway of lung function reduction[31]

C. Morphological changes

Morphological studies have revealed a reduction in the proportion of oxidative (type I) fibers accompanied by an increase in glycolytic (type II) fibers of the vastus lateralis muscle in COPD patients.[32]So,weakness of the diaphragm is part of a generalised process, involving all (respiratory and peripheral) skeletal muscles. Causative factors for respiratory muscle dysfunction in COPD include disturbances in electrolytes, hypercapnia, forward failure prolonged use of oral corticosteroids[33]and exposure to noxious particles, such as cigarette

smoke and air pollution over a period can lead to lung inflammation with an associated increased number of neutrophils and neutrophill- activating inflammatory mediators such as IL-8 and LTB-4, as well as neutrophil-derived oxidants in the airway lumen and macrophages in the respiratory epithelium and parenchyma.[34,35]In addition, destruction of alveolar walls and loss of alveolar attachments is associated with destabilisation of small conducting airways, leading to premature airway closure during expiration and airflow limitation.[36]Wright and colleagues found that the wall thicknesses of membranous and respiratory bronchioles for each bronchiolar diameter were increased in almost all size ranges in smokers when compared with lifetime non-smokers, indicating that smoking is associated with an increase in airway wall thickness independent of airway size and regardless of the presence or absence of emphysema. However, for the same level of function, andcan show other abnormalities, probably elastic recoil losses, influenced the degree of flow limitation.[24]And two hallmarks of smoking-induced by COPD are squamous cell metaplasia and goblet cell hyperplasia. The glands are enlarged and increased in number which translate to hypersecretion and airway obstruction.[37]Recent studies have also identified dysfunction of the vastus lateralis muscle (VLm), a functional group of muscles active during systemic exercise such as cycling and walking, in COPD patients. And this dysfunction occurs due to the decreased muscle mitochondrial (oxidative) capacity and phosphocreatinine breakdown during in COPD patients.[38,39]It has also been proposed that as much as 70% of COPD patients may be affected by peripheral muscle dysfunction and strength and endurance is decreased in COPD patients as compared with age matched healthy subjects.[27]



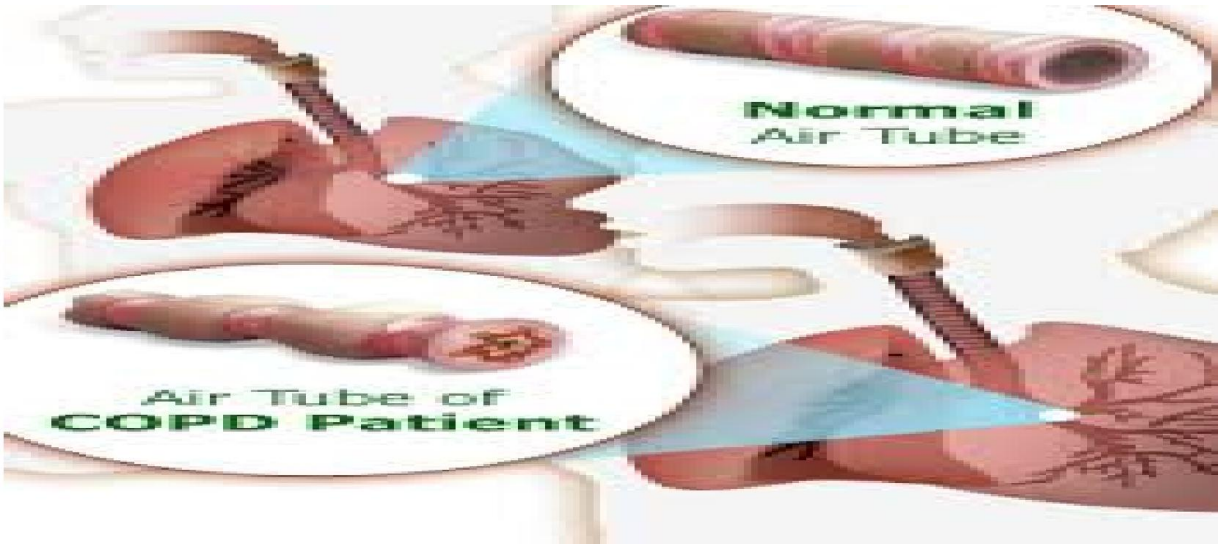


Fig :-Morphological changes associated with COPD.

