



eLITERATURE
REVIEW

eDiabetes Review
Podcast Issue

Jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing

Supported by educational grants from Eli Lilly and Company, Bristol-Myers Squibb, and Novo Nordisk, Inc.



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VOLUME 1 – ISSUE 2: TRANSCRIPT

Featured Cases: Intensifying Therapy for Glycemic Control

Our guest author is Nestoras Mathioudakis, MD, Assistant Professor of Medicine, Division of Endocrinology, Diabetes, & Metabolism and Associate Director, Inpatient Diabetes Management at the Johns Hopkins University School of Medicine in Baltimore, Maryland.

After participating in this activity, the participant will demonstrate the ability to:

- Describe the advantages and disadvantages of available glucose-lowering medications as add-on therapy to metformin.
- Evaluate treatment options in patients with the suboptimal glycemic control already on three glucose-lowering medications.
- Summarize the indications for insulin therapy and the principles involved in adjusting insulin dosing.

This discussion, offered as a downloadable audio file and companion transcript, covers the important topic of glycemic control and strategies to intensify therapy in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 1, Issue 1 *eDiabetes Review* newsletter—[Strategies for Intensifying Therapy for Glycemic Control](#).

MEET THE AUTHOR



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Dr. Mathioudakis has indicated that he does not have any relevant financial interests or relationships with any commercial entities.

Release Date
April 30, 2014

Expiration Date
April 29, 2016

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The target audience for this initiative includes: endocrinologists, primary care clinicians, nurse practitioners, physician assistants, Certified Diabetes Educators, and other health care practitioners whose work/practice includes treating patients with T2D.

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- Clinicians do not appropriately intensify therapy as necessary to maintain glycemic control.
- Conflicting data about the safety of incretin agents may unduly deprive patients of treatment benefits.
- Clinicians are not aware of and/or are not implementing strategies to maximize the value of SMBG readings to improve patient outcomes.
- Clinicians do not adequately understand or treat to control CVD risk factors in their patients with T2D.
- Clinicians do not have a sufficiently current knowledge base to effectively consult patients about potential T2D therapeutic advances.
- Clinicians do not adequately counsel and treat their overweight/obese patients with T2D.

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General Counsel, Johns Hopkins Medicine (4/1/03)
Updated 4/09

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MR. BOB BUSKER: Welcome to this *eDiabetes Review* Podcast.

Today's program is a follow-up to our newsletter on Strategies for Intensifying Therapy for Glycemic Control. With us today is that issue's author, Dr. Nestoras Mathioudakis, Assistant Professor of Medicine, Division of Endocrinology, Diabetes, & Metabolism, and Associate Director, Inpatient Diabetes Management at the Johns Hopkins University School of Medicine in Baltimore.

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Learning objectives for this audio program include:

- Describe the advantages and disadvantages of available glucose-lowering medications as add-on therapy to metformin.
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- Summarize the indications for insulin therapy and the principles involved in adjusting insulin dosing.

Dr. Mathioudakis has indicated that he has no financial interests or relationships with any commercial entity whose products or services are relevant to the content of his presentation, and that his discussion today will not reference the unlabeled or unapproved uses of any drugs or products.

I'm Bob Busker, managing editor of *eDiabetes Review*. Dr. Mathioudakis, thank you for joining us today.

DR. MATHIOUDAKIS: Thank you for having me.

MR. BUSKER: We want to talk about how to recognize when a patient's glycemic control isn't where it should be despite being treated, and some of the strategies to intensify therapy. You reviewed some of the most relevant literature in your newsletter issue — what I'd like to do today is have you translate that information into clinical practice. So if you would, please, doctor — start us out by describing a patient.

DR. MATHIOUDAKIS: This was a 40 year old gentleman I'd seen for initial consultation for diabetes management. He had struggled with obesity his entire life, he was obese he said since first grade, gained weight steadily throughout his adolescence and reached the peak weight of about 240 pounds in college. Around that time he was told that he had prediabetes, and then a few years later at the age of 33 he was officially given the diagnosis of type 2 diabetes.

