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https://reachmd.com/programs/cme/obesity-a-looming-cardiovascular-threat-pathophysiology-diagnosis-and-impact/24574/

Released: 05/31/2024
Valid until: 04/26/2025
Time needed to complete: 55m

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Obesity: A looming cardiovascular threat – Pathophysiology, diagnosis and impact

Dr. Sattar:
Hello, everybody. My name is Naveed Sattar. I'm Professor of Cardiometabolic Medicine at the University of Glasgow. I'm going to talk about obesity: a looming cardiovascular threat - pathophysiology, diagnosis and impact.

Here are my disclosures.

So in terms of diagnosis of obesity, as all of you know, we traditionally use BMI above 30 as signifying a level of obesity. What is now apparent, however, is where you put your weight, and also your height are relevant to your risk. So waist to height ratio may well be a better predictor of future obesity-related cardiovascular risk. It's more predictive for many outcomes than just as BMI. Equally, if you have comorbidities or symptoms linked obesity, that can also help us determine who has a particular level of obesity that requires treatment, i.e., to diagnose obesity. There's a new Lancet commission that will discuss these aspects that will come in the next few months. So look for that.

But the key point here, though, is that, as we've done reasonably well over the last 25 years in reducing atherosclerotic cardiovascular disease, at the same time, obesity levels have gone up and up and are threatening to reverse cardiovascular gains. And that's really important.

I'm going to show you one or two slides in each of these aspects. So how does obesity relate to cardiovascular disease? What's the evidence? Well, from epidemiological, genetics, some of the pathways, and also some weight loss evidence from bariatric surgery.

Let me just start with the following. This is taken from UK Biobank. As you can see in these four figures, there's a rise in BMI on the X axis and the top two, and the rise in waist circumference and the bottom two, and on the Y axis is the incidence of cardiovascular events on the left and two in men and right in women. BMI has the typical sort of J-shaped relationship, but at the top level, the risks are about twofold higher when BMI is about above 40.

For waist circumference, however, the relationships are much more linear, and it again confirms that waist circumference is a more robust marker of atherosclerotic cardiovascular risk mediated by obesity, but that the associations go to roughly two- to threefold, so modest.

However, if you contrast the relationship between adiposity and atherosclerotic disease to that relationship to heart failure, have a look at the middle figure here. This is the BMI rise in young women who were entering the army and their risk for dilated cardiomyopathy, which is in a sense, a precursor of heart failure. Here, the risk goes up linearly, and instead of two- to threefold, as BMI approaches 40, the risk is almost 16-fold higher. So in other words, obesity is more strongly related to processes that lead to heart failure than atherosclerotic cardiovascular disease. And that's important because heart failure has not fallen to the same extent as has MI and stroke.

We see the same associations genetically, people who are living lifelong with genes that give them higher BMI. If you look at the sort of second panel down, heart failure risk is up 12% for every unit higher BMI. If you look further down for coronary artery disease, it's 7%. So again, genetic evidence that high BMI is causal for many cardiovascular complications and more strongly for heart failure processes than atherosclerotic processes.

How do we tie them all together? Well, this is a review we've published in *Diabetes Care*. It came out this year. But if you look at the top panel, weight gain is important, and depending on your genes, your age, your ethnicity, and your sex, sooner or later, you will put fat into your ectopic tissues, so the liver, muscle, pancreas, around blood vessels. And ectopic fat also leads to high triglyceride levels, worsened lipids, it leads to diabetes eventually, it can be accompanied by excess salt intake to lead to higher blood pressure. But fat can also permeate into the heart and also contribute to atrial fibrillation and chronic kidney disease. So ectopic fat is really atherosclerotically damaging and also damaging to the pump, i.e., the heart, and also some of the filters, like the kidney as well.

This is genetic evidence that, again, confirms that where you put your fat matter. So if you look at type 2 diabetes at the top, those people with open triangles have got favorable adiposity, so they're able to store fat peripherally in their thighs and their arms. If you're able to store fat peripherally, in fact, you have a lower risk for diabetes, whereas the dark triangles is unfavorable adiposity. So genetically, if you carry more fat centrally into your liver or muscles or your pancreas, you have a high risk of diabetes. And that association is also true for hypertension. It's also true for coronary artery disease on the bottom. In other words, once again, it confirms that where you put your fat matters to risk, and that's really important.

In another paper we did, we put together some clinical signs and symptoms that allows you to work out who has ectopic fat. So if a patient presents with high triglyceride, but they don't drink too much or have other conditions like nephrotic syndrome or underactive thyroid, but if they also have, for example, a raised liver function test, particularly ALT or gamma GT, and they have dysglycemia, that combination of race, triglyceride, dysglycemia, abnormal liver function tests, in most people, it signifies that that individual is living with ectopic fat. And those three or four signs, along with excess weight, can be used to understand when the patients have ectopic fat. And it could also be used as biomarkers for when people lose weight, that these biomarkers should improve to signify less ectopic fat, and that's really important.

So going back to this review we published in *Diabetes Care* this year, we now recognize that excess adiposity, there are a range of risk factors that we usually treat, glucose, statins treat non-HDL, blood pressure, and slow atherosclerosis, but that unless we treat the obesity at the same time, we will less likely slow heart failure or kidney disease, and that's what we're finding. And the new disease-modifying drugs SGLT2 and GLP-1 receptor agonists are able to tackle some of the hemodynamic and cellular elements that links excess adiposity to heart failure and kidney disease, so distinct from atherosclerotic benefits. So it's a useful review to get at how the newer classes or drugs are starting to improve risk beyond the usual risk factors.

Without looking at trial evidence, which you'll hear in another talk from other colleagues, but looking at observational data in people who've had bariatric surgery, this is data that comes from a study of people living with diabetes, half of whom, or a proportion of whom had bariatric surgery in the red and others who did not. The average BMI was roughly 40 to 41. And over the course of 8 years, you can see that those individuals who had bariatric surgery experienced less macroalbuminuria, experienced roughly a halving of severe renal disease incidence, roughly halving of heart failure, and a lower decrement in nonfatal cardiovascular disease. In other words, this provides observational evidence that large scale weight loss may well benefit cardiovascular outcomes, particularly those that affect pumps, i.e., heart and the kidneys, more so than arthrosclerosis. And you will see that that evidence is now going to be transmitted into trial evidence with drugs that cause weight loss.

Finally, why should we all be interested in obesity? Well, I would suggest to you that obesity is the major driver of multimorbidity. And that if we don't tackle obesity at the same time as we tackle chronic diseases, we will actually promote more multimorbidity. And in this paper, written along with colleagues that you're familiar with, John McMurray, Ian McInnes, Vanita Aroda, and Mike Lean, we argued, based on multiple evidence, that nowadays, more and more people are living with obesity for longer in life, because not only is obesity rising faster, but we've reduced premature mortality for many conditions. But that excess aggregated exposure to obesity in many conditions is leading to multiple other conditions. So the patient with heart failure having diabetes and kidney disease, and, for example, osteoarthritis; therefore, we need to upscale weight management much earlier in many chronic conditions and upscale preventative policies. And that's really important going forward. Otherwise, many health systems are simply not able to cope with the number of people living with long-term multiple conditions linked to their adiposity.

Thank you very much.