JOHNS HOPKINS MEDICINE eLITERATURE REVIEW

eDiabetes Review

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

Vol 3: Supported by educational grants from NovoNordisk, Sanofi, and Merck & Co., Inc.

VOLUME 3 - ISSUE 8

LISTEN TO PODCAST | DOWNLOAD PODCAST | PHYSICIAN POST-TEST | NURSE POST-TEST

Intensifying Glycemic Therapy with a Fixed Ratio Basal Insulin/GLP-1 RA Combination

- Review the use of a GLP-1RA as add-on or in a fixed ratio combination (FRC) as an intensification strategy after basal insulin.
- Evaluate a GLP-1RA as add-on or in an FRC in a patient with macrovascular and microvascular complications.
- Describe how a GLP-1RA as add-on or in an FRC can reduce regimen complexity as well as hypoglycemia risk.

Guest Faculty Disclosure
Dr. Mehta has indicated that she has no financial interests or relationships with any commercial entity whose products or services are relevant to the content of her presentation.

Unlabeled/Unapproved Uses
Dr. Mehta has also indicated that there will be no reference to the unlabeled or unapproved uses of any drugs or products.

MEET THE AUTHOR

Roopa Mehta, MBBS, MRCP
Endocrinologist
Instituto Nacional De Ciencias Médicas y Nutrición Salvador Zubirán
Mexico City, Mexico

Release Date:
July 10, 2018

Expiration Date:
July 09, 2020

LISTEN TO PODCAST NOW | DOWNLOAD PODCAST | SUBSCRIBE NOW | PHYSICIAN POST-TEST | NURSE POST-TEST

OTHER RESOURCES

Download the podcast transcript

Go to the companion newsletter

NEWSLETTER ARCHIVE | SHARE WITH A COLLEAGUE

PROGRAM DIRECTORS

Nestoras Mathioudakis, MD, MHS
Assistant Professor of Medicine
Clinical Director, Endocrinology, Diabetes & Metabolism
Johns Hopkins University School of Medicine
Baltimore, Maryland

Kathleen Dungan, MD, MPH
Associate Professor
Associate Division Director for Clinical Services
Division of Endocrinology, Diabetes and Metabolism
The Ohio State University
Columbus, Ohio

Susan Porter, MSN, CRNP, CDE
Clinical Nurse Practitioner and Certified Diabetes Educator
University of Maryland, St. Joseph Medical Group Owings
Mills Internal Medicine
Baltimore, Maryland

Podcast Transcript

BOB BUSKER: Welcome to this *e*Diabetes Review podcast.

I'm Bob Busker, managing editor of *e*Diabetes Review. Our guest today is Dr. Roopa Mehta, Endocrinologist at the Instituto Nacional De Ciencias Médicas y Nutrición Salvador Zubiran in Mexico City. And our focus is on intensifying glycemic therapy with a fixed ratio basal insulin/GLP-1 RA combination.

***e*Diabetes Review is jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. This program is supported by educational grants from Merck & Co. Inc, NovoNordisk, and Sanofi.**

Learning objectives for this audio program include:

- **Review the use of a GLP-1RA as add-on or in a fixed ratio combination (FRC) as an intensification strategy after basal insulin.**
- **Evaluate a GLP-1RA as add-on or in an FRC in a patient with macrovascular and microvascular complications.**
- **Describe how a GLP-1RA as add-on or in an FRC can reduce regimen complexity as well as hypoglycemia risk.**

Dr. Mehta has indicated that she has no financial interests or relationships with any commercial entity whose products or services are relevant to the content of her presentation. She has also indicated that there will be no reference to the unlabeled or unapproved uses of any drugs or products.

MR. BUSKER: Dr. Mehta, thank you for joining us today.

DR. MEHTA: Thank you for inviting me.

MR. BUSKER: In your recent newsletter issue you presented some of the current research about intensifying therapy in patients whose diabetes is no longer effectively controlled on basal insulin. Our objective today is to see how some of that new information can be applied to clinical situations. So please start us out with a patient scenario.

DR. MEHTA: Let me tell you about this 49-year-old lady with type 2 diabetes. Her diabetes was diagnosed about nine years ago and she is presenting for routine follow-up in the outpatient clinic. She's testing her glucose levels about twice daily and mentions morning readings from 110 mg/dL to 130 mg/dL and nonfasting levels that are typically above 180 mg/dL.

She reports that she has occasional hypoglycemia, generally if she skips a meal, but there is no history of severe hypoglycemia requiring outside assistance. She is frustrated with continued difficulty controlling her weight, but she does attempt to stick with a consistent number of carbohydrates per meal and tries to limit portion size. For exercise she says she takes her dog out for a walk every day.

