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Pompe Disease: A review on rare disorder of glycogen storage

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ABSTRACT:-
Pompe disease also called as acid maltase deficiency. It is commonly known as Glycogen Storage Disease type II is an autosomal recessive metabolic disorder. The accumulation of glycogen in the lysosome occurring as a result of deficiency of the lysosomal acid alpha-glucosidase enzyme is the main reason of the disorder. It is transmitted as an autosomal recessive trait which implies that healthy parents can have affected children. It is caused by mutations in the gene encoding the acid α-glucosidase (GAA). As Pomp disease is a glycogen storage disease type II, there are total 15 types of GSD are characterized. Each of them is caused by genetic enzyme defects.
Hence, they are classified based on enzyme deficiency and affected tissue. The disorder has three types: classic infantile-onset, non-classic infantile-onset, and late-onset Pompe disease. Pompe disease may show the symptoms like muscle weakness and trouble in breathing. Liver, heart, and muscles are seen to be affected. The treatment is approved for Pompe disease is Enzyme Replacement Therapy (ERT).The drug named alglucosidase alfa is administered intravenously through patient's vein.ERT has provided the scope to the scientific community for development of next generation of therapies.

I. INTRODUCTION:-

Pompe disease, also called as Type II glycogen storage disease (GSDII), is a rare autosomal recessive neuromuscular disease that affects people of all ages. This serious, often fatal disease has earned a well-deserved reputation as the first recognized lysosomal storage disorder, a group which now includes more than 50 entities.[1]In the 1960s, some thirty years after the first description of Johannes Cassianus Pompe disease,[2] the mystery behind the great accumulation of glycogen in Many tissues in the autopsy reports of those affected have been resolved: the patient is missing enzyme, acid alpha-glucosidase (GAA), has an optimal acidic pH, and glycogen is stored in a membrane organelle, indicating its lysosomal origin.[3]This enzyme is unique responsible for the complete hydrolysis of glycogen to glucose in the lysosome, and its deficiency is manifested as a multi-system disease mainly involving skeletal muscle and myocardium. The estimated frequency of the disease is often cited as 1 in 40,000 live births ,[4]but recent implementation of newborn screening (NBS) for Pompe disease revealed a much higher frequency.[5][6] The first such a program was enacted in Taiwan in 2005 ,[7]followed by several other countries including the US, where the recommendation by the Advisory Committee on Heritable Disorders in Newborns and Children to add Pompe disease to the Recommended Uniform Screening Panel was finally approved in 2015. The severity of the disease depends largely on the nature and extent of the genetic defect.

Changes in residual enzyme activity produce a wide range of phenotypes that differ in age of onset and rate of progression.[8][9] Although this situation represents a single disease continuum, Two different phenotypes are widely accepted the more severe infantile form and the more rapidly fatal infantile form. And the lightest form of late onset, respectively, with or without cardiac involvement.

Alternative names for Pompe disease is acid maltase deficiency, glycogen storage disease type II (GSDII), acid alpha-glucosidase (GAA) deficiency.[10]

II. HISTORY: -

Pompe disease, a severe metabolic myopathy, is caused by mutations in the gene coding for acid alpha-glucosidase (GAA), the enzyme that breaks down glycogen in acidic milieu of the lysosome. Once in the lysosome, glycogen can escape following complete degradation by

