Obesity and cardio-metabolic health

ABSTRACT

Obesity is a major and growing global health problem. It is associated with increased mortality as a result of an increasing number of complications, including type 2 diabetes, dyslipidaemia, hypertension, non-alcoholic hepatic steatosis, cardiovascular disease, sleep apnoea, gallbladder disease, obesity-related renal disease, increased risk of falls and injuries, and mental health problems as well as increased risk of certain malignancies. This article discusses the metabolic derangements associated with obesity. These include insulin resistance, dysglycaemia, low and dysfunctional high-density lipoprotein, formation of small dense and oxidised low-density lipoprotein, and high circulating levels of free fatty acids. This article reviews the aetiology of these derangements and their relationship to cardiovascular disease, and discusses the concept of metabolic health.

Obesity is a major and growing global health problem and has been recognized as a disease entity on its own right. In 2016 the World Health Organization (2017) estimated the global prevalence of overweight or obesity of both men and women to be 39%. This has risen from 20% in men and 23% in women in 1975. The financial impact of treating obesity and obesity-related disease is substantial. There are also societal costs in terms of hours of work lost as a result of obesity-related absenteeism.

Obesity is associated with increased mortality. It has been estimated that 5.0% of adult deaths among black men and 15.6% among white men were associated with overweight and obese body mass index levels; the corresponding figures were 26.8% in black women and 21.7% in white women (Masters et al, 2013). This increased mortality is the result of the link between adiposity and a number of complications, including type 2 diabetes, dyslipidaemia, hypertension, non-alcoholic hepatic steatosis, cardiovascular disease, sleep apnoea, gallbladder disease, obesity-related renal disease, increased risk of falls and injuries, mental health problems as well as increased risk of certain malignancies (endometrial carcinoma, colorectal carcinoma, post-menopausal breast carcinoma, ovarian carcinoma, oesophageal adenocarcinoma, gallbladder cancer and pancreatic carcinoma). This article focuses on the cardio-metabolic consequences of overweight/obesity.

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Anthropometric measures of adiposity

The most commonly used measure of adiposity is the body mass index (weight in kilograms (kg) divided by the square of the height in metres). A body mass index of 20–24.9 kg/m^2 is defined as normal, 25–29.9 kg/m^2 as overweight, ≥30 kg/m^2 as obese and >35 kg/m^2 as morbidly obese. Although these cut-offs are useful to categorise patients, they are arbitrary as risk rises exponentially with increasing body mass index.

The concept of body mass index was originally developed in the early 1970s as the measure depended less on height than other indexes such as weight, weight:height ratio, ponderal index (weight divided by the cube of height), or weight expressed as a percentage of the average weight for the subject's height and age. In other words, the body mass index was developed in order to standardise weight for height. Although body mass index has withstood the test of time, it has a number of limitations. It uses total body weight as a surrogate marker for fat mass, so muscular individuals might have a disproportionately high body mass index in relation to their degree of adiposity. Conversely, sarcopenic individuals might have a normal body mass index in spite of increased adiposity. Furthermore, it does not distinguish subcutaneous fat from visceral fat, which is thought to be more harmful. There are also racial differences between the relation of body mass index to fat distribution and therefore to disease prediction (Luo et al, 2019).

Another commonly used measure of adiposity is the waist circumference, which is a good marker of visceral fat including cardiac and hepatic fat (Lee et al, 2017). It predicts risk of type 2 diabetes independently of, and more strongly than, body mass index (Neeland et al, 2012). There are gender- and race-specific cut-offs for waist circumference; the most commonly used are the International Diabetes Federation cut-offs used in the definition of the metabolic syndrome (*Table 1*).