She does not have any history of microvascular complications, and her current medication regimen consists of insulin glargine 42 units per day and metformin 1 gram BID. On physical examination she has a blood pressure of 132/80, her body mass index is 32, but otherwise everything else is essentially normal. Her glycated hemoglobin is 8.1%.

MR. BUSKER: How would you approach her glycemic management?

DR. MEHTA: She mentions her fasting plasma glucose levels were between 110 mg/dL and 130 mg/dL, but that is generally where I would like most of my patients to be. She is on target. However, she mentions that her postprandial levels are a little high, around 180. So, we can say that her fasting plasma glucose is optimal and that indicates that her basal insulin dose is probably adequate.

The other aspect that she mentions is that she is getting hypoglycemic episodes, but only when she skips meals. She is not really having any severe hypoglycemic episodes, but we interrogate her a little more closely to assure ourselves that this really isn't a major problem.

If we try to titrate up the basal insulin, we may end up provoking more hypoglycemia. And the fact that her fasting plasma

glucose is on target seems to indicate that the basal insulin should probably not be touched in this patient and she can maintain that same dose. However, she does have an elevated glycated hemoglobin level of 8.1%, and the postprandial glucose levels are above 180 mg/dL, so we should really be addressing postprandial elevations here.

How can we really control postprandial hypoglycemia in this patient? We can add in prandial insulin, we can switch to a premixed insulin, or add in a GLP-1 receptor agonist. And that's what the latest ADA guidelines recommend.

MR. BUSKER: So adding prandial insulin, switching to premixed insulin, or adding a GLP-1 receptor agonist. What determines that treatment decision?

DR. MEHTA: We must always consider the full patient profile. We need to look at all aspects of this patient, what her concerns are, and what she wants should also be taken into account. She has already mentioned that she's concerned about weight gain, she's having hypoglycemia occasionally, and the glucose-lowering efficacy should also be an option here.

Now her diabetes is not controlled: she has an A1c level of 8.1%. If we add more insulin, she may well gain more weight, and she is already complaining about that, so this might not be the most desirable option. She mentions hypoglycemic episodes, and insulin may increase the risk of that.

So, in her case, adding a GLP-1 receptor agonist alone or switching to a fixed ratio combination may well be the best option. Studies have shown that adding a GLP-1 receptor agonist will achieve similar glucose lowering efficacy to the other two options. But the added advantage here is that we're not increasing the risk of hypoglycemia or weight gain.

MR. BUSKER: What are the differences among the GLP-1 receptor agonists?

DR. MEHTA: We have several choices: the once weekly GLP-1 receptor agonists, including exenatide-LAR, dulaglutide, and semaglutide. We also have once daily ones which include liraglutide and lixisenatide. And we have the short acting GLP-1 receptor agonist exenatide-BID. This list will keep growing, but these are the basic GLP-1 classes.

When we consider the fixed ratio combinations, these are generally the combination of a long-acting insulin analog with a GLP-1 receptor agonist. We currently have two combinations on the market: the combination of degludec with liraglutide, and glargine with lixisenatide. In these fixed ratio combinations, the long acting insulin is combined with either the once daily or weekly agent. The advantages of having this fixed ratio combination are, you may end up reducing injection burden, you may have the possibility of reducing insulin dosage, and they may be better tolerated than the GLP-1 receptor agonist by itself. They may possibly have lower insurance copays because fixed ratio combinations count as one drug. Also, if we are considering either adding in a GLP-1 receptor agonist by itself or switching over to a fixed ratio combination, we need to take into account the properties of the GLP-1 receptor agonists we're adding.

Remember that short acting agents may have more side effects than the longer acting agents. And they may also be more effective for postprandial hypoglycemia, whereas the longer acting ones may better control fasting hypoglycemia.

All of this needs to be taken into account when we make the decision on how to intensify in this patient.

MR. BUSKER: How would you implement intensifying therapy in this patient?

DR. MEHTA: We've decided that for her a GLP-1 receptor agonist is probably the best option. Her fasting glucose is on target, so we'd maintain that on her basal insulin, but we may need to reduce the dose a little before initiating the GLP-1 receptor agonist. With a once weekly GLP-1 receptor agonist, we may have to wait for it to take effect, so a fixed ratio combination would probably be a good option here.

MR. BUSKER: And your choice of agent?

DR. MEHTA: We have the combination of degludec with liraglutide and the combination of glargine with lixisenatide. Let me tell you how we would start these agents.

