DEFICIENCY STATUS OF ALPHA-1-ANTITRYPSIN GENE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is the most prevalent clinical disorder. It is generally considered to be due to an imbalance between proteolytic enzymes and their inhibitors. A specific trypsin inhibitory protein was isolated along with the alpha-1-globulin of human serum. It was named as alpha-1-antitrypsin (α1-AT), as most of the serum trypsin inhibitory activity was found to be associated with the alpha-1 globulin fraction. Alpha-1-antitrypsin drew clinical interest when Laurell and Eriksson described the absence of plasma α1-AT in patients with degenerative lung disease leading to death in middle age. Genetic deficiencies resulting in the reduced levels of α1-AT in human plasma are particularly prevalent in individuals of north European descent. Deficiency of α1-AT is a recognized risk factor for COPD and is characterized by the progressive obstruction of airways, which is not fully reversible. The condition was hereditary and was likely to occur in individuals homozygous for mutated or deleted alpha-1-antitrypsin (aat) gene. Heterozygosity was found to exhibit half the normal proteolytic activity of α1-AT. Alpha-1-antitrypsin deficiency is widely under-diagnosed in many populations with majority of the individuals remaining undetected due to the delay in the onset and variability of respiratory symptoms. WHO stated that 2-3% of all alpha-1-antitrypsin deficient individuals were homozygous for PiZ and recommended screening for α1-AT deficiency in individuals with COPD, all adults and adolescents with asthma as well as neonates, children and adults with unexplained liver disease.

KEY WORDS: COPD, Genetic predisposition, Alpha-1-Antitrypsin Deficiency

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is the most common chronic disease of the lungs characterized by a slowly progressive irreversible airflow obstruction (Stockley, 2000). Emphysema and chronic bronchitis are the most important conditions that compose COPD. Emphysema and chronic bronchitis occur together frequently as they share a common etiologic agent, tobacco smoke (Boschette et al., 2003, Seifart and Plagens, 2007).

In chronic bronchitis, irritation of the airways by smoke or other irritants results in excessive mucus secretion. Airway obstruction results from narrowing of airway by thick mucus and from bronchial inflammation and edema. Excess mucus secretion also results in plugs in the small peripheral airways. These plugs reduce the functional air exchange area and leads to the destruction of the alveoli. In contrast, emphysema is characterized by destruction of the distal airspaces including the bronchioles, alveolar ducts and alveolar sacs. This results in the loss of elastic recoil. The forced expiratory volume is maintained by the elastic recoiling. If decreased, the ductal airways will collapse during expiration and trap air (Goldsmith and Weber, 1996).
COPD begins with complex biochemical and cellular events in the small airways and surrounding alveoli. The lungs begin to increase in size with an increase in forced expiratory vital capacity (FVC). This leads to early physiological alterations that can be readily identified by simple spirometry. By the time that both clinical and radiographic signs are present, COPD is in a moderate to advanced stage. Airflow obstruction in COPD patients is found to respond to various therapeutic efforts, but mostly once initiated this is largely irreversible (Petty, 2002).

COPD is becoming a greater health problem with the growing use of cigarettes around the world (Lomas and Silverman, 2001; Rennard and Farmer, 2002). COPD is responsible for >29 million disability adjusted life years and one million years of life lost per annum around the world (Silverman et al., 2002). COPD is predicted to explode in developing countries such as India, Mexico, Cuba, Egypt, South Africa and China (Peto et al., 1999). COPD is currently the 12th leading cause of disability worldwide (Stang et al., 2000). It is expected to become the third leading cause of death after ischemic heart disease and cardiovascular diseases and the fifth leading cause of disability by 2020 (Lundback et al., 2003).

GENETIC PREDISPOSITION

Exposures to environmental factors such as tobacco smoke or occupational air pollutants play a significant role in the pathogenesis of COPD (Higgins, 1991). WHO (1996) estimate that there are approximately one-third smokers in the world or approximately one third of the global population ≥ 15 years old are smokers.

