[MUSIC PLAYING]

MARTIN WIJKSTROM: All right, so I have too many slides. I'm going to go a little bit fast. If we have questions from a coordinator perspective, I'm very glad we have Antoinette Carol here who will help me with those.

So this is the pancreas in the center of the belly just around the belly button. And it has a tail-- let's see if this works. It's hard to see. So tail and a head and it's around the duodenum which is the first part of the small bowel after the stomach. So it's very central. It's abutted too-- or many big vessels go near it and through it, so it's a complex organ from a surgical standpoint.

So the function are exocrine, it helps with the digestion of sugars and lipids. And also endocrine function, which is our focus. That's what we want to replace with a transplant. So it makes insulin. That's the majority of the hormone. It also makes glucagon. So insulin brings sugar down in blood. Glucagon brings sugar up in your blood. Several other hormones also, like pancreatic polypeptide, and there's also somatostatin, and VIP, and some others. So the physiology is basically-- so if the sugar is low, you make glucagon and the sugar goes up. And then insulin is needed to bring sugar down. So from digestion, into the blood, and then insulin helps bring the sugar into the cells.

So there are several types of diabetes. So type 1 is typically then the one that hits young patients, children. It's an autoimmune disease. Type 2 hits older patients, obese patients. And then type 3c is the diabetes if you have diseases primarily from the pancreas, like chronic pancreatitis for example. And then gestational diabetes typically goes back after you're done being gestational, and then with your increased risk of being type 2 diabetic after.

So the word comes from Greek. So diabetes means siphon, mellitus means sweet, and insipidus, which is another type of diabetes when you lack a hormone from the brain and so you pee water basically. And that is without flavor. We don't use that test anymore, the flavor. So the diabetes is defined by a fasting sugar of more than 200 or-- so 200 after food and 126 after a fast. And if you have a question, if you're

near 126, then you would do a glucose load and if it's more than 200, then you're diabetic.

So it's a little bit surprising but it wasn't until 1993, it was actually established that tight insulin control, tight sugar control, reduces long term complications. And this is the classic graphs I've chose that as A1C goes up-- so poor sugar control here-- then you have progression of retinopathy as one example of a secondary complication. So the worse the sugar control, the more eye disease you had. And the better control, you have better control of your eye disease. But then on the other side you could also have then severe hypoglycemic events if your sugar are low. So if you're sugars are low means good A1C, then you have many more hypoglycemic events.

And the difficult thing is for patients who have brittle diabetes it's tricky to control, so then they have lots of both. Their sugars are high and low. So they're A1C may be fine but they have high glucose excursion. And then they have risk of both secondary complications and death in their sleep from hypoglycemia. So type 2 diabetes comes from insulin resistance. And I'm not going to go into detail, but it typically presents in the middle age in obese patients.

So I talked about this a little. So type 1 is typically young patients, thin, sudden onset, and they don't make an insulin and they must take insulin. So type 2 diabetics are older, overweight, they slowly get symptoms. And they have decreased need of insulin compared to type 1s because they actually make a lot of insulin already, and they may require more. We can also give them pills to stimulate the pancreas to make more insulin.

So chronic complications, secondary complications, is macroangiopatic, so that can hit the big vessels. You can get atherosclerosis, then you get strokes, ischemic problems in your legs and brain and bowel. Peripheral vascular disease, you have foot ulcers and the highest risk of amputation after trauma is from diabetes. So microangiopathic disease then causes small vessels to get diseased, and those are in the eyes that get symptoms, and also in the peripheral, so feet, and also the small vessels in the kidneys. So diabetic retinopathy is the number one cause of diabetes in adults. And diabetic nephropathy is number one cause of kidney disease, 43% of new cases, especially if you add hypertension to that. And neuropathy is very common. So 60% to 70% of diabetics have mild to severe disease.

