Insulin Management

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Thank you, and I want to thank the Division of Diabetes Treatment and Prevention for inviting me to speak today and to Jan and Wendy for the facilitation and hosting. My name is Marie Russell. I am an internist by training. I am currently the Deputy Chief Medical Officer of the Phoenix Area. I'm currently serving as the Acting Chief Medical Officer for the Phoenix Area.

Just a little bit on my background. I actually have been in the Indian Health Service now for about 12 years. I spent 11 of those years at the Phoenix Indian Medical Center helping to manage their diabetes program and their diabetes grant there. I've been here at the Phoenix Area Office for about one year now.

The topic that I've been asked to cover today is insulin management. And I think if many of you were able to catch Chris' talk a couple of weeks ago on diabetes medication. He gave an excellent overview of the medications that we have in our armamentarium to treat diabetes. He covered a little bit about one of the newest long-acting insulins, which I am not going to cover today. But overall, he just gave a fantastic presentation on the oral agents and some of the newer non-insulin injectables.

What I plan to cover today are some important studies to kind of give frame and reference for why we try to control blood sugars in diabetes and frequently why insulin might be used. I want to cover the general approach to hyperglycemia management. Often times, we think it's quite confusing and complicated. I'll show you some algorithms that really do point to the fact that it can be quite confusing and complicated, but if you look at it from a patient-centered approach and logical approach, I think that we can boil it down to things that work for our patients ultimately to improve their care.

We'll talk briefly about the pathophysiology of insulin. We'll go through the different types of insulin, remind us of some of the side-effects of insulin and then discuss some insulin regimens. Then lastly, we will end with three different case studies that hopefully will help to illustrate how we can utilize insulin in our management of our patients, and then one specific case of which we want to be cognizant of what we do for our patients when they're on insulin.

The first thing that I want to start with is to remind us a little bit about why we have goals and why we treat patients, and I hearken back to the UKPDS trial which really was the largest and longest study that we've had on Type 2 diabetic patients that had been performed at the time. Essentially, what UKPDS showed us was that in terms of microvascular disease, retinopathy, nephropathy, and neuropathy that by lowering blood glucose levels for folks who have Type 2 diabetes with some intensive therapy, achieving maybe a goal of hemoglobin of 7% versus 7.9% that we were able to decrease the microvascular complication rate. That was seen that there was a continuous relationship between the risks of the microvascular complications for every percentage point decrease in a hemoglobin A1C.

So, there is benefit from going from a 10 to a 9, or a 9 to an 8; and that for instance from a 9 to an 8, there was a 35% reduction in the risk of complications. Really, what they showed as well in UKPDS was that there wasn't a significant effect of lowering of the blood glucose on cardiovascular

complications, though they saw a 16% reduction, it was not considered statistically significant. But we do know that the lowering of blood sugars really is important in our folks for both microvascular and macrovascular complications.

That caused folks to try to treat people fairly aggressively and lower their blood sugars. Then, ACCORD came along, and ACCORD said, it was actually a trial designed to determine if lower was better. So, a strategy of targeting normal hemoglobin levels down to 6, and if that would reduce the risk of serious cardiovascular events in middle-aged and elderly people who had Type 2 diabetes.

They needed to start with an A1C greater than 7.5 at that time. The importance of this was the fact that the trial had to be terminated early at 3.5 years because they didn't find a significant reduction in cardiovascular events in the intensive group but they did find a higher mortality. This is real important because as they looked at it they said, and I know that this is maybe a little small and hard to see, this slide shows actually a continuation of an additional 17 months. So the trial was terminated, the intensive arm was terminated to 3.5 years but this is actually a graph showing in this middle panel that they actually followed these folks out to five years. The importance of this was that they showed that there actually persisted even in those folks, at the time when they terminated the aggressive group, they actually allowed their A1C's to come back up.

After the intensive intervention was terminated, the median A1C for the intensive group rose from a 6.4 to a 7.2. But the important part that they found was that there still persisted even at the five years an increased mortality in the folks that have been treated to tighter targets to begin with.

That really is important as we talk about how we use insulin and what we want to do to treat folks. So, really, this is a great slide that I think helps us sort of approach how we manage hyperglycemia. I think that it's very important because typically, when we get to insulin, we're looking to really hopefully be, in many times in a more stringent control. Sometimes, we need to use it even to get good control.

But if you look at this, what it really breaks it down to is this issue of whether you're trying to be more stringent in your glycemic control or less stringent. There are some things that I think that we as clinicians and as patients need to consider as we approach our patients with insulin treatment or diabetes treatment in general. And that is, what is the patient's attitude and the expected treatment effort? So, if you have a highly motivated individual who is adherent and has excellent self-management capability, then you could probably get away with the more stringent diabetes care regimen, and maybe this is somebody who really would do very well on insulin and specifically in multi-daily dosing of insulin.