A marked variability in the development of airflow obstruction in response to smoking has been reported (Burrows et al., 1987). Interestingly many countries with high rates of smoking have a low prevalence of COPD. For example, despite the highest tobacco consumption, the prevalence of COPD in China is reported to be very low (Halbert et al., 2003). In Caucasians, only 10-20% of chronic heavy cigarette smokers develop symptomatic COPD. This suggests that other factors are likely to be important in determining which cigarette smokers are at the risk of developing airflow obstruction (Sandford et al., 2002).

Population studies of families and twins have demonstrated familial aggregation of respiratory symptoms (Kueppers et al., 1977; Khoury et al., 1986; Tager et al., 1988; Redline et al., 1989). Larson and Barman (1965) showed aggregation of COPD in families favoring a genetic basis for COPD. Familial aggregation of reduced lung function was observed in relatives of COPD patients suggesting a genetic basis for the development of COPD (Kueppers et al., 1977; Redline et al., 1989). Case control studies also demonstrated an increased prevalence of COPD in relatives of COPD patients (Khoury et al., 1986; Tager et al., 1988).

Difference in the prevalence of COPD among different racial groups indicates that genetic factors may play an important role in the development of COPD (Cox et al., 1980; Marcus et al., 1988; Buist et al., 1995; Blanco et al, 2001). COPD is more common in whites than blacks and other racial and ethnic groups (Cox et al., 1980; Zhu, 2001). The susceptibility to develop COPD was found to vary between different racial and ethnic groups with Caucasians being more susceptible and Asians and Africans less susceptible (Blanco et al, 2001). The prevalence of COPD in Japanese Americans was found to be very low when compared with Caucasian Americans (Roberts et al., 1977; Marcus et al., 1988). It is also uncommon in Chinese living in the USA (Buist et al., 1995). These reports indicate a genetic predisposition for the development of COPD.

The association of COPD to inherited severe deficiency of the serine protease inhibitor α1-AT has been known since 1963, and remains the only proven genetic risk factor for severe, early onset of COPD. Alpha-1-antitrypsin serves
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primarily as an inhibitor of neutrophil elastase (Snider et al., 1985). Laurell and Eriksson (1963) observed that members of families who have low concentrations of serum α1-AT have a high prevalence of pulmonary emphysema than the usual smoking population that acquired emphysema. Gross et al (1964; 1965) reported that when lung tissues of rats were treated the elastolytic enzyme papain, it degrades them to produce parenchymal destruction resembling centrilobular and panacinar emphysema.

Subsequently, it was demonstrated that the normal human neutrophil contained a potent serine elastase (Janoff and Schere, 1968). The serum from patients with α1-AT deficiency also showed less inhibitor capacity specifically for elastase (Turino et al., 1969). These observations led to the protease-antiprotease imbalance hypothesis for the development of lung destruction in pulmonary emphysema. The proteinase-antiproteinase hypothesis originated with the observation that subjects with inherited deficiency of plasma alpha-1-antitrypsin were particularly susceptible to the development of emphysema. Thus research into human emphysema concentrated on the role of α1-AT and neutrophil elastase in the pathogenesis of the disease.

ALPHA-1-ANTITRYPsin: STRUCTURE, FUNCTION AND MOLECULAR GENETICS

Alpha-1-antitrypsin is the archetypal member of the Serine Protease Inhibitors (Serpins) family that is widely distributed throughout the plant and animal kingdoms performing a diverse array of functions. The major function of α1-AT is to protect the elastic tissue from proteolytic attack (Potempa et al., 1994). Alpha-1-antitrypsin exhibits broad substrate specificity, inhibiting a variety of serine proteases including neutrophil elastase, cathepsin G, kallikrein, pancreatic trypsin, rennin and urokinase (Beatty et al., 1980). However, kinetic studies have shown that the neutrophil elastase is the primary target for α1-AT especially in the lung (Heidmann and Travis, 1986).