He was started on metformin at a low dose of 500 mgmg daily and that had really been the only medication he's taken since he got his diagnosis. He had no diabetes-related complications, but he did have several cardiovascular disease risk factors, including obesity, he had a BMI of 40, and hyperlipidemia, and was being treated with a statin.

He had really tried to make some diet and lifestyle changes to control his diabetes, he was working out on a treadmill 20 to 30 minutes a day, was lifting weights about two to three times per week, avoided fast food, tried to limit his carbohydrate intake, and had seen a nutritionist who gave him a 2,000 calorie diet limit. In the past he had been able to lose a significant amount of weight on an Atkins-like diet.

When I first saw him, he brought in his glucometer and we downloaded his glucose readings. He had a mean glucose of 170, his prebreakfast glucose was 173 and postdinner was 130. A point of care A1c taken in the office that day was 6.7%. Three months earlier it had been 8.3%.

MR. BUSKER: Interesting numbers. What's your impression of this patient's glycemic control?

DR. MATHIOUDAKIS: One thing I noted about his glycemic control was that there was a disconnect between his A1c at that visit, which was 6.7%, and the average of his glucose readings off of his meter, which was 170. That average would predict an A1c of about 7.6%. It wasn't clear why that might be unless, of course, there are periods in the day when his glucose was lower and he wasn't checking, or there was some other reason for spurious A1c. Regardless, I think from his glucose meter it was clear that this patient had fasting hyperglycemia and that was his biggest problem, waking up with a glucose of 170, better glucose control during the day with postdinner readings around 130. I noted right away that he had

been on a very low dose of metformin, and his severe obesity was clearly his biggest risk factor for his long-term glycemic control.

MR. BUSKER: At this first visit to you, what did you change about his glucose-lowering regimen?

DR. MATHIOUDAKIS: The first thing I did was to maximize his metformin dose. As we discuss in this newsletter, in the article by Hirst, et al,¹ metformin has a maximal effect when it's increased to a dose above 1,500 mg a day, so this patient was on a clinically insignificant dose. The main problem that he had was fasting hyperglycemia, which as we know is a reflection of insulin resistance at the level of his liver. He had better glucose readings throughout the day, which was probably a reflection of the fact that his insulin sensitivity was improved with physical activity as he was up and about during the day. He should be on a maximum dose of an insulin-sensitizing agent like metformin to try to control his overnight hyperglycemia. And we know that high-dose metformin can make a difference.

Metformin is the only drug in diabetes management that has proven benefits with respect to cardiovascular disease outcomes. We know that other drugs have effects on cardiovascular risk factors but not on hard cardiovascular outcomes, per se. For my patients I continue metformin as long as possible unless there is some contraindication or they are not tolerating it. We learned that from the UKPDS trial. At that initial visit we did talk about possible second-line agents should things change.

MR. BUSKER: Share with us your thoughts there, if you would, please.

DR. MATHIOUDAKIS: Given the fact that he was morbidly obese, I thought a GLP-1 agonist would be a good option for him, but a GLP-1 agonist targets postprandial glucose values rather than fasting glucose values. So his issue being mainly a fasting problem, you know, that wasn't necessarily going to be addressing that problem. A DPP4 inhibitor is also a good option since he just had mild hyperglycemia, but by the same token as the GLP-1 agonist really is not going to have much of an impact on the fasting glucose.

What was clear to me at that visit is that I would avoid sulfonylurea in this man with a BMI of 40. You want to avoid agents that will promote further weight gain.

After talking to him about these options he wanted a trial, three more months of lifestyle and weight loss to see if he could bring down his fasting glucose with weight loss on his own. I should say that we did broach the subject of bariatric surgery with his BMI of 40, but the patient was not interested in doing that, and in the past he'd been able to lose a significant amount of weight on a low carb diet. I referred him to the weight management center and he pursued a low carb diet, which had worked for him in the past.

MR. BUSKER: Now his SMBG — his self monitored glucose number — in your opinion, what should that be?

