Overview and Integration of Cellular Metabolism

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Lecture 15: Glycogen Metabolism (IV)

Welcome back. So, we were in the sessions of overview and integration of cellular metabolism. And in the previous lectures we have learned about different mechanisms of glycogen metabolism that is glycogen synthesis via glycogenesis as well as glycogen breakdown via glycogenolysis. Then we also discussed about the regulations of these two mechanism how they are reciprocally regulated. Now, today we will discuss few clinical conditions related to the related to disordered glycogen metabolism or defective glycogen metabolism. Now, in today's session actually we will discuss glycogen storage disorders.

So, basically this glycogen storage disorders we will discuss the different diseases where this glycogen synthesis or breakdown is hampered. So, glycogen storage disorders are mostly all are those all of them are actually inherited disorder inherited disorder of enzymes actually. Those enzymes which were involved which are involved in synthesis of glycogen or degradation of glycogen they are defective. Defective either by the function or by their deficiency their numbers their count.

So, this is a this is a group of disorder where glycogen synthesis and degradation are hampered. Now, for that glycogen is present either in abnormal quantity or in defective or poor quality or both. Now, these glycogen storage disorders are named as numeric type in chronological order as in the chronological order how they were discovered. Now the frequency of these glycogen storage disorders are mostly 1 in 20000 life bars. So, let us see what are the different enzymes we have discussed in the previous class which actually was involved in glycogen synthesis as well as breakdown.

So, first if you remember that glycogen was forming glucose 1 phosphate in between that there was limit dextran and that limit dextran was formed with the help of phosphorylase. Phosphorylase either present in muscle or present in liver. Now limit limit dextran to glucose 1 phosphate is formed by deblanching enzyme. Again that glucose 1 phosphate is forming UDP glucose in circulation that UDP glucose once again

is utilized in glycogen synthesis. So, here up to this or the glycogen breakdown mechanism then here we are talking about glycogen synthesis and that in that synthesis if you remember there was branching enzyme which was actually creating the alpha 1 6 glycosidic bond.

Then again glycogen inside lysosome breakdown of glycogen occurs in different in different locations of cell, but in lysosome that degrading enzyme is acid alpha glucosidase or sometimes we call it acid maltase as well. Now again there is another enzyme if you remember which activates this phosphorylase is the phosphorylase kinase. So, defect can be there as well then again glucose 1 phosphate which enters to form glucose finally, via the enzyme glucose 6 phosphatase can be defective or this glucose 6 phosphatase has a 1 transporter which helps in activation of this glucose 6 phosphate. So, that transporter can be defective as well. So, these are the different locations where different enzymes rather which can be defective ultimately giving rise to one of the glycogen storage disorder.

So, let us see one by one there are multiple types of glycogen storage disorder and I as I told they are named in chronological order numerically they are number and the numbering is done with which one discovered first that is type 1 then onwards. So, all the glycogen storage disorders are actually known as glycogenesis. So, basically these glycogen are stored inside tissues. Now glycogen if you remember they are found in most of the tissues, but the most important organs were liver and muscle. So, the accumulation in case of glycogen storage disorder accumulation occurs in this organs mostly.

Now, if you remember the two different function of glycogen in liver and muscle once again I am highlighting the fact that liver glycogen is basically a source of glucose to maintain normoglycemia in circulation. So, basically liver senses glucose liver actually acts as a sensor of glucose. So, it senses if there is a fall of blood glucose level or a rise of blood glucose level as well and accordingly on requirement it releases glucose to circulation via glycogenolysis, but in case of muscle once again this glycogen break down the product is glucose 6 phosphate remember glucose 6 phosphatase enzyme is absent in muscle. So, from glucose 6 phosphate glucose cannot be formed. So, the end product in of glycogenolysis in muscle is actually glucose 6 phosphate and that glucose 6 phosphate is utilized for production of ATP which helps in skeletal muscle contraction.

Now whenever there is defect in glycogen synthesis or breakdown. So, what will happen ultimately the on requirement glycogen breakdown will not happen properly. So, how these two organ will suffer? Number one is in case of muscle it will not get that ATP for its contraction. So, there will be energy deficiency which will lead to fatigue

muscle weakness then easy fatigue ability most importantly easy fatigue ability the persons the patients who are suffering from glycogen storage disorder where muscle is affected they are easily fatigued. Then when liver is affected what will happen firstly the glycogen stored in liver they will be accumulated.

