Overview and Integration of Cellular Metabolism

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Week 04

Lecture 19: Diabetes Mellitus and Metabolic Alterations

Hi, everyone. Welcome back to your lecture session on Overview and Integration of Cellular Metabolism. We are almost at the end of fourth week and this is the last topic that will be covering on Carbohydrate metabolism. Definitely we will be covering more about carbohydrate metabolism when we go into the integration and overview of integration metabolism phase, but for now our today's topic is diabetes mellitus and the metabolic alterations in diabetes mellitus. Now as all of we us are aware the diabetes mellitus itself is a such a huge disease and there are specialties and super specialties and thick books that are written on the topic. So, the overview of diabetes mellitus will be what that is we will be covering in this lecture because if we start getting in deep into each and every topic the entire lecture series can be covered by just taking diabetes right.

So, that being said keeping that in mind we will be discussing our lecture today on the following headings we will be learning how to diagnose, how it is a diagnostic criteria of diabetes mellitus, we will be learning what is the difference between type 1 and type 2 diabetes mellitus, we will also be learning what are the metabolic alterations that is our main focus in diabetes mellitus as well as we will also learn what is the metabolic basis of the diabetic complications all right. So, this I will start with this slide which is actually the recall slide from the previous class where we discussed the regulation of blood glucose right blood glucose homeostasis and over there I discussed these are the few check milestones which we need to keep in mind for diagnostic as well as for multiple choice questions right. So, I discussed that this whole thing will be discussed in much detail in later class which is today's class all right. So, I hope this slide is very familiar with you with this basic knowledge let us go ahead.

Now, what is diabetes? Since diabetes is a disease a strict definition cannot limit because it has got so many things, but just for sake of stating what the disease is to us we can say diabetes mellitus is a chronic metabolic disorder, chronic means it develops over time, chronic metabolic disorder characterized by what is the problem excess glucose the only and only culprit is high blood glucose in blood and urine ok. So, this thing often it

is missed all right due to what is the reason defective insulin action or deficiency in its secretion. So, either insulin is less or insulin is more and it cannot act which leads to the problem of increase blood glucose and urine glucose and it develops over time ok. So, this is the whole definition or statement about diabetes that we need to know. Now, regarding the diagnostic criteria of diabetes the diagnostic criteria that we all follow in standard text books as well is American Diabetes Association criteria.

It was coined in 2011 and it remains same till date that is 2023 you can check the same information in American Diabetes Association website as well. So, what are the cut off points or the criteria based on which diabetes is diagnosed? Well the whole thing not only diagnosis diabetes, but it also gives us an idea about the normal blood glucose level, what is the pre diabetic condition, what is diabetes right. So, you can find out the normal means we are a person or individual does not have any disease. So, what are the cut off limits? In fasting whenever the person has not taken anything after overnight fasting that is the blood glucose level should be below 100 mind it below 100 means up to 99. You see loosely we often say it is 70 to 100, but according to American Diabetes Association that is ADA criteria we often abbreviate it as ADA it is pre diabetic.

So, the 100 mg per deciliter falls under the lower limit of pre diabetic. Again I told you in many text books specially in older text book the criteria that still holds true or even in many medical under graduate text books it is 110 mg per d l right. But if we follow you have to follow one standard criteria we follow ADA criteria and it is up to 99. So, 70 to 99 is the normal fasting blood glucose level. Again one term I would like to request all of you who are listening to this lecture hence forth do not use the term sugar right.

But sugar is the misnomer because we are only dealing with diabetes by the level of blood glucose. Sugar means many other carbohydrates other than glucose right. So, even if mistakenly I say sugar you know this that I am wrong what I mean is glucose rate. So, that being said the normal blood glucose level fasting is up to 100. So, 70 to 99 and what is postprandial we have heard this term PPBG or PPBS for example, postprandial blood sugar the correct term is postprandial blood glucose.

The correct cut off limit is up to 140 unit for everything glucose is milligram per d l right up to 140 the lower limit being 70. So, 70 to 99, 70 to 139 right 140 again falls into prediabetic territory. And this prediabetes what is prediabetes it means a state of altered metabolism where it is neither normal nor a state of frank disease right. So, what is the criteria or cut off criteria of frank disease where we definitely need treatment this is 126 more than equal to 126. So, 126 mg per d l is diabetic and for postprandial it is 200.

Well we do not see the word PP ok we see OGTT. So, what is this? This stands for oral

glucose tolerance test oral glucose tolerance test. What is done? In postprandial blood glucose what used to be done with the dictum is we ask a patient or a case or a normal person who has come for routine blood glucose checkup that you take a meal and after 2 hours you check the blood glucose right. In oral glucose tolerance test in OGTT it is a finite amount that is 75 gram of glucose is asked to be taken in case of a adult patient. And this actually varies depending on his weight, but the standard for a standard adult healthy adult 75 gram of glucose after 2 hours the whole value is taken.