DR. MATHIOUDAKIS: You know, that's actually not an easy question. There was a recent publication last month actually in *Diabetes Care*, this was in the February issue of *Diabetes Care*, Nancy Wei, et al, showed that the blood glucose targets that we'd been recommending for patients for many years are lower than required to achieve an A1c less than 7%.² I think this patient's A1c goal is less than 6.5%, he's relatively young, he has no diabetes related complications, in light of the new data by Wei et al, a fasting glucose between 110 mg/dL and 120 mg/dL and a postprandial glucose less than 150 mg/dL will probably achieve an A1c of less than 6.5%.

MR. BUSKER: I want to let our listeners know that a link to that paper by Wei et al can be found in the transcript version of this podcast.

So Doctor Mathioudakis, let me ask you: if this patient's A1c were to go above 7.0, you said you might decide to start a GLP-1 agonist — what practical considerations should clinicians and patients be aware of?

DR. MATHIOUDAKIS: I think one of the most important factors is cost. Some insurance companies will not cover newer agents like the GLP-1 agonists, and so if there is any financial barrier to using them, I'd consider another agent. Within the class of GLP-1 agonists, between liraglutide and exenatide, my preference is for liraglutide for several reasons.

First, it's a once-daily injection, so compared to twice-daily exenatide there is a convenience issue. But more important, as data from the DURATION-6 trial showed, and that's addressed in this newsletter, they're better outcomes, with respect to both glycemic lowering and weight loss with liraglutide compared to

exenatide with both the twice-daily exenatide and the once-weekly extended release of exenatide.³

I think extended release exenatide is a good option for patients who would benefit from that convenience if it would improve compliance. The DURATION-6 trial showed that it's nearly as effective as once-daily liraglutide, and in fact is associated with fewer gastrointestinal side effects, so that's one thing to consider. On the other hand, these injections require a lot of preparation on the part of the patient. They have to connect parts, mix the medication, and fill the syringe, which for some of my patients is a barrier to use; the pens would be a better option for them.

MR. BUSKER: I want to bring up the idea of clinical inertia. We know it's pretty common in patients with diabetes: they're not reaching their A1c targets, but their treatment is not being intensified. What can be done about it? In your practice, what do you do to avoid clinical inertia?

DR. MATHIOUDAKIS: Tough, tough problem, especially with diabetes being such a chronic disease. I think the most effective way to address this is to have a team-oriented approach, to have multiple clinicians and practitioners working closely with a patient. At our institution we have several diabetes nurse practitioners who work closely with our providers and we will have the patients alternate visits with them as frequently as needed until they're at target. However, I don't think this minimum of three month visits applies to all patients. If I have somebody struggling to get their A1c down or somebody I'm intensifying therapy for and there could be potential side effects, I'll have them back to see the nurse practitioner within two weeks to review glycemic control and to make some changes.

The key is that if the A1c is above target for your patient, some change is needed, whether that's titrating an existing medication, adding another medication, or emphasizing lifestyle modifications, because it will be impossible to attain good glycemic control for a patient who is adhering to a poor diet and is physically inactive. So we rely heavily on our diabetes educators and our registered dietitians.

Another important thing is to inform the patient about the natural history of type 2 diabetes at their initial diagnosis. Long before their insulin deficiency has developed, we encourage our patients to adopt a

lifestyle that will preserve their pancreatic function, but we let them know that over time there will be some decline in beta cell function and possibly progression to needing insulin, and if they need insulin therapy, that should not necessarily equate to failure on the patient's part. I tell them that early on so that there is no stigma with insulin therapy, if it's needed in the future.

In this newsletter we review a study by Khunti et al that showed there is an exceedingly long delay to starting insulin therapy in patients who are already on maximal doses of three agents, as long as six years.⁴ We know it's well established that timely treatment of diabetes has beneficial effects on both microvascular and macrovascular outcomes, and that effect can persist for a long time after so-called "metabolic memory." So avoiding clinical inertia is important.

MR. BUSKER: Thank you, Doctor. And we'll return with Dr. Nestoras Mathioudakis from the Johns Hopkins University School of Medicine in just a moment.

