Advances in Insulin Therapy Using Non-Insulin and Insulin Injectables

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Part One - Advances in Insulin Therapy Using Non-Insulin and Insulin Injectables

DR. IRL HIRSCH: Good day, everybody. My name is Irl Hirsch. I'm at the University of Washington in Seattle. And today, we are going to be talking about advances in insulin therapy using non-insulin and insulin injectables. These are my dualities, and let's get started.

So I think we all know there are multiple metabolic abnormalities related to hyperglycemia in type 2 diabetes. And we know that there are abnormalities with the entire islet both with the beta cell and the islet cell, in the brain, at the kidney, gastric emptying is abnormal, and we have abnormalities with lipolysis of the fat tissue, decreased glucose uptake and insulin resistance of the muscle, and an increase in hepatic glucose production at the liver.

So, these are the abnormalities we know about, and the GLP-1 receptor agonist, which became commercially available in the United States about 15 years ago with our first one works at multiple sites. It works at the islet both with the beta cell and the alpha cell. It works in the brain to reduce food intake and satiety. It works with gastric emptying. It slows the gastric emptying. And, this is how they work; they work without causing hypoglycemia because the effect on the beta cell does not cause insulin secretion if the glucose level is low and it's very important, very different, for example, than what we see with sulfonylureas.

Insulin, on the other hand, works at the liver, at the muscle and in the fat tissue, and that's why one of the themes of this discussion is the fact that these drugs can work synergistically because they have different targets of their mechanism of action. So, let's talk about updates with the GLP-1 receptor agonist. First, the GLP-1 receptor agonists are now first-line injectable therapy for type 2 diabetes, and this is per the American Diabetes Association standards of care, but I should point out that the general recommendations around the world, based on the evidence, suggests that due to their mechanism of action, the lack of hypoglycemia, and the ability to cause weight loss, these drugs are now first-line injectables.

Secondly, the GLP-1 receptor agonist and for that matter the SGLT-2 inhibitors for cardiovascular or renal benefits for people with type 2 diabetes should now be considered independently of baseline or target hemoglobin A1c. Now, this quote came directly from the American Diabetes Association Standards of Care. To be fair, the italics for emphasis are mine, not the ADA; but, I want to repeat that. These drugs should be considered independently of glucose control for people with cardiovascular disease or renal disease, and we'll talk a little bit more about that in just a moment.

I do think we should take an overall look at the evidence, and I don't want to go through every study one by one, but I do think we should look at some of the big meta-analysis.

For example, this one on cardiovascular death. We're looking at a variety of studies from the study that was published in 2020, and if we look at the totality of the evidence, we see this hazard ratio of 0.88; this 12% risk reduction of cardiovascular death with all these trials with GLP-1 receptor agonist.

But, what's important about this, and very important with all of the heart failure we see in people with type 2 diabetes, these drugs have no effect on heart failure, and this becomes important when we look at the guidelines for when to use and not use these drugs most efficiently.

DR. HIRSCH: Now, the GLP-1 receptor agonists continue to be developed for weight loss with or without diabetes. Let me show you the data with the high-dose semaglutide. This is the STEP 1 trial that was published in the New England Journal in 2021, and with a high-dose semaglutide, you see this approximate 16% change in body weight compared to the placebo after the 68 weeks of the trial. And in people with type 2 diabetes, we see also this tremendous weight loss with a high-dose semaglutide. It wasn't as much; it was a little under 10% of the weight which was lost, but it's still a significant amount of weight in this particular study.

So these drugs are effective not just for glucose control, not just for cardiovascular benefit, but also for weight loss. So, let's take a look at the most recent American Diabetes Association standard of care on how we should use these drugs. Well, the first-line therapy is still going to be metformin and comprehensive lifestyle management.

Now, I will tell you that there are rumblings amongst the experts should this still be first-line therapy, with all the benefits of metformin, it's cheap, it's effective. My personal belief is, yes, I don't think we're ready to change that from first-line therapy, and, indeed, that is what the current standard still is. But then, what the guidelines say is that if somebody has high risk or established atherosclerotic cardiovascular disease, CKD chronic kidney disease, or heart failure, then we're going to look at this algorithm a bit differently. We look at those individuals who have no ASCVD or indicators of high risk, those people who have a diagnosis of heart failure, and those individuals with a diagnosis of CKD.

If we look at the ASCVD and indicators of high risk for a moment, what the guidelines tell us if they have established ASCVD or they have indicators of high ASCVD risk, that is they're greater than 55 years old with coronary, carotid or lower extremity artery stenosis more than 50% or they have LVH, what the guidelines say is we should start with a GLP-1 receptor agonist with proven CVD benefit or an SGLT-2 inhibitor with proven CVD benefit.

No, there's nothing here about thiazolidinediones and sulfonylurea. And so forth, because this is what the evidence suggests, and again, independent of hemoglobin A1c. If they have heart failure, well, and in particular if they have an ejection fraction under 45%, in this situation, we are going to start based on the evidence on the SGLT-2 inhibitors that have proven benefit with this population and I need to point out as you saw in the previous slide, you would not use the GLP-1 receptor agonist here.

