AHEAD Podcast 2 – Updates in Diabetes Pharmacotherapy

Transcript

[Jazzy instrumental intro music]

[Voiceover] Michael Konstan: Welcome to the AHEAD Initiative podcast series focused on sharing evidence-based practical strategies to improve diabetes outcomes and advance diabetes health equity. I'm Dr. Michael Konstan from Case Western Reserve University School of Medicine, and I serve as a principal investigator for the Northeast Ohio Quality Improvement Hub, a collaboration of Case Western Reserve University with Northeast Ohio Medical University. The Northeast Ohio QI Hub is funded by the Ohio Department of Medicaid and provides quality improvement infrastructure for primary care clinics in our region. We hope you enjoy today's ahead initiative podcast.

Shari Bolen: Welcome to our AHEAD podcast series for the Northeast Ohio Quality Improvement Hub. My name is Dr. Shari Bolen, and I am the co-PI of the NEO QI Hub and AHEAD initiative, a professor of medicine at Case Western Reserve University School of Medicine and the Metro Health System. I am delighted to talk with Dr. Dr. Betul Hatipoglu today about some of the newer diabetes medication options. Dr. Hatipoglu is the center director for diabetes and metabolic care at University Hospitals and professor of medicine at Case Western Reserve University as well as the endocrinology lead for the AHEAD initiative. Thanks so much for joining with us for this discussion.

Betul Hatipoglu: Oh, it's my pleasure. I'm really excited to talk with you today.

Shari: I thought I would get us started really on discussing a little a little bit about the newer diabetes medications that are currently used in care. So, could you share a little bit about what those classes are?

Betul: Yeah, of course. You know, in the last 20 years, we have been so lucky and observing newer medications and tremendous improvements in technology for people with diabetes. However, at the same time, we are also observing this rising hemoglobin A1C in this group instead of better control. You and we all know that decreasing A1C dramatically changes microvascular complication as well as reduces death from all cause for diabetes. So, the three new groups of diabetes medications have changed transformed how we treat diabetes because it's not just focusing on the glucose lowering effect but their impact on overall cardiovascular health, for example, which started around 2008 when the FDA required diabetes medications to also be tested for cardiovascular safety. The first group is the glucagon like peptide one, the GLP-1 receptor agonist, which we have been using since around 2005. Nothing necessarily new

about them, but the second group that was recently approved is an extension of GLP-1 receptor agonist with a touch of glucose dependent insulin tropic polypeptide—even difficult for me to say it—which is GIP. So, it has a dual action. And the last group is the sodium glucose cotransporter 2 which we know as SGLT2 inhibitors that we have been using since 2014.

Shari: So given these three newer classes of diabetes medications, even though some may have been not super new, they're still relatively newer in use. When might you choose one option of these medication classes over another? And what are some of the critical factors that help affect your choice?

Betul: You know, this is an excellent question. I think the recent recommendations from different professional associations such as the American Diabetes Association or the American Association of Clinical Endocrinology show that choosing a medication is very much about personalization of the treatment. It is critical. We are observing more and more emphasis on the personalization of medication choice. This applies to our own QI Hub recommendation as well. What this means is that we look at the comorbidities, other factors that might affect our choice such as heart failure, kidney disease or other cardiovascular events. For example, we know today that we need to start with SGLT2 inhibitors in a patient with diagnosis of heart failure. This is very important. These drugs have been approved by the FDA in heart failure patients with or without diabetes. They have tremendous benefit by lowering cardiovascular death and events even up to 40% in studies in patients with diabetes and rehospitalization rates in heart failure patients. However, if an individuals with type two diabetes comes to me, comes to us with coronary artery disease already established but they want to lose weight, they need to lose weight, these individuals can be started on a GLP1 receptor agonist instead which we know also decreases mortality as well as has weight loss benefit. I mean what can you ask for more, right? A couple months after we started GLP1 receptor agonist it might be then reasonable to add an SGLT2 inhibitor for example. So, it's not really necessarily that we choose one medication over another. Sometimes we have to just prioritize initial medication based on what we want to target in comorbidities and what is the patient preference and then add the next or the other medication later.

