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Carolyn: I'm Carolyn Coyne. I'm a Scientist in the Division of Pediatric Infectious Diseases.

Brian: And I'm Brian Martin, Vice President of Medical Affairs here at UPMC Children's Hospital of Pittsburgh. We'd like to welcome Radhika Muzumdar today to our podcast. She's the Chief of the Division of Pediatric Endocrinology here at Children's Hospital and she's also an Associate Professor in Pediatrics and Cell Biology at the University of Pittsburgh School of Medicine. She arrived at Children's in 2014 from Albert Einstein College and the Children's Hospital Montefiore in the Bronx, New York. And we welcome her today and look forward to hearing a bit about what brought her to Pittsburgh and some of her research interests and clinical interests here at Children's. Welcome Radhika.

Radhika: Thank you Brian. What brought me to Pittsburgh? I think I came here, like you said in 2014. And I would say what brought me here is the reputation of Children's Hospital, especially in care of children with diabetes. And diabetes is an area that's always been of interest, not only in clinical care of these kids, but also my research focuses on diabetes and especially type two diabetes. And what factors regulate insulin resistance and what can we do to help kids or adults with type two diabetes.

Carolyn: So when did your interest in diabetes first start? So at what stage of your training and how did you get involved in the research aspect of it?

Radhika: That's an interesting question and maybe a cliche answer, but I do come from a family with a lot of members with diabetes. So the interest started pretty young. And my mentor, I always look at my dad is one of my mentors and he had diabetes, so that always solidified my interest. But I think overall working with the children and getting interested in pediatric endocrinology, it combined my interest in math, it's all algorithmic everything. So I guess that's what brought me to the field of diabetes.

Brian: That's interesting stuff. Could you speak a little bit about how your with insulin like growth factors and peptides has influenced your perspective over time. And maybe a little bit of background about where and how that started and where you see that going.

Radhika: So as I say, I'm a pediatric endocrinologist by training and growth hormone and insulin like growth factors, IGF-1, are kind of the bread and butter of pediatrics. And when I was looking at research labs to go into, there was a lab which I was very interested in Einstein, that worked on insulin resistance and the biology of fat. And I wanted to do something related to that. And that was an aging lab. So they were looking at age-related factors. So I wanted to bring something from my pediatric endocrinology experience to that field. And so my earlier work was studying the role of growth hormone and IGF-1, which is insulin like growth factors and its binding proteins in insulin homeostasis. So I was able to bridge my pediatric endocrinology background with the research labs expertise, which was insulin resistance and type two diabetes in adults.

Carolyn: And how do you feel that the basic research has influenced your clinical work or vice versa?

Radhika: Very much. I think basic research just alters the way you think. You kind of imagine everything happening inside the body. I think that helps us understand physiology, so that helps us understand what best will help the kids. So for example, one of my earlier work was to look at the different types of fat. Every fat person is not the same. Where you deposit fat is important. So that was one of my earlier work that showed that if you had a belly fat or apple type of distribution of fat, so that fight is more harmful because that fat is deposited in your abdomen and that's what we call the visceral fat. And that's different from somebody who has a pear shaped obesity where the fat is mostly in the back rear region or in the ties.

Radhika: That's a better type of fat deposition. My work looked at specifically looking at different proteins and peptides that are secreted from the two fat depots. The subcutaneous fat or the fat under the skin versus the visceral fat. And we showed that the visceral fat is more harmful because it makes many more peptides that increased the risk of diabetes, high blood pressure and inflammation. So bringing that back to clinical setting and we can look at [inaudible 00:04:57] circumference as one of the indices of those belly fats. So you're able to understand the biology of the fat, understand that all fat is not equal. And then you can bring it back to clinical to understand who is at higher risk for comorbidities like diabetes and hypertension.

Carolyn: And how do you model these different sort of fat deposits? Do you use sort of a mouse model?

Radhika: Yeah.

Carolyn: Do you give the mice lots of cookies? How do we ...

Radhika: Yeah, there are different ways of doing that.

Brian: Where is your lab?