And, to me, what's the most exciting part of all of this as the data will continue to come out over the next few years is what we know and what is being studied with regards to CKD. If they do not have DKD with albuminuria, but rather if we come down here and they have CKD with an estimated GFR below 60 and thus had an increased risk of CV events, we can start with the GLP-1 receptor agonist with proven CVD benefit or an SGLT-2 inhibitor with proven CVD benefit, and we can start right away down here. And I should point out that there's no doubt about the SGLT-2 inhibitors with CKD. The GLP-1 receptor agonist data, the data on CKD is mostly secondary outcomes, but the primary outcome data for the kidney disease with a GLP-1 receptor agonist, those trials are now ongoing.

The more common scenario where you have albuminuria with the DKD, the first-line therapy based on the evidence with the albuminuria is an SGLT-2 inhibitor with primary evidence of reducing CKD progression. I should point out that dapagliflozin for example has this indication with or without diabetes. That's how good these drugs are with this DKD and albuminuria. An SGLT-2 inhibitor with evidence of reducing CKD progression and cardiovascular outcome trials.

Again, both of these, the SGLT-2 inhibitors are recommended. The GLP-1 receptor agonists are included here. In my view, we don't have a stronger data yet, but I do believe in the next few years, that will change. But, this is how the guidelines have changed over the past few years, very different than what we saw three, let alone five years ago.

We should think about the limitations of the GLP-1 receptor agonist compared to insulin therapy. As far as the former is concerned, of course, we know about the GI side effects; this is always the number one problem with these drugs, which is why we have to start slowly and increase the dose slowly, sometimes more slowly in some patients. There is still a pancreatitis contraindication, although the data for that I will acknowledge is actually quite weak, but it's still in the package insert. With these drugs, you have to give an injection or with the two newer drugs, the semaglutide and the dulaglutide; these injections are just once a week. And, of course, with any new drug, we have to worry about costs.

As far as insulin is concerned, there is obviously hypoglycemia, which we don't see with a GLP-1 receptor agonist unless it is used with insulin or with a sulfonylurea. We have the obvious issue of weight gain with insulin, which was literally observed a hundred years ago. We have the need for frequent glucose monitoring and, especially for individuals who need to take meal-time insulin, continuous glucose monitoring is the better way to go; I think everybody would agree with that, no matter if type 1 or if type 2; and certainly in the United States, Medicare agrees with that as those patients are approved for CGM from the CMS Guidelines. And insulin right now is cost. I am hoping that our US Congress and the Senate and the current bill that is currently being scrutinized will go through and, if I'm allowed to give this talk a year from now, cost will not be the big issue that it is now.

Now, another factor to consider is the cost of the GLP-1 receptor agonist and other non-insulin agents. Now, this came out in 2021, this is a very recent study, and I want you to look at the total payment to the pharmacy compared to the out-of-pocket yearly costs.

And if we look at the total payments to the pharmacy, you can see this huge spike up around 2014 and 2015, there is this huge spike up in the total payment and of all the drugs that are the most expensive, it's the GLP-1 you see over here in blue.

But if we look at the out-of-pocket yearly cost, and what it costs to those individuals who are insured, what you see is very little change going back all the way to 2006 to 2018, 2019. So, the out-of-pocket yearly costs have not been as bad as what the costs of these drugs actually are to the entire community and society. So, an increase in costs from the launch of the DPP-4 inhibitors, the GLP-1 receptor agonist and the SGLT-2 inhibitors were 88%, 78% and 37%, respectively.

We are focused on the GLP-1s, 78% increase in cost, but the out-of-pocket costs were relatively stable. And this was something that was unknown to me, especially from talking to patients who have been very vocal about the cost of the medication; but at least when you look at the entire US, at least those individuals insured, it wasn't as bad at least as I thought it was.

What about the GLP-1 receptor agonists? Why they make so much sense to use with basal insulin? Well, I talked about this a little bit earlier. We have beta cell and alpha cell dysfunction in type 2 diabetes, and the GLP-1 receptor agonist, as you recall, improves both beta cell and alpha cell function. It also obviously works on the stomach. It works on the brain. Whereas insulin, on the other hand, and we're going to really focus now on basal and not prandial insulin, it targets the liver to suppress hepatic glucose production. It does this by reducing gluconeogenesis and glycogenolysis. So, it turns the glucose production off, and these two have complementary actions, which is why many of us feel, especially for patients with high hemoglobin A1cs, using these drugs together make so much sense.

And in the United States, we actually do have two preparations that are fixed-dose GLP-1 insulin preparations; one is IGlarLixi, that's glargine nd lixisenatide; and the other is IDegLira, which is degludec and liraglutide; and let's just look at both of these drugs for a moment.

First, the registration studies, and this shouldn't be surprising to anybody that if you use two drugs instead of one drug, you're going to get a better A1c loss, and it doesn't matter if we use IDegLira or IGlarLixi. But what I'm not showing you here is the fact that when you give the GLP-1 receptor agonist on top of the basal insulin, you mitigate the weight gain you see with the basal insulin alone. So, again, this is generally an obese population, so there are multiple reasons why the combination of these two drugs makes so much sense.

