

# **Transcript for PROMINENCE – Obesity pathophysiology lecture**

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**Slide 1** - introduction slide (*no text*)

**Slide 2** - As already briefly mentioned, obesity is really a complex multifactorial chronic relapsing disease. And in many individuals, multiple causes of obesity might be at stake. We know that in most individuals, obesity is a consequence of both biological, but also psychological factors, socioeconomic factors, and of course the environment where we live in. In my talk, I will not address all these causes, because I think that will be also discussed by colleagues talking later at this meeting (ECN Winter Meeting EASO). So, I will more focus on the consequences of obesity.

**Slide 3** – But we know that obesity is associated with a reduced life expectancy, with, I think that is even more important, a lower number of healthy life years, a reduced quality of life, and it is associated with enormous healthcare costs. So, I think we all hopefully agree that it is really, really important to put more emphasis on and to put more efforts in both the prevention as well as the treatment of obesity and its complications.

**Slide 4** - Why all that? Because obesity is, as I said, a gateway to many health complications, and more than 200 illnesses and complications have been linked to obesity. But just to highlight maybe the ones that are most familiar to you: an increased risk of cardiovascular disease, type 2 diabetes, metabolic dysfunction-associated liver disease (so, steatosis), but also multiple types of cancers are more prevalent in people living with obesity. Same as arthritis and pain associated with osteoarthritis. Infertility, both in men and females, kidney disease, chronic kidney disease, respiratory disease, and also mental health issues. Therefore, it is really important that we prevent and treat obesity because I think obesity is really upstream of many of these health complications. So, if we can prevent that, we can prevent a lot of complications, reduce healthcare costs, improve quality of life.

**Slide 5** - When talking about obesity, there is a lot of discussion ongoing, and we also hear that in the discussion after Jennifer's talk (ECN Winter Meeting EASO; lecture not included), about how to define and how to diagnose obesity. According to the WHO, we still use the BMI criteria, right? BMI equal or higher than 30, we say somebody is living with obesity. And I think it is important to mention that BMI is still a very useful measure. It certainly has retained its value in epidemiological research. We know that on average, countries with an average higher BMI have also a higher prevalence of several chronic diseases. It is still very useful. However, at the individual level, we know that BMI is really not a good measure of cardiometabolic health. And the reason is, for example, that BMI does not distinguish between adipose tissue mass and lean mass, and mainly muscle mass. You can imagine that when two individuals have a similar BMI, body composition does impact health outcomes. You can say, well, this is an extreme example: on the left-hand side, somebody living with abdominal obesity and on the right-hand side, maybe a bodybuilder, very muscular. But you can also think about looking at BMI throughout the life course. So if you have, let us say, a healthy BMI in your 20s, but if you have still the same BMI when you're age 75 years old, for example, with that same BMI, it is highly likely that you have a lower muscle mass and more adipose tissue mass, due to the decline in muscle mass with aging, which occurs in most individuals. So, we need to move beyond BMI when we want to say something about cardiometabolic health in people with higher BMIs.

**Slide 6** - And then you should say, but then you are arguing that we should pay attention to adipose tissue mass because, as was already mentioned, obesity is defined as excess fat mass that represents an increased risk for health. That is true, but I would like to confuse you maybe a little bit by showing a few examples that makes clear why there is not a tight relationship between total fat mass and metabolic health, in this case insulin sensitivity, so how your body responds to the hormone insulin to get, for example, glucose into your muscle. And the first example I would like to give is the situation of a female premenopausal with a certain BMI compared to a man, same age, same BMI. We know that premenopausal women are relatively protected against cardiometabolic diseases and have better glycaemic control and a higher insulin sensitivity, despite, on average, increased fat mass compared to men. Second example, patients that undergo liposuction, so the surgical removal of adipose tissue subcutaneously, up to 8-10 kilograms sometimes. Following liposuction, there is no change whatsoever in insulin sensitivity. So metabolic health does not improve shortly after liposuction. Less fat, but no change in metabolic health. And a final example that

I would like to give you is patients living with lipodystrophy, so the partial or complete lack of subcutaneous adipose tissue. These patients are severely insulin resistant, and most, if not all, will develop overt type 2 diabetes, despite the fact that they have very little adipose tissue mass subcutaneously. So, take home message from these examples, I would say, is that, as I mentioned already, there is no strong relationship between fat mass and metabolic health, even not at the individual level.