The liver is the predominant source of α1-AT. It is subsequently secreted into the blood stream where it accounts for 90% of the protease inhibitor capacity in serum (Perlmutter, 2002). The major site of action of α1-AT is alveoli of the lung, where it functions to protect elastic tissues from excessive hydrolysis by neutrophil elastase. A normal serum concentration of α1-AT (1.3 g/L) is necessary to maintain the normal structure and function of the human lung (Gadek et al., 1980).

The synthesis of α1-AT is controlled by a pair of genes at the Pi (Protease inhibitor) locus and is inherited as co-dominant alleles (Gadek and Crystal, 1983). The gene-encoding human α1-AT resides in an approximately 320kb gene cluster of serine protease inhibitor genes. This region also includes the genes encoding α1-antichymotrypsin, protein C inhibitor, kallistatin, corticosteroid binding globulin and an antitrypsin related pseudo gene. These six genes are organized into two discrete sub clusters of three genes each, which have similar genomic organizations (Rollini et al., 2000).

The aat gene locus is highly polymorphic and is mapped to chromosome 14q 31-32.3 (Byth et al., 1994). Long et al (1984) obtained the complete cDNA sequence of the aat gene. The gene length was 12.2kb with a 1,434bp coding region. According to the gene structure, aat is composed of seven exons separated by six introns. Exon I, the 5' prime portion of exon II and 3' prime portion of exon V are non-coding regions. The first intron contains a 143 amino acid open reading frame, an Alu family sequence and pseudo transcription initiation region. The major transcription site starts from the middle of exon Ia. Cis acting promoter sequences are present in the 5’ to exon Ia and in the middle of exon Ic. Two different hepatocyte nuclear proteins bind in the region between Ib and Ic. C-jun protein binds within exon Ib region. The start codon (ATG) lies in the exon II followed by sequences coding for a 24 residue signal peptide. The sequences for the matured protein start in exon II and end in the exon V. Three identical carbohydrate attachment sites, two in the exon II (Asn46 and Asn83) and one in the exon III (Asn 247) are present. The sequence for the active residue is in the exon V.
region. There is a promoter region specific for hepatocytes and an alternate promoter for monocytes and macrophages.

The \textit{aat} gene is expressed in liver hepatocytes and mononuclear phagocytes as a 1.75kb mRNA, translated and secreted into the ER. In the rough ER, N-linked carbohydrates are added to each of the 3-asparaginyl residues- 46, 83 and 247. The protein is translocated to the golgi bodies where the high mannose carbohydrates are trimmed and the glycosylated \(\alpha\)-AT is secreted as a mature protein of 394 amino acids. The mature protein circulates in the plasma with a half-life of approximately 5 days and diffuses into all tissues where it functions to inhibit neutrophil elastase (Perlmutter \textit{et al.}, 2000).

The 3D conformation of \(\alpha\)-1-AT is determined by nine \(\alpha\)-helices and three \(\beta\)-pleated sheets made of parallel and anti parallel strands. An exposed mobile reactive loop presents a peptide sequence as a pseudo substrate for the target proteinase. In \(\alpha\)-1-AT, this loop is occupied by the P\(_1\)-P\(_1\)' residues (methionine- serine) and act as “bait” for neutrophil elastase. The methionine residue can be easily oxidized resulting in the functional inactivation of the protein (Moraga and Janciauskiene, 2000). The crystallographic study of serpin protease complex indicates a conformational change initiated by reaction of the active serine of the protease with the active residue of \(\alpha\)-1-AT. The reactive loop cleaves and moves to the opposite pole while displacing the tethered protease along with it. After docking, the proteinase is inactivated by a mouse trap action that swings it from the upper to the lower pole of the protein in association with the insertion of the reactive loop as an extra strand in \(\beta\) sheet A). This complex is then recognized by hepatic receptors and cleared off from the circulation. The reactive loop \(\beta\)-sheet A interaction of the serpin is crucial for their role as effective antiproteinases. It also renders them liable to undergo conformational transitions that cause diseases. Mutations in the mobile regions lead to the loss of function, with consequences that reflect in the physiologic role of proteinase inhibitor (Lomas and Mahadeva, 2002).

