KRISTEN G. HAIRSTON: Thank you very much to the coordinators of this meeting for inviting me. I feel like a little bit of a fish out of water as an endocrinologist amongst a lot of cardiologist folks. But I also see a lot of friends in the crowd. My goal is for this to be an informal type of discussion to give you some information, some background from our perspective in endocrinology and metabolism physicians. And then for you to ask some questions about how does this intersect with what you see and what you do on a daily basis?

So I'll start a little bit about really how this idea of cardiometabolic syndrome developed. So everyone's goal is to improve quality of life and try to prevent premature death. And really that's the goal of any health care provider. And for years, we all in our various specialties have come at it our specific angles. So we want to prevent kidney disease, or prevent heart disease, and primary care with screening, and endocrinologists with diabetes. And that's really been how we approached it.

But what we realized is that as we talk to each other, which is amazing now much we learn when we talk to each other, that we were seeing similar patients that seemed to have a similar grouping of symptoms and ended up in all of our clinics getting similar types of therapy. And it was with thought process that started to move to this idea of a syndrome, which is a collection of symptoms. And the cardiometabolic syndrome is a constellation of physical and biochemical traits that increase your risk of developing diabetes and/or cardiovascular disease. And you'll hear me use diabetes and cardiovascular disease almost interchangeably because as I hope to convince you through this presentation, what we're starting to learn is that they're not necessarily the same thing, but maybe their mechanism underlying it may be very similar.

So this is a little bit of a busy slide. But the idea is to show you the progression of this notion of metabolic syndrome. So way back in 1922, we had a physician that began to start clustering symptoms. And it started with a clustering of hypertension, hyperglycemia, and gout. And he noticed that patients that seemed to have that constellation behaved similarly. And over the years, we added more and more to the syndrome. And really when we got down to Reaven, which is really a hallmark for us, particularly in endocrinology-- this was at a ADA conference-- that's when really the idea about Syndrome X was coined because they added insulin resistance as part of this definition.

So what we have here are really the idea of what we considered traditional risk factors for cardiovascular disease. As people age, they tend to have more issues; gender; what is their blood pressure, trying to get your blood pressure control; type 2 diabetes. And it's really just at the weight we've talked about glucose regulation, not just overt diabetes, but type 2 diabetes; what is your lipid profile; and smoking status.

But over time, we've learned through research and experience that there may be more factors that related to this constellation, rather than the standard ones that we've always used. And what we've come up with are we call these emerging factors, which are now insulin resistance, and really looking at this as a clinical entity, a prothrombotic profile. This is when we were collecting-- and some of you do this-- inflammatory factors. That's what they're trying to construct there, thrombotic profile, inflammatory state, very similar. And one of particular interest to me is abdominal obesity, sadly as a personal and research topic.

So what we've transitioned to is this idea of global cardiometabolic risk. So we're not compartmentalizing it, as we've done in the past. But saying we recognize that all of these symptoms travel together. And what the evolution has been is really finding that the core of these is really this intra-abdominal adipositity or insulin resistance that's tied to adiposity.

So what I want to spend the rest of the time on is really taking you through how that's been a change in how we think about cardiometabolic risk in the research world, but there's been a lag in us implementing this in the clinical world. And this is where there's some room for improvement really in all disciplines to start adding this as a risk profile measurement.

So I think we're all familiar with this picture. And this is from 1947, with the idea that you're either an apple, which typically men are described as an apple android, with central adiposity, or you're a pear. Women are typically pears, more adipose tissue in the bottom half. Now, we know that you can have the same distribution in the opposite sex as well. But this is typically what we see. And for years, we attributed this to why we previously saw more cardiovascular disease in men because they tend to carry more weight centrally and women tend to carry it lower.

And what we know over the years is yes, there is a correlation between abdominal obesity and cardiovascular events. It's not just an aesthetic thing or how people are designed. There's significant risk attached to it. And I'll promise I'll try to limit these kind of slides. But is it's good to know that I'm just making it up.

So the HOPE study, which was very important, showed very clearly that cardiovascular death, MI, and all-cause mortality were significantly and linearly related to your weight size. Another study looking at the waist circumference, the larger the waist circumference, the higher the risk of coronary heart disease. Again, the higher the waist circumference, the higher your risk of developing type 2 diabetes.

