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Review Article

THE ROLE OF NUTRIGENETICS AND FITNESS GENETICS IN THE PREVENTION AND MANAGEMENT OF ASTHMA AND COPD

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A B S T R A C T

Asthma and COPD are the two common respiratory diseases with overlapping pathophysiological features, symptoms and signs, associated with considerable morbidity worldwide in different countries over the recent decades. If left untreated, both can lead to worst outcomes over time involving various body systems. Various Genome Wide Association studies, linkage and nucleotide polymorphism studies have provided sufficient data to prove that these airway abnormalities, particularly airway inflammation in both are linked to variations in genes on different chromosomes .Identification of the influence of genetic profile in Asthma and COPD provides the basis of effect of dietary factors and exercise on gene modifications. Consumption of diet rich in antioxidants, vitamins, and polyunsaturated fatty acids can lower the expression of inflammation related genes in these diseases. Similarly, exercise training reduces the inflammatory process by regulating the expression of antioxidant and inflammatory genes and up regulating the immune systems of the body.

INTRODUCTION

The increase in the prevalence of asthma and allergic diseases in most countries around the world in recent decades poses a substantial global health burden to people of all ages and ethnic backgrounds. Asthma is characterized by episodic or chronic wheezing, cough and a feeling of tightness in the chest particularly at night as a result of bronchoconstriction. These recurrent episodes of symptoms cause widespread airflow obstruction that is reversible either spontaneously or with treatment. Most dominant pathological change in asthma is airway narrowing and airflow limitation. Three airway abnormalities are present: airway obstruction, airway inflammation and airway hyper responsiveness to a variety of stimuli. Proteins released from eosinophils in the inflammatory reaction may damage the airway epithelium and contributes to hyperresponsiveness.[1] Increased number of eosinophils often correlate with greater asthma severity. Leukotrienes, histamines and prostaglandins are released from mast cells, and can aggravate bronchoconstriction. Numerous other amines, neuropeptides, chemokines, and interleukins have effects on bronchial smooth muscle or produce inflammation and are involved in the pathogenesis of asthma. During acute exacerbations of asthma, exposure to cold air, allergens or irritants cause bronchial smooth muscle contraction (bronchoconstriction). As the disease progresses and inflammation becomes more persistent, other factors further limit airflow.

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These include mucus hypersecretion, formation of inspissated mucus plugs, airway edema, structural changes including hypertrophy and hyperplasia of airway smooth muscle, sub epithelial fibrosis and thickening of basement membrane.

Symptoms of asthma include shortness of breath, tightness of chest, cough which is recurrent in nature and wheezing. Both genetic (host factors) and various environmental factors like inhaled allergens, smoke exposure, air pollution play a critical role in the pathophysiology of asthma. [2] These factors are-

Host factors

Airway inflammation in asthma may represent an imbalance between two types of lymphocytes Th1 & Th2. Th1 cells play a crucial role in cellular defence mechanism against infections by producing interleukin -2 (IL-2) and interferon- gamma(IFN γ) . While Th2 cells produce interleukins: IL-4, IL-5, IL-6, IL-9 and IL-12, that are important mediators for allergic inflammation. Immune system of newborn produces more Th2 response. As the child grows up, environmental stimuli such as infection (particularly TB, hepatitis A, measles), exposure to other children and less frequent use of antibiotics activate Th1 responses and they create the balance between Th1 and Th2. With absence of these conditions, genetic background of the child shows more Th2 response. Th2 response leads to production of IgE antibodies (immunoglobulins) to various environmental allergens, for examples dust mites, cockroaches, animal danders etc. This gene environment interaction in a susceptible host causes sensitization and increased production of IgE antibodies. Various studies have shown the association of genetic factors with development of

asthma. Many genes have been discovered that are involved with the development of asthma.

Environmental factors

Two major environmental factors associated with development of asthma are airborne allergens and viral respiratory infections. Exposure and sensitization with house dust mite, animal danders, cockroaches etc are risk factors for development of asthma. Respiratory syncytial virus (RSV), para influenza virus infection in infancy causes bronchiolitis, which can result in development of childhood asthma. Besides these factors, other minor factors which may have role in development of asthma include tobacco smoke, air pollution, diet, and occupation.