So, it gives a unified uniform idea because suppose I am taking some idli and someone might be taking 10 rasgulla the value of postprandial per say might be erroneous. So, OGTT gives us a gives us an uniform idea. So, that being said that is after meal 2 hours after meal the cut off is 200. So, considering the prediabetic state that is the condition in which I have abnormal metabolism, but still the disease can be reversed by lifestyle modification and there are many things I mean I have not reached the alarming stage the cut off to that prediabetic state is 100 to 125 in case of fasting and in case of OGTT it is 140 to 199 units being mg per bl milligram per deciliter very important. The cut off criteria is so important that is why I am spending so much time and we are dedicating so much time because you need to learn this right and to remember it by heart diagnostic everything multiple choice question exam result common knowledge everything right.

One additional criteria is there that is regarding the parameter A1C glycated hemoglobin we will be discussing that separately in an upcoming slide, but for now just know this the lower cut off for normal I mean the higher cut off for normal is 5.7 the unit is gram percent ok or gram per deciliter unit of blood glucose was in mg this is gram and for diabetes the cut off is above 6.5 more than equal to 6.

5. So, 5.7 to 6.5 falls in prediabetic state ok. So, this is all about the diagnostic criteria of diabetes mellitus according to American diabetes association guidelines ok. So, let us move forward. So, how can we classify diabetes? Earlier or if you see text books in I mean older text books we will find the names are actually different earlier the nomenclature of diabetes or the type of diabetes was given based on the age either it was based on age or the type of therapy which was used to treat the diabetes. Nowadays it is not used the dictum is not used nowadays we now name the diabetes types based on the pathogenic process.

So, now it is actually type 1 and type 2 it is actually very easy right. I will discuss in more details what was the earlier names and what are the differences very soon, but you should know that in both the types be it type 1 or be it type 2 the problem lies in abnormal glucose homeostasis. So, the class that we had preceding this class that is blood glucose homeostasis regulation of blood glucose that whole thing is jeopardized

that is why blood glucose goes up. I told you any problem only insulin is there to keep the blood glucose down. So, any problem in that hormone just single player which keeps the blood glucose in control.

So, any problem blood glucose will go high right. So, let us see what are the differences between the two varieties of diabetes right. So, we have the features over here as well as type 1 and type 2. So, previous name for type 1 diabetes was IDDM or insulin dependent diabetes mellitus because it needed only and only insulin for therapy right without insulin type 1 diabetes cannot be treated. Also earlier depending on the age of onset I told you.

So, it was juvenile onset diabetes mellitus it was also known as juvenile diabetes mellitus. Well mind it nowadays also we loosely use this term, but strictly speaking correct term is type 1 diabetes mellitus ok. This IDDM juvenile diabetes mellitus often means one and the same thing, but if you are to choose the right thing you need to state type 1. Similarly in type 2 it was known as NIDDM non insulin dependent diabetes mellitus and since it happens in old older patients it is also known as maturity onset right. So, generally it happens in older patients.

So, maturity onset diabetes mellitus. Now since depending on the nomenclature we already know what can be the next difference that is the age of onset. The age of onset in type 1 is usually in case of small children or below puberty for that matter in pediatric age group. Now so during childhood or puberty there is an exception the disease specifically that is mentioned LADA that is latent autoimmune diabetes in mellitus means the pathogenesis since now we are classifying diabetes based on pathogenesis. Now this type the LADA variety is actually the pathogenesis autoimmune, but we have to consider it in type 1.

If it were we were doing in based on the earlier classification we had to say ok since it happens in adults it would have been type 2 ok I mean the non insulin dependent, but now since the classification is based on pathogenicity we need to consider LADA in type 1 because both in case of type 1 and LADA the pathogenesis is autoimmunity ok. And again the age of onset for type 2 diabetes is old individual old cases more than 35 years what is the exception maturity onset diabetes of the young. We are not going to details of the pathogenesis, but the insulin resistance is the pathogenesis that actually are found in these cases, but these are patients that are actually younger patients earlier they could have been considered in juvenile, but not no longer. Now we are strictly considering on the pathogenesis right. So regarding pattern of onset they develop rapidly type 1 suddenly develops the underlying pathogenesis may go on for years, but the symptoms are all of a sudden whereas, it very it is very slow in case of type 2 diabetes mellitus .

