

Division of Diabetes Treatment and Prevention

Identification and Treatment of Type 1 Diabetes in AI/AN Populations

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June 2014

Michael Bryer-Ash:

I've been at IHS for about four years, just over four years, I spent my career prior to that in academic medicine doing research and teaching, saw a lot of patients during that time. So I always had my hand in with patient care. I actually spent several years in Canada at the University of British Columbia and had some responsibilities for accrediting diabetes centers among First Nations in the interior British Columbia, although I didn't work for First Nations, I was familiar before I joined the IHS.

I do go to all eight of our facilities here, and some of the things I'm going say today are based -- I know this presentation is titled "Advancements." This is based on some of the things that I think are relevant in terms of my practice out at our centers and the things I encounter, some of the issues, so I hope they're of practical value to you.

So I'm going to start now and list my objectives. As you know, type 1 diabetes is by very much the minor part of diabetes among the Native American community. In the world in general, type 1 diabetes is about 5% to 10% of all diabetes. Among Native Americans, it's about 2%, but nonetheless, it's important to recognize it and manage it appropriately. And there are certain unique features that one needs to consider in a population with a very high prevalence of type 2 diabetes and insulin resistance, and that will come up during the course of what I'm about to say.

So, I'm going to review the natural history of and lab tests for the diagnosis of type 1 diabetes. And then talk a little bit about how we can differentiate type 1 from type 2 diabetes, and then mention a couple of issues that are important when we see our American Indian and Alaska Native patients with type 1 diabetes.

Under current treatment guidelines, I'm not going to restate the guidelines to you, but I'm going to mention a couple of issues that I think are important and that I find challenging going out to our centers in implementing to make sure that insulin treatment, which is really what it comes down to in type 1 diabetic patients, is being done appropriately.

Then I've been asked to make one suggestion for recommended change that you can make in your practice. It's my hope that as a result of this, there'll be three or four things to choose from that you might want to implement as a change if you're not already doing it.

So, let's review the natural history and laboratory tests for the diagnosis of type 1 diabetes. Well, let's do that by reviewing the causes of diabetes, and I know this will be all quite familiar to virtually all of you. In this cartoon representation, we have simplistic terms, we put carbohydrate, but basically all forms of nutrients enter the gastrointestinal tract. I know I have to pull this arrow over there hopefully, but let's see. Here it is.

So we have our nutrients entering the gastrointestinal tract, and being absorbed under normal circumstances, and then under the influence of insulin, which comes from the pancreas. In this case,



the case of diabetes, there is deficiency of insulin coming from the pancreas. In the case of type 1 diabetes, it's an absolute deficiency. In the case of type 2 diabetes, it's a relative deficiency.

So, the patient with type 1 diabetes becomes diabetic because they have essentially no or very little insulin production. In the case of type 2 diabetes, they have insulin resistance shown by the yellow arrow, principally into the muscles. So there's reduced glucose uptake this is as a result of genetics, weight gain, aging, lack of exercise, et cetera, and one or two unusual causes. Also, we have excessive glucose release from the liver. So we have failure to take glucose up from the circulation into the insulin-sensitive tissues, and an excessive release from the liver and this is therefore, as you see on the bottom right, resistance to the action of insulin and leads to hyperglycemia.

So now, talking about type 1 diabetes and its natural history, let's start with looking at family risks. Most cases of type 1 diabetes are what we call sporadic. They arise in families who have no history of diabetes. There may be history of other autoimmune disease, most commonly thyroid disease, but only about 10% to 15% of individuals affected with type 1 diabetes, have a first-degree relative, i.e. brother, sister, parent or child who have type 1 diabetes at the time of diagnosis. This was exemplified by - many of you may remember the Diabetes Control and Complications Trial, which was the first trial in type 1 diabetes to show the importance of tight control in preventing diabetes complications. Of the 1,500 patients there, there were about 80, I think it was either 83 or 85 who had a brother or a sister or first-degree relative with diabetes. It's actually less than 10% so it's a small percentage.

The risk of developing diabetes is 5%, if a first-degree family member is also affected with it. The general population risk is about 0.4% to 0.5%. So it's about 20 times the risk if you have a first-degree relative with type 1 diabetes. However, a risk of only 5% is not enough really, in most cases, to discourage one from having children because of the risk. But it's a significantly increased risk but it's still small.

Interestingly, the children of a father with type 1 diabetes have a higher risk than the children of a mother with type 1 diabetes, even if that mother has diabetes at the time when she's carrying the child. One might think that as we increasingly know that the uterine environment during which the child develops may have a profound effect on this susceptibility later in life. You think it would be the other way around. We're not sure why, but it might be that there's a higher spontaneous miscarriage rate when both the fetus and the mother have the type 1 genes. Now, it would have to be very early because as far as I know, there isn't a higher spontaneous abortion rate measured, so it would be very, very early on.

So moving on to talk about family risks, so in spite of what I've just told you, which is that there's a 20-fold increase of having diabetes if you have a close relative with it, the concordance rate, meaning that both have it, in identical twins for type 1 diabetes, is only 50%. So since they're genetically identical by definition, this means that there must be a strong environmental influence.