SUSAN PORTER: Hello. I'm Susan Porter, Clinical Nurse Practitioner and Certified Diabetes Educator at the Johns Hopkins University School of Medicine. I'm one of the program directors of *eDiabetes Review*.

If you found us on iTunes or on the web, please be sure to subscribe. This podcast is part of Johns Hopkins *eDiabetes Review*, a new educational program providing monthly activities certified for CME credit and nursing contact hours, with expert commentary and useful practice information for clinicians treating patients with type 2 diabetes.

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Thank you.

MR. BUSKER: Welcome back to this *eDiabetes Review* podcast. I'm Bob Busker, managing editor of the program. Our guest is Dr. Nestoras Mathioudakis, Assistant Professor of Medicine, Division of Endocrinology, Diabetes, & Metabolism, and Associate Director, Inpatient Diabetes Management, at the Johns Hopkins University School of Medicine. And our topic is Intensifying Therapy for Glycemic Control.

We've been discussing how some of the new information Dr. Mathioudakis reviewed in his newsletter issue can be applied in clinical practice. So if you would, Doctor, please describe another patient for us.

DR. MATHIOUDAKIS: This was a 64 year old woman whose type 2 diabetes was diagnosed about 10 years earlier when she was 54. She had controlled her diabetes with diet and exercise for about five years, and then metformin 500 mg daily was added, but she stopped the medication after taking it for just two days because of palpitations and diaphoresis. And at that point, because she was deemed to be intolerant to metformin, she was transitioned to glipizide XL.

About 18 months before I saw her, sitagliptin was added to her regimen, and then three months before I saw her, detemir insulin, 30 units, was added at bedtime. This patient had a unique situation where she needed bilateral knee replacement, but her surgeon said he would not operate on her until her A1c was less than 7%, rather pressing her to improve her glycemic control. She had no diabetes complications, although she did have several cardiovascular disease risk factors.

At her initial visit with me she had a mean blood glucose of about 180 mg/dL. Her prebreakfast glucose was 150 mg/dL, predinner it was around 180 mg/dL, and bedtime was around 190 mg/dL. She had had no hypoglycemic episodes. A point of care A1c at that initial visit was 7.7%.

MR. BUSKER: Your initial impressions of this patient — what stood out?

DR. MATHIOUDAKIS: This was a woman with a 10 year history of type 2 diabetes who surprisingly had no diabetes-related complications, despite periods of suboptimal control over that 10 year timeframe. Her average glucose was elevated, her A1c was high at 7.7%, and I thought a goal A1c for her should be less than 7%.

MR. BUSKER: As you described her, she is not on metformin. What do you make of that?

DR. MATHIOUDAKIS: I noted that when I first saw her. She had taken the metformin for only two days, and her side effects of palpitations and sweatiness were rather atypical, so I question whether she truly

had an intolerance to metformin. Could she tolerate another challenge now, perhaps on an extended release formulation which we know is often better tolerated from a GI standpoint? I thought that was important to help improve her insulin sensitivity.

It was clear from her glucose pattern that she had inadequate insulin production at that point on three medications, a basal insulin, detemir; the DPP4 inhibitor sitagliptin, and a sulfonylurea, the glipizide XL. Thinking through her options, one option would be to maximize the glipizide XL to 20 mg daily. The pros of that would be improved fasting and postprandial glycemic control — sulfonylureas are very effective agents; the obvious cons would be weight gain and hypoglycemia. The other thing worth noting is that she is already on a basal insulin, so is there a role for maximizing a sulfonylurea in her case?

Another option is to continue titrating her detemir insulin. That would obviously attain better fasting glycemic control. If you look at weight-based estimation at 1 unit/kilo/day, which would be for a patient who is insulin-resistant, would be about 93 units. If we take about half of that, 40% to 50% of that being her basal insulin, that's 37 units. So she was already on 30 and probably close to her basal insulin requirement, so I didn't think that would have much of an impact.

Another option is to add a rapid-acting insulin analog before meals and transition her to an intensive insulin regimen, the basal bolus insulin.