As far as the IDegLira is concerned, 100 units of this preparation is 100 units of the long-acting insulin degludec, 3.6 mg of liraglutide, which we've had now for over a decade. It's recommended that for those individuals receiving basal insulin gets 16 units, and the reason why this dose is recommended is that this is the usual dose we start liraglutide with if we're using it alone, because this is really going to be the rate-limiting step, the GI side effect, so we're going to start at the rate-limiting effect of the liraglutide. And the recommendation is to titrate up by 2 units every three to four days, based on the

fingerstick, glucose testing or maybe the continuous glucose monitoring if they're using that.

So even though the side effect profile is more impacted by the liraglutide, we talk about this drug in terms of units as far as the degludec is concerned. The pen will deliver 10 units, so 10 units of degludec is 0.4 mg of liraglutide, this is the lowest dose; and the highest dose is 50 units, which is 50 units of the insulin and 1.8 mg of liraglutide, and that's not an accident. This is the highest dose of liraglutide we can use for type 2 diabetes if we're just using the drug by itself.

Now, IGlarLixi is the other one that is available commercially, and this is 100 units per mL or 33 mcg per mL of the lixisenatide, which is the GLP-1 receptor agonist. For those individuals who are taking less than 30 units a day, we would start at 15 units of the IGlarLixi, which is 5 mcg of the lixisenatide, the GLP-1 receptor agonist. And for those individuals who are on more than 30 units a day, for the IGlarLixi, it would be 10 mcg of the lixisenatide, and this is the highest dose you can go to, 60 units a day. And again, the data between these two combination drugs are very similar.

So, I think it's important that we all talk to patients about starting a GLP-1 receptor agonist and what they can expect because just writing them a prescription and not having this discussion, I don't feel, it's very clear to me, will reduce compliance, will reduce the ability for these patients to stay on these drugs. You need to obviously talk about advantages, about efficacy, about weight loss. It does lower blood pressures by the way. What we know about cardiovascular disease and the secondary renal endpoints in the trial, and again, in a few years, I think we'll be able to say primary renal endpoints, and you really need to talk about adverse events, the nausea, other GI adverse events, that these generally resolve over time. Some people may only be able to tolerate a lower dose; some people will have to go up more slowly than others; and, I've seen the other situation where patients start on a higher dose, sometimes it's even accident.

I had a very recent patient who didn't read the directions and started on 0.5 mg instead of 0.25 mg of the semaglutide and had no problems at all. So, there is extreme variability and this all needs to be discussed with the patient.

So, if you have a patient with an A1c above 10% on metformin monotherapy, with or without atherosclerotic cardiovascular disease or CKD, the toxicity of the hyperglycemia needs to be treated while awaiting other drugs to take effect, and I won't even mention, but I am mentioning obviously, the hassle of the pre-authorization, patients finding out when they get to the pharmacy they can't afford the medication and so many issues.

If I see a patient with an A1c of 12, I don't want to wait two months before they actually get their medication. And one of the reasons for that is this old study where from the UKPDS where you see this rising risk of risk with microvascular complications, but if you look at the risk of myocardial infarction, you flatten out at an A1c of about 9.5%. And if I have somebody at 10%, 11%, 12%, I just don't want to wait. And so, why not just start basal insulin or even better yet, basal insulin with a GLP-1 receptor agonist while on the steep part of this curve and avoid the clinical inertia that many of us see in our practices every day.

And so, last year, my colleague, Dr. Gaudiani and I, we actually wrote a commentary in JAMA and we believe that even for A1cs in the 9% and 9.5% range or higher, it is not unreasonable to consider basal insulin or basal insulin with a GLP-1 receptor agonist when you have blood sugars this high. I don't think there's any problem with that at all.

So let's get into more of the details. First about basal insulin. The primary role of endogenous basal insulin is to fine tune lipolysis and glucose production from the liver as I keep mentioning in the fasting state, especially overnight, while maintaining sufficient glucose for brain function. That's what basal insulin does. Whether it's exogenous or endogenous, think basal insulin, think the liver. The goal of exogenous insulin with severe insulin deficiency, what we are trying to do is recreate constant low levels of insulin overnight and between meals which with the correct dose will maintain euglycemia for 24 hours in the fasting state. That's the goal.

And how well do we do in achieving that? Well, that's when we talk about how do you know what the correct dose of basal insulin is? I know when glargine was first introduced in the United States in 2001, the goal was fix fasting first, and there's nothing wrong generally with that, but there are some caveats with that I want to show you. Traditionally, with somebody with severe insulin deficiency, especially somebody with type 1 diabetes, we would say 50%, 50% prandial insulin. That often doesn't happen, especially with the GLP-1 receptor agonist now because we often don't need 50% prandial and, in fact, there are many situations we don't need any prandial insulin with the GLP-1 receptor agonist.