Now interestingly, if one of a pair of a pair of identical twins has type 2 diabetes, then the concordance rate is much higher. It's between 70% and 90%. We know especially that it's well exemplified by the experience among Native Americans, that environment, in spite of carrying susceptible genes for type 2 diabetes, environment plays an enormous role.

There's a famous epidemiologist who spent his career among the Pima American Indian community in Arizona, Dr. Peter Bennett. He gave a Banting Lecture about -- it was probably close to 20 years now, it was probably in the mid '90s I suspect. He noted that while nowadays, among Pima American adult men, 40% have diabetes, sorry, Pima Indian. Pima Indian adult women, over 50% have type 2 diabetes. A hundred years ago, there was only one identified member of that Nation that had type 2 diabetes. So clearly, genes haven't altered themselves that dramatically in a hundred years, so there's

a tremendous impact of environment. In spite of that, the concordance rate is very high and much higher than it is for type 1 diabetes.

Now, I mentioned to you in the previous couple of slides that you have a 5% risk if you have one parent or sibling affected, but that's, again, much lower than type 2 diabetes. If you have one parent with type 2 diabetes, statistically, your likelihood of having type 2 diabetes yourself is about one in three, and it's about two in three if both of your parents are affected. So, this just restates that there's a powerful environmental component interacting with genetic components to confer risk of type 1 diabetes.

So, I want to look now at the natural history of diabetes, how does it evolve? So we know that you start out life and here you are in utero, in the red box here, with a genetic predisposition. And that there are possibly intrauterine precipitating factors, which we don't, certainly don't understand fully at this point, but given that the uterine environment may play a role on your risk, clearly, there are environmental factors. A factor or factors, it may be more than one factor in one case that may be one powerful factor in another. But we know that there are environmental factor or factors that play a role. This leads to detectible immunologic immune abnormalities.

So that often, many years before any abnormality of glucose metabolism is detectible, we can measure immunologic markers. I'll talk a little bit more about that in the slides following. For a sizeable amount of time, normal insulin release is maintained. Indeed, in a number of patients, and perhaps in the majority of the patients, the process may be arrested.

So in family members of patients with type 1 diabetes, you can find detectable antibodies with an increased frequency, but as I mentioned it by no means guarantees that those patients are going to go on and get diabetes. So, there is some other factor, other than the initiation of autoimmunity that is either precipitating or protecting the patient against going on to get diabetes. Then we can detect declining insulin release, but this again doesn't always lead to full-blown diabetes with severe insulin deficiency of the type that we're familiar with in a patient with obvious type 1 diabetes. The process may be arrested.

In fact, in up to 20% of the patients who we diagnose as type 2 diabetes may have a form of partially arrested type 1 diabetes, so-called latent, latent autoimmune diabetes of the adult. They may arrest at pre-diabetes or they may have a usually somewhat unusual, atypical form of type 2 diabetes. They may be less responsive to oral agents; they may clearly be more insulin-deficient than insulin-resistant. They're more often lean rather than heavy. But sometimes they follow a type 2 diabetic course. So you can see here that we're talking about a spectrum of disease that in the cases that we're most familiar with ends up with severe insulin-deficiency and overt diabetes.

So autoantibodies. So by the time clinical onset occurs after the timeline that I had shown you, that can be anything from months, I mean sometimes babies are born with congenital type 1 diabetes. It can also occur later in life. 90% of the patients who will develop type 1 diabetes will develop it before the age of 35, but there's a substantial minority, about 10% that will develop it in later life. I've seen it, frank type 1 diabetes, developed as late as 80 years of age.

So at clinical onset of diabetes, less than 10% of the residual beta cell or insulin-producing mass remains in the pancreatic islet and we'll talk more about that later too, and there are a number of measurable immune abnormalities.

In humans, we see that the pancreatic islet is infiltrated by inflammatory cells, and this is most active and most obvious in patients newly diagnosed with the disease. As a result, or at least possibly in partnership with this process, these islet cell antibodies are formed against proteins in the insulin-producing cell. So 90% of patients with newly diagnosed type 1 diabetes have one or more associated antibodies.

As you can see from the natural history that I showed you earlier, by no means does having an antibody guarantee that the patient will get diabetes or will get diabetes in the immediate future. The commonest of these antibodies are these five antibodies: islet cell antibody, ICA; insulin antibody, IAA; the glutamic acid decarboxylase antibody, which is called 65 because this particular protein, glutamic acid decarboxylase, comes in different size fragments and this antibody is against the 65 kDa fragment, but for practical purposes, don't worry it's just the GAD, antibody of a GAD65 antibody.

There's a couple of less common and more recently identified antibodies here. So what is the practical utility of knowing these antibodies? The most useful and commonly measured antibodies are these two, the GAD65 antibody and the insulin antibody. Now, I personally find that the GAD65 antibody which is available to be measured at all of our service units, is the most useful marker, because insulin antibodies can develop as a result of insulin administration, and it's seldom that we are measuring these antibodies in patients before they have been exposed to insulin.

