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Recognizing the Pervasiveness of Hypoglycemia in Adults with T2D

Announcer:
You're listening to ReachMD, and this episode of *Diabetes Discourse* is sponsored by Lilly.
Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. Charles Turck and joining me to discuss the pervasiveness of hypoglycemia in adults with type 2 diabetes is Dr. Brian Frier. Dr. Frier was a physician and diabetologist in the Royal Infirmary of Edinburgh in Scotland and is currently an Honorary Professor of Diabetes at the University of Edinburgh, where he is affiliated with the Queen's Medical Research Institute. Professor Frier, welcome to the program.

Dr. Frier:
Well, thank you for inviting me. It's good to be here.

Dr. Turck:
To start us off, Dr. Frier, what could you tell us about the incidence of hypoglycemia? How often does it occur in people with type 2 diabetes?

Dr. Frier:
It's been thought for many years that hypoglycemia is a major problem in type 1 diabetes and that it isn't an issue in people with type 2 diabetes. And that's probably partly because a lot of people with type 2 diabetes are either treated with diet alone, or they're on oral medications which don't cause hypoglycemia, the exception being the sulfanurias. But it's now readily apparent that people on type 2 diabetes, once they're on insulin, they're exposed to frequent hypoglycemia. And defining hypoglycemia as non-severe and severe. Non-severe is any episode that you can treat yourself, the patient itself is treating. Severe episode is one where necessitates recovery, help from somebody else. It doesn't mean coma, but it means that they have cognitive impairment and can't take the necessary action to treat themselves.

So, to give an idea of the approximate number, the person with type 1 diabetes will have approximately two non-severe episodes in a week. Starting with type 2 diabetes on insulin, less than one. So, it's less frequent. And overall, with several studies, it's shown that hypoglycemia, whether non-severe or severe, is about three times higher in people with type 1 diabetes than type 2 diabetes. Now, that's not to diminish the problem in type 2 diabetes, there's still a lot of both severe and non-severe episodes occurring.

It partly depends on how it's measured. If you ask people retrospectively then they forget the number of episodes, so you get a much lower number than if you do it as prospective measurement, as should be done in clinical trials. Now, this was very clearly shown in the very large, international, global study called the HAT study where they compared retrospective with prospective measurement. It was very, very much higher when done prospectively. And in fact, some of the rates were incredibly high, much higher than had been anticipated from studies in North America and in Northern Europe.

So prevalence, overall, looking at large number studies together, type 2 diabetes is about 20 percent in the year, annual prevalence, and the incidence about one episode per patient, per year. So, that gives you a sort of approximate measure of the frequency.

Dr. Turck:
So, you'd mentioned differences in prevalence and incidence, are there any other reasons that hypoglycemia might be overlooked in patients with type 2 diabetes?

Dr. Frier:
Yes. One of the major problems in type 2 diabetes, this is both the fault of the medical providers, as well as the patients themselves, is it's not discussed. No inquiry is made at routine review consultation about the problem of hypoglycemia. And curiously, many patients don't mention it. We've done some work on this, be surprised about how few people mention severe, even severe events. So, this is, in itself, a communication problem.

And then, recall can be poor. People sometimes have amnesia after a severe event of hypoglycemia. And the other major issue is that symptoms are age-specific. Now, everybody is familiar with the typical symptoms, the autonomic symptoms, the shaking, the sweating, the hunger that you get during hypoglycemia, and also the effects on the brain, the neuroglycopenic symptoms difficulty concentrating, and drowsiness, and so on. These are all very typical symptoms in the younger population. But if you look at an older population, now the symptoms change or there is a new group of symptoms emerges, both being described as neurological symptoms, effects on their vision, effects on balance the, sort of, thing which, if presented to a clinician, they will immediately start thinking about trans ischemic attacks or cerebral vascular disease. So, the diagnosis of hypoglycemia is missed or is attributed to some other condition. And this is a problem as many people with type 2 diabetes are coming into the older age group and their symptoms are different from the classical, typical ones, which everybody's familiar with.