So over time it was becoming clear that there was some connection with the abdominal girth and these disease states. And so part of what my recent research has been about is distilling down this idea of obesity. And we've all had patients in clinic-- or it's maybe it's just my clinic-- where they kind of go around and around that BMI doesn't apply to me. And even though it might say that I'm overweight on a chart, you can't tell. And I'm big-boned and everyone in my family looks like that, and-- yes.

But to their point, we have realized in clinical medicine and in research that every person with a BMI of 32 or 35 does not look the same. They do not have the same risk profile. So we started to distill down this idea of obesity, which was just a raw number, and started to look at what is the distribution of the obesity?

So we started with obesity here. We came down to central adiposity, which we can do with waist circumference. And now, even more, we looked with imaging modalities, CT scans, of the fat tissue that's in the midsection, where exactly is it? And this is a cartoon that describes exactly what I'm talking about.

So if this person comes to clinic, we may get a waist circumference. But we don't really have a good idea about exactly where is his fat deposition. If it's mostly in the subcutaneous, which is that orange, he might not like it. It might be unsightly. But in terms of his cardiovascular risk, it's less than if all of the adipose tissue leading to his increased waist circumference is in the intra-abdominal region.

So where we've moved is how can we start to learn more about these different compartments, rather than just the waist circumference? And in the research world, we've asked, well, OK, if it seems to be connected to being intra-abdominal, what's the driving factor of that? And as an endocrinologist, we always talk about the other little known endocrine organ, which is the fat cell.

What we have learned about the fat cell is it is a nasty player. It creates a lot of bad things. And again, this is a little bit of a busy slide. But if you look at this, these hormones and proteins are, I'm sure, very familiar to a lot of you in cardiovascular world. But what we found is that one of the main culprits in the production of these hormones is that adipocyte.

And when you trace back down to what's the cause of the inflammation in that atherosclerotic plaque, what may be the harbinger of those macrophages that might be coming to create disease, we come back to the adipocyte. And it's been linked numerous times in studies to inflammation, hypertension, insulin resistance, thrombosis. And these are just the types of proteins that we typically connect to these disease states. But we found that their origin is in the adipocyte.

And what we appreciate is if these are nasty proinflammatory, prothrombotic proteins and hormones, would you rather it be right under your skin or right next to your liver, your colon, your kidneys, where it can exert an even worse effect on those organs? So that's what we're finding out.

And here just describes a little bit about how we've tried to tie together this from proinflammatory state with risk. And C-reactive protein can be a bit of a challenge because if you look at a lot of the literature, it may suggest that that's something to check and follow all the time. But it becomes a challenge when you try to quote, unquote, "treat it." So we get in the discussion about risk versus something that's treatable.

So we know that a high CRP may be correlated to an MI. And that if you use aspirin, or have weight loss, or put someone on a statin, we can decrease their CRP, but not necessarily a person that has a lower CRP will always have less cardiovascular disease. So that connection isn't always there. But we know that it's an increased risk.

And again, this is just another graph pulling together what I was just describing. We have the cardiometabolic risk in the middle. And the blue section is really where the field is moving. So it's not just the general metabolic syndrome that we talked about in that first slide, with blood pressure, age, weight, do you have diabetes or not? We've really moved to this idea of central adiposity, inflammation, insulin resistance and trying to characterize that as a cause of the metabolic syndrome.

So some of the advances in risk assessment, so as a obesity researcher and as an endocrinologist I find that first of all-- and I'm sure you can collaborate this-- we don't always do a great job of even getting our patients to go with the stuff we know work, like blood pressure and statins, let alone adding a new risk assessment tool like weight circumference.

I struggle a lot in a very well-controlled research study. We get questions about where exactly is their waist. Is it above the belly button? Is it below? I can't quite tell. So we know that this can be very helpful in risk assessment, but it can be a little bit of a challenge.

So as we look at the cardiometabolic profile-- and really you can use the metabolic syndrome interchangeably-- but the language has moved a little bit more to cardiometabolic because we know that these same things are related to heart disease, what really needs additional attention and focus is the hemoglobin a1c or glucose management, waist circumference-- and that is how do we measure that accurate and integrate that into risk assessment-- and sleep history, which is important. Very, very clear in the literature, its relationship to negative outcomes, but not always something that we give.