If you've got someone who is less motivated and not adherent, then maybe you need to be a little less stringent both in your management attempts as well as your glycemic control. I always tell people, I mean, I can put people on hundreds of units of insulin but if they're actually not compliant and not going to use it, it doesn't matter how much insulin or medications that we're going to use.

You also need to consider as you're approaching your patient, what are the risks potentially associated with hypoglycemia are. As we know, insulin has a risk of having hypoglycemia. Some of the oral agents don't. So there are some individuals, especially older individuals as we'll see, that it's not in their best interests to trigger hypoglycemic episodes. Maybe that's something that you need to consider as you are determining your treatment plan as to what the risk associated with hypoglycemia would be for that patient.

Disease durations, so one of the things that came out of ACCORD was it was a study that looked at older folks, middle-aged to elderly folks and so part of the discussion that came out of ACCORD was really the risk was for the older individuals, that perhaps more stringent targets are more appropriate for younger individuals who have had lesser disease duration. Again, life expectancy, the elderly don't do as well with the tighter control.

Then, the other issue is established vascular complications. So, those folks that have established cardiovascular disease who we think sometimes we want to be overly aggressive in, do not do so well with being overly aggressive. So that's one thing that we need to take into consideration.

And then as we design our approach to hyperglycemia management, we need take into consideration resources and the support system. As we'll talk a little bit about the cost of different types of insulin, as well as some of the other newer diabetes medications, the cost of those are an issue. Sometimes some of those medications are on our formulary, some are not. Some folks have the ability to pay for them, sometimes they don't.

Again, as we talk about insulin and potentially things like multi-daily dosing, what's the support system that goes along with that? Because that can be quite complex and we need to make sure that the patients can handle the regimens that we're going to be putting them on.

Again, when we look at glycemic management and definitely insulin management, not one size will fit all. Again, when you think of your glycemic targets, you need to think of the duration of which the patient had diabetes. What is their age? Do they have established cardiovascular disease? What is their readiness for a change? Are they going to be willing to give themselves an injection, multiple injections, doing Accu-Checks or blood glucose checks several times a day? Are they really willing to invest in what needs to be done? Because, again, it needs to be a team approach to how we are delivering this care and we need to make sure that everybody's on the same page.

Consideration of a patient's predisposition to hypoglycemia, the important comorbidities, and then as we discussed what resources they have. There was an interesting article that actually just came out in Diabetes Care this month and basically, it talked about the clinical inertia for treatment in people with Type 2 diabetes. It was a retrospective study that was done in the U.K. that looked at about 80,000 people. So, what's the A, B, and C stand for is, 1A, is one oral agent, B is two oral agents, and three is more than or three oral agents or insulin.

What this shows is that the probability of patients with poor glycemic control taking the one, two, or three oral agents. The probability of them intensifying treatment at the end of follow-up was about 21% to 43% of people at the end of seven years who were on either one or two agents, or only about 5% to 12% of folks who are on insulin. The mean A1C at the time of intensification of additional oral agents or insulin for people taking the one, two or three, was a mean A1C of 8.7%, 9.1%, or 9.7% depending upon whether they were on one, two, or three agents.

Again, the table that came out of that article is a little bit hard to see but what you'll see is that for folks that have, and this table breaks it down to folks who started with the greater than 7, greater than 7.5, or greater than 8, and you'll see the number whether they were on one, two, or three oral agents. What is most striking is, this column where you'll see that, for instance, median time from the above A1C cutoff to intensification with additional oral agents was 2.9 years, 1.9 years, or 1.6 years depending upon their A1C and the number of oral agents. Patients with treatment intensified with insulin, it was an average time of 7.2 years, 7.1 years, or 6.9 years.

What this article really showed us is that that we as a medical community and as our patients really tolerate high A1C's for quite a while and we don't do a great job about intensifying our regimens. I think that there are many reasons for that and a lot of it comes down to the fact of resources, and team management, and patient care. But as we talk about antihyperglycemic therapy and we talk about medications, I always like to remind people that before we even get to medications, we really do need to talk about therapeutic options. Again, we can give people a lot of medications, give people a lot of insulin, but ultimately, we also want to be able to coach folks on lifestyle, on what's the weight optimization is, what's a healthy diet, what's their activity level.

Again, as providers, it really takes a team approach in order to do this. So, it takes the patients, it takes the diabetes educators, it takes the dietitians, it takes the pharmacists, it takes the providers, it takes the family members, and it really takes the community that we want to engage in how we're delivering care to the diabetics and how we're controlling their glycemic management.

