



eLITERATURE  
REVIEW

eDiabetes Review  
Podcast Issue

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VOLUME 1 – ISSUE 8: TRANSCRIPT

## Featured Cases: Role Of GLP-1 Receptor Agonists In The Treatment Continuum Of Type 2 Diabetes

Our guest author is Rajesh Garg, MD, Assistant Professor of Medicine at Harvard Medical School, Brigham and Women’s Hospital in Boston, Massachusetts.

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

- Explain why GLP-1 agonists should be considered early in the treatment of T2DM in obese patients.
- Discuss why GLP-1 agonists may be a better choice than basal insulin in selected obese patients with T2DM.
- Describe why adding GLP-1 agonist to a treatment regimen that already includes basal insulin may be better than adding nutritional insulin in obese patients with T2DM.

This discussion, offered as a downloadable audio file and companion transcript, covers the important topic of the Role of GLP-1 Receptor Agonists in the Treatment Continuum of Type 2 Diabetes in the format of case-study scenarios for the clinical practice. This program is a follow up to the Volume 1, Issue 7 *eDiabetes Review* newsletter—[Role of GLP-1 Receptor Agonists in the Treatment Continuum of Type 2 Diabetes](#).

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Rajesh Garg, MD discloses that he has received research funding from AstraZeneca.

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

Today's program is a follow-up to our newsletter on "The Role of GLP-1 Receptor Agonists in the Treatment Continuum of Type 2 Diabetes." With us today is that issue's author, Dr. Rajesh Garg, assistant professor of medicine at Harvard Medical School, and Brigham and Women's Hospital in Boston, Massachusetts.

*eDiabetes 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 Eli Lilly and Company, AstraZeneca, and Novo Nordisk, Inc.

Learning objectives for this audio program include:

- Explain why GLP-1 agonists should be considered early in the treatment of obese patients with type 2 diabetes.
- Discuss why GLP-1 agonists may be a better choice than basal insulin in certain obese patients with type 2 diabetes.
- Describe why adding a GLP-1 agonist to a treatment regimen that already includes basal insulin may be better than adding nutritional insulin in obese patients with type 2 diabetes.

Dr. Garg has indicated that he has received research funding from AstraZeneca. 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. Garg, thank you for joining us today.

**DR. GARG:** Thank you, Bob, it's my pleasure.

**MR. BUSKER:** In your newsletter issue, you reviewed the recent literature describing where GLP-1 agonists fit into treatment decision-making for patients with type 2 diabetes, and the important role these agents can play in more effectively individualizing therapy. Today I'd like to focus on how that information can be translated into practice. So if you would, Dr. Garg — start us out by describing a patient.

**DR. GARG:** Okay, let me give you the example of the first patient. He's a 49 year-old male with type 2 diabetes who has been well-controlled on metformin

2.5 grams daily for the last six years. However, his most recent HbA<sub>1c</sub> when you test in your clinic is 8.9%. He has no diabetes-related complications at this time. His current BMI is 36 kg/m<sup>2</sup>. Your records show that the patient has been gaining weight over time, and he has gained 13 pounds in the last one year.

You ask the patient to meet with your nutritionist and advised him to exercise at least half an hour daily on most days of the week. You see him three months later and repeat the A<sub>1c</sub>, which is 8.7%. To your best clinical assessment he is following lifestyle changes and he's compliant with his medications.

**MR. BUSKER:** So Dr. Garg — am I right in assuming that this is a common clinical situation?

**DR. GARG:** Yes, Bob, this is a very common clinical situation, and most physicians would have encountered one or many patients like this in their practice. We know that type 2 diabetes is a chronic disease, it's a progressive disease, as time goes by the patients will need more and more medications. This is because their beta cells, the pancreatic beta cells, they fail over time and produce less and less insulin. There have been several long-term studies including the UKPDS that was a large clinical trial, that have established the sad effect that over time there is progressive beta cell failure in type 2 diabetes, and that's why patients will need more and more medications as time goes by.

Now this patient has been controlled with metformin alone for six years, which is a long time, and we know that at some point metformin alone is not going to be enough. And I think at this point of time when we know that the A<sub>1c</sub> is high and we think he is following, doing his best with his lifestyle measures and taking medication, it's time to go to a second agent. And that's what are the guidelines from the American Diabetes Association, as well as the European Diabetes Society.