Another option would be to stop the DPP4 inhibitor and replace it with a GLP-1 agonist. We know that the GLP-1 agonists are more effective from a weight loss standpoint. They also provide better prandial coverage than the DPP4 inhibitors. The cons would be those are the most costly agents, and it's an injection instead of a pill. But that was less of an issue since she had already been on the injections with the detemir insulin.

Finally, re-challenging the patient, as we discussed earlier, with metformin to improve her insulin sensitivity, potentially lower her insulin requirements, and provide some cardio protection.

MR. BUSKER: Considering all these options, what did you ultimately recommend for her?

DR. MATHIOUDAKIS: I put her back on metformin ER, 500 mg daily just to see if she would tolerate the low dose, and in fact she did. She had none of her initial symptoms. We were able to titrate the dose up to 1,000 mg daily, and my goal is to get it to a dose of 1,500 mg or more as illustrated by the article that we discuss in this newsletter by Hirst et al, showing a better benefit from higher-dose metformin.

I also switched her sitagliptin to the liraglutide, and we maximized that to the 1.8 mg dose. She tolerated that quite well and had a real appetite suppressive effect from the medication. I also stopped her glipizide since she was already on a basal insulin and there is increased risk of hypoglycemia. It is also worth pointing out that sulfonylureas and GLP-1 agonists, when taken together, have a higher risk of hypoglycemia. So we typically don't think of GLP-1 agonists causing hypoglycemia except when taken in combination with a sulfonylurea.

With respect to the insulin I had her titrate her detemir dose up to 40 units daily, aiming for a fasting glucose between 90 mg/dL and 130 mg/dL. I also asked her to check her blood glucose before each meal.

MR. BUSKER: How did your patient respond to this approach?

DR. MATHIOUDAKIS: So she did quite nicely. She returned to clinic with her meter, and her downloaded average was about 140 mg/dL, her prebreakfast average was 125 mg/dL, prelunch about 155 mg/dL, and predinner around 150 mg/dL. Her glycemic control was quite stable, she had no hypoglycemic episodes in the three months that followed, and her A1c three months later had come down to 6.3%, which allowed her to have uneventful knee replacement surgery.

MR. BUSKER: Thank you for that that discussion, doctor. Let me ask you now to describe one more clinical scenario for us, if you would, please.

DR. MATHIOUDAKIS: This was a 56 year old beer delivery man who had diabetes for about six years and had been obese since his 30s, with a peak weight of about 250 pounds and a BMI of 32 when I first saw him. His primary care physician started him on on glimepiride as his first line medication and subsequently added metformin. Over the years, the

glimepiride was switched to glipizide for some reason. About a year before his initial visit with me, sitagliptin was added to his regimen.

In reviewing his glycemic control he typically had an A1c somewhere between 7.5% and 8.5%, most recently about 7.5%. He did have some complications of diabetes, including albuminuria and peripheral neuropathy, as well as cardiovascular risk factors including hypertension and hyperlipidemia.

At his initial visit, his diabetes medications included metformin at 1,000 mg twice daily, sitagliptin 100 mg daily, and glipizide 5 mg in the morning and 15 mg in the evening. We downloaded his blood glucose meter, and his prebreakfast range was somewhere between 200 mg/dL and 265 mg/dL, predinner anywhere between 100 mg/dL and 140 mg/dL, and his 30 day blood glucose average was 194 mg/dL.

He told me that he was having hypoglycemia several days per week, mainly during the day, late afternoon, early evening, and these episodes were associated with an intense hunger at dinner time and what he described as a tendency to overeat at dinner as a result. He said his diet was very high in fats, fried foods, carbohydrates, and sweets, and he was getting little to no exercise at all.

MR. BUSKER: Some of the things you just described sound very typical for a lot of patients. What were your initial recommendations for this beer delivery man?