Regarding the prevalence what is the prevalence if we are considering 100 patients of diabetes only 10 percent have been found to be of type 1 more than 90 percent or almost 9 out of 10 patients are type 2 right. Considering the genetic predisposition means we often here my maternal uncle has diabetes my mother has diabetes. So now, in being that part of the family you are also predisposed to diabetes. So what type of diabetes are they referring to they are referring to type 2 because genetic predisposition of type 2 diabetes is very strong it is not that much strong in case of type 1 diabetes ok. It is moderate it is there I mean the tendency to have autoimmune destruction of pancreas which is the main pathogenicity can happen there may be genetic predisposition, but mostly the factors that help in development of insulin resistance are the they are in type 2.

Nutritional state at the type of diabetes how will the patient look like the patient of type 1 diabetes will look like lean and thin under nourished ok skin and bones if you can define that thing. And it is mostly obese fat in case of type 2 diabetes mellitus again what is the biochemical defect autoimmune destruction of beta cells in 90 percent of the cases and remaining 10 percent of the case it is still not noticed still research is being pursued what is the reason of those cases in which there is not no destruction by autoimmune mechanism right. Whereas in case of type 2 diabetes mellitus it is the insulin resistance combined with the ability of beta cell to produce inappropriate amount of insulin. So, first insulin resistance develops and then at the later stage beta cell dysfunction develops right. So, as you have guessed rightly plasma insulin is almost low to absent in case of type 1 in case of type 2 it is high in early stage there is something must compensatory hyper insulinemia, but as we go on the beta cell dysfunction happens and again it is low right.

So, the acute complications being diabetic ketoacidosis it is abbreviated as DKA in case of type 2 diabetes mellitus it is known as hyperosmolar non ketotic coma HONK ok hyperosmolar non ketotic coma HONK. Frequency of ketosis very common ketosis a mild amount of ketosis may be found in type 2 diabetes mellitus, but is mostly common in type 1 diabetes mellitus all right. And rigander treatment insulin is always needed oral hypoglycemic drugs are ineffective and in this case lifestyle modification that is diet exercise and oral hypoglycemic drugs are quite effective and insulin may also be required in severe cases right. So, this is the natural course of the type 1 diabetes let us see what happens. So, initiating event is there is a exposure to any virus or toxin that will lead to the autoimmune trigger.

And in course of time it will slowly decrease the beta cell mind it if we just look at the insulin secreting capacity when the beta cell destruction is going on still the pancreas

secretes adequate amount of insulin. So, that the disease is undiagnosed. Now suddenly when the destruction has reached a certain level suddenly the symptoms develop there is ketosis there is hypoglycemia all the features of type 1 diabetes and ultimately the features I mean this is the case that happens ok. And in case of type 2 diabetes mellitus what happens? Initially an obese patient starts with obesity right it start patient develop starts developing insulin resistance it can run up till many years. Then what happens? Patients are diagnosed when patients are diagnosed initially in initial stage I told you some there is something as compensatory hyperinsulin amies of blood glucose rise is not that much, but ultimately in the long run it will be very very very high right.

So, next so, so this is all about the natural course of type 1 and type 2 diabetes. Now regarding another parameter that we just discussed that is a hemoglobin A1C or HB1C what is HB1C? You see whenever there is glucose in the system it has a tendency to attach to any non carbohydrate molecule right then that is known as glycation and that increase and that corresponds to the amount of blood glucose that is present. So, when blood glucose is very high there will be glycosylation of multiple products and that is a covalent bonding. However there is also something that is non enzymatic covalent glycation ok. This is also proportionate to the amount of blood glucose that is present and what we what ligand or what moiety we are focusing whether that is hemoglobin.

So, it means normally hemoglobin is attached with glucose to form HB1C that is normally below 5.7 gram percent, but when it is very high so, when glucose is very high so, the amount of glycation also increases. So, HB1C level will be high. Now why HB1C is actually very useful? You see blood glucose level can go up and go down very suddenly depend on our metabolic activity depending on taking of drug or depending on whether we are somebody is injected insulin or not. But once HB1C is formed once a hemoglobin is glycated the life span of an RBC is 120 days.

So, the status if once today is glycated it will run for the next 3 months. So, even if today my glycated hemoglobin level is very high and I now my blood glucose level is more than 200 my glycated hemoglobin level is more than 6.5 right. I fit in all the criteria of diagnostic diagnose get diagnosed by diabetes mellitus. I am suppose I am taking insulin shots along with that.