Even with the semi-synthetic insulins, to which there are very seldom allergic or immune reactions, we still see insulin antibodies the longer a patient has been on insulin. You can see this in type 2 diabetic patients. So the GAD65 antibody is a more specific marker. These other antibodies are less commonly available or measured, but if you're going to measure an antibody, my recommendation is to measure the GAD65 antibody.

So if a patient has one positive antibody, then you can see they have a five-year risk of only 5% of getting type 1 diabetes. Five years is a good spell of time, and that's even for a risk of 1 in 20. So antibody marker alone, while it does confer increased risk, it by no means guarantees that the patient is going to get diabetes and we shouldn't unduly alarm our patients. We should just be more vigilant. However, four positive antibodies, and we're seldom going to get most of our facilities to measure four positive antibodies, but they confer a much higher risk. The more antibodies you have, the higher your risk of getting diabetes within the next five years, it's about 80%.

So what are the environmental factors? Well, unfortunately, they remain unknown although these have been studied for as long as diabetes has been identified and there have been pretty intense studies over the last, this particularly 25 to 30 years. There is fairly a good supporting evidence for some or all of these, and it may be that it's not just one precipitating factor. It may be that the precipitating factor is different in different regions of the world.

Interestingly, the parts of the world with the highest risk of type 1 diabetes, are quite different climatically and socially and probably, economically, and also in terms of their ethnicity. They are Kuwait, Sardinia, and Finland. I think if you put the average person from Kuwait and Sardinia and Finland in a room, they are from, in general, I mean the world is a very heterogeneous place now but I think, there would be a tremendous amount of difference between them in a number of areas, and yet, those are the three highest areas.

So, exposure to viruses, there's fairly good evidence for a rubella, mumps, Coxsackie B virus, or possibly other microbial pathogens. Early exposure to cow's milk has received a lot of attention. The reason for that is that there's a sequence on bovine serum albumin, which is a protein found in cow's milk, that it has similarity to this GAD65 enzyme that I mentioned to you against which antibodies are raised.

Then we have diminished breast milk consumption. It's found that babies, children who move from breast milk to either formula or cow's milk early have a higher likelihood of getting diabetes. We know that early exposure to cereals -- and this is with or without gluten. It's not just a matter of gluten. There is a higher prevalence of celiac disease, which as you know, is gluten sensitivity, with gastrointestinal disease. There's a higher prevalence of type 1 diabetes. In fact, if I see -- and this is higher in patients

from Northern Europe; if I see a patient with diabetes who is blue-eyed and blonde hair, I always ask them or I'd be concerned about the possibility of coexistent celiac disease because they have a higher risk of it.

It's also been shown that Vitamin D supplementation early in infancy seems to have a protective effect. That doesn't mean that Vitamin D deficiency is causative, because the infants who received early Vitamin D supplementation were not considered to be Vitamin D-deficient but there's -- as you know, the role of Vitamin D in glucose metabolism and diabetes in general has received a lot of interest and attention in the last few years as it has for a number of other diseases. It's almost where Vitamin C was about 30 or 40 years ago. Whether that will stick, whether that will turn out to be important is unclear, but that has been an additional fact that has been noted.

The other thing which I've called, for lack of a better word, clean environment. We know that children who -- interestingly, children who go to daycare from an early age have a lower incidence of type 1 diabetes. If siblings are separated from families, what often happens is that the first child may or may not go to daycare and time may be taken but as more children are born, maybe it's more likely that they'll go to daycare or sometimes less likely for whatever reasons. But the children that spend more time in daycare have a lower prevalence of type 1 diabetes. Interestingly, there's also a lower prevalence of leukemia. This may lead us on to what are the possible mechanisms for what I've shown you here. One possible mechanism is the mimicry of components of the islet cell by components of these agents, such that the immune response turns on to clear, or to get rid of, for example, a virus such as rubella or mumps. It turns on an immune response but then it goes on to attack the islet.

Because of the association within family members and, indeed, within individuals, that if you have one autoimmune disease, you're significantly more likely to have another and I'll talk more about that again a little bit later. We know that type 1 diabetes is not necessarily standing in isolation. A predisposition to autoimmunity is a disorder of immune handling and, as such, it's not the deficiency; it's really that the immune system is over-vigilant.

You can think about this rather like after there's been a battle on the battlefield, and the losing defeated army has been routed, then the soldiers of the victorious army often go house-to-house to search out the stragglers and people who are hiding down in the basements, et cetera. And they may have difficulties recognizing which, you know, were on the opposing army and which are innocent civilians. That's the problem facing the immune system of those who are predisposed to get autoimmune diseases.

There may be proteins or structures on some of these bacteria or viruses that resemble proteins and structures on the islet cell and the person with autoimmunity is going to take no chances. After getting rid of the virus, it will then turn its attention to try to get rid of the islet cell and that will give diabetes a chance to occur.