DR. MATHIOUDAKIS: I felt his the late-day hypoglycemia was most likely due to the sulfonylurea and was possibly driving his hunger in the evening, so his tendency to overeat was making his weight loss effort even more challenging, despite the morning dose of glipizide being lower than the evening dose. So I had him stop the 5 mg glipizide in the morning. In addition, you know, this man was obese and having trouble losing weight, so I felt a GLP-1 agonist was a good option for him and recommended he stop sitagliptin and start liraglutide. We started at a 0.6 mg dose and increased to a 1.2 mg daily dose after a week and I did mention to him that there is a risk for hypoglycemia when a GLP-1 agonist is taken with a sulfonylurea.

I also maximized his metformin and recommended that he continue it and emphasized the importance of

improving his lifestyle. I encouraged him to begin walking 30 minutes a day, tracking his calories and aim for about a 20 pound weight loss over the next four to five months.

MR. BUSKER: How did your patient respond to these recommendations?

DR. MATHIOUDAKIS: His A1c eight weeks later was 7.2%, but there was a discordance again between the A1c and his glucose readings. So there was not much of an improvement, if not worsening of his glucose readings by his meter. His average prebreakfast readings were about 210 mg/dL and predinner now about 170 mg/dL, whereas they were more like 100 to 140 range previously. And we tried to find reasons for that discordant A1c, perhaps anemia or some other problem, but it wasn't clear to me why that was happening.

Fortunately, he had no further episodes of late-day hypoglycemia after stopping the morning sulfonylurea. I did additional lab work, a fasting lipid profile. He was found to have severe hypertriglyceridemia with a triglyceride level of over 1,100 mg/dL and a total cholesterol of 264 mg/dL. So to me, the hypertriglyceridemia and the persistently elevated fasting glucose suggested insulin deficiency and I recommended that we move directly to insulin therapy.

MR. BUSKER: Talk to us, if you would, about the decision-making process for determining his starting dose of insulin, and also, what changes you made to his other glucose-lowering medications when the insulin was added.

DR. MATHIOUDAKIS: I started him on a weight-based dose of glargine insulin at the 0.2 unit/kilo/day conversion. He weighed about 100 kilos, so this translated to 20 units of glargine. There were a couple of other issues here. He had severe hypertriglyceridemia, which poses a risk of pancreatitis. Since the GLP-1 agonists have been associated with pancreatitis, I was concerned about his continuing the GLP-1 agonist and asked him to stop the liraglutide. I do want to mention to your listeners that results of a recent large meta-analysis of randomized control trial showed that there is no increased risk of pancreatitis. So my recommendation may have been a bit conservative, and hypertriglyceridemia in and of itself is not a contraindication to using a GLP-1 agonist.

I continued his metformin, of course, and since I was starting a basal insulin, I had him stop his evening sulfonylurea. This is a question I get often from primary care physicians, as I'm starting the basal insulin, what should I do with the sulfonylurea? Should I reduce the dose, should I stop it completely? It's not entirely clear and there aren't clear guidelines about this. Some endocrinologists will just gradually titrate off the sulfonylurea while starting the basal insulin, others will completely stop it and just start insulin therapy. I personally prefer to just stop the medication and titrate the insulin so I have a clear sense of what exactly the insulin is providing to the patient.

MR. BUSKER: When patients need to increase their basal insulin dose, what advice do you give them?

DR. MATHIOUDAKIS: I think it's important to have patients self-titrate. If you start somebody on a basal insulin and then have them back in three months, you've lost time. So take advantage of patient self-titration to get to goal more quickly. I usually have my patients increase their basal dose by one to two units every two or three days or so, until the fasting glucose is at the target that I specify for them. For most patients, that is somewhere between 90 mg/dL and 130 mg/dL, although in light of some more recent data, perhaps it can be higher, even like 130 mg/dL to 150 mg/dL range.

This titration approach is used also by Testa and colleagues as reviewed in this issue of the newsletter,⁵ although their self-monitored blood glucose targets were a bit more stringent.

MR. BUSKER: How did this patient respond to self-titrating his basal insulin?

DR. MATHIOUDAKIS: He came back to clinic a week later to see our nurse practitioner, and by that point he was up to 30 units of glargine; he'd gone up by 10 units, but unfortunately things got worse for him, in that week. He had prebreakfast readings between 200 mg/dL and 300 mg/dL and his average blood glucose was now 250 mg/dL.

