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TYPE 1 DIABETES – UPDATED PODCAST

Developed by Cassidy Chapman and Dr. Elizabeth Rosolowsky for PedsCases.com.
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Introduction:

Hi everyone! My name is Cassidy Chapman. I'm a 4th year medical student at the University of Alberta. This podcast was developed with Dr. Elizabeth Rosolowsky, a pediatric endocrinologist at the University of Alberta.

Welcome to our updated review of Type 1 Diabetes (T1D) in children and adolescents. PedsCases podcasts last covered Type 1 diabetes in 2013, and a lot has changed since then!

By the end of this podcast, the listener should be able to:

1) Briefly describe the pathophysiology of T1D
2) Describe the clinical presentation, diagnostic criteria, and new staging system for T1D
3) Discuss the management options for T1D, including advances in insulin therapy and glucose monitoring
4) Identify acute complications of T1D and be aware of the updated management protocols for these complications

Of note, a separate PedsCases podcast covers Diabetic Ketoacidosis. Please refer to that podcast for more detail on this very important complication.

Case Overview:

Let's begin with a case: Imagine that you are working in a pediatric clinic and are scheduled to see a 13-year-old female patient accompanied by her parents for a follow-up appointment for Type 1 Diabetes. The patient's diabetes was first recognized when she presented to the Emergency Department with DKA, 11 years ago! Hmmm, this sounds like it might be the same patient as the original T1D podcast! Anyways, now that the patient is older and is starting to become more independent with her self-management, her parents want you to review T1D with her. They have heard that there have been some recent developments in the management of T1D and are interested in hearing about these. What key points would you want to cover? Feel free to pause the podcast now to gather your thoughts before we proceed.

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Objective #1:

Pathophysiology of T1D:

For our first objective, let's start with discussing the pathophysiology of T1D. T1D is an autoimmune disease, in which the immune system attacks and destroys the pancreatic beta cells, the cells responsible for secreting insulin. As functional beta cells are lost, this leads to worsening insulin deficiency and therefore worsening glucose intolerance. There is a subclinical or 'honeymoon phase' in which the remaining beta cells have adequate function, but when about 80% of the beta cells have lost their function, the patients develop the signs and symptoms of diabetes. Type 1 diabetes occurs due to a combination of a genetic predisposition combined with exposure to certain environmental triggers. From a genetic standpoint, The HLA allotypes DQ8 and DQ2 on chromosome 6 are risk factors for developing T1D, and HLA type in first degree relatives also indicates an increased risk for developing T1D. However, T1D is not caused solely by genetic factors, and in fact, 90% of new cases of T1D have no family history.

Type 1 Diabetes Diagnosis:

Clinicians can suspect diabetes mellitus with clinical symptoms such as unintentional weight loss, unusual thirst, frequent urination, and low energy. In the context of these clinical symptoms, a random plasma glucose greater than 11.1mmol/L or a fasting plasma glucose greater than 7.0mmol/L are diagnostic[1]. Type 1 diabetes is favored as a diagnosis over other types of diabetes when there is evidence of an autoimmune etiology. Specifically, in T1D, the immune system attacks and destroys the pancreatic beta cells, which are the cells responsible for secreting insulin. As functional beta cells are lost, insulin deficiency and glucose intolerance arise, leading to the signs and symptoms of T1D[2].

Objective #2:

New Staging System for T1D:

Recent advancements have improved our understanding and diagnosis of T1D. It is now recognized that the presence of two or more pancreatic autoantibodies is a significant marker for diagnosing T1D, even before clinical symptoms appear. Examples of these autoantibodies include those against specific beta cell proteins such as insulin, glutamate decarboxylase, and islet antigen 2, to name a few[3].

A new staging system has been introduced based on this improved understanding of the development of T1D. This new staging system includes three stages[4]:

- Stage 1: Beta cell autoimmunity with 2+ autoantibodies, normal glucose tolerance, pre-symptomatic
- Stage 2: Beta cell autoimmunity, abnormal glucose tolerance, pre-symptomatic
- Stage 3: Beta cell autoimmunity, raised blood glucose above diagnostic thresholds, classic signs and symptoms of T1D

Previously, T1D was diagnosed at stage 3 with the onset of clinical symptoms and abnormal lab investigations, but now, it can technically be diagnosed in stage 1 when autoantibodies are present, even without symptoms. Although the pre-clinical staging is currently not that relevant

for clinicians because commercial tests for these antibodies are not widely available, research focusing on pre-clinical groups might help to find interventions to delay or prevent the onset of T1D!

