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A NEW CONCEPT ON PREVENTION AND CURE OF DISEASES BY A BROAD SPECTRUM PROTEASE INHIBITOR (A2M)

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Abstract

Different types of proteases may play influential rolesacross a spectrum of diseases. Correspondingly, protease inhibitors have been known to play crucial roles in the patho-physiology of diseases. We hypothesize the activity of the broad spectrum protease inhibitor, alpha-2-macroglobulin (A2M) may hold unexplored roles in diseases as well. Clinically measuring levels of variant proteases in combination with the monitoring of A2M, in plasma, can be a novel approach to further our understandingof diseases related to protease activity. There is evidence showingadministration of purified human A2M to animal models with bacteria induced septic shock usingPseudomonas aeruginosaresulted in the reversal of the pathological effect. In addition, recent evidence has also shown the beneficial effectsof treatment with autologous A2M in post-traumatic osteoarthritis patients. We have measured levels of protease (trypsin) and A2Mduring the chronic ill patients (n=31) and compared their values to normal healthy donors (n=31). Our results show protease activity in blood went up from 516.16 ±17.17 to5021.22 ± 61.63 mg/ml ($p<0.001$) and A2M levels went down from 2013.30 ± 52.00 to 487.64 ± 9.70 ($p<0.001$). All critically ill patients showed a significant increase in protease levels and also a significant decrease in protease inhibitor (A2M). These results further support evidence suggesting an inverse relationship taken on by protease and protease inhibitors in severe to terminal cases.

Key Words: *Proteases, alpha-2-macroglobulin, Life-saving protein, Diseases, Medicine*

INTRODUCTION

This publication examines the levels of the life-saving protein alpha-2-macroglobulin (A2M) present in the blood of terminally ill patients who have received all possible methods of treatment, and endeavors to reveal new information about these diseases while considering the levels of A2M - a broad spectrum protease inhibitor - in the blood.

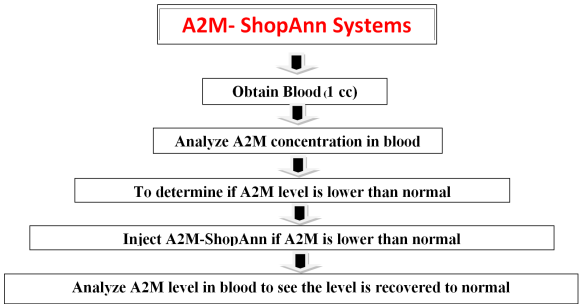
If blood test results show less-than-normal presence of A2M (1-2 mg/ml)[1], the effects of toxicity associated with potentially harmful proteases can be considered factors in the development of several diseases. This is due to the fact the main element which can remove this toxic protease is the protein A2M. A deficiency of this protein can allow increased levels of toxicity - which, in turn, impairs the body's defense mechanisms, ultimately leading to serious illness. Therefore, this publication considers it possible that many diseases may be prevented at onset if depleted levels of A2M in the body are replenished through the simple system**A2M-ShopAnn Systems.**

The new, life-saving method of treatment A2M-ShopAnn Systems can open up new horizons in the field of medical science. I have recently patented this method of treatment in the US. After extensive examination, the United States Patent and Trademark Office (USPTO) has recognized that A2M-ShopAnn Systems plays an important role in the treatment of several diseases as described in the patent.

This may also mean that the following terminal diseases can someday be cured using this method of treatment: Diabetes; Hypertension; Viral infections (including HIV); Flu; Cholera; Malaria; Diarrhea; Dengue; Chicken pox; Rheumatic fever; Infection; Septicemia; Septic shock; Cerebrovascular diseases (Stroke); Cardiovascular diseases; Heart attack; any clot formation and clotting disorders; any form of Cancer; Alzheimer's disease; Autoimmune

diseases; Psychiatric disorders (including Autism and Schizophrenia); Genetic disorders; Kidney disorders; Joint pain; and other diseases where the involvement of protease(s) can be traced.

A brief introduction of the method of A2M-ShopAnn Systems is given below



A2M levels. These 31 inpatients (in a hospital in Bangladesh) were found to have almost one fourth of the normal level of A2M.

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The scientific analysis of these tests has been published in an online journal (http://www.rarediseasesindia.org/septicshock/proteasprevalence) and also been published in the Journal of Clinical & Experimental Pathology[2,18]. Never before were patients tested for the level of A2M in the blood during illness, indicating that this may shed light on a new area of medical science.