Radhika: Oh the mice models, oh they are different kind of fat we can give them. They love the fat. They love the chocolate donuts.

Carolyn: Smart mice.

Radhika: Smart mice of course. So we can give high fat, we can also give western diet, which is high fat and high sugar. A donut is high in sugar and high in fat, that combination is worse. So we can model all of these, take it in the mouse model and find out the different side effects or you can call it a complication and how it affects insulin resistance. That helps us tell kids or families on what kind of diet is good for them.

Carolyn: And do you find that that's something that kids with diabetes have as a major obstacle to them is optimizing their diet, controlling their diet? And do you think that that's a

difficulty? I will say my husband's a type one diabetic and so I'm very aware of the mathematical calculations of carbs and how that then influences how much insulin you take. Do you think that is one of the biggest obstacles to ...

Radhika: Yeah. It's a very big thing. When people think of diabetes they think of insulin, just insulin or a medicine to treat diabetes. But when we look at it, we always think diet is just as important as insulin. So you can take the right insulin but eat the wrong diet. Your diabetes is going to be worse or vice versa. When you think of diet in a diabetic, it depends on the child whether they have type one or type two diabetes and again whether they have any comorbidities. So for example, type one diabetes, if you're a lean type one and if your problem is blood sugar control and if you are on right doses of insulin, yes one has to eat healthy. But we are more concerned about simple sugars.

Radhika: Whereas a type one can have a dyslipidemia or lipid problems and if they have lipid problems then we would tell them to watch that. And a child with type two definitely we worry about other diseases like diabetes, high blood pressure, high cholesterol, high triglycerides, all of which either alone or in combination can increase their risk for cardio-metabolic side effects. So we do advise them and it is one of the biggest hurdles for not only kids with diabetes, but for the whole family. Which we try [crosstalk 00:07:39].

Carolyn: Oh, absolutely.

Radhika: Yeah.

Brian: I do not pretend. So full disclosure, I do not pretend to be well read in this in any way whatsoever. But I did take notice of a paper that was published in this month's journal of Pediatrics regarding a Paleo Diet regimen or a very low sub 24 gram carbohydrate diet regimen, which seemed to have a positive, a really quite a positive impact on hemoglobin A1c levels. I think the average was like 5.36 average, like over 36 months, somewhere in there. Is there a relationship or at any part of the studies, not necessarily the basic science studies that are going on in our division of endocrinology, but specifically about how your division interfaces with the dieticians and others on your team in regards to such a finding?

Radhika: Very good question. And I think it's a very long question, so I'll try to answer the question in parts.

Brian: Yeah I apologize for that.

Radhika: No, no, no.

Brian: Quite a soliloquy there.

Radhika: No. Your question about Paleo Diet, but as you can see there are multiple types of diet where you can modify the different macronutrients to different levels, but ultimately the broad goals we try to follow, the more complex carbohydrates the better. Avoid

simple carbohydrates, avoid saturated fat. Those foundations still hold same. And in terms of what we are doing as a division, so we have multiple Dietitians who come to all the diabetes clinic and obesity clinic and we are trying to do some things innovative. So right now one of the things we are working on is to bring a test kitchen or a model kitchen to our clinics when there's diabetes or obesity clinics. So someone can actually come introduce kids to healthy diet.

Radhika: Often we find many of our kids have not, they don't like fruits and vegetables, especially vegetables. And some of them have not gone beyond corn or carrot. So we want to introduce them to new vegetables. So we are thinking of having a test kitchen kind of thing during clinic. Introduce them to one healthy grain or a vegetable, give them some fun facts about it and then engage them and then let them taste so that maybe they can go home and try that. So that's one thing. We are now also doing a study looking at video game based nutrition education. We kind of tell people about eat this, eat that. But many times they haven't heard us or they haven't processed what we've said. So we are working with a company in California about a game based education. So basically by playing the game, the character gets stronger by eating fruits or vegetable and gets weaker when he eats a donut or a pizza.

