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What is the Importance of Hypoglycemia Awareness in T1D Patients?

Announcer:
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Dr. Rickels:
Hello, I'm Mike Rickels from the University of Pennsylvania, and we're going to discuss the topic What is the Importance of Hypoglycemia Awareness in type 1 diabetes patients? Impaired awareness of hypoglycemia represents one of the most significant risk factors for experiencing a severe hypoglycemic episode in individuals with type 1 diabetes. This can be defined by a questionnaire, survey, or Clarke score of 4 or more. Other surveys such as a Gold score can also be utilized. Impaired awareness of hypoglycemia has been associated with a sixfold increase in the risk of experiencing future severe hypoglycemia. For individuals that have complete unawareness of hypoglycemia, this risk is increased twenty fold. The development of impaired awareness of hypoglycemia is tightly linked to exposure to hypoglycemia that serves to decrease the ability to recognize autonomic symptoms generated during hypoglycemia by the induction of hypoglycemia-associated autonomic failure. Exposure to hypoglycemia is also related to glucose variability, with excessive glucose variability increasing risk of hypoglycemia exposure, and of course, individuals that have experienced severe hypoglycemia remain at risk for future events.

Other factors are not modifiable such as disease duration, the presence of autonomic neuropathy, requirement for beta-adrenergic blockade, and the development of absent endogenous insulin secretion in established disease. This is a case of an individual with hypoglycemia unawareness where continuous glucose
monitoring is shown here with a different color representing individual day. What can be appreciated is that this individual spends very little time in the normal glucose range of 70 to 180 or 3.9 to 10 millimoles, and really only passes through this range as they're moving from hyper to hypoglycemia, and back again. So, this
is indicative of marked glucose variability, and also highlights marked exposure to hypoglycemia. In particular, prolonged exposure during the nocturnal period poses extremely high risk for severe hypoglycemic events. It's been documented that the dead-in-bed syndrome of type 1 diabetes occurs when severe hypoglycemia occurs in the overnight period and with failed arousal, as well as failure of glucose counterregulatory mechanisms to restore glucose concentration to normal, individuals may expire and contribute to the increased mortality of type 1 diabetes.

This risk for hypoglycemia and failure to counterregulate is in part driven through adaptation to the experience of hypoglycemia by the brain, which includes working to utilize alternate fuels such as lactate, and increasing brain glucose availability through transport mechanisms. These serve to increase GABA in the ventromedial hypothalamus, which reduces autonomic output that normally would be increased in response to the sensing of hypoglycemia by the brain. This decreased autonomic output limits the increase of epinephrine secretion and the generation of autonomic symptoms that normally serve to exert glucose counterregulatory defenses and symptom awareness that would normally alert an individual to ingest food. The impairment of epinephrine secretion and autonomic symptom generation contribute to the syndrome of hypoglycemia associated autonomic failure, and there's further impairment of

epinephrine secretion by increases of epinephrine itself, such that the secretory capacity of the adrenal chromaffin cells declines with further exposure to hypoglycemia.

These mechanisms of impaired counterregulatory defenses start prior to individuals developing impaired awareness of hypoglycemia. In this study, individuals with hypoglycemia unawareness, shown in purple, who spent more than 10% of time in the hypoglycemic range on continuous glucose monitoring compared to a group of type 1 diabetes individuals with intact awareness of hypoglycemia who meet the current recommended target of not more than 4% time spent with hypoglycemia. When we look at the epinephrine response to hypoglycemic clamp, and for reference, levels during a euglycemic control experiment are shown in the gray shaded region, and you can see that there's marked impairment of the epinephrine response to hypoglycemia in those in two cohorts of those with impaired awareness of hypoglycemia, and that while epinephrine secretion is greater in individuals with intact awareness of hypoglycemia, these individuals with type 1 diabetes still have markedly reduced epinephrine secretion when compared to non-diabetic controls.

Is epinephrine important for generating endogenous glucose production from the liver? We see here that relative to the euglycemic control data, individuals with hypoglycemia unawareness generate no increase in endogenous glucose production during hypoglycemia. While there is more endogenous glucose production produced during hypoglycemia in those with intact awareness, it remains impaired relative to
individuals without diabetes. Importantly though, this group with intact awareness does demonstrate normal autonomic symptom generation during the hypoglycemic clamp, such that this remains the last defense against developing severe hypoglycemia. Strategies to alert individuals through the use of continuous glucose
monitoring have helped significantly in reducing clinically important and severe hypoglycemic episodes, but do not entirely eliminate exposure to hypoglycemia, as shown in this example tracing of individual with hypoglycemia unawareness, who is receiving appropriate alerts and alarms to predicted and actualized hypoglycemic exposure. This has been shown in the study reference here, as well as in larger randomized clinical trials to reduce hypoglycemic exposure by about 40%.

However, in individuals with hypoglycemic unawareness, that reduction of hypoglycemic exposure fails to improve the epinephrine response to hypoglycemia after six, or even 18 months of intervention, while there has been demonstrated modest increase in hepatic glucose production after 18 months of intervention with
continuous glucose monitoring. The autonomic symptom response also modestly improved, but remains impaired even after 18 months of intervention with continuous glucose monitoring. The only interventions to date to restore normal autonomic symptom responses to hypoglycemia in individuals with hypoglycemic
unawareness has been pancreas or islet transplantation, and that can be appreciated by this example of our initial case who underwent islet transplantation resulting in the achievement of complete normal glycemia as can be appreciated, no time spent in the hypoglycemic range, and also normalization of glucose
variability.

So to summarize, hypoglycemia exposure and related glucose variability mediate increased risk for severe hypoglycemia through compromising physiologic glucose counterregulation and hypoglycemia symptom recognition to defend against low blood glucose. Impaired adrenomedullary epinephrine and endogenous glucose production responses exist in longstanding type 1 diabetes, even when symptom awareness of hypoglycemia remains intact. Hypoglycemia exposure may require targeting less than 2% time below range in order to preserve or restore physiologic counterregulatory defenses against hypoglycemia and symptom awareness, as demonstrated by islet transplantation. Thank you very much for your attention.

Announcer:
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