Human Physiology
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Hello everyone, welcome to another brand-new class of human physiology. In our last class, we discussed glucose homeostasis, and we saw that if there is any disturbance in glucose homeostasis, then a persistent condition of hyperglycemia can lead to diabetes. In this class, we will discuss various ways to measure blood glucose, and we will also see some preliminary treatments for diabetes. Let us start with it. So, what are the different contents we will first see, such as how blood glucose can be measured in our body, what the different regular ranges of blood glucose are, and what the blood glucose levels would be in a diabetes condition? We will see different factors affecting blood glucose measurements, and we will examine some very preliminary therapies that are well known, especially regarding drug therapies or pharmacological therapies. We will discuss a little bit about insulin therapy, different routes of insulin delivery, and factors that affect insulin therapy.

Finally, we will discuss insulin pumps and a little bit about the SGLT inhibitors. So, what is blood glucose measurement and why is it important? Blood glucose measurement is essentially like quantifying the amount of glucose that is present in the blood at a given time. It can be during the research or in clinical settings, mostly trying to understand what the glucose concentration is in the body. Because studying the glucose concentration can be crucial to understanding if our body is maintaining regular proper glucose homeostasis or experiencing any disturbance or condition leading to hyperglycemia or hypoglycemia.

Why it is important, as we said, is that hyperglycemia and hypoglycemia can be detected by measuring the blood glucose. Hyperglycemia can cause a lot of significant damage to the tissues and the cells, and it can also cause similar damage to various organs. Hypoglycemic conditions can cut off the glucose supply to the brain, causing unconsciousness or coma. So, you can see a very general picture where excess blood glucose in the blood can be termed hyperglycemia and low blood glucose in the blood can be termed hypoglycemia. And then let us see what the normal blood glucose levels are in cases of non-diabetic animals.

So, these are like different conditions; for example, if we fast for over 8 hours, what will happen? So, mostly in a fasting condition, we will see a blood glucose level of about 70 to 100 milligrams per deciliter, or it can also be mentioned as about 3.9 to 5.5 millimoles per liter. Before the meal, it has generally been seen to maintain a similar level of blood glucose as during fasting, but after the meal, it becomes more or less about 140 milligrams per deciliter. So, if you measure randomly at any time of the day, we will mostly see around 140 milligrams per deciliter.

And one more important marker, which is HbA1c. It is also called the glycated hemoglobin test. And what is being measured? It measures your average blood glucose level over the past two to three months. So, this is very important. Generally, doctors can test this marker, which is called HbA1c.

That is nothing but measuring the average blood glucose level over the last 2-3 months, which provides significant insight into any pre-diabetic or diabetic condition. And HbA1c levels in cases of normal blood glucose have generally been found to be less than about 5.7 percent. Then what happens in the pre-diabetic case? As you can see, in cases of pre-diabetes, the glucose level is about 100 to 125 milligrams per deciliter. So, for normal, it was less than 100, but for the pre-diabetic, even with the fasting condition, it goes from about 100 to 125 milligrams per deciliter.

After the meals, mostly after 1 to 2 hours, you will see about 142 to 100 milligrams per deciliter. And what would the HbA1c level be? The average level in the last 2 to 3 months has been observed to be about 5.7 to 6.4 percent. And let us see what happens in cases of diabetes.

So, in cases of hyperglycemia and persistent high glucose levels in the body, it creates the condition called diabetes, and in the case of diabetes, we will see the fasting level will be more than 126 mg per deciliter. After a meal, we can experience blood glucose levels higher than 200 mg per deciliter. And even after any time, like randomly in a day, if the blood glucose is measured, we will always see a high blood glucose level, which would be more than 200 mg per deciliter. And if the average blood glucose levels are monitored, you will see that the HbA1c level would be about 6.

5 percent. So, what is the HbA1c level for a normal case if you do the glycated hemoglobin test, which is generally around 5.7 percent, that goes up to about 6.4 percent for a pre-diabetic case, and for a diabetic case, it goes higher than 6.5 percent? So, by measuring both the blood glucose and the HbA1c level, it can be determined if the body or the person is either in a normal condition, in a pre-diabetic condition, or in a diabetic condition. Now, it is very important to measure the blood glucose, right? So, what are the different ways we can measure the blood glucose? There are different laboratory-based blood glucose analyses, and we can also measure them from home, right? So, a very common one is this glucometer, right? It can be easily used to prick your finger and take a drop of blood, and using a strip, the blood glucose can be instantly measured, which can be seen at the top of the screen of this glucometer, right? Also, in the pathology lab, they can collect your blood and measure or monitor various enzymes like glucose oxidase or hexokinase.