So, what about type 2 diabetes? How do we dose basal insulin? Well, something that I read about and I've been a fan of, and what I teach all of our fellows here in Seattle, is the BeAM factor; that's the Be stands for bedtime, the AM is AM glucose, and pretty much every patient, I'm looking at the BeAM factor, type 1 or type 2 diabetes. So, a BeAM factor is considered positive if the bedtime glucose is higher than the morning glucose; that's the majority of patients.

So, if the bedtime glucose is 200 and the average fasting glucose is 100, the BeAM factor is 100; it's 200 minus 100. Okay, that's a positive one. A negative one, which is much less common is the bedtime glucose is lower than the morning glucose. So, there is not enough basal insulin or the liver is overproducing glucose. So, here, if you have an average glucose at bedtime of 120 and an average fasting glucose of 180, that's a delta of 60, but it's going in the opposite direction; so that's a negative BeAM score, much less common, but we see it.

Well, let's focus now on type 2 diabetes and the BeAM scores. Adding basal insulin in type 2 diabetes. So, putting these together, we're dealing with a lot of patients, close to 2,000. And when we look at these patients, we look at the baseline BeAM score and we look at the Week 24 BeAM score, we can see that we have a BeAM score of 60, whether we look at the initial exploratory analysis or the main study, a BeAM score of 60. So, that's a difference of 60 from the higher blood sugar at bedtime compared to the lower blood sugar in the morning, but it doesn't tell us if the bedtime blood sugar was 200, if it was 240, if it was 160; we don't know. We just know that the difference from this is 60.

So, a BeAM of 60 is due to the lower fasting without a change in bedtime glucose; and, this is just with basal insulin, and the whole point is how do we know when these patients are overbasalized is what we call it, and this is really the key point of this discussion. So going back to these same data, the higher the BeAM, the higher the A1c, and the higher the contribution of post-prandial hyperglycemia. And you can see, as the A1cs go up here, you have these higher BeAM scores that go quite high. So the higher the BeAM score, the higher the contribution of the post-prandial hyperglycemia, because none of these patients were receiving prandial insulin. And so, those with the highest A1cs, they needed some basal insulin, prandial insulin I should say, so they were overbasalized.

But it gets more interesting. If you draw a line here at 60, and this is my line, not their line, but I just drew the line here at 60, look what you see. If you draw a BeAM score at 60, you don't see A1cs under 7%. If the BeAM is over 60, that means you have so much post-prandial hyperglycemia, your BeAM score is going to be over 60, and the reason is you're using basal insulin to control prandial glycemia.

That's what happens when you have a BeAM above 60. And in fact, I would like a BeAM even lower than 60, but this is the data, so this is really one of the key points, I think, of this entire discussion.

In individuals with type 2 diabetes with basal insulin alone, it appears that a BeAM level above 60 is associated with A1cs above 7. Should the goal in type 2 diabetes be based on basal insulin, a BeAM less than 60? I think yes, as a minimum goal, because if you have a BeAM of 70 or 80, you need to do something else; whether it's mealtime insulin, whether it's a GLP-1 receptor agonist, whether it is an SGLT-2 inhibitor, we didn't have all these choices before, but you should not have BeAM scores above 60; that's the bottom line for this discussion.

Let's talk about basal insulins now. I think we would all agree they're not all the same. We use NPH insulin occasionally in type 1 diabetes for multiple injection patients with a severe dawn phenomenon. We use it in the morning for steroids; it works very well in that situation with all people whether they have type 2 diabetes, prediabetes, you get a big slug of prednisone in the morning, morning NPH works very well. But the problem with NPH if you use it typically in type 1 or type 2 diabetes, you see more nocturnal hypoglycemia because of that well-known peak.

With U100 glargine, this is still the most common basal insulin used in the world, and I want to point out that all of these insulin analogs just here in the fall of 2021 were put on the World Health Organization essential medicine list, meaning it was decided by the World Health Organization that all of these long-acting analogs should be considered essential medications in low and mid-income countries. Many of these countries that have difficulty in getting these insulins, hopefully that will change.

We now have U300 glargine here in the US, and we have insulin degludec, which we mentioned earlier here in the US. And what's really important to know is these insulins are not all the same. This is the same dose of insulin, the red being degludec, the blue being glargine, and this is looking at the CLAMP studies that is giving glucose to keep the blood sugars stable, and you can see that these insulins are quite different.

What you can also see looking at U100 glargine versus U300 glargine, again, looking at this glucose infusion rate in the CLAMP, it is different, and that is, specifically, the U300 glargine lasts longer. But here is the problem. The problem and, as a clinician, you need to know this, this is one insulin where a unit of insulin is not a unit of insulin. You need 15% more insulin with the U300 glargine than the U100 glargine.

What about glargine versus degludec and U300 glagine? Well, here's sort of the bottom line from a lot of data. The degludec consistently shows less hypoglycemia, both in type 2 and type 1 diabetes. The U300 glargine some, but not all, studies with less hypoglycemia, especially in type 1 diabetes; in type 2 diabetes, the data are more clear. The bottom line, in my view, is that both degludec and U300 glargine are better basal insulins than U100 glargine based on the hypoglycemia data. As a rule of thumb, you should get them if you can, especially for type 1 diabetes where we see so much more hypoglycemia than in the type 2 population.