Just a quick slide on again the pathophysiology of Type 2 diabetes. Our medication regimens are essentially focused on the different pathophysiological defects that occur. Specifically, of course with insulin, it's the fact that the pancreas ultimately decreases its output of insulin and then our tissues increase the resistance of insulin or to the insulin requiring more insulin. We know that our body will produce sugar regardless of what we do and so we need a mechanism to control that.

We have various societies and organizations that give us algorithms in order to treat diabetes. This first algorithm that I put up is the American Diabetes Association Antihyperglycemic Therapy Algorithm, published back in June of 2012. It goes through again, initial drug therapy, two-drug combination, three-drug combination, and then normal complex insulin strategies. I bring your attention to the fact that they do start talking about basal insulin as part of the two-drug combination strategy. And then, again, as it gets more complex and they talk about failure; adjusting every three months, adding additional agents and that sort of thing.

Often times, we look at these algorithms as providers and it's confusing. There are a lot of choices and basically it's also given up to us to decide what we want to do. There's not a lot of evidence-based literature out there past metformin as to what is the next best step. There is currently a study that is being conducted, GRADE, that is trying to answer that question as to what in combination with metformin is going to be the best next step in helping people improve their outcomes. And so that trial will be forthcoming.

But, in the meantime, what we're left with are algorithms that really leave a lot to choice. There are a lot of choices out there and not all of them are necessarily the appropriate ones for all of our patients. And I would hearken back to some of the issues that we talked about earlier, which is folks' readiness to change, resources, and I mean really what you're trying to achieve with that glycemic control.

The American Association of Clinical Endocrinologists, this is their algorithm. They actually talk about different entry points for whether you want to start with monotherapy, dual therapy, triple therapy, and then entry of A1C greater than 9. When this came out, and this just came out in the past year, there was a lot of buzz in the community because even the providers can't understand this algorithm. Again, we tend to make things very complicated because there are many choices. As Chris talked about last time, a lot of the choices that are out there don't necessarily have that great of an impact on our diabetic control, may be costly, and may not be the right choices for our patients.

I bring to you now what the IHS has done in terms of their hyperglycemic or antihyperglycemic algorithm. To me, I actually love this algorithm. I think it's very simple. I think it's based in our reality which is one of the limited resources. I think it's a great place to start and it's not to discourage folks from looking at the ADA or the AACE algorithm, I think it's great to understand it and know it, but I do encourage you to go to the IHS website if you're looking for something that's very simple and really based in the reality of what works in our system.

Here, if you look at it, I would show that really what they'll talk about is insulin therapy if any of the following exist. So, if your fasting blood glucose is greater than 250, if your glucose is greater than 300. If your A1C is above 10 then why don't you consider just starting with insulin? If you've got active liver disease or alcohol abuse that may be contraindications for some of the other oral agents. Ketonuria or weight loss. Again, it's just a great resource that we have within our system and I encourage folks to take a look at that.

What are we trying to do with insulin? Well, ultimately, we're trying to duplicate how the pancreas works in releasing insulin for someone who is not a diabetic. What does that look like? This is important because we need to understand the variations of the insulin excretion and why we need it. One of the things that we need to always remember and one of the case studies will cover this which is we have a basal need for insulin. So, regardless of whether we eat or not, our body is producing insulin because our body is also producing sugar, and the sugar needs to get controlled.

Then, as we eat, our body is excreting more or giving out insulin to cover the food that we eat and so we tend to have valleys and peaks throughout the day where we have more insulin going back to our basal level depending upon what we eat, again increasing and decreasing.

When we try to design or when we try to administer insulin to our patients, ultimately, where we'd love to get to, is just a replication of what our normal body does. So, we need to understand what that is and understand the requirements as we look to our patients for the regimen. As we look toward what or how to utilize insulin in our patients and what possible insulin there are, again, this is a card from the IHS DDTP site and it goes through the different types of insulins. We have basal insulin which again is that insulin that's going to cover our patient for their basic baseline needs. There's intermediate and long-acting insulin.

One of the mainstays is NPH. NPH is on our formularies, great drug. It has an onset of about one to three hours, peaks in about 6 to 10 hours, lasts somewhere in our body 12 to 20 hours. The issue with NPH is the one that it is a twice daily drug, if you're trying to completely cover or make sure that we are covering the physiologic basis of our insulin secretion.

We have newer agents that are long-acting insulin, Levemir or detemir, and Levemir and glargine. The onsets of these insulins are a little bit quicker and they are more stable. I'll show you a graph in a sec. But they are considered, or we like to talk about them as being peakless insulins. They don't have the up and down. I'll show you the graph in a sec on NPH where obviously, as it peaks and it goes down you're going to have some lack of coverage and some other things.