So, your blood glucose level can also be measured by different types of enzymatic assays. Then there are continuous glucose monitoring patches, like this CGM patch; these can also be put in our bodies. This basically uses a subcutaneous sensor for real-time glucose tracking. It also minimizes the requirement for frequent blood sampling. This is really suitable for long-term studies, and using an insulin pump, this can be coupled with this continuous glucose monitoring (CGM) patch, which can ensure that whenever there is a high blood glucose level, the insulin pump will be able to pump or jab a few rounds of insulin into the body.

So, this is a very useful technique using continuous glucose monitoring, and there are also intravenous glucose monitoring options. During those, sampling can be done using either a syringe or a catheter from the femoral vein or another part of the body. Now let us see this procedure; this procedure we have recorded in the lab will show how blood can be collected from a mouse tail, and using a glucometer, you can easily see the blood glucose level. So, the research fellow is now wiping the tail with ethanol to sterilize it so that there is no bacterial presence on the tail, and she is using a needle to prick the tail so that a drop of blood comes out. So, she is causing the small prick not a big prick and as you can see like a drop of blood is coming out and you can little bit press also and now the blood will be collected to the strip.

And this glucometer will take the blood and sense the glucose, and it will show how much the blood glucose is, 226 milligrams per deciliter. So, this is how you can also use a blood glucometer at home by pricking your fingertips to get a drop of blood and measure the blood glucose. And one more important thing: how much blood glucose was observed? It was 226 mg per deciliter. So, can anyone tell me what this blood glucose level is? Is it normal, pre-diabetic, or diabetic? Yes, you are right; this is the diabetic level of blood glucose because what we said is that anything above 200 mg per deciliter is generally considered a diabetic level. And also, an important disclaimer here: this animal study, or the observation of blood glucose using the animal, is ethically approved by our institutional committee.

We try to maintain as little pain as possible in the mouse during the study. What are the different factors that affect blood glucose measurement? Like blood glucose, as you know, it can vary due to many factors, especially beta cell insulin function or alpha cell glucagon function. But during the blood glucose measurement, many other important factors can also partially vary the blood glucose level, and that can give a wrong result because it is so important to accurately measure the blood glucose; otherwise, the doctor may not be able to properly detect or diagnose the condition in your body. So, some technical factors that can play an important role, such as glucometer accuracy, improper steep storage, or higher blood volume, can cause improper blood glucose detection during the measurement. And there are also many biological factors, as you can see.

For example, stress, acute stress, trauma, infections, or surgery can elevate glucose levels due to stress hormones like cortisol and catecholamines. And then, gestational diabetes alters normal glucose tolerance and insulin response. Then, of course, food intake can increase blood glucose simultaneously, just as fasting can also cause lower levels of blood glucose, which we already know. Blood pressure can also affect blood glucose measurements by altering peripheral perfusion. Lastly, anemia may lead to falsely high glucose readings on some devices due to reduced red blood cell mass.

So, these are some of the biological factors. If there are certain variations in those factors, the measurement of blood glucose can be hampered or can give us inaccurate results. Then let us discuss some common therapies for diabetes. The foremost and primary treatment is insulin therapy. So, insulin therapy is very important for the management of diabetes, especially with type 2 diabetes and type 1 diabetes.

Insulin is required almost all the time for type 1 diabetes. Why? Because in cases of type 1 diabetes, there are no beta islet cells, as all the beta islet cells are destroyed by autoimmune activity. So, the body needs the insulin that is not being produced by the destroyed beta cells. So, insulin therapy is the only important and foremost therapy that is always required for type 1 diabetes. For type 2 diabetes, it can generally be managed by a healthy lifestyle, including regular exercise and dietary management.

Along with that, sometimes, like occasionally, this insulin therapy may be needed. But insulin therapy can also create resistance in case of frequent use. So, that is a significant limitation that continuous insulin therapy can activate these glycoprotein-type receptors in the cell, causing resistance, like drug resistance. And we already know that, in the last few classes, we have been discussing how insulin maintains glucose homeostasis. So, we are not discussing any of that, as you know, like insulin; by expressing or over-expressing the insulin receptor, it activates the

glucose uptake proteins, like the GLUT receptors, and glucose is generally distributed to the cell.