So this is a graphic we have in our clinic just to remind people how you measure waist circumference. And admittedly, it can be a challenge because your landmarks are the iliac crest, which is the hip bone. Sometimes that's a challenge to find that. [LAUGHTER] I'm just saying.

But that's your landmark. And you want to bring the tape around at the iliac crest. And you want to bring it around level.

Some patients would like for us to measure their hip the way they wear the belts. Wear it low so you have a-- but no, alas. And it needs to be parallel to the floor is what we tell them. But this is a good side that we have. NHLBI came out with this to help clinics realize the appropriate way to check waist circumference.

And what we know is that waist circumference isn't perfect. But there's a great correlation between waist circumference and intra-abdominal fat. So though I can't put everybody through a CT scan, but at least if I can get this measurement and follow it along the same way we're dogmatic about blood pressure and dogmatic about glucose, it could be very helpful because we know that they're correlated.

What we don't see as much correlation is this waist-hip ratio. So that's actually good news that you don't have to feel like you're a seamstress, get the hip, and the bust, and the waist. Waist circumference is clean.

And the other piece of this for risk stratification is once you get the waist circumference, we've also found that you can then start combining risk factors. So often the question I get is, well, how do I know what they look like on the inside even if I do a waist circumference because people look differently? But what we know is when we start combining risk factors-- so they may have the same exact waist circumference-- but the person that has the elevated waist circumference and elevated triglycerides is at more risk than the elevated waist circumference and normal triglycerides.

And again, that's the notion of a syndrome. You're starting to accumulate risk factors.

Another instrument that's being used-- and again, this is a little bit more in the research world. But we're transitioning into more clinical-- is the sagittal diameter. Which you would mount this to the wall the same way that you would do-- or to the bed the same way that you do when you do stadiometer height. So this would be attached to the bed or to the wall. And you just do that measurement for patients.

And what we find is that sagittal diameter and waist circumference both have great correlation with intra-abdominal fat. So again, another clinical way that we can get to understand what's on the inside.

Another measurement that people are using, since it feels like people get CTs for everything, is that you can also look at the density of the liver in terms of fat mass, again to give you a measure of what the intra-abdominal fat content may be. Because we now know that fatty liver is really what we call an overflow phenomenon. There's so much adipose tissue in the intra-abdominal cavity that it begins to kind of seep into the liver. And with weight loss, you get regression of adipose tissue from the liver. So measuring the fattiness, if you will, of the liver is also a clinical measure that you can ask your radiologist to look at in a CT scan that was done for belly pain or something else.

DEXA scans, I use this a lot for osteoporosis. But this also is able to give you a total fat mass as well. So again, making use of tools that your patients already have, but then being able to extract some of that information to help you with cardiovascular risk.

And then the ultrasound is also used to look at the changes in tissue density to just try to get a general idea. Is it right under the skin or is it more intra-abdominal?

So now we get to the fun part, the how do I make this relevant to me? So we know about physical activity. It's good. Smoking, stop and don't start.

Glucose management-- as endocrinologist I have to pause here. So this is another area when we know that insulin resistance is part of the overall syndrome that's leading to cardiovascular disease. We've really moved from a very black and white description, you have diabetes, you don't, to understanding that glucose metabolism is really a spectrum.

And where there's room for improvement in clinical care of all of the disciplines I mentioned earlier is we as providers need to be more aware where that patient is on the spectrum. And we need to make the patient more aware of where they are on the spectrum.

For example, you're not diagnosed as having type 2 diabetes until you have a fasting glucose greater than 125. So there are several patients who get fasting blood work. Their fasting glucose is 110. The next year, it's 117. The next year, it's 122. And every they get that postcard that says your lab work looks great. And there's a little check on there, right?

And then, two years down the line, when they pop up and have a fasting glucose of 150, they feel like how did happen? I was just fine last year. And I feel like that's a bit of a dropping the ball on our part as clinicians. Instead of saying, OK, this is that time-frame when your fasting glucose is between 100 to 125, we need to be creating a teachable moment for patients.