PATHOPHYSIOLOGY

COPD is a group of conditions characterized by airflow obstruction and is largely irreversible.[40] Chronic exposure to cigarette smoking or other secondhand smoke, air pollution[41]which impacts numerous cell types of the immune system including bronchial epithelial cells, alveolar macrophages, natural killer cells, dendritic cells, and B and T lymphocytes.[42] An elevated concentration of peptides, amines, expression of MHC, and proinflammatory cytokines: IL-8, IL-6.[43]Narrowing of the airways reduces the airflow rate to and from the air sacs (alveoli) and limits effectiveness of the lungs. In COPD, the greatest reduction in air flow occurs when breathing out (during expiration) because the pressure in the chest tends to compress rather than expand the airways. In theory, air flow could be increased by breathing more forcefully, increasing the pressure in the chest during expiration. In COPD, there is often a limit to how much this can actually increase air flow, a situation known as expiratory flow limitation.[44]Clinically, COPD is divided into chronic bronchitis and emphysema. In chronic bronchitis, the lungs have thickened bronchial walls with luminal narrowing, and mucous plugging or mucopurulent debris within the airways. In emphysema, the alveolar walls are destroyed, resulting in enlarged air-spaces distal to the terminal bronchioles. Progressive destruction can cause impairment of lung function. COPD inflammation research's in the 1960's classic elastase:antielastase hypothesis that the balance between protease and there inhibitor determined whetherthe lung was resistant or susceptible to air space enlargement. The loss of elastin, due to gene induced or smoking induced loss of anti elastase, causes collapse or narrowing of the smallest air passage and destruction and enlargement of alveoli.[18,45]

ACUTE COPD EXACERBATION

Exacerbation means worsening or a "flare up" of COPD.[46]In fact, the chronic and progressive course of COPD is frequently aggravated by exacerbations.[47]Acute exacerbations of COPD lead to further erosion of quality of life, absenteeism, and greater use of health care resources.[48] According to Anthonisen and colleagues the definition for Acute COPD exerbation is, the presence of all 3 features such as worsening of dyspnea, increase in sputum production, and increase in sputum purulence indicates a severe exacerbation, 2 features indicates a moderate exacerbation, and 1 major feature in conjunction with 1 minor feature (eg. increase in wheezing or coughing, fever, upper respiratory symptoms in the past 5 days, and increase in heart rate or respiratory rate by approximately 20%) indicates a mild exacerbation.[49]In 2000, a consensus panel of respiratory physicians from Europe and the USA suggested that an exacerbation of COPD should be defined as:– "a sustained worsening of the patient's condition, from stable state and beyond normal day to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD"[50]

AETIOLOGY OF EXERBATION

Exacerbation means worsening or a "flare up" of COPD.[46]In fact, the chronic and progressive course of COPD is frequently aggravated by exacerbations.[47] The main aetiological factors of exacerbation in patients with COPD are usually triggered by either bacterial or viral infections and air pollutants. Between 30–50% of patients with COPD have a positive sputum culture for bacteria, largely Haemophilus influenzae, Streptococcus pneumonae and Moraxella catarrhalis.[51,52] And the role of infections in both the development and progression of COPD is receiving increased attention, including the role of adenoviral infections in emphysema and the role of intracellular infections (e.g., mycoplasma) in asthma.[53]

Pathogen (% of Cases) :-

- *Haemophilus influenzae* (30-70%)*
- *Moraxella catarrbalis*(3.3-28)*
- *Streptococcus pneumoniae*(15-25)*
- *Staphylococcus aureus*
- *Pseudomonas aeruginosa*
- *Mycoplasma pneumoniae*
- *Chlamydia pneumoniae*
- *Enterobacteriae*

Other Gram-Negative Rods

Viruses (3-32%)

- *Rhinovirus*
- *Influenza*
- *Parainfluenza*
- *Adenoviruses*
- *Respiratory syncytial virus*

* These organisms together accounts for 70% of all infective exerbations while 30% may be related to viral infections.