So this is a pancreas transplant. I'm not going to go through every little-- oh, sorry. This is a carotid artery. So this is a patient had stroke. You go in and take away the plaque in the carotid artery. And this is more common in diabetics, and so they're two to four times more common to have a stroke. And it causes lots of disease and mortality in diabetics. So treatment of diabetes typically then in the '70s was one daily injection with 17:30 insulin. And you checked your sugar in your blood, in your urine. In the '90s insulins were purified. And we then also had long-acting and short-acting insulin.

Then in the 1990s even, patients had diet restrictions. So they weren't supposed to eat candy. More than just healthy, they were told to not eat things with sugar. Now they're still supposed to eat healthy, but now we can count calories and give them insulin based on what they eat. And we have many different sorts of insulin, so short, medium, or long-acting insulins. And we can also treat secondary complications a bit differently so the outcomes are better. But despite perfect control, or better control now with modern technology, we still have the complications of low sugars and sometimes death from that.

So intensive therapy is-- the rules have actually increased. So for a while, the A1C goal was 6.5, now it's 7.5 for intensive therapy just because hypoglycemic events are so dangerous. Now in recent times, we have continuous glucose monitoring and insulin pumps. There's sensors. Sensors you can put also in the skin, and dual pump systems in Europe. I don't think they're in the US yet, but you can inject both glucagon and insulin.

So despite the best efforts, we cannot completely normalize the blood sugar, and much of the difficulty is with the sensing part. So even if you have an implanted sensor, you don't get minute or second-to-second sugar levels in blood. And the cost is very high. And these patients are also limited from driving and they can't maybe be pilots. In severe cases, they can't take care of themselves or their families.

So this is what a pancreas looks like after it's out from the donor. There's an artery, the splenic artery goes to the tail and the superior mesenteric artery goes to the head and the duodenum that must come with the pancreas from the donor. And

then we connect those two vessels to one iliac artery down in the groin from the donor system to make the connection one in the recipient. So this is then the perfect glucose sensors. So the islets in the pancreas feels exactly what the sugar level is and then it gives off exactly the right amount of insulin. So we treat diabetes but the cost is lifelong immunosuppression.

So then we just have to find a balance. What is the burden of diabetes on this particular patient? Risks of hypoglycemia unawareness and maybe death. And long term, of course secondary complications versus burden of transplant to the immunosuppression and the risk of surgery. So we have to do precision medicine to find the correct organ for the correct patient. So it's a big job and we have lots of coordinators. And I think Antoinette is-- we have to update a little bit but many of them are still here.

So the pancreas transplant candidate is evaluated similarly to a kidney patient. But we also need the input from the endocrinologist because we have to make sure their insulin control is the best it can be. If it's not the best it can be, then it has to become the best. And at that point maybe they don't benefit from a pancreas anymore. So we check blood testing here with c-peptide, make sure they're type 1 or type 2. We do heart evaluation which is a little bit more in depth than for just a kidney. And we do normal workup basically as for a kidney. And then of course, the endocrine consult is very important to make sure they are in optimal therapy.

So type 2 diabetics can also be treated with pancreas transplants. So if we look at the insulin requirement from a normal type 1 patient, that's about 0.7 units per kilo per day. If you're type 2, you may require up to 5 or 7 units per kilo per day. So it could be much more insulin requirements and that may not be treatable with just one pancreas. So then in for organ allocation purposes to give the pancreas to patients that have a good chance of doing well, we have limited-- or UNOS has limited the type 2 diabetic patients to have a BMI of less than 28. So patients first have to lose weight to optimally treat their diabetes, and then some patients don't even need a pancreas after they reach that.

And the age cutoff is based on what we typically have found in individuals over 55. So normally patients over 55 don't qualify, so we have set that limit so we don't unnecessarily work up patients who are older. So this is a patient who has

hypoglycemia unawareness, and that's a patient who doesn't feel they have low sugars. So they can be driving or taking care of their child and then they just pass out. So to assess that, we use the Clarke score. So it's a questionnaire, and we ask patients basically how often they need help from others, how often they need to go to the ER, how often EMS is called to their house, and what level of sugar they feel their sugar is low.