The diagnosis of asthma can be reached by performing forced expiratory manouvers with spirometry. The earliest change associated with airflow obstruction in small airways is slowing in the terminal portion of the spirogram. This slowing of expiratory flow is mostly reflected in a concave shape on a flow -volume curve.[3]Quantitatively, it is reflected in a proportionally greater reduction in the instantaneous flow measured after 75% of the FVC has been exhaled ($FEF_{75\%}$) or in mean expiratory flow between 25% and 75% of FVC than in FEV_1.As airway disease becomes more advanced and/or more central airways become involved ,timed segments of the spirogram such as FEV_1 will, be reduced out of proportion to the reduction in VC.[4] An obstructive ventilatory defect is a disproportionate reduction of maximal airflow from the lung in relation to the maximal volume (i.e.VC) that can be displaced from the lung. It implies airway narrowing during exhalation and is defined by a reduced FEV_1/VC ratio lower than the 5th percentile of the expected value. [5]

Chronic Obstructive Pulmonary Disease (COPD)

The Global initiative for chronic obstructive lung disease (GOLD) defines chronic obstructive pulmonary disease (COPD) as a disease associated with airflow obstruction that is not fully reversible. COPD is also associated with extra pulmonary consequences that may contribute to severity or outcomes.[6] According to World Health Organization (WHO) reports, COPD will be the third leading cause of death by 2030.At present, very limited disease modifying therapy is available for COPD, hence we need an improved understanding of pathogenesis mechanism, which can lead to novel therapeutic interventions and preventive strategies in future.

COPD is a progressive inflammatory disease of lung and airways, characterised by chronic bronchitis, airway thickening and emphysema. The airflow limitation is not fully reversible in COPD, and is due to combination of airway and parenchymal damage (alveoli, alveolar ducts and bronchioles). Symptoms of COPD include shortness of breath, chronic cough, excessive mucus production and frequent infections.

Most important risk factor for COPD is smoking. Almost 85% of the COPD cases develop due to tobacco smoke and rest 15% of the cases are classified as non- smoking COPD. The risk factors for non smoking COPD cases include indoor air pollution created from cooking with biomass fuels (eg. wood, cow dung) in poorly ventilated homes over 25 years at least. Biomass fuels on burning release air pollutants like carbon monoxide (CO), nitrogen dioxide (NO_2), sulphur dioxide (SO2) and particulate matter smaller than 10 micron in size, which leads to development of COPD on chronic exposure.[7] Another important risk factor for non smoking COPD is prolonged exposure to occupational smoke or dust for eg. fertilizer manufacturing, ammonia exposure in petroleum refining, grain dust in farmers, crystalline silica in cement industry, pottery, and ceramic work etc. Besides these risk factors, various epidemiological studies provide strong evidence that genetic factors also influence the development of COPD. High occurrence of COPD in families has led to recognition of a genetic component to this multifactorial disease.

Spirometry testing assist in differentiating Asthma from COPD. Airflow obstruction that is fully reversible after administration of a bronchodilator is indicative of asthma while partially reversible or irreversible is suggestive of COPD. [8]Increase in airway resistance and reduction in airway calibre, causes reduced airflow particularly during expiration, prolonging the removal of air from the lungs. This feature of COPD can be detected by spirometry by performing forced expiratory manoeuvres. The findings include reduction in FEV_1 [forced expiratory volume of air in 1 second], and the ratio of FEV_1 & FVC [total volume of air removed during forceful expiration after maximal inhalation] as less than 0.7(FEV1/FVC < 0.7). [9,10]

COPD is a complex disease involving many inflammatory pathways that initiate and potentiate disease process.[11] The two major mechanisms implicated in pathogenesis of COPD are oxidant- antioxidant imbalance leading to oxidative stress and persistent inflammation. Macrophages, neutrophils and T lymphocytes are the key inflammatory cells involved in the pathogenesis of COPD disease. Unlike asthma, inflammatory cells in asthma do not respond to steroids. These cells release inflammatory mediators like chemokines, cytokines & protease enzymes that produce a chronic inflammatory state. [12]