Levemir and glargine, I think the issues here, and I'll talk about some PIMC data on Levemir, is glargine really can be used to the once a day administration. Levemir, not so much. It says 12 to 24 hours, certainly some experience that we've had really suggests that it's really better off as a twice daily administered drug.

Then, you have our shorter-acting insulins. We have our mainstay, regular, which has been around for awhile. We know that the onset of action there is 30 to 60 minutes, so it takes a little while. This takes some thought in our patients because they have to know when they're going to eat because they need to take it about 30 minutes before that they're going to eat in order to cover those spikes that we're going to see and would be how our pancreas would have reacted. Regular insulin peaks in about one to two hours, it hangs around for about five to eight hours. This sometimes can be an issue depending upon how people are using it and may lead to some issues referred to as stacking.

So, as you give multiple daily dosing, you may end up having a little bit more insulin left over and ultimately you're going to stack that as you go through the day. Sometimes, that can lead to some hypoglycemia.

We've got newer agents on the short-acting that are a little bit easier to use and a little bit friendlier for our patients because they can use them right at the time that they're eating. So, Aspart, Lispro, and then a newer or one that we don't use so often which is the Apidra. These onset at about 15 minutes to 30 minutes, peaks at about 30 minutes to 90 minutes, and it lasts a little bit shorter. It's a little more like how our pancreas would normally output the insulin.

Then you have premixed insulin, the 70/30s of the world. I'll give you my two cents on premixed insulins now, which is I don't like them. They do have some use and so folks tend to use them for people that may need the combination of regular or shorter-acting and basal control. They're really hard to manipulate because they're mixed. Often times you need to actually adjust the basal or you need to adjust the bolus insulin, but you don't need to adjust both of them at the same time.

Those tend to be a little harder. I know, sometimes people use them when they just have noncompliant patients and they want to get the patient on something, but I'm not a real fan of them. I think a lot of times, folks get into trouble with these and they'll end up with some hypoglycemia.

Here's the graph that talks about what we just talked about, which is just graphically how the insulin works. Again, we have the basal insulin, so you've got the intermediate acting of NPH which again kind of has a slower onset of action goes at peak and then ends. Often times, what we need to do in order to stimulate our pancreas is we need to give two doses a day so you get that curve going twice a day. You'll see the longer-acting insulins, the glargine and detemir, they have a much faster onset of action so they start covering sooner and they're more stable. They are peakless. They don't tend to have the same upward trend as the NPH, although detemir I think really does act more like shorter or intermediate acting insulin.

Then, you have regular which again has a little bit longer acting onset of action than the lispro and the aspart and then hangs around a little bit longer. Again, if you think about if you're eating here and you take it, and then you're going to eat around here and you're going to take another dose but you haven't completely gotten rid of the earlier dose, you can see that over time, you may end up into some trouble.

Then you have the rapid-acting which really can be quite nice because it gives patients a lot of flexibility in how they're going to use that. I just want to talk about, and I want to give a shout a big thanks to Raeanne Fuller who is one of the pharmacy residents at PIMC. She was nice enough to allow me to share this data with you guys. That was some experience that we looked at a couple of years ago after we switched our long-acting insulin from glargine to detemir, back in February of 2011.

Anecdotally, the providers and the patients said, "We just feel like the patients aren't as well-controlled after the switch." I feel like a lot of the patients just said, "I don't like it. I want to go glargine. My control isn't as good." So, she was nice enough to actually look at it from a data-driven perspective and give us the data that we needed.

Basically, she went back and looked at folks who were switched over, over about a year period of time. They were all patients who had Type 2 diabetes. They have been prescribed glargine for at least six months prior to the switch and then converted over to detemir. And then you can see some of the exclusion criteria there.

The interesting thing here, if you look that the primary outcome was A1C control. And so what you can see is that initially, if the baseline A1C, six to twelve months before the switch was 9.1, 9.4 is the time of the switch. About three months after, what we saw was actually, right, which was patients didn't seem to be as well-controlled, but then as those patients that stayed on detemir for 12 months, you could see that we began to get better control of them, and I really think anecdotally as the provider who kind of went through this, I suspect that part of it was we learned a lot in terms of how to utilize detemir over the course of the time and so ended up being able to control our patients.

One of the very interesting things and one of the things that we do know and is well-documented with detemir, is that folks actually did see a decrease in weight. As you know, one of the side effects and we'll talk briefly about this momentarily is patients don't like to go on insulin because they gain weight. In detemir, in this group that we looked at, there actually was a loss over the one year of about five pounds. So, that was a plus for the patients.