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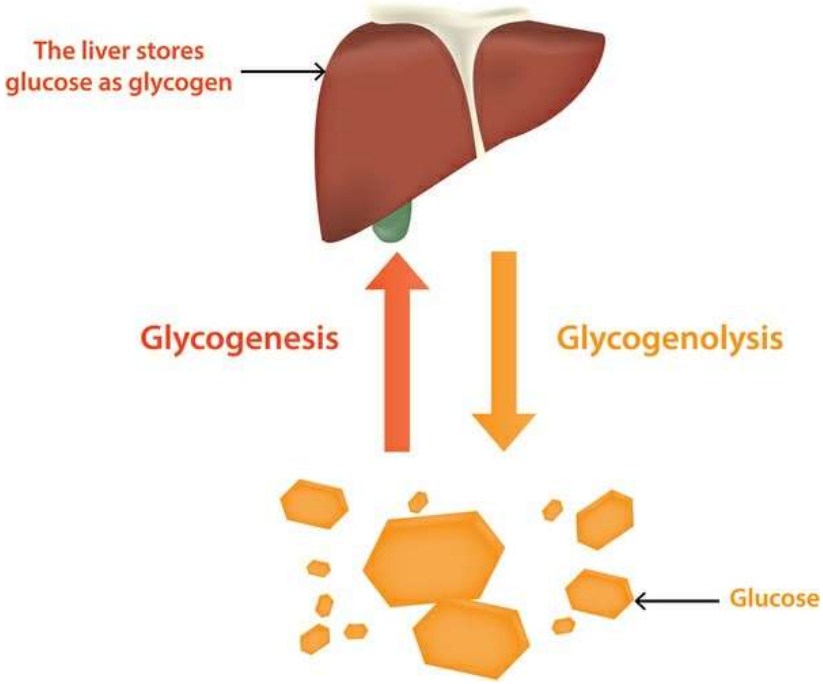
GAA in the form of glucose. A deficiency of the enzyme leads to lysosomal accumulation of glycogen in multiple tissues, but cardiac and skeletal muscles are most severely affected. The disease also goes by the name "Type II glycogen storage disease (GSDII)" or "Acid maltase deficiency." [11] Pompe disease is a rare disorder with an estimated frequency of 1:40,000.[12][13]

In 1932, Johannes Cassianus Pompe, a Dutch pathologist, described the disease in a 7-month-old infant who died of idiopathic hypertrophy of the heart; in addition to the cardiac problems, the infant had generalized muscle weakness. Dr. Pompe made the crucial observation that the baby's symptoms were associated with massive "vacuolar" glycogen storage in virtually all tissues.[14][15] Decades later, basic science breakthroughs led to the discovery of the metabolic pathway of glycogen.

III. ETIOLOGY: -



Pompe disease cause due to mutation in the GAA gene instructions for producing an enzyme called acid alpha-glucosidase (also known as acid maltase) are provided by GAA gene.[16] This enzyme is active in lysosomes which are structures that serve as recycling centers within cells.[17] This enzyme breaks down glycogen into glucose which is main source of energy for all cells.[18] Glycogen is a form of sugar that the body stores mainly in the cells of the liver and skeletal muscles.[19]

The acid alpha-glucosidase which is used to break down glycogen effectively is provided by gene GAA at the time of its mutation.[20] In lysosomes this sugar builds up to toxic level due to this enzyme. This sugar level increase damages organs and tissues throughout the body, particularly the muscles, leading to the progressive signs and symptoms of Pompe disease.[21]

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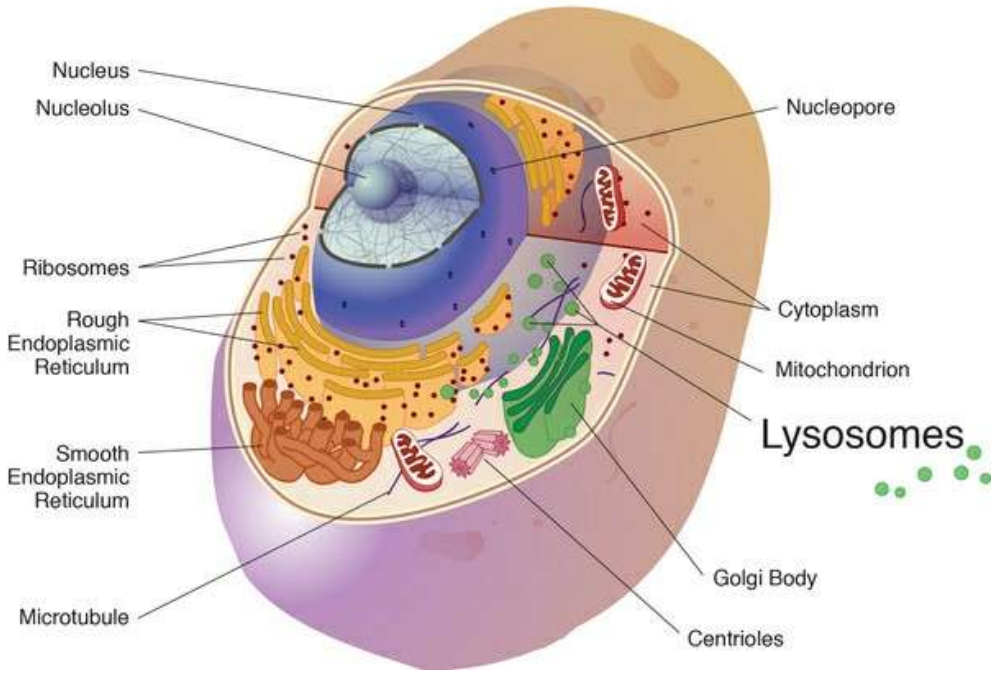