If the breakdown is not happening properly definitely glycogen will be accumulated that will give rise to hepatomegaly. Hepatomegaly is basically increase in size of the liver. Then again there will be hypoglycemia remember as I told that the dietary dietary glucose supply soon depleted then our body depends on the stored glycogen which will be providing glucose, but in case of glycogen storage disorder where liver is affected their supply from liver glycogen will not occur. So, what will happen there will be fasting hypoglycemia. So, during the time of fasting when there is a long gap between two meals or there is fasting in those cases glycogen will be unable to supply glucose and that will cause fasting hypoglycemia.

So, the manifestation of glycogen storage disorder are actually based on the manifestations which is coming from liver or manifestations which are coming from muscle or they can be generalized. So, the symptoms or the presentations are divided in three main group. Now the liver glycogen storage disorder or liver glycogenosis they are the types glycogen storage disorder type 0, 1, 4 and 6. Then in case of glycogen storage disorder type 3 and type 9 the hepatic presentations manifest as liver glycogenosis. So, these are about the liver glycogenosis these types actually affect liver where as I told there will be fasting hypoglycemia there will be hepatomegaly these patients with will manifest with these things.

Now the muscle glycogenosis they mostly present in two way actually. Now the first group comprises type 5, type 7 then the muscle form of type 9 then also phosphoglycerate kinase deficiency also type 10, 11, 12, 13 there are multiple types of glycogen storage disorder. Now these group this first group actually manifest as exercise intolerance. So, basically the person is fine when at rest then while doing exercise they are tired easily they are fatigue easily that is called exercise intolerance. And what will happen when they will exercise they will be having muscle pain, muscle cramps so, exercise induced myalgia cramps that will be present.

Finally sometimes these symptoms are followed by rhabdomyolysis and myoglobinuria. So, there will be muscle proteins which will be degraded remember when actually normally what happens when there is long prolonged fasting in those cases when the muscle glycogen storage is depleted there is no further glycogen to supply energy then after a long time muscle proteins start to break down to provide energy. So, here the same thing will happen because they are the glycogen stored glycogen from skeletal

muscle is actually not happening. So, the muscle protein will start to break down and that will finally, give rise to rhabdomyolysis myoglobinuria. But the thing is that these persons when finally, they come to take rest these conditions reverse.

So, this is a reversible condition where if there is excessive exercise or prolonged exercise that causes the symptoms. Whereas, in the second group which are actually myopathic forms here there is chronic or subacute myopathies and there is a generalized weakness mostly even this weaknesses are manifested in body limbs and then also in respiration respiratory muscles are also facing myopathies. Apart from that there are involvement of other organs as well like RBCs, nervous systems, heart, liver these organs can be affected. So, basically these group the second group is not only causing myopathy rather they affect other organs as well. So, these are muscle glycogenesis remember.

So, there are two forms. Next we will discuss about the type 1 glycogen storage disease this is the most important one which is known as Von Jerky's disease. It is named basically with the with who has described it that is Von Jerky he has first described the disease. Now the cause of this disease is related to the enzyme glucose 6 phosphatase. Now this glucose 6 phosphatase if you remember that it is finally, that glucose after while glycogen is breaking down it is forming glucose 6 phosphate which is finally, broken down by glucose 6 phosphatase.

So, remember this glucose 6 phosphatase is not only the enzyme of glycogen degradation it is also involved in actually neo glucosinesis. So, in these disease type 1 glycogen storage disorder glycogen metabolism is hampered as well as neo glucosinesis is also hampered. Apart from that this is type 1 A where directly the catalytic subunit of this enzyme is deficient whereas, in type B there is deficiency of a translocase that is glucose 6 phosphate translocase that is which is present in ER endoplasmic reticulum. Then again there are other two types which are sometimes described as they are denoted as a separate type like the endoplasmic reticulum phosphate translocase if they are deficient that is sometimes designated as GSD 1 C type 1 C. Then a transporter deficiency that is glucose transporter deficiency that is type 1 D, but remember all apart from this 1 A 1 B 1 C and 1 D they are sometimes clubbed together under 1 B only.

So, we are concerned about finally, what happens with all of these type glucose 6 phosphatase function is affected. So, there is no formation of glucose from glucose 6 phosphate. Now, what will be the manifestation in in those cases? So, in case of neonate there is hypoglycemia as well as lactic acidosis. On further progress in case of infancy finally, glycogen accumulation starts which leads to hepatomegaly and also it affects the central nervous system. So, it is causing seizures hypoglycemic seizures.

Now this is a typical presentation of glycogen type 1 glycogen storage disorder von geerkes disease the babies actually or the kids they present with a doll like features. So, they are having obesity a protruded abdomen then prominent cheeks, hypertrophic my hypotrophic muscles sorry hypotrophic muscles and growth retardation as well. So, finally, the extremities which how it appears the extremities are actually very thin whereas, abdomen is protruded giving rise to a feature of obesity. So, this is a doll like feature which we say. Now what they are suffer from the most important one is hypoglycemia.