The thing that we learned over time was that you needed an increased dose. I can tell you that as a provider making the switch, we sort of did a one-to-one switch and we also said, "This is a long-acting insulin so we're just going use it once a day." Well that didn't worked out so well for us and so it took a period of time for us to realize, part of the issues and the reason why it wasn't working was because we actually needed to increase the dose.

As you can see that, again, so for patients the six to twelve months glargine before the switch we're using about 68 units, 72 at baseline, the initial dose for detemir it was about 75, so it was about a one-to-one switch. But after about a year, we needed to increase the doses and so they ended up on more insulin, specifically more basal insulin. But they also ended up on more insulins total, so those folks that did multi daily also in bolus doses, we ended up having to increase all of the doses of insulin.

So, what we found, anecdotally we experienced and then were sort of validated by looking at the data, was that at three years we did see that the A1C went up over time, but it was able to be brought down at a year and that difference was not statistically significant from where we started at the baseline. We did have about 12% of the folks that discontinued the detemir, and the main reason why people discontinued it was because they really just felt like that we couldn't good control of their insulin, or their blood sugars.

Then, we did have some uncommon adverse drug reactions with the detemir such as leg stiffness, jittery feelings, some palpitations, and metallic taste. We did see that the insulin requirements were more, both on basal insulin and the total insulin dosing. I think that the most important thing I think for me is a provider, what we actually realized earlier on and then was validated by the study was that, we really needed to go to twice daily dosing, that one daily dosing was just not working for the vast majority of the patients.

One of the things that also showed was that we saved a lot of money. Glargine is very expensive and I'll show you a table in just a sec how expensive for us it is, but we did save a lot of money when we switched from glargine to detemir. Just a word on the basal insulin. Again NPH, I have a preference to use NPH, I've used it for a long time. We as a provider group have the longest experience with it. It is the cheapest that you'll see in a moment, and it works really, really well.

So, I have to have some overriding reasons why I'm going to switch to a longer-acting insulin, because most of the time I'm really able to get my patients controlled, to folks utilizing the NPH. Detemir, it does have less weight gain than the other insulins and that may be very attractive for some patients and maybe something to consider when you're thinking about what basal insulin to use. But for me, I know I'm going to have to use it twice daily anyway and so often times it's not an overriding reason for me to try to use it.

Glargine definitely has a role. I think that for folks that have a tendency toward hypoglycemia, for folks who really will, from a compliance standpoint, even do better with once daily dosing, I do think that glargine is a great drug and actually can be utilized, but I really try to work with patients to make the other things work before I jump to that. The other thing I just wanted to mention briefly on glargine because you'll some of it in the literature, is that there is some preliminary or some case reports on increased cancer incidence for breast and pancreatic cancer with glargine. The more recent studies don't necessarily show that to be significant, but I just put it out there because your patients may ask about it and it's something that probably needs some more follow up over time.

So, talking briefly about short-acting insulin. Basically, I'll start with regular insulin. Regular insulin is less costly, but it actually does have some problems or some downsides to the fact you have to kind of pre-plan it. So, you have to know when you're going to eat, you need to take it 30 minutes before, it hangs around a little while. Novolog or Humalog, it's really what we call food on fork.

Basically, the great thing about that is, patients can take it as they're eating and its onset of action is so quick that it will cover them and the duration of how long it sticks around is more in line with how patients will digest their food. Having said that, a lot of our patients who have gastroparesis however, that there may be other issues and maybe regular insulin would work better. There is less activity also before bedtime with the shorter-acting insulin, so you maybe less likely to have night time hypoglycemia. Again, experience that you have less likely to stack it because it doesn't stick around quite so long.

Here is basically a table that shows, I say the IHS cost of insulin, this is basically the cost of insulin for PIMC and whether it exist on the formulary or not. So if you look on the top three of the basal insulin, NPH, again, the cost per vial very cheap, $4.79, cost per pen $3.42 for the 300 unit pen versus $11.40 for 1,000 unit pen. The detemir is the long-acting insulin that is on the national formulary. It is $19.99 for the vial versus the $26.66 for the pen, but sometimes that $26.66, if you're looking to use a pen may come in handy for you. Glargine is expensive. It is not on our national formulary, I know at PIMC we have to put in a non-formulary request for it. Certainly, in our environment you really want to think about why you're using it, whether it's appropriate for that patient and use it appropriately.

Regular insulin, just like NPH is the least costly of the shorter-acting insulins. It is obviously on our national formulary. Regular insulin does not come as a pen. The nice thing about aspart or NovoLog is it is on the national formulary. It comes both as a vial and a pen and it actually comes at the same price as a vial and a pen. It actually, though, is more expensive obviously than the regular insulin, for a lot of our patients if they're going to get to the point of doing bolus dosing, and meal time insulin, and you can get it at the same price as the pen as the vial, it really is a great option to consider.