IV. SIGN & SYMPTOMS: -

The sign and symptoms of Pompe disease are characterized according to their types: -

◆Classic infantile-onset: -

It may have muscle weakness, problems with eating, breathing, or hearing problems, respiratory infections, an enlarged heart or liver, and weight faltering - difficulty gaining enough weight or growing as quickly as expected.

◆Non-classic infantile-onset: -

It may have weak muscles and an enlarged heart. The development of a child's motor skills, such as turning and sitting, can also be delayed.

◆Late onset: -

Frequently noted muscle weakness and increased pain in the legs and trunk, which can lead to difficulty walking and frequent falls. They may have shortness of breath or fatigue and frequent lung infections.[49]

V. PATHOPHYSIOLOGY: -

Pompe disease is a rare autosomal recessive disorder caused by mutations in an enzyme that degrades glycogen. The gene located on chromosome 17 (17q25.2-q25.3) codes for the enzyme acid alpha-glucosidase (GAA or acid maltase), which catalyzes the hydrogenation of branched glycogen compounds (glycogen and maltose) to glucose-6-phosphate within the lysosomes.[22] Mutations in this gene result in glycogen storage disease type 2. The GAA gene provides instructions for producing an enzyme called acid alpha-glucosidase (commonly called acid maltase). This enzyme is lively in lysosomes, which are systems that function the cell's recycling middle. The enzyme normally breaks down glycogen right into an easier sugar known as glucose, which is the main energy source for most cells. Mutations inside the GAA gene save you acid alpha-glucosidase from breaking down glycogen, permitting it to accumulate within the body's cells. Over the years, this buildup damages cells at some point of the frame, especially muscle cells.

GAA is an important enzyme, which is found in all the tissues of the body. The lysosomes get swelled and ruptured due to continuous accumulation of glycogen and deficiency of GAA enzyme, which further causes cellular damage. The various studies of pathophysiology as well as accepted mechanisms suggest that it leads to progressive degeneration of skeletal, respiratory, and cardiac muscles. That eventually results in loss of function. Progressive weakness arises in milder forms of the disease due to glycogen accumulation in skeletal muscles. When severity increases, glycogen gets accumulated in liver, cardiac tissues as well as in respiratory muscles. This leads to cardiomegaly, hepatomegaly, elevation of liver