Neutrophils release elastase, proteinase3, cathepsin B & cathepsin G, matrix metalloproteinses (MMP) which cause damage to elastic lung tissue. Neutrophils also release interleukins like IL- 8 and leukotriene B4 which attract other neutrophils to the inflammatory site. Similarly, macrophages release IL-6, IL-8, IL-10,TNFα (Tumour Necrosis Factor α, reactive oxygen species to activate other inflammatory cells & proteinases like MMP9, MMP 12, MMP 14, Cathepsin k, l & s which cause tremendous damage to elastic lung tissue. [13] Lymphocytes causes apoptosis of the alveolar epithelial cells by releasing enzymes like perforin and granyzme B. Oxidative stress causes imbalance of protease- antiprotease enzymes and inactivation of surfactant leading to mucus hypersecretion, membrane lipid peroxidation, alveolar epithelial injury, reduction in elastin, collagen synthesis and remodelling of extracellular matrix. Decreased elastic recoil, due to elastic lung tissue damage, structural narrowing of airways combined with the effects of cholinergic vagal bronchoconstrictive tone causes impaired pulmonary function in COPD.[14]Chronic airflow obstruction and loss of elasticity in the lungs in COPD causes air trapping and hyperinflation. [15]

In Emphysema, alveoli are damaged to a great extent causing reduction in surface area for gas exchange to occur. The proteolytic enzymes released by various inflammatory cells cause destruction of the walls of air sacs, which break down into larger air spaces, forming ‘’bulla’’. Airway narrowing and

hyperinflation results in hypoventilation and feeling of breathlessness. In chronic bronchitis, there is increased mucus production, persistent inflammation causing irritation of bronchi and bronchioles. Diagnosis is made when symptoms and signs are present for two consecutive years, and mucus production is on most days for three months. Increased vagal tone and excessive mucus production cause airways constriction. Impaired clearance of secretion due to damage to airway cilia result in frequent infections in chronic bronchitis .[16]

Influence of Genetic profile in Asthma and COPD

Influence of genetic profile in Asthma

Risk factors involved in the development of asthma may be endogenous or environmental in origin. The genetic contributions for asthma has been reported to vary between 35% and 95%.Such large contribution suggest that the influence of genetic makeup of an individual is significant which itself is a major risk factor.[17] There is high concordance rate for asthma in identical twins. The impact of genetic inheritance is also revealed when a patient gives a family history of asthma.[18]It is also a challenge to identify specific genes as many other manifestations like allergic rhinitis, atopic dermatitis and other allergic diseases have a similar etiology and also they share a common pathway of pathogenesis. [19]

Screening of genetic profile by genome-wide linkage study of linkage analysis and single nucleotide polymorphisms have shown that it is of polygenic in origin.[20]Therefore, a number of genes may be involved and they have different representation in a particular group of people. Recently genome -wide association studies (GWAS) are being done which take into consideration all the regions of the genome without any preliminary hypothesis about the site of the genetic contributor to risk variants. Next Generation Sequencing (Next Gen) is the future sequencing study which comprises of re-sequencing of genes, exomes or whole genomes in large samples of subjects to know about any variation.[21]

About 100 genes have been described in various studies to be linked with asthma. But explaining all of them is beyond the purview of this chapter. The important ones are the following : Orsomucoid - like 3 (ORMDL3) and Gasdermin (GSDML) genes -

The first genome wide association studies of asthma identified ORMDL3/ GSDML as a novel asthma susceptibility locus on chromosome 17p21.ORMDL3 is an allergen and cytokine (IL4) inducible endoplasmic reticulum gene expressed predominantly in airway epithelial cells.[22] GSDML induces 5 lipooxygenase, which further induces transforming growth factor (TGFβ) to increase airway remodelling over months. The variation in the locus on chromosome 17, had been associated with asthma in around 1000 cases. The variation in this gene is also a risk factor for childhood asthma.[23] In animal experiments, it has been shown that mice expressing altered ORMDL3/GSDML gene is characterized by airway hyper responsiveness and increase in airway remodelling in absence of airway inflammation.