Radhika: But with that, we have incorporated nutritional advice. If they want to, older kids can click on it to see why they got weaker. What about the fat and glucose? So we are just doing a study in diabetics to see if that avoids all the yo-yoing up and down of blood sugars and whether we can influence kids' behavior. Instead of us telling us this is good, maybe they should feel that it's good. That if they ate a broccoli they got stronger. Maybe we subconsciously influenced them to eat better. So that's one of the thing. And we are creating puzzles and crossword games and find the word, etc., but based on fruits, vegetables and grains. We are distributing them in the clinic waiting area. So they learn some fun facts about the food. So we're trying to, in addition to standard nutrition education and that's what we are comparing the video game based education to.

Brian: That is interesting. And I'm sure this is as much a family engagement as it is a child because we sort of had the parents as our patients as well and these situations.

Radhika: Absolutely. I think if the parents are not involved or not have not bought in, it doesn't work. Because they do all the grocery shopping at home.

Carolyn: Oh, absolutely.

Radhika: Yeah.

Carolyn: What do you see as sort of the the next steps in treatment or care of diabetes? So certainly even during my husband's lifetime, the kind of advent of the pump based system, which has I think really changed the quality of life, at least of my husband, I think of a lot of other people as well. But where do you see sort of the challenges that remain and how even just basic science and research could help us get to the point where maybe you wouldn't even have to use a pump?

Radhika: Right. So two part answer to that. First is, can be prevent diabetes from happening. And second, how effectively we managed the diabetes and are we managing it or we treating it. So far we are treating the glucose but we have not treated the diabetes. So we are hoping some fundamental breakthrough will come. In terms of the Beta cells are cells that make insulin and those get destroyed in diabetes. So there's effort from groups here with Dr Gittes and others trying to see, even our division is involved in that, to see whether if the Beta cells are getting destroyed can be changed, some of the cells into Beta cells.

Radhika: But the hurdles that we still have to sort out is are these cells also targeted by auto immunity and will they be destroyed. So it's in evolution, it'll happen, but that's the longterm vision for diabetes. But short term, how to improve the lifestyle. Because they have to check blood sugars multiple times, dose multiple times. So an average child can get six to eight times blood sugar checks plus five injections or five to seven injections. That's like 15 times poking your skin. Can we minimize that? That's where pumps and continuous glucose monitoring come in. And every day there are advances in the glucose monitoring. CGM or continuous glucose monitoring can noninvasively check your blood sugar every five minutes and show you a graph on your phone so you know when your sugar is going to drop. It can give you indication when your sugar's high.

Radhika: So there's lot of technology that is there, but as we use the technology we are identifying limitations but the industry is keeping up and trying to solve. A new CGM has just come out I think yesterday, Monday, going out so that that does not need calibration. Otherwise you had to calibrate the CGM. The new CGM does not need calibration. But I think the next step in innovation, which is already approved for 14 and over and we are now going to do a study in younger kids, is semiautomatic pumps. Have a glucose monitor that feeds blood sugar readings into an insulin pump that adjust the basal insulin on its own. So it's semiautomatic because you still have to put in what you're eating and adjust for high blood sugars, but that's going to improve quality of life a lot. Right now that got approved for 14 years and older and at Children's here we are going to do a study in younger age group and we are doing the paperwork for that. I think that's the next step that is semiautomatic and a fully automated one will be the next step.

Carolyn: Well and for kids I imagine that would be very important. I mean it's difficult enough I think for adults and I speak just from my own personal experience to sort of manage this and deal with this and I imagine for kids having something that would be ...

Radhika: Absolutely. Imagine a kid in the middle of soccer. I've had my son's friend crying in the middle of the game. You don't know if they're crying because the blood sugar is low or they missed a kick.

Carolyn: Yeah.

Radhika: And if you had the CGM telling you, you just pull out and see, oh it's not a low blood sugar, he can continue. Or if the sugar is low, you know when to pull the kid back.

Carolyn: And these pumps actually will send the signal even to the parent's phone, correct?

Radhika: Right.

Carolyn: And that's I think a major improvement.

Radhika: It can send as many as five phones.

Carolyn: Yeah.

