Obesity and Cardiometabolic Risk

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Obesity is a major risk factor for a number of diseases. It is associated with increased risk of many types of cancer, osteoarthrosis, gall bladder disease, sleep apnoea, falls and injuries and psychological problems. Importantly it is associated with the metabolic syndrome and its component elements, namely hypertension, abnormal glucose tolerance, insulin resistance and dyslipidaemia. These, in turn, increase the risk of cardiovascular disease.

Metabolic Derangements

Adipose tissue releases a number of biologically active molecules that are thought to have a causative role in the pathogenesis of insulin resistance and vascular disease. Serum free fatty acids (FFAs) are generated by lipolysis (breakdown of stored triglycerides). They are increased in obese individuals as a result of increased adipose tissue mass. FFAs induce insulin resistance, possibly by competing with glucose as an energy substrate and by having an inhibitory effect on insulin signaling. The liver takes up FFAs to synthesise triglycerides and packages them with proteins to form very low density lipoprotein (VLDL). FFAs therefore mediate the association between obesity and hepatic steatosis ('fatty liver') and with hypertriglyceridaemia.[1] High serum triglycerides, in turn, result in small dense LDL and low HDL. These lipid abnormalities help explain the association between obesity and cardiovascular disease.

FFAs are also thought to be deleterious to the ß cells of the pancreas (lipotoxicity).[2] They decrease the sensitivity of the pancreas to glucose, so that it secretes less insulin for a given plasma glucose concentration.[3] They also increase apoptosis (programmed cell death) of ß cells, resulting in decreased ß cell mass.[2] The combination of increased insulin resistance and diminished ß cell function predisposes to abnormal glucose tolerance and diabetes.

Other cytokines released by adipose tissue that contribute to increased cardiometabolic risk include tumour necrosis factor alpha (TNFalpha), plasminogen activator inhibitor-1 (PAI-1) and interleukin-6 (Il-6).[4] These molecules decrease insulin sensitivity and are pro-inflammatory. PAI-1 is also pro-thrombotic. Adipose tissue is also an endocrine organ, releasing a number of hormones. These include leptin (see below), resistin (which increases insulin resistance) and adiponectin (which decreases insulin resistance and inflammation).

Metabolic Memory

There is evidence that the metabolic milieu of adipose tissue early in life causes long-term or even permanent changes in their metabolic profile. Undernutrition *in utero* or in early postnatal life, especially if followed by unrestricted access to food later in life, leads to hyperplasia and hypertrophy of adipose tissue and a shift towards release of pro-inflammatory cytokines and insulin resistance.

Visceral vs Subcutaneous Fat

Visceral fat is more strongly associated with cardiometabolic risk than subcutaneous fat. It secretes more FFA, PAI-1 and IL-6. Furthermore, since these molecules are released directly into the portal rather than the systemic circulation, they have a greater effect on the liver, their main site of action.[5] Visceral fat is also more insulin resistant than subcutaneous fat. Furthermore the balance is shifted towards production of resistin rather than adiponectin.

Visceral fat can be measured by CT scan, MRI or other specialized imaging techniques such as dual X-Ray absorptiometry (DXA). However, it is impractical to assess visceral obesity by using these modalities repeatedly in all patients. Fortunately, waist circumference has been found to be a useful indicator of visceral fat. Because it is so easy to measure, it is now used in the definition of 'central obesity' or 'abdominal obesity' in most guidelines.

Control of Food Intake

Obesity is a very difficult condition to treat. It is caused by an interaction of genetic and environmental factors. A key to unraveling both its pathogenesis and its treatment, is an understanding of the physiological control of food intake and hence body weight. This is a very complex subject and only a very brief outline will be given here. The role of the endocannaboid system will be discussed in the next section.

Two centres in the hypothalamus regulate the desire to eat. The feeding centre stimulates eating. The satiety centre inhibits the feeding centre. The activity of the hypothalamic centres is in turn regulated by a number of sensing mechanisms. The hypothalamus can thereby respond to ingestion of a meal (gut hormones), body fat mass (lipostat or adipostat signals) and nutrient status (blood nutrient levels).

A number of gut hormones inhibit food intake in response to food in the gastro-intestinal tract.[6] These include glucagon-like peptide1 (GLP-1), cholecystokinin (CCK), pancreatic polypeptide (PP) and peptide YY. GLP-1 and CCK also stimulate insulin release. Grehlin is a hormone secreted from the stomach in response to starvation and cachecia; it stimulates food intake as well as secretion of growth hormone from the pituitary.

The hypothalamus also receives chemical signals about the body fat mass. Leptin is secreted by adipose tissue in proportion to its mass.[7,8] Leptin acts centrally to inhibit feeding.[9,10] Adiponectin may also serve as an adiposity signal and inhibits feeding. Insulin levels correlate with adipose mass and are increased after meals. Like leptin, insulin's central action is probably to inhibit feeding.

The hypothalamus can also sense directly the levels of certain nutrients in the blood; these include glucose and fats. For example, oleic acid (a constituent of olive oil) inhibits food intake.[11]

continues on page 27

Obesity and Cardiometabolic Risk

continued from page 17

The endocanniboid system (ECS)

It has long been known that the plant *cannabis sativa* stimulated appetite and had a number of metabolic effects. These effects are receptor-mediated. This had long raised the suspicion that there must be endogenous cannabinoids. These have indeed now been identified and characterized. The endogenous cannabinoids are arachnidonic acid derivatives produced by cell membranes. They act locally and are rapidly inactivated. Their receptors are expressed in many tissues including the hypothalamus, adipose tissue, liver and skeletal muscle. Overactivity of the ECS results in hyperphagia, fat accumulation, decreased glucose uptake by skeletal muscle, increased lipogenesis in the liver and adipose tissue, decreased adiponectin production and insulin resistance.[12]

The ECS therefore presents a novel and exciting target for pharmacological intervention, since its blockade may not only be useful in the treatment of obesity but also directly improves many of the metabolic derangements that contribute to the cardiovascular risk associated with it. Indeed the Rimonabant in Overweight/Obese (RIO) trials have shown very promising and exciting results.[13-16] Blockade of the ECS by rimonabant, reduced weight and waist circumference (central obesity), and improved blood pressure, blood glucose, triglycerides, insulin sensitivity, small dense LDL and HDL. In diabetic patients there was a lowering in HbA_{1c}. Furthermore, many of these metabolic effects occurred independently of its effect on obesity and are therefore attributable to a direct effect over and above that associated with a reduction in obesity. These included a decrease in triglycerides, fasting insulin, HBA_{1c} and a rise in HDL.

Conclusion

Obesity should be regarded as a disease since it is associated with significant mortality and morbidity. Much of this is due to an increased risk of vascular disease as a result of various metabolic derangements. Obesity should therefore be treated aggressively. Unfortunately, treatment has proved difficult. Blockade of the ECS offers another exciting new tool on our armamentarium that targets not only obesity but also its associated cardiometabolic risk.

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