ADAM 33 gene

ADAM 33 gene located on 20p13 chromosome has been reported to play important role in asthma. ADAM33 gene is highly expressed in fibroblasts and smooth muscle cells of the lungs. Therefore, disturbance in expression of ADAM 33 gene may result in alterations in airway remodelling and repair processes. Selective expression of ADAM 33 in mesenchymal cells of asthmatic airways suggest that alteration in its activity may result in abnormalities in the function of airway smooth muscle cells and fibroblasts linked to bronchial hyper responsiveness and remodelling in asthma. [24]

DPP10 and PHF11 genes

Plant homoeodomain zinc finger protein 11 and Dipeptidyl peptidase 10 were shown as asthma susceptibility genes in the previous studies.PHF 11 on chromosome 13q14 has been suggested to genetically impact asthma via serum total IgE regulation and altered Th1/Th2 cytokine release. Recently, it has been shown by a study that PHF 11 regulates the expression of Th1 type cytokines genes and its reduced expression causes increased Th2 responses characterizing asthma and allergic diseases.DPP-10 is located on chromosome 2q14, regulates the activities of chemokines & cytokines, and is strongly associated with asthma susceptibility. Alterations in DPP10 gene cause higher levels of serum IgE which is a strong risk factor for asthma.[25]

NPSR1 gene

Neuropeptide S receptor 1 gene encodes a member of vasopressin/oxytocin subfamily of G protein coupled receptors. The encoded proteins act as receptor for neuropeptide S, which mediates various types of cellular processes through its signaling. In asthma, NPSR 1 gene is over expressed in ciliated cells of respiratory epithelium and in bronchial smooth muscle. Polymorphisms in these gene loci 7p14 have also been associated with asthma susceptibility.

HLA-G gene

It is a non classical, class Ib, major histocompatibility complex antigen, encoded by a gene on chromosome 6p21 within HLA complex. HLA-G is normally expressed in pregnancy to maintain immune tolerance towards foetus, but it has also been associated with inflammatory disease. Various diseases have demonstrated expression of soluble isoform of HLA G, sHLA-G5, in airway epithelial cells and of increased plasma levels of sHLA-G5 in children having atopic asthma. Presence of HLA-G in airway epithelium suggests that its deregulation could contribute to airway inflammation in chronic asthma.[26]

FMRP interacting protein 2 gene-

CYFIP2 (Cytoplasmic Fragile X mental retardation interacting protein 2 gene) is located on chromosome 5q33.Polymorphism in this particular gene have been associated with asthma in various studies. Increased levels of cytoplasmic FMRP interacting protein 2 gene in lymphocytes has been associated with development of atopic asthma in humans.[27]A polymorphic proinflammatory gene is located in chromosome 5q for TH2 cells IL-4 (IL-4 5q31-33 IgE switching, TH2 polarization, up-regulation of VCAM-1, induction of mucus genes), IL-5, IL-9 (IL-9 5q31-33 Mast cell growth factor) and IL-13.

Influence of genetic profile in COPD

Various polymorphic genes are involved in COPD. [28] Various genes involved in metabolism of toxic substances in cigarette smoke, antiproteolysis, inflammatory response to cigarette smoke and the efficiency of mucociliary clearance in the lungs have been found to be implicated in pathogenesis of COPD till date. The expression of these different gene combinations, perhaps affects the heterogenous, histopathological and clinical profile of COPD seen among different individuals. [29] A number of studies have examined candidate gene loci with the help of association studies, comparing the distribution of variants in genes hypothesized to be involved in development of COPD in patients and control subjects. Similarly linkage studies and genome wide association studies have identified genome variations associated with disease phenotypes. [30,31].The important gene associations which have been studied in COPD are described below:

Genes involved in proteolysis and antiproteolysis

The most common and well established genetic risk factor identified for COPD is SERPINA 1 gene located on chromosome 14q32 which codes for serine protease inhibitor, α 1 antitrypsin (AAT-1).Disturbance in expression of SERPINA 1 gene leads to deficiency of AAT-1, resulting in uncontrolled proteases activity and development of emphysema. A polymorphism that predispose smokers to develop COPD (Taq-1 G→A) had been detected by the restriction enzyme Taq-1 in the 3' non - coding region of α 1 antitrypsin gene. This Taq polymorphism cause reduction in production of α1 antitrypsin leading to uninhibited protease activity and development of COPD.[32]

Mutations in plasma proteinase inhibitor, increases the susceptibility of smokers for COPD. Two point mutations that alter the amino acid sequence (229Pro→ Ala & 55 Leu→Pro) in the α 1 antichymotrypsin gene (SERPINA 3) leads to inactivation of α1 antichymotrypsin.

