Pakistan Journal of Pharmaceutical Research
Faculty of Pharmacy, Bahauddin Zakariya University Multan, Pakistan
ISSN: 2410-6275 **July, 2017** **DOI:** 10.22200/pjpr.2017299-105

Review Article

Alpha -1-antitrypsin deficiency, associated diseases and treatments: a review

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Received: Sep, 7, 2016
Revised: Apr, 26, 2017
Accepted: May, 3, 2017
Online:

Abstract

Alpha-1-antitrypsin (AAT) *is produced in the liver and one of its most important function is to protect the lungs from the neutrophils elastase level enzymes, normal level of AAT in the blood is 1.5-3.5gm/ml, when the AAT is up to 60% the lungs function normally but when it drops below 15% patients are likely to develop Emphysema and liver cirrhosis. Alpha 1-antitrypsin deficiency is heterogeneous genetic disorder due to mutation of chromosome no 14q32.1 (SERPINA1) that leads to the protease anti-protease imbalance. Alveolar And hepatocyte damage were observed causes which is due to the deficiency of Alpha 1-antitrypsin. Disease effects every system of body like respiratory, hepatic and biliary. The aim of study is to evaluate various diseases associated with AATD. Data was collected from internet using sciencdirect.com, googlescholar.com, pubmed.com. The most common associated diseases with alpha 1 antitrypsin deficiency are emphysema, asthma, liver cirrhosis and hepatitis depending the deficiency level of AAT. The best treatment is considered the adminstration of anticholinergics and ipratropium bromide improves the lung functions, however use of bronchodilators improves asthmatic attack also vaccination is carried to prevent the Hepatitis and liver cirrhosis.*

Keywords: Antitrypsin, Alleles, SERPINA (serine protease inhibitor) ,Hepatic, Respiratory,

Introduction

liver produces Alpha-1-antitrypsin (AAT) and its function is to protect the lungs from the neutrophil elastase enzymes (Needham M *et al*, 2004). Normal blood level of AAT are 1.5-3.5gm/ml. in individual with alleles named as PISS, PIMZ and PISZ phenotypes the level of AAT is reduced up to 40-60% of normal level, this is sufficient to protect the lungs from the elastase in peoples who do not smoke. However, in individual with PIZZ phenotype the level of AAT levels are less than 15% of patients are likely to develop emphesema at the early age, 50% of these patients will develop liver cirrhosis because AAT is not secreted properly and instead accumulates in the liver. Smoking directly inactivates AAT by oxidizing essential methionine residue to sulphoxide formation and thus decreasing the enzyme

activity by 2000 (Brantly ML, *et al* 2005; Bals *et al*., 2007). Also increases inflammatory reaction in the airway. AAT is a heterogeneous genetic disorder that affect approximately 3.4 million individual worldwide and about 116 million population is carrier of disease (Emer Kelly *et al*, 2011). AAT deficiency was first time documented by Laurel and Erikson in 1963. They carried out a pains taking review of 1500 serum protein electrophoresis gels in which the band for the alpha 1 was absent. Differences in protease inhibitor of common homozygous allele with MZ, MM, MS, and ZZ phenotype are observed as shown in (figure1) (Brantly ML *et al*, 2005; M. Sh. Badawy *et al*, 2013). Mutation of chromosome no14q32.1, serine protease inhibitor (SERPINA1) gene and protease inhibitor locus are considered the reason of disease (Robert Balsa *et al*., 2007; Sabina M. *et al*, 2011). The term SERPINA was introduced as by Carrel and Travis in 1985 to describe a super family of serine protease inhibitors of plasma (Figure 2). Serpent like gene and over a 1000 member of the disease have been identified in animal, poxviruses, plants, bacteria and archaic. AAT genes are

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located on the long arm of chromosome 14 and have successfully sequenced and cloned. There are almost 75 Alleles for AAT variant that have been described but only 10-15% is associated with severe (AATD) Alpha 1 – antitrypsin deficiency. These alleles are basically divided into four groups.