Objective #3:

Back to the Basics: Insulin Therapy:

Now for our next objective, let's discuss the management options for T1D. Insulin replacement remains crucial for individuals with T1D to mimic natural pancreatic insulin production. Effective management involves not only administering exogenous insulin, but also monitoring glucose levels regularly and adjusting insulin doses as needed.

There are many types of insulin which vary in terms of their time of onset, time to peak, and duration of effect. There are 3 main categories of insulin based on their time of onset: Rapid-acting, intermediate-acting, and long-acting insulin. Rapid acting insulin has various names including Novorapid (Aspart), Humalog (lispro), Apidra (Glulisine), and Fiasp, with onset in 5-15 minutes, peak in 1-2 hours, and duration of 3-5 hours. Intermediate acting insulin includes NPH, and Humulin-N, with onset in 60-180 minutes, peak in 5-8 hours, and duration of up to 18 hours. Long-acting insulin includes Levemir (Detemir), Lantus (Glargine), Basaglar, and Tresiba, with onset in 90 minutes, a steady release and therefore no peak, and duration of about 24 hours.

Advancements in Insulin Therapy:

Today, we want to discuss updates in insulin therapy. Recent advancements include faster-acting insulins, which provide a quicker onset and peak compared to traditional rapid-acting insulins. An example of this is a rapid-acting insulin called Fiasp (insulin aspart), which has its onset in about 2 minutes[5]! Another update is the advent of ultra-long-acting insulins, which offer a steady insulin release over an extended duration of over 24 hours. Tresiba (insulin degludec) is an example of an ultra-long-acting insulin, with a duration of action of over 42 hours[5]! The introduction of biosimilar insulins has also been a significant advancement in recent years. Biosimilar insulins provide cost-effective alternatives to branded insulins, while maintaining similar safety and efficacy, enhancing patient access to diabetes medications. Three biosimilars are currently used in Canada[6]:

1. Basaglar, a long-acting insulin, and biosimilar of Lantus/Glargine
2. Admelog, a fast-acting insulin, and biosimilar of Humalog/Lispro
3. Truapi, another fast-acting insulin, and a biosimilar of NovoRapid/Aspart

These biosimilars have made insulin therapy more affordable and accessible, including for pediatric patients.

Insulin Delivery Methods:

Now, let's talk about the timing of insulin delivery. Insulin delivery schedules can be thought of in two broad categories: basal-bolus regimens and continuous subcutaneous insulin infusion (CSII) regimens[7].

Starting with basal-bolus therapy, it is also known as multiple daily injections, or MDI for short. In MDI dosing, long-acting insulin is given once a day (normally at supper or bedtime). This

long-acting insulin provides a background or basal level of insulin overnight and throughout the day. This background or basal insulin is needed to prevent one's body from producing too much glucose when fasting. Then, rapid insulin, also known as bolus insulin, is given at each mealtime to cover blood glucose spikes when eating. While MDI is the most physiologic basal-bolus regimen, you might also hear about regimens such as twice a day (or BID), and three times a day (or TID) dosing. BID and TID regimens require fewer injections than MDI, and are therefore occasionally used at initial diagnosis when patients and their families are getting used to injections. BID and TID regimens are also sometimes used in school-aged children who are not yet able to deliver their own insulin at school. This is because in BID and TID regimens, the intermediate-acting insulin given at breakfast peaks in about 4-6 hours, around the child's lunch time. This is a large advantage of BID and TID dosing: the child does not need to receive another lunchtime insulin injection at school because the peak of their morning intermediate-acting insulin is already covering this lunch period!