Then, the other possible problem/mechanism, which addresses the issue of the clean environment, is that inadequate immune system priming early in life is needed to train our immune system to distinguish "self" from "non-self". Now, you can imagine back in cave man days. In the days, I'm not sure if it was male or female-dominance, but the men, for better or worse, were sent out to dodge saber-tooth tigers and forage for food and hunt. Women sat, generally, in communities with the babies in their midst for protection. They weren't dotted in individual places around the town, such as there were in those days. But the children were basically playing among the dirt and getting exposed to all sorts of antigens and infectious agents. Sometimes, this was very deleterious and they suffered and, of course we know that there were high death rates and there still are in some parts of the world from overexposure to infections, but probably, this was beneficial to many children because it allowed their immune systems to be primed and they could recognize what was dangerous to them and foreign from what was "self".

So that's where that stands. Now, don't worry about this slide. It's a bit busy. I don't know. I suspect that none of you are immunologists, I certainly am not. But these are parts of the so-called HLA or histocompatibility localizing haplotypes, or the genes that gives or confers susceptibility to diabetes. I raise this because patterns of these types of immune molecules have been found among Caucasian populations but when you look at the type 1 diabetes in African-Americans, for example, it's much less reliable and much less frequent. I looked up for Native Americans and I could only find one so-called allele. And this is actually protected, it was this DRB1*1402.

Everybody on this call is familiar with the fact that the Native American community is a very heterogeneous community. Even if we're talking about those of you who are pure-blood Native Americans, you still may be from quite different stock, from different regions. For example, Pima Indians migrated across from Alaska about 20,000 or 30,000 years ago. They may have little genetically in common with their cousins from, say, the eastern and southern part of the United States. Similar is true of African-Americans who were brought here from different parts. Native Americans evolved in very different communities with somehow, often times quite separated in North America and Central America. So that explains why it's very hard to do a genetic typing and reliably say yes, you have a very high risk of diabetes.

I mentioned the increased risk of other autoimmune diseases in patients with type 1 diabetes and that is certainly true. The main disease which patients with type 1 diabetes are at risk of is Hashimoto's thyroiditis. Almost every other autoimmune disease is at increased prevalence. Now, these may be fairly rare diseases so it doesn't mean it's significant, but for example, Addison's disease, adrenal insufficiency, it's well known that it's more likely to have a family history of lupus, rheumatoid arthritis, inflammatory bowel disease, hypoparathyroidism, premature testicular or ovarian failure in patients with type 1 diabetes.

But Hashimoto's thyroiditis or hypothyroidism is by far and away, the most common. A patient with type 1 diabetes has about a one in three lifetime risk of developing autoimmune thyroid disease, and nine out of ten cases of this, or more, will be hypothyroidism. In families who have a high risk of autoimmune thyroid disease alone, it could be hyper, overactive thyroid, or underactive thyroid. If you have type 1 diabetes, for some reason, you're much more likely to get an underactive thyroid. You have a 4% risk of adrenal insufficiency and 1% or lower for some of the other disorders that I've mentioned.

Now, I'm showing a couple of slides here, two or three slides here, which you don't have to worry about anything except what's written in orange. These are the atypical forms. These are from the American Diabetes Association classification of diabetes. These are the different forms of diabetes that don't fall classically into type 1 or type 2. Yet, these can certainly mimic type 2 or type 1, and have features of some or both. I want you to just to draw your attention to this Class C type here, exocrine pancreatic disorders, because those are the disorders that are most likely to mimic classic type 1 diabetes because they are diseases of the exocrine pancreas in which the insulin-producing islet cells are about 2% of the mass of the pancreas.

They get, for want of a better term again, and I'm sorry I'm turning to military descriptions, but I suppose when you've got inflammation in your pancreas, it's like a war going on, they get caught in the crossfire. When you have diseases that cause generalized damage or failure to the pancreas, then you can catch your islet cells and your beta cells in the crossfire and get almost complete destruction. This can, for all intents and purposes, look like type 1 diabetes.

Pancreatitis is probably the most common example, and probably the commonest example of the cause of that is going to be alcohol. When the patient has severe and recurrent alcohol-induced

pancreatitis or pancreatitis for any other reason, then they can develop insulin-deficient diabetes and a condition that looks very much like type 1. I'm going to show you in a minute that it isn't type 1.

Then, there's trauma to the pancreas. There's pancreatectomy and pancreatic cancer, if for any reason you've had your pancreas removed or you have pancreatic cancer, then you can get extremely insulin-deficient. There's a condition called tropical calcific pancreatitis, which develops. It's probably related to repeated dehydration if people who are not familiar with it. You get stone and mineral formation in the pancreas and severe damage. Then, there's this interesting condition, cassava or tapioca toxicity. And in the interest of time, I can't go into that in detail but suffice to say that if tapioca or cassava is not appropriately prepared by being soaked in water for several hours after being harvested, it will produce cyanide. So, you have to soak it and prepare it on -- I know we may come from the same country but I'm no Gordon Ramsey, so I can't give you the details about this, but there has to be a great deal of care in tapioca preparation or it can become toxic.