Shari: Yeah, that's a great point and has been a big switch in recent years in terms of diabetes treatment where we used to start with metformin for everyone and now really looking at prioritization related to comorbidities and preferences. So important. So how do you approach starting diabetes medications in adults with diabetes who also have kidney disease?

Betul: And this is very important as well. I want to just remind our audience though that ACE and ARBs and, you know, statins and we are not talking about those. We're just focusing on diabetes medications in this cases because they still remain the important piece of targeting kidney disease in people with diabetes. So, an individuals in type 2 diabetes with type two and with kidney disease for example will definitely benefit from taking an SGLT2 inhibitor to reduce kidney complications. Reviewing details of these studies can be another podcast and I'll be happy to come back as the studies are diverse, but the results are very consistent. So also, we can add a GLP-1 receptor agonist such as semaglutide for instance after few months of SGLT2 that also have some benefits for the kidneys; the GLP1 group is not as strongly established in

this area as the SGLT2s are. Therefore, when you are starting a medication, a patient choice, the effect of the medication on comorbidity really becomes very important which as you said is really a change from the past where we were encouraged to use metformin as a first choice and then other diabetes medications. We're really looking into what conditions the patients has and what diabetes medication to recommend that will benefit them the most.

Shari: Well, thank you so much for sharing about kidney disease because it is so prevalent in people with diabetes. So, another area that we get a lot of questions about is weight. So, a lot of people with diabetes are trying to lose weight—especially type 2 diabetes. How might you approach starting a diabetes medication if the patient is really interested in being on a medication that can have effects on weight loss?

Betul: And it's very important and very popular subject in the media and in our clinics. If you're looking into the weight loss effect of the medication while also helping with diabetes, the first two choices are going to be a GLP1 receptor agonist that has both cardiovascular and kidney benefits as well. However, if the patient cannot tolerate this medication or we start and we don't see much benefit, which sometimes we can see, then it is reasonable to choose the second choice which is the GLP1 and GIP agonist, the tirzepatide. It is a possibility, and I have seen that in some patients who might not respond to GLP-1 receptor agonist, or they plateau or they have very strong side effects like nausea and vomiting. They can be switched to this new group. However, it is important for our audience to note that we do not have any studies showing cardiovascular or kidney benefits of this medication yet. We will see what the results of the ongoing studies for this medication class will show in the next year or two.

Shari: Great. Can I ask you a question with the GLP1 GIP agonists? Are is it just one medication, tirzepatide, in that class right now that's FDA approved?

Betul: Yes, correct. We do have some in the pipeline, but currently the only one we have available to be able to write to our patients is the tirzepatide, or the other brand name is Mounjaro, for diabetes treatment.

Shari: Thanks for clarifying that because I know that is relatively new. So since we get a lot of patients with diabetes who do want to lose weight and following up on that question that I just asked, can you tell us a bit more about the average weight loss that is seen in the GLP-1 receptor agonist and the SGLT2 medications as a class and any differences between drugs that might be important for us to know?

Betul: Yeah, this is a very good question and honestly when if the audience wants to know more there is this great 2023 network meta-analysis that is published in British medical journal by She and colleagues. They synthesized data from 800 plus trials with over 400,000 people on diabetes medications for an average of six months follow-up and they found that SGLT2 inhibitors—which I don't personally see them as a weight loss drugs in my practice in any ways—but they are still effective in reducing the weight around 4 to 5 pound on average. The GLP-1 receptor agonist, they separated them since the effect on weight is not necessarily similar in all of them; it varies by drug type. And I think it's important to note that semaglutide for

example on average can cause 10 to 14 pounds weight loss at the amount that we use for diabetes management and dulaglutide is around 3 to 6 pounds—is a little bit less nevertheless significant. The latest group that we just discussed, the dual agonist the GLP1 and GIP agonist, the tirzepatide, it causes average around 15-to-20-pound weight loss which looks like the most probably the effective one for the weight management piece.

Shari: I wanted to ask you a little bit about what choices we might want to use if we're trying to avoid hypoglycemia.