**GENOTYPES OF PROTEASE INHIBITOR (PI) SYSTEM**

During serum electrophoresis in an acid gradient, the \(\alpha\)-1-AT protein moves towards the anode and splits into three major and five minor antitrypsin bands. Difference in the speed of migration of different \(\alpha\)-1-AT variants on serum electrophoresis has been used to identify the Pi phenotype. These differences in migration relate to variations in protein charge resulting from nucleotide base alterations (Fagerhol and Cox, 1981). Based on the mobility the variants are named: F-Fast, M-medium, S-slow. The E, F, G and I variants are electrophoretically faster than the M protein, while the P, S, V, W, X and Z proteins are slower than the M protein.

With respect to circulating \(\alpha\)-1-AT levels, Pi alleles may be classified as “normal” (normal levels of functional \(\alpha\)-1-AT protein), “deficient” (low serum \(\alpha\)-1-AT protein level), “dysfunctional” (normal level of a non-functional \(\alpha\)-1-AT) or “null” (no \(\alpha\)-1-AT detectable). From the viewpoint of \textit{aat} gene evolution, \(\alpha\)-1-AT variants can be categorized into two groups: the variants derived from the oldest human \textit{aat} gene- PiM1 Ala213 (example: PiZ, PiM Heerlen, and PiNull Granitefalls) and those derived from the newer \textit{aat} gene PiM1 Val213 (example: PiM3, PiM2 and PiNull Bellingham) (Crystal \textit{et al.}, 1989).

The normal M alleles represent by far the largest group of \textit{aat} alleles. The normal \textit{aat} alleles are characterized by their association with normal levels of \(\alpha\)-1-AT in serum and normal function of the \(\alpha\)-1-AT protein. Inheritance of anyhomozygous or heterozygous combinations of the M family proteins is associated with “normal” levels of \(\alpha\)-1-AT. Among the Caucasians of northern European descent, M1 (Val213) allele is the most common allele (allelic frequency- 44-49%) followed by M1 (Ala213)- 20-23%, M2- 14-19% and M3- 10-11% (Blanco \textit{et al.}, 2001).
The deficiency group is characterized by \textit{aat} genes that code for \(\alpha_1\)-AT present in serum but in amounts insufficient to protect the lower respiratory tract from progressive destruction by neutrophil elastase. Deficiency alleles of \textit{aat} gene represent the clinically relevant group and include mainly the PiZ and PiS alleles. The PiZ variant differs from the PiM variant by a single nucleotide substitution of G by A at codon 342 exon V resulting in the amino acid substitution of Glu (GAG) to Lys (AAG). Based on the assumption of random recombination, origin of PiZ was proposed to be approximately 2000 years old. With frequency higher in the northern Europe it has been accepted that the PiZ gene had first arose in the northern Europe and subsequently spread to other European countries. It has an allelic frequency of 1-2\% in Caucasians of northern European descent (Crystal, 1990).

Individuals carrying the PiS gene exhibited reduced \(\alpha_1\)-AT plasma levels (60\% for PiSS, and 80\% for PiMS. Molecular characterization of the PiS allele revealed an A to T transversion resulting in a Glu to Val substitution at residue 264, exon III (Long \textit{et al.}, 1984). It is hypothesized that the origin of PiS allele occurred around 10,000 to 15,000 years ago making the PiS mutation much older than the PiZ allele. The PiS allele has an allelic frequency of 2-4\% in Caucasians of northern European descent and varies from 10\% in the southern Europe to 5\% in the north, a distribution gradient with opposite direction to Z allele frequency.

