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# T1D Pathophysiology and Disease Management: What We Currently Know

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**Dr. Rickels:**
Hello. I'm Mike Rickels from the University of Pennsylvania, and we're going to discuss Type 1 Diabetes Pathophysiology and Disease Management: What We Currently Know. Type 1 diabetes is caused by the autoimmune destruction of the insulin-producing islet beta-cells. Currently, approximately 1.6 million individuals are affected in the United States, and there is an increasing incidence of type 1 diabetes, with 5 million individuals anticipated to be affected by the year 2050. Presently, multi-dose injection or continuous subcutaneous insulin infusion, or pump therapy, is required for survival. Also currently, only approximately one in five adult patients receiving specialized diabetes care in the United States are achieving the American Diabetes Association recommended glycemic control target of a hemoglobin A1C less than 7% or 53 mmol per mol. In addition, more than 7% of adult patients report having experienced a severe hypoglycemic episode resulting in seizure or loss of consciousness in the last three months.

Beta-cells can also be replaced by transplantation of allogeneic islets isolated from deceased donor pancreas. Islet transplantation has completed phase 3 investigation in the United States for patients with impaired awareness of hypoglycemia experiencing severe hypoglycemic events. Multi-dose injection or pump delivery of insulin is shown here with the top left demonstrating the pharmacokinetics of insulin of appearance in the circulation with use of varying insulin analogs that have altered absorption kinetics to provide either basal insulin activity to suppress hepatic glucose production or more rapid-acting insulin to promote glucose disposal at the time of meal ingestion.

These insulins can be given by a syringe and vial or, as shown in the bottom left, by a pen injection, and an alternative is to provide a rapid-acting analog of insulin continuously via an insulin pump, shown in the top right, where the basal insulin is provided by a continuous insulin infusion, and bolus insulin of rapid-acting analog is delivered prior to meal ingestion or at the time a elevated glucose requires correction. Currently, insulin pumps can be informed by continuous glucose monitor, shown the right side of the abdomen of the individual in the photo. The bottom right shows the continuous glucose monitoring tracing that informs automated insulin delivery from the insulin pump, where the pink shows automated increases or suspensions of basal insulin delivery, and the purple ovals show the bolus insulin delivery dictated by user and/or carbohydrate contents at the time of ingestion of meal or snacks.

This automated increase or suspension of insulin delivery serves to help prevent both hyper and hypoglycemia from developing throughout the course of the day. However, our current data from the United States show that as many as 7% of individuals will still experience a severe episode of hypoglycemia resulting in seizure or loss of consciousness in the past three months, and it's important to note that this occurs regardless of hemoglobin A1C levels. So the idea that raising a hemoglobin A1C level will allow for avoidance of severe hypoglycemia is no longer applicable in the present use of modern insulin analogs and delivery systems.

To understand this risk for severe hypoglycemia, it's important to understand the evolution of islet defects in type 1 diabetes, and so,

currently, type 1 diabetes has been staged by the start occurring with an inciting event triggering autoimmunity when glucose homeostasis remains normal. Stage 2 is now defined by the first occurrence of impaired glucose tolerance in an individual with established autoimmunity against insulin producing beta-cells, while the traditional onset of diabetes is considered stage 3 type one diabetes, where symptomatic hyperglycemia ensues, and individuals require the initiation of insulin therapy.

After a variable period of time, continuing loss of islet beta-cell mass occurs such that individuals with established type 1 diabetes for many years can develop a form of brittle diabetes where significant glucose variability and hypoglycemia become problematic. While there are some beta-cells remaining at the onset of stage three diabetes, already, at that stage of disease, the glucagon response that normally defends against development of hypoglycemia is lost. These data show glucagon response during hypoglycemic clamp as being markedly impaired in individuals at diagnosis of type 1 diabetes and a year later, following the achievement of glycemic control.

Importantly, epinephrine response to hypoglycemia is intact at diagnosis, and this serves to be a key counterregulatory defense against individual with type 1 diabetes developing more severe hypoglycemia. However, throughout the course of many years living with type one diabetes, it's well-established that the occurrence of even mild hypoglycemia blunts the sympathoadrenal response to increase epinephrine and generate symptoms during a subsequent exposure to hypoglycemia, and this has been demonstrated in both non-diabetic humans, shown on the left, and in individuals with type 1 diabetes, shown on the right.

So while normally, in response to a decline in plasma glucose, our primary defense, our islet cell response is to decrease insulin secretion, which provides a paracrine signal within the islet to activate the alpha-cell to increase glucagon secretion that normally is sufficient to increase endogenous glucose production from the liver and prevent further decline in plasma glucose concentration. However, with the development of near total loss of insulin-producing beta-cells in type 1 diabetes, these primary islet cell defenses, both the ability to remove insulin from the circulation that's been dependent on subcutaneously-administered therapy, as well as the inability to increase glucagon, leaves individuals dependent on their secondary sympathoadrenal responses.

But it's just shown exposure to even mild hypoglycemia leads to the development of hypoglycemia-associated autonomic failure, where the increase in epinephrine and generation of autonomic symptoms become impaired. This importantly precludes the individual from physiologically increasing glucose production from the liver to defend against development of low glucose. To summarize, the achievement of target glycemic control and avoidance of severe hypoglycemia remain major challenges for most patients living with type 1 diabetes. Absent islet cell responses predispose a cycle of hypoglycemia begets hypoglycemia, resulting in impaired glucose counter regulation and the syndrome of hypoglycemia-associated autonomic failure. Thank you so much for your participation.

**Announcer:**
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