With IDegLira, because she is already on basal insulin she is not insulin naïve, you would probably start with 16 units. That 16 units is combined with 0.58 mg of the liraglutide component. If you start this agent in an insulin naïve patient, you'd start with 16 units and the liraglutide combination would include 0.36 mg. With this agent in the pen the maximum dose is 50 units of degludec with 0.58 mg of liraglutide. How do we adjust the dose? We adjust the dose based on self measured blood glucose targets, similar to the way we adjust the basal insulin.

The recommendations for iGlarLixi are slightly different. If the basal insulin dose is less than 30 units a day, we can start with 15 units of the combination therapy. If the basal insulin is greater than 30 units a day, you can start at 30 units and titrate up. The minimum dose with this combination is 10 units and the maximum dose is 60 units. Like the other fixed ratio combination, the adjustment is based on self measured blood glucose levels and you're basically adjusting two to four units weekly.

Please remember that you are really titrating up the basal insulin. And because it's a fixed ratio combination, as a consequence of titrating up zero to two units every three to four days, you are also gradually titrating up the GLP-1 receptor agonist. This must take into account the characteristics of the basal insulin, and both degludec and glargine have longer half-lives than the typical human insulin.

MR. BUSKER: Thank you for that case and discussion, Dr. Mehta. We'll return in just a moment.

MR. BOB BUSKER
This is Bob Busker, managing editor of *e*Diabetes Review. *e*Diabetes Review is a combination newsletter and podcast program delivered via email to subscribers. Newsletters are published every other month. Each issue reviews the current literature in areas of importance to clinicians treating patients with type 2 diabetes.

In the month following each newsletter, a case-based podcast discussion, like the one you're listening to now, is available to help translate that new clinical information into practice. These podcasts are also available as downloadable transcripts.

Subscription to *e*Diabetes Review is provided without charge or prerequisite.

Continuing education credit for each newsletter and each podcast is provided by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. For more information on this educational activity, to subscribe and receive *e*Diabetes Review without charge, and to access back issues, please go to our website: www.ediabetesreview.org

Thank you.

MR. BUSKER: Welcome back to this *e*Diabetes Review podcast. We're here with Dr. Roopa Mehta, from the Instituto Nacional De Ciencias Médicas y Nutrición Salvador Zubiran in Mexico City, and we've been discussing the clinical utility of fixed ratio basal insulin/GLP-1RA combinations. So, to continue in that vein, please bring us another patient scenario.

DR. MEHTA: A 59-year-old man with a 12-year history of type 2 diabetes. He has coronary artery disease and had two stents put in two years previously. He also has heart failure with New York Heart Association grade 1 categorization. He presents to the clinic because he is quite frustrated by his glycemic control.

He's been checking once or twice daily and just notes the blood glucose levels are high, routinely above 200. He also complains of fatigue and says he's thirsty and goes frequently to the bathroom. The current blood glucose lowering medications include metformin 1000 mg twice daily, glimepiride 2 mg once daily, and dulaglutide once weekly. On examination he has a blood pressure of 140/90 and a body mass index of 30. Peripheral vascular exam demonstrates weak pulses, venostasis changes, and a stocking and glove peripheral sensory neuropathy. His current glycated hemoglobin is 10.2% and the laboratory results show a creatinine of 1.6 mg/dL with microalbuminuria and an eGFR of 40 mL/min.

MR. BUSKER: What's your assessment of this patient?

DR. MEHTA: This case is a little more complex than the last patient. We have a history of 12 years of type 2 diabetes, but he now has macrovascular and microvascular complications. He mentions coronary artery disease and heart failure, and he also has peripheral neuropathy and some degree of renal impairment. So in this patient it's really important to have individualized glycemic targets. The target for the A1c here would be around 7.5% to 8%.

We need to look into the renal function, as well. He's taking metformin and may well be fine with the current dose for a little longer, but if his GFR drops below 45, metformin may no longer be the best option.

Because he's at high cardiovascular risk, one category of agents that has shown great benefit in this type of patient is the SGLT-2 inhibitors. Empagliflozin could be an option in this patient, but with a GFR below 45, it may not be effective for glycemic control.

The other aspect is considering a GLP-1 receptor agonist. Certain GLP-1 receptor agonists have shown cardiovascular benefit, but again, we must take into account the renal function.

One of the most pressing concerns in this patient is that his diabetes is very uncontrolled. He has symptoms of hyperglycemia, he mentions polyuria, polydipsia, and blood glucose levels above 200, so in my opinion adding in insulin is probably the best option for this patient. Generally, a basal insulin would be preferred.

MR. BUSKER: Can you walk us through your recommended treatment plan?

