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# SYMPTOMS, DIAGNOSIS AND TREATMENT OF TARUI DISEASE: AN AUTOSOMAL RECESSIVE DISORDER

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## ABSTRACT

Tarui disease is also named as glycogenosis 7, glycogen storage disease VII (GSD VII), GSD7, muscle phosphofructokinase deficiency, PFKM deficiency, and phosphofructokinase deficiency. It is named after his scientist and due to the enzyme; phosphofructokinase, deficiency which is occur in this disease. Due to this enzyme deficiency glycogen will not able to be broken down and start to be accumulated in the muscles. It is a disease of glycogen storage metabolism. On the basis of symptoms and signs it is further divided into classical form, sever infantile form, late-onset form, and hemolytic form. Its symptoms include muscle cramp, pain, spasm, mild jaundice and pain at lower back. PFKM gene mutation causes Tarui disease. The inherited condition is in the pattern of autosomal recessive. Investigations should be carried out to differentiate from other possible jaundice causes. Diagnosis is performed by blood test, urinalysis, imaging and electrophysiology and muscle biopsy and then treatment should be carried out. It involves avoidance from carbohydrate diet, hard exercises and using ketogenic diet. When we use low carbohydrate and high fat diet, body will use fatty acid instead of glucose as a main energy source.

**KEYWORDS:** Phosphofructokinase, Autosomal recessive, Ketogenic diet.

## INTRODUCTION

All storage diseases of glycogen are regarded as metabolic disorders which are inherited. A disease that interacts with the metabolism is the metabolic disorder. The process by which energy is generated by the breakdown of food, called metabolism (Di Mauro, 2007). Simple sugar glucose is a carbohydrate. In many foods, this sugar is the primary energy source for the body. In our body, storage form of glucose is the glycogen. Glucose joined to made glycogen by forming 1, 4 linkage interrupted by branch points at distance of every 4 to 6 residue by forming 1, 6 linkage. Glycogen is formed when there is more carbohydrate in the body and broken down when energy is required (Haller & Vissing, 2004).

There are a number of disorders present related to glycogen metabolism involving synthesis, breakdown and regulation. When glycogen stores in abnormal amount in the body it causes glycogen storage diseases. They are characterized according to the chronology of discovery of defects of enzyme. These disorders mostly affect muscles and liver because glycogen is mostly store in these organs (Garcia *et al.*, 2009). Muscle and liver are the main organs for glycogen storage. In liver its disorder causes hypoglycemia and hepatomegaly. While in muscles it causes muscle weakness, intolerance of exercise, fatigue, muscle cramps. Synthesis and degradation of glycogen take place with the help of a large number of enzymes and regulation take place by hormones. Storage diseases of glycogen are a group of genetic disorders that cause improper formation or degradation of glycogen in the body. Glycogen accumulated in the abnormal amount cause disturbance and cause disorders in the body (Zahedan, 2012). There is fig. 1 showing the structure of the glycogen.