**MR. BUSKER:** He needs a second medication to control his diabetes — which agent would you recommend for this patient?

**DR. GARG:** In the past we used to follow an algorithm. Most physicians would add a sulfonylurea drug like glyburide or glimepiride or glipizide.

However, in the last two to three years, the guidelines have changed, and both the American Diabetes Association and the European Diabetes Society now recommend that next line of agent should be individualized. In other words, there is no single algorithm that is good for every patient. So in this patient, who is young and continues to gain weight over time in spite of the maximum dose of metformin, an agent that will help him lose weight will be preferred, and so we need to choose from among all the other antidiabetic agents available, but the preference will be one that will help him lose weight or at least not gain more.

**MR. BUSKER:** What glycemic goal do you see for this patient?

**DR. GARG:** The glycemic goal for this patient should be a HbA1c less than 7%. Now even the HbA1c goals need to be individualized, that is the latest recommendation from most of the societies, but this patient is young, 49 years old, and has a relatively short duration of diabetes with no complications, so our goal for his glucose control should be a HbA1c less than 7%.

**MR. BUSKER:** What agent would you recommend to achieve that goal? And how would you explain that recommendation to the patient?

**DR. GARG:** What agent to use — for that, there are several factors that need to be considered. We already discussed the weight issue, which is particularly important for this patient and for most other patients with type 2 diabetes. Then we need to discuss with this patient the various available therapies and explain to him what is available, what is the cost, what are the oral agents, what are the injectables, and I think for this patient a GLP-1 agonist should be considered as one of the many choices that should be discussed with this patient, and he should be given the choice whether to take it or not.

**MR. BUSKER:** Doctor, how would you explain a GLP-1 agonist to this patient? What would you say to him?

**DR. GARG:** For this patient, weight loss is as important as glycemic control because that's going to have a major impact on his health. So we need to give him the various options, we need to extend to him whatever other agents are available, and out of all the agents, for example, DPP4 inhibitors or SGLT2

inhibitors, that maybe weight-neutral or helpful in losing a little bit of weight. GLP-1 agonists have been shown to cause the most weight loss. So this should be one of the choices — not that this is the only choice and we need to force it on the patient, but we should explain that this is one of the options that will help him lose weight. However, this is an injectable, and there can also be issues with his insurance. Many insurance companies may not cover a GLP-1 agonist as the second-line drug after metformin, and the copayments may be high. So all those issues need to be discussed with the patient, and then we should arrive at the consensus which drug to add.

**MR. BUSKER:** Thank you, doctor. And we'll return, with Dr. Rajesh Garg from Harvard Medical School, 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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**MR. BUSKER:** Welcome back to this eDiabetes Review podcast. I'm Bob Busker, managing editor of the program. Our guest today is Dr. Rajesh Garg, from Harvard Medical School and Brigham and Women's Hospital in Boston. And our topic is the Role of GLP-1 Receptor Agonists in the Treatment Continuum of Type 2 Diabetes. We've been looking at how the information in Dr. Garg's newsletter issue can impact clinical practice. So to continue, doctor — let me ask you to bring us another patient now, if you would please.

**DR. GARG:** So let me give you another example of the patient who is a 58 year old man with type 2 diabetes for 12 years who has been taking metformin at 2,000 mg/d and glipizide 10 mg/d for several years; linagliptin was added about two years ago

because his A1c had started going up, and on his last visit his A1c had gone higher. It had been maintained around 7% before that but now it is 8.3%.

So you again advise the patient about diet control, exercise, you reinforce what you have done before, and he returns to your office three months later and his A1c is 8.5%. His BMI is 34.4 kg/m<sup>2</sup>, and his weight has been unchanged for the last one year. He has signs to suggest some complications of diabetes like numbness in his feet, and he also has microalbuminuria.

He thinks he is doing everything he can do to follow diet and exercise, and he takes his medications regularly, and obviously he is worried about his sugars and developing the complications of diabetes.

**MR. BUSKER:** He's showing some neuropathy as well as some kidney dysfunction. In your opinion, how advanced do you think his diabetes is at this point?

**DR. GARG:** Well I think he has moderately advanced diabetes, but he's not at the stage where one has advanced complications or comorbidities where we start thinking that maybe we should relax glycemic control because tight control is not going to benefit them. I think for this patient our goals for his diabetes control, still a HbA1c less than 7%. So he obviously has advanced beta cell failure because he is already on three drugs and still his A1c is going up and it's quite clear that he needs more medications.

