EPISODE 30: PREDIABETES

Dr. Rita Kalyani, MD: Welcome to ***Diabetes Deconstructed***, a podcast for people interested in learning more about diabetes. I'm your host, Dr. Rita Kalyani at Johns Hopkins. We developed this podcast as a companion to our Patient Guide to Diabetes website. If you want a trusted and easy-to-understand resource for diabetes or to listen to previous podcasts, please visit hopkinsdiabetesinfo.org.

On today's podcast, we are thrilled to welcome Dr. Nes Mathioudakis, who will be speaking with us about prediabetes. Dr. Mathioudakis is an endocrinologist at Johns Hopkins, focusing his clinical practice on the care of patients with endocrine disorders with a particular clinical interest in research focused on diabetes. His research is focused on health informatics approaches for Diabetes Prevention and Management. Dr. Mathioudakis received his medical degree from the Johns Hopkins University School of Medicine and completed his internal medicine residency at Johns Hopkins Bayview Medical Center. He did a fellowship in Endocrinology, Diabetes and Metabolism at the Johns Hopkins Hospital and then joined the faculty in the division in 2012. Dr. Mathioudakis has also received his Master of Health Science degree in Clinical Investigation. After receiving his master's degree, he served as the Clinical Director of the Division of Endocrinology, Diabetes and Metabolism from 2016 to 2021. Dr. Mathioudakis is currently an associate professor of medicine at Johns Hopkins and the Co-Medical Director of the Baltimore Metropolitan Diabetes Regional Partnership, a five-year grant funded by the Maryland HSCRC to scale patient access to diabetes prevention programs and diabetes self-management training programs across the state. Welcome, Dr. Mathioudakis.

Dr. Nes Mathioudakis, MD: Well, thanks so much for having me. Pleasure to be here.

RK: Thanks so much for being here today. I wonder if you could start off by telling us: What is prediabetes? And why is it important to identify?

NM: When I talk to my patients about prediabetes, I often use the analogy of the check engine light in the car. You can kind of think of prediabetes like the check engine light for diabetes. So imagine you're driving along and your car's check engine light comes on, your car's still driving fine to you [and] you're not noticing any difference in how its operating. But that light coming on as an early warning system to you. It alerts you that if you don't do something about the problem soon, you might have serious engine trouble down the line.

Prediabetes is when someone has higher than normal blood sugar levels, but not quite high enough to be classified as Type 2 diabetes. It's sometimes referred to as impaired glucose tolerance or impaired fasting glucose, depending on what test was used to detect it. And why should we care about identifying prediabetes early? Well, it's pretty simple. It's quite important, actually. Once that prediabetes check engine light turns on, if we don't step up and make some healthy changes, like upping our physical activity, eating healthier, losing some weight, if we need to. There's a good chance that we might slide into type two diabetes in the next few years, which of course carries an increased risk for other health problems like heart disease, stroke, kidney issues, and vision loss. But more importantly, catching prediabetes early gives us a chance to do something about it. You can maintain your vehicle in very good condition because of the check engine light. Now we can slow down or even stop that slide towards diabetes with the right lifestyle changes and sometimes even medications.

RK: I really liked that analogy of the check engine light, especially since as you mentioned, sometimes, you know that can come on and unless you get it checked right away, it can really evolve into something more serious. Would people know if they have prediabetes? Would there be any warning signs or symptoms? Or would it be something that they would just find out about, like you said, on a blood test as a warning sign?

NM: That's a great question and an important one too. You know, the tricky thing about prediabetes is that usually there aren't any symptoms that people notice, which can make it harder to detect. But we're really reliant on clinicians identifying risk factors for patients and screening them. Some patients may notice some signs of prediabetes, one of which is darkening of skin on certain parts of the body; areas like the neck, armpits, your elbows, your knees, and knuckles. That's a condition called Acanthosis nigricans. And it's often associated with insulin resistance, which is a hallmark of prediabetes. But again, the signs are pretty subtle. Most people won't see any symptoms at all. And it's why regular checkups with primary care clinicians is so important, especially if you have risk factors for prediabetes, like being overweight or having a family history of Type 2 diabetes.

RK: That's really interesting. One of the questions that I feel like I get a lot in clinic is the naming, 'prediabetes.' Is this a condition that necessarily leads to diabetes? Often people will tell us they had been told they have a touch of diabetes or borderline diabetes. I wonder what you tell your patients when they ask you about that? Is this really a precursor to diabetes?