Now, we see a lot of hypoglycemia in the type 2 when you look at the numbers of people with type 2 diabetes; but for individual patients, it's the type 1s where we see much more hypoglycemia. And so, this has just been a by-product of the innovation in insulin therapy over the last decade or so, and what we will be seeing soon, and the data has been published on this, is weekly insulin. There are two companies right now making weekly basal insulin.

Let's move for a moment to prandial insulin. Prandial, again, is not the liver so much, it's mostly skeletal muscle. So that's what you should think about. Liver is basal insulin; muscle is mealtime insulin. And it's important to know the difference when we talk about PK versus PD; this happens to be lispro, our first rapid-acting insulin analog. The PK is just looking at the insulin levels; and this is what most people think about. I know this is what my fellows think about. This is what's on the package insert. You see, this peak of the lispro in an hour, and after three hours, it's almost gone; after four hours, it really is gone. This is compared to regular human insulin, which is a much longer duration of action. But I have to tell you, as a clinician, and certainly for our patients, I would argue this is the wrong graph to keep in mind when thinking about the activity of our mealtime insulins.

Instead, we should think about the PD, which is the pharmacodynamics, where we give a dose of insulin and then what we do is we give glucose, a glucose infusion to keep that blood sugar exactly at 100. This study happens to be insulin aspart by my friends in San Diego, and what they showed was that when you look at aspart, and lispro by the way is identical, what you see is you don't have this one hour peak, but it's much longer. It's really this plateau you see here at about two hours; because what has to happen is once the insulin finally gets into the blood, to the subcutaneous tissue, it then has to go find itself an insulin receptor on that muscle, it then has to bind to that insulin receptor, and all of these things have to happen inside of the cell to get that glucose into the cell, and that's exactly what you're seeing here in the green with aspart, and in the red with human regular insulin, which obviously is much longer, and you can see how long this tail of regular insulin lasts, which is why when all we had was NPH and regular insulin at dinner, why we saw so much hypoglycemia in the middle of the night.

Now, lag times, and, you know, we've been talking about this for a long time, and this is the amount of time between giving the insulin injection and eating. And these are type 1 studies, the first one with lispro, the second one with glulisine, these are both rapid-acting analogs, and what you can see is the longer you wait, the longest here being 30 minutes between giving the insulin and eating, the less of the post-prandial spike. And in fact, if you wait until 15 minutes after the meal, you have the greatest spike. And this is what a lot of our patients do; they eat and then they give their insulin and then they spike. We see the same general trend with the least amount of spike with the 20-minute wait between eating and the injection. So, we've been talking about this for years, and it's very important.

But, let's move to type 2 diabetes. We don't have as much data with type 2 diabetes. I know that I see with my patients on continuous glucose monitoring, and I see in many of these patients what we see in the type 1 population, but that is not consistent with the data in the literature. Let me show you. This was a study in type 2 diabetes using insulin aspart at two different lag times, 15 minutes and 30 minutes at one dose, and then 30 minutes at another dose, a higher dose, and what you see is no difference in the post-prandial blood sugars in these three arms of the study. Compared to placebo, of course, you do see the spike, but I will just point out this data about lag times is not as solidified in type 2 as it is in type 1 diabetes.

Now, this comes up a lot in type 2 diabetes, more so than in type 1. We want to get the insulin in faster. What tricks do we have? And I use this a lot on the inpatient service, when we have patients who need very high doses of insulin often due to steroids and their illness. And, this happens to be a type 1 study, but it's also true in type 2 diabetes. And this is a study using aspart and looking at giving either 18 units of insulin in one shot or two units of insulin in 9 shots. And all this is about is the surface area of 9 small depots of insulin compared to one larger depot of insulin, and what you see with the 9 small depots of insulin, greater surface area from these depots, you get a significantly faster rise in insulin levels and it doesn't last as long, which is actually what you want to see.

Now, we have an ultra-rapid-acting lispro. We have lispro. We have aspart. And now we have a fast-acting aspart, and this is again looking at what happens with just the insulin concentrations, these are not CLAMP studies, but what you see with these rapid-acting analogs, it doesn't look as impressive with the ultra-rapid-acting lispro or the rapid-acting aspart when you look at these graphs. But, down here, it's the same graphs, but the first hour is blown up, and what you see with these blown up first hours is that the rapid-acting insulins get in faster. Well, that's all well and good, but what does that do to the more important outcomes? Well, as far as post-prandial glucose is concerned, and this is the lispro-aabc, which is the ultra-rapid-acting lispro, what you see is a reduction in post-prandial glucose, that's obviously a good thing; but you don't see in this type 2 study any difference in A1c comparing the ultra-rapid-acting lispro compared to the usual lispro. It's really exactly the same, which in my mind is obviously disappointing because we would like faster rapid-acting insulins.

