Transcript Module 6

[0:16] Dr. Richard Bergenstal:

Welcome everyone to "DKA Fundamentals: Making Sense of Pathophysiology, Ketones, and Euglycemic Risk." This is part of ACT Now- Advancing CGM Training. I'm Rich Bergenstal, Senior Research Investigator and Executive Director Emeritus of the International Diabetes Center in Minneapolis, Minnesota, and a clinical professor at the University of Minnesota. I'm happy to co-chair this with my friend and colleague Ketan Dhatariya. Please introduce yourself.

[0:47] Dr. Ketan Dhatariya:

Hi, everybody. Hi Rich, thanks for this. I'm Ketan, a diabetes doctor from Norwich in the UK, and it's a real pleasure to be here.

[0:55] Dr. Richard Bergenstal:

Great. We're going to have a great session today. We're talking about DKA, and there's no better place to start than why DKA still matters. It's not talked about as much in the office and clinic as other conditions around diabetes, but it needs to be. There is a great clinical burden and there are consequences of delaying recognition. DKA, which many people don't realize, is the most common hyperglycemic emergency in people living with diabetes, more than severe hypoglycemia or hyperglycemia admissions.

It's a leading cause of death for children and young adults with diabetes under age 58. There's high mortality, long length of stay and high healthcare cost, not only for people with type 1 diabetes but for those with type 2 who get DKA. And people come back with repeat admissions. If you've had one episode of DKA, you're very likely to have another, and the second is even more costly. There's even early work suggesting a single episode of DKA in children may lower IQ scores. It's a short study, but it shows that early detection is crucial to prevent this cost and these complications.

[2:40] Dr. Richard Bergenstal:

DKA is increasing in burden. This is a really nice study with 21 years of follow-up in the UK of DKA episodes in both type 1 and type 2 diabetes. Look at the numbers: 78,000 people with type 1 and over half a million with type 2. Of the people with type 1, 16.4% experienced at least one DKA episode, so it really does happen. A smaller percentage of people with type 2 are affected, but there are so many more of them that it's quite a number. The rates seem to be going up, and we're not exactly sure why. They're now around 4%-5%, meaning a one-in-twenty chance in a given year that someone with type 1 could have an episode. You saw how costly and dangerous it is.

[3:43] Dr. Richard Bergenstal:

The strongest predictor is recurrence. The UK study also found that women, younger age and socioeconomic deprivation were associated with DKA, which is probably not surprising, and so was multimorbidity. It's dangerous, common and seems to be increasing.

[4:08] Dr. Richard Bergenstal:

Who's at risk? A previous history of DKA: really watch those people and emphasize ketone monitoring. A prior hypoglycemic crisis, which suggests a lot of swinging low and high, potentially venturing into ketoacidosis. Absolute insulin deficiency, which is type 1 diabetes but also other circumstances. Comorbidities, alcohol or substance use, and very high A1Cs put you on the edge to tip over. And unfortunately, people who ration their insulin because they can't afford it. If you don't have insulin, that's another cause of insulin deficiency. SGLT2 inhibitors, which we'll come back to, and social determinants of health.

[5:14] Dr. Richard Bergenstal:

There are special types of ketosis-prone type 2 diabetes. They're not as common, but be aware that type 2 can have a funny presentation. Often it masks what is really type 1 and we misdiagnose it. Some people with type 2 present with high ketones, then clear, but can go into ketoacidosis and later not even require insulin.

[5:41] Dr. Richard Bergenstal:

On the right-hand side is euglycemic risk, which we'll talk about more. People on SGLT2 inhibitors can have DKA at a lower glucose, and pregnant women, whose glucose tends to be lower and who may have starvation-type ketosis in the morning, are at risk. All of these put people at risk, and it's quite a number of people, so we need to focus on this condition. This is a good time to have my colleague Ketan tell us about the pathophysiology, what's going on behind the scenes.