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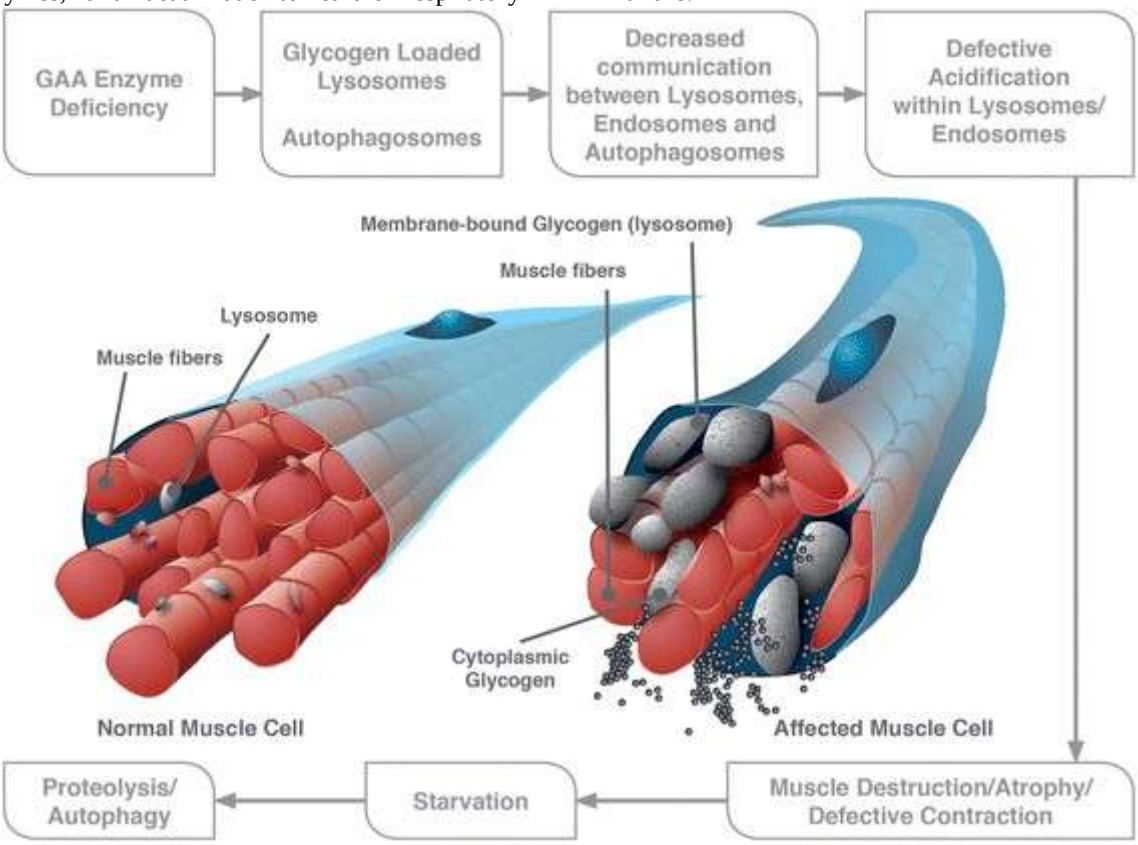
enzymes, and death due to cardio respiratory failure.[23]



COMPLICATION OF POMPE DISEASE: -

Without treatment, newborn children with Pompe disease will die.

Most individuals will utilize oxygen and wheelchairs,

Respiratory (breathing) issues

Heart issues

Nearly all are tormented with muscle shortcoming point.[24]

Complications of Pompe disease may be partitioned into cardiac and
respiratory complications.

● CARDIAC COMPLICATIONS: -

Cardiac complications comprise of cardiac arrhythmias counting ventricular tachycardia, ventricular fibrillation, bradycardias, and systolic arrest.[25]

The pathophysiology behind these arrhythmias is complex. The impressive hypertrophic cardiomyopathy and decreased cleared out ventricular volume result in tall cleared out ventricular filling pressures. Great hydration and adequate preload are fundamental to guarantee an adequate cardiac yield. It is additionally crucial for diastolic blood weight to stay tall in arrange to guarantee an appropriate coronary perfusion weight. Any lopsidedness to this framework, such as might occur during soporific acceptance, can result in coronary ischemia.[26]

In a broad case arrangement of 139 patients, 6% (9 patients) endured cardiac arrhythmias on acceptance. In this arrangement of captures, ventricular fibrillation (VF) happened on 5 events, ventricular tachycardia (VT) on 3 events, and bradycardia on 3 events. 3 patients passed on as a result of these arrhythmias; ventricular fibrillation being the irregular beat on each occasion.[27]

● RESPIRATORY COMPLICATIONS: -

Lack of respiratory function as a result of the hypotonia and neuromuscular shortcoming in Pompe disease. Delayed mechanical ventilation is in this manner a hazard of surgery for patients with Pompe disease.[25] Rhabdomyolysis and hyperkalemia can happen in patients with Pompe disease as a result of utilizing suxamethonium.[28]

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VI. THERAPY:-

- Enzyme Replacement Therapy: -

First attempt to treat with enzyme replacement therapy. Gaucher disease caused by β-glucosidase Purified from the placenta in 1974.Physiotherapy is an important part of management. Recently, recombinant acid α-glucosidase purified from rat milk has been mannose 6-phosphate receptor intracellular and corrected for enzyme deficiency in patient fibroblasts. Preclinical studies also suggest that high doses of recombinant enzymes are required for a positive response. For example, the effect of high doses much better treatment than low dose treatment.