So when they have lots of points, they don't feel the low sugars and then they become hypoglycemic unaware. So for patients who have more than four, they do have hyperglycemia unawareness. And if you have that, then you would benefit from a pancreas transplant even if you don't need a kidney. So that would be a pancreas transplant alone.

So this is the questionnaire. It's probably too small there but-- so patients then basically can lose-- so this guy now can do flying lessons after he treats his diabetes. And some of course, if your pilot, you can't work. So we have to sort out who benefits or not. So if you are type 1 diabetic only, then you would benefit from a pancreas if you have unawareness. But if you have marginal kidney function, with the Prograf we can push you into kidney failure needing dialysis.

So in Minnesota in the '80s and '90s when they figured this out, they found that 30% of patients who had pancreas transplants alone were pushed into dialysis. And that's not good. So now we limit the patients to those-- pancreas alone to the patients who have adequate kidney function. So we talked about the evaluation already. So this is Lillehei and Kelly who did the first pancreas transplant in Minnesota in 1966. And it worked for a few days and they had a leak. So there are lots of technical issues, so they actually just didn't drain the pancreatic juices. They just tied off the duct. So the pancreas got pancreatitis and then they had clotting and leaks and lots of complications. So then over the next decades it was worked out how it's done. And we really haven't changed the technique in the last 15, 20 years.

So the different types of pancreas, we talked about pancreas transplant alone already, so that's those who have good kidney function but hypoglycemia unawareness. If you don't have a living donor, then you can wait for cadaveric organ. Then you could benefit from a simultaneous kidney, pancreas and that's the majority of them. And then if you have a living donor, it's better to do the living

donor kidney first, followed then with the pancreas after that.

So contraindications to transplant is chronic infection or untreated infections, irreversible rehab potential, or persistent non-adherence to follow medications or follow up, and active substance abuse. That's very similar to kidney and any other organ. Other contraindications is malignancy. And this is again some anatomical pictures of the pancreas and how it looks when it comes from the donor. So it has the spleen attached and then on the back table we do this work where we connect the vessels. And we take off the spleen here, and we shorten the duodenum. And we make sure it doesn't bleed after we reperfuse it.

So we can either connect the duodenum, which brings the pancreatic juices to the bladder, or we can connect it to bowel. And to the bowel is more common now. It's more physiological. You don't lose bicarb then in your urine. One negative thing is that when we connect the pancreas to the bladder, we can then measure amylase and lipase in urine, and that's a very quick and easy way. Now in these cases, we have to measure amylase and lipase in blood, and it's pretty nonspecific.

So this time it's a pancreas. So this is the artery anastomosis here and the vein is over here I think. It's hard to see on the picture. So then nursing care is of course key to successful outcomes because they need intensive care for at least one night, and then they typically stay in the hospital for about a week after. We monitor the pancreas function by measuring sugars. And typically it goes down to normal within 20, 30 minutes and stays down. It can fluctuate a little bit after the patient starts eating or if the patient gets graft pancreatitis after. And we don't treat that. We just watched it, make sure it doesn't cause any systemic effects with fevers and things like that.

We look at the wound closely because it's a higher rate of infection after a pancreas transplant because we do a bowel anastomosis that is uncontaminated. The most common reason for a technical failure is graft thrombosis. And we actually have to take out 7% of the grafts within a week after transplant and that's pretty high. So all the patients know this going into it that they may lose 7 to 10-- of a 10% risk of losing the graft.

And then sometimes we have to go back to the operating room to look at the

vessels, make sure the blood flow is good, that the positioning is good. And maybe we have to wash out infection and remove blood clot around the pancreas. So that's not uncommon, so we also tell the patients about that. And then after discharge we follow them very closely, so daily for a while on our outpatient clinic on Seven West, and then closely in the outpatient clinic for life after.