DR. MEHTA: We'd start with a basal insulin, either 10 units daily or 0.2 units per kilogram. We should probably consider stopping the sulfonylurea or at least reducing the dose to minimize the risk of hypoglycemia. In this high cardiovascular risk patient, we really don't want to be provoking hypoglycemic episodes.

The GLP-1 receptor agonists should be continued, and further along the line when glucose levels are better controlled on basal insulin, we may consider switching to a fixed ratio combination. In particular, with iDegLira, the liraglutide component may give us certain cardiovascular benefits.

MR. BUSKER: With this treatment plan, what response would you expect to see in terms of A1c, weight, hypoglycemia?

DR. MEHTA: Initially, I would titrate up the basal insulin to get his diabetes controlled. That would lower the glycated hemoglobin, but it would not provoke weight loss, and I would have to be careful that I'm not provoking hypoglycemic episodes. But once I get the glucose levels a little lower, I could then consider switching the patient to a fixed ratio combination.

One of the reasons to do that would be to maintain efficacy, and the combination therapy would be more effective in reducing glycated hemoglobin than each of the individual components by themselves.

Hypoglycemia would be expected to increase if we just added insulin. With insulin by itself, weight gain is a concern, but using the fixed ratio combination may limit weight gain and minimize the risk of hypoglycemic episodes and possibly the dosage of the basal insulin needed to control his diabetes.

MR. BUSKER: Thank you for that case and discussion, Dr. Mehta. Please bring us one more patient scenario.

DR. MEHTA: The final patient is a 76-year-old man with a 14-year history of type 2 diabetes who comes to the office with his daughter. He's recently widowed, and his wife formerly performed the injections of his insulin therapy. The daughter is concerned with her father's ability to self-manage his diabetes and he is currently living alone. He brings along glucose logs, and you can see that the checking is sporadic. He reports waking up in the middle of the night with sweating and confusion at least three times per week. He keeps glucose tablets by his bed. And he mentions a fall two weeks ago requiring stitches.

His current regimen is glargine 20 units daily. He also has short acting insulin lispro, 5 units with each meal, plus a correction dose of 1 unit per 50 mg/dL over 150 mg/dL. He tends to take the lispro sporadically and he does not tolerate metformin.

On physical examination he's alert and orientated, blood pressure 128/64, body mass index 28. His weight has been stable over the last year. He has a glycated hemoglobin of 6.5% and his renal function is normal.

MR. BUSKER: What do you see as the most important priorities in managing this patient?

DR. MEHTA: This is an elderly man who lives by himself, so I think there were two main concerns here. One concern is safety. There does appear to be a hypoglycemia risk. He may well also be eating less, since his wife has recently died and she seemed to be his main support, so he's not really managing his self-care at all. Falls are another risk. He's had one in the last two weeks requiring stitches, so I think that is what I would be most concerned about.

The other aspect I find so surprising is that he seems to be on a full basal-bolus regimen. In an elderly patient, we want to simplify the treatment, we don't want to complicate their lives any more than we need to. When I initially assessed this patient, I would obviously explore all these safety concerns, but I would also ask very particular questions to assess his cognitive function. A mini mental examination would be necessary here, and also to look into his mental health status. He may well be extremely depressed and this could be why sometimes he doesn't inject or sometimes not even eat.

DR. MEHTA: So, the best option for this case to address at least the hypoglycemia risk is probably to suspend the prandial insulin doses. He has a glycated hemoglobin of 6.5%, which I think is a very strict target in this patient. So, removing the lispro and maybe adjusting the basal insulin further would be necessary.

MR. BUSKER: What about simplifying his regimen? How would you go about that in practice?

DR. MEHTA: I've already mentioned that we need to stop the prandial insulin, so the lispro would be removed. And to adjust the basal insulin, I'd probably begin by reducing the dose by at least 20%. I would educate the patient so he would recognize some of these episodes he's having as hypoglycemia. I'd also ask him to keep a log so I could further reduce the basal insulin dose if necessary. I'd also reinforce that he eats his meals and should at least maintain his treatment.

To simplify the regimen further, a fixed ratio combination of a basal insulin with a GLP-1 receptor agonist would have a place. It would also help if the daughter could come home in the evening and inject her father, making it much easier for him so he wouldn't have to be so concerned about managing his medication. However, before considering a fixed ratio

combination, we do need to educate the patient and the daughter about possible GI side effects related to the GLP-1 receptor agonist component and give them advice on how to manage this.

MR. BUSKER: Thank you, Dr. Mehta, for today's cases and discussion. Let's wrap things up now by reviewing what we've talked about today in light of our learning objectives. Our first objective: using a GLP-1RA as add-on or in a fixed ratio combination as an intensification strategy after basal insulin.