Betul: You know, this is such an excellent question, one that is really close to my heart because I have a strong desire to eliminate hypoglycemia in the lives of people living with diabetes. I believe it causes huge distress in their life and affect their loved one as well. So, we want to utilize diabetes medications that have low hypoglycemic risk in anyone at high risk for these events. I mean these are individuals who are stroke survivors or someone with impaired hypoglycemic awareness or someone who had a concerning or serious hypoglycemic event that required external help in the last year or two; someone that lives with a established coronary artery disease because you know that hypoglycemia in these individuals can trigger really unwanted undesirable side effects such as arrhythmias, seizures—I have seen coma, I have lost patients to hypoglycemia. So, the medication classes with low hypoglycemic risk like GLP-1 receptor agonist that we just talked about, SGLT2 inhibitors, DPP4 inhibitors in appropriate patients and the thiazolidinediones? (we have pioglitazone in the market) or the biguanide like metformin can be utilized.

Shari: Well, thank you so much for answering that important question. What are some of the common side effects seen with the new diabetes medications?

Betul: You sound like my patients. When I tell them all these good things, they are like, "Doc, well, this is too good to be true." And that is kind of true. They have some side effects even though they are excellent drugs. So, the GLP1 receptor agonist as well as the dual analog, they have very similar side effects. You know, they can cause nausea. Sometimes this can result into vomiting. You can see diarrhea or constipation. They are definitely contraindicated or I wouldn't use it—there is a warning about it in patients with pancreatitis, history of pancreatitis or recurrent pancreatitis. We need to keep in mind that patients with nausea and vomiting can get dehydrated and this can cause worsening of kidney function which has been reported. Semaglutide is in the GLP-1 receptor group in a study was also linked to a worsening of retinopathy in the first six months which we all believe was linked to the improvement of glucose control. But you know if you have a patient who has a retinopathy and you're starting this medication and they suddenly have some visual changes they need to see ophthalmology. It does stabilize and reverse itself, but it is important to be aware of this side effect as well. Abdominal pain has been also described in the literature as well as in clinical practice.

Shari: Yeah, it's something we often have to chat about with patients is the potential side effects and some of those issues that might arise if they take the medicines. One that comes up rarely but occasionally a patient will have read the warning on the drug insert which GLP1 receptor

agonist and ask about medullary thyroid cancer. Wanted to ask your opinion on what you say to patients related to this?

Betul: There is a increased risk in rats for medullary thyroid cancer when this was tested in multiple different doses in higher doses. I actually tell the patients that the rats who are not exposed to this drug are at risk to develop medullary thyroid cancer. So, it's not like humans; they have a tendency. So, when the ones that were exposed to higher levels of the drugs during the studies develop more of of this rare cancer type. So, there is no indication or recommendation to do serial ultrasounds or checking calcitonin in these patients. It is not contraindicated to be used in other thyroid cancer types like follicular thyroid cancer or the papillary thyroid cancer for example. You can use these drugs. However, if someone has themselves medullary thyroid cancer or history of multiple endocrine neoplasia type two or they have a family history of that, we should not use these drugs.

Shari: So really no data in humans showing this, but we want to be careful if they have that exact same history of a medullary thyroid cancer.

Betul: Absolutely.

Shari: So, I know we've talked about the GLP-1 receptor agonist side effects. Let's give equal time to the SGLT2 side effects. What about those?