The waist index is the waist circumference divided by the gender- and race-specific cut-off, so a value of >1.0 is abnormal irrespective of race or gender. An individual with a high waist circumference or waist index is said to have central or abdominal obesity. Sagittal abdominal diameter is another measure of central obesity but it is rarely used as it requires imaging by magnetic resonance

Table 1. Definitions of the metabolic syndrome as proposed by different organizations

Clinical measure	World Health Organization (1999)	European Group for the Study of Insulin Resistance (Balkau et al, 2002)	National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (2002)	American Association of Clinical Endocrinologists (Einhorn et al, 2003)	International Diabetes Federation (Alberti et al, 2005)
Insulin resistance	Impaired glucose tolerance, impaired fasting glucose, type 2 diabetes mellitus or lowered insulin sensitivity Plus any two of the following	Plasma insulin >75th percentile Plus any two of the following	None But any three of the following	Impaired fasting glucose or impaired glucose tolerance Plus any two of the following	None
Abdominal obesity	Men: waist:hip ratio >0.9, women: waist:hip ratio >0.85 and/or body mass index >30 kg/m^2	Men: waist circumference >94 cm, women: waist circumference >80 cm	Men: waist circumference >102 cm, women: waist circumference > 88 cm	Body mass index >25 kg/m^2	Ethnic specific Plus any two of the following
Blood pressure	>140/90 mmHg	>140/90 mmHg or on treatment	>130/85 mmHg	>130/85 mmHg	>130/85 mmHg or on treatment
Lipid profile	Triglycerides >1.7 mmol/litre and/or Men: high-density cholesterol <0.9 mmol/litre, women: high-density cholesterol <1.0 mmol/litre	Triglycerides >2 mmol/litre or on treatment or high-density cholesterol <1.0 mmol/litre or on treatment	Triglycerides >1.7 mmol/litre Men: high-density cholesterol <1.03 mmol/litre, women: high-density cholesterol <1.29 mmol/litre	Triglycerides >1.7 mmol/litre Men: high-density cholesterol <1.03 mmol/litre, women: high-density cholesterol <1.29 mmol/litre	Triglycerides >1.7 mmol/litre or on treatment Men: high-density cholesterol <1.03 mmol/litre, women: high-density cholesterol <1.2 mmol/litre or on treatment
Glucose	Impaired glucose tolerance, impaired fasting glucose or type 2 diabetes mellitus	Fasting plasma glucose >6.1 mmol/litre	Fasting plasma glucose >5.6 mmol/litre	Impaired glucose tolerance or impaired fasting glucose but not diabetes	Fasting plasma glucose >5.6 mmol/litre or diagnosis of type 2 diabetes mellitus
Other criteria	Albumin:creatinine ratio >30 mg/g			Other features of insulin resistance based on clinical judgement	

or computed tomography, or use of special calipers. Other uncommonly used markers of adiposity include waist:hip ratio, skin fold thickness, neck circumference, arm circumference and percentage body fat.

Metabolic derangements associated with adiposity

Insulin resistance

The most central defect associated with obesity is insulin resistance which in turn leads to hyperinsulinaemia. Both body mass index and waist circumference are predictors of hyperinsulinaemia and of insulin resistance (González-Gil et al, 2017). Mendelian randomization studies strongly suggest that these associations are causal (Wang et al, 2016). Postulated mechanisms linking obesity with insulin resistance include high circulating levels of free fatty acids as a result of an expanded adipose tissue mass (Rachek, 2014), and the release of a number of cytokines (referred to as adipokines) from adipose tissue. Adipokines implicated in causing obesity-related insulin resistance include tumour necrosis factor-α (da Costa et al, 2016), interleukin-6 (Rehman et al, 2017), fetuin-A (Pérez-Sotelo et al, 2017) and resistin (Santilli et al, 2016).

Furthermore, there is evidence that adiponectin resistance as well as low adiponectin levels (Engin, 2017) contribute to insulin resistance in obese individuals. Adiponectin is an adipokine which stimulates free fatty acid oxidation and thereby decreases plasma triglyceride and free fatty acid concentrations, and fat content in liver and muscle (Fruebis et al, 2001). It also improves glucose homeostasis (Holland et al, 2017).