**Slide 7** – We know for many decades already, I would say, that it is much more important where the body fat is located. So, body fat distribution matters a lot. And we know that it is really the abdominal fat accumulation that increases the risk of cardiometabolic complications. And I think it is very interesting to know that even with a higher BMI, if you store the adipose tissue mass, the excess adipose tissue mass at the lower part of the body, so the hips, the thighs, the buttocks, you are relatively protected against these chronic diseases like diabetes and cardiovascular disease.

**Slide 8** – You can just believe me based on what I said, but I would like to show some evidence for this. As an example, I would like to show the results of the INTERHEART case-control Study, a large study (more than 27,000 participants from over 50 countries participated). And what you can see in this figure is on the x-axis, the different BMI categories, so normal weight, overweight, and obesity. On the y-axis, you can see the odds ratio, so the risk for acute myocardial infarction. And within each BMI category, you see these blue squares that are the quintiles for the waist to hip ratio. So, a higher value means that somebody has relatively high amounts of abdominal fat. And what you can appreciate, hopefully, is that within each BMI category, the higher the waist-to-hip ratio, the higher the risk for acute myocardial infarction. But what I would like to point out here in this figure is if you just look at these two red circles, it means that somebody with, let us say, a BMI of 29, but a relatively high amount of abdominal fat mass, so a high waist-to-hip ratio, has a higher risk of acute myocardial infarction compared to somebody with a BMI of 31 with relatively low amounts of abdominal fat.

**Slide 9** – So, what this data show, I think, is that we not only need to look beyond BMI, but we should also look beyond fat mass and pay attention to body fat distribution. And one way to do this already in the clinic, on a daily basis, when you see patients, you can just also measure

waist circumference, for example. That already gives additional information about health status on top of just BMI.

**Slide 10** – But if we really would like to understand the different phenotypes of obesity, that was one of the questions after the previous talk. We have **obesities**, it is not one disease, it is multiple phenotypes, multiple biological phenotypes as well. But then we need to understand what is going on in adipose tissue, and why there is a difference between upper and lower fat mass. So, we need to zoom in into the adipose tissue to really understand what is going on. And that is also what my team in Maastricht in the Netherlands is doing a lot. We try to understand underlying mechanisms.

**Slide 11** - So how does abdominal obesity increase this cardiometabolic disease risk?

**Slide 12** – Well, then we need to understand what is happening when fat mass is expanding.

**Slide 13** – And we know that in adults when body weight gain occurs, there is an expansion of fat mass, abdominal fat mass expansion, and that is solely due to enlargement of existing fat cells. So, you will develop adipocyte hypertrophy.

**Slide 14** – And that is also what you can see here on this picture taken from one of our own studies. So, when we take an adipose tissue biopsy, we can make sections, we can stain these sections and make these pictures under the microscope. And what you can appreciate on the right-hand side is that these fat cells of a person living with obesity are clearly larger compared to somebody with a healthy weight, same age, same sex. And why is this important? Well, we know that enlargements of subcutaneous abdominal fat cells is an independent marker of insulin resistance and it even predicts the future development of type 2 diabetes. So, to me, that highlights that adipose tissue dysfunction plays a key role in the development of complications, in this case type 2 diabetes. But why, that is the next key question, why are these enlarged fat cells predisposing towards complications?

**Slide 15** - Well, then we need to understand the normal function of adipose tissue, and that is to buffer the daily influx of calories. So, when we do not eat in between meals or during the night, the stored calories can be liberated, can be released from the adipose tissue. For example, the fatty acids can be used by other organs, like the muscle when we exercise, or other organs even when we are just sitting behind our desks.

**Slide 16** - But in people with obesity, these enlarged fat cells are already overloaded with stored fat, with stored triacylglycerol, and therefore the lipid buffering capacity is severely impaired. And the consequence of that is that after meal intake, there will be higher lipid concentrations in the circulation for a more prolonged period of time. And exactly that is also what we see in these patients with lipodystrophy I was referring to. So, if you lack the subcutaneous fat to store the lipids and the calories, where do they go? They remain in the circulation. And why would that be a problem? Well, the consequence of that is that there will be an excessive flux of lipids towards non-adipose tissues, just the muscle, the liver, the pancreas, and the heart. And we know for many years already that lipid accumulation in the muscle and in the liver is directly linked to insulin resistance. So, these lipids can interfere with insulin signalling. Lipid accumulation in pancreatic beta cells might reduce the insulin secretory capacity. And lipid accumulation within the cardiomyocytes, but also surrounding the heart, so the epicardial fat, that is linked to cardiac dysfunction, mainly diastolic dysfunction.