Now, we're talking about pharmacology of insulins and the GLP-1s, but I would say there's another important tool about after meal spikes that our patients need to know, and that's

the whole topic of exercise. There is a lot of research on this. It's not discussed enough. Post-meal exercise. No surprise. It reduces after meal spikes. Pre-meal exercise, this, to me, is the more important issue. It reduces both pre-meal and post-meal glucose levels. And the other thing about pre-meal versus post-meal exercise is that if you are using meal-time insulin and you exercise while that rapid-acting analog is spiking, you're more at risk of hypoglycemia if you just do the exercise post-meal where you're getting all of that calorie burn while that insulin is peaking. So, pre-meal exercise is a better way to go if there is an option.

So, I would like to conclude that GLP-1 receptor agonists have been a tremendous benefit to people with diabetes due to their ability to lower glucose and weight, in addition to what we have learned about cardiovascular disease outcomes and probable renal benefits. Although they can be expensive, and I showed you the data, they are the most expensive drugs in diabetes, the cost of these agents to those with insurance have actually been reasonable in terms of the out-of-pocket costs have not increased, at least based on that one study, which I found surprising but really interesting.

The GI side effects of these drugs are usually, but not always, manageable. We have a few patients, and I certainly have them, that they cannot tolerate these drugs at all. The good news is that is the exception and not the rule. Fixed ratio of the GLP-1 receptor agonists with basal insulin is an important tool to remember. It's in our armamentarium. I don't feel we use these drugs enough, but they make a lot of sense, especially with the high A1c patients.

Furthermore, there are many choices of basal insulin, all with slight differences, but these agents should be started sooner than they currently are with those with very high A1c levels. The BeAM scores which we talked about are an excellent tool to assess basal insulin dosing. Prandial insulin choices have increased over the years. And patients need to learn about the various pearls on how to best use these insulins including exercise.

In type 2 diabetes, dosing of prandial insulins does not need to be complex compared to type 1 diabetes and fixed doses with or without corrections often work well, they really do. So with that, I'd like to thank you for your attention, and I trust this has been helpful. Thank you again.

Part Two - Smart Pens in 2022 and Beyond

DR. HIRSCH: Hello again, my name is Irl Hirsch from University of Washington School of Medicine in Seattle and in this discussion, we're going to talk about Smart Pens in 2022 and moving forward.

Now, there's been an interesting evolution of Smart Pens to 2021. Right now in late 2021 and into 2022, we have two FDA-approved Smart Insulin Pens.

Now, what do we mean when we talk about Smart Pens? Well, let's talk about the core components of Smart Insulin Pens. First, from the Pen, we have to have some sort of wireless connectivity between the pen, the app, and a continuous glucose monitor.

Ideally, it's a CGM. You can use a Smart Pen without a CGM, but it really makes the Smart Pen, in my view, so much more helpful.

I had a patient the other day who was not using CGM and this patient just loved her Smart Pen because it helped her dose her insulin much better than she could on her own but the CGM as will show you makes this much more helpful.

The other core components include a digital dose capture between the pen and the application on the smart phone, integration with a bolus calculator, and in the future where we we're going with this is integration with AI for basic and trend arrow dosing adjustments. So, for somebody who is using it continuous glucose monitor, if the pen recommends to give 5 units of insulin but there is an arrow going up, meaning the blood sugar is rising, the pen will make the recommendation, the suggestion to give a higher dose of insulin. This is the promise of the Smart Pens.

In my opinion, the inability of clinicians like us to see multiple daily injection dosing has been our greatest gap in insulin management. For those of you who see a lot of insulin pump patients, watching the patients bolus, how they bolus, how they get the information for their bolus with an insulin pump is great, but until we have a Smart Pen, the only way to know what patients were really doing with their insulin was if they wrote it down and very few people including me have time to go through those type of log books with every single patient.

Smart Insulin Pens allow both patients and providers to see this granularity of insulin dosing, again, only seen previously with pumps. You can see missed doses, you can see late doses and what happens with the calculator on the app on the phone is these doses are calculated to avoid stacking of insulin and therefore avoiding hypoglycemia. The access of data on the download to allow both the clinician and the patient to see the data together and promote shared decision making for appropriate insulin dosing and adjustments.

And now that we have access to Smart Pens and I have a lot of my patients using these, who are on multiple injections, these comes up with almost every patient, where we will make decisions together what we should do with the mealtime insulin dosing based on the data we see in the download. So, right now, we have two connected pen options in the United State. We have the InPen from Medtronic, which connects with the Medtronic Guardian Connect or the Dexcom G6 and we also have the BigFoot Unity. The BigFoot Unity connects with the Libre 2.

Both of these are now on the market and we have three different ways patients can dose insulin and this really can be individualized and I find it and this is the example of the companion impact to be extremely helpful. Many of my patients especially the type 1s, but not all the type 1s, they're used to carbohydrate counting. So, what they do in the app is they put the glucose in the app from their blood sugar, usually on their CGM. They then put the amount of carbs they're going to eat and then you get a calculation on how much insulin is recommended.