In some parts of the world when the rice harvest fails, the local population will turn to tapioca as an alternate source of carbohydrate and if they're not familiar with this, if these only occur every few years, a certain number of folks will not know how to prepare it and will give themselves pancreatic damage from it. Then, the other is a kind of -- I think it's a weed killer called Vacor that can cause severe pancreatic damage. All these others that I've listed here, they can cause significantly milder pancreatic damage. You're not going to confuse it with type 1 diabetes.

Then, we must remember the case of gestational diabetes. Gestational diabetes, is diabetes which is first recognized in pregnancy and most will be true gestational diabetes that will go away at the end of the pregnancy, albeit giving the woman an increased risk of getting type 2 diabetes later in life. Some will be previously unrecognized type 2 diabetes that will not resolve when the pregnancy is concluded, but a very few will be evolving type 1 diabetes that you just happen to pick up during the course of the pregnancy. That's rare, I've probably seen that two or three times in my whole career, but we're sure to keep it in mind. Diabetes must be reevaluated and reclassified after delivery.

What about prevention of type 1 diabetes? How much success have we achieved in that? Well, I think, the top line in yellow here summarizes it best, which is that no intervention to date has been conclusively shown to be effective in preventing type 1 diabetes. And indeed some of the recent clinical trials, because they are immune modulators because there are a considerable amount of side effects and they suppress immunity, cannot get approved for use in patients who have the immune set-up for type 1 diabetes because the risk outweighs the benefit. They've been used in patients with early type 1 diabetes.

Now, I mentioned in a previous slide that by the time you get diabetes, 90% of your islet mass and your beta cells have been destroyed. This may be too late. We may be intervening too late to try to rescue somebody when their pancreas is 90% destroyed, but that's where we are at the moment.

This is going back over about a 15- to 20-year period, I'm just summarizing briefly. These various projects, there was an attempt to use nicotinamide as the diabetes prevention drug, using insulin based on the principle that if you rested the pancreas and gave parenteral insulin very early before a patient got frank diabetes would possibly rest it and restore its function, that didn't really work; avoidance of cow's milk products was inconclusive, probably not effective; I mentioned about, we don't prescribe multiple infections in childhood even though exposure to them does seem to have a protective effect probably there the risk outweighs the benefit, too; there were studies of the immune suppressive drug, ciclosporin, but again, showed insufficient benefit to justify the toxicity of the drug. Trials with other immunosuppressants such as azathioprine, linomide, use of BCG vaccination, which is what we use for TB and all insulin, were also ineffective. Then, there was a recent study called The Protégé Study where they used an anti-CD3 antibody, Teplizumab. Some beneficial results but they didn't meet the primary outcome measure, which was to maintain the hemoglobin A1C below 6.5. There were other

trials here with two other antibodies that have shown early promise, but again, they're not at level of phase 3 so we're not going to be seeing them in clinical use anytime soon. So right now, type 1 diabetes prevention is not really effective.

I don't think that I need to spend much time on this slide especially since I don't have a great deal of time and I've got some other things to cover. But obviously, in the presence of severe insulin deficiency, everything starts to break down. This is the metabolic consequence of the type 1 diabetes, you have high blood sugar, you have osmotic diuresis with severe dehydration, acidosis, and electrolyte imbalances, which leads to the classical clinical picture. You get fatty acid release from your fat which breaks down and that's what leads to the production of the ketones and further acidosis, muscle breakdown, protein breakdown, and you then it all combines to lead to the classical acute clinical picture which we're very familiar with. And I won't restate this for you - the symptoms, the signs and then these laboratory features, which again, you're seeing more or less on most days in various degrees of severity, and that's the classical picture. But I put that there because part of this talk is about distinguishing between type 1 and type 2 diabetes, and even with that classical clinical picture, it's not often possible to reliably distinguish.

I wanted to just spend a moment to talk about this pseudo-type 1 diabetes forms. Now, if you remember, when I showed you that slide of the ADA classification, those two slides, the forms highlighted in orange, such as pancreatitis and tapioca toxicity, et cetera. You might think that for practical purposes, however the islet damage is mediated, whether it's through the immune system or whether it's through alcohol, or whether it's through tapioca, that the form of diabetes is going to be the same if the insulin deficiency is severe, but that actually isn't true. The reason it isn't true is because the immune system may not be working very well to distinguish self from non-self in the case of classical type 1 diabetes, but it does know only to attack the beta cell.

This is an islet, which I mentioned, is about 2% of the mass of your pancreas, sitting there interspersed among all the enzymes. These islets, or little islands, are arranged in a very specific way. The yellow here are the beta cells that produce insulin and around the outside of the islet, around the periphery are the pink glucagon-producing cells, and then you have in white here, the somatostatin producing cells. We're not really going to talk about that because it's not really a player in this scenario for now.