This therapy also has some disadvantages, for example; the development of nephrotic syndrome, allergic reactions, including anaphylactic shock, the development of antibodies Patients receiving treatment within the first 3 months treatment. Recent studies have shown that after receiving enzyme replacement therapy and counteract the therapeutic effect. Human cell products are better than animal cell products that can be part of recent developments, and this development needs to overcome challenges, especially in enzyme targeting.[35][36] For example, the combination of oligosaccharides containing 6-phosphate mannose and acid α-glucosidase can improve muscle delivery and glycogen clearance in Pompe mice. In addition, acid oligopeptide labeling can improve the delivery of drugs to bones, and phosphorylated regals can be delivered to a variety of tissues, including bones, which means a potential enzyme replacement therapy for IVA-type muco-32 polysaccharide disease.[37]Carbohydrate remodeling of recombinant human acid α-glucosidase to improve its affinity for mannose 6-phosphate cation independent The receptor represents a possible approach to improve the effectiveness of enzyme replacement therapy for Pompe disease.[38]But there are many other related complications. Use human recombinant acid α-glucosidase as less effective for skeletal muscles.[39]

- Gene Therapy: -

The number of gene therapy candidates used to combat human disease has increased dramatically, and Pompe disease is no exception. The limitations of ERT currently exist; as does the need for frequent intravenous infusions throughout life and the inability of therapeutic enzymes to overcome BBB, make the development of gene therapy for Pompe disease an attractive option.

In the past over the years, the field has seen an explosion of gene therapy studies testing different types of vectors, different promoters, multiple elements of gene expression cassettes, and routes of use in preclinical settings. Several recent reviews analyze these studies.[40][41][42] Here, we focus on the initiated and planned gene therapy-based clinical trials using non-pathogenic adeno-associated virus (AAV) as a vector. Unlike wild-type viruses, the recombinant AAV genome remains largely fragmented in the nucleus and shows a low frequency of integration into the host cell genome.[43] AAV is rapidly becoming the media of choice for genetic therapy for Pompe disease.

Based on the results of the first preclinical study evaluating the effect of systemic or intramuscular injection of AAV vectors in KO mice [44][45], the first human trial of Pompe gene therapy the disease began in 2006, thus marking a milestone in the field. This is an open-label phase 1/2 trial
(NCT00976352) that uses rAAV2/1-CMV-hGAA to be injected directly into the diaphragm of a small group of children, although ERT requires assisted ventilation. Research has confirmed safety and shows a tendency to improve respiratory function in some the patients.[46][47]

- Substrate replacement therapy: -

Substrate replacement therapy is a combined synergistic therapy designed to reduce the accumulation of glycogen in muscles. The approach should target the enzyme involved in the muscle glycogen biosynthesis pathway and regulate and maintain hepatic glycogen stores to avoid disturbances in glucose homeostasis. Several studies suggest that modulation of glycogen synthesis offers a new treatment option in Pompe disease. Glycogen synthesis is regulated by phosphorylation by various kinases. Thus, glycogen synthesis may be partially regulated by mTOR (a target of mammalian rapamycin).Serine/threonine kinases are part of different multiprotein complexes, such as (mTORC1 and mTORC2).Recently, it has been shown that acid α-glucosidase knockout mice treated with rapamycin (an inhibitor of mTORC1) significantly reduced muscle glycogen storage due to phosphorylation-mediated inhibition of glycogen synthesis, and It has also been demonstrated that the mTORC1 pathway regulates muscle glycogen storage. Synthesis without affecting liver glycogen synthesis.[48]

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VII. TREATMENT OF POMPE DISEASE: -