Normal M Alleles (phenotype MM) 90% of USA population have normal lung functions. Deficient alleles Z observed 2-3% of the USA population plasma level less than 35% of normal. Null no detect AT least common and most severe form of diseases. Dysfunction patient have abnormally AAT level, but the enzymes does not function properly. Every 3out of 5 patients developed Emphysema at young age. AAT deficiency is a genetic cause of chronic obstructive pulmonary Diseases (COPD). National health information survey in the USA with approximately 3.1 million Americans developed emphysema which is caused by AATD. The clinical diseases present in a number of ways but the most frequent organs affected are lungs and liver.

The protease activity of human plasma was first discovered by Fermi and Penrose in 1894. However, the isolation and characterization of individual proteins emerged much later with the availability of new techniques. Serum trypsin inhibitor responsible for anti-protease activity was first isolated in 1955 by Schultz and named AAT because of its occurrence in the alpha 1-Globulin fraction and its ability to inhibit trypsin (Sabina M. *et al*, 2011). Single amino acid substitution i.e. Glutamic acid for Lysine may lead to impaired product which leads to Protease and anti- protease imbalance ultimately increased alveolar damage (Carla Spınola *et al*, 2009). Majority of population of lung and liver diseases were also the potential candidate (Loutfi S. *et al*, 2009). AAT in is a leukocyte protease inhibitor due to this deficiency serpent is known to be at greater risk of chronic air flow obstruction (Bals *et al*., 2007).

Alpha 1 antitrypsin deficiency disease can almost effect every system of the body however most commonly it effect the respiratory system, hepatic and biliary system (Eden, *et al*, 2006; Edward Edena *et al*, 2010). Respiratory system diseases are emphysema, asthma, COPD and up to some extent tuberculosis, while in case of hepatic disorders hepatitis, liver fibrosis, liver carcinoma and cystic fibrosis are more commonly reported (Aralast, *et al*" 2003). The aim of current work is to study the various diseases associated with the AATD diseases. The diagnosis of the associated disease and various treatments currently used to cure the AATD and other associated disease.

Material and Method

The data was collected from the various published material available on internet variousearchengine like sciencedirect.com, googlescholar.com, pubmed.com, springerlinks.com, willeyblackwell were used. Data of various diseases associated with the AATD, how they were diagnosed and the possible treatments that can prevent the disease. Associated diseases were segregated successfully by using Microsoft excel 2007. Important parameter studied from the various sources are described below

AATD associated diseases

Various diseases associated with the AATD are COPD asthma, wagers granulomatous, pancreatitis, gallstones, primary sclerosing cholangitis, autoimmune hepatitis,

emphesema and cancer. These are some of the complication /diseases associated with the AATD. These disease may arise due to the deficiency of alpha1 antitrypsin. The disease is characterized with shortness of breath with or without exertion and other symptoms of COPD. Symptoms of severe liver disease unintentional weight loss and wheezing. Other associated diseases with the alpha 1 antitrypsin deficiency may include hepatitis A, Band C.

Diagnosis of diseases

Physical Diagnosis: physical examination may reveals barrels shaped, chest, wheezing, or decreased breathing.

Laboratory Diagnosis

These tests includes arterial blood gas, chest X-ray, CT-scan of the chest, Genetics testing, lung function test (Stoller *et al.*, 2006).

Treatment of alpha1 antitrypsin deficiency and associated diseases

Preventing the progression of lung disease is one of the major goal of (AATD) management. Which decreases pro inflammatory stimuli in the alveolus, these stimuli may include smoking, asthma, respiratory infection, besides achieving these goals. Augmenting or replacing the deficient enzyme, and thereby moderating inflammatory stimuli, is also to be considered a major factor in prevention of lung disease from progression. Most patients are identified only after they develop lung disease, and the goals of treating AATD emphysema are similar to those for treating all forms of emphysema. To decrease the risk of liver disease, vaccination against hepatitis A and B is recommended (Stoller JK *et al* 2007).