So, basically there is absence of glucose supply from glycogen. So, there is hypoglycemia more more specifically fasting hypoglycemia along with that lactic acidosis is also present then hepatomegaly as already told then bleeding tendency because of platelet functions are altered skin's entomosis present gouty arthritis this why we will discuss later also gouty arthritis joint pains the patients present with this symptoms and in case of specifically type 1 b with the deficiency of the translocase enzyme neutrophils are also hampered giving rise to neutropenia that is low neutrophil count. So, these are the manifestations of von geerkes disease. Now the hallmark of these disease are these 4 symptoms hypoglycemia, lactic acidosis, hyperlipidemia and hyperuricemia. Now why this happen actually hypoglycemia as I have discussed already that there is glycogen cannot provide glucose defective breakdown of glycogen or neo glucogeneses is also hampered.

So, that is giving rise to hypoglycemia during fasting. So, what happens if there is glucose 6 phosphatase deficiency basically glucose 6 phosphate cannot be converted to glucose. So, there will be accumulation of glucose 6 phosphate. Now these glucose 6 phosphate if you remember that can be that can enter in different other pathway like it can enter HMP shunt. In HMP shunt you have already read that HMP shunt is important because it gives those pentose sugars which is finally, giving rise to nucleotides.

Now uric acid is a breakdown product of nucleotide basically it is the end product or breakdown product of purine metabolism purine is one type of nucleotide. So, excess entry excess HMP shunt due to entry of look accumulated glucose 6 phosphate it is giving rise to excess amount of nucleotide which is finally, giving rise to on break breaking down it is giving rise to uric acid which is causing hyperuricemia. So, this is about increased production of uric acid, but then again because kidney is hampered. So, if kidney is hampered then in case why kidney is hampered because there is once again there is storage of glycogen in kidney as well. So, the function of kidney is hampered.

So, clearance of this excessively synthesized uric acid is also hampered. Production is

excess as well as clearance is decreased that is giving rise to hyperuricemia and these hyperuricemia manifest as gouty arthritis remember uric acid level when it is increased it is manifest the manifestation is gout. Then hyperlactic acidosis which is due to excess production of lactic acid in system and that is hyperlactatemia why once again it is the consequence of excess glucose 6 phosphate accumulation. Now, because these glucose 6 phosphate cannot be hydrolyzed to glucose it is entering in excess in glycolytic pathway giving rise to pyruvate which is finally, giving rise to lactate. So, that is causing hyperlactatemia that is and that is causing lactic acidosis.

Now important thing is if you remember the feeder pathway of glycolysis they are galactose, fructose, glycerol they also they are also dependent on this liver glucose 6 phosphatase enzyme to be metabolized to glucose. Now once again if these type of sources carbohydrate sources are ingested in form of sucrose lactose they are also finally, giving rise to hyperlactatemia then hyperlipidemia. Once again remember glycogen is causing hypo glycogen storage disorders are causing hypoglycemia hypo on hypoglycemia is sensed by glucagon and that glucagon is actually inducing more production of triglycerides and that is causing hyperlipidemia and it is actually giving rise to milky appearance in blood. So, we have discussed about the 4 important hallmarks of Von Jerkis disease that is hypoglycemia, lactic acidosis, hyperlipidemia and hyperuricemia. So, finally, how these Von Jerkis disease is diagnosed? It is most important that the clinical manifestations are concerning in these patients.

So, basically neonates who presents with fasting hypoglycemia growth retardation seizures they are checked for this glycogen storage disorders presence of these disease. Now how they are detected in laboratory by assessing the enzyme activity enzyme glucose 6 phosphatase activity which is obtained from liver biopsy. But these days basically the the diagnosis is mostly dependent on the identification of specific mutations which are giving rise to these diseases. So, mostly these days enzyme activities are not measured the diagnosis is mostly dependent on the molecular technology molecular diagnostic technology even it can be diagnosed prenatally. So, prenatal screening can be done from chorionic villi sampling presence of these mutations G6 PC or G6 PT alleles they are mutations which are causing Von Jerkis disease.

So, prenatally that can be screened. And finally, the line of treatment is basically because the majority of the manifestations the acute manifestations are actually from hypoglycemia. So, if that is checked other metabolic derangements like hypertriglyceridemia hyper hyperuricemia those can be checked. So, the goal of the treatment is to prevent hypoglycemia. So, basically these are the different types of glycogen storage disease. Now type 0 is one very fatal one where glycogen synthase the main synthesizing enzyme of glycogen is present and there is definitely hypoglycemia

and hyperketonemia which is finally, causing early death in patient.