- Role of Targeting Intercellular Adhesion Molecule-1: - Targeting intercellular adhesion molecule-1, a protein involved in inflammation and over expressed on most cells under pathological conditions, provides broad biodistribution and lysosomal transport of therapeutic cargoes. Delivery of this is improved by coupling acid α-glucosidase to polymer nanocarriers coated with an antibody specific to intercellular adhesion molecule-1. Radioisotope tracing in mice demonstrated enhanced acid α-glucosidase accumulation in all organs, including Pompe targets. Along with improved delivery of Niemann-Pick and Fabry enzymes, previously described, these results indicate that intercellular adhesion molecule-1 targeting holds promise as a broad platform for lysosomal enzyme delivery.[29]
- Role of Hyaluronidase: - In order to enhance acid α-glucosidase activity into the muscle in Pompe Disease, Matalin et al.2006 examined the efficacy of hyaluronidase in the heart, quadriceps, diaphragm, kidney, and brain of mouse model of Pompe disease. These studies suggest that hyaluronidase enhances penetration of enzyme into the tissues including muscle during enzyme replacement therapy and therefore hyaluronidase 43 pre-treatment may be important in treating Pompe disease.[30]
- Role of c.546G>T Mutation: - Mutant acid α-glucosidase in patient fibroblasts carrying c.546G>T mutation is stabilized without cytotoxic effect by treatment with proteasome inhibitor as well as pharmacological chaperon N-butyl-deoxy nojirimycin. In this study, researchers characterized the effect of two proteasome inhibitors, bortezomib and MG132, on maturation, sub cellular localization and residual activity of mutant acid α-glucosidase in the patient fibroblasts carrying c.546G>T mutation. These studies indicate that proteasome inhibitor may be a novel drug as potential pharmacological chaperone therapy for Pompe disease patient carrying chaperon responsive mutation.[31]
- Role of Angiotensinogen Converting Enzyme: - In a study researcher reveals the role of angiotensinogen converting enzyme in early symptoms of Pompe Disease and also severe motor dysfunction in patient. According to a research angiotensinogen converting enzyme have three genotypes DD, ID, II out of which DD alleles encode for angiotensinogen converting enzyme influence. Patient with D allele had increase action of angiotensinogen converting enzyme it decreases half-life of bradykinin and increase level of angiotensinogen II that is vasoconstriction. The angiotensinogen converting enzyme genotype work in place of reduced endothelium acquired vasodilation and decrease the substrate delivery to the muscles by this mechanism it decreases the stored glycogen and muscles are dependent on circulating glucose to meet their needs. D allele is also responsible for increase in level of type II fiber those are less rich in mitochondria and therefore more susceptible for oxidative stress and are related to the Autophagy. These studies conclude that ACE enzyme have relevant action on the early onset of disease.[32]
- Role of BMN-701: -A new molecule BMN-701 which is a fusion protein of insulin-like growth factor 2 and acid α-glucosidase for the treatment of late-onset Pompe disease is in clinical trial. The results show improvement on maximal inspiratory pressure and maximal inspiratory pressure which are the important parameter of respiratory muscle function. The clinical trials are proceeding for the entity BMN-701 and will replace with a glucosidase alfa used now days.[33]
- Role of Cancer Drugs: - Immune response against enzyme replacement therapy is treated with a cocktail preparation of chemotherapy drugs rituximab and methotrexate, plus the intravenous gamma globulin immune booster to prevent the immune response to the enzyme replacement therapy.[34]