Betul: Oh my goodness. Well, this is another group that we have to warn the patients about the side effects that is mainly linked to the glucosuric effect, right? The urination, increased amount of sugar in the urine, especially we see that when people have high A1C's to start with. So, I warn the patients about the increased risk of urinary tract infection and yeast infection and also, I tell them that they can get possibly dehydrated. This might cause their creatinine to go up. So, I usually check their creatinine in a month to make sure they are okay. If a patient is on other diuretics, the dose might need to be adjusted honestly within a week or two; might need to look at the blood pressure of the patient and see how they are doing just to make sure. Otherwise, you can cause dizziness, decrease blood pressure that can result into falls which is not safe for the patient. For my own practice and in general our groups, after two to three of the most urinary tract infection or yeast infection, I usually give these medications a break. In women in my clinical practice, they are more used to yeast infection concept and how to deal with it. It's a little bit less common in men and the teaching needs to be done for them. It has been also described in the literature, and I have seen one case of Fournier's gangrene. So, it's important to really talk to them about careful hygiene which needs to be a little bit maybe more than their usual hygiene when you are spilling so much more sugar. Some of my patient uses bidet to wash after urination to decrease the sugar from sticking to the external genitalia for example; they can use flushable wipes that are available in the market if they feel that they are getting or they are prone to get infections urinary or yeast infection. So, one other warning that I realize that not a lot of physicians or healthcare providers who use this group of medications are aware of is the risk of diabetic ketoacidosis with these drugs. We are talking about sometimes a euglycemic diabetic ketoacidosis in individuals who are type 2 diabetics who were started on SGLT2. This is not very well understood pathophysiologically yet. There are some theories behind it. However,

what I would say is I do not use it in type 1 diabetes. It's not approved for type 1 diabetes and in type two you might want to be just open-minded about this possibility in case you get a call about the patient not feeling well, suddenly feeling nauseous and things like that.

Shari: Yeah, that's a great point to mention, although rare with type two to just be cautious of. Is there a way to prevent dehydration with this medication sort of in advance? What you might say to someone?

Betul: Yeah, I actually tell them, "Listen, this is going to make you urinate a lot. So, make sure you drink enough fluids including water." It is very important to give heads up to the patients that they will need to really replenish what they are losing. Keeping in mind as healthcare providers to adjust the diuretics that you are giving the patients—furosemide, hydrochlorothiazide—they might need to be really cut down in amount at the beginning at least until you know how they are going to respond to the medication.

Shari: I think that's really important because we do see so many adults in primary care with diabetes who are very tenuous and we want to make sure that they don't have that problem, and I feel like it comes up more frequently than I might have guessed. So, I think it's an important thing to think about. I had heard that it might benefit to get an A1C a little bit lower and then start the SGLT2, that it might reduce excessive urination that you see once the sugar's a little bit lower. And I don't know if that's just a myth that's out there—and no real data on that—but I know that I had heard that and had been doing that for a while where I'd start, you know, a GLP-1 and then I'd add the SGLT2 and the A1C got a little bit lower. So, I didn't know if you had thoughts about that when the A1C is very high and starting an SGLT2?

Betul: I don't have necessarily a cutoff that I use myself. However, I think it's reasonable to understand that if someone has enough high A1C that you believe the sugars are so high that they might even need insulin to bring it down, I would take care of that first before I give them an SGLT2 that further increases glucosuria. The other part that I was not thinking before is, as you were asking me the question, it came to my mind that if someone has such a high A1C, they might be relatively insulin deficient at that time and they might recover from that relative insulin deficiency in the coming months. But what I mean is that that can cause a higher predisposition to develop even diabetic ketoacidosis because they have that relative insulin deficiency. So, I think it is wise to put all these together—risk of more dehydration, need for insulin, recovery of insulin production internally—and then wait a couple months and then introduce the medication.

Shari: So now that we've talked a little bit about the side effects, how do you discuss starting an injectable like GLP-1 medications compared to sort of starting an oral medication?

Betul: Yeah, you know, many years ago when I was trying to really start writing these drugs, I thought I will have a lot of resistance and to my biggest surprise, I did not. So, it has not been very challenging. Honestly, it depends on how you maybe present it to the patient because there's a lot of misconception in our patients that they think any injection is insulin. You have to make sure they know this is not insulin. When I mention that it might help the heart, the kidney, and they might lose weight, they just go for it. And then the idea that it might even put the