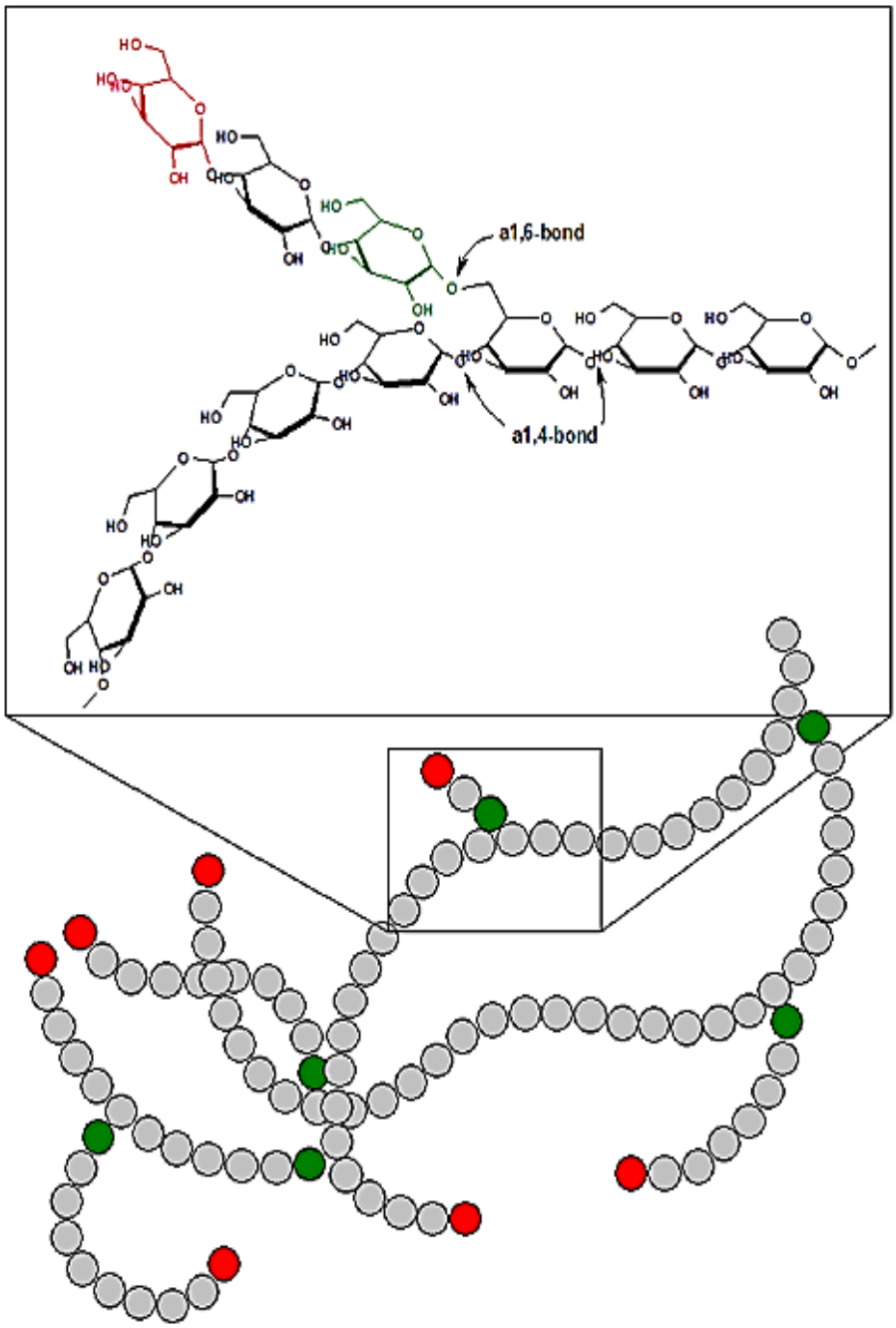


**Fig. 1 Glycogen**

In 1965, Seiichrio Tarui a Japanese physician and his co-workers described Tarui disease which is also well-known, as "glycogen storage disease type VII". It is also known as "phosphofructokinase deficiency". In the muscle tissue, there is deficiency of an enzyme phosphofructokinase. Glycogen is a complex sugar which could not be broken down in the absence of this enzyme. It is very rare disease very few cases are encountered affected both females and males, worldwide (Di Mauro, 2007). Phosphofructokinase (PFK) is the main enzyme involves in the glycolysis regulation and catalysis the fructose-6-phosphate to fructose-1, 6-diphosphate. A complex isozyme PFK comprising of three subunits: Liver type (L), Muscle type (M) and Platelet type (P) or Fibroblast type (F). Three autosomal genes controlled the enzyme. Muscle subunit (PFK-M) encodes by the gene present on chromosome 12, liver subunit (PFK-L) encodes by the gene present on chromosome 10, and platelet subunit (PFK-P) encodes by the gene present on chromosome 10 (Nakajima *et al*., 2002). There is fig. 2 showing the pathway of glycogen metabolism.