Now once someone has been on three oral agents and still the glucose control is not adequate, I think we should consider insulin or one of the injectable therapies to add onto this patient or to switch to insulin.

**MR. BUSKER:** To your mind, doctor: is there any chance that an additional oral agent or a change in oral agents might prevent him from having to go to an injectable therapy?

**DR. GARG:** I will think it's very less likely that adding another oral agent will help this patient now he is already on a sulfonylurea and metformin, and a DPP4 inhibitor, the other agents that we have on our list are pioglitazone, that will make him gain weight, and SGLT2 inhibitors that are relatively new but then his renal function has to be good to use those agents. So I think at this stage most of us, most physicians will

consider insulin therapy, especially because his HbA1c is now more than 8% and so we need an agent that will be relatively potent.

**MR. BUSKER:** How would you discuss injection therapy with a patient like this?

**DR. GARG:** Most patients at this stage who have had diabetes for more than 10 years have been taking all these drugs and trying to do their best with diet and exercise. They are aware that at some stage they are going to need an injection. However, it is important to discuss with the patient, see how much comfort, discomfort they have, it's always helpful to show them how to inject insulin or another agent, show them the pen, and the needles, it's really thin, and most patients will feel reassured when they see the device. And another thing is that the patient should be given the choice that not just insulin but there are also GLP-1 agonists which are injectable but not insulin and we need to discuss both the pros and cons of adding insulin or selecting the GLP-1 agonist with this patient.

**MR. BUSKER:** Insulin or a GLP-1 agonist — which would be the most logical choice for this patient?

**DR. GARG:** The most logical choice in my opinion for this patient will be a GLP-1 agonist, because he's obese and has type 2 diabetes with very few complications, so one of our goals will be weight loss. Now adding insulin will be relatively cheaper, but it will cause weight gain and it also has the high risk of hypoglycemia. GLP-1 agonists are more expensive and they may cause side effects like nausea and vomiting, and they may not be as effective as insulin in lowering A1c, but it makes sense to try them before we try insulin in a patient like him. If the patient cannot tolerate GLP-1 agonists or they are not effective enough, then we can always switch to basal insulin. But however, in this patient I think it makes all the sense that we should try a GLP-1 agonist along with metformin and see if it works or not. There have been several clinical trials comparing basal insulin to GLP-1 agonists and what we have seen is that for several years, for as long as up to three years, glucose control with basal insulin and GLP-1 agonists has been excellent. So with the additional advantage of weight loss and low risk of hypoglycemia, if he can tolerate GLP-1 agonists — and I think most insurances these days will cover this therapy at this stage — it makes sense to try this agent first.

**MR. BUSKER:** So to intensify his therapy, you would recommend trying the GLP-1 agonist in addition to metformin. Would you stop the sulfonylurea and/or the DPP-4 that he's already on?

**DR. GARG:** Yeah, so in this patient who is on three oral agents, when we start injectable therapy we will stop with glipizide and linagliptin. Linagliptin doesn't make sense given in addition to the GLP-1 agonist because it's going to work through the same mechanism, it's the DPP4 inhibitors that increase the endogenous levels of GLP-1 and if you are giving a GLP-1 agonist it is going to be more potent and additional linagliptin is not going to be helpful. Glipizide, mostly as we discussed before, the sulfonylureas fail within about five years of the onset of diabetes, so most likely in this patient glipizide is not even helping to control diabetes. And moreover, GLP-1 agonist is going to also help in some insulin release, increasing insulin release from the beta cells. So I think it will make sense to stop glipizide in this patient. We will keep him on just metformin, which is an insulin sensitizer and works in a different mechanism, and GLP-1 agonists which will be insulin secretagogues, and will also have other mechanisms that are incretinomimetic mechanisms.

**MR. BUSKER:** Thank you Dr. Garg, for that patient presentation and discussion. Let me ask you now to bring us one more patient, if you would, please.

**DR. GARG:** Let's take another example of a patient. This is a 54 year-old Hispanic woman who has type 2 diabetes for the last nine years and has been treated with oral agents for six years, and then insulin was added three years ago. Currently she's on insulin glargine, 55 units at night as basal insulin, and metformin at the maximum dose of 2.5 gm daily in divided doses. Her HbA1c three months ago was 7.9% and today when you see her in the clinic it is 8.3%. You go over her blood glucose log and you see that most of her sugars in the morning are 100 mg/dL to 150 mg/dL range, but at bedtime her sugars go up to as high as 250 mg/dL, 200 mg/dL to 250 mg/dL most of the time. She has gained six pounds in the last three months. Her current BMI is 39.7 kg/m<sup>2</sup>. She currently has no diabetes-related complications, but she does have hypertension and high cholesterol for which she is taking medication. She works as a home cleaner, and her work schedule makes it really inconvenient for her to test so many times a day or take multiple injections. Her eating schedule is not always regular.