Matrix metalloproteinases(MMP) are proteolytic enzymes that play an important role in tissue remodeling. MMP 12 has elastase activity due to which it has been suggested to play an important role in COPD. In the past, animal experimental study depicted that MMP12 null mutant mice were entirely protected from cigarette smoke induced emphysema. This means less MMP12 expression protects against COPD.

SERPINE 2 is an inhibitor of thrombin, urokinase & plasmin. However, SERPINE 2 is postulated to be positional candidate susceptibility gene for COPD, which is influenced by gene-smoking interaction and repair in development and inflammation. [33]

Genes involved in antioxidant function

Oxidant-antioxidant imbalance results in oxidative stress which plays an important role in development of COPD. Lung is protected normally by antioxidant enzymes like Glutathione-S- transferase, superoxide dismutase and catalase. Alterations in genes encoding these enzymes, increases oxidative stress and development of COPD.

Glutathione-S-transferase (GST) enzyme can detoxify noxious chemicals of tobacco smoke. Functional polymorphism including one single nucleotide polymorphism in GSTP 1 and three alleles of GSTM1, each decreases the enzyme activity, due to which protection to oxidative stress is lost. Superoxide dismutase enzyme scavenges reactive oxygen species, which damages the lung tissue. Polymorphism in Superoxide dismutase 3 (SOD3) gene have been found to associated with emphysema in COPD. Microsomal epoxide hydrolase (MEH) enzyme is expressed in human bronchial epithelial cells and detoxifies reactive oxygen species of cigarette smoke. Single nucleotide polymorphism in MEH/EPHX1 gene has been associated with severe COPD cases and rapid decline in FEV_1 in smokers.[34]

Inflammation and inflammatory mediators related gene

Many inflammatory mediators have been implicated in the pathogenesis of COPD including (Tumour Necrosis Factor α) TNFα, IL-8 and TGFβ (Transforming Growth Factor β). [35] Cigarette smoke activates macrophages to release TNF α , LTB-4,IL-8.TNFα promotes release of IL-8 from other cells in the respiratory tract by NF-κB mediated gene transcription.TNF α indirectly increases neutrophilic inflammation and release of proteases. Disturbance in TNF α gene expression leads to uninhibited release of protease enzymes and development of COPD. TGFβ activates fibroblasts, which plays a key role in pathogenesis of fibrosis. TGFβ gene is located on chromosome 19q. Various animal experiments suggest that disordered activation of TGFβ is related to the pathogenesis of COPD. [36, 37]

Gene-diet interaction and Impact of diet in Asthma and COPD

The food that we consume have a great impact on our health. A large number of studies have proved that the overall human diet interacts with the genetic composition of an individual. With the food technology industry showing a rapid growth, the availability of the processed foods has increased to the masses. The dietary pattern in different regions of the globe have been found to influence the development of various diseases like hypertension, coronary heart disease, allergic diseases and asthma.[38]

Two major types of dietary pattern are observed: the Western diet and the Mediterranean diet. Western diet is mostly consumed in developed countries. It comprises mainly of high quantity of highly processed foods leading to greater consumption of refined grains, processed meats, sweets and deserts, fried foods, potatoes and dairy products containing high fats. This diet provides high energy, saturated fats, sugars and sodium.[39] In addition, the Western diet possess a high omega-6 to omega-3 polyunsaturated fatty acid ratio which is involved in etiopathogenesis of many inflammatory diseases.[40,41] Both omega -6 and omega-3 fatty acids have an impact on genetic expression. Mediterranean diet is mostly prevalent in southern regions of European countries .It comprises of mainly fruits and vegetables, whole grain cereals, olives, legumes, nuts, seeds and low fat dairy products. It also contains high quantities of seafood which is a rich source of omega-3 fatty acid, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and docosapentaenoic acid (DPA). Therefore, Mediterranean diet is enriched in antioxidants, flavonoids, micronutrients, carotenoids, polyphenols, omega-3 polyunsaturated fatty acids and monounsaturated fatty acids.[42,43]