When you have classic type 1 diabetes, the beta cell is specifically targeted for destruction by the immune system. So, you get loss of insulin production and only loss of insulin production as a result. But in these other forms of general pancreatic damage you get these pseudo-type 1 diabetes forms, which are, because all the islet cell types are damaged, the alpha cell, the delta cell and the beta cell. So the net result here is different. You lose both insulin and very importantly, you lose glucagon production. You know that glucagon is what we call the counter-regulatory hormone. When your blood sugar is getting down low, then glucagon is produced, and in fact of course many of you will prescribe or make sure your patients have glucagon pens in order to raise their blood sugar when they have unexpected hypoglycemia.

So, it's an important counter regulatory hormone, the most important counter regulatory hormone. And if it's lacking due to generalized pancreatic damage, then the form of diabetes that these patients have is very brittle. Also, this will usually be complicated by the fact that they usually have severe damage to the rest of the pancreas. So, they have malabsorption and they're going to need eventually pancreatic enzyme supplementation. So this is going to make their food absorption variable and unreliable. So this is a very complicated form of diabetes to treat.

So, I'm just going to move now to the laboratory tests. Actually, as a practical issue differentiating between type 1 and type 2 diabetes is actually less important than it sounds. Why do I say that? Not because I don't care, but because the principle of therapy is to treat hyperglycemia with the least

aggressive and most convenient modality that will achieve stable glucose level and to treat all detected cardiovascular risk factors.

And then, because many patients will have features of both type 1 and type 2 diabetes in varying degrees, and all of these must be addressed. And because as I showed you a little bit earlier in the natural history, diabetes is a spectrum ranging from classic type 1 through a number of intermediate and partial forms to classic type 2. So, it's often not really possible to give a patient a label with certainty. But as long as you treat their metabolic abnormalities appropriately, if you make the odd mistake and you see an evolving patient with type 1 diabetes that turns out later to have type 1 diabetes, which you catch them early in the course - you try oral agents, you're not successful then you move to insulin. As long as you don't send the patient away for six months with no glucose monitoring and no follow up, then you're going to pick up these things. So, a therapeutic trial is often just as good of a way of doing diagnosis in the field.

So, here are the features that don't differ between type 1 and type 2 diabetes with enough frequency to actually be diagnostically helpful, and essentially they are classical features of hyperglycemia and the classical laboratory findings of uncontrolled hyperglycemia in more severe cases. So, we can't really use these. But if we were to take the classic patient with type 1 diabetes and compare them to the classic patient with type 2 diabetes at the far end of each spectrum, there would be little overlap.

The classic type 1 diabetes is prone to ketoacidosis; will have positive antibodies, has a low C-peptide level; will have an anion gap in their decompensated severe hyperglycemia. They will not have the typical lipid abnormalities of type 2 diabetes, and they will not likely have hypertension early in the course of the disease, and they're more likely to be lean. And the opposite is true in all of the patients with type 2 diabetes. When you are in those circumstances and that's the majority of patients, it's relatively easy to make the distinction and confidently get the patient a label, and most of our patients will be type 2 diabetes. There is no required number of these criteria. It's always a clinical judgment because it's a disease spectrum.

So, I'm giving you an example here in this slide with an exception to ketoacidosis as a reliable diagnostic criterion for type 1 diabetes. About 20, 25 years ago, actually, he's a pathologist at the University of Florida, Dr. William Winter, described this unusual form of -- at the time, they thought it was unusual, of maturity onset diabetes in young African-Americans. About 10% of African-Americans presenting in Gainesville with youth onset diabetes would present with weight loss, ketoacidosis, and would absolutely require insulin to turn them around. But later, they would gradually follow a non-ketosis prone insulin independent course and it was possible to withdraw insulin. They clearly didn't need it and they were followed for many years. In his initial series, he followed them for up to I think it was eight or nine years. And in spite of presenting with typical features of type 1 diabetes and extreme insulin deficiency, ketoacidosis, they remained non-insulin requiring; they were antibody negative after many years of follow-up.

So, what this reminds us is that ketoacidosis generally indicates severe virtually complete insulin deficiency. But it can occur in a setting of moderately severe insulin deficiency along with extreme insulin resistance. And I think we've all known a patient who we thought was classical type 2 and then they got some kind of infection, maybe a foot wound or a severe illness, and under an extreme amount of physical stress, they develop ketoacidosis because they had marginal insulin production, and when enormous insulin resistance was added to it through the stress, then they behave like a type 1 diabetic.

So, is there a gold standard test for the diagnosis of type 1 diabetes? And, yes, if there is such a test, it is the stimulated C-peptide. Now, it has to be said that often the main utility of this test is to satisfy insurance company requirements for providing insulin pumps if their policy is only to provide it to patients with type 1 diabetes. Unfortunately, the majority of cases that I see where this was done, it

wasn't done correctly and I'm not just saying in our IHS facilities but I've seen this throughout my career but it's not done correctly.

So, why is it important to perform it correctly and why is it C-peptide? Well, C-peptide which is this orange -- this is the structure of insulin. The C-peptide is so called connecting peptide and it's here, when the insulin is in the inactive storage form of pro-insulin and it connects the blue alpha chain to the red beta chain. When it's cleaved off, when insulin is released, and this signal peptide is cleaved off, you end up with the 2a and 2b chains of insulin joined together and they float around like this. But no synthetically manufactured insulin contains C-peptide. It wouldn't make sense. It would therefore be inactive.