The first question which arises concerns the function of A2M in the blood. Since A2M is a broad spectrum protease inhibitor, its main function is to prevent any formation of protease. Scientific research has shown that protease is a potentially harmful chemical and the main cause for numerous diseases. Protease attacks the proteins in the body's immune system, thus impairing the body's defense mechanisms. Therefore, to remain healthy, it is necessary to remove this protease from the body.

The task of removing protease from the body is done by A2M: an amazing protein associated with protection against disease.

It can accurately be said that the main function of A2M is to maintain our body's immune system. Separate from its effect on protease, A2M also works in the body to continuously remove redundant chemicals such as growth factors; cytokines; hormones; and soluble beta-amyloid. For various reasons, these present as abnormal and harmful elements in the body during the development of several diseases.

Thus it could be keeping us healthier than we may currently ascertain.

Similar to the continuous manner with which pathogens enter the body, the body saves itself by constantly destroying these pathogens with the aid of various types of cell and chemical substances with resistive properties. Due to this resistive power, the body is able to decide what does not belong in the body, and even removes it entirely. This is how, under normal conditions, we are able to remain healthy. However, there are times when the body loses its immunity and that is when we begin to feel sick. No matter how they enter the body, these microscopic pathogens start fighting for their own existence. The result of this battle determines our well-being. In most cases, the body wins, and the pathogens are defeated, and for this reason we do not feel constantly ill.

Scientific Analysis

Below is a typical diagram illustrating the manner in which pathogens entire the body with the help of protease, and the way in which the blood's supply of A2M continuously prevents the creation of an environment favorable to pathogens, by immediately finding and removing proteases from the body, thus keeping up healthy.

Figure 1.

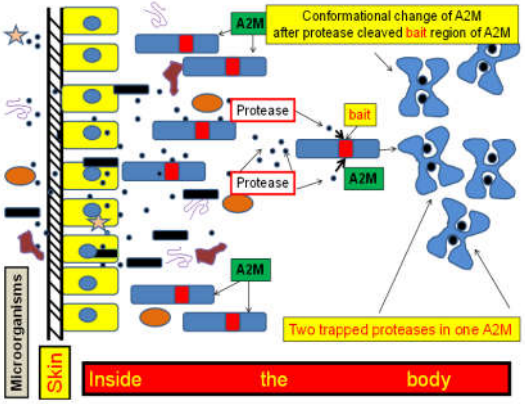


Figure 1 This diagram shows the interactions of various types of proteases( ) and the protease-resisting protein, A2M( ).

With the help of various proteases ( ), many types of pathogen (, , , ,) continuously penetrate the skin or other organ membranes in the body. After entering the body, these pathogens start secreting different types of protease for their own survival. These proteases attack a particular part of A2M ( ) containing 35 amino acids. Situated in the blood, this bait region in red ( ) attracts protease, and this attraction is suicidal for it. The protease ruptures this bait region, and the normal structure of A2M ( ) immediately changes into a trap-like shape ( ). In this manner, A2M traps two proteases[11] (A2M-Protease complex -). This "A2M-Protease Complex" is then added to a special kind of receptor (CD 91) situated within the cell coating (macrophage, hepatocyte, neuron, syncytiotrophoblast). Subsequently, through another process, this CD91-A2M-Protease is expelled along with other waste products from the body [2, 15].

Through the process of removing protease, A2M destroys any environment in which pathogens can live and reproduce. In this way, A2M is continuously protecting us from the attacks of pathogens and performing other protective functions without our knowledge. Therefore, fewer pathogens result in less protease secretion, and ultimately less A2M usage. Similarly, more pathogens result in more protease secretion, and, as a result, more A2M usage. In this manner, A2M continues to resist pathogens without our knowledge. Problems arise, however, when these pathogens exceed the levels of A2M. More protease is secreted and thus more and more A2M is used. Since there is only a fixed quantity of A2M in the body, A2M levels decrease with increased usage. When A2M levels are depleted, protease can attack other proteins freely,

weakening our body's defense mechanisms, and thus creating an environment favorable to the survival and reproduction of pathogens. It is at this time that we begin to feel the symptoms of sickness.