Apart from this some air pollutants causing exacerbation are

- Nitrogen dioxide
- Sulphur dioxide
- Particulate matter (PM10)
- Ozone[50,40]

COPD AND CARDIOVASCULAR COMPLICATIONS

The precise mechanism(s) involved, COPD patients are at increased risk of cardiovascular events. Indeed, cardiovascular events (e.g., strokes, acute coronary syndromes, and cardiovascular deaths) are the leading causes of morbidity and mortality in this population.[31]COPD causes accelerated decline in forced expiratory volume in one second (FEV1).[54]In fact, for every 10% decrease in FEV1, all cause mortality increases by 14%, cardiovascular surgery,(CVS) mortality increases by 28%, and non-fatal coronary events increase by 20 percent. Moreover, if the patient is having arrhythmias the risk of coronary events increases by two-folds.[55]Nicotine increases the amount of bad fats (LDL,triglycerides, cholesterol) circulating in the blood vessels and decreases the amount of good fat (HDL) available.These silent effects begin immediately and greatly increase the risk for heart disease and stroke. In fact, smoking 1-5 cigarettes per day presents a significant risk for a heart attack.[56]

COPD AND DIABETES MELLITUS(DM)

The risk of developing type 2 diabetes is increased in patients with COPD, even in those with mild disease.[57]The pulmonary function in diabetics is characterized by restrictive lung defect.[58] And both these COPD and DM are associated with an enhanced cardiovascular risk profile. COPD patients have a two to three fold cardiovascular related mortality when compared to the general population rates. Cardiovascular disease is the second cause of death among COPD patients and the first one among patients with DM.[59]

CHARECTERSTICS OF CIGARETTE SMOKING AND ITS HARMFUL EFFECTS

Cigarette smoke is a complex mixture of more than 4,700 chemical compounds, including free radicals and other oxidants at high concentrations,which are well characterized toxins and carcinogens (International Agency for Research on Cancer [IARC] 2004).[60]Some smoke components, such as carbon monoxide (CO), hydrogen cyanide (HCN),nitrogen oxides which are gases; formaldehyde, acrolein, benzene, and certain N-nitrosamines which are volatile chemicals; nicotine, phenol, polyaromatic hydrocarbons (PAHs), and certain tobacco-specific nitrosamines (TSNAs)which are submicron-sized solid particles.[9]The mean size of

those particles is 0.1-0.5 µm, so they are capable of reaching small airways.10-30% of the particles are deposited in the lungs. 40% (as documented in inhaled radiolabeled particles measurements) to 90% (in mathematical models) of these are deposited in the gas exchange region.[61]Cigarette smoke is often separated into two phases (tar and gas), which both contain free radicals. The gas phase is less stable and contains approximately 1015 radicals per puff; and the more stable tar phase has been estimated to contain more than 1017 free radicals per gram.[60]