So, if you want to distinguish internal endogenous insulin production by the pancreas from any insulin that the patient might have received from injections or self-administered, et cetera, then you can do that by measuring the C-peptide. So the presence of C-peptide means that any insulin that was produced came from the person's pancreas.

So, to perform this challenge correctly, how do we need to do it? Well firstly, insulin therapy must be withheld because the reason is that insulin suppresses its own production. It feeds back on its own production and if you get a shot of insulin, then you're likely to produce less insulin, even if your glucose is not at an ideal level. So, we have to withhold the outside insulin, but only for a safe period. The glucose must be elevated above normal postprandial levels in order to stimulate the patient's pancreas to produce maximum insulin.

The third feature which is most commonly forgotten, which is the patient needs to be fed and the reason for that is you have to activate the enteroinsular-axis. Now, the enteroinsular-axis is this axis, which again, because we now have mediations directed at it. When you eat a meal, long before the calories were absorbed, and this is a bit of liberties with this cartoon because this looks as if it's being released from the colon, while actually it's from the upper small intestine. But these two incretin peptides, GLP-1 and GIP are released, and they travel to the pancreas and stimulate the beta cell to release insulin, and they do this in the glucose dependent manner. If the glucose level is below 100, then they won't stimulate insulin release. But as the calories come in from your meal and as the glucose rises then, GLP-1 and GIP are important stimulators of insulin production. They are cleared by this enzyme called DPP4. So, in order to keep them around, you're all now very familiar even though the topic of this talk is not type 2 diabetes, but this is the glucose dependent insulin production, that we now have DPP4 inhibitors. These are the gliptins or sitagliptin, linagliptin, saxagliptin, the improved ones that will prevent them being broken down, keep them around longer and promote more insulin production.

We also have the tides like exenatide, liraglutide or extended-release exenatide that will take the place of the semisynthetic copies of animal versions, actually lizard versions of GLP-1 and GIP that will also stimulate the pancreas and they're not broken down readily by the DPP4 enzymes. So they're very potent and they hang around for longer.

So, it's important that you activate this axis to find out what the patient's insulin reserve is. So, in order to do the C-peptide challenge correctly, we need to withhold long-acting insulin the previous evening and on the morning of the test. We allow the patient to have the usual short-acting insulin dose for the evening meal the night before the test. The patient then eats their breakfast and presents to the clinic one hour later, when their glucose should be pretty high, they haven't had insulin and if their likely to have type 1 diabetes. And their capillary glucose must be tested. When the reading is above 150, then the patient is sent to laboratory where glucose and C-peptide are drawn. In this case, when the test is done correctly, and if you have strictly gone by the book, you would give a specific mixed meal, but for practical purposes just eating a normal breakfast is satisfactory. A value of less than 0.6 nanomoles

per liter, then it indicates type 1 diabetes. Often, we don't need to do that but if you're going to do it, it's important to do it properly.

So, I'm running -- I guess we started about seven or eight minutes late. I'm running up on time but I'd like to get to this last section, whether I get to the treatment slides I'm not sure. But just to talk about, because I think there are important considerations of type 1 diabetes in Native American patients that we need to consider. Insulin resistance is an underlying mechanism in a number of disorders so here are the factors that predispose to insulin resistance and we talked to all about them earlier today. And insulin resistance is at the basis of a number of these diseases, the hypertension, the dyslipidemia, arterial disease, and in women, polycystic ovarian syndrome.

So, these are features that can be clinically useful parameters to identify insulin resistance. We're familiar with acanthosis nigricans. It's the thickening and darkening of skin in the neck and other skin folds under the arms, the groins, and skin tags. And then the little red cherry angiomas that look like little red dots or ticks that are capillary overgrowths on the skin. Those are pretty highly sensitive for insulin resistance and then these other features here have varying degrees of sensitivity, for instance, interestingly merely having impaired glucose tolerance isn't a particularly sensitive indicator. And I'm sorry that I've omitted to include the source of this data. It seemed that should be higher than this, but high fasting insulin, high insulin after glucose, and then the typical triglyceride abnormalities, low HDL, being overweight and high waist circumference. These are all pretty reliable indicators of insulin resistance. Now, if we look in our patients who have type 1 diabetes, we don't have these because the patient already has diabetes. We can't test for these. They're not producing their own insulin and they already have type 1 diabetes. But it's important to know if they have insulin resistance superimposed.

So, we need to consider these other factors. If our patient with type 1 diabetes is hard to manage on a high dose of insulin and they have acanthosis nigricans, skin tags and angiomas. If they have high triglycerides, low HDL and especially if they are obese then, we need to consider that insulin resistance is playing an important role here. This leaves us with the question, if you have type 1 diabetes, does this therefore preclude you from having the risk factors for getting type 2 diabetes, or can you just as easily have the risk factors for type 2 diabetes and develop them and express them other than the insulin deficiency, which you've already got because you've got type 1 diabetes. The answer of course is that there is considerable overlap.