**MR. BUSKER:** She's on insulin, but her A1c continues to go up. What do you think is going on?

**DR. GARG:** She's one of the typical patients who gets into the cycle of getting more insulin, gaining more weight, and requiring more insulin. She is already close to morbid obesity. Her BMI is really high and as you give more and more insulin she will keep gaining more and more weight. I think she does need something different; she needs something to control her post-meal glucose levels, which are quite high. We look at her glucose levels, 200 mg/dL to 250 mg/dL at bedtime, so clearly if we were to control her glycemic levels to bring down her A1c, she needs additional insulin. But again, the problem with more insulin will be to give her more weight, so that's the dilemma we are facing in this patient.

**MR. BUSKER:** So right now she's on metformin, plus the basal insulin. Would you consider adding additional oral agents to her treatment regimen?

**DR. GARG:** Well she's already on insulin and she has been on oral agents so I think she's at a stage where most of the oral agents are not going to work and she is already requiring insulin and. I think she does need either nutritional insulin or some other agent that will prevent postprandial hyperglycemia in this patient. And because her A1c is 8.3% at this stage, she needs an agent that will be relatively potent, and most of the oral agents are not going to be adequate to get her to the goal A1c of less than 7%. So I will think of another injection in this case.

**MR. BUSKER:** A second injectable therapy — as we've been discussing, that means either adding nutritional insulin or a GLP-1 agonist. How would you make that decision?

**DR. GARG:** In this patient like in most other type 2 diabetes patients, weight is a major issue. I think both treatments, if we give her nutritional insulin or GLP-1 agonist, we'll be able to control her diabetes, and there have been clinical trials comparing head to head GLP-1 agonists with nutritional insulin added on to basal insulin that have shown equivalent results in terms of glycemic control. But the advantage of giving GLP-1 agonist to this patient will be to stop her weight gain or more likely to help her lose weight, which is extremely important in a patient like her. So giving nutritional insulin will help to control diabetes, but make her gain weight, and nutritional insulin will also most likely be needed 3 times a day for her. And many

patients find it inconvenient, especially if they are working, to take insulin in the middle of the day. So taking one injection of a GLP-1 agonist will be a more convenient option and if we were to go that route I will add it to basal insulin. So giving basal insulin to control her fasting hyperglycemia and a GLP-1 agonist that will be more effective for her postprandial hyperglycemia, will be a really nice option that will control her glucose and help her lose weight or at least not gain more weight.

**MR. BUSKER:** Talk to us a little more, if you would, about the advantages — and also the disadvantages — of controlling postprandial hyperglycemia with a GLP-1 agonist.

**DR. GARG:** One advantage that we already discussed is weight loss. Another will be the cardiovascular risk profile. We know that even mild weight loss in patients with type 2 diabetes has a major effect on their blood pressure, cholesterol, and triglycerides — that is, the cardiovascular risk factors. The major disadvantage for this or any other patient is the cost of the drug. Most insurances will cover the cost, but the copayment may be high. So that is something that we need to discuss and make sure the patient can afford it.

The other consideration why many patients and providers may be hesitant to use GLP-1 agonists is the concerns about pancreatitis and pancreatic cancer that have been circulating in the media for sometime. However, when we look at the data, those concerns are still unconfirmed and there are no really scientific data to support those claims.

**MR. BUSKER:** Through today's case presentations, Dr. Garg, you've shown how important a role GLP-1 agonists can have in individualizing diabetes treatment in most areas of the diabetes treatment continuum. Why do you think overall that these agents are not more commonly used?

**DR. GARG:** The one big issue, Bob, with these agents is that they are an injectable form. The other incretin mimetics, that is DPP4 inhibitors, even though they are milder drugs in terms of glycemic control, they are one of the most commonly used antidiabetic drugs these days. But because GLP-1 agonists are injectable, their acceptance by the patient and the provider community is lower than with most of the oral agents.

They also have side effects like nausea and vomiting, and many patients may not be able to tolerate them. However, over the last five or six years, there have been attempts to design agents that will cause fewer side effects. The drugs that are used once a week cause less nausea and vomiting than the original exenatide used twice a day.