MR. BUSKER: His glycemic control got worse after starting insulin. That's fairly unusual. Why do you think that was happening?

DR. MATHIOUDAKIS: What I think happened in his case was that stopping the sulfonylurea cold turkey

removed some endogenous insulin that was being used to control both his fasting and his postprandial glucose. When you start a basal insulin, you are controlling fasting hyperglycemia but you are not providing much in the way of nutritional coverage. In addition, we stopped his GLP-1 agonist, which was also providing nutritional coverage. So I think discontinuing both sulfonylurea and the GLP-1 agonist meant that that basal insulin was not sufficient to maintain normal glucose.

MR. BUSKER: What were your next steps?

DR. MATHIOUDAKIS: At that point it was clear that he be on a basal bolus insulin regimen, so I told him that we'd have to move to mealtime injections and continue his metformin. This was clear to me, because his prebreakfast readings were around 200 mg/dL, rising by late evening to as high as 300 mg/dL, which indicated the lack of nutritional coverage.

MR. BUSKER: Now here's a challenge, I think, that many clinicians have, and that's: when you initiate a basal bolus insulin regimen, first of all, how do you know what changes to make to the basal insulin dose? And how do you decide what the nutritional coverage dose should be?

DR. MATHIOUDAKIS: That's an important question. As an endocrinologist I often see patients coming to me on extremely high doses of basal insulin. We use the term "overbasalization" to describe this scenario where the patient is on an excessive amount of basal insulin and usually has inadequate nutritional insulin coverage. Early in the management of type 2 diabetes, we add a basal insulin to help the beta cells maintain stable fasting glucose levels. But this assumes that your beta cells are still functioning well enough to cover your meals with endogenous insulin.

And if you expect to achieve prandial control with basal insulin, you put the patient at risk of fasting hypoglycemia and persistent postprandial hyperglycemia. You cannot control the complete pattern of glycemic variation with just basal insulin alone. So when I start a patient on basal insulin, if you use a weight-based dose of 0.6 to 0.8 units/kilo/day, which is appropriate for most patients, and you make half of that total daily dose as the basal; typically for most patients that's a basal dose less than 50 units, unless you are dealing with a patient who is severely obese.

If you're seeing doses higher than 50 units of basal insulin, chances are the patient should be on nutritional insulin. So when I switch somebody to basal bolus insulin, I calculate a weight-based dose for their total insulin requirement for the day, so let's take, for example, a 70 kilogram patient at 0.6 units per kilo per day, that equals a total daily dose of 42 units. And if we take 40 to 50% of that and make that basal, that's 21 units of basal insulin, and take the remaining 50% of the nutritional, that's 21 units divided by three meals a day, that would be equal to 7 units, then we give the 7 units with each meal.

There are several approaches to starting a mealtime insulin, one is just give the mealtime insulin with the largest perceived meal of the day; for most people that's dinner. The ADA EASD recommends a starting nutritional dose of 4 units, the ACE guidelines are 5 units with meals, and having the patient titrate by about 2 units every few days until that peak postprandial glucose is less than 180 mg/dL or their fasting glucose is at goal.

Another thing that you can do to have the patient titrate their nutritional insulin is to have them gradually increase their dose until their peak postmeal glucose, which for most people is usually one to two hours after the meal, is no more than 50 points higher than their premeal blood glucose value.

Finally, for very motivated patients, carb counting is an option. And a rule-of-thumb estimate for calculating the carb ratio is to take 450 and divide that by the total daily dose, which gives you the insulin-to-carb ratio. I find that for most of my patients with type 2 diabetes, except those on insulin pumps, carb counting is not something that people tend to want to do, so we usually just do more of a fixed mealtime insulin dose.

MR. BUSKER: How did your patient respond to this basal bolus regimen?