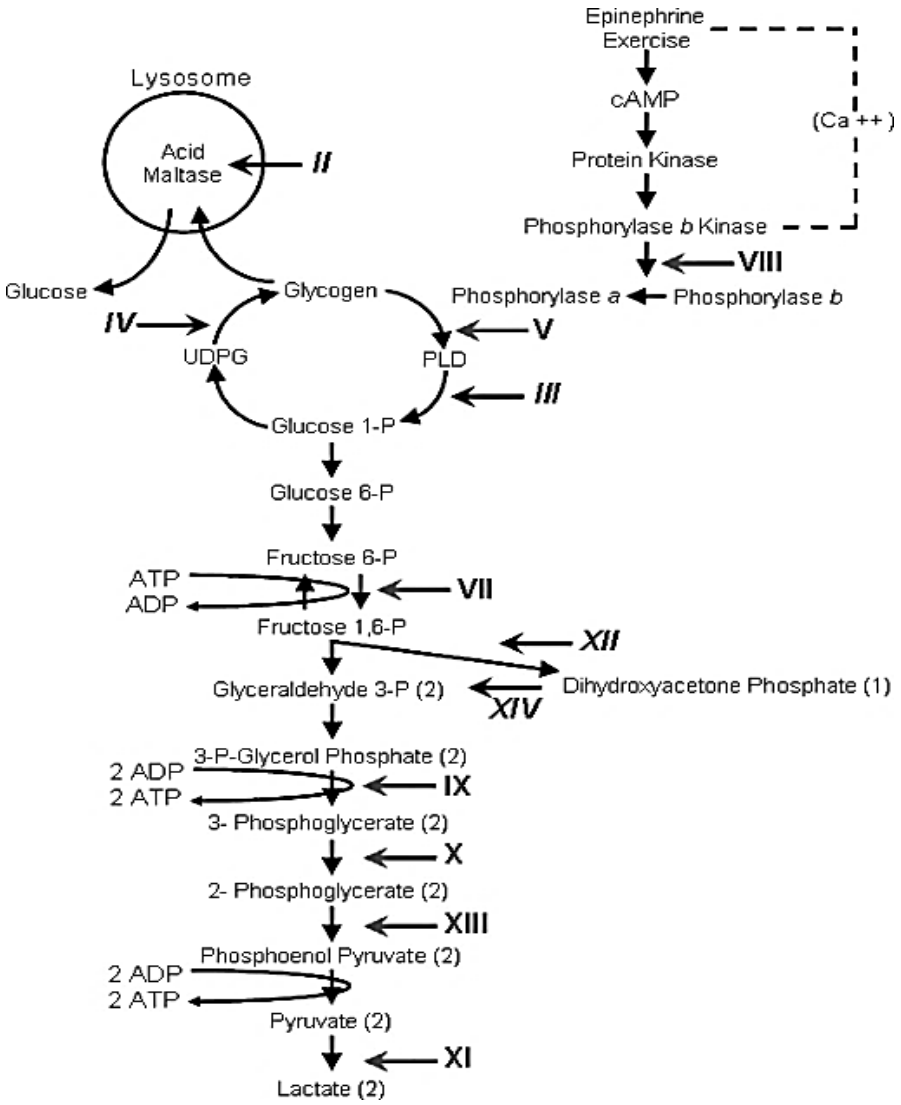


**Fig. 2 Glycogen Metabolism**

**TYPES OF PFK DEFICIENCY**

Tarui disease is divided into four different types according to their symptoms and signs and age of presentation.

**The classical form**

It is very common and mostly present in childhood. It is described by the pain and cramps in muscles mostly after performing some exercise. Exhausting exercise could lead to vomiting and nausea. Muscle tissues are broken down abnormally during exercise releasing myoglobin protein. Kidneys processed this protein and discharge in the urine, myoglobinuria. Kidneys could be damaged if myoglobinuria is untreated and cause kidney failure (Zahedan, 2012).

Due to increase of high levels of "uric acid", a waste product in the blood which is called "hyperuricemia", take place in the people having Tarui disease classical form, because their kidneys are damaged and are not able for the uric acid removal effectively. Blood of the affected individuals may contain high levels of bilirubin that causes jaundice, whites of the eyes and skin become yellowing. Creatine kinase an enzyme present in high amounts in the blood of individuals having Tarui disease classical form (Musumeci *et al.*, 2012).

**The severe infantile form**

It influences the babies present with floppiness, low muscle tone, it causes weakness of muscles that could progressively critical. Children who are affected have enlarged and weakened heart, cardiomyopathy and face difficulty in normal breathing. This form of Tarui disease is very severe and past their life first year, the survival of the individuals is difficult due to breathing problems or infection (Haller & Vissing, 2004).

**The late-onset form**

It is found in people during the age of 40s or 50s, mostly cause weakness of muscle and some people have difficulty with continued exercise that they observed initiating in childhood. Muscles are mostly affected by weakness near the body center; proximal muscle (Toscano & Musumeci, 2007). There is fig. 3 showing the GSD effect on carbohydrate metabolism.

**The hemolytic form**

It is described by "hemolytic anemia"which causes red blood cells shortage due to break down, hemolysis, of red blood cells prematurely. People having hemolytic form of Tarui disease do not face any symptoms and signs of muscle weakness or pain relevant to the disorder. This form is very unusual (Al-Hassnan *et al*., 2007).

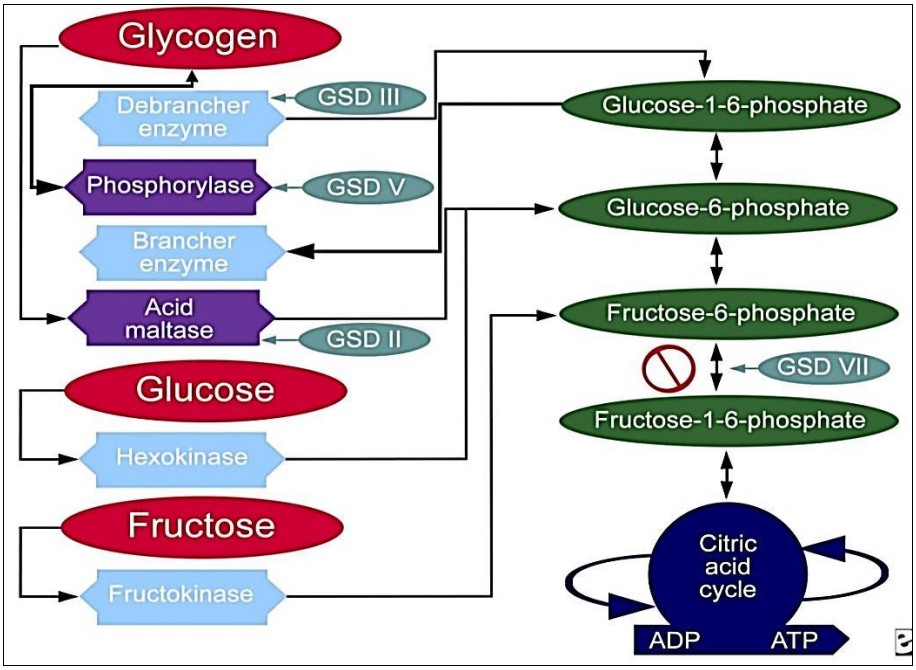


**Fig. 3 GSD effect on carbohydrate metabolism**

**SYMPTOMS**

The indications are because of the muscles not having enough vitality to work typically. This implies the cell needs to discover different wellsprings of vitality and results in muscle cell "harm" and "degeneration". The condition causes torment, cramping, defect and muscle firmness in exercises having effort, for example, strolling, running, carrying or lifting. In an exceptional people muscle movement, demanding energy prompts to the "breakdown of muscle protein". There may likewise be an expanded creation of uric corrosive, which is the reason for excruciating irritation of the joints; gout (Nakajima *et al*., 2002).