[6:25] Dr. Ketan Dhatariya:

Thanks, Rich. That was an important reminder of why DKA is important. I'll go through the pathophysiology. Many of you will know that in people with type 1 diabetes it's because they're absolutely insulin deficient. What puts people with type 2 diabetes, or people who are really unwell, at risk is excess counter-regulatory hormone production. They're not necessarily absolutely insulin deficient day to day, but if counter-regulatory hormone concentrations go up, the insulin-to-glucagon ratio can change and they become ketotic. Counter-regulatory hormones also drive lipolysis, which drives ketosis.

[7:14] Dr. Ketan Dhatariya:

So you have insulin deficiency or excess counter-regulatory hormone production, which leads to lipolysis and the liberation of free fatty acids into the circulation. Free fatty acids are taken up by liver mitochondria and converted into acetyl-CoA, which is condensed to form the ketones we're familiar with, acetoacetate and beta-hydroxybutyrate.

Acetone is breathed off in the deep Kussmaul breathing you characteristically see in people with DKA, and you can smell it on the breath. It smells like pear drops or nail varnish remover, and you know that person is in ketoacidosis.

[8:11] Dr. Ketan Dhatariya:

Beta-hydroxybutyrate and the other ketones go back into the circulation and are taken to the kidney, where you can get both glycosuria and ketonuria. But don't forget that the ketones in urine are acetoacetic acid, not beta-hydroxybutyrate.

If you're using urinary ketones to measure what's going on, that is not the ketone that's in the blood, because beta-hydroxybutyrate is broken down into acetoacetic acid, which is then excreted into the urine. You may falsely think that because there are still ketones in the urine there are still ketones in the blood, but the beta-hydroxybutyrate may be gone. The other thing to remember is that urinary ketones are an average of what happened since the bladder was last emptied. So urinary ketones are not necessarily very good, but Rich will talk more about that shortly.

[9:18] Dr. Ketan Dhatariya:

Acetoacetic acid is also taken up by muscle, particularly the heart, and by the brain, as the substrate of choice when there's no insulin around. It's insulin that drives glucose into cells. If there's no insulin, or it's not working, glucose isn't getting into the cells. The cells are effectively starving, which is why ketones form, to provide an alternative energy substrate during insulin deficiency or insufficiency. I'll hand back to you now, Rich, to talk about ketone testing: what, when and how.

[10:00] Dr. Richard Bergenstal:

Thanks, Ketan. What a biochemistry refresher. It's good to get that straight in our heads again. To emphasize the need for ketone testing and to understand what we're testing, people with diabetes need to know when to test first, and then how. They need to test anytime they're feeling unwell: nausea, vomiting, fatigue, symptoms that can be precursors or early stages of ketoacidosis but can also happen when you're not feeling well for any number of reasons. Don't assume you always have the flu. Check ketones if you've felt unwell for an extended period.

Also test when your blood sugar is over 250 mg/dL for more than two or three hours, a persistent level over 250. Lots of times blood sugars go up and we know why and we get over it, but if they stay up, it's time to check ketones.

Also when sick, dehydrated or under mental distress, when things really aren't going well. Fasting for long periods leads to elevated ketones. If you do it gradually you can get accustomed to it, but an acute fast, an illness on top of it, or interrupted insulin, whether a dose missed by accident, running out of insulin or a dislodged infusion set, are all reasons to test or advise patients to test.

[12:01] Dr. Richard Bergenstal:

How do they test? That's an issue today. There's the urine test Ketan described, which measures acetoacetate, not the one in the blood, not beta-hydroxybutyrate (BHB), and gives an average. It's cheap, but not very convenient, and patients don't like to do it. It is the least expensive option, so

many have the strips, but they open the vial and the strips get outdated. Not ideal, but it does check some ketones presence.

[12:44] Dr. Richard Bergenstal:

Blood ketone meters are pretty good. They're very accurate and measure beta-hydroxybutyrate (BHB), but you have to poke your finger. Many people with diabetes today say, "I'm on continuous glucose monitoring, I'm trying to get away from poking my finger," but that's what you have to do to test this. The devices are relatively expensive and, at least in the US, not always covered by insurance, so there's a cost outlay. And people don't really routinely carry a ketone meter when traveling or outside the home. They have their phone and their continuous monitor.