Therefore, when A2M levels in the body decrease due to overuse, the requirement for it in the body also increases. A2M is produced within the liver, and when A2M levels are depleted, the body tries to produce greater quantities of it. In the beginning, as protease increases within the body, A2M levels in the blood gradually decrease, even though there are sufficient quantities in the blood for the removal of protease. Our liver works hard to produce more A2M, and in so doing its ability decreases gradually, and it ultimately fails to produce the required amount. A gap is then created between supply and demand of A2M in the body. At this point, a great deal of A2M is needed.

This was observed in scientific research carried out on animals. Pathogens were introduced artificially into the bodies of guinea pigs and they were observed under Septic Shock Model until death. A2M levels were measured every hour and it was observed that the levels decreased as the guinea pigs were collapsing. Just before death, the level of A2M was reduced to 30% of that present before the pathogens were introduced. This is why the guinea pigs did not recover [7, 8]. In this same study, it was clearly demonstrated that when A2M was injected into the bodies of dying guinea pigs for treatment, 100% of the treated guinea pigs survived. A2M was shown to be a similarly life-saving protein when injected into the guinea pigs as a preventative measure before the introduction of pathogens. In this second test, 100% of the guinea pigs survived. The efficacy of the amazing, life-saving A2M, demonstrated here in research on animals, can open up a new horizon in the treatment of humans, as levels of A2M present in the human body during the development of many deadly diseases have been observed to be diminished[2,7,8,18].

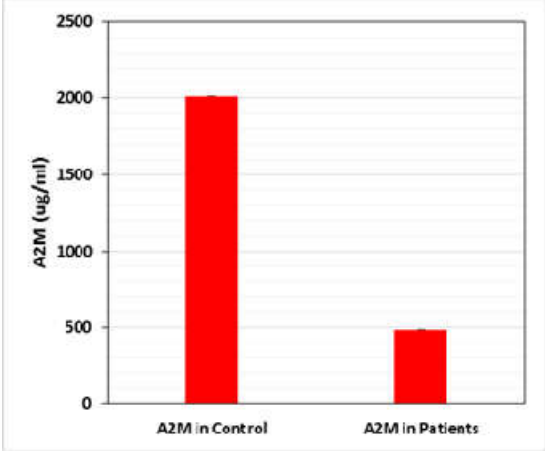
In the same way that excessive bleeding poses a life threat, depleted levels of A2M in the body can similarly bring about serious harm. Therefore, just as additional blood is required for treatment of profuse bleeding, it is necessary to increase the levels of A2M in the body when they are diminished.

During the treatment of any patient, it is desirable that the blood should be tested to assess the presence of pathogens; the amount of protease secreted by these pathogens; and the amount of life-saving A2M protein in the body, as well as other key components. When it is not possible for medical science to explain the cause of a particular illness, or when it becomes impossible for conventional treatments to cure a patient, the concept of the effectiveness of A2M can open up new possibilities.

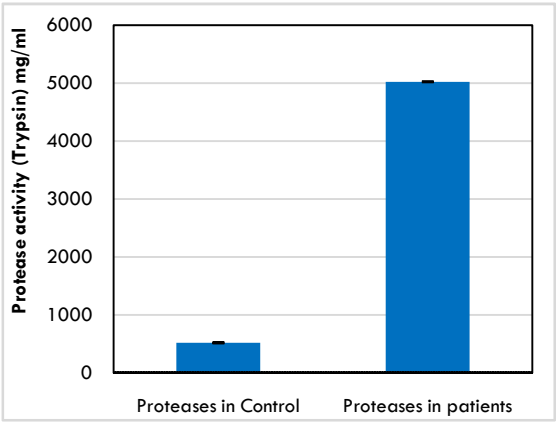
In many studies, it is surprising to observe that the Creator has bestowed the animal kingdom with A2M. Almost from the very beginning of creation, A2M has been present as a life-saving protein in all vertebrate and invertebrate [11-15]animals (nematodes, arthropods, mollusks, echinoderms, urochordates).

In the begginining, I mentioned the blood test results of 31 patients in a hospital in Bangladesh suffering from various diseases. This is described in Figure 2. This is the first time A2M levels were tested for in the blood of patients. It was observed that all of them had very low levels of A2M: about a quarter of the normal amount. At the same time, quite expectedly, it was found that the efficiency of protease in the blood was increased (about nine times the usual level). Here it can be mentioned that this is the first time comparative results of the efficiency of A2M and proteases in blood test reports were published from Bangladesh [1-18].This will open up a new path for medical science to investigate the causes of many diseases.

Figure 2.