Smoking has a greater effect than any other treatment for emphysema, to prevent the disease progression make an effort to inform the patients about the most common consequences of smoking on AATD.

The 4 stages in the process of helping patients become nonsmokers: ask about smoking habits; advice about health effects; assist the patient with encouragement, education, and nicotine replacement; (Brantly *et al.*, 2005). Improving lung function. Administration of short-acting beta-adrenergic agents and ipratropium bromide bronchodilators improves the lung function up to a certain level. One of the preferred method for administration of these drugs is metered dose inhaler because they have a lower incidence of adverse effects than other routes. Inhaled corticosteroids have not been studied in patients with AATD emphysema, but many patients have significant bronchore activity. Long-acting inhaled beta-adrenergic drugs and anticholinergics provide improved bronchodilation and symptoms for patients with COPD. They have not been studied in a population with AATD, but they are likely to provide the same benefits. Long-term administration of corticosteroids does not protect the lung from progressive emphysema, but it is associated with many detrimental adverse effects. Limit oral steroid use to brief courses of 1-2 weeks. Theophylline may lessen the degree of dyspnea in some individuals, and a therapeutic trial may be indicated for selected patients. The therapeutic range of theophylline is relatively small, and its metabolism frequently is altered by other drugs or illness, which can lead to frequent episodes of drug toxicity or the need for frequent monitoring of serum levels. Most programs combine education, exercise conditioning, breathing training, chest

physical therapy, and respiratory muscle training with nutritional counseling and psychological support (Brantly ML, 2005).

Therapy does not improve pulmonary function test results, but well-controlled studies document significant improvement in exercise endurance, exercise work capacity, level of dyspnea, quality of life and reduction of health-related expenses (Stoller JK *et al* 2006).

Replacing enzymes

AATD individuals who have or show signs of developing significant emphysema can be treated with Prolastin, a pooled, purified, human plasma protein concentrate replacement for the missing enzyme that has been screened for HIV and hepatitis viruses, although practitioners should immunize patients against hepatitis regardless. It also is heat-treated as an additional precaution against transmission of infection. The US Food and Drug Administration (FDA) has approved 2 other alpha1-antitrypsin protein concentrates, Aralast and Zemaira, for augmentation therapy. Weekly IV infusions of AAT protein concentrates restore serum and alveolar AAT concentrations to protective levels. No controlled studies have proven that IV augmentation therapy improves survival or slows the rate of emphysema progression. Results from the NIH patient registry and a comparison of Danish and German registries have been published, and both suggest that augmentation therapy has beneficial effects. Although they were not controlled treatment trials, the similarity of the results suggests that the findings are significant(Stoller JK *et al* 2006).

The NIH report described an overall death rate 1.5 times higher for those who did not receive augmentation therapy and a rate of FEV_1 decline (54 ml/y) in AATD individuals, about twice that of healthy nonsmokers but about 50% that of smokers (108 ml/y). Prolastin augmentation therapy did not improve the average FEV_1 decline (54 ml/y); however, participants with moderate airflow obstruction (FEV_1 35-60% of predicted value) had a slower rate of decline (mean difference 27 ml/y).

Lung transplantation

If patients are at substantial risk of early mortality and poor health conditions, they may be candidates for lung transplantation. Contact a local transplant center before patients become too ill (cachexia, inactivity, frequent infections). With a recent change in the system for allocation of lungs for transplantation, patients with emphysema are being more carefully evaluated for listing. Many transplant programs have adopted the (Body mass index, airflow obstruction, dyspnea and exercise) BADE index to identify patients with emphysema who are most likely to benefit from transplantation. The uncertainties of emphysema exacerbations and complications that might prevent transplantation make it imperative that patients be referred when their BADE index is 5-6 or if they have experienced an episode of acute hypersonic respiratory failure.