Any additional excess glucose is generally converted to glycogen in the liver. Then let us see what the different types of insulin treatments are and how fast the actions are. So, there are different types of rapid-acting insulin formulations in the market clinically. So, these are some of the drugs you can see: Lispro and Aspart. So, generally these are rapid-acting, which means the initial onset is about 5 to 15 minutes, and within 30 to 90 minutes, the peak insulin concentration arises, and then the overall treatment duration lasts up to about 5 hours.

There are some regular or short-acting insulin formulations, such as Hemulin R and Novolin R. Their initial onset is about 30 minutes to 1 hour, and the peak can rise up to 2 to 3 hours, with the treatment duration lasting up to 8 hours. There are some intermediate-acting and long-acting. For long-acting specials like the Largin from Lantars and then the Detemir from Levimir, these are some of the drugs that can be used for a long-acting or long-lasting insulin formulation. Their initial onset can be up to 1 to 2 hours to increase the insulin level, and it generally maintains for more than 24 hours.

And there are recently some ultra long-acting drugs that can also maintain the glucose level for more than 42 hours. So, depending on the patient's situation, either a short-term formulation, a rapid-acting formulation, a long-duration formulation, or an ultra-long-duration formulation can be used depending on the patient. Insulin can generally be given via various routes; it can be taken orally, given intravenously, or taken via inhalation. So, you can see there are different areas you can give. For example, you can give the insulin jabs in the hand; it can be given in the peritoneal area or abdominal area; it can also be given in the thigh area.

Generally, if it needs some rapid-acting insulin, you can use the intravenous method, but for daily insulin administration, subcutaneous is the most common. There are inhaled types of versions of inhalation, like insulin, but their use is generally limited due to concerns about lung function. They can also act very rapidly. What are the different factors that can affect insulin therapy? For example, like physiological factors, food intake. If you take carbohydrate loads, that can affect insulin needs; physical activity, like exercise, increases insulin sensitivity, and stress and illness can also increase insulin requirements.

And finally, liver and kidney function can also affect insulin metabolism. Medication interactions can also be a cause of affecting insulin therapy. For example, if the patient is using a steroid type of drug or a diuretic type of drug for another condition, it can promote increased blood glucose or a hyperglycemic condition, which means it will require more insulin. So, under steroids and diuretics, this type of drug can affect the body in terms of causing side effects such as a higher insulin requirement. What are the different types of side effects? Over insulin, like more insulin, if the insulin level all of a sudden goes high, it can cause a hypoglycemic condition because more insulin eventually will distribute all the glucose from the body, causing a lack of glucose present in the blood, and that can cause hypoglycemia.

Insulin can also cause ocular imbalance. It can cause cardiovascular risks. It can cause weight gain. It also has challenges with renal inefficiency or insufficiency. So, there might be challenges in cases of a high amount of insulin therapy. So, that needs to be properly monitored without giving like unlimited amount of insulin jabs.

First and foremost, over-treatment with insulin can cause insulin drug resistance, and if there is any insulin drug resistance, then insulin will eventually not affect maintaining the blood glucose level, even if you give too many injections. In those cases, the only options would remain as organ donation, cellular replacement, or cell-based therapy. In our next class, we will discuss in detail topics such as the artificial pancreas, how organ donation can happen, and how an artificial pancreas can be created in the lab. And we will also discuss how we can replace the damaged beta-ylate cells in terms of cell therapy. So please tune in with us for the next class, which will be very interesting.

Finally, there is this insulin pump that can also be coupled with a continuous glucose monitoring patch. So, you can basically measure the blood glucose level continuously, and whenever there is a requirement for blood, like insulin in the body, if you see a hyperglycemic condition from this pump, a certain amount or certain unit of insulin will be immediately injected into the body. These are very important for type 1 diabetes patients, where insulin levels need to be maintained most of the day because in cases of type 1 diabetes patients, there are no surviving beta islet cells, causing severe irregularities in blood glucose levels and prolonged hyperglycemia. So, for those patients having this insulin pump, the continuous glucose monitoring patch is very helpful. Whenever there is a blood glucose level that goes high, the pump can eventually jab or inject a few units of insulin to maintain glucose homeostasis.

Finally, we will also discuss the SGLT1 inhibitor; these are sodium glucose cotransport inhibitors. So, you remember that in the cells we have this sodium-glucose co-transporter, right? These are secondary active transporters. What happens in those cases is that when sodium comes into the cell, it also helps the glucose, which is high outside, to come inside. Right, and this is called the sodium-glucose secondary active co-transport mechanism. We say "secondary" because it is dependent on the primary sodium-potassium ATPase transport to initially create this ionic gradient.