The other reservation about these drugs has been the publicity they received about pancreatic effects. Some case reports, and some basic science data from labs testing these agents on cells or on animals raised concerns that these drugs might increase chances of pancreatitis or even pancreatic cancers. However, those claims have never been confirmed, and most of us now feel that there is no reason to be concerned about pancreatitis or pancreatic cancer with these agents.

I think overall the providers especially and patients just need to be more informed. Educational activities like this one and other activities provide the right information that will be helpful and will help our patients to get the most advantage of available therapies.

**MR. BUSKER:** Along those same lines, doctor — talk to us about some of the developments that are currently underway in relation to GLP-1 agonists?

**DR. GARG:** I think one of the major developments is the use of GLP-1 agonists in addition to insulin or in combination with insulin. There are agents that are being tried in combination with insulin, so the same injection or the same pen device will have both insulin as well as a GLP-1 agonist. I think that will improve the acceptance because of the fewer number of injections; that option is likely to become available in the near future.

The other development that will be really helpful is an oral form of GLP-1 agonist, because, as I said, one of the major issues for low acceptance of GLP-1 agonists is their injectable form. Many companies are working to produce an oral form of GLP-1 agonists, but I don't see that it will be available in the very near future.

Then there are clinical trials going on to maximize the weight loss effect of these drugs in combination with other agents that also help in weight loss like SGLT2 inhibitors. So results of those trials when they come out will be helpful to guide us further.

Then several agents have come to market like exenatide once a week that are longer acting so there are less injections, exenatide once a week, albiglutide that was approved by FDA, is also an injection once a week, and that is another helpful thing for the patient that not only they have less injections but also the side effects with those longer acting preparations seem to be less than daily injection or twice daily injection of GLP-1 agonists.

**MR. BUSKER:** Thank you for sharing your thoughts, Dr. Garg. Let's wrap things up by reviewing today's discussion in light of our learning objectives. So to begin: why GLP-1 agonists should be considered early on in the treatment of type 2 diabetes in obese patients.

**DR. GARG:** Weight loss is a major issue for most patients with type 2 diabetes and out of all the available therapies, GLP-1 agonists are most effective for weight loss and glycemic control at the same time. And also there have been clinical trials showing their effect is sustained for as long as up to 3 years and in fact longer than sulfonylureas. So it makes all the sense to use these agents early in the therapy.

**MR. BUSKER:** And the second learning objective: why GLP-1 agonists may be a better choice than basal insulin in certain obese patients.

**DR. GARG:** The GLP-1 agonists again could be an option for patients who are going on to need basal insulin because at that point when the patients need basal insulin they are already sort of prepared to take injections and so the acceptability of these agents will be higher, at least they are not refusing because it's an injectable form. And the clinical trials have shown that basal insulin and GLP-1 agonists, if they are compared head to head, they have equal effect on glucose control but the GLP-1 agonists have the advantage of helping patients lose weight and not causing hypoglycemia.

So I think before patients go on to take basal insulin, which will be required at some stage in most patients, it makes sense to try a GLP-1 agonist in those who are eligible and are able to tolerate it.

**MR. BUSKER:** And our third learning objective: why adding a GLP-1 agonist to a regimen that already includes basal insulin may be better than adding nutritional or postprandial insulin.

**DR. GARG:** At this stage when a patient needs multiple insulin injections, that's when adding GLP-1 agonists along with basal insulin may be able to avoid nutritional insulin in many patients. If it can help patients take less injections, weight loss, less hypoglycemia, while getting equivalent glycemic control, that obviously is a better choice than giving multiple insulin injections.

Now there have been head-to-head clinical trials showing GLP-1 agonists when added onto basal insulin can achieve as good a glycemic control as adding nutritional insulin for several years. So I think this will make sense to try a GLP-1 agonist in a patient who is already on basal insulin, or we can add basal insulin to someone who is already on GLP-1 agonists but other than give multiple insulin injections of nutritional and basal insulin.

**MR. BUSKER:** Dr. Rajesh Garg — from Brigham and Women's Hospital and the Harvard Medical School — thank you for participating in this eDiabetes Review podcast.

**DR. GARG:** Thank you, Bob, it was really my pleasure to work on this CME program.

**MR. BUSKER:** To receive CME credit for this activity, please take the post-test at [www.ediabetesreview.org/test](http://www.ediabetesreview.org/test).

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