Liver transplantation

Liver transplantation is the definitive treatment for advanced liver disease.

Diet

Patients with advanced COPD are characterized by a significant reduction in fat-free muscle mass. This pulmonary cachexia is common in patients with AATD and is associated with a decline in clinical status. The syndrome is a result of multiple factors, including hyper metabolism, drug

therapy, inactivity, and aging. Prolonged glucocorticoid administration accelerates the process. Protein-calorie supplementation, as one component of a comprehensive treatment program, may reverse the loss of muscle mass, and dietary counseling may aid patients at high nutritional risk. Adding fat-based no protein calories may benefit patients with respiratory failure who are receiving mechanical ventilation. However, other than this special circumstance, little evidence exists to suggest that this dietary manipulation aids ambulatory patients.

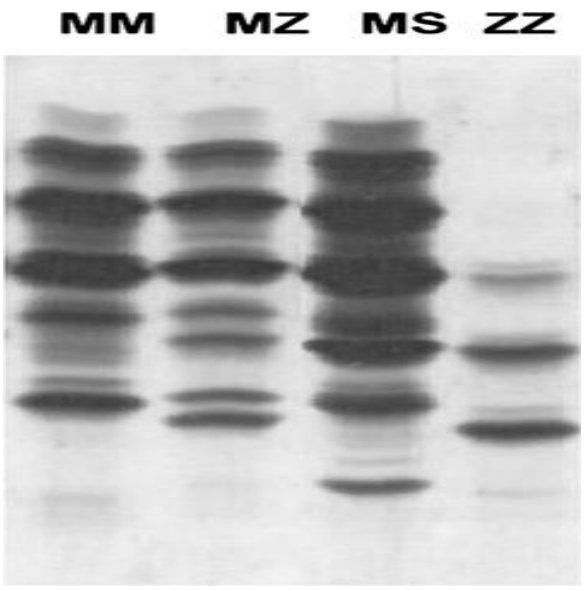
Result and Discussion

AAT is produced by the liver and its function is to protect the lungs from the damage caused by the ex-cassava release of neutrophils. Normal level of the AAT reported in the range of 1.5-3.5g/ml. It is reported that if the level of AAT is below the normal level the individuals who are deficient in the AAT have no of diseases associated with the AAT deficiency. The common diseases associated with the AATD include asthma, emphysema, chronic obstructive pulmonary disease, liver cirrhosis, hepatitis. The disease is diagnosed with either the physical examination or laboratory. The possible treatments quit smoking and on current adminstration of adrenergic drugs with the ipratropium bromide which provides the relief to the patient however disease can be prevented from further progression by improving the lung functions. Disease can be completely eradicated by improving diet, liver transplantation and lung transplantation (Eden E *et al*., 2006).

AATD diseases are found to be rare in Asian and Mexicans. It is uncommon in Black American (2.6/1000) and more common in Hispanic(9.1/1000).14 out of 1000 white Americans are effected (Kyrsten D. et al, :2008;). Severe deficiency of first symptoms appeared in 35.0 years. Diagnoses age is 41.3 years due to its complication which appears late (JAMES k *et al*, 1994). Social environment are uncertainty including criticism having a family member with illness and participation in a support group. AATD disease may be due to a dominant susceptibility to Wagner's granulomatous (WG). Most of the study revealed that almost 5-27% of the patients with AATD must have WG, however it is not clear that these Z allele is the associated factor for the disease (Mahr *et al*,2010).