Then we have discussed about Von Jerkis disease type 1a then type 1b also and they are different manifestation. Now, remember once again as I have told already that type 1b it manifest as neutropenia. Now neutropenia neutrophil is basically dealing with our immunity. So, whenever there is neutrophil functions hampered in those cases there will be recurrent infections. So, these patients are manifesting with recurrent infections.

Now, glycogen storage disorder type 2 which is known as Pompey's disease. Now, Pompey's disease is actually related to the deficiency of acid maltase which is a lysosomal glucosidase. So, definitely the manifestation is accumulation of glycogen we inside the lysosome these patients the manifestation is juvenile variant. So, juvenile persons manifest with these muscle affected with muscle hypotonia and finally, heart affected. So, death from heart failure at very early age sometime there is another adult variant which is causing muscle dystrophy.

So, remember once again type 2 here heart muscle is affected it is Pompey's disease. Then type 3 4 5 6 now 3 a here both the debranching enzyme present in liver and muscle they are affected which is giving rise to accumulation of limit dextrins. So, this is known as Forbes disease or Corey's disease again there is fasting liver is affected. So, there is fasting hypoglycemia hepatomegaly then muscle affected and that is causing muscle weakness. Now type 2 b type 2 a where debranching enzyme of both liver and muscle are affected whereas, in case of type 3 b only the liver isoenzyme is affected giving rise to only the liver symptoms generated from liver hepatopathies, but the muscle manifestations are not there.

Then type 4 it is known as Anderson's disease here the defect is in case of glycogen synthesis with the defect in enzyme branching enzyme. Now again there is hepatosplenomegaly and liver failure or heart failure which is the ultimatum in those patients. So, we read in the previous slide that in type 2 there is manifestation of heart affect the cardiac muscles are affected then again type 4 there is cardiac muscle is affected here moving to type 5 which is known as McArdle's deficiency is in phosphorylase muscle isoform of phosphorylase enzyme. So, the manifestation will be from muscles. So, again here is exercise intolerance we have discussed muscle glycogen are used up easily exercise intolerance which is giving rise to hyper lactatemia in these patients.

Now this is the muscle isoform which when affected is the type 5 remembers muscle for McArdle's M4M and in type 6 which is known as Hirsch's disease the liver isoform of phosphorylase is affected and the manifestation is the liver symptoms like hepatomegaly

fasting hypoglycemia is present already then also accumulation of glycogen in liver which is causing hepatomegaly actually and also mild hypoglycemia. Now you can see that this type 6 is giving rise to mild hypoglycemia. So, basically this hypoglycemia is the cause which is finally, targeting other metabolic pathways causing other metabolic derangements. So, whenever there is mild the those glycogen storage disorder which presents with mild hypoglycemia they are their prognosis are actually good.

So, here type 6 is having a good prognosis. Now these are the few important points like type 3 here you can see hepatopathy myopathy as well as cardiomyopathy. So, here also heart muscle is affected. So, we include type 3 as well. Then type 4 where the branching enzyme is affected they manifest at very early age in infancy or in childhood leading to hepatic failure or liver failure as we have discussed that is causing death in them actually. So, this one is a serious one which is causing early death.

Next the other glycogen storage disorders like type 7, 8, 9, 10 they are with the involvement of if you remember the enzymes that is enough actually. In type 7 there is muscle and RBC's phosphoructokinase affected. Then in type 8 liver phosphorylase kinase is affected. In type 9 both isoform of phosphorylase kinase present in liver and muscle they are affected. And finally, type 10 where cyclic AMP dependent protein kinase A if you remember which is actually the one important regulating enzyme of glycogenesis and glycogenolysis that is affected.

Now, this type 6 we have discussed in the last slide that type 6 hearse disease and here type 9. They are the least severe forms of glycogen storage disorder with a mild tendency to fasting hypoglycemia. And what happens the hepatomegaly which is actually caused from glycogen storage that is cleared with age. So, the liver size normalizes with age and finally, patient reach a normal adult growth in those patient. So, these are in these types type 6 and type 9 the prognosis is good.

So, this is all about glycogen storage disorder. We have learned from these sessions the different types of glycogen storage disorder and those are all due to either defective enzyme synthesis or defective enzymes function which ultimately is causing defective glycogenesis or defective glycogenolysis. The manifestations of glycogen storage disorder are at the level of liver or at the level of muscle causing hepatopathies or muscle related problems. The most important one which is mostly discussed is Wannier case disease which is due to the enzyme deficiency of glucose 6 phosphatase. And the line of treatment for all the glycogen storage disorder are the most important one is tackling hypoglycemia. So, basically a constant provision of carbohydrate to the circulation.

So, this is all about glycogen storage disorders these are my references. So, see you in the next session.