The point at which muscle cells are harmed; myoglobin (a substance which is the cause of red shading of muscles) escapes from muscle cells to the blood plasma. The point at which the blood plasma is sifted over the kidneys the pee gets to be distinctly red shaded (myoglobinuria). Myoglobinuria is a genuine difficulty requiring intense doctor's facility mind, as high conjunctions of myoglobin in blood plasma causes kidney damage. Some myoglobinuria patients form extreme renal disappointment demanding "dialysis" (Musumeci *et al.,* 2012). A prolonged rate in the "breakdown" of red platelets (hemolysis) can prompt to fluctuating degrees of jaundice (icterus). As a rule the condition displays as a yellow discoloration of the "whites" of the eyes. Likewise prolonged calcium particle content in the red platelets now and then "miracles" the cell films, which thus may trigger the coagulation procedure bringing about the improvement of blood clumps and cardiovascular intricacies (Haller & Vissing, 2004). There is table. 1 showing the signs and symptoms assigned by HPO.

**Table. 1 The Human Phenotype Ontology (HPO) assigned symptoms in patients**

| Signs and Symptoms | Approximate number of patients |
|---|---|
| Anemia | Very frequent (present in 80%-99% of cases) |
| Increased muscle glycogen content | Very frequent (present in 80%-99% of cases) |
| Myotonia | Very frequent (present in 80%-99% of cases) |
| Hyperuricemia | Frequent (present in 30%-79% of cases) |
| Skeletal muscle atrophy | Frequent |

| | (present in 30%-79% of cases) |
|---|---|
| Autosomal recessive inheritance | - |
| Cholelithiasis | - |
| Exercise intolerance | - |
| Exercise-induced muscle cramps | - |
| Exercise-induced myoglobinuria | - |
| Gout | - |
| Hemolytic anemia | - |
| Increased total bilirubin | - |
| Jaundice | - |
| Reduced erythrocyte 2,3-diphosphoglycerate concentration | - |
| Reticulocytosis | - |
| Variable expressivity | - |

**GENETIC CHANGES**

Phosphofructokinase lack is an uncommon hereditary condition coming about because of a transformation or mistake in a man's DNA or qualities. Phosphofructokinase inadequacy causes brokenness in the body's capacity to process sugars (Di Mauro, 2007). Ordinarily, cells in our body, including platelets and muscle cells, change over the starches that we devour, for example, sugar, into vitality that permits them to work. A man who has a phosphofructokinase insufficiency can't change over these sugars into vitality and which prompts to side effects including muscle issues, muscle shortcoming, and dull pee (Al-Hassnan *et al*., 2007).

Changes in the PFKM quality cause Tarui malady. The quality codes for a protein which shapes one section (the PFKM subunit) of a catalyst called phosphofructokinase. PFKM quality transformations causes the generation of PFKM subunits; that have practically no capacity. The phosphofructokinase chemical is comprised of four sections (produced using 3 subunits) which join in various approaches to make 3 unique sorts of working protein for the muscle, liver, and platelets (McArdle, 1951). In ordinary muscles, employed for development (skeletal muscles) the chemical is made totally of PFKM subunits. This implies the transformed subunit can't make a working catalyst and the muscle cells can't separate glycogen into glucose. Accordingly, somewhat split down glycogen; then develops in muscle cells (Toscano & Musumeci, 2007). There is fig. 4 showing the normal and deficient situations of PFK.