NM: I think the connotation of precursor implies that there's some sort of inevitable progression. I like to think of it as, like I said, the check engine light or even like a yellow traffic light so that if you continue on the current course then diabetes may be an outcome for you. But by no means does it mean that you are destined for diabetes. There is a very good chance that you could revert back to normal blood glucose control with lifestyle changes. There's a lot of debate over the term itself and whether this is actually a disease. I know the FDA actually doesn't consider this a disease state in terms of drug indications. And so I think it's just better to be thought of as an early warning sign and an opportunity to reverse the trajectory to diabetes, which of course, is not inevitable.

RK: I agree. I think that the pre-term sometimes can be confusing to our patients.

NM: Yup.

RK: But it's definitely important to emphasize that this is the opportunity to really change the trajectory, to change whether this does develop into diabetes or not. So it seems like identifying prediabetes at an early stage really could be a benefit for people so that they can act upon it. How common is prediabetes in the United States?

NM: Yeah. So, an important point to discuss; quite frankly, the numbers are a bit alarming. So, prediabetes is very common in the US. According to the CDC, more than 96 million American adults, that's more than one in three, have prediabetes. And while that statistic is concerning in and of itself, I think what's more concerning is the fact that the vast majority of people who have prediabetes, that's eight in 10, don't even know that they have it. And so this sort of a silent tide creeping in. And that's really worrying, because without intervention, prediabetes often does lead to full blown diabetes within a few years.

RK: It sounds like it's a tremendous public health issue, and really one where increased awareness could have tremendous benefit. You mentioned the testing that can be done to diagnose prediabetes. Can you talk a little bit more about the tests that people could take if they're curious if they might have prediabetes?

NM: Sure. So, the tests that we do for prediabetes are the same that we use to diagnose diabetes. It's just that the cutoffs that we use are shifted a bit lower, as you might imagine. So, there are three tests: the fasting glucose, the glucose tolerance test, and HbA1C, or we often just referred to A1c. For the fasting glucose test, you know, this measures your blood sugar when you've haven't had anything to eat or drink, except for water, for at least eight hours. And people with prediabetes have a fasting glucose between 100 and 125. So, 126 is the cutoff for diabetes. For the glucose tolerance test, you come in fasting, but then as part of the test you drink a sugary drink containing 75 grams of carbs and then two hours later, we measure the blood glucose and people with prediabetes have a glucose tolerance resolved between 140 and 199, where diabetes is 200 and higher. And then for the A1C test, the good thing about this test is it can be done at any time, even if you've recently eaten and it's an indication of what your blood sugar levels have been like for the past two to three months. So people with prediabetes will have A1c levels between 5.7-6.4 and 6.5-higher is diabetes. Which tests to choose really depends on your clinical situation. The A1C test is more convenient - you don't need to fast, but there are some conditions that can make it less reliable. Anything that affects hemoglobin, iron deficiency, if you're pregnant, it may not be as accurate [as well as] if you've got chronic kidney disease. And there actually is some indications [or] some research to show that there's some ethnic variation in A1C. Black individuals for the same levels of fasting glucose and 2-hour glucose results may have slightly higher A1C levels compared to white people, which could lead to a higher false positive diagnosis of prediabetes in black people. So we do like to look at the whole picture. Sometimes we're looking at more than one test to make the diagnosis.

RK: It sounds like there are many tests, or at least a few tests available. But the decision about which one may be individualized, is that right?

NM: For diabetes, we have to have two abnormal test results. There aren't clear guidelines for prediabetes. Now, do you have to have one result repeated twice? Do you have to have two different tests? But often clinicians will look at these tests are often obtained clinically anyway, certainly a fasting glucose, we may look at the trend over time and your fasting glucose together with an A1c to make this diagnosis of prediabetes.

RK: And what this be a test that someone would get screened for routinely by their primary care provider? Or would this be a test that they'd need to ask about?

NM: As for current guidelines by the US Preventive Services Task Force or that all adults between the age of 35 and 70, who are overweight or obese be screened for prediabetes every three years. So it should be offered to you. If it's not, if you fall in that age bracket or

you're overweight, you should ask your healthcare provider to screen you. Once you have a test that puts you in the prediabetes category, then you would be followed annually with lab testing just to make sure you're not progressing to diabetes.

RK: That's so good to know. It sounds like really anyone who is 35 or older should be screened for this and especially those who are overweight or obese. What about children? Can screening occur in children as well?

NM: Yeah, so the guidelines don't typically recommend screening for children. But we know that the rates of Type 2 diabetes in children are increasing. A lot of pediatricians will screen appropriately for this just based on their clinical judgment. Especially if the child is of a certain racial or ethnic background, or have they have a family history of Type 2 diabetes and are really struggling with weight management, it would certainly be appropriate to screen. Generally, we think of age as being a risk factor for prediabetes and children being at younger risks just by virtue of their age. We are seeing more and more diabetes in children and screening is appropriate, you know, on a case-by-case basis.