Insulin resistance in turn increases the risk of type 2 diabetes. Pancreatic β-cell function has to increase in

> Adverse cardio-metabolic parameters associated with obesity include hyperinsulinaemia and/or insulin resistance, high serum levels of fatty acids and triglycerides, low levels of high-density lipoprotein, and dysglycaemia.

a hyperbolic manner as insulin resistance increases in order to maintain euglycaemia (Stumvoll et al, 2005), explaining why the risk of type 2 diabetes increases exponentially with increasing body mass index. For example, in a study of American male health-care professionals, the relative risk of type 2 diabetes was 2.2 in men with a modestly increased body mass index of 25–26.9 kg/m^2 compared to men with a body mass index of <23 kg/m^2, after adjusting for age, smoking and family history (Chan et al, 1994). The adjusted relative risk increased to 42.1 in men with a body mass index >35 kg/m^2.

In women, the association between obesity and risk of type 2 diabetes is even greater. In the Nurses' Health Study, women with a normal body mass index of 23–23.9 kg/m^2 already had a 3.6 times increased risk of developing type 2 diabetes over an 8-year period compared to women with a body mass index of <22 kg/m^2, and the risk increased dramatically to 93 times in women with a body mass index >35 kg/m^2 (Colditz et al, 1990).

Weight gain in both men and women is also associated with increased diabetes risk. The association between central obesity and risk of developing type 2 diabetes is even stronger (Neeland et al, 2012).

Lipid abnormalities

Increased adiposity (both increased body mass index and central obesity) is also associated with a number of lipid abnormalities (Klop et al, 2013). The most readily detectable lipid abnormalities in everyday practice are elevated triglyceride levels and low levels of high-density lipoprotein. High triglyceride levels are a consequence of high levels of circulating free fatty acids (one of the substrates for the synthesis of triglycerides) and diminished lipoprotein lipase activity (which breaks down triglycerides) as the latter is insulin-dependent. The increased triglyceride levels in turn result in more triglyceride-rich high-density lipoprotein, which is cleared more rapidly than triglyceride-poor high-density lipoprotein.

Abnormalities in other lipid parameters associated with increased adiposity are not usually available to the clinician but are nonetheless important as they contribute to increased cardiovascular risk. They include increased levels of circulating apolipoprotein B, free fatty acids, very low density lipoprotein, intermediate density lipoprotein, small dense low density lipoprotein and oxidised low-density lipoprotein (Linna et al, 2015) as well as dysfunctional high-density lipoprotein (Vazquez et al, 2012). Another important metabolic abnormality associated with obesity is oxidative stress (Santilli et al, 2015). All these metabolic derangements contribute to the known excess risk of cardiovascular disease associated with increased body mass index and with central obesity (Carlsson et al, 2013).