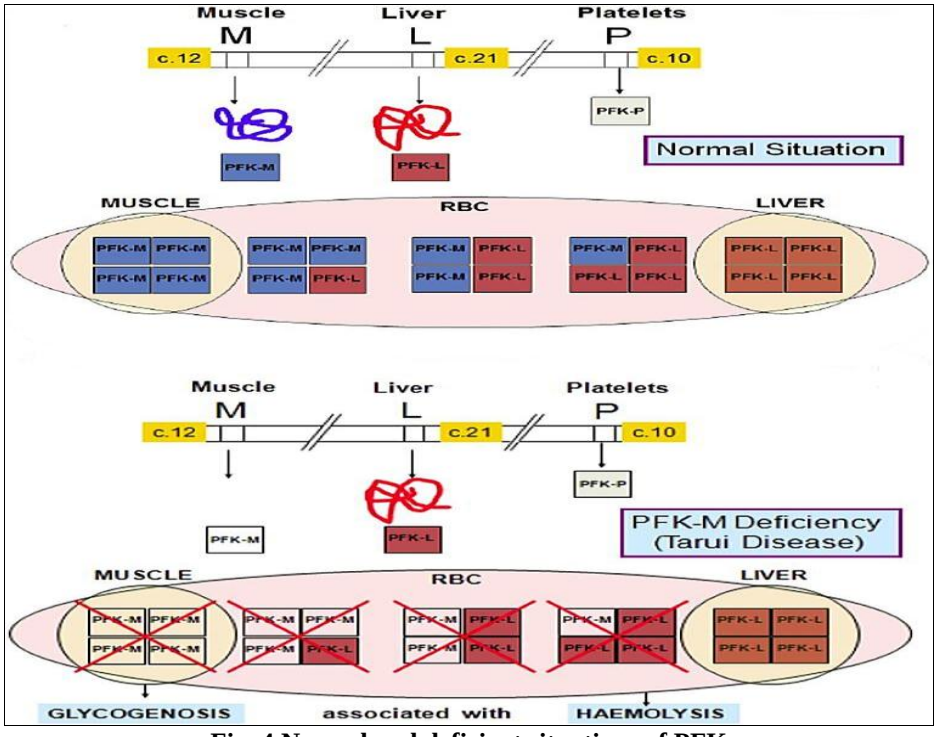


**Fig. 4 Normal and deficient situations of PFK**

Muscles that don't have entry to glycogen as an energy source get to be definitely weakened and cramped after direct strain, for example, work out, and at times, start to detached. Be that as it may, in red platelets there is a blend of compound sorts which implies that there is just an incomplete nonattendance of the protein in these cells, around 50 for every penny (Ozen, 2007). Glycogen is likewise establish and separated in the liver yet the PFKM subunit is not a subunit of liver phosphofructokinase which is the reason the liver is not influenced by "Tarui ailment". Swedish specialists have distinguished a relationship between PFKM insufficiency and expanded spillage of "calcium particles" into red platelets. The unusually high centralization of calcium particles lessens the versatility of the red platelet films, which is most likely the immediate reason for the quickened crumbling of red platelets (hemolysis) and jaundice in patients with Tarui ailment (Roach, 2002). There is fig. 5 showing the Human muscle having phosphofructokinase deficiency.

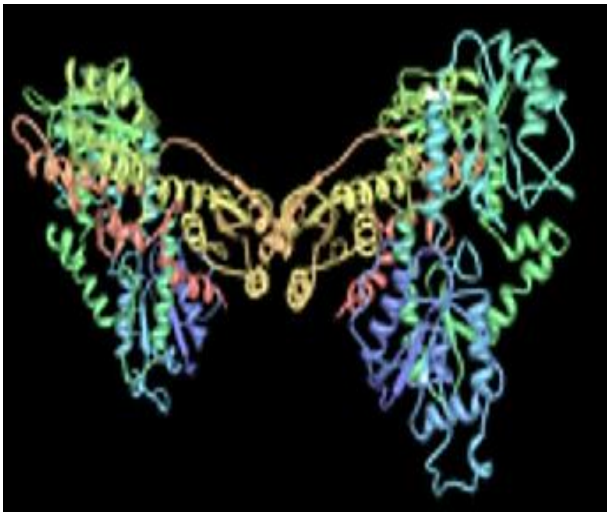

**Fig. 5 Human muscle having phosphofructokinase deficiency**

**INHERITANCE**

This condition is acquired in an autosomal latent example. We as a whole have two duplicates of every chromosome aside from the sex chromosomes. In passive conditions both duplicates of the quality must be inadequate for the illness to grow completely. In this circumstance each parent is a transporter of one deficient quality (Di Mauro, 2007). What's more, in every pregnancy they have a 25% shot of have a youngster influenced with the condition. Hereditary directing is accessible to families who have had an analysis of phosphofructokinase insufficiency. This administration gives data, helps families comprehend legacy designs and what this implies in their family, and in addition empowering individuals to settle on more educated family-arranging choices. You can get to this through your GP, self-allude or a MDA Fieldworker can help you (Nakajima *et al*., 2002). There is fig. 6 showing possibility of disease in a child.

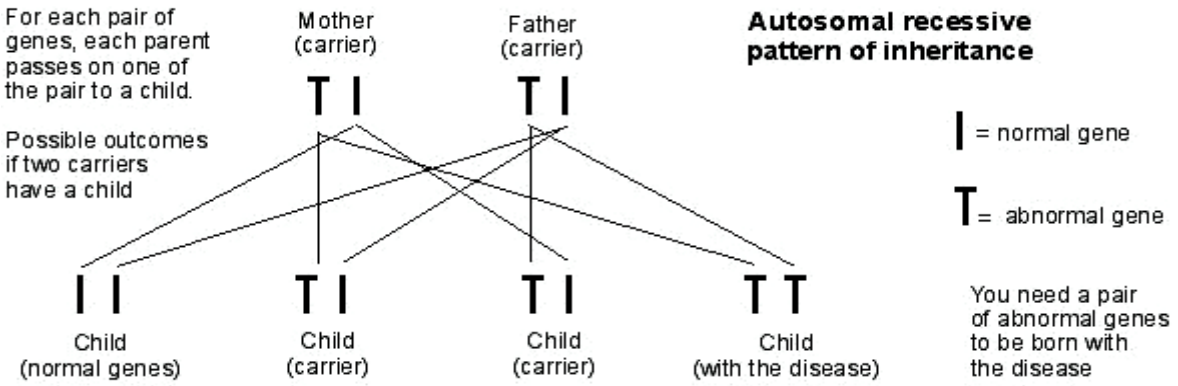


**Fig. 6 Possibility of disease in a child**

**PATHOPHYSIOLOGY**

PFK is required for glycolysis. The chemical lack brings about the gathering of glycogen in the tissues. The catalyst inadequacy can likewise prompt to expanded uric corrosive creation and in this manner conceivable gout. There might be a rewarded hemolytic "weakness".