So, we've got problems with communication, problems with identification during medical consultations and there's also a big problem with limited knowledge, both amongst patients and their relatives. They don't know a great deal about hypoglycemia and may not realize what's going on.

Dr. Turck:
So, let's talk about the clinical impact of hypoglycemia. How does it affect glycemic control?

Dr. Frier:
Well, the major problem, if people have hypoglycemia, it engenders anxiety and increasing fear of hypoglycemia. This is a well-recognized problem. And that itself affects behavior. The tendency then is to actually reduce the insulin dose or allow higher glucose, prevailing glucose level, so to avoid the risk of hypoglycemia. Now that's not good, of course, because it leads in the long-term to increased risk of complications. But is also an issue with chronic hyperglycemia, that in itself can have symptoms. There's an element of psychological morbidity attached to this. It reduces the quality of life, it reduces treatment satisfaction, and it, therefore, has an effect overall on glycemic control. And again, we mustn't blame patients for this because clinicians are often responsible for not putting people onto insulin early enough when they need it. There's a delay in conversion to insulin therapy and the deliberate avoidance of investigational therapy and that itself promotes poorer glycemic control, in an effort to avoid hypoglycemia.

Dr. Turck:
As we know, patients with type 2 diabetes already have an increased risk of experience in cardiovascular events, does hypoglycemia play any role in cardiovascular morbidity?

Dr. Frier:
Well, this is a major area of interest at present. Several large trials have shown that there's an association between severe hypoglycemia and both cardiovascular events and mortality. Now, that in itself doesn't prove causality, it just shows an association. And it may be that the people who are having recurrent hypoglycemia are those who have general ill-health. They're sicker patients who have this problem. But nonetheless, there's a definite interest in the risks of hypoglycemia causing cardiovascular events. And certainly, survival is reduced after severe hypoglycemia in people with type 2 diabetes. There's one study which followed people for five years after a severe event, the mortality compared to a matched control group who did had no hypoglycemia was three times higher. And survival after hospitalization for severe hypoglycemia is much less. So, there is clearly an association going on, here.

Well, the question then is, how would hypoglycemia affect the heart? Well, it's a major stress on the heart. There's a big autonomic response to hypoglycemia, you get a lot of catecholamines released, adrenaline, epinephrine, there's a big increase in the workload of the heart, cardiac output is increased. Now, if you've got a young, healthy heart, normal coronary arteries, that's no problem. But of course, many people with type 2 diabetes and who are in the older age group already have cardiac disease. They have coronary heart disease, they may have a heart the heart muscle disease you get with diabetes, they may get autonomic abnormalities of the heart. So, they're a risk then of an effect on causing ischemia marked ischemia, even infarction, and there's plenty anecdotal evidence for this, or changes in electrophysiology of the heart. So, you get cardiac arrhythmias developing.

A lot of interesting work on this done in recent years a group in Sheffield in the UK have shown that the arrhythmias are worse at night, during sleep. So, if somebody has a hypoglycemia episode during sleep, they're much more at risk of having a bradycardia or atrial ventricular ectopics and these can go on to life-threatening arrhythmias. This has been looked at in some detail now in type 1 diabetes

and you probably heard of the Dead in Bed Syndrome, which is thought to be sudden death during hypoglycemia in young people with type 1 diabetes. Fortunately, rare, but I am quite convinced that this also happens in type 2 diabetes.

So, there are plenty of good pathophysiological mechanisms which could underly heart disease and hypoglycemia being a major problem.