Table 1: phenotypes and the likely clinical consequences

Phenotypes	Serum conc.umol/l	COPD risk
Pi-MM	20-53	General population
Pi- MS	20-48	Very low /general population
Pi- SS	15-33	Low
Pi- MZ	12-35	Low
Pi- SZ	8-19	Variables
Pi- ZZ	2.5-7	High
Pi- z-null	<2.5	Very high
Pi- null-null	None	Very high



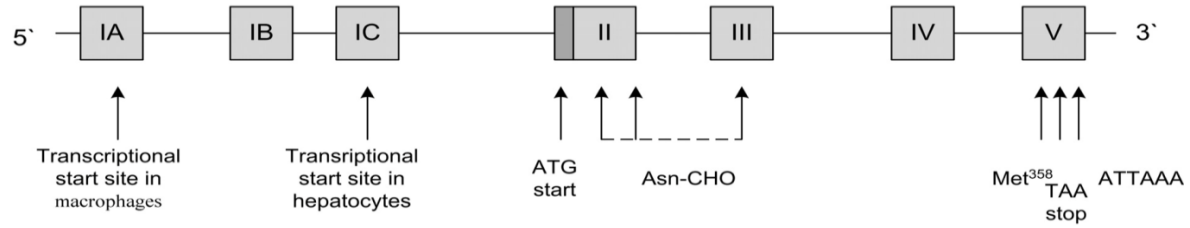


FIGURE2: *SERPINA1* gene structure. Boxes IA to V donate exons. Exons IA, IB, and IC have regulatory elements for normal A1AT expression. ATG start codon is localized in the second exon. As-CHOs are three carbohydrate attachment sites. Active site Met358, the TAA stop site, and polyadenylation signal are localized in the fifth exon.

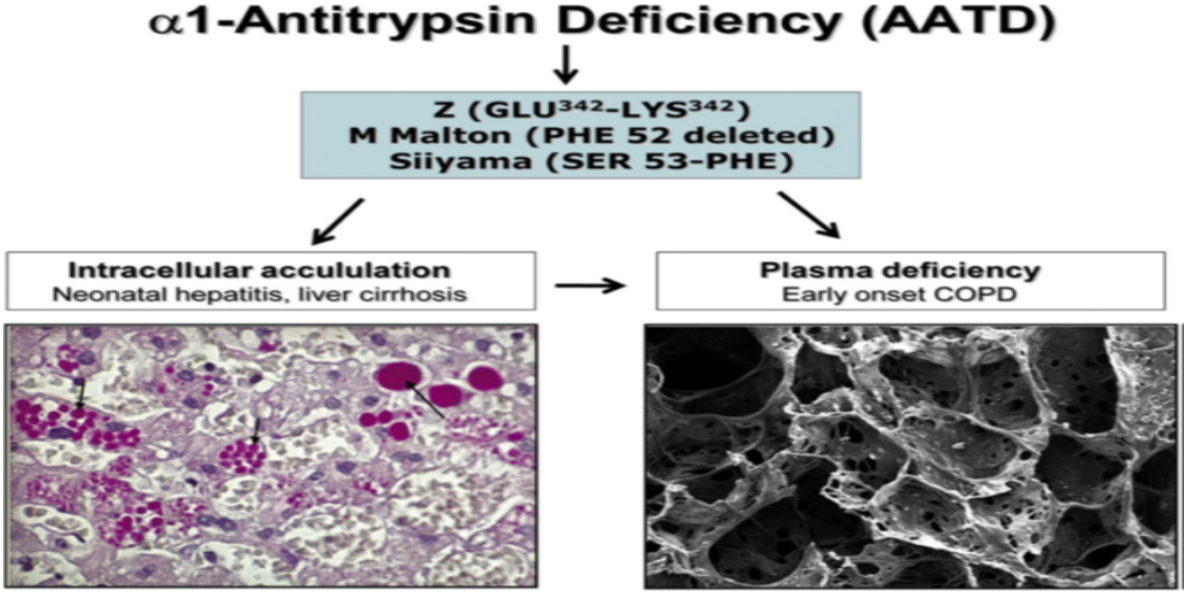


figure3: AATD and associated diseases

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