DR. MATHIOUDAKIS: He responded beautifully. Over the next eight weeks he had very close follow-up with our nurse practitioner. We titrated his glargine up to 50 units, and he was ultimately put on mealtime insulin of 18 units of aspart insulin with meals, as well as some correctional insulin. At his follow-up visit six weeks later he had an average blood glucose of 155 mg/dL, prebreakfast average was 163 mg/dL, prelunch was 155 mg/dL, and predinner was 154

mg/dL. As expected, he did have a slight weight gain of about three pounds with the insulin and also had a few hypoglycemia episodes.

MR. BUSKER: What dosing adjustments did you make to address the hypoglycemia?

DR. MATHIOUDAKIS: Typically we'll reduce the total insulin dose by about 10% to 20% as one approach, or the insulin specifically that will address the time of the day when the hypoglycemia is happening by that same amount of 10% to 20%. For example, if a patient is having nocturnal hypoglycemia, that means they need a reduction in their evening basal insulin, if they're having postprandial hypoglycemia, they need a reduction in their nutritional insulin dose.

It is important for your listeners to realize that the job of the basal insulin is not to bring the glucose down, but to maintain a steady glucose. If a patient goes to bed with a glucose, say, of 110 mg/dL, they should wake up with a reading that does not deviate more than 30 points from that bedtime reading. If you find that a patient's glucose drops significantly from their bedtime reading to the morning, they're getting too much basal insulin, and they are prone to dropping when fasting later in the day.

In his case, I reduced his glargine dose from 50 to 40 units and I reduced his aspart dose from 20 to 15 units with meals, about a 20% reduction in his insulin overall. And if you have got a patient who is on premixed insulins, you will want to make sure that you rely on your pre-dinner blood glucose readings to adjust your morning dose, and vice versa, your pre-breakfast readings to adjust your evening dose.

When this patient came back a few months later, his A1c was 5.8%, which to me indicated too tight glycemic control, so I had to reduce his insulin doses even further.

MR. BUSKER: Dr. Mathioudakis, thank you for today's discussion on Strategies for Intensifying Therapy for Glycemic Control. I'd like to review what we've talked about in light of our learning objectives. So to begin: available glucose lowering medications as add-on therapy to metformin — the advantages and disadvantages.

DR. MATHIOUDAKIS: First key point is that metformin should be maximized. Factors to consider when adding a medication to metformin include the

drug's glycemic efficacy, the potential for weight gain, the risk of hypoglycemia, other drug side effects, and medication costs. Weight-neutral medications, for example, DPP4 inhibitors, or drugs that promote weight loss such as GLP-1 agonists, would be ideal options in overweight or obese patients.

MR. BUSKER: And our second objective: options for treating patients who are already on three glucose-lowering medications but still have suboptimal glycemic control.

DR. MATHIOUDAKIS: Metformin is the cornerstone of any combination regimen since it improves insulin sensitivity and may have cardio protective benefits. The combination of metformin, a GLP-1 agonist, and basal insulin is an effective strategy. And again, the same factors that we consider when choosing add-on therapy to metformin would apply when considering a third agent. So you want drugs with the lowest cost, the lowest hypoglycemia risk, the lowest weight gain potential, and the greatest glycemic lowering efficacy.

MR. BUSKER: And finally: the indications for insulin therapy and the principles that are involved in adjusting insulin dosing.

DR. MATHIOUDAKIS: Insulin therapy is indicated when a patient has failed to achieve an A1c target on a combination of optimal doses of either two or three glucose lowering medications. Basal insulin should be started according to the patient's body weight and titrated to achieve fasting blood glucose targets. And if the A1c is not achieved on basal insulin alone, nutritional insulin should be added. The total daily dose, which is determined by the patient's weight, should be divided roughly into 40% to 50% basal and 50% to 60% nutritional insulin.

MR. BUSKER: Dr. Nestoras Mathioudakis from the Johns Hopkins University School of Medicine, thank you for participating in this eDiabetes Review Podcast.

DR. MATHIOUDAKIS: It was my pleasure, thank you for the opportunity.

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eDiabetes Review is supported by educational grants from Eli Lilly and Company, Bristol-Myers Squibb, and Novo Nordisk, Inc.

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