Many of our patients with type 1 diabetes as they get older are going to express insulin resistance and be difficult to manage because they have many other features genetically and environmentally of type 2 diabetes. So, it's important to consider that many of our patients with type 1 diabetes can develop the metabolic features of type 2 and these should be treated. Insulin sensitization can therefore be an important component of treatment of patients with type 1 especially as they age.

I'm going to move to my last few slides, which is talking about principles of insulin therapy. These are more principles that I think are very important and often overlooked and they are not necessarily the current treatment guidelines summarized in a specific way, but the simplest regimen that achieves diabetes glycemic control should be employed. We shouldn't just give the patient any more complex regimen than is necessary because they are less likely to follow it.

An initiation adjustment of insulin should be based on appropriate availability of his monitoring data. I'm constantly surprised and I believe many of my patients, when they say that their doctor or provider never asks for their meter, never asks to look at it. And I know many of you are because we have the downloads in our EHR and on our desktops. So, meters are being downloaded and then data is being looked at. But a lot of the time it isn't and that's unfortunate.

Sliding scale insulin alone is never a suitable prescription and shouldn't be permitted on quick orders. And the insulin that's administered now should be dosed based on historical data of glucose at a later

time point. If you are administering short-acting glucose at lunch, you're administering it to achieve a good glucose value at supper, and so the previous days, you can't look ahead for today's supper, but the previous days supper time readings should be used to adjust the patients or the patients should use these. Of course, there's carbohydrate counting, et cetera, so they're accounting for their food intake. It's clear to me that our patients are just, are not understanding this simple concept that the insulin you give now is dosed and measured against the glucose you are going to achieve later.

So, we know of a number of reasons why sliding scale insulin alone is discouraged especially in patients with type 1 diabetes. I'm going to move through these slides in the interest on time, because they just exemplify what I was talking about in terms of when insulin should be dosed, and I think they just say it visually so I'm going to go through these. If you choose to print out the slides, then you will be able to look through those. Sorry that the line came out in black in the insulin curves and that wasn't supposed to but somehow it got changed.

So, it's important to remember that NPH and Detemir insulin do have a peak and they are only once a day insulins in a fairly low dosage, usually 30 units or less. Glargine is a true once a day insulin, of course within our system it's many times the price so we tend to use Detemir first. But once you get above 30 to 50 units of Detemir then, you need to consider that you're going to be seeing a peak about 10 hours after administration and that you need to split this.

So, additional considerations are, in patients with coexistent features of insulin resistance, consider the benefits of using insulin sensitizers. Pioglitazone sensitizes up to 35%, metformin up to 15% to 20%, and these effects are additive so you can substantially lower an insulin resistant patient's insulin dose by using insulin sensitization. The insulin dosing should not be based on postprandial readings alone. Even the American Diabetes Association guidelines mention that you can increasingly use this, but remember that the preprandial glucose is the dose determining value. If you have high postprandial glucose and you don't know the preprandial glucose, it's still possible for patients to get hypoglycemia because you're not looking at their lowest dose limiting glucose value, which is going to be right before the next meal. You need to know this to safely dose insulin.

This is a representation of me in my fighting days because this is something, an issue I'm prepared to fight on because I think it's very important and that's why I put my Union Jack shorts on. So, supplemental -- I call myself Doc Rocky but you don't have to. So, supplemental dosing of short acting insulin postprandial is also discouraged. I see this a lot where patients are testing their blood sugar an hour or two after and if their blood sugar is high, they're giving additional insulin. Our new synthetic insulins were specifically designed to work with the profile of being given when the food is taken. And if you give it afterwards then, you're having a considerable amount of insulin action when the meal has been absorbed. Not only that, but the patients end up taking seven shots a day sometimes which is really miserable for them. So, you get stacking with overlapping shots of insulin, piling up and causing late hypoglycemia. So again, I'm prepared to get out and get punchy about that.

So last slide, it's one recommendation to change that you can make in your practice as a result of today's presentation. So, I'd like to offer these four to choose from. If you're doing the stimulated C-peptide challenge to diagnose a type 1 diabetes, be sure to do it properly. Hold the insulin, feed the patient. You don't have to personally feed them of course and verify glucose is above 150 milligrams in order to get a valid result.

The second one that I'd like to be take-home point was consider the potential benefits of insulin sensitizer use in type 1 diabetic patients who have clinical laboratory evidence of insulin resistance. Third one, this is a Doc Rocky point, which is avoid sliding scales in ambulatory patients, and there should be no quick orders. In my world, there would be no quick orders for sliding scale insulin in your pharmacy menu. Have a look when you go back and if they're there, please consider having them removed. Dose both short- and long-acting insulins proactively against their desired action point and

make sure that our patients, in your education of them, understand this. And then, finally, stacking is for chairs and pancakes, but not for insulin.

So, I'll try to address, for those of you who are still on, I'll try to address some of the questions or comments. This is where you get to flatten me. So, thank you.

Jan Frederick:

Thank you Doctor Bryer-Ash.