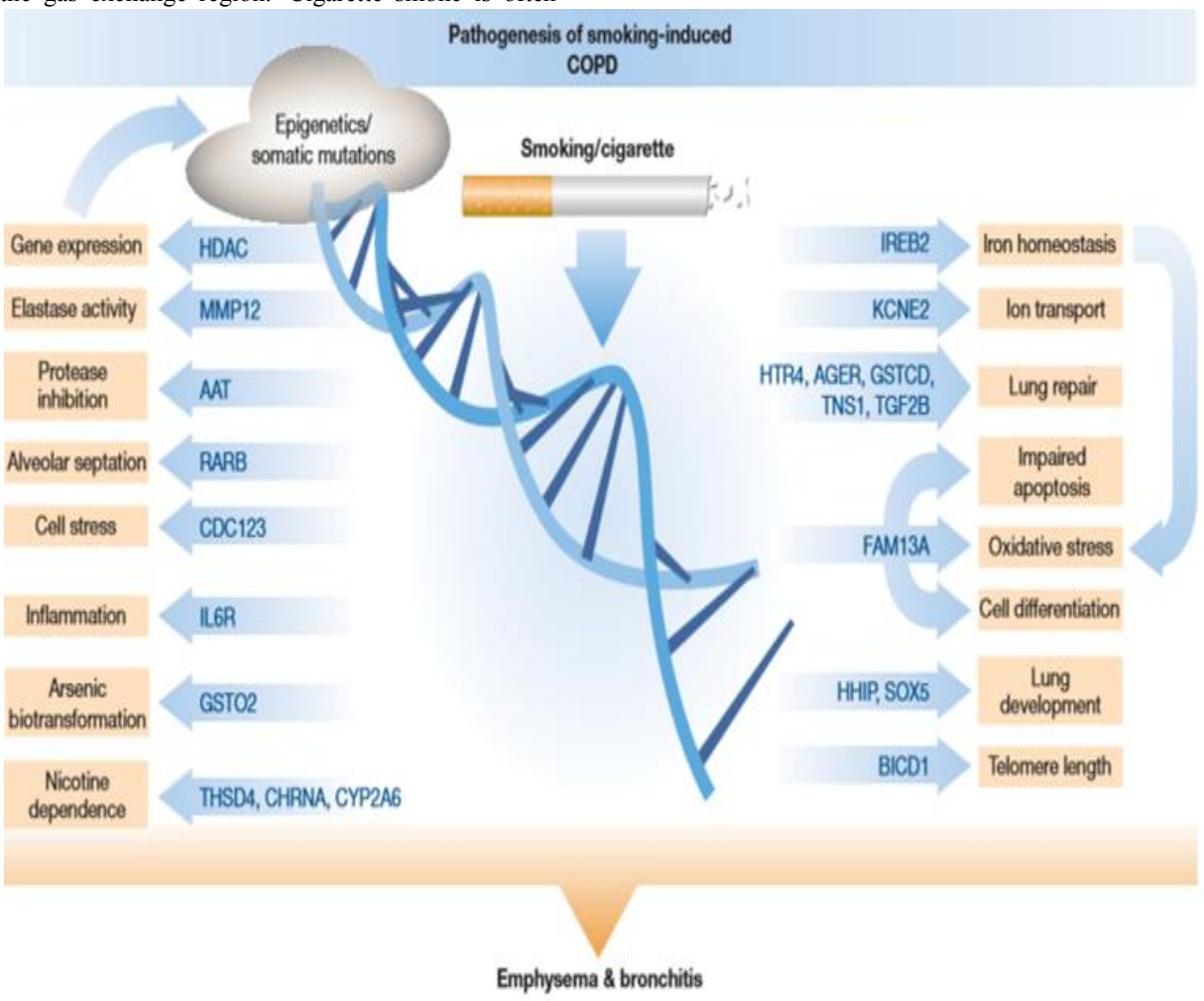
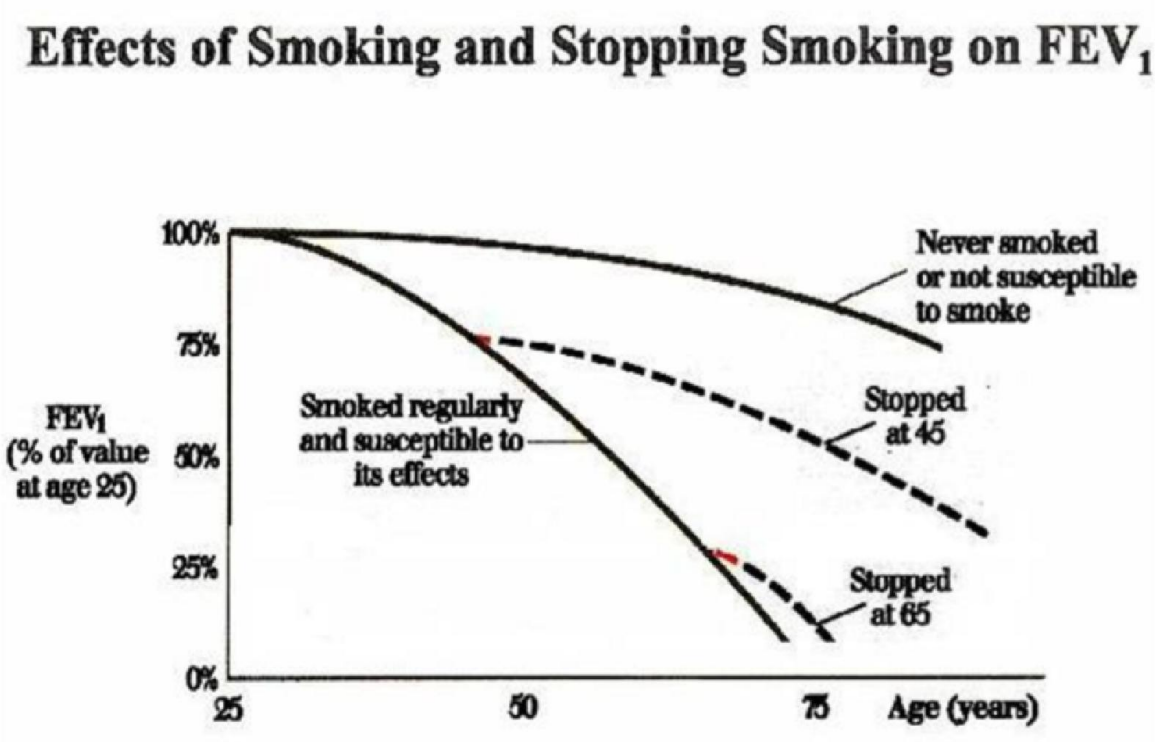