RK: I agree. It's certainly alarming the rise and diabetes that we're seeing in children, especially among ethnic subgroups, like you mentioned, or those who might have other conditions such as obesity as well. Definitely people of all ages, it sounds like, depending on their other clinical conditions could potentially benefit from the screening. How often would young adults get screened for this otherwise, if they didn't have any risk factors?

NM: So, the screening frequency is every three years. So, if you have a normal test result, then you know, checking again three years later and continuing on is what's recommended. But again, more frequent once the diagnosis is made, at least annually.

RK: That's good to know. You mentioned some of the risk factors already for prediabetes. I wonder if we could just talk about those in a little bit more detail. And also, I've heard about these risk tests and definitely talked about them with patients that I see. I wonder how often you talk about those with your patients and what you recommend for someone who you might be considering for screening?

NM: Yeah, so the risk factors for prediabetes are weight, age, family history, ethnicity, physical activity, and there are others. For all of these risk factors there is a prediabetes risk assessment tool that you can do that incorporates all of those in addition to your weight and gives you a score. And if you're above a certain threshold, it's really recommended that you'd be screened. Let's talk about them in a little more detail.

For weight, we know that excess weight, especially weight around the belly is a big risk factor. It's like carrying around extra baggage that puts a lot of strain on your body's ability to use insulin properly. So we use a BMI cut off of 25-29.9 for overweight and over 30 for obesity, but there are different cutoffs in Asian populations are a little bit lower.

Again, as I mentioned earlier, age is a big piece of this puzzle. So as we get older, especially once we hit 45, our risk of prediabetes goes up; our body's not quite as efficient as it used to be in regulating blood sugar.

Family history - Type 2 diabetes is a strongly heritable condition. So if you've got a parent or a sibling with type two diabetes, you're at higher risk

Also certain ethnic groups, so African Americans, Hispanics, American Indians, Asian Americans, and Pacific Islander patients are at higher risk.

Now lifestyle- So being physically inactive is a key factor. We know that regular physical activity not only helps control weight, but makes your cells more responsive to insulin and addresses that underlying insulin resistance that causes that diabetes in the first place.

And gestational diabetes is another strong risk factor. So, women who've ever developed diabetes during pregnancy, or given birth to a baby who's weighed more than nine pounds, have an increased risk of pre diabetes.

So it's a mix of different factors. Some of them you can change, like your weight and your physical activity, others you can't. But it's important just to be aware of these risks so that you can kind of take the right steps to reduce the ones you can and manage your health effectively.

RK: As you mentioned, you know, some of these risk factors are what we call 'modifiable ones' that you can change and others are not modifiable, such as family history or age, or even ethnicity. Focusing on the ones that you can change- the modifiable risk factors. If someone was concerned that they were at risk for developing prediabetes or diabetes, what do you usually tell your patients about how they can change their risk, how they can reduce their risk of developing prediabetes and diabetes?

NM: I mean, the first thing that I emphasize is that it is doable, and it's doable with small changes.These don't have to be extreme changes. From a weight perspective, we're talking about 5-7% weight loss being linked to significant reduction in risk. And for most people, 5% is within reach in terms of weight reduction.

Then physical activity, you know, we're aiming for 30 minutes per day for five days per week with no more than two days per week being inactive. So, a total of 150 minutes per week. And in some patients, they need to work up to that so it's balance maybe if 10 minutes at a time a few times in the day. It may not need to be continuous activity. And those two changes alone can have a big impact on reducing risk, particularly the weight.

RK: I agree the weight loss and the changes to diet and exercise can have such important effects on health and reducing the risk of diabetes. But they're definitely easier said than done, aren't they?

NM: Sure.

RK: It can be hard to implement those changes in practice. I know one of the studies we often talk about a lot is the Diabetes Prevention Program. I wonder if you might want to just touch about the findings of that study and why it was so important. And then maybe how in actual practice you recommend to your patients to implement these changes in real life? Because sometimes that can be different than what we find in studies, can't it?