Often times, I actually go through sort of the machination in my mind in terms of resources and that sort of thing, I will go to the short-acting analog before I would go to the longer-acting glargine if I wanted to try to manipulate the insulin a little bit more and get under tighter control.

Just briefly, because as we talk about insulin, one of the things that we need to educate our patients on and we need to be concerned about is hypoglycemia. I put that in there just mainly to remind people signs and symptoms as well as to give you guys again what treatments of hypoglycemia. But it is very important if you're going to be using insulin in your patients that they're well-versed in the signs and symptoms and more importantly, or as importantly really how to treat those when they happen. Again, it's not just the patients that need to know that, but it's the family members as well.

Insulin ultimately, one of the main things patients are going to tell you is, "Everybody I know gained weight on it." Unfortunately, it is a reality. In general, there's about a two to four kilo increase in body weight when people start insulin. Mechanism is unclear, possibly explained by reductions in glycosuria and resting energy expenditure when the glycemic controls improved. There has been some debate about that recently. Again, at least the PIMC data when we reviewed it, it definitely did show that there was less weight gain with detemir than NPH. Well, definitely than glargine, but also for NPH, and the data out there does support that.

It's one of the things where you just have to have the honest conversation with your patients, in terms of what that is and just how to mitigate those circumstances. This again came out of the ADA recommendations in terms of glycemic management and really it's about sequential influence strategies.

When we talk about how we're going to utilize insulin, I hearken back to that first graphic that I showed in terms of hyperglycemic management and less stringent or more stringent goals. This is the same idea which is, there are times where you're going to have folks that are more flexible and less flexible, and depending upon what their flexibility is, your regimen could be more complex or less complex. That's something that you need to consider, and why you really need to have a conversation with the

patients, and their families, and the team as you look to determine what insulin strategy you're going to follow.

Here's the algorithm that the AACE puts in for adding or intensifying insulin. Again, a lot of times you'll see this reference to total daily dose based on unit per kilogram and so if you strictly want to go by the book, what you do is you would go ahead and determine, look at the patient's weight, you do some multiplication, and you determine what their total daily dose was.

Then, there's a whole analysis then in terms of whether you're going to start with just basal insulin or you're going to divide that total daily dosing into multi-daily dosing. Some of the total daily dosing for an A1C less than 8 is going to be less than the total daily dosing for an A1C greater than 8%. And then this whole algorithm goes through -- you're going to titrate it every two to three days to reach the glycemic control based on what your fasting blood glucoses are, and this is really only for both basal and prandial manipulation. I sometimes look at this and I go, "Well, that's really, really confusing."

Then, I hearken back to what the Diabetes Division for Treatment and Prevention has given us which is really a very simple thing and a simple algorithm to use. So, they just have three steps. They say, "We're going to target first the fasting plasma glucose and so we're just going to think about basal insulin." We could figure out what people total daily dosing is by trying to multiply by how many units per kilogram and that sort of thing. But often times, it's just easier to look at somebody and say, we're going to give you 10 units at night and we're going to see how you do. Then basically you could tell folks, we want you to increase that dose two units every three days until your fasting blood sugar is 70 to 130. What does this mean for the patient? Well it means a couple of things. One, that it means you're asking them to check their blood sugars every morning and we'll go through a little bit of that when we get to the case studies. But you're also asking them for an investment of time, because they're going to have to record their blood sugars, they're going to have to know how to increase it and so that again takes the fairly committed patient as you'll find out.

Then, it goes to step two. Basically, if you've done and you've gotten down the fasting glucose then the step two is going to say, well let's target meal time. So, the first thing that you're going to do is look at pre-meal glucose, so you're going to be checking that blood sugar before you eat and then adjusting the insulin based on that.

The DDTP algorithm suggests four units as a start and then increasing again two units every three days based on a goal of pre-lunch blood glucose of less than 130. Then, if you want to get even more savvy you can go to postprandial glucose and you can have people checking their blood sugars before they eat, and checking their blood sugars two hours after they eat, and then you can really fine tune it.

I have to say that again kind of hearkening back a little bit too to where I started, which is a lot of patients just don't want go on insulin and there's a lot of reasons why, and we as providers and as medical system are included in those reasons. Patient barriers are a huge thing. I frequently will have a conversation with patients when I bring up insulin and I'll say, you know we as a medical community did patients a disservice, because 10 years ago, 15 years ago, 20 years ago, we threatened people with insulin. We said, "If you don't do what you need to do, and lose weight, and eat right, then we're going to put you on insulin." So everybody was scared of that and so nobody wanted to go on insulin and so we threatened people with insulin. So, instead of saying, "You know what? Your body produces insulin on its own and if you want to control your blood sugars, this is the best way to do it," we used to threaten people with it.