I would say, in summary of this, we have some tools, but they're not ideal and not used very frequently. We really need to know where ketones are and whether they're going up or down, and that requires continual testing, which people don't seem to do very often.

[13:57] Dr. Richard Bergenstal:

In summary, there isn't much testing being done. In the clinical office we often don't talk about ketone testing. We're busy and talk about glucose, A1c and complication prevention, and we don't always get to the ketone message. People aren't sure: there are devices, but when do I test? Do we give a clear message and a testing schedule? And if I do test, what am I supposed to do with the data, from the patient and clinician perspectives? We'll get into that later because it's so important. But our current tools don't serve us well for early detection of ketone levels. Let's talk more about the glucose-ketone relationship, and I'll turn it back to Ketan.

[14:59] Dr. Ketan Dhatariya:

Thanks, Rich. I want to reinforce that the mechanisms for hyperglycemia and the mechanisms for elevated ketones are different. On the left, with elevated glucose, it's absolute insulin deficiency or insufficiency in the face of raised counter-regulatory hormones, leading to increased gluconeogenesis and hepatic glycogenolysis. And because of the lack of insulin, or insulin insufficiency, glucose doesn't enter the cells, so you get impaired glucose utilization. Meaning the glucose stays in the blood and you get worsening hyperglycemia, which can lead to volume depletion and everything else we know happens in DKA.

But because glucose isn't entering the cells, they're effectively starving and want that alternative energy substrate, so that's where ketones come in. So if you have insulin deficiency, and as you know insulin switches off ketosis and ketogenesis, so if you have no insulin, or it's not working well, you get lipolysis, release of free fatty acids and fatty acid oxidation in the mitochondria, leading to a rise in ketones.

[16:27] Dr. Ketan Dhatariya:

So two different things are going on: a rise in glucose, but independently a rise in ketones. Do we need to monitor both? The answer is probably yes, because a rise in glucose does not equate to a rise in

ketones. They are separate. So what we've been using for many years is this relationship we've assumed that if glucose is high, ketones will be high.

[16:58] Dr. Ketan Dhatariya:

There are data showing that's not necessarily the case. This study by Jennifer Sherr at Yale took 20 people with type 1 diabetes on a pump into a lab and stopped their insulin. Over about eight hours she measured everybody's glucose and ketones. Now this looks a bit messy, but I'll show you three patterns. On the left, glucose and ketones rose at a similar rate in this individual, which is what most people are familiar with: "My glucose is high, so I need to check my ketones because they might be high." That's what we always say. If your glucose is above 250 mg/dL, or 13.9 mmol/L, check your ketones, and your machine may tell you that too.

But that's not always the case because they're independent. In the middle, glucose, in light blue, went up quite quickly, but ketones rose very slowly, so there was dissociation, with glucose rising much faster than ketones. On the right is an individual whose ketones rose much more quickly while the glucose stayed the same. That's euglycemic DKA. The glucose can be completely normal or minimally raised, but they can be in frank DKA because their ketones are really high, with all the symptoms of metabolic acidosis, deep breathing and so on. We need to spot when ketones are rising regardless of what glucose is doing.

[18:45] Dr. Ketan Dhatariya:

And that's where new technology comes in. As you'll be aware, the FDA recently authorized a new device, the Libre Duo, a 10-day device, for use in people with diabetes.

[19:04] Dr. Ketan Dhatariya:

On the left are the glucose ranges we're all familiar with from CGM downloads: very low, low, time in target, high and very high. In the international consensus document that Rich and I were part of, we came up with similar ranges for ketones so people have some familiarity. Normal ketones are less than 0.6 mmol/L. If anybody starves overnight, children particularly, their ketones can be high, but below 0.6 mmol/L is completely normal physiologic ketones and there's no need for concern.