PFK has muscle, liver and platelet subunits. In muscle tissue, it is made out of muscle "subunits" yet erythrocyte PFK is made out of both "muscle" and "liver subunits" (Di Mauro, 2007). This involves in exemplary PFK insufficiency, there is no PFK movement in muscle and around half action in "erythrocytes". Due to the shortage of an enzyme, carbohydrate metabolic pathways are blocked; so that the additional glycogen stores in affected tissues (Zahedan, 2012).

Every "GSD" signifies a particular enzyme deficiency. Each enzyme is specific in most body tissues. Basically, Phosphofructokinase catalyzes the rate-limiting step in "glycolysis "which is very important. Enzyme deficiency, generally decreases the rate of conversion of "fructose-6-phosphate" to "fructose-1, 6-diphosphate". Basically tarui disease is an "autosomal recessive condition". Phosphofructokinase is present in red blood cells and muscle tissues. Garcia et al observed the effects of phosphofructokinase deficiency in" tissue", other than skeletal muscle on the pathogenesis of "GSD type VII" (Roach, 2002).

Authors who study the phosphofructokinase-deficient mice, have this assumption that because the animals' erythrocytes kept only 50% of their phosphofructokinase activity, due to this "Spartan hemolysis" extensively decreases in 2, 3-bisphosphoglycerate levels (impairing the extraction of oxygen from hemoglobin).As a result of this compensatory reticulocytosis and splenomegaly occurred. Reduced levels of cardiac phosphofructokinase activity, which combined with the other hematologic changes, are found as well. They directed to the development of "cardiac hypertrophy" (Toscano & Musumeci, 2007).

Madhoun et al reported an exceptional case of a man with phosphofructokinase deficiency who also offered with portal and mesenteric vein thrombosis PFKM gene mutations has outcome in the production of "PFKM subunits". These subunits have little or no function. As a consequence, no functional "phosphofructokinase" is prepared in skeletal muscles. So that the glycogen cannot be fully broken down (Ozen, 2007). Glycogen, which partially broken down, then forms in muscle cells. Muscles that do not have access to glycogen (as an energy source) become weak. They also become cramped and causes the moderate strain, for example "exercise". In some cases, they start to break down. Other subunits (in other tissues) that make up the "phosphofructokinase" enzyme probably compensate for the other tissues that are not affected by "PFKM gene variations". It is uncertain that why some persons suffering with "GSDVII" are affected with more "Spartan forms" of the syndrome than others (Garcia *et al.*, 2009). There is fig. 7 showing mechanism of glycogen breakdown.

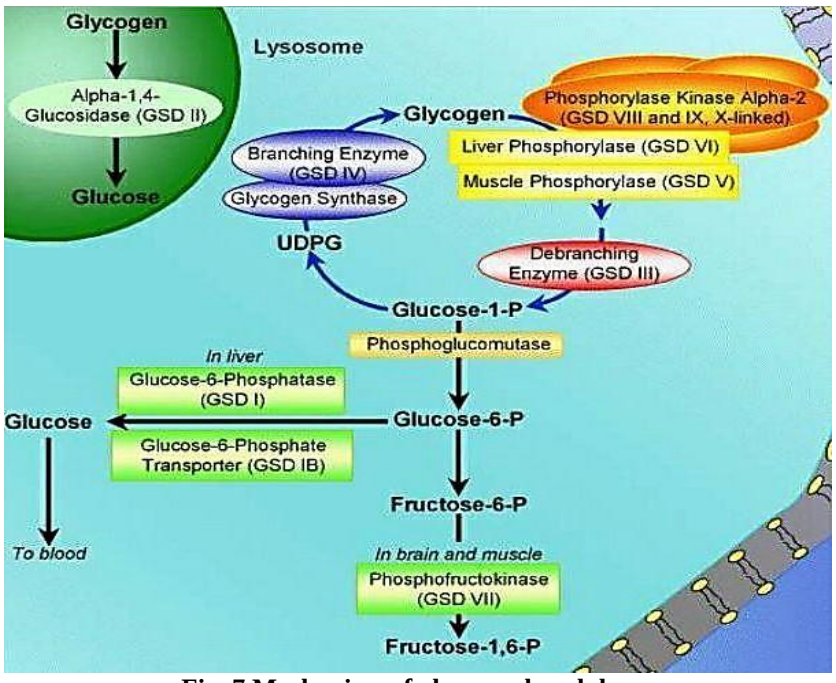


**Fig. 7 Mechanism of glycogen breakdown**

**EPIDEMIOLOGY**

It is very uncommon and has been accounted for in around "100 patients" (around the world). Manifestations might be mellow in a few people so there might be a few cases that go unrecognized. Guys give off an impression of being inclined more commonly than females. It is more usual in "Ashkenazi Jews". Herling and his colleagues studied the "incidence" and "frequency" of inherited metabolic circumstances in "British Columbia". GSDs are found in 2.3 children per "100,000" births per year (Ozen, 2007). Prompt illness increases from exercise intolerance, which also occur in McArdle

disease. Haller and Vissing found no constant second wind phenomenon in "GSD VII", but this phenomenon is found in McArdle disease. This disease seems to be predominant in the people of "Ashkenazi Jewish descent". Generally, GSDs present in childhood. Later onset associates with a less "unadorned form" (Haller & Vissing, 2004).