One other, just briefly, wasn't just think only of heart problems because there's considerable morbidity attached to hypoglycemia itself the effect on the brain, obviously, there's a lot of interest in whether it causes cognitive decline. There's a paper just published online from the follow-up with DCCT/EDIC study in type 1 diabetes showing that after thirty years, recurrent hypoglycemia causes a decline in cognitive function. Several studies now in type 2 diabetes showing similar problems and possibly precipitating dementia. So, there's a lot of problems with morbidity of hypoglycemia, other than the heart.

Dr. Turck:
For those just tuning, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. Charles Turck and today I'm speaking with Dr. Brian Frier about the pervasiveness and effect of hypoglycemia in adults with type 2 diabetes.

Dr. Frier, are there strategies that you would recommend to mitigate the impact of hypoglycemia on people with type 2 diabetes?

Dr. Frier:
Yes. We're trying to both reduce the frequency and also severity of hypoglycemia. I think to try and irradicate it completely is a major ask. But we certainly should be able to try and reduce the exposure to this problem and its potential morbidity.

I think one of the things, most important things is to choose appropriate glycemic targets for the individual patient. That means that in frail, elderly patients, who, particularly people who have got perhaps limited life expectancy, going for intensive therapy and trying to lower the hemoglobin A1C down to near non-diabetic levels is really not wise.

So, I think appropriate glycemic targets are essential. And one of the major things for both patients and relatives is education. We need to tell people about hypoglycemia. We need to know that they can identify the symptoms or the signs of this and know how to treat it. And then there are particular conditions like exercise where hypoglycemia may be a risk. Knowing how to avoid that is also very important. From the clinician's point of view, obviously, we want to use medications or injectables in people with type 2 diabetes that don't need insulin, which have a lower risk of hypoglycemia. When they do need insulin, then there are various insulin regimens that can be used which are less likely to cause hypoglycemia and particularly the use of the insulin analogs; these have less risk of glucose variability and they prevent a lot of nocturnal events, the hypoglycemia during sleep.

So, there are various ways that medications or changes in therapy can be used to avoid hypoglycemia. That's another reason why we should be reviewing medications regularly. I think crucial thing is to discuss the hypoglycemia regularly at reviews and then take action if there's clearly a problem.

Dr. Turck:
And finally, do you have any other recommendations you could share with our audience to help manage hypoglycemia in patients with type 2 diabetes?

Dr. Frier:
Well, think the new technologies which are now becoming much more widespread in their usage could be very useful here. I'm thinking of flash glucose monitoring and continuous glucose monitoring, which are a way of identifying hypoglycemia, particularly at times say at, during the night, during sleep, because the newer forms of these devices have alarms systems. The tendency has been to use these only in people with type 1 diabetes, but I think there is a very strong case for using these newer forms of technology to identify hypoglycemia in people who are on any form of insulin.

I think screening patients is important for their risk factors, with severe hypoglycemia. There's an established list such as having a previous history of hypoglycemia, that should be a red flag at an MD taking the consultation. Things like renal impairment. Impaired awareness of hypoglycemia, big problem in type 1 diabetes, much less, though in type 2, but it still occurs, about one in then people on insulin will develop that syndrome. And again, reviewing medications at regular intervals.

Finally, I would say, there's a need to have access to glucagon. Glucagon is not for the patient to use, it's for their relatives or carers and to treat a severe event. But it's really very underused. I think one of the big problems was that it had to be reconstituted, there was a powder, you had to a dilutant very tricky method of administration, several steps involved. Now, that should no longer be an issue because there have been new forms of glucagon produced recently. There's nasal glucagon, just squirt it into the nostril. Or there's also aqueous forms and coming in also injectors, which make the administration of glucagon very much easier. So, these are the things which I would recommend that clinicians keep in mind when treating people with type 2 diabetes on insulin.

Dr. Turck:
Well, with those helpful strategies and recommendations in mind, I want to thank you, Dr. Brian Frier for coming on to discuss hypoglycemia in adult patients with type 2 diabetes. It was great having you on the program.

Dr. Frier:
Thank you. It was my pleasure to be with you.

Announcer:
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