In pathogenesis of asthma airway inflammation is a major change taking place. [44] Mediterranean diet provides anti-inflammatory factors such as omega-3 polyunsaturated fatty

acids, monounsaturated fatty acid and antioxidants. Eicosapentaenoic acid and docosahexaenoic acid lowers the expression of genes for the inflammatory mediators particularly the interleukins: IL-6 and IL-8 .So, this type of diet provides a protective environment for the lung epithelium.[45,46] Various studies have proved that there was a decrease in the levels of acute phase reactant C-reactive protein (CRP), interleukin -6(IL-6) and intracellular adhesion molecule-1 (ICAM-1) in individuals consuming this diet. Also, there was decrease in number of neutrophils in patients of asthma following restriction in diet containing saturated fatty acid.[47] Olive oil is a major ingredient of the Mediterranean diet .It decreases oxidative injury and inflammation and helpful in prevention of recurrent attacks in asthma sufferers and thus is beneficial in these patients.

Lack of antioxidants in the diet makes a person more prone to lung injury as they are more susceptible to oxidative stress because the free radicals have the potential to damage the deoxyribonucleic acid and the proteins of the cell. The higher amount of saturated fatty acids in the blood lead to activation of inflammatory cascade causing harm to the airway epithelium. Antioxidants have the capacity to modify the effects of the oxidation process occurring in the body.

If the fetus is exposed in utero to tobacco smoke, perinatal infections or microbial products the chances of childhood asthma increases. [48] Maternal diet during the period of pregnancy enriched in Vitamin D, Vitamin E and fish oil have shown a decline in incidence of wheeze in childhood period. Also, exclusive breast feeding have shown to have protective effect on the development of asthma at an early age. [49]

The main objective to manage COPD patients is to stop the progression of the disease, improve the pulmonary function parameters and provide a quality life to the diseased. In COPD chronic inflammation proceed to the obstruction of airways and lung parenchyma destruction and therefore it is essential to herald this ongoing inflammation process. The oxidative injury plays an important role in the pathogenesis of development of COPD . Oxidative damage to the underlying pulmonary tissue results from smoking and environmental air pollution. The free radicals released from the ongoing inflammatory and the oxidation process damage the outer cell membrane of the lung tissue .Free radicals also has the ability to cause conformational changes in the protein structure of the protease inhibitors and the enzymes for repair. Hence, antioxidants especially Vitamin A, Vitamin C and Vitamin E play a significant role in prophylaxis of COPD. [50] Antioxidants are reducing agent that act by donating electrons to various enzymatic and non-enzymatic reactions. They help to protect cells from damage caused by unstable molecules called as free radicals. [51]

Dietary interventions in the form of consumption of fresh fruits and vegetables have been found to be beneficial in these patients. [52]Fresh fruits and vegetables are a rich source of multivitamins especially Vitamin A, Vitamin C and Vitamin E .Vitamin A or beta carotene is a fat soluble vitamin .It has both antioxidant and anti-inflammatory property. It collects the generated free radicals in the tissues. Studies on mice have proven that administration of Vitamin A has caused reversal of the airway obstruction. Foods that are particularly high in Vitamin A are carrots, sweet potatoes, apricots, spinach,red bell pepper, grape fruit, pistachios, broccoli, goji berries, mango and butternut squash. Vitamin C or ascorbic acid is a water soluble vitamin. It is found both in intracellular and extracellular parenchyma fluid. Its role is maintenance of hydration in the airway passages and therefore its deficiency leads to dryness of the underlying mucous membrane of the airways. Foods rich in Vitamin C are papaya, orange, grapes, lemon, strawberries, kiwi fruit, guava, broccoli, blackberry, pineapple cauliflower, brussels sprout, tomato, cranberry and apple. Vitamin E is a fat soluble compound. It is also a powerful antioxidant. It is found in extracellular lung fluids and in cell membranes. [53] Here, it helps in converting the oxygen and peroxyl free radicals to less reactive forms minimizing their damaging effects. Good sources of Vitamin E include almonds, peanuts, sunflower seeds, spinach, broccoli and vegetable oils. [54]