## CLINICAL FEATURES

Recently, a clinical characterization has been accounted for separating patients with "GSD VII" into four various clinical subclasses: traditional shape, late-onset frame, puerile frame and hemolytic shape. The established frame is portrayed by exercise bigotry, muscle spasms, torment and, some of the time after extreme physical endeavors, sickness and spewing. It is additionally conceivable to watch jaundice joined by lifted "creatine kinase" (CK) levels, hyperuricemia, reticulocytosis and expanded serum bilirubin (Roach, 2002). The late-onset frame presents with "spasms" and 'myalgias" in later life in spite of the fact that activity capacity is low as of now in adolescence; a mellow muscle shortcoming may show up in the fifth period prompting to extreme disability. Patients with the puerile shape may show as "floppy infants" and they bite the dust inside the main year of life. They can likewise exhibit confirmation of arthrogryposis and mental impediment. The hemolytic frame presents with inherited non-spherocytic hemolytic pallor, however with no muscle "exhibitions" (Nakajima, *et al.*, 2002).

## MORPHOLOGICAL FEATURES

Muscle biopsies commonly show inward "vacuolization with glycogen" stockpiling, that can be uncovered by PAS recolor regardless of the fact that, now and again, morphological viewpoints are practically typical. Electron microscopy can uphold the "glycogen testimony" in sub-sarcolemmal and between myofibrillar zones (Toscano & Musumeci, 2007).

## DIAGNOSIS AND TREATMENT

An investigation would take place to remove all other possibilities of jaundice. The diagnosis is carried out by analyzing the activity of an enzyme phosphofructokinase in the red blood cells. Mostly the results of the test indicate slightly less activity. Phosphofructokinase subunit and glycogen concentrations in biopsied muscle tissue mostly pick up from the outer thigh are measured by a microscopic analysis. In some circumstances, PFKM mutation could be identified by diagnostics which are DNA-based. Its symptoms might have similarity with McArdle's glycogen storage disease but more worse (Ozen, 2007).

### Investigations

In **Blood tests**, bilirubin and serum creatin kinase are mostly increased. Hyperglycemia and hyperuricemia. Diagnose LTFs (Liver failure). Anemia could be shown by FBC due to increased reticulocyte count. If myoglobinuria exist, perform tests of renal function.

In **Urinalysis**, after exercise there might be myoglobinuria (Haller & Vissing, 2004).

In **Imaging and electrophysiology**, in the infantile form, ventricular dilation and cortical atrophy might be discovering on brain imaging. Electromyography (EMG) might indicate alteration regular with myopathy or could be normal (Di Mauro, 2007).

In **Muscle biopsy**, in muscle tissue, PFK assay indicate reduced levels and could provide a definitive diagnosis (Zahedan, 2012). There is fig. 8 showing structure of muscle.