[19:55] Dr. Ketan Dhatariya:

If ketones start rising to between 0.6 mmol/L and 1.5 mmol/L, we classify that as elevated, and you may have some symptoms, which we'll come to on the next slide, along with what people need to watch for and what action to take. If ketones continue to rise to between 1.5 mmol/L and 3 mmol/L, that's high, and people may become more symptomatic. If ketones are above 3 mmol/L, which is the current threshold, people need to seek urgent medical attention because they're at risk of overt DKA. Depending on how you feel, there are some actions you can take to help yourself before you get that help. I'm going to hand back to you, Rich, to talk about what people should be doing.

[20:45] Dr. Richard Bergenstal:

Thanks, Ketan. I love that series of slides from Jennifer Sherr's work, teaching us that glucose and ketones are not the same and don't always go in sync. And then the establishment of these key

thresholds. It was the best work our international consensus group could do to come up with 0.6 mmol/L, 1.5 mmol/L and 3.0 mmol/L, but I think they make clinical sense. Now that the Duo is available, one small sensor that measures both glucose and ketones, it's really good for all clinicians and people with diabetes to get familiar with these terminologies and thresholds.

[21:36] Dr. Richard Bergenstal:

Both people with diabetes and clinicians need to be aware. When people get over 0.6 mmol/L, which Ketan said is the normal range, and yes, you can go above 0.6 mmol/L occasionally with a prolonged fast, they should watch for nausea, abdominal pain and fatigue, and more if it gets higher. Everything Ketan mentioned about the pathophysiology: difficult breathing, fruity breath from ketones being expressed through the lungs, confusion, and nausea, vomiting and abdominal pain, probably the main ones. Then fatigue, even confusion, and when you get deep breathing, dry lips and orthostasis. Frequent urination often occurs if your glucose is high, but remember glucose doesn't always have to be high, so you might not have it. People with diabetes need to be aware of these symptoms and correlate them with ketone testing, or let them prompt ketone testing. If they have the dual glucose-ketone sensor, just look at it, and you'll probably get a warning when reaching certain of these levels. We'll learn about that as this becomes available.

[23:09] Dr. Richard Bergenstal:

Next, what will people with diabetes do? I won't go into great detail, but they need to take action: test more frequently, test their glucose, follow their ketones, take fluids, and get medicine for nausea. But if it's ketones, the best medicine is to get those ketones down by getting some insulin and some carbohydrates in.

And know when to call your healthcare professional. If things aren't going well, nausea and vomiting continue, and you're trying to do all the right things, taking extra insulin, carbohydrate and fluids, it's time to call he healthcare professional.

[23:59] Dr. Richard Bergenstal:

Now, clinicians listening: what will you do when someone calls? What advice should you give? I think you all know it's fluids, carbohydrates and insulin. Insulin is the main factor, but getting fluids on board is really important because people are often very dehydrated at the same time.

You need insulin, but you can't take insulin if you don't have enough carbohydrates. If your sugar is 300 mg/dL or 400 mg/dL, you have plenty, so take some insulin. If your sugars are lower, if you're in that euglycemic state, as with an SGLT2 inhibitor, you need to take glucose and insulin. This table will be a nice resource. On the left are different elevations of ketones using the same thresholds, and across the top are different levels of glucose.

[25:07] Dr. Richard Bergenstal:

You match them up: how high are the ketones, and where is my glucose? That gives you a sense of how much extra insulin you need and whether you need carbohydrates to cover that insulin. Not mentioned on this slide: if you're on an SGLT2 inhibitor, in the middle of these symptoms, with

elevated ketones, stop your SGLT2 inhibitor until you talk to your healthcare team about when to restart it. Don't take another dose while you're getting your ketones back in line.

[25:45] Dr. Richard Bergenstal:

With these tools we can move into ketoacidosis prevention mode. In the past we've been teaching people how to treat it. Now we'd like to prevent it, arming the patient and clinician with tools like this. Dual glucose-ketone sensing may go a long way toward preventing DKA.

[26:12] Dr. Richard Bergenstal:

That's the message for today. I'm really pleased to have worked with Dr. Dhatariya as always, and I hope we've learned more about the importance of ketones. Preventing DKA should be part of our day-to-day clinical practice. Thanks very much for participating in this event.

[26:34] Dr. Ketan Dhatariya:

Thanks, Rich, and thanks everybody.