And then people also have a tendency to associate the initiation with insulin to it being the end game. A lot of people have family members who didn't go on insulin, who put off going on insulin for so long that by the time they finally went on insulin, they subsequently very quickly went on dialysis, lost a limb, lost eyesight, or died. So, patients go, "Oh my God you're telling me that I'm going to have one of these bad things happen." Because we as a community used to threaten people and we delayed the

start of insulin. We don't want to do that anymore but we need to recognize that patients really have predispositions to it.

They also have predispositions to the fact that they're going to gain weight as we talked about that maybe they're afraid of having low blood sugars. It's a lifestyle commitment, more so than taking pills. There are all sorts of issues, but we as a community also need to understand that often times we perceive the patient's resistance. We actually put up those barriers, we believe that patients may not be able to ever do it, that we believe that patients may become hypoglycemic. The question is whether we've actually had that conversation with the patients or not.

The system is over-burdened. This is a team effort. Treating diabetes in general is a team effort, but putting somebody on insulin requires many members of the team. So, in a resource-poor environment, you as the provider may think, "I just simply can't support it." We know from the clinical inertia data, we don't do a good job about intensifying therapy whether it's oral agents or insulin. These are things and these are conversations that you need to have with your patients and with your team in order to be able to optimize the management of the patient.

Again, just a few things on general strategies for initiating it and mainly it is have that conversation with the patient. Make it easy, emphasize the importance of lifestyle management, make sure that they understand why you're doing it and really do it as a team. It's not something that you're doing to them. It's not something that you're doing for them or anything else. It's something that, you're working with them to achieve better outcomes for their health. I only have a few minutes left and I want to go through these cases really quickly just to illustrate a couple more things.

The first case study, just 52-year-old male, 10-year history of type 2 diabetes, current medications, he's on two oral agents Glucophage, 1,000 milligram twice a day and Glipizide XL 20 milligrams po q day. Glycemic controls are not great. He still has an A1C of 9.3 and a fasting blood sugars that are roughly at 250 on average.

What would you do next? I bring us back to the DDTP algorithm and say, well, you know what, I would probably start with the basal insulin. We know his fasting blood sugars are high and we want these fasting blood sugars to be somewhere between 70 and 130. I could go ahead and calculate out what his total daily insulin dose is, but in this case, I would just start him at the 10 units at bedtime.

For those of you that sat and listened to my blood glucose monitoring talk, you've seen this slide before. Again, how do people monitor their blood sugars once they start insulin? Well, this gentleman who's already on oral medications and bedtime insulin, you're going to have a start phase, an adjust phase, and a maintenance phase. So, if you adjust that insulin, you're also going to be adjusting how often they're going to have to be checking their blood sugars. When you're first doing it and you're first giving them the basal insulin, then you're going to want them to check their blood sugars every morning during that first week and then follow back up with them.

So, our patient goes ahead and does that and he comes back. I also instructed the patient to go ahead and increase, by the algorithm, if he was over a certain amount by four units. He's actually done a really nice job as to looking in his fasting blood sugars, and going ahead and increasing over the course of the week to try to bring his blood sugars down.

By the time he comes back to me on day seven, he has actually increased already up to 16 units from the 10 units that I started him on and his fasting blood sugars down to about a 160. At this point, I would probably say to him, "You've done a great job." I probably would tell him, let's keep in mind, our goal is 130, but he can adjust that on his own. We're going to follow up. The team is going to follow up and then we're going to proceed from there.

Again, in just talking about some points to be aware of, some of the things that happen when folks start taking insulin and things that you need to tell patients about is some early morning hypoglycemia. If patients are having that, you might need to tell them to take their NPH later. I mean it should be taken around bedtime. Another reason why you don't like the 70/30 is because you end up taking the basal portion too early in the evening. You may need to tell them to start taking it later to delay the peak. You may need to reduce their nighttime dose of insulin. And over-correction of that early hypoglycemia can result in fasting hyperglycemia. In other words, if they're waking up at 02:00 a.m., they've got a low, they over-correct, now they've got fasting blood sugars, and you kind of start in a circle. The other reason that you could have some fasting hyperglycemia, is again that maybe you're just taking your night time insulin too early or that you need to increase the dose.

Patient number two, is our patient comes back now. Remember our clinical inertia. Now he is two years older. He's had diabetes for two years longer. Over the course of the time, he had increased his NPH from 16 units at our last time of seeing him. Now he's on NPH at 40 units twice a day. He's still on the Glucophage. He's still on the Glipizide which is a whole another conversation as to whether you continue the sulphonylurea once they're on insulin or not, but in this case, we did.