So, I take my insulin now I get my blood tested my blood may show 120 mg per dl. To a physician who does not know that I have a history of diabetes mellitus I may appear to be absolutely normal right. So, the glucose level can be fooled for example, if even if I do not take insulin shot if I skip my meals at some point of time all my blood glucose will be used up and all the glucose level will fall and that means, a false low blood glucose level. This and similarly it can in opposite direction also suppose I take 10

rasgulla the there is a sweet sweet dish and immediately I test my blood the blood glucose level will be falsely high. But the glycation of hemoglobin cannot be fooled because once it is glycated it will continue the state will be continued for next 120 days.

So, that is why even if fasting and plus postprandial blood glucose are essential HB1C is also one diagnostic criteria according to ADA guideline the cut off point being more than 6.5. And we have to ensure that where the laboratory where you are measuring has to be standardized using NGSP that is National Glycomeoglobin Standardization Program. It is a type of accreditation program by which they certify whether the lab is actually using the correct protocol. So, that the basically what it means the reliability of the HB1C result from the lab.

So, this is all about HB1C that we need to discuss in this class regarding metabolic alteration of diabetes mellitus. Now, what is the exact metabolic alteration that happens right? Two things basically what what the roles of diabetes mellitus they are what are the roles of insulin they are reverse because there is either absolute or relative means functional deficiencies of insulin. So, there is decreased glucose uptake or in that leads to an increased glucose production. The uptake happens in muscle and adipose tissue on action of insulin and glucose production in happens in liver. So, if the glucose uptake is not occurring and glucose is being continuously produced in liver ultimately there will be hyperglycemia.

So, this is the intra I mean inter tissue relationship in diabetes mellitus. So, what happen see in type 1 diabetes mellitus basically glucose level is low ok. So, when glucose level is low cells cannot uptake glucose ok. So, when insulin deficient cells cannot uptake glucose. So, intracellularly a cell cannot sense it is senses glucose deficiency.

So, all it I mean it tries in every way to compensate for that by undergoing what is known as gluconeogenesis. So, all the substrates for gluconeogenesis are being pushed for towards the liver and there is increased production of glucose ok because there is deficiency of insulin. Now, what happens inside the cells I mean the since glucose is absent alternate sources of metabolism alternate source storage sources are broken down to produce energy that being fatty acids. Now, fatty acids when broken down you will be reading all this very soon. So, I am not going to much detail fatty acids when they are broken down they produce acetyl coenzyme A.

This acetyl coenzyme A cannot enter the TCA cycle due to deficiency of oxaloacetic. Why? Because oxaloacetic is a substrate for gluconeogenesis it is being used up. So, TCA cycle is not functioning that is why all the acetyl coenzyme A is now diverted towards production of ketone body. So, there is excess glucose there is excess production

of ketone body ok. So, this is the thing that happens in cell as well as in liver that leads to production of diabetic ketoacidosis.

Well in case of type 2 diabetic stimulators the mechanism is almost similar, but there are some insulin that actually in initial stage of course, there are compensatory hyperinsulinemia and in course of time when insulin deficiency happens or beta cell dysfunction happen often cases of type 2 diabetic stimulators can mimic type 1 diabetic stimulators, but the amount of ketosis ketone bodies produced are much less compared to type 1. All other pathogenesis remaining same increased gluconeogenesis increased glycogenolysis and that leads to hyperglycemia ok. So, these are the major metabolic changes in diabetes mellitus. So, what happens in carbohydrate metabolism glucose uptake is reduced by muscle adipose tissue there is increased glycogenolysis and gluconeogenesis clear. What we will be discussing in lecture session ahead now moving forward that is what the alterations regarding lipid and protein metabolism.

So, just for now you should know this in case of lipid metabolism there is increased fat breakdown, increased fatty acid oxidation and production of ketone bodies in the liver. These are all catabolic processes insulin is an anabolic hormone it helps in all the metabolic pathways that are anabolic. So, when it is deficient all the catabolic processes are up regulated by the counter regulated hormone that is glucagon. Same happens in protein metabolism decreased protein synthesis and increased protein degradation. So, once you understand the concept everything will become very clear.

So, what is the signal what is the basic alteration in the hormone signaling that happens in the diabetes mellitus ok. See in liver what happens liver is supposed to regulate it acts as a store house of glucose I told you regarding the mechanism of hexokinase and glucokinase. So, mainly it regulates the pathway of glycogenolysis and gluconeogenesis. So, if that is under imbalance hyperglycemic will occur. How it occurs? Since there is increase decreased secretion of insulin, insulin has got an inhibitory effect on glucagon.