A



B

Figure 2

A. The A2M levels in the blood of 31 patients was found to be reduced to 487.64 ± 9.70 µg/ml, which is around four times less than the A2M level in the blood of 31 healthy people 2013.30 ± 52.00 µg/ml ($p<0.001$).

B. It was also found that the efficiency of protease in the blood of these 31 patients was increased to 5021.22 ± 61.63 mg/ml, which was about 9 times more than the efficiency of protease of 516.16 ± 17.17 mg/ml ($p<0.001$) in the blood of 31 healthy people.

From these results, it can be understood clearly that when A2M levels in the blood are reduced, the efficiency of protease is increased because there is nothing to remove it from the blood. At this point, the effectiveness of protease is unrestricted, and this can be considered the main reason for the onset of any kind of disease. Therefore, when A2M levels are reduced in the blood, we can anticipate the advent of disease. By replenishing diminished levels of A2M, it is possible to protect ourselves at the onset of any disease by preventing unrestricted activity of protease in the blood. The method of treatment by increasing levels of A2M is known as "A2M-ShopAnn Systems".

What is the harmful chemical, Protease?

Protease is a specific kind of protein (enzyme) which is able to break down other proteins through its incredible power [19-24]. A protein is made up of different types of amino acids, and a number of peptide bonds helps these amino acids cohere by means of bridge-like structures [20,21]. Protease can break down the structure of peptide bonds in the proteins through a process called hydrolysis [21,22]. Protease is also known as peptide or proteinase. Proteases can be found in animals [23], plants [24,25], bacteria [26], archaea [27] and even in viruses [28]. Around 500 types of protease have been found so far in the human genome. Most of these proteases are involved in many normal physiological processes, such as coagulation system activation or complement system activation etc. Again, proteases like HIV-1 protease and Dipeptidyl Peptidase IV-(DPP-IV) protease have been identified as the main reason for harm caused by deadly diseases such as AIDS and diabetes respectively [29]. Six types of protease have been found so far: Serine protease, Threonine protease, Cysteine protease, Aspartate protease, Metalloprotease, and Glutamic acid protease [30].

What is the lifesaver Alpha-2-macroglobulin?

In order to survive, all animals (vertebrates and invertebrates) and plants are born with their own immune systems. The various components of the body's autoimmune system either directly inactivates the harmful pathogens, or neutralizes the harmful chemicals secreted by those pathogens. Among many harmful chemicals, the main toxic element responsible for pathogens entering and reproducing within the body is protease. This protease is involved with most of the diseases from which humans suffer (described earlier). The fact that a disease can be cured, or its onset prevented, simply by preventing the activity of protease in the body has yet to be considered by medical science. From the very beginning of the creation of flora and fauna, the protein which has been continuously preventing the activity of protease, keeping us healthy without our knowledge, is **Alpha-2-macroglobulin (A2M)**. This is also called a broad spectrum protease inhibitor. This is because the body's own A2M alone is able to inactivate all currently known proteases. For this reason, A2M is highly significant in the field of treatment.

A2M is mainly produced in the liver. It is also produced by certain cells such as macrophages, fibroblasts and adrenocortical. Maybe the greatest non-immunoglobulin glycoproteins (mw= 720 kD) are present in large quantities in the blood (1-2 mg/ml)[2] to protect our body. The complete description of the structure of A2M is available in notable publications [2,15,78,81]. A short overview of its functionalities was described earlier in Figure 1. Aside from inactivating various proteases (serine, cysteine, aspartic and metalloproteinases), A2M also keeps us healthy by continuously removing many harmful toxic substances without our knowledge, such as different types of growth factor cytokines: TNF-α, IL-1β, IL-6 and TGF-β etc., which are being produced constantly in our body as carrier proteins[3,4-8,11,12,30].

The onset of a disease only occurs when A2M levels in the body are diminished, thus allowing proteases to harm the body. Proteases begin by damaging the body's defense systems, and, as a result, humans fall ill. Therefore, it can easily be said that, if after a blood test, A2M levels are suboptimal and these lost levels of A2M are replaced in the blood, it is possible to stop any disease at onset. The importance of analysis of the levels of A2M in the blood may be a new milestone for medical science.

One day, we might be protected from many diseases by analyzing the level of A2M in the blood, and replenishing diminished levels of A2M in the blood by the method of treatment "A2M-ShopAnn Systems" whenever we fall ill.

In conclusion, I wish to state that one day this new innovation in medicine will play a vital role in saving the lives of the animal kingdom.

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