NM: Yeah, absolutely. The Diabetes Prevention Program is a landmark study. It was published in the early 2000s. It was a study that randomized people to receive really no intervention for prediabetes, a placebo group. A group that got intensive lifestyle modification, focusing on things like diet, physical activity, and weight, and then a group that got the medication, Metformin, which we use to treat Type 2 diabetes. And the results were really impressive. So they found that the lifestyle intervention reduced the risk of progressing to diabetes by 58% compared to Metformin, which reduced the risk by 31% compared to the placebo. So really, really strong evidence. In fact, the strength of this evidence was greater than many of the recommendations that other drugs that we use in medicine for other indications. So, this is a lifestyle program that had a very, very strong level of effectiveness. And so yes, that to your point about, you know, this was a research study and so you've got the support of research coordinators, and you've got a really dedicated team developing, delivering the intervention and implementing this in practice can be a little more challenging. That being said, fortunately, the CDC recognized that this brings such value to patients that they developed the National Diabetes Prevention Program in which essentially local programs that have adapted the intervention that worked in that clinical trial can get recognized as a lifestyle change program. And patients can be referred to these programs to get the intervention that we know works. I tried to keep it simple. We know what works. This worked in a clinical trial. There is a real-world version of this out there today and patients need to get what we know works. And so referring people to a Diabetes Prevention Program should be standard of care for people with prediabetes.

RK: That's so amazing that we've seen such support from the Center for Disease Control for these National Diabetes Prevention programs, like you said, modeling them on what was done in the large trials, but really, for real-world settings. Are these funded? Are these covered by insurance? If someone has prediabetes, how could they find out about these programs?

NM: Most insurers will pay for the Diabetes Prevention Program. The programs themselves will, you know, of course bill for the service they're delivering and charge to the insurance to cover the costs of the program. There are thousands of lifestyle change programs throughout the country, and if you're looking to find one near you, the CDC website is the best resource. So you can just Google search 'find DPP near me' and the first sight that should pop up is the CDC's online registry, and you're going to want to look for recognized organizations. So, in order to be listed there by the CDC, the program actually has to report their outcomes data back to the CDC. They need to demonstrate that a certain proportion of their participants achieve the outcomes that we know are linked to preventing diabetes like 5% weight loss and increased physical activity. And at Hopkins our program, the Brancati center, DPP, actually has full plus recognition based on really impressive outcomes. So, I would encourage you, if you're interested in this, the CDC's website is a great resource to check out.

RK: That's great to know: 'find DPP near me.' That's a catchy website name and one that I think people can easily remember. And so great to know that these are covered by insurance. It seems like it's a win-win for people to enroll in them, it can only lead to better health outcomes. What are the barriers? Why do you think it's so hard sometimes to get people into these programs? Are they long, cumbersome programs for people to follow? Or what are some ways that we can facilitate people getting into these programs?

NM: That's an excellent question, Rita. And we've done a lot of work through this partnership that I've been leading in the state to identify the barriers to people getting into the DPP. Historically, despite all the evidence for benefit, about 5% of people who are eligible for the Diabetes Prevention Program, participate in it. And there's been some studies out of Johns Hopkins on this topic. Part of it is the patient is unaware and the clinician is also unaware there's a DPP that can help the patient, so there's low rates of referral. Now admittedly, this is a big commitment. Let's say you're identified, and you're referred; this is a year-long lifestyle change program. So, participants meet weekly

for the first six months, and then it's every other week for the remaining six months. So that can be, you know, people are busy, and they've got jobs and finding a group time that works for them can be a challenge. But one thing that has made one, you know, silver lining with COVID, is that our DPP really shifted almost entirely to zoom-based delivery, and patients have loved it. It's convenient, you can log in at the start of your day, your lunch break, the end of your day; meet with a group of people and lifestyle coaches who are trained to kind of guide you through this process and provide advice and encouragement to you. And the outcomes are similar to what we were seeing with the in-person. I think the barriers historically have been lack of awareness and the commitment for people.

RK: It is great. I think, in some ways, like you mentioned, that the pandemic has brought about these other ways for us to reach out to patients. And particularly for the program that you're talking about the Diabetes Prevention Program, having that Zoom or virtual option can be really great, especially if you are working full-time, and like you said, you can cap it on to the end of your workday, or even maybe during a lunch break. I think meeting people with prediabetes where they are and really having a program that fits their needs sounds like it's key. Now, the National Diabetes Prevention programs around the country are certainly an amazing resource. And for people interested in them, like you said, perhaps letting their provider know that they're interested. The awareness factor can go both ways so for people listening, bringing it up to their provider, I knew that you're also involved in newer technologies, AI-based programs are apt to facilitate and support people who are engaging in these kinds of programs too. I wonder if you want to talk a little bit about the role they have in supporting people with prediabetes.