**Slide 17** - But adipose tissue does more than just regulating lipid metabolism. We know that adipose tissue is an endocrine organ, so it produces and secretes a variety of hormones and peptides called adipokines. And in that way, adipose tissue can talk to a variety of organs in our body. And it is not surprising that adipose tissue, therefore, regulates many, many physiological processes, not only lipid and glucose homeostasis.

**Slide 18** - But also, adipose tissue plays a key role in immune function, in blood pressure regulation, angiogenesis, but also the regulation of appetite and energy balance. And if I just have to name one adipokine that might be familiar to you, that is leptin, produced by the adipose tissue and that acts in the hypothalamus to reduce appetite and to increase energy expenditure.

**Slide 19** - And the point is, that in people with obesity that are characterised by these enlarged hypertrophic fat cells, the adipose tissue is functioning less well. So, there are impairments in this endocrine function. Also, when we talk about inflammation, we know that these enlarged fat cells produce more pro-inflammatory cytokines that can enter the circulation and contribute to low-grade systemic inflammation, something we know is present in many individuals living with obesity.

**Slide 20** - And when I am talking about adipose tissue, I should not only focus on fat cells. We have many cells in our adipose tissue, endothelial cells, fibroblasts, but also different types of immune cells. And the main message I want to highlight here in this slide is that during the progressive development of obesity, many pro-inflammatory immune cells infiltrate the tissue, and that contributes to inflamed adipose tissue, and it also contributes to low-grade systemic inflammation.

**Slide 21** - So, if I summarise this first part of what I've been telling you, is that during a prolonged positive energy balance leading to weight gain, we know that these fat cells enlarge and that causes issues with the normal functioning of the tissue. So, we get these impairments in lipid metabolism, impairments in the endocrine function of the tissue that not only impacts the adipose tissue itself but it has effects at the whole body level because we know if these lipids spill over to other tissues and also this low-grade systemic inflammation can directly impair the function of other key metabolic organs such as the liver, the muscle but also the heart. And that is of course a direct link with for example type 2 diabetes, and the development of cardiovascular diseases.

**Slide 22** - So, I already pointed out earlier that the causes of obesity can differ between individuals, but what about the consequences?

**Slide 23** - And then I would like to show you this figure. It is already an old study published more than 15 years ago by the group of Matthias Blüher in Leipzig. And what you can see here on the x-axis is BMI, and on the y-axis, the glucose infusion rate. That is a measure of insulin sensitivity. The only thing you need to remember, the higher the value on the y-axis, the better your insulin sensitivity. So, what you can see, if you look at this blue line, is something that you would expect, I think. You know, people with a higher BMI on average have a lower insulin sensitivity. We know that obesity, excess fat mass is linked to insulin resistance, so this makes sense. But look at the BMI category here

between 40 and 50. Let us say a BMI of 45. What you can see is that there is huge inter-individual variation in insulin sensitivity. So, the individuals on the lower part of this graph, show insulin resistance, with a BMI of 45. But there are individuals with a BMI of 45 that have completely normal insulin sensitivity. On the left-hand side, you see a health-weight reference group, and you can see that insulin sensitivity is comparable between this healthy-weight reference group and people on the top of this graph, with a BMI of 45, so normal insulin sensitivity. Having said that, I think it is also important to point out that this is a snapshot. These individuals were examined at a certain point in time. We know that even people are considered metabolically healthy, a term that is commonly used in literature, that they do have an increased risk of cardiometabolic diseases when they are followed up in time. I think that is important to emphasise.

**Slide 24** – And why is that, why are some individuals with high BMIs, also with high fat mass, also with abdominal obesity in the study I just showed you, why are some individuals even relatively protected against these diseases. Well, many studies have been done, to understand this. And what I can say is that one of the key things you see in these relatively protected individuals, is that adipose tissue seems to function normally. So, fat cells do not show enlargement, there is no inflammation in the adipose tissue, there is less liver fat, less muscle fat, less visceral fat and insulin sensitivity is therefore also normal. So, it is important that we understand that this can be the case in certain patients with high BMIs. About 10-30% of the people living with obesity show this metabolically healthy status.

**Slide 25** – So, the consequences of obesity can also differ. Fortunately, we have many interventions nowadays.