We're not saying that you have diabetes. And I don't use words like you have a touch of sugar or you have a little bit of sugar. Because I think that trivializes is what I'm trying to share with the patient. I say your body is trying to tell us that it is struggling maintaining a normal glucose. This is your opportunity to turn the wagon around, weight loss, physical activity. Sometimes starting a medication can help jump start that.

But we've got to start helping patients understand that it's no longer I have it or I don't. It's really a continuum. And there have been some advances as well in diagnostic testing using a1c, c which is easier because you don't have to be fasting. You can get that in clinic. But again, an a1c between 5.7 and 6.4, that same gray zone where the patients need to be aware, OK, your body is struggling.

And last piece I'll mention about glucose management, as well as if we have a patient that is on steroids, and they say I was fine until those steroids gave me diabetes. What I often use as a correlator for patients, I say steroids are like a stress test for your pancreas. The whole reason we give you a stress test is we try to push your heart to the limit and see can it accommodate that demand? And if it can't, we try to figure out why.

Well, steroids really increase insulin resistance. That's a negative side effect. But that's one of the ways that they work. So if in the face of increased insulin resistance, your pancreas cannot keep up, then that lets me know that your pancreas is probably barely hanging on.

So if everything is perfect-- and what do they always say? When I don't eat anything, my blood sugar is perfect. Well, but you don't live in a state of fasting. You eat. And so if your body can't accommodate when you eat, then we have an issue. OK. Enough about the glucose.

Hypertension, I think we all know what we need to do better with that, bringing that discussion up. And I know I'm guilty of this. You have a long list of things to get through. And sometimes you're tempted to let the "I ran in front of my car, or I couldn't find a parking space, I've been really stressed out," you allow those excuses to be why we don't really press for that blood pressure to be better that day there in clinic.

And then I go back through my notes and I'm like, OK, a year ago it was they couldn't find a parking space. And then three months, it was still high. And it was their daughter had an issue, and the three months after that. And I let it go a whole year and not really address that.

And then "Others." Some of the research work that we've done shows that fiber is very important in reducing that intra-abdominal fat and insulin resistance, and good sleep. So not only sleep quality, but that optimal six to eight hours.

When you get less sleep than that, we've shown that people increase their visceral fat substantially. When you get over that, there really is no change. So it's not like you can make it up by sleeping 10 hours.

So ideally, what you want to six to eight hours. And I bring that up because often it's important to ask our patients with all these other risk factors, about sleep, about snoring, about sleep apnea, those things that we often don't ask about.

So as I try to wind down I get a lot questions because the idea about metabolic syndrome has been around for a while. And a lot of my cardiology colleagues and nephrology colleagues say, well, OK, I get this small list. And you want me to check all these things, and put it in a chart. But at the end of the day, is it really a valid predictor of cardiovascular risk?

And honestly, study after study has shown that for major cardiovascular disease, a person that has this constellation that that we mentioned is twice as likely to have an event as someone that doesn't have the constellation. And the more of these that you have, the higher your risk is. And in terms of type 2 diabetes, it's five-fold when you have this constellation.

And even further, they found that your risk for cardiovascular disease if you only have type 2 diabetes is less than if you have type 2 diabetes, and a increased waist circumference, and poor sleeping. So there's something about how these factors work together that increased the risk out of proportion to the individual parts.

So how should I use this clinically? Again, as you have a patient that you are noting is accumulating more, and more, and more, and more of these risk factors, that should really charge you to be even more diligent about managing these risk factors.

So example, a person who has impaired fasting glucose and their fasting number is 115, 120, if they have three or four of these other conditions, I may be more inclined to start them on a Metformin to really prevent that progression, rather than do this extended, let's do life style for six months, and then let's send you to the weight management for six more, and let's-- you know this protracted trial. I probably would pull the trigger a lot faster on that patient because they have increased risk.

Then the other question is, well, you mentioned lipids, hypertension, diabetes, well, that's what the cardiologist is for, the endocrinologist, and the nephrologist. Let's just handle all of the parts. But again, what our data has shown us is that the sum is greater than the parts.

It's like what I thought when I had two children, instead of just one. It was more than just two children together. It was a lot more work. So there's synergistic effect with each risk factor that you add.