But you can do meal estimation where you can have low, medium, or high carb for each meal. This is all programmed into the app. You get the same dose and the other thing that is very common are fixed doses. Especially with some of our type 2 patients where you have a fixed dose for breakfast, lunch, and dinner, but what the patient can do is put the glucose level in, so you have a correction factor to give more or ever less insulin for a low blood sugar but the patient sees what the calculator recommends with the hope of having more uniformity and standardization on what they're doing with their mealtime insulin.

So this does reduce the fear of hypoglycemia because it does help with reducing insulin stacking, it improves confidence in the accuracy of their insulin bolus doses. And I should say, with regards to accuracy, what's very nice about the Companion InPen is the fact that in insulin-sensitive patients, you can give half units of insulin and patients really like this. I mean they really like this; my type 1 patients in particular. But I want to point out, I do use this also for type 2 diabetes.

So, this is the dashboard of the InPen and you can see the ambulatory glucose profile. You can see the average glucose. You can see that the time and range that we use with continuous glucose monitoring in this patient is 62%. The time of below range is 1% in this example. You can see this patient is using the calculator in 96% of the boluses and you can also see what's happening with the amount of long-acting and short-acting insulin and what's to me extremely important, it's very easy to see what the doses are.

This is a carb-counting patient and you can see that in this patient who's counting carbs that they're getting more insulin with 1:10 ratio here for dinner. They're getting the same correction dose of 1 unit for every 40 throughout the day. You can also see the duration of action of insulin action here. All of this is programmed in to the calculator when the calculator is set up.

Now, previously, we talked about the BeAM score and that's all this is doing. It's calculating the BeAM score for you but it's actually doing it in a very cool way because if a patient gives correction dose or meal-time insulin at that time, it doesn't count it. So, what you see here is that in the last 14 days, two of these days were not counted due to bedtime rapid-acting insulin and so when looking at the basal insulin, it counted 12 of the 14 days and you can see the BeAM score here of -22. It went from 179 to 157. It went down by 22 points.

Now, how to help patients with mealtime insulin? Let me give you an example. This is a 60-year-old patient who is a Math teacher. She happens to have type 1 diabetes, but she doesn't do all that great with her diabetes. Her A1c is usually in the high 7s and the low 8s. And the question is why? She has been on multiple injections for years. Well, it's really easy to tell why.

First of all, this is the basal insulin. She is on 9 units of glargine twice a day. This is the prandial insulin and when you see the checkmark, the checkmark means they are giving the amount of insulin that is recommended by the calculator. But look what happened here, she gave 3-1/2 units of insulin for a 40-gram low. She actually got low, she treated the low. I would say she didn't over treat it. She got her blood sugar here in the middle

of the target but here she ate. She gave her insulin. Looks like she ate lunch and then she gave her insulin at 1. Her blood sugar was already 281. She gave the dose recommended and her blood sugar came way down here into the lower end of the target.

Well, that's good but again, look what happened here with this Math teacher. She ate here, she gave her insulin here for her 45-gram low. She gave her insulin after she ate; doesn't work especially for type 1 diabetes. She then gave the amount of insulin recommended by her calculator. She then had 25 grams right here. She did what it said and she got low again, doing what it said even though the calculator will take insulin away to prevent insulin stacking.

So, we can make some pretty interesting recommendations when we see what she's done. And what I can say is, her mealtime insulin appears too aggressive. She's getting too many lows and this forces her to give insulin late. So when talking to her, the reason why she's doing this is that she knows she's getting too much mealtime insulin and it's been like this for her for years. When we set this app up for her, we were just doing what she was always doing but this is why she has not done well with her diabetes. The problem was, I couldn't see it until now. I could not see what she was doing.

Here's another one, an obese person BMI 33 on glargine and lispro and you can see what is happening here. The food, the basal insulin, the food, the prandial insulin, and you can see it again here. So, let's walk our way through this. First of all, it looks like the basal insulin here is okay. There was a correction dose given before bed but the blood sugars stay pretty much the same overnight. It just wasn't enough correction dose. But here you can see, it's pretty good.

So, the basal appears good, but look what happens. Again, this individual is late for their insulin. Here, they gave their insulin on time, things actually worked well. Here they ate, blood sugar went up. So, this is the prandial insulin often but the correction dose insulin seems to be working fine.

This is an interesting one. This is a 35-year-old woman with type 2 diabetes for five years, severe insulin resistance, and the question is, is this gastroparesis, is this polycystic ovarian disease, is this hypothyroidism, is it a prolactin-secreting adenoma, or is it a marijuana smoker? You can see the average is 165. The time and range isn't horrible at 60%. But what you see is this huge, huge spike overnight while she is asleep and what the real issue is here is could this be gastroparesis? Well, I guess it could be but if you do a history, what you found out is at least here in Washington State, we're seeing more of these. The right answer here is E.

This is somebody who is smoking a lot of marijuana at night and she gets very, very hungry and her blood sugars spike because she is not giving enough insulin. And I can see that. I know exactly what's going on. But you have to ask her on it in a very diplomatic, nonjudgmental way.