DR. MEHTA: In patient whose fasting plasma glucose levels are uncontrolled but the A1c is elevated, you need to consider intensification. We have three options and in particular the case we talked about, the GLP-1 receptor agonist is preferred because the lower risk of hypoglycemic episodes, less weight gain, and the possibility of reducing the basal insulin dose. But it is important to say that this may not be the best option in all cases, such as those with very high insulin doses. The fixed ratio combinations have an upper limit. Renal function needs to be taken into account. It may not be the best option in patients whose diabetes is very uncontrolled when maybe just adding in more insulin would be the best option. And with the fixed ratio combination education is extremely important, for both the patient and the physician.

MR. BUSKER: And our second learning objective: a GLP1-RA as add-on or in a fixed ratio combination in a patient with macrovascular and/or microvascular complications.

DR. MEHTA: The second patient had both microvascular and macrovascular complications and had quite severe hyperglycemia. In this case I think the best option is initiating basal insulin. There are three steps in that process: initiation, optimization, and intensification in the future.

How do we initiate basal insulin? 10 units or 0.2 units per kilogram, you titrated based on two to three fasting finger prick measurements a week. I mentioned that once we had the patient better controlled on their basal insulin, a fixed ratio combination could be considered, possibly the combination of degludec with liraglutide, because liraglutide has shown cardiovascular benefits in a recent study. Semaglutide is the other GLP-1 receptor agonist that has shown cardiovascular benefit, and this could also be an option.

MR. BUSKER: And finally: how a GLP-1RA as add-on or in a fixed ratio combination can reduce regimen complexity and hypoglycemia risk.

DR. MEHTA: Our final patient was an elderly man who was having hypoglycemic episodes and falls and had a very complex insulin regimen. One of the most important aspects is simplifying the regimen and reducing the hypoglycemia risk.

We discussed removing the prandial insulin doses and reducing the basal insulin, and we could consider switching his patient to a fixed ratio combination to reduce injection burden to once daily, and in that way tackle both the fasting and the prandial glycemic excursions. A fixed ratio combination could be possible in this patient, but on the other hand, he may just need his basal insulin. Assessing each patient in an individualized manner is extremely important.

MR. BUSKER: Dr. Roopa Mehta from the Instituto Nacional De Ciencias Médicas y Nutricién Salvador Zubiran in Mexico City, thank you for participating in this *e*Diabetes Review Podcast.

DR. MEHTA: Thank you very much again for having me. I hope the discussion of these cases has helped people understand better when to use GLP-1 receptor agonists or the fixed ratio combinations. Thank you very much.

MR. BUSKER: To receive CME credit for this activity, please take the post-test at www.ediabetesreview.org

This podcast is presented in conjunction with the *e*Diabetes Review newsletter, a peer-reviewed literature review certified for CME/CE credit, emailed monthly to clinicians treating patients with type 2 diabetes.

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 credit*™. Physicians should claim only the credit commensurate with the extent of their participation in this activity.

The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

For nurses, this 0.5 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hour.

This educational resource is provided without charge, but registration is required. To register to receive *e*Diabetes

Review via email, please go to our website: www.ediabetesreview.org**.**

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only.

Use of the names of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing implies review of educational format, design, and approach. Please review the complete prescribing information for specific drugs, combinations of drugs, or use of medical equipment, including indication, contraindications, warnings, and adverse effects, before administering therapy to patients.

***e*Diabetes Review is supported by educational grants from Merck & Co., Inc., NovoNordisk, and Sanofi.**

CME/CE INFORMATION

ACCREDITATION STATEMENT

Physicians:
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Nurses:
The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

CREDIT DESIGNATION STATEMENT

Physcians:
The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 credit™*. Physicians should claim only the credit commensurate with the extent of their participation in this activity.

Nurses:
For nurses, this 0.5 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hour.

POLICY ON SPEAKER AND PROVIDER DISCLOSURE

It is the policy of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing that the speaker and provider globally disclose conflicts of interest. The Johns Hopkins University School of Medicine OCME has established policies that will identify and resolve conflicts of interest prior to this educational activity. Detailed disclosure will be made prior to presentation of the education.

INTERNET CME/CE POLICY

DISCLAIMER STATEMENT

STATEMENT OF RESPONSIBILITY

STATEMENT OF NEED

INTENDED AUDIENCE

CONFIDENTIALITY DISCLAIMER FOR CME ACTIVITY PARTICIPANTS

HARDWARE & SOFTWARE REQUIREMENTS

COMPLETE CME INFORMATION

This activity was developed in collaboration with DKBmed.