

# OBESITY MANAGEMENT: The Window of Opportunity for Cardiometabolic Clinicians

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## Introduction



### Raul Santos

- High prevalence of obesity leads to a high burden of morbidity and many years of life lost due to excess body weight.
- Obesity is not only related to increased arterial hypertension, atherogenic dyslipidemia and consequent atherosclerosis, but also other important cardiovascular diseases such as heart failure, atrial fibrillation, and sudden cardiac death.
- Obesity is also associated with sleep apnea and non-alcoholic fatty liver disease.
- Obesity treatment can reduce the burden of complications and even prolong life expectancy of those suffering from severe forms.
- GLP-1 agonists can reduce body weight, improve risk biomarkers, and reduce the risk of cardiovascular disease in people with type 2 diabetes.
- Understanding the pathophysiology of obesity is very important for the development of new therapies.

# Module 1: Epidemiology and Pathophysiology of Obesity and CVD



## Naveed Sattar

- Excess body weight is linked to atherosclerotic cardiovascular disease, heart failure, atrial fibrillation, and chronic kidney disease.
- Obesity-related cardiorenal outcomes, such as chronic kidney disease and heart failure, can be triggered by the hemodynamic impairment as well as other cellular effects of overnutrition at the cell level.
- Obesity can cause remodeling that leads to cardiomyopathy and consequently heart failure.
- Increased BMI or abdominal circumference is related to increased risk of stroke and coronary artery disease, independent of the usual risk factors, suggesting that there are other mechanisms involved.
- Weight gain leads to rapid increases in liver fat, triglycerides, blood glucose, and blood pressure, but takes longer to generate cardiac remodeling and atherosclerosis. Weight loss very quickly leads to reductions in triglycerides, liver fat, glucose, and blood pressure, however cardiac remodeling can take a few months to improve, and reductions in atherosclerotic cardiovascular disease risk can take several years.
- Studies with medications for weight loss should also show cardiorenal benefit, in addition to a reduction in atherosclerotic disease.



## Samia Mora

- Visceral adiposity results in increased blood free fatty acids. These increased free fatty acids target the liver where ApoB particles are generated. There is an increase in the production of triglycerides and VLDL, which will give rise to LDL.
- Production of small and dense LDL particles occurs by the action of hepatic lipase.
- Atherogenic dyslipidemia associated with visceral adiposity is characterized by high triglycerides, low HDL-C, and small dense LDL particles. ApoB measurement, to evaluate pro-atherogenic particle number, can be useful in patients with normal or low LDL-C.
- Patients with visceral adiposity, metabolic syndrome, diabetes, and pre-diabetes may have normal or low LDL-C but elevated ApoB. This phenomenon is called discordance and is associated with increased cardiovascular risk.
- Weight loss with diet and physical activity improves lipid changes.



## Viviane Rocha

- Observational as well as genetic studies and clinical trials show the importance of inflammation in atherosclerotic disease.
- The higher the body mass index, the higher the inflammatory levels of various mediators such as C-reactive protein.
- In the obese state, there is a shift to a more pro-inflammatory phenotype.
- Inflammation associated with obesity appears to be related to increased insulin resistance.
- Anti-inflammatory therapies show conflicting results on glycemic control.
- There are medications used in the treatment of obesity that have an anti-inflammatory effect. One example is GLP-1 receptor agonists. Whether this anti-inflammatory effect is actually mediating cardiovascular risk reduction or glycemic control remains to be demonstrated.