NM: There are different modalities for delivery of the DPP. We've just talked about sort of the distance learning which is a Zoom-based method; there's in-person. But there's also a digital modality and so that might consist of an app or you know, logging onto a website and checking in with a lifestyle coach. That, you know, that flexibility may be attractive to some people who can't commit to the scheduled check in frequency for the DPP. You know, their products like Omada and Noom, that have evidence behind them and are really effective. And so, if patients find that committing to the in-person DPP is challenging, I'd encourage them to explore other options like that. Even Weight Watchers is a recognized DPP. We are very interested in the role of AI technology in providing coaching support. So, we have an ongoing NIH-funded trial to compare a fully automated app, which delivers personalized push notifications to patients together with a digital scale, encouraging all the things you talked about for the DPP versus the standard of care, which is the human coach-based DPP. But, you know, we don't know whether a computer, using machine learning algorithms, can deliver the same results as a human coach and this is something that needs to be tested. If it can, then thinking through the scalability issue for, you know, there's so many people affected by prediabetes and people are busy may not be able to make it to the DPP, this might be an option to just reach more people and hopefully make a dent on this public health problem.

RK: AI or artificial intelligence is so exciting.

NM: Yup.

RK: Definitely, it is the way of the future. And as you mentioned, there's so many programs out there; commercially available, and also through the government that people can look into. What about people who just want to do it on their own? Perhaps they're not interested in enrolling in a program? Do you think that could be successful, home-based regimens? Or what do you recommend?

NM: You know, I have a lot of patients who are really serious about reversing this and you know, they'll tell me "Hey, Doc, look, next time I come in, I guarantee you my fasting sugar will be normal and my A1c will be in range." And I trust them because they are committed and you know, there are a lot of tools out there. Maybe it's a calorie tracking app, like My Fitness Pal, where you're putting in your calories, you've got a calorie goal set for you, you're weighing in. The important thing is monitoring. We've got wearable devices-Fitbit, Apple watches -that people can use to make sure they're getting to that goal. All of these would be expected to yield the results. I still think that there is value; if a person is able to commit to going to the DPP, for more intensive education. You know, this is something [that] is going to be a long term issue for the patient and you want to be able to sustain this and so there's a lot of emphasis on strategies on how to troubleshoot when things get a little tricky - when life gets in the way, your stress levels are up, and you revert back to old eating habits; what to do if you've got some barriers to physical activity because of health issues or whatever. Yes, I think you can do it on your own and of course, that would be encouraged if people can't commit. But if they're able to, I try to push people to get the evidence-based intervention.

RK: And aside from the physician who might be the primary care doctor or the endocrinologist, or even another physician - who are other members of the care team that usually recommend people with prediabetes see, in order to achieve these health care goals?

NM: Yeah, it's a tricky question. You know, you were talking about often nutrition is a big component of this. So, you might think that, you know, referring a person to a registered dietician would be helpful, and medical nutrition therapy is certainly valuable. The problem is that not all insurance companies will cover medical nutrition therapy for prediabetes. There's good coverage when you have diabetes, but if a patient's insurance will cover a visit with a registered dietician, I think there's certainly value there. You know, aside from that, I think a lot of the resources may actually not be within the healthcare team itself. So maybe it's your personal trainer, who is an extension of the healthcare team. If it's about physical fitness, or physical activity levels. I think it depends. It depends on the individual. If, for example, weight is a big part of the problem, referral to a weight management center, where we're thinking about medications that might promote weight loss, things like the GLP-1 receptor agonist that's been, you know, all over the media this last year, because of the shortage can certainly be helpful for prediabetes as well.

RK: It definitely does take a comprehensive approach, as you mentioned, and it could be many members of both the health care team and really, like you mentioned, the extended fitness or health team at home that could contribute. Even family members to prepare meals.

NM: Oh, for sure.

RK: Talking a little bit about nutrition and diet. Do you have a specific type of diet that you mention or recommend to people with prediabetes? Or what do you usually tell them in terms of how to modify their food intake?

NM: There's not a single diet that we can say, you must follow for diabetes prevention. But there are some principles. We do want to avoid, you know, processed foods, sugary drinks, high-calorie meals, foods that are very high in saturated fat. You know, the diabetes prevention program itself actually tested a low-fat, low-calorie diet. And that was, you know, that was two decades ago and there's since been a lot of shift in thinking towards, you know, lower carb, ketogenic diet. When you look at the evidence for diabetes prevention, there haven't been very many diets that have been rigorously tested, but there are certain [diets] - like the Mediterranean diet does have some data to show benefit. And that, you know, that's a diet that's going to be high in fruits and vegetables and healthy nuts, lean poultry, and moderate intake of fish lower in the red meat intake. Those are just general principles, regardless of the diet that you're following that should help with diabetes prevention, I think I would encourage , patients may have a preference for a specific diet. Sustainability is going to be key, you know, we have intermittent fasting, we've got ketogenic diets. All of these certainly work for weight loss. Some may be harder to sustain than others. And this is a marathon, this isn't a sprint. We're trying to make some, like permanent changes in metabolic setpoints for an individual and so I do think trying to find a diet that you can stick to in the long term is going to be really key.

