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Investigating the Link Between Type 2 Diabetes & Obesity

Dr. Wysham:

The association of obesity with diabetes, hypertension and cardiovascular disease are well known, but increasingly, we are recognizing the impact of obesity on multiple organ systems, including the ovaries. Polycystic ovarian syndrome is incurring with increasing frequency as we see the increase in frequency of obesity. And it can be a harbinger of future health risks.

Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. Carol Wysham and joining me to discuss her research on Type 2 diabetes and its link to polycystic ovarian syndrome and obesity is Dr. Kristen Nadeau, a professor of pediatric endocrinology at the University of Colorado School of Medicine. Dr. Nadeau, welcome to the program.

Dr. Nadeau:

Thank you.

Dr. Wysham:

Now Dr. Nadeau, you're regularly seeing and treating adolescent female patients. Having first-hand clinical experience, what trend have you seen in your practice regarding obesity in this population?

Dr. Nadeau:

What we're noticing in girls is that we tend to see more problems with low physical activity and obesity in our girls that are teenagers when compared to our boys, and as a result of that, the rates of developing type 2 diabetes are higher in girls versus boys, and one of the other aspects that also goes with risk for developing type 2 diabetes is developing polycystic ovarian syndrome, or PCOS. Obviously, only girls get that, so they're gonna have more than the boys, but we are seeing more evidence of insulin resistance, which is the underlying cause, we believe, that leads to both PCOS and type 2 diabetes, and links them together. And it may be partly because puberty happens a year earlier in girls than it does in boys, so that we're seeing more of those insulin resistance related complications in girls than boys, because they're having that whole process of puberty happening sooner than it happens in boys. But we also think that physical activity is really important, and some research from our group has shown that once puberty starts, that sex differences arise, where girls have much less physical activity than boys do, whereas prior to puberty, they're quite similar.

Dr. Wysham:

Well, that's very interesting. Are there other aspects in your research between polycystic ovarian syndrome and obesity other abnormalities that you're seeing besides polycystic ovarian syndrome?

Dr. Nadeau:

Yes, other things that we're commonly seeing in our adolescent population, in girls in particular, would be fatty liver disease, and we do see higher rates of fatty liver disease both in girls with type 2 diabetes and in girls with PCOS. And then we also are seeing higher rates of high blood pressure, and having what we call the metabolic syndrome, so the constellation of having glucose abnormalities along with blood pressure abnormalities, and then abnormalities in the lipid profiles, which would include high triglycerides and low HDL cholesterol. And then another aspect that we're recognizing more recently is that sleep apnea and problems with sleep are more common overall in our adolescents with obesity, but in girls that have PCOS, they seem to have a higher degree of having sleep apnea and sleep problems than other girls do. Usually, we see more of a male predominance with sleep apnea, but with PCOS, it is causing these girls to have a higher rate than we would expect of having problems with sleep apnea and sleep trouble.

Dr. Wysham:

So that's very interesting. I personally wasn't aware of the high prevalence of sleep apnea in these adolescents. So, if you look at

patients with polycystic ovarian syndrome. As you have pointed out, they are at higher risk of developing several other metabolic complications, including type 2 diabetes. Were there specific risk factors for the development of diabetes that you identified in your research?

Dr. Nadeau:

Yes, specifically in girls with PCOS, those that were at higher risk of developing diabetes did have several features. Overall, we found that girls with PCOS had eighteen times the rate of developing type 2 diabetes when compared to girls with obesity that didn't have PCOS, so PCOS itself gives much higher rate of development of type 2 diabetes. And then within the girls with PCOS, those that were more likely to develop diabetes were those that had elevations in their hemoglobin A1C, so if they had a hemoglobin A1C in the prediabetes range, they were much more likely to go on and progress. In addition, if they had an elevated ALT, so if there was evidence of liver inflammation that would go along with nonalcoholic fatty liver disease. And then finally, also, being of Hispanic ethnicity also was a higher risk. So, what we saw is the girls that were the most likely were those that were Hispanic with an elevated ALT and an elevated hemoglobin A1C.

Dr. Wysham:

That's very interesting. For those just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. Carol Wysham, and I'm speaking with Dr. Kristen Nadeau about the risk of type 2 diabetes in adolescent females who present with polycystic ovarian syndrome and obesity.

Now, Dr. Nadeau, what should we be aware of when we're seeing an obese patient who presents with polycystic ovarian syndrome? Are there any screening or prevention methods we can be doing better?