Now, his A1C is still 8.9 and so you ask him, "Can you check some other sugars? You've been checking the fasting blood sugars but can you check the pre-meal blood sugars?" You'll see that his pre-meal blood sugars are not optimal either and so the question then was, well what do you next?

Then, you're talking about doing multi-daily dosing. Really that's the most complicated. It's the most time intensive. It is most like our pancreas but what we need to remember as we've discussed before is it's really not for everyone.

How to monitor people who end up taking multiple daily doses? Again, you're going to have the start phase, the adjust phase, and the maintenance phase. You're really talking about having them check their blood sugars maybe four to six times daily. These are pretty motivated individuals. The other thing, and a shout out to our diabetes educators and to our nutritionists, is carb counting. Ultimately, if you're going to go forward on and do insulin boluses, you really need to teach carb counting because you don't just want to do a sliding scale. You don't want to just do static insulin. You want people to be able to do corrective dosing insulin depending upon what they eat and in order to do that, you're going to teach have them carb counting.

Again, just briefly, according to the algorithm that we are using, we go ahead and add four units of regular insulin before his largest meal. He'd have to check his blood sugar pre and two hours post. So, again, somebody highly motivated to check their blood sugars that often then you would go ahead and increase the bolus insulin by two units every three days until the two-hour postprandial is less than a 180. Then, depending upon his blood sugar readings, you go ahead and add in regular or the short-acting insulin to his other meals based on the blood sugar readings. Then, you need to teach the carb counting, because really you want to use corrective dosing and not sliding scale. I know we're running out of time but I just want to cover one last thing in this last case study, because this is a really important thing for folks that are on insulin that our patients sometimes get harmed on.

That is, a 56-year-old female, long-standing diabetes on a lot of insulin, NPH 100 units twice a day and regular insulin 100 units twice a day. The patient has a surgical procedure planned for tomorrow. What do you tell the patient to do with her insulin in the 24-hour period prior to her surgery? The reason why I think I'm on this at the moment is because it actually happened recently to my patient. So, this is a patient of mine just recently.

So, very quickly, insulin therapy before surgery; there's really three steps that you need to think about. Think about the type of diabetes. Mainly in our folks who's going to be type 2, so it's not quite as important, but in many of our folks it is important. You need to adjust the basal insulin dose, and note, you need to adjust the basal insulin dose. Then, you need to stop the prandial insulin. Those are really

the three steps. We want to control hyperglycemia in the preoperative period because if we don't, it can result in the delay of surgery, delayed wound healing, wound infections, fluid and electrolyte shifts and high hyperglycemic states that can either end up in DKA or hyperosmolar.

What I've done here, in the interest of time I won't go through it too much because I've made a little bit of a table for you guys in terms of how to adjust the insulin whether you're on long-acting, intermediate-acting or 70/30. The thing that I need to stress the most is that you're going to stop all prandial insulin. You're going to give, depending upon whether they have -- they tend toward hypoglycemia or not. You may adjust it a little bit more, but the biggest message that I have to give is do not stop all of their insulin. So, depending upon whether they're on intermediate-acting, if they're going to eat well and normally the day before, you're going give them the full dose before. You can give them 50% the morning of the surgery, and then so on and so forth with the long-acting insulins.

Again, post surgery, you're going to resume, assuming they're eating a normal diet that night. You resume the normal insulin dosing that night, but the key that I want to say is that patients requires some form of the insulin even in a fasting state. I can tell you that what happened to my patient was, the pre-op nurse told her, "Don't take any insulin the morning of your surgery." So, she showed up for her surgery and a she had a blood sugar of 350 and they sent her home and they had to reschedule her surgery.

Again, in her case where she used a lot of NPH she would have just taken no prandial insulin the morning of her surgery and she would have taken 50 units of the NPH that day.

In summary, good glucose control equals improved outcomes. Diabetes management can be complicated but it doesn't have to be. You need to individualize the treatment plan, one size does not fit all. Don't let your patients or yourself be victims of clinical inertia. It really does take a team in order to treat diabetes, specifically to do insulin management.

As I end I'll just leave you with the care model again for the Indian Health Service. All of these things in the chronic care model are needed in order to successfully deliver diabetes care insulin management to our patients. Probably one of the most important is the effective relationship that we have as a care team with our patients, because it's hard work to take care of, to deliver insulin management, to do it successfully, but it's worth it because we can improve the outcomes of the patients. With that, I really thank you for your time in listening to me and I know we're already a little past the hour, but I don't know if there are questions or not. So, thank you very much.

Wendy Sandoval:

Marie this is Wendy Sandoval. I just wanted to thank you on behalf of the Division of Diabetes for taking time to present this great seminar. There are few questions in the chat, I think you can probably see them there --