Glucagon has always got a tendency to increase blood glucose ok because increase in blood glucose in emergency mechanism it always tries because not only there are multiple other factors by which blood glucose rises that we already discussed in the previous class. So, if inhibitory effect of insulin is gone the glucagon will be more and more that will it increase glycogenolysis and gluconeolysis and that will release more glucose into the blood stream and increase plasma glucose will happen. This is the alteration that happens in liver. Similar alteration also happens in muscle and adipose tissue lack of insulin leads to all the catabolic pathways. So, proteins are broken down to form gluconeogenic I mean a substrates for gluconeogenesis that is glucogenic amino acids are produced and that also increases plasma glucose.

Similarly, in adipose tissue lack of insulin means lack of glucose uptake from plasma glucose are taken up in cells if insulin and insulin helps in that. If there is no insulin there will be no glucose uptake and ultimately plasma glucose will rise. So, now let us look at the complications of diabetes. Mind it I have not gone into details regarding the clinical features of diabetes mellitus that is polyphagia, polydipsia, polyuria and polyneuropathy. So, let me discuss in brief right over just before going into the complication right.

So, diabetes is I mean the one very important symptom of diabetes is polyphagia. Patient suffers from increased hunger why that is so? You see blood glucose has got a tendency to regulate the hunger center right. Means what when we have got when we are well fed means the hunger center is suppressed because the satiety center is also addressed. You mean to say I mean just listen to me once when there is increased blood glucose level the body does not need more glucose. So, there is no need to eat when there is low blood glucose the hunger center is stimulated because the inhibition of satiety center over the hunger center is gone and we sense to take more and more food that is that happens in case of normal individual.

But when a patient is having diabetes means insulin is not acting then the person feels as if he needs to take more and more food in spite of having full stomach or in spite of having high blood glucose. So, that is one pathogenicity both hunger and thirst that we need to keep in mind. The same mechanism is happening for food intake as well as water intake and since there is more and more glucose in blood there are multiple osmotic complication that leads to polyuria. Now, going into the complications of diabetes mellitus the major complications are addressed by three mechanisms. Number 1 formation of advanced glycation end products, number 2 sorbitol pathway that all we already discussed in galactose and fructose metabolism and number 3 is the production of reactive oxygen species.

So, the first mechanism is advanced glycation end product. What is glycation I told you covalent non enzymatic attachment of carbon to multiple compounds right. So, there are some compounds to which if glucose or any carbohydrate is added in excess for example, excess amount of glucose is attached to some compound such as few amino acid, few protein, few fat lipid particles. They actually trigger a chain of immune reaction which leads to a destruction in blood vessel. Specifically the interaction between those advanced glycation end products and their receptors. Their receptors are known as RAG that is receptors for advanced glycation end product.

Mind it this is itself a huge topic and if you are interested there are references in the

reference section you can read it, but for now just know this excess glycation of certain products leads to micro vascular complication by interaction with the receptors and whole thing is mediated by inflammation and pro inflammatory cytokines. The next mechanism I already discussed in fructose and galactose metabolism that is how there is increased sorbitol inside the cell because in case of these slides are common to those classes right. So, I will not be covering these in details because you already know and I already told you because we will be referring this slides again in diabetic complications. So, the thing is the enzymes sorbitol dehydrogenase is absent in the organs of lens, retina, nerve cells and kidney. That is why the sorbitol when it is formed in case of excess blood glucose cannot be washed out and they lead to all the complications of diabetes that is diabetic retinopathy, diabetic neuropathy, diabetic nephropathy so on and so forth.

And ultimately lastly that is the major complication which is the triggering mechanism for all other micro vascular complication is reactive oxygen species mediated damage. I already discussed about reactive oxygen species during HMP shunt and glucose 6 phosphate dehydrogenase deficiencies you already have some idea. Basically what happens is this excess amount of sorbitol and an imbalance between NADH to NAD ratio that is redox imbalance that happens diabetes mellitus leads to an increased amount of reactive oxygen substances that leads to something known as oxidative stress. And that oxidative stress actually hampers with multiple normal cellular mechanism that is solar proliferation, apoptosis, cellular I mean that includes dysfunction of cell and damage and ultimately that leads to the all the micro vascular complication. And along with that an excess of advanced glycation end products, excess fructose that is bypassing the glycolytic path when entering into the cell creating an hyperglycemic state and also excess sorbitol that leads to the formation of all the problems including problem in eye that is cataract and other electrolyte imbalance.

So this is the conclusion that this class has covered the diagnostic criteria of type 1 and type 2 diabetes mellitus. We have also discussed what the differences between type 1 and type 2 diabetes mellitus. We have also covered what is the natural courses, metabolic changes, the basis of metabolic complications as well as the basis of clinical features in a brief. So these are my references and you can read them at your will and this is the end of it.

We will be moving very soon to lipid metabolism in the next class. I thank you for your attention.