RK: I agree. I think, you know, the dietary changes, the exercise regimen, you know, the weight loss that can occur 5 to 7% is so important to delay the progression or prevent the progression to diabetes. How long can diabetes be delayed or prevented? Can it be delayed you think indefinitely? Or what have the studies shown, as for how long people can really put off, [or] delay the transformation from prediabetes to diabetes?

NM: You know, when you look at the statistics on the rate of progression. So a little different than your question. But you know, every year about 10% of people in the pre-diabetic state will progress to diabetes. When you look a little bit longer, there was actually a meta-analysis, which is, you know, pulls together results from multiple studies looking at people for up to 24 years, this was about a quarter of a million patients. And it shows that over like a 12-year period, about a third to 40% of people will go from prediabetes to diabetes.

Going the other way, regressing to normal and how long you sustain it, there's similar data to show that the results are pretty favorable. So, this was there was a study actually, right now, 47 cohort studies of over 100,000 people and a considerable proportion of people with prediabetes returned to sustained normoglycemia, which is a fancy way of saying normal blood sugar levels, at about one to five years of follow-up. This was achieved by about a third-60% of people and in the 6–11-year follow-up of the intervention it was about 20 to 40%. So those are pretty high numbers for a pretty long period of time. Overall, the rates do tend to go down with longer follow-up, as you might imagine. That's partly due to age, but also just sustaining the intervention. I think the key thing is sustaining. So you know, whatever intervention you implement that worked initially to get your glucose to control, it's a matter of keeping that up and maintaining your glucose levels in that range.

RK: It's great to know and a key point to emphasize that with a diagnosis of prediabetes it is not inevitable that you will develop diabetes. And that really, it is the opportunity, as you mentioned, to focus on interventions; changes to lifestyle, weight loss that can either stave off the progression, or really, in some people, as you mentioned, revert back to normal, which is pretty amazing, to a decade later, if not longer. And for those people who have tried, you know, lifestyle changes, diet and exercise, and for whatever reason, haven't been able to sustain it or hasn't given the desired health benefits, when do you consider medication for prediabetes and which ones to usually consider?

NM: Medications definitely can play a role and we use them often, but their effectiveness varies compared to lifestyle. And overall, I do want the takeaway message to be that lifestyle has been shown to be more effective than medications. Even medications that we use for diabetes, which is kind of counterintuitive, but two of the drugs that I use, and you know, there's some variability here because these are used to off-label. But Metformin is typically used first line and then the other that I mentioned earlier is semaglutide or it goes by the trade name Wegovy if it's being used for weight management or prediabetes. So Metformin, as I mentioned earlier, in the Diabetes Prevention Program, lowered the incidence of Type 2 diabetes by 31%. And it was shown to be more effective in some subgroups of patients. These are people under the age of 60, people with a BMI over 35, of women with a history of gestational diabetes, as well as people whose glucose levels were on the higher end of the prediabetes range. Fasting glucose of 110, or more, or an A1c of 6 to 6.4 of that 5.7 to 6.4% range. And so in those people, if they've tried lifestyle, and it's not working, we will certainly add Metformin on early. All drugs have side effects, Metformin can have some GI side effects; diarrhea, abdominal bloating. It can also affect the absorption of vitamin B12. So if we're going to use it for pre diabetes in an off-label fashion, we want to make sure that we're monitoring for side effects. And then the semaglutide that I mentioned, this is a drug that's used for diabetes that has a significant weight loss benefit, it was tested in a trial called the Step 1 trial; they gave it to overweight adults, many of whom had prediabetes, and they did show significantly lower rates of Type 2 diabetes compared to the people who didn't get it. The one thing we don't know about any of this is how permanent it is. You know, when you're using the medications, you're losing weight, you're improving your insulin sensitivity. But if you were to come off of these drugs, how permanent are these effects in the changes in your metabolism? We do need longer term studies to know that specifically. And you know, there are other drug classes have been tested for diabetes prevention, and they've shown some modest benefit, but all the other drugs generally have more side effects than potential value, and we don't tend to use them for diabetes prevention.