Null phenotype is defined as the total absence of immunologically cross-reactive \(\alpha_1\)-AT in serum. The two parental \(\alpha_1\)-AT genes are not expressed, such that they produce no or insufficient \(\alpha_1\)-AT to be detected in the serum. It is estimated that among the Caucasians, null \(\alpha_1\)-AT alleles have a haplotypic frequency of approximately 0.001. When inherited with certain deficient haplotypes such as Z or with other null haplotypes, the affected individuals are at high risk for the development of emphysema. The molecular mechanisms responsible for absence of serum \(\alpha_1\)-AT include splicing abnormalities, deletion of \textit{aat} coding exons and premature stop codons. Some of the null variants are Null Granitefalls, Null Bellingham, Null Hong kong (Crystal, 1990).

Dysfunctional variants are present in normal levels but do not function normally. In the P\(_1\)-P\(_1\) loop of Pi Pittsburg, methionine is replaced by arginine residue. This results in the inhibition of the highly effective coagulation proteases-thrombin instead of neutrophil elastase. The consequence is life threatening hemorrhagic disease (Lewis \textit{et al.}, 1978).

**ALPHA-1-ANTITRYPsin DEFICIENCY IN EMPHYSEMA AND COPD**

The normal function of the respiratory system is to exchange oxygen (O\(_2\)) and carbon dioxide (CO\(_2\)) so that O\(_2\) is delivered to and CO\(_2\) is removed from the blood. CO\(_2\) is the major stimulus for the respiratory centre, which is located in the medulla of the brain. When the partial pressure of CO\(_2\) (PaCO\(_2\)) is increased, ventilation is stimulated resulting in increased removal of CO\(_2\). This process is supported by the components present in the respiratory tract-a conducting system, respiratory exchange unit and a vascular supply. The conducting system (upper respiratory system) is composed of the nose, pharynx, trachea and bronchi. The respiratory exchange units (lower respiratory tract) include the bronchioles, alveolar ducts, alveolar sacs and alveoli. The normal acinus is supplied by a terminal bronchiole. The terminal bronchiole undergoes three orders of branching, first into respiratory bronchioles with alveolar walls then into alveolar ducts and finally into alveolar sacs. The alveoli (tiny air sacs) remove carbon dioxide from the blood, releasing it into the lung to be breathed out, and also absorb oxygen, transferring it into the blood. This exchange is essential to survival and is the key function of the lungs. Normal airway integrity is maintained through the relationship of pressure in and around the airways and the elasticity of the airways.

During inflammation, activation of airway neutrophils release neutrophil elastase (Lucey \textit{et al.}, 1988). Neutrophil
elastase, a 29kDa extra cellular protease is produced by white blood cells to help fight bacteria and clean up lung tissue. Extra cellular release of neutrophil elastase occurs after cell death, phagocytes or neutrophil activation by a variety of stimulants. Despite its useful role in fighting infection, neutrophil elastase also has the potential to be harmful, damaging healthy lung tissue and when in excess, the protective effects are overcome by the destructive effects. The elastases also stimulate macrophages to release the chemoattractant leukotriene B4 (LTB4). This further recruits neutrophils to the site of inflammation. In the lung, elastases and proteases released from neutrophils are capable of digesting parenchymal tissues including basement membranes, capillary endothelium and alveolar walls. The consequences result in the connective tissue destruction especially the elastin breakdown. This destructive role of elastase is balanced by a sufficient amount of alpha-1-antitrypsin in the circulating blood.

In alpha-1-antitrypsin deficiency, the alveoli and bronchial tubes are destroyed due to excessive proteolytic action of the uninhibited neutrophil elastase. The oxygen-carbon dioxide transfer becomes much less efficient and the stale air is trapped in the isolated sacs. More air is required to provide the same amount of oxygen to the blood via the parts of the lung that are still functioning (Goldsmith and Weber, 1996; Pierce, 1997). This need for more air eventually leads to lung over-inflation. As the lung over expands, it gradually enlarges, completely filling the chest cavity and causing a sense of shortness of breath (Sandford et al., 1999; Hogg and Senior, 2002).