Fig:-COPD is caused by chronic enviromental insults (in particular cigarette smoking) in individuals with predispositions due to variations in one or multiple genes. The combinations of enviroment and genes lead to distinct aberrant pathophysiological process/pathways, the combination of which causes COPD.[19]

SMOKING CESSATION[62]

Cigarette smoking is an addiction.[18]And cessation of smoking is the most important step in the treatment of COPD. Smoking cessation has been found to reduce the decline of FEV1.[16]That is why Dr. Renée Arnold says:

" If you stop smoking, you will put a stop to the accelerated loss of lung function. You will prevent disability from chronic lung disease. It is never too late to quit! "



Quitting smoking takes practice and most people who smoke stop smoking by their own method. But if it is required nicotine replacement therapy can help to reduce the withdrawal symptoms that some smokers experience while trying to quit.

Examples include:

• Nicotine patch

• Nicotine gum

• Nicotine lozenges

• Nicotine inhaler

There are also prescription medications to help you quit smoking (e.g., bupropion HCl, also called Zyban).[63,46]

CLASSIFICATION OF COPD BY SPIROMETRY:

Severity of COPD based on Spirometry:

STAGE	SEVERITY	POST-BRONCHODILATOR FEV1/FVC	FEV1 % PREDICTED
0	At-Risk	>0.7	≥80
1	Mild	≤0.7	≥80
2	Moderate	≤0.7	50-79.9
3	Severe	≤0.7	30-49.9
4	Very Severe	≤0.7	<30

FEV1: Forced expiratory volume in one second ;
FVC: Forced vital capacity 64

Symptoms:

- Stage 1:-
  - Occasional or remittent dyspnoea
  - Mild airflow limitation
  - Chronic cough and sputum
- Stage 2:-
  - Shortness of breath on exertion

- Chronic respiratory symptoms or an exacerbation forces the patient to seek medical help
- Chronic cough and sputum

- Stage 3:-
  - Chronic cough and sputum production
  - Greater shortness of breath on exertion
  - Worsening airflow limitation
  - Reduced exercise capacity
  - Fatigue
  - Repeated exacerbations
  - Reduced quality of life
- Stage 4:
  - Chronic respiratory failure
  - Cor pulmonale possible
  - Frequent, possibly life threatening exacerbations
  - Significantly impaired quality of life
  - Severe air flow limitations.[65]

CONCLUSION

From the above informations we can easily say that the primary risk factors for the development of COPD is exposure to toxic dusts and fumes,and among them the most significant is cigarette smoke. And these agents causes harmful effects in lungs, which in course of time changes the normal physiology and histology of the lungs. The major symptoms are chronic bronchitis and emphysema. These agents also causes alteration in the immunological system and results in the above mentioned complications. So, for proper management spirometry should be performed to observe the severity of the diseases.

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