And again, this is a nice slide that I really like from a report that was done in 2011, that this really pulls together again this idea of this global risk factor and the continuum. A patient starts with impaired fasting glucose, which is likely a manifestation of insulin resistance. We also have hyperinsulinemia, which I didn't go into. But we've also found that hyperinsuinemia brings on its own set of cardiovascular risk, just like hyperglycemia. Which is why being insulin resistant, even if your glucose is normal, is a problem. OK. Does that sense?

So hyperinsulinemia, insulin resistance-- and in those folks we start to see maybe some of the issues with subclinical atherosclerosis. And below that come the traditional risk factors with metabolic syndrome.

And then as we progress, you see that top line beginning to be a progression of glucose dysregulation because we find that they work together. As you get more inflammatory, that feeds back on your insulin resistance, which feeds back on your pancreatic function. And it's a cycle.

Then you progress to advanced atherosclerosis. Often that's co-occurring with the diagnosis of type 2 diabetes. We see issues with retinopathy. Because you know that approximately 20% of patients that time of diagnosis of type 2 diabetes already have some issues with in-organ damage, neuropathy and nephropathy. And then when we're at the end of the continuum is when we have the CAD hard endpoint.

And this is just a slide reiterating what we know that even if you take all the parts of the cardiometabolic syndrome and treat them individually, the risk reduction you would expect by having perfect lipids, perfect blood pressure, it still does not seem to erase that person's or that patient's risks totally. So they have what we call a residual risk effect. That can be a little bit frustrating. But the upside of that, for those in researches, can we develop an agent that does a better job handling the syndrome factors and how they work together rather than each individual part?

So just to recap, we've kind of worked from just general cardiovascular risk factors in isolation to the idea of a metabolic syndrome, to now the field really has a thought that the insulin resistance-- central adiposity is at that core, driving what we see in the development of cardiovascular. And so the question is what will be next? I'm glad you asked.

So in 2012, someone made up a new syndrome. I think it was a cardiologist because they were sad that the endocrinologists seemed to be the people talking about it all the time. But it's a new term called "circulatory system," where there's more emphasis on what I would consider the plumbing, the vessels, vasculature, and the disease state that comes there. And it's that relationship. So as vessels become occluded and blood pressure becomes more of an issue, how does then that come back onto insulin resistance and inflammation?

So this is a new model that's out there. And there's been also a lot more collaboration with the idea about heart failure and where does heart failure fit in with inflammation, insulin resistance? So that's also included in the model. And I didn't make this out. This is a friend.

So looking towards the future, so absolutely we all can do better at making sure that the risk factors that we know need to be addressed, we're addressing them. Is the blood pressure well controlled? Did we make the comment about glucose metabolism?

Did we make the comment about BMI? Nobody likes to talk about it. But we need to talk about it every visit if it still is an issue.

The best pharmaceutical agent is still physical activity and diet. And I know I'm preaching to the choir. But it's amazing. I'll have patients that go on vacation and they say, yeah, we went to the canyon and we hiked every day-- and oh, OK.

Even though we hiked every day and I ate ice cream every day, my blood sugar was so low. And there were a couple times I didn't even give myself my meal time because I was low going into it. I just don't know what happened.

And I said, well, tell me what you did? Well, we had to walk up to the little breakfast place. And then we canoed every day. And then we hiked. And the I was so tired after that. I usually went to bed around 10:30.

And I said, really? And I said that proves to you A, your metabolism is not broken-- which I get that consult frequently-- and the impact that even in the short term that lifestyle and physical activity can have on these numbers.

So we joke about it. But I really try to help people see you're proving your own point. And not that you have live your life hiking and those things, but if you can do one of those things, you might have a better effect.

And also there's a big movement, and the American Heart Association is even moving to the notion of health factors versus risk factors and trying to change our language and thought process, to help with policy changes, insurance reimbursements, to help prevent disease rather than always treat it. And change our collective consciousness.

And I don't mean that of providers, I mean that of patients as well. That you have to put a little elbow grease in it. I don't have a magic pill. If I did, I wouldn't be here.

And that the next pharmaceutical agent really needs to address more than just those individual parts. We really need to look at how does this agent that we give someone do more than just fix the blood pressure or fix the glucose? Does it treat those things that we don't quite measure in clinical settings, like inflammation and thrombotic state? Is it having an impact on those? And that really would make for a good agent.

So with that, I will close.