## Module 2: Obesity and Target Organ Damage



### Aruna D. Pradhan

- Adipose tissue has the role of storing energy, but in excess it increases the risk of type 2 diabetes mellitus.
- There is a consistent linear relationship of body mass index with type 2 diabetes. This relationship is consistent not only across geographic regions of the world, but also across races and ethnic groups.
- Obesity causes:
  - decrease in adiponectin
  - increase in inflammatory mediators, which become important for the pathogenesis of type 2 diabetes.
  - release of free fatty acids, which causes insulin resistance.
- Inflammatory markers such as C-reactive protein and interleukin-6 are associated with the risk of type 2 diabetes mellitus.
- Insulin resistance and inflammation lead to pancreatic beta cell failure and progression to diabetes mellitus.
- BMI does not reflect the distribution of fat, so measuring waist circumference is important. There are individuals considered obese by BMI but who have lower visceral fat content and greater cardiorespiratory fitness, better insulin sensitivity, thus, they would be metabolic healthy.
- The measurement of abdominal circumference and triglycerides can help to define obese individuals at higher cardiometabolic risk.



### Kris V. Kowdley

- There has been an increased prevalence of obesity, type 2 diabetes mellitus and non-alcoholic fatty liver disease (NAFLD) in recent decades.
- Obesity and metabolic syndrome are associated with the development of nonalcoholic fatty liver disease that is characterized by steatosis, steatohepatitis (NASH), and fibrosis.
- More severe non-alcoholic fatty liver disease is associated with greater risk of cirrhosis, liver cancer, and need for liver transplantation.
- Risk factors for developing steatohepatitis are obesity, advanced age, female gender, type 2 diabetes, and high blood pressure.
- Using a tool like FIB4 score can help identify those at higher risk of liver fibrosis.
- Weight loss is a fundamental part of the treatment of non-alcoholic fatty liver disease.



### Subodh Verma

- There is a relationship between obesity and heart failure with preserved ejection fraction (HFpEF).
- Visceral adiposity is associated with decreased cardiopulmonary performance, decreased left ventricular compliance, cardiometabolic vascular interactions, and changes in vascular compliance.
- Obesity-related HFpEF is associated with BNP deficiency, so it is better to measure NT-proBNP in the context of obesity.
- Pericardial/epicardial fat can generate external constriction and consequent pericardial restriction.
- Endothelial dysfunction and microvascular endothelial dysfunction are very important in the pathophysiology of heart failure.
- Obesity treatment reduces inflammation and acts in the prevention and treatment of HFpEF.
- SGLT2 inhibitors appear to be of benefit in patients with increased BMI and HFpEF.
- Clinical trials with GLP-1 agonists to assess their benefit in obese patients with HFpEF are ongoing.

# Module 3: Pharmacotherapies for Obesity and CVD Prevention



## Jean-Pierre Després

- There is heterogeneity in the distribution of body fat from one individual to another. The presence of visceral fat in greater quantity is related to a worse prognosis.
- Factors associated with prognosis in obesity:
  - Increased waist circumference for a given BMI range is related to increased mortality
  - Low cardiorespiratory fitness is associated with risk of coronary heart disease
  - Type of diet (Mediterranean diet is associated with reduced cardiovascular events)
  - Level of physical activity (performing physical activity reduces the risk of coronary disease)



## Karol E. Watson

- Weight reduction with bariatric surgery is associated with reduced mortality.
- There is a relationship between obesity and arterial hypertension. A previous study demonstrates that intensive blood pressure control had a greater benefit in individuals with a BMI of around 30 Kg/m<sup>2</sup>.
- Obesity is related to atherogenic dyslipidemia with increased triglycerides, reduced HDL-c and small and dense LDL pattern. The treatment of LDL-c with statins presents similar benefits in different BMI ranges.



## Alice Y. Y. Cheng

- The benefit of weight loss in obese patients has been well documented with bariatric surgery, but this is not available or not indicated for all patients. Therefore there is a role for pharmacotherapy.
- GLP-1 receptor agonists represent a great tool in the treatment of obesity. The first medication liraglutide demonstrated that 25-30% of people can achieve more than 10% body weight loss in individuals with obesity and without diabetes mellitus.
- Semaglutide 2.4mg once a week demonstrated that 60-75% of subjects achieve 10% or more weight loss in subjects with obesity and without diabetes mellitus.
- The studies that demonstrate a reduction in cardiovascular events with GLP-1 receptor agonists were done in patients with diabetes. We are waiting for the results of SELECT trial with people living with obesity.



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