diabetes into remission is very attractive to the patient. And I will just define remission for our audience. It is defined as an A1C less than 6.5 that occurs either spontaneously or following an intervention. It can be a drug intervention, but it has to be there for three months without any glucose lowering pharmacotherapy. Even though the intervention was a pharmacotherapy, the remission description is without pharmacotherapy. So usually, my experience that patients are very open to starting GLP-1 medications even the injectable forms. Sometimes I do have them do the first injection if they are hesitant about injection, it helps so much in front of me; I'm watching them do it, that really removes the fear of needle. They are so surprised how easy it is when they do it and they feel comfortable when they leave my office and they go home. Rarely though, I would admit some patients would be very against injectables, and we do have an oral as we discussed GLP1 semaglutide which has many of the benefits of the injections and one could try if really you cannot go for injectable form for patients with severe needle phobia. It can be challenging of course to get this medication. And if you realize the patient has a neophobia, I have used this opportunity to try to get them into psychological help as well because that might in the future affect their care further by not accepting insulin when they need insulin.

Shari: Yeah, that's a great point. There's sort of the fear of using needles that can be overcome and then there can be some very severe needle phobia that may even benefit from having psychotherapy. And I liked how you talked about the injections because I found the same thing that if I've had more resistance to insulin injections than to the GLP-1 injections, which is really speaks to the benefits of those medication classes and how people would like to use those. So, given these newer medicine classes and their benefits, what about medication coverage for these newer medicines?

Betul: Yeah, we are so actually lucky. Most insurers, including Ohio Medicaid, will cover one at least of the medications within each of these two newer diabetes medication classes, the SGLT2 inhibitors and GLP-1 receptor agonist. However, you know, coverage does differ by payer, can be confusing to the provider. So, we encourage people to use tools and apps to assess coverage prior to prescribing medications to patients. The Medicaid patients in the state of Ohio, there is a unified preferred drug list; they have actually great tables. I love the way their tables are made which can be accessed on the Ohio Department of Medicaid website and lists which medications are covered within these drugs.

Shari: Thanks so much. I know that'll help people start to look at that and think about that as they prescribe the medications. Are there protocols you follow for titration of medications to make it easier for yourself or others in your team?

Betul: Yeah, thank you. I think some of it of course comes from my 30 years of endocrinology experience for myself. But I do go back and follow the American Diabetes Association and American Association of Clinical Endocrinologist treatment algorithms. They are very helpful. They are very practical and FDA's approved those guidelines. Of course, we always look at them. We have, as you know, Sherry, we worked hard on that treatment protocol and additional resources for our audience around medication management, including initiation of insulin and how to address hypoglycemia within our diabetes quality improvement clinical toolkit on our

website. And I will just spell the website for our audience if they want to know. It is www.NEOQIHub.org.

Shari: Thank you. I think that those are great resources to have and look at in case people want to see those and use those as they're starting to use these medications more frequently. Well, given that we covered a lot of material today, what are some key points you would want our listeners to take away?

Betul: Yeah, I think remembering the newer medication that have strong impact in preventing diabetes complication, reducing mortality beyond just controlling blood sugar, that should be as strongly considered as both initial and add-on choices of treatment. We should really each patient deserves to be considered for this group if it's appropriate. They also have strong weight reduction which can benefit the patient even reverse their diabetes, put it into remission. Important to remember and the last but probably not the least is remembering that we take care of human beings. So shared decision making is critical in describing the benefits, potential harms of the patient and allowing empowering the patient in choosing which medication is right for them.

Shari: That's a wonderful and strong point to end with. I really want to thank you Dr. Hatipoglu for talking with me today about some of the approaches for incorporating some of the newer diabetes medications into a treatment regimen for adults with type 2 diabetes. So important.

Betul: Thank you very much for having me.

Shari: And thank you for listening to the AHEAD podcast. Subscribe on your favorite podcast platform so you never miss an episode.

[Voiceover] Konstan: This concludes today's AHEAD Initiative podcast. To learn more about the Northeast Ohio QI Hub, visit neoqihub.org. The Northeast Ohio QI Hub is part of the regional quality improvement hub project funded by the Ohio Department of Medicaid and administered by the Ohio Colleges of Medicine Government Resource Center. Views stated in this podcast are those of the presenters only and are not to be attributed to the Ohio Department of Medicaid or to the federal Medicaid program.

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