We serially do labs, so amylase and lipase are checked with labs. And we also measure A1C and c-peptide to make sure the pancreas is working well. So if the enzymes are elevated in blood, that could indicate rejection. So then we would do a biopsy. But it's not perfect, so if you look at a 5 year survival of a kidney, it's probably around 85, 90%. 5 year survival of a pancreas, if we do it from a combined, it's maybe about 70%. So it's a 10, 15% difference, and that's just because we cannot track or monitor rejection as well from the amylase and lipase. The kidney's more sensitive, so we basically just follow the kidney and treat the pancreas as it comes from the same organ. If we do the pancreas from a different donor, so pancreas after kidney, then the results are worse. So then they're about 65% to 70% at 5 years for this particular reason.

All right, so the Prograf levels have to be a little bit higher, 10 to 12 for life, than in the kidney that we can go down to 4 to 8 in about a year or so. And that's because of this rejection rate. So if we see the amylase and lipase go up higher, and especially if the sugars go up, it's too late. Then we can't rescue the pancreas. We'll try to prevent rejection more than is necessary in the kidney. That also explains why the PTLD rate and the cancer rates are higher in pancreas. So they're also expected to follow up with their general health care maintenance with their PCP and nephrologist, and they need standard cancer follow up as for all our transplant patients, and for other issues.

So the post of course, we had talked about this, so I see you first and then in the floor for about seven days. So some data here. So graft thrombosis, so it's a little bit depended on if it's a kidney combined with the pancreas, it's 5.5%. It's 12% from a pancreas alone. And that's possibly that the patients who have kidney failure have less risk of thrombosis. That's probably the reason. Wound infection rate is pretty high, 11 to 18%. The infection rate after normal surgery and non-immunosuppressed patients, about 5%. The leak rate is about 5 to 9%. Most of

them we can just treat with a drain. And the graft pancreatitis we don't really treat, we just watch them.

Outcomes we talked about a little bit. This shows that the outcomes have improved over time. So in the era from 1966 to '87 the results were not great, but now they're improving. But despite the techniques improving, we still have early draft loss so it's not perfect. And this is a more survival graphs. Can skip that. So you can see-- so Prograf and Cellcept are our standard immunosuppression. Some patients who have lots of antibodies also needs steroids. Results are improved. So the recent outcomes are improving certainly from the past.

So post, we talk about complications. So if we had a kidney, then of course, we have the standard kidney transplant complication risks of leak and stricture. And this is a picture of what rejection looks like in a pancreas, all these little blueberry cells are t-cells and they are not supposed to be there. We talked about graft function already and can skip that. So this is indications we talk about for isolated pancreas transplants, so severe hypoglycemia or difficult to control diabetes, if their sugars are high and low at the same time.

And we talked about the allocation systems that was changed in 2014 to prevent patients-- so we have over 20 million patients in the US with diabetes. 19 million of those 20 have type 2 diabetes, and the type 1 diabetic patients basically would benefit more from a pancreas transplant. So in order to protect them from type 2 patients using up all organs, we have limited-- or the UNOS has limited allocation of organs to patients who have already maximized treatment with non-transplant means, for example, by losing the weight. So to qualify you have to have a BMI of 28 or less and you have to have a proven c-peptide positive for type 2.

So we have to pick a good risk patient. We have to minimize the risk of complications and picking good organs. And with the new technology with the pumps, we may see fewer patients referred to us. And with the older population of donors, we may have fewer donors. So a total in number of transplants for pancreas have gone down all over the country. So good patients are those less than 55, BMI less than 30, or 28 for type 2, the insulin use should be less than one unit per kilo per day but it's not a fixed limit there, and of course they should have minimal coronary artery disease and peripheral vascular disease to minimize complication.