Now for Continuous Subcutaneous Insulin Infusion (CSII), we think about insulin pumps! Insulin pumps may be considered after initial management with MDI has been established, particularly when a patient struggles with optimal blood glucose control, requires flexible dosing, or seeks a more convenient insulin delivery method. In CSII, an insulin pump delivers a continuous flow of basal insulin into the subcutaneous tissue, and can also be activated to deliver insulin boluses when needed, such as at mealtimes, and when glucose levels are high for other reasons. Insulin pumps use only rapid-acting insulin and can deliver insulin doses as small as 0.05units/hour, which facilitates more precise control of blood glucose levels compared to MDI dosing.

Blood-Glucose Monitoring:

When giving exogenous insulin, blood glucose monitoring is required for adjusting insulin doses accordingly. Blood glucose levels can be checked through either capillary blood glucose checks, or with a continuous glucose monitor (CGM for short). A CGM is a small wearable sensor device placed under the skin that measures interstitial fluid glucose levels throughout the day. This means that CGMs technically measure interstitial fluid glucose, not blood glucose. New and improved CGM models continue to be introduced, leading to constant updates in T1D management! For example, updated CGMs can be paired with modern insulin pumps, allowing for improved insulin delivery systems. Some current examples of insulin delivery systems using a CGM and insulin pump include sensor-augmented insulin pumps, hybrid-closed loop systems, and the concept of 'looping'[8].

Insulin Delivery Systems:

These insulin delivery systems can be quite complicated, so let's start with a big-picture overview. An ideal insulin delivery system would closely mimic the action of our pancreas; It would have a pump that automatically delivers both basal and bolus insulin based on real-time blood glucose information, and without any input from the user. As of our podcast, there is no commercial system that does this, but there are some systems which are coming close. So, let's review the current options!

With sensor-augmented insulin pumps, individuals can use their CGM data to guide insulin adjustments on their insulin pump device. However, these insulin adjustments are not automatic, and still depend on input from the individual using the insulin pump. Building on this,

hybrid closed loop systems automatically increase or decrease basal insulin delivery to keep baseline blood glucose levels within a target range. Hybrid closed loop systems reduce the amount of manual input by the user, as basal insulin delivery is somewhat automated! However, hybrid closed loop systems still require input from the user for mealtime or correction insulin doses. Next, you might also hear about people creating their own insulin delivery systems, called do-it-yourself (or DIY) insulin delivery systems, in a concept called "looping". Looping involves a continuous feedback system between a CGM and insulin pump, and automatic adjustment of insulin delivery based on current and predicted glucose levels. While looping comes close to full automation, it still requires the individual to notify the device when they are going to be eating a meal, to deliver correction insulin accordingly. Although these DIY looping systems are not yet commercially regulated in Canada, and they require technical expertise to set up, they offer highly personalized and tight glycemic control[7].

Glycemic control is important to prevent long-term complications of T1D such as cardiovascular disease, neuropathy, nephropathy, and retinopathy. Regular screenings, including follow up doctors' appointments, lab investigations, and regular eye exams, are essential for early detection of these issues. By achieving good glycemic control, patients can significantly reduce the risk and severity of these complications, underscoring the importance of proactive diabetes management.

Objective #4:

Now that we've talked about the basic management of T1D, let's talk about managing various acute complications. Remember that individuals with T1D must manage the associated risks, including hypoglycemia and DKA.

Managing Hypoglycemia:

Hypoglycemia, often caused by the administration of exogenous insulin, is defined as a plasma blood glucose level less than 4.0mmol/L. Signs and symptoms of this include sweating, shakiness, dizziness, headaches, mood swings, extreme hunger, and altered level of consciousness. For mild hypoglycemia, the individual needs to ingest a fast-acting carbohydrate source such as juice, syrup, or candy, to quickly raise blood glucose levels. Severe low blood glucose, known as severe hypoglycemia, is not a specific blood glucose level per se, but is when the person is unable to participate in their treatment. Their mental status and bodily functions are altered. In the case of severe hypoglycemia, patients require glucagon. Glucagon is a hormone that stimulates the liver to release stored glucose. Traditionally, intramuscular glucagon was used as first-line treatment for severe hypoglycemia. More recently, an intranasal route of glucagon administration was invented. This intranasal glucagon is called Baqsimi. Baqsimi is a non-invasive and easy-to-administer option for severe hypoglycemia[9,10]. Unlike with intramuscular glucagon, no mixing or reconstitution of glucagon is needed with Baqsimi. It's all ready to go, which makes it so much easier to use, especially in a stressful situation such as a severe glucose low. Baqsimi has been approved in children ages 4 and up and is now first-line in this population, whereas intramuscular glucagon is reserved for very young children and when mini-glucagon injections are needed.