Radhika: So grandparents, parents, babysitters. So kids can go on overnight camping trips and parents can watch their blood sugars from home. Kids can be on the bus and parents don't have to have to worry. So technology has made significant strides. Yeah.

Brian: And I imagine as well on the providers side that also allows you to interrogate that data and then kind of customize your treatment approach and your engagement approach in much more real time rather than relying on a handwritten log or other kind of a cumbersome things by the patient or family.

Radhika: Absolutely. It's also increased the complexity of the things we are looking at at a visit. So the more data, the more time it takes to analyze. But we are looking at different ways of optimizing that by setting limits, red flags that can draw our attention to that. And so that may be allow us to look at this tons of data in a efficient way. Instead of all shiny pennies everywhere. Kind of look at goals, the red areas, where are the greens. And we can use informatics to better management of diabetes. And that's one of the things we are hoping to achieve. Better integration of all these technology based data into our electronic records as well as into our clinical visit.

Brian: I'd love the gearshift a little bit if it's okay with you and I was perusing some of your research interests. And I'm interested, I'd love to hear a little bit about your work with the hypothalamus and energy metabolism. And where do you see that research interest with. What were sort of the genesis of that and how are you carrying that out here at children's?

Radhika: Yeah. So when people think of glucose metabolism, often people thought of liver, skeletal muscle and adipose tissue. So for years we have worked on the role of hypothalamus because that's a region of the brain for the non-physicians out there. So the hypothalamus is a key area that integrates signals from all over the body and regulates our food intake. It regulates our energy expenditure but it also regulates our glucose metabolism. So some of our work has looked at growth factors and how they work on the hypothalamus. And we showed that even among the family of growth factors, they have opposing effects and they have independent effects on the brain in the way they regulate. We also know that factors like Leptin act on the hypothalamus and curb our food intake. But what has complicated matters a little bit is that with obesity, the brain also becomes leptin resistant just like the body becomes insulin resistant.

Radhika: It's important to understand what parts of the body regulate metabolism. It's also important to know how can we change the sensitivity and how we can use that to improve. So compared to mouse models which we study, where we can give the peptide of interest directly into the hypothalamus, in humans we have to rely on the peptide to cross the blood brain barrier and actually get to the brain. So we are always looking at ways using mouse models to differentiate between the two. Is it important for the peptide to get to the brain or are the effects a combination of central versus peripheral? And that's what we are looking at. Our lab is also looking at another new, relatively new protein, called humanin. Which it binds the idea of BP3, which is in the growth factor family.

Radhika: And we are looking at this peptide's role in insulin secretion, insulin action, insulin resistance. But this is also an anti-apoptotic peptide. So we are looking at ways wherever there is cell death, can we minimize cell death. And that offshoot research has taken us into cardiovascular research. And we showed in mouse models that single dose of this peptide after the mouse heart attack, which simulate a heart attack, we give this peptide, we are able to decrease the heart damage by more than 50%.

Radhika: So we are now working with a center in New Orleans, which does pig models and we are now applying for grants to NIH to study this peptide in a heart attack model in a pig with the understanding that the pig heart is very similar to human heart. And many of the translational thing, what works in the mice doesn't always work in the humans. But if it works in the pig there is a good chance it'll work in humans. And we have preliminary data to show that even in a pig when we induce heart attack, but we treat with the single dose of this peptide, we can decrease infarct size and damage. So we are very excited by that research and that's the hottest thing happening in our lab right now.

Brian: That's fascinating. All through apoptic...

Radhika: All through apoptotic and metabolism. We think humanin improves glucose metabolism. And that's where the connection between metabolism and myocardial infarction. Because there's data to show that if you make the heart use glucose when there is stress in ischemia reperfusion, the heart survives better. You have to innovate fatty acid oxidation and favor glucose oxidation. And we have shown that this peptide does that and favors glucose oxidation, reduces oxidative stress and decreases apoptosis. So three different effects, we feel it is affecting in infarct size. And so that's where we are. We are looking at pig models, we are looking to see if it prevents heart failure.

Carolyn: Well thank you for joining us. It was great to hear about your research here, your clinical work, and we look forward to hearing more about you.