Linoleic acid is a polyunsaturated omega -6 fatty acid. It is found as lipid component of cell membranes. Dietary sources include safflower oil, sunflower oil, salicornia oil, nuts, margarine and fatty seeds. The metabolism of linoleic acid leads to formation of arachidonic acid. The arachidonic acid is further converted to eicosanoids. The eicosanoids include prostaglandins, thromboxanes and leukotrienes. They promote the inflammatory process in the body and hence have deteriorating effect on the lung parenchyma. Linoleic acid is precursor of arachidonic acid and it is converted to prostaglandins particularly PGE_2 which inhibits interferon gamma and accelerates inflammation process in bronchial asthma.[55]Fish oils has more content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and they achieve higher omega-3 polyunsaturated fatty acids (PUFA) .Hence they play a defensive role. [56,57]The components of fish oils helps in decreasing the inflammatory reaction especially triggered by allergens and they also lowers the airway hyperactivity. This all helps to achieve a higher pulmonary function test result in the concerned. [58]

The 5-lipoxygenase (5- LO) pathway in the inflammatory process in bronchial asthma lead to production of metabolites mainly the leukotrienes. The leukotriene LTE_4 is excreted in the urine and therefore used in research purposes. According to the response of the patients to fish oil, there are two types of patients-responders and non responders. The ones who have high urinary secretion of leukotriene E_4 (LTE_4) are responders and the ones with low secretion are non responders. In urine, the LTE_4 levels are measured by immunoassay based on radioactivity or enzyme activity. The difference in urine concentrations of different individuals may be due to polymorphisms present in the genes of biosynthetic pathway of leukotrienes. Also, the genetic variability along with the host and environmental factors affect the production of the leukotrienes. By preliminary genotyping these cases can be recognized. [59]

Nutrigenetics is concerned with the relationship between genetic factors and nutrition. It is basically the effect of genetic variation on the dietary response. It is concerned with the interindividual variation in response to diet based on the genetic factors. Nutrigenomics is the role of nutrients and bioactive food compounds on gene expression. [47]It helps to provide better nutritional consultation to the affected individual so that an appropriate diet plan can be suggested to the concerned. It involves interplay of nutrition, genetics and biochemistry.

This knowledge can be applied to find out nutrient -gene interactions. It helps in improving health outcomes in genetic subgroups and individuals. [60]It is important because i) there is large variation in the inherited genetic material between ethnic groups and individuals which affects nutrient bioavailability ii) individual intake of food vary largely as they come from different cultural, economical and geographical background and iii) the state of malnourishment whether deficiency or excess exert an influence on the genetic expression and also on the stability of the genome.

A wide range of asthmatic cases are present and there is numerous clinical phenotypes present which gives variable response to the pharmacological as well as to non pharmacological (diet and exercise) program. Thus, suggestions related to dietary intake on the basis of genetic testing that is identifying changes in chromosomes, genes or proteins will aid in the preventive management of the disease.

Gene-exercise interaction based intervention in prophylaxis and management of Asthma and COPD

Lifestyle modification is an important step to adopt in the prevention and management of asthma and COPD. It is also necessary to educate and counsel the diseased to maintain these habits on day to day basis with a lifetime commitment. [61]It is well known that regular physical activity is essential for the total day to day energy expenditure. It decreases the risk of developing several chronic diseases, improves the health outcome and decreases the chances of excessive weight gain. Also, a better rate of utilization of oxygen in the lungs is achieved as the blood circulation improves. It enhances the muscle function. Exercise is also beneficial in obesity management. Obese people are at more risk of developing asthma. Also, these individuals have poor asthma control. Hence, weight loss will be beneficial to them as it would lead to an improvement in pulmonary function parameters and a better asthma control. All these measures will improve the quality of life of the individual and will bring increment in years lived in good health. Exercise have a relaxing effect on mind and body and helps in decreasing mental stress. Awareness and education about the exercise training program is an essential step in management of these patients.