Dr. Nadeau:

Yes, absolutely. We would suggest that an adolescent girl with PCOS, who has obesity, should have screening for other comorbidities that go along with the metabolic syndrome, and that would include looking at a fasting lipid profile, specifically looking for elevations in triglycerides and low HDL. The HDL we wouldn't intervene on clinically, other than recommending exercise, but the triglycerides sometimes do need treatment. We would also recommend looking at ALT levels as a marker for fatty liver disease, but knowing that it's a very insensitive marker, and so if there's a higher rate of suspicion, then we start to think about using other imaging, which usually is just in a research setting currently, but at least the ALT can give you an idea if there's inflammation going on in the liver. In the future, there'll be more access to things like FibroScan or using MRI with, markers of fibrosis as well as fat, that will likely be what will be recommended more in the future, but usually those are only available in research settings currently. And then we would screen for, sleep apnea, so taking a sleep history and considering a sleep study; looking at blood pressure, to be screened for hypertension; and then depression as well is quite common in this population and can really make treatment more difficult. And then the glucose itself, of course, looking at hemoglobin A1C is a good way to screen for glucose abnormalities. As far as the treatment, I usually prefer in a girl with PCOS that is obese, to start with a combination of insulin sensitizing medications and lifestyle treatment. So usually, that would be working on exercise and diet, along with metformin. And the reason is that metformin can get at the underlying insulin resistance, and by helping to improve insulin sensitivity, the pancreas doesn't have to make as much insulin, and by lowering insulin levels, we think that this helps to decrease the drive to make testosterone from the ovary. And then there are also other ways to improve insulin sensitivity. There's still more in the research realm, but increasing evidence that things like a GLP-1 analog or other medications that are currently being used more for type 2 diabetes may be effective in PCOS as well.

Dr. Wysham:

Well, that's very interesting and very helpful for those of us that are in the clinic. Now you'd previously mentioned that being of Hispanic heritage increased the likelihood of developing diabetes in this population. Were there other differences in the non-Hispanic white versus Hispanic versus non-Hispanic Black adolescents?

Dr. Nadeau:

Yes, we did see several racial and ethnic differences in the populations that we've looked at. In the non-Hispanic white group, we found more evidence of markers of insulin resistance, and specifically higher triglycerides, or the ratio between triglycerides and HDL cholesterol. And then in the Hispanic population, we saw more evidence of elevations of liver enzymes and of liver fat, so when we did an MRI looking at fat, there was more steatosis or development of fat in the liver. In contrast, in the non-Hispanic Black population, we see much less liver fat, and instead, in the non-Hispanic Black population, more evidence of glucose elevations, so more girls having prediabetes in the non-Hispanic Black population. And then usually the non-Hispanic white population is coming out intermediate, with having liver fat that's less than the Hispanic population but more than the non-Hispanic Black population. And we also saw more evidence of insulin resistance in the fasting state, so if you use a measure called the HOMA-IR, or the homeostatic model of estimated insulin resistance, that also appeared to be highest in the non-Hispanic Black population. So overall, there are differences in fat

distribution, where the Hispanic population seems to have more, liver and visceral fat, and then in the African American population, there appears to be more pancreatic dysfunction and lower beta cell function.

Dr. Wysham:

Oh, that's very interesting. Well, to tie all this together, Dr. Nadeau, what key messages would you like to leave with our audience today?

Dr. Nadeau:

A really important message is that knowing that girls with PCOS, whether they be of normal weight or overweight, have underlying insulin resistance when compared to other populations, and so it's critical, no matter what weight they're at, that we be doing things to help improve insulin sensitivity, which would include exercise and healthy diet, but that becoming obese or overweight then tends to worsen the picture of PCOS, and actions to try to prevent weight gain, or once it's there, working at trying to help weight loss, would be the most important. But it's a lot harder to lose the weight once it's there, so the most important thing we can do is in younger populations be encouraging regular physical activity and healthy diet and doing things for the whole community that helps girls to exercise more and to stay at a normal weight, so that we're not having to work as much on weight loss. But on the extreme end we're also interested in looking at girls with severe obesity that have more difficulty losing weight, and then using medications such as weight loss medications or adjunctive therapies used in type 2 diabetes, or even things like bariatric surgery. And so there's a lot more research to be done yet to see how we can best help the girls that are of the highest weight. And then I think the final comment would be that when there are symptoms that are more related to cosmetic symptoms, like acne and hirsutism, then there's a different class of medications that often is needed in addition. So, there is where we're gonna be using birth control pills, or things like spironolactone. But in particular, we need also more research about what birth control pills, and that type of an approach is doing to cardiovascular risk and diabetes, because it's not well known as much, although you can have improvement in periods and in cosmetic symptoms, whether there is, increase in risk in cardiovascular disease with birth control pills, and so that's another area that we really need new studies.

Dr. Wysham:

That's a great way to round out our discussion on the risk of type 2 diabetes in females with polycystic ovarian syndrome and obesity. And I want to thank my guest, Dr. Kristen Nadeau, for joining me in this discussion. Dr. Nadeau, it was great having you on the program.

Dr. Nadeau:

Well, thank you.

Dr. Wysham:

I'm Dr. Carol Wysham. To access this and other episodes in our series, visit ReachMD.com/DiabetesDiscourse, where you can be part of the knowledge. Thanks for listening.