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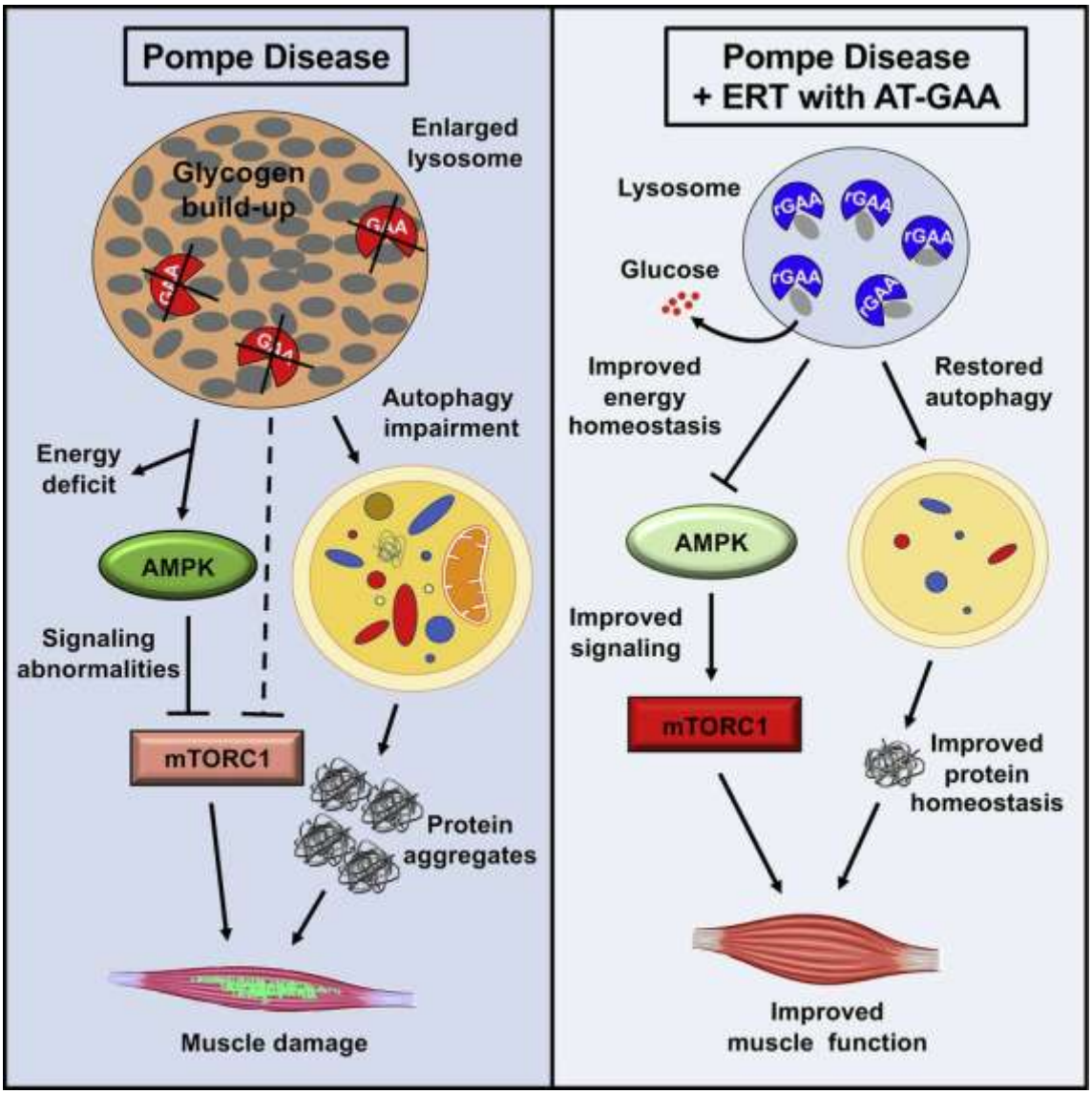

COST OF TREATMENT: In the context of IOPD, total support costs (excluding treatments) were €
32,871 over a life expectancy of 0.4 years, (compared to a total of US$ 41,667 adjusted for currency and inflation at US$ 2017). The average annual expenditures for adult LOPD were €22,475 (adjusted $28,489) for each
patient.[50]

Pompe disorder is a rare, progressive, metabolic disorder and the first inherited muscle disorder to be treated. AL glucosidase alfa enzyme replacement therapy (ERT) is a disease-specific and unique drug authorized to treat Pompe disease. As with most orphan drugs, the cost of ERT is very high. In comparison with supporting treatments in adult patients with Pompe disease, this study examined the economic effectiveness of ERT.[51][52][53]

There was estimate of substantial survival incremental years – in scenarios without and after the observed period of survival extrapolation, reduced incremental years of ERT varied from 1.9 to 5.4 years. For patients receiving ERT, quality of life was also considerably better. There were significant incremental costs and the cost of ERT consisted primarily of them. For scenario 1 and €1,8 million for scenario 2, the QALY incremental costs amounted to EUR 3,2 million.[54]

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VIII. CONCLUSION: -

We concluded from this study that Pompe disease is an autosomal recessive metabolic disorder. It is serious and fatal disorder and the diagnosis as well as the treatment is needed to improve as the frequency of cases in newborns is expected to get increase in upcoming period. The clinical manifestations of Pompe disease are quite different. The findings of signs and symptoms are slightly different from infantile-onset and late onset of the disease.

Cardiac and respiratory complications are frequently detected in patients. Enzyme Replacement Therapy (ERT) has achieved a good response, especially in infantile-onset of the disease; in addition there are several other drugs and enzymes which are found to be effective with ERT and other therapies. Survival of patients treated with these forms of Pompe disease will help to better understand the course of the disease.

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