There exist a genetically determined component affecting exercise -related phenotypes such as maximal oxygen consumption (VO_{2max}), body composition and body fat distribution and plasma lipid profile. These traits are multifactorial in origin. A great body of literature working in potential gene physical activity have included an exercise, fitness and performance paradigm in their studies.[62]They observed a heterogenic response to various exercise programs .They concluded that there was a substantial differences in person -to-person response to an exercise regimen and also there was a significant component relating to or occurring in the family or its members.[63,64]Genes are constituent of chromosomes that gives uniqueness to an individual and is responsible for the varied responses in the particular person.[65] For example, Glutathione S- transferases (GST) is a crucial antioxidant gene responsible for the protection of the cells. It plays a key role in pathophysiology of bronchial asthma. In the lung parenchyma, mainly two forms of Glutathione S-transferases are expressed: $GSTP_1$ and $GSTM_1$.A study reported that individual possessing null genotype of $GSTM_1$ was related with higher chances of developing bronchial asthma and decline in pulmonary function. Also, children living in high ozone atmosphere and who have a particular allele have very lower probability of developing asthma following exercise .[66]

Training exercises have proved to play a defensive role in chronic smokers having pulmonary health problem. Cigarette smoking in COPD is responsible for damage to the lipid and protein constituent of the cell and also to the nucleic acid. All this puts an oxidative stress on the body organs especially the working muscles; one of them is the diaphragm (the most important muscle involved in respiration). In an experimental study, it was found that regular physical exercise lead to alteration of genes involved in the antioxidant pathway. It has a protective effect on diaphragm muscle wasting caused due to smoking in COPD patients.[67] Exercise training reduces the inflammatory process by upregulating the immune systems of the body. Therefore, there is a need to begin a methodical exercise training program in the concerned individual as early as possible. [68]

A family of genes known as Sirtuins is present inside the nucleus of the cell .It prevents the ageing process in the body. In COPD, the researchers found that one of the sirtuins (SIRT1) is involved in regulating the inflammatory process and decreasing the oxidative process. Therefore, it leads to decrease in progression of the disease process. Exercise increases the messenger ribonucleic acid levels and protein expression of the enzyme SIRT1 and some antioxidant enzymes namely FOXO1 and FOXO3. [69]Experiments in mice have proved that constant involvement in physical activity decreases the chances of lowering of pulmonary functions. It reduces the probability of development of COPD in individuals involved in smoking. It also increases the quantity of cells producing the antioxidant enzymes glutathione peroxidise and superoxide dismutase.[70]

Human Gene Map for physical performance and health-related fitness phenotypes (2005) showed that a number of genes were involved including one hundred and sixty five autosomal , 5X chromosomal gene and seventeen mitochondrial genes. The genes included are associated with the body composition, hemodynamics, plasma lipid, lipoporotein and hemostatic, endurance, speed and muscle strength, exercise intolerance and physical activity. [71] Many studies have concluded that there is involvement of genetic component corresponding to exercise training .For example, one of the cause of development of COPD is factors present inside the organism (intrinsic) which is genetically controlled. One factor is angiotensin converting enzyme gene. It has three genotypes on the basis of insertion (I) and deletion (D) within the deoxyribonucleic acid. They are DD homozygote, II homozygote and DI heterozygote. The DD genotype of ACE is linked with development of pulmonary hypertension during exercise in sufferers of COPD .The level of lactic acid is higher in these cases due to impairment of peripheral tissue oxygenation. The DD genotype is related with increase in serum concentration of ACE .The allele II is correlated with an increased response to exercise training. It is a disease modifying gene and beneficial in long term course in COPD patients. This knowledge helps in monitoring the progression of disease in COPD patients. [72]

However, the research on molecular genetics of physical activity and health related fitness and outcomes is still in its initial stages and more research on gene-activity interactions

in this area will find out the advantage of regular exercise on genes. Molecular research includes the identification of the genetic loci which plays a significant role in capability to gain good results from a well planned exercise regimen.[62]

Thus, the significance of lifestyle changes cannot be underestimated. A healthy di*et al*ong with exercise habits lead to significant loss of body weight, a better lung function test result and a good quality of life. [73]The combined effect of a healthy dietary pattern along with the regular exercise program would be a productive effort to enhance the improvement in the condition of asthmatics and COPD sufferers. Therefore, a multidisciplinary approach in the form of both pharmacological and non pharmacological measures would help in management of these patients. [74, 75,76]

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