RK: I think this is a question that probably both you and I get all the time in our clinic, you know, "should I take medication for my prediabetes?" And that's really great to hear about the subgroups in the Diabetes Prevention Program where Metformin, as the drug that was studied in that trial compared to lifestyle, may have had a benefit. I agree, I see blood sugar is rising, people are trying lifestyle for the years and A1c continues to rise, that might be a time we think about medication. Or gestational diabetes, in particular too, as you mentioned, women who have a history of that, or severe obesity. These medications are relatively well tolerated as you talked abou,t the Metformin and the semaglutide, Wegovy, just with some GI side effects in some people. Are these drugs approved for the treatment of prediabetes?

NM: Yeah, they're actually not approved. And so we've talked to all my patients about that, up front, that this is an off-label indication. And you know, most patients understand as long as we go through the side effects and talk about the risks and benefits are willing to move forward with it. But you know, the drugs were developed initially for diabetes management, and that's what they got their approval for. The other thing I'd like to just mention briefly about who to treat with medications, there was actually a recent study published in JAMA Internal Medicine in 2021, which was a little bit controversial in making the claim that older adults may not derive as much benefit for management of prediabetes in general. So, this this was a study of 3400 people with prediabetes followed in another observational study and the mean age of the patients was 75 years. They found that during the six years of follow-up, it was much more likely that patients would revert from prediabetes to normal than they would progress to diabetes or actually, unfortunately, die from some other cause. If you've made it, if you're older, you know, your 70s or beyond and your HbA1c is in the prediabetes range and holding, there is a chance that it will continue to stay in that range. And it's a little bit controversial about whether you would derive benefit from lifestyle modification, or weight loss at that point. I think this depends, again, it's made on a case-by-case basis; what the patient's other health issues are and what I think their long-term longevity is predicted to be, to kind of figure out what that return on investment is for them.

RK: Thanks for bringing up that study. I think there were a lot of questions asked after that study came out about what are the benefits of diagnosing someone with prediabetes, even giving some of the label of prediabetes at any age. That's always you know, that's the cost, if you will about diagnosing people with this condition. As I recall in that study, it relied primarily on A1c and fasting glucose and we know that the physiology might be a little different in older adults, that two hour glucose levels might be more predictive to people that have complications. But, I agree, I think that has to be individualized for the goals of the person who has this diagnosis. And then also, knowing that Medicare, I believe, also does cover the Diabetes Prevention Program. Is that right?

NM: Yes, absolutely.

RK: Yeah. And we know that in the Diabetes Prevention Program, the greatest benefits for intensive lifestyle are found in our older adults. So, it's not an easy decision. It's definitely a discussion to have with patients, and definitely one that continues to be debated. And part of the reason I think that we've had these challenges, don't you think in getting people into these programs?

NM: Yes. Yes, it is. For sure. I think that this decision really does need to be made on a case-by-case basis. And insurance coverage is a big part of it. My recommendation would be first, I mean, if you are interested yourself in participating, the program can help you figure out whether you're covered. And so just a quick call, a screening intake and if it's not covered, and it's not right for you, they can certainly provide you with other options.

RK: One of the topics that we haven't covered, and I wonder if we could just talk about briefly is: What causes prediabetes? Why does this occur in the first place? We talked about risk factors, but you know, what causes prediabetes? And are there other health care conditions, let's say like high blood pressure that if someone has, do you think they should be screened perhaps earlier?

NM: That's an excellent question, a very important one. And you know, we talked about prediabetes. First and foremost, we need to talk about insulin resistance. Insulin is a hormone made by the pancreas. And we like to think of it like the key that lets sugar in your blood enter your cells where it can be used as energy. You know, in your brain and your heart and your muscles and your liver where it can be stored as a fuel source for later. Imagine that the locks on your cells start getting a bit rusty, and that key, insulin, doesn't work as well and sugar starts to build up in your blood instead of going into your cells where it's being used as an energy source. And that's what we call insulin resistance. It's a major player in prediabetes. It's the same pathophysiology we see in Type 2 diabetes. Now, why does insulin resistance happen is a complex question. It's not completely understood, but it does often have to do with excess weight and lack of physical activity as well as to some extent the genetic predisposition. It's like our bodies were designed to be on the move when we don't keep active or when we're carrying extra weight, the system for managing blood sugar can really get out of whack. Insulin resistance starts many years before the diagnosis of Type 2 diabetes and over time, the pancreas, to compensate for this insulin resistance, has to produce more insulin to overcome that barrier. And that can be really taxing on the cells of the pancreas, and then that the insulin production can start to decline. And that's when sort of diabetes starts to manifest. So we want to kind of address the insulin resistance upstream before we start to see problems with insulin production.