So, we can conclude that Smart Pens fill the gap with insulin dosing and allows clinicians to help their patients not possible before. These pens also help patients remember if they

have taken their insulin or not and most importantly, to help prevent insulin stacking to prevent hypoglycemia.

These tools will become a common part of diabetes management in the next few years. We have two of these pens on the market, but there will be more pens coming on the market within the next few years and I would suggest it would be good to get familiar with them now. So with that, I hope this was helpful and thank you very much.

Part Three – Patient Cases

DR. HIRSCH: Hello again. This is Irl Hirsch from the University of Washington and we are now going to talk about a patient case, advanced glycemic management.

So, here is the case. You are seeing a new patient, a 54-year-old woman with five years of type 2 diabetes who has not seen a physician in two years because of the pandemic. And we are seeing a lot of these types of patients in our clinic. She takes metformin monotherapy. She has no cardiovascular disease but she takes atorvastatin and lisinopril for hypercholesterolemia and hypertension. Her father died from cardiovascular disease and he had an MI at the age of 61. Important point. Her BMI is 36. A more important point. She has gained 12 pounds and on metformin monotherapy over the pandemic, her A1c has had a huge increase from 7.1% to 11.2%.

So, here's the question and these are the different options. What do you want to do? Do you want to add dulaglutide? Do you want to add long-acting exenatide? Do you want to add bedtime glargine? Do you want to add bedtime glargine with mealtime lispro? Or do you want to add the combination of degludec and liraglutide at the same time?

So, let's think about this. We have an obese woman with a strong family history of heart disease. She herself doesn't have cardiovascular disease but she has this very high A1c and I think the first thing that goes without saying and I don't think we give it enough time for discussion is the entire topic of what's going on with the diet and the exercise? And there needs to be a discussion when you are talking to her. But after having that discussion, we have a very high, in my view, scary A1c.

We're not going to get to where we want to with A1c certainly by adding a GLP1 receptor agonist by itself. And as a matter of fact, even though we have this high BMI and we could expect weight gain with glargine, we know from the treat to target trial which was published 20 years ago now that glargine by itself with an A1c above 8.6 and certainly above 9. You're not going to get even close to target A1c.

Prior to that GLP1 receptor agonist, this would have been the right answer. The problem with this is the complexity, the need for very frequent glucose testing, the issue of quality of life on the patient, the multiple injections, that would have been the way to go. But now that we have all of our experience and we have these newer GLP1 receptor agonist, I would argue a of these answers and that A1c, a combination degludec and liraglutide is the best answer here.

Now, if you're going to tell me that's really high A1c, the patient doesn't have an insurance that will cover a GLP1 and in fact, I'm not even sure we can afford the glargine, you can always use basal insulin. We now have a biosimilar glargine, there are other options but for the answers in this question, E is the right answer.

Now, let's move forward. So, she was started on the combination IDegLira and after six months, her A1c actually did improve from 11.2% to 8.3%, now at the highest dose, which is 50 of the degludec, 1.8 of the liraglutide. Her BMI came down a little bit. She is still obese obviously.

The fasting and premeal glucose levels are generally in the low-to-mid-100s, but after eating, she really spikes quite high. So, what is the best option now? Is it mealtime lispro? Is it pioglitazone? Is it dapagliflozin? Is it change in the liraglutide to semaglutide and take the degludec separately? Or is it to invest in a pharmaceutical mutual fund?

Well, maybe you think the right answer is E. I'm not going to even go there. There would be nothing wrong with using lispro. Pioglitazone, I would not use with that high BMI of 34. So, that is clearly wrong. I actually believe the right answer here and it is a shame this is virtual because maybe not everybody would agree with me, I would use C, dapagliflozin because what I'm going to do with that is I'm going to reduce everything down.

I may have to be a little concerned about watching the fasting glucose levels since they're now in the low to mid-100s. But if I can take this mid to high 200s to high 100s and occasional low 200s, I think we will be doing her a great service. If you're going to tell me you're comfortable with prandial insulin, you want to do that, you have the time to deal with prandial insulin when she comes in with each appointment, it's hard for me to argue with that but I think the other thing about dapagliflozin is the further weight loss with the high BMI, not to mention her high risk of CVD and potentially renal disease. So, I like C best for this one.

So, concluding, the same patient wants to start an exercise program of fast walks alternating with swimming. What is the best time of day for her exercise? Would it be in the morning before she eats breakfast? Immediately after dinner when her blood sugars are the highest? In the middle of the afternoon? Or at bedtime? And based on the data, assuming she is not waking up with very low blood sugars, it's really in the morning before breakfast because there you have effectively exercised throughout the morning and maybe even into the afternoon. Whereas if you do it after dinner, that will help you but it won't help you at the other times of the day when she may have spiking blood sugars, the same in the middle of the afternoon. And bedtime, I would not recommend exercise then due to my concerns of nocturnal hypoglycemia. So with that being said, again, I hope this was helpful and thank you very much.