Managing DKA:

As previously mentioned, DKA is another common acute complication of T1D. For a full review on DKA, please refer to the existing PedsCases resources. Recall that one serious complication of DKA is cerebral edema. As an update, our improved understanding of the pathophysiology of DKA-related cerebral edema emphasizes its link to cerebral hypoperfusion as well as osmotic shifts[11]. Cerebral hypoperfusion in DKA is caused by a combination of factors such as systemic hypotension due to severe dehydration and altered autoregulation. These can be worsened by rapid changes in glucose levels and fluid shifts, further contributing to cerebral edema. Our improved understanding of DKA pathophysiology has clinical implications, such as choosing isotonic IV fluids such as 0.9% sodium chloride for initial fluid resuscitation. It also highlights the importance of a slow rate of fluid administration to avoid abrupt changes in blood glucose and electrolyte levels[11]. In terms of the initiation of insulin in DKA, recall that we start with a continuous insulin drip to shut off ketogenesis and glucose production, and to promote glucose uptake into cells. Once the DKA resolves based on several lab markers, the patient can be converted to a subcutaneous insulin regimen, such as the ones we covered above. As an update since the previous podcast, recent guidelines now emphasize more conservative insulin dosing in DKA, particularly in milder cases in DKA, to avoid rapid drops in blood glucose levels and to prevent complications.

Case Revisited:

Let's revisit our clinical case! Recall the patient that you were asked to see: a 13-year-old female with a history of T1D diagnosed about 11 years ago. In this follow-up visit, you start by checking in to see how she has been doing and clarifying any questions that she has about T1D. You inquire about her current management with insulin administration and blood glucose checks. You explore any T1D-related symptoms that she has been experiencing, including any blood glucose 'highs' or 'lows'. If she has experienced any acute complications of T1D such as hypoglycemia and DKA, you ask how she has managed these.

In speaking with the patient and her family, you find out that she has been doing very well with her T1D management. She is using an MDI insulin dosing schedule, using generic long-acting and rapid-acting insulins. She does finger prick blood glucose checks about 4-5 times per day. She has occasional 'lows' requiring fast-acting carb sources. She always carries her intramuscular glucagon with her in her backpack, but thankfully she has not had any episodes of severe hypoglycemia requiring its use!

With the above information in mind, think about a few changes to management that you could suggest based on your updated knowledge of T1D! Please pause the podcast if you'd like a minute to reflect before we give some ideas.

Some potential changes to T1D management that you could discuss with the patient include:

1. You might discuss the benefits of biosimilar insulins as a safe and cost-effective alternative to the generic insulins that she has been using.
2. You might explain the benefits of a continuous glucose monitor (CGM) to replace capillary blood glucose checks.
3. You might discuss the option of switching from her current basal-bolus (MDI) insulin delivery schedule to a continuous insulin delivery system with an insulin pump. Recall

that an insulin pump can also be paired with a CGM to automate some aspects of insulin delivery!

4. You might suggest an updated prescription for intranasal glucagon (Baqsimi), instead of her current intramuscular glucagon, as a less invasive and easier-to-use treatment option in case of severe hypoglycemia.

The patient and her family members are very impressed with your knowledge on T1D and are excited to incorporate some of these updates into her management plan. Way to go!

Conclusion:

To wrap up this podcast, let's do a brief review of the material that we have covered. Here are 3 key points to remember:

1. The traditional diagnosis of T1D occurred at the time of clinical symptom onset, but we now know that it can be diagnosed even earlier using pancreatic autoantibody markers!
2. Advancements in insulin therapy and blood glucose monitoring technologies allow more fine-tuned control of blood glucose levels.
3. Acute complications including DKA and hypoglycemia are now managed with updated protocols based on our improved understanding of these presentations.

This concludes our podcast on Type 1 Diabetes. Thank you for listening!

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