**ALPHA-1-ANTITRYSIN DEFICIENCY RELATED LIVER DISEASES**

In addition to obstructive pulmonary disease, liver disorders are also found. Liver disease in association with alpha-1-antitrypsin deficiency was first recognized by Sharp et al (1969) and has a less common prevalence than lung diseases. It is associated with PiZ homozygotes, PiM Malton, Pi Siiyama and the compound heterozygotes PiSZ, PiZ-aat variants (Seyama et al., 1995). The suggestive mechanism in the development of liver abnormalities in these variants is that the base change from the normal sequence reduces the rate at which the α1-AT peptide folds to form the tertiary structure. This slow folding allows the peptide monomers to come together by a loop sheet insertion mechanism to form polymer, which is retained within the endoplasmic reticulum (Primhak and Tanner, 2001).

**FEATURES OF ALPHA-1-ANTITRYSIN DEFICIENCY**

Alpha-1-antitrypsin deficiency shows a recessive mode of inheritance in familial conditions. Individuals with α1-AT deficiency have two deficient alleles for the protein. Brothers and sisters of deficient individuals have a 25% chance of inheriting the condition. Children of deficient individuals can be expected to be heterozygotes for the deficiency. The risk is high only if the partner of the deficient individual is a carrier (Cox, 1989). Alpha-1-AT deficiency related emphysema patients have the lowest survival rate (Burrows et al., 1987). Estimates of longevity in patients with α1-AT deficiency predicted a life span shortened by 10 to 15 years, compared with the normal population. They also have the highest rate of decline in pulmonary function (Brantly et al., 1988; Boschetto et al., 2003). Symptomatic obstructive lung disease in α1-AT deficiency usually presents at a mean age between 32 and 41 years in individuals with a history of smoking (Eriksson, 1965; Brantly et al., 1998).

**PREVALENCE OF ALPHA-1-ANTITRYSIN DEFICIENCY**

Studies on Caucasian populations gave a frequency of 1 in 2,857 (Silverman et al., 1989), 1 in 5,097 (Wall et al., 1990) and 1 in 3, 694 (Colp et al., 1993). Crystal (1990) reported that α1-AT deficiency occurs at a frequency of 1 in 2000-7000 Caucasians but only rarely in African or Asian populations. In a worldwide analysis on the racial and ethnic distribution of α1-AT deficiency, α1-AT deficiency was reported to be prevalent in populations of African blacks, Arabs
and Jews in the middle east, central, far east and southeast Asians, whites in Australia, Europe, New Zealand and north America (de Serres, 2002; 2005).

**CIGARETTE SMOKING ACCELERATES COPD IN PRESENCE OF ALPHA-1-ANTITRYPSIN DEFICIENCY**

Alpha-1-antitrypsin deficiency in smokers is associated with an accelerated development of emphysema and premature mortality (Gadek et al., 1980). Cigarette smoke is thought to cause emphysema by creating a functional protease imbalance in peripheral lung areas (Hunninghake and Crystal, 1983). In α1-AT deficient smokers, more neutrophils were found within airspaces than in emphysematous lungs of individuals with normal α1-AT plasma levels (MacNee et al., 1989). Hutchison et al (1987) found a decline of the overall forced expiratory volume in 1 second (FEV₁) in smokers. This was supported by other studies indicating a significant decline in FEV₁ in smokers when compared with non-smokers (Janus et al., 1985; Pittulainen and Sveger, 2002).

Cigarette smoke also stimulates neutrophils and macrophages to increase the production of proteinase, stimulating them to produce oxidants such as HOCl₂, H₂O₂, a component of cigarette smoke is involved in the inactivation of α1-AT (Luisetti and Travis, 1996). The wild type α1-AT is also susceptible to oxidative impairment due to conversion of the reactive site methionine (Met358) to its sulphoxide derivative by oxidants contained in cigarette smoke or released from phagocytes resulting in loss of inhibitory activity (Johnson and Travis, 1991; Taggart et al., 2000).