RK: Yeah, I think that's an important point that by the time people are found to have prediabetes, the process has been probably going on for about five years, at least in terms of the insulin resistance, and it's a warning sign, but it's a warning sign of a process that's been going on for a few years. For people who have other metabolic conditions, do you think they're at greater risk for developing prediabetes?

NM: Yes, prediabetes often goes hand-in-hand with other features of the metabolic syndrome, so high blood pressure and high cholesterol are often found to be bystanders here. And so that check engine light is actually a check engine light for multiple conditions. So, if you are found to have prediabetes, you are often evaluated for high blood pressure and your cholesterol is checked. Addressing all of those issues can really reduce your risk of cardiovascular complications down the line.

RK: That's really good to know and we talked so much today about the opportunities for intervention; for lifestyle; for medications for those who might need it as well. But for those who, for whatever reason, aren't able to delay the progression of diabetes, or maybe it's discovered too late, and prediabetes persists. Besides the risk of developing diabetes, what other complications are they at risk for? You mentioned cardiovascular disease, that can occur even in people that prediabetes?

NM: Yes, it can. And so, to your point earlier about, prediabetes may be around for a long time before we even know it. It turns out that many patients with prediabetes will already develop some of the complications that we associate with diabetes itself. And so those are complications that affect the small blood vessels, microvascular complications, as well as the larger blood vessels in the body that’s macrovascular complications. So, prediabetes is an independent risk factor for macrovascular complications, mainly around cardiovascular disease and stroke. And there's actually been some studies showing, higher rates of heart disease and mortality compared to people who don't have prediabetes. And similarly, there are higher rates of microvascular complications like retinopathy issues with the eyes, neuropathy, or nerve damage, and nephropathy, kidney damage. As high as 8% for retinopathy and prediabetes and somewhere between 8 to16% of patients will have neuropathy at the pre-diabetic stage. And I often have patients come to me because they're having numbness and tingling in their feet at the prediabetes stage. It's actually interesting that pathology can start so early. But again, I think if you're catching this at this stage earlier, even if you've got these complications, you know, reversing the prediabetes to normal should be expected to kind of delay the progression of those complications itself as it would if you were diagnosed with diabetes.

RK: It's so important to know that even at the prediabetes stage, you could be at risk for those complications, the cardiovascular disease, the retinopathy, and the neuropathy and further underscores the importance of diagnosing and identifying and treating this condition.

NM: For sure, you know, it's interesting is that even though there is this higher risk of these complications, professional organizations don't formally recommend screening for these complications in people with prediabetes because there's really not enough data yet to show that

it's effective and cost-effective. But I think what is important is to know that you have prediabetes as the starting point, because they will often be detected as part of the evaluation there.

RK: Well, thank you, Dr. Mathioudakis, for this informative and really great discussion about prediabetes, the awareness that's important and what people can do, who are concerned that they might be at risk to find out and the opportunities to support people with prediabetes and attaining their health care goals. I wonder, in closing, what parting words you might have for listeners who are either concerned they have prediabetes, or diagnosed with prediabetes, and are motivated to try and delay the progression to diabetes? What would you recommend as their next steps?

NM: Well, I would say if you're concerned about your risk for diabetes, or prediabetes, and you don't know whether or not you have it, step one is getting screened. And as Dr. Kalyani had said earlier, you may be the person that brings this to your clinician's attention, get screened if you've got the risk factors. If you have prediabetes, the good news is that this is a reversible condition with lifestyle changes. And there are programs that are proven to reverse your risk. That is the Diabetes Prevention Program. And as I mentioned, the CDC registry to find the program really encourage people to look there. And the other thing that I would say if you are a Maryland resident interested in the DPP, you can also check out the healthier2gether.org website. That's the healthier2gether website and provide you some information about the Hopkins and University of Maryland programs. But I've really enjoyed speaking with you about this really important problem. And, you know, thanks for opportunity to kind of increase awareness around this.

RK: Well, thank you so much for being here. This was such a great discussion and a really important public health issue that I hope gets some more awareness as well. So that people can get the treatment that they need. I'm Dr. Rita Kalyani, and you've been listening to Diabetes Deconstructed, we developed this podcast as a companion to our Patient Guide to Diabetes website. Our vision is to provide a trusted and reliable resource based on the latest evidence that people affected by diabetes can use to live healthier lives. For more information, visit hopkinsdiabetesinfo.org.

We love to hear from our listeners. The email address is hopkinsdiabetesinfo@jhmi.edu.

Thanks for listening. Be well and see you next time.