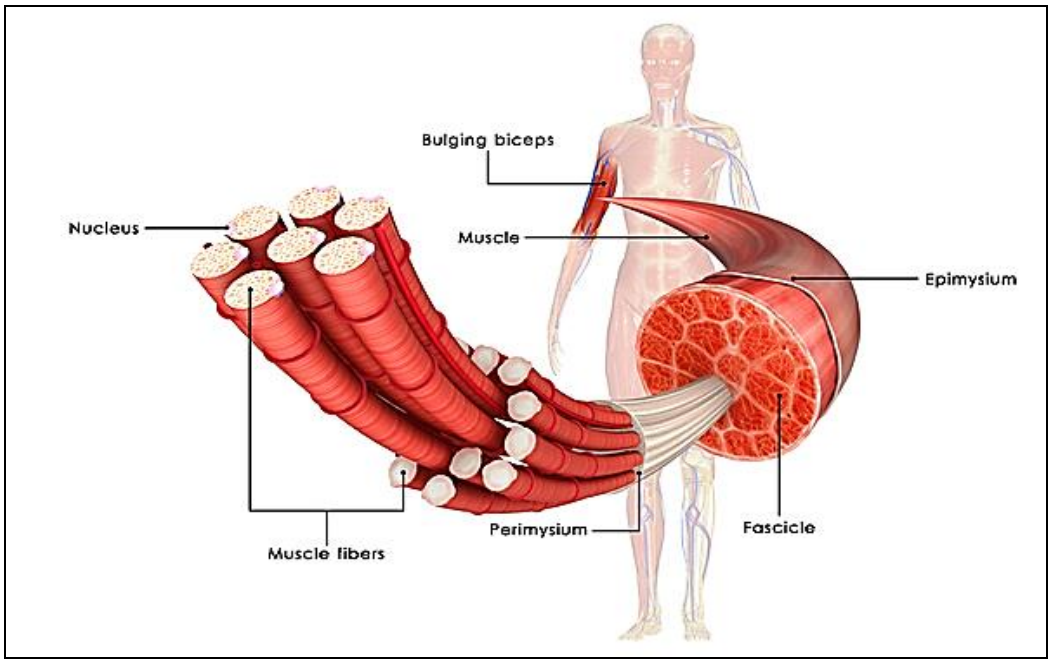


**Fig. 8 Structure of muscle**

In humans: A diagnosis is carried out by a muscle biopsy that indicates accumulation of high level of glycogen. Due to interruption in the breakdown of normal glucose that regulates glycogen breakdown, as a result in the muscle glycogen is deposited. Phosphofructokinase activity is measured by conducting blood tests, patients would have lower count. Patients also exhibit commonly high creatine kinas enzyme (Ozen, 2007). In dogs: Diagnosis involves blood tests similar in humans. Total activity of erythrocyte PFK is measured by blood tests. DNA testing is also present. Phosphofructokinase deficiency treatment involves changes in potential diet and minimizing intensive exercise (Nakajima, *et al.*, 2002).

In humans: Patient should avoid hard exercise to stop muscle cramps and pain. Carbohydrate avoidance is also suggested. An infant with deficiency of PFK symptoms could be improved by a ketogenic diet. Behind this treatment, the logic is that the high fat, low carbohydrate diet causes the body to utilize fatty acids as a primary source of energy in spite of glucose. In glycolysis the enzymatic defect is bypasses, lowering the mutated enzymes PFKM impact. The studies are not widely sufficient to prove this treatment viable but testing is proceeding to explore it (Swoboda *et al*., 1997). In dogs: Supportive care is mostly involved for treatment. Dogs are mostly keeping out of exciting or stressful situations avoiding hard exercise and high temperatures. Hemolytic signs should be observed. From the population of breeding, gene of mutated form should be completely removed, in order to lessen the onset of the condition (Gerber & Harvey, 2009). There is fig. 9 showing phosphofructokinase tetramers.

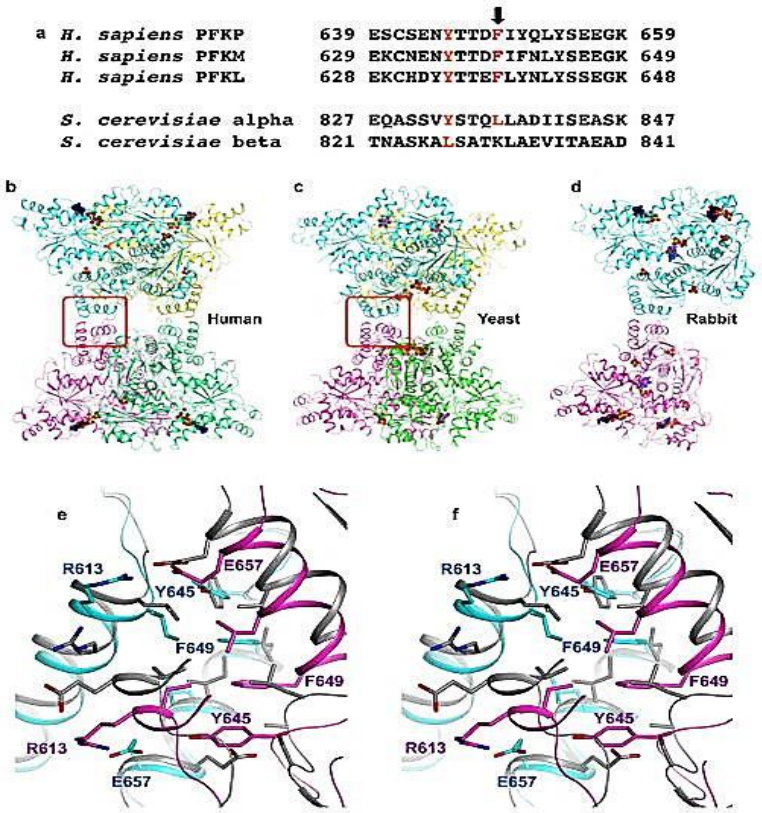


**Fig. 9 Phosphofructokinase tetramers**

Phosphofructokinase exists as tetramer. The diagram showing the structures of phosphofructokinase in humans, yeast and rabbit. The quaternary structure is also shown which have several domains and subdomains (Ozen, 2007).

## PROGNOSIS

A very poor prognosis is for infantile variant, its death in early childhood and infancy. For other variants prognosis is very good but stiffness and weakness invariable occur in groups of muscle subjected to prolonged or vigorous exertion. In future gene therapy could be used. However, a case of three days old boy with the deficiency of PKF is reported whose seizures were controlled by medication (Al-Hassnan *et al*., 2007).

## CONCLUSIONS

In the previous 15 years, a large amount of information relevant to distal glycogenosis and PFK deficiencies reported but many problems are still unsolved. In fact correlation of genotype-phenotype is still weak and at present there is no therapy. In this field extensive study on more patients are vital to understand these disorders pathophysiology in better way and to suggest better options of treatment, as obtained recently in Acid Maltase deficiency (GSD type II) or pomp disease. However, there is no specific treatment for this disease.

This disease may lead towards kidney injury, jaundice, myoglobinuria, hemolysis, gout and gallstones. So proper treatment should be requiring.

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