**MOLECULAR DIAGNOSIS OF ALPHA-1-ANTITRYPSIN DEFICIENCY**

Identification of the aat phenotype or genotype provides important information relevant to the relative risk for emphysema and / or liver disease and plays an important role in the laboratory diagnosis of α1-AT deficiency. The accurate diagnosis of α1-AT deficiency is critical for proper evaluation, treatment and the genetic counseling of the individuals and their family members. The main advantage of early diagnosis is that patients may be persuaded to stop smoking. Hence diagnosis will enable the individuals to institute lifestyle changes that may slow down the progress of deterioration.

Alpha-1-antitrypsin deficiency is diagnosed from measurements of plasma or serum concentration of antitrypsin. This is done by radial immunodiffusion on commercially available agarose plates that contain specific antibody. Other widely used techniques include immuno electrophoresis, turbidometric assays and enzyme-linked immunoassays (Pierce, 1997). The laboratory diagnosis of α1-AT deficiency is most frequently made by using isoelectric focusing of α1-AT in serum (Pi typing) but is very tedious and prone to errors. Recent molecular methods such as restriction fragment length polymorphism (RFLP), allele specific oligonucleotide hybridization (ASO) and allele specific amplification (ASA) have advantages over conventional methods and find application as current diagnostics tools.

**CURRENT THERAPY**

Intravenous administration of a pasteurized pooled human plasma α1-AT product (Prolastin, Bayer Corporation, Clayton, North Carolina) is used to increase α1-AT levels in deficient individuals. In individuals with moderate airflow obstruction, augmentation therapy has found to confer better benefits than in those with severe airflow obstruction. Transplantation has been found successful in severe cases of liver or lung diseases. In advanced liver diseases, liver transplantation is the therapeutic option for some patients. Restoration of alpha-1-antitrypsin levels to the normal range after orthotopic liver transplantation was observed in seven white patients who had end-stage liver disease due to alpha-1-antitrypsin deficiency. Similarly in a randomized controlled trial in patients with severe emphysema, lung reduction
surgery was found to improve FEV1, walking distance and quality of life.

Other measures include nonspecific or supportive measures for the clinical manifestations of liver or lung diseases. They include bronchodilator medications such as beta agonist salmeterol and formoterol. This is the mainstay of current drug therapy for COPD and causes a small increase in FEV1 in COPD patients. These drugs may improve symptoms by reducing hyper inflammation and thus dyspnoea. They also improve the spirometric measurements. Additional treatment includes antibiotics, oxygen therapy and systemic glucocorticosteroid (Goldsmith and Weber, 1996).

CONCLUSIONS

Worldwide, COPD is the only leading cause of death that still has a rising mortality. It has been estimated that by year 2020, COPD will be fifth among the conditions that will be the most burden to society. It is therefore, essential that strategies be implemented on a global scale to assess the prevalence of COPD, and to study the causes and outcomes of the disease and how best the burden of COPD might be mitigated. Understanding the pathogenesis of and developing novel tools for the early diagnosis for COPD represent enormous challenges as it has environmental and genetic components as stimulating factors. Alpha-1-antitrypsin deficiency is the only established genetic factor for the development of COPD. Studies on the prevalence of α1-AT deficiency have demonstrated that α1-AT deficiency will, in the near future, become one of the most common serious hereditary disorders in the world. However Alpha-1-antitrypsin deficiency appears to be widely under diagnosed. Based on the predicted gene frequencies, even in the most intensely studied populations, only a small proportion of those predicted to have α1-AT deficiency have been diagnosed. Studies on the prevalence of α1-AT deficiency have demonstrated that α1-AT deficiency will, in the near future, become one of the most common serious hereditary disorders in the world. Thus studies to identify α1-AT deficient individuals in all populations should be undertaken as unidentified individuals lose opportunities for important life style changes and preventive measures.

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