What happens is that the SGLT1 or SGLT2 inhibitors work on these SGLT1 receptors, which are present in different areas of the body. For example, the SGLT1 receptor is present in our gastrointestinal system, mainly in the small intestine and sometimes in the kidney as well. What it does is enhance the glucose absorption from the foods. But if we use this SGLT1 inhibitor, for example, this drug is like sotagliflozin.

So, this is the sotaglyphlogine. If you use this SGLT1 inhibitor, what will it do? It will basically stop the absorption of glucose from food into the blood, right? So, if less glucose is absorbed into the blood, the glucose level will slowly go down. So, in this way, SGLT1 inhibitors can be used to treat hyperglycemic conditions. In the same way, SGLT2 inhibitors are similar to sodium-glucose secondary active co-transporters. So, they also improve the reabsorption of glucose during urination or in kidney filtration. So, do you remember the discussion we had in the kidney class? That during kidney reabsorption, especially in the proximal convoluted area, this type of SGLT2 receptor is present.

What do they do? They promote glucose reabsorption. Why does PCT do that? Because glucose is a very essential component of our body, our body does not want to lose any essential molecules. But in cases of diabetes, do we really need this reabsorption? No, right, because our body is already high in glucose. So, in these cases, you can use different SGLT2 inhibitors, for example, Dapagliflozin or Empagliflozin. So, these are different types of brand names of SGLT2 inhibitors that will basically stop the glucose reabsorption process in the kidney. So,

basically, glucose will be released in the urine, right? So, in this way, this type of inhibitor can be successfully used to either reduce the absorption of glucose in the blood or to remove the excess glucose through the urine.

This is the same thing we discussed here. You can go through the diagram, and if there is any confusion, please drop us your questions; we can also discuss further during the live interaction, right? So, if you remember, we thoroughly discussed this glucose-like sodium glucose secondary active co-transporter pump during our cellular transport mechanism, which also depends on the sodium-potassium ATPase primary transporter pump. So, SGLT1 and SGLT2 inhibitors basically stop either the SGLT2 pump or the SGLT1 pump, causing a lack of reabsorption of glucose either in the intestine or in the urine or in the renal cells to the blood. And one other important drug that is very commonly used nowadays is metformin. Metformin can also be coupled with insulin to treat high blood glucose levels. And what are their different mechanisms of action? You can see that metformin inhibits gluconeogenesis, which means metformin reduces the activity of the enzymes that produce glucose in the liver.

Metformin also improves insulin sensitivity. So, metformin, if combined with insulin, enhances the body's response to insulin to control blood glucose levels. Metformin also decreases the absorption of glucose. So, from the food in the intestine, it will reduce glucose absorption; in this way, a lower amount of glucose will be absorbed in the body. So, these are different ways metformin is a very important medicine that is generally combined with insulin to treat diabetes. Okay, there are other pharmacological therapies, aren't there? Like you can see, these are different types of drugs.

The six most different classes of drugs that can also be used. It can be like alpha-glucosidase inhibitors; it can be like dipeptidyl peptidase 4 inhibitors, right? It can be like meglitinide analogs; it can be like sulfonylureas. So, these are different classes of drugs that are sometimes used to treat conditions like diabetes in specific cases. They may have different side effects, such as increased urination, increased thirst, a high risk of genital yeast infection, and a high risk of urinary tract infection; but, of course, they can control blood glucose levels, and sometimes blood pressure can also be controlled.

They can also help reduce body weight. So, there are some side effects and benefits for all these drugs. If you are interested, go through each of those drugs, their details, do a detailed study of how those drugs are being used and what the different conditions are in which they are used. So, please think about why the fasting blood glucose is considered a more reliable indicator of diabetes than the random blood glucose level. Also, try to find out what challenges healthcare providers face in ensuring patient adherence to insulin therapy and how these challenges can be addressed.

Hopefully, you enjoyed the class. If you are more interested, read these books, and you can also read web content. If you have further questions, please don't forget to leave questions for us, and we can also discuss them during the live session. Thank you for attending this class where we discussed various ways to measure insulin, how to measure blood glucose, and also how different types of therapies exist in cases of hyperglycemia, including insulin, metformin, SGLT inhibitors, etc. Hopefully, you enjoyed the class. Let's hope to meet with another new class in human physiology very soon.