The link between metabolic health and cardiovascular disease

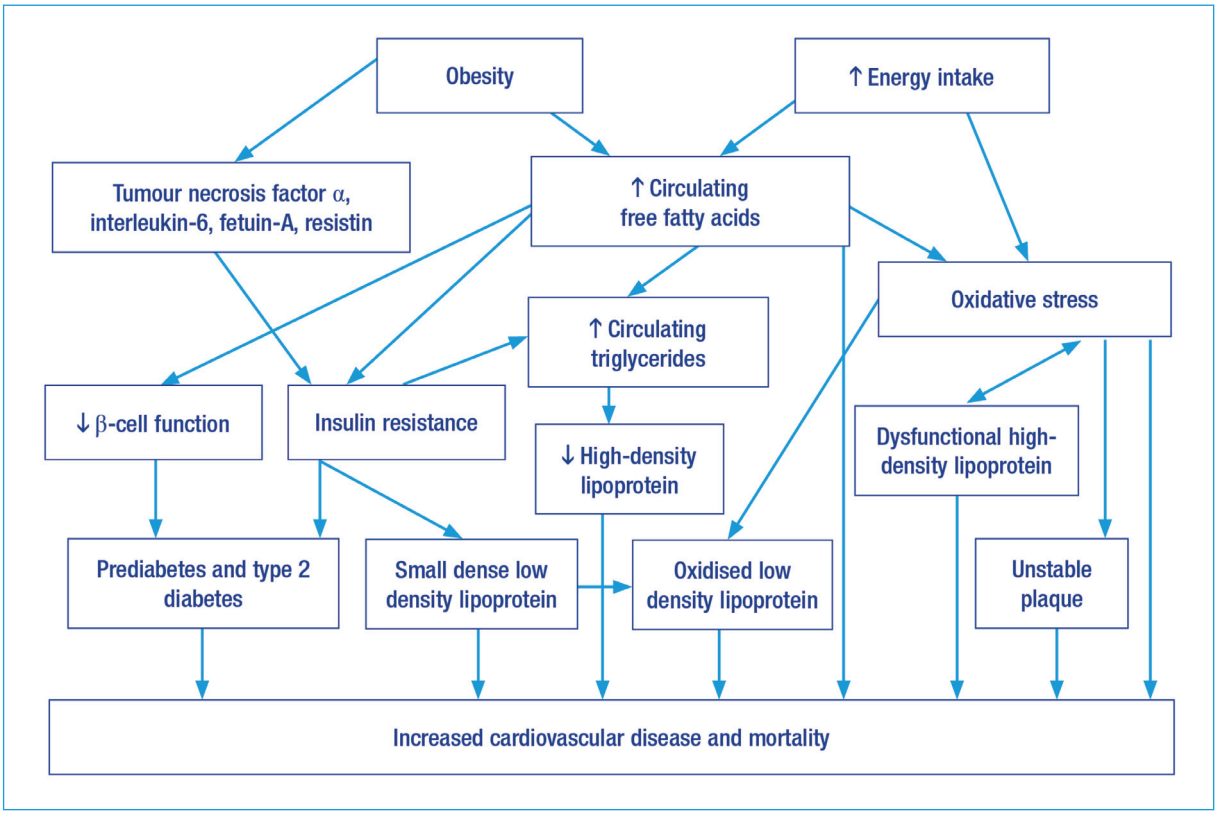
The term metabolic health refers to the status of a number of metabolic parameters which affect cardiovascular risk. As discussed above, adverse cardio-metabolic parameters associated with obesity include hyperinsulinaemia and/or insulin resistance, high serum levels of fatty acids and triglycerides, low levels of high-density lipoprotein, and dysglycaemia. All of these have been individually associated with increased cardiovascular risk (*Figure 1*). In the Helsinki Policemen Study (Pyörälä et al, 2000), investigators performed an oral glucose tolerance test in 970 men who were free of cardiovascular disease and diabetes at baseline and calculated the area under the curve for insulin as a measure of hyperinsulinaemia. They found that men in the highest quintile of the area under the curve for insulin had an age-adjusted hazard ratio for all-cause mortality of 1.94 after 10 years follow up and 1.51 after 22 years, compared to the combined lower quintiles.

Apart from causing increased triglyceride synthesis and contributing to increased insulin resistance as discussed above, free fatty acids also result in endothelial dysfunction, oxidative stress, subclinical inflammation and apoptosis of endothelial cells, and activation of the renin–angiotensin system. Serum triglycerides have been consistently linked with higher cardiovascular risk but it is unclear whether this is a causal relationship or whether triglycerides act as markers of increasing circulating fatty acid levels and insulin resistance or hyperinsulinaemia. A low level of high-density lipoprotein is a well-established marker of increased cardiovascular risk. High-density lipoprotein is involved in reverse cholesterol transport (transporting cholesterol away from cells) and also has antioxidant properties. Obese individuals not only have low high-density lipoprotein levels, but oxidative modification renders their high-density lipoprotein dysfunctional. Both its reverse cholesterol transport (Vazquez et al, 2012) and antioxidative functions (Hansel et al, 2004) are adversely affected.

Insulin resistance and hypertriglyceridemia drive the formation of small dense low-density lipoprotein particles, which are more atherogenic than normal sized low-density lipoprotein particles because they are more readily oxidised and have a lower affinity for the low-density lipoprotein receptor (Diffenderfer and Schaefer, 2014).

The presence of oxidative stress in obesity also contributes to low-density lipoprotein oxidation. Oxidised low-density lipoprotein is highly atherogenic (Diffenderfer and Schaefer, 2014). Oxidative stress in

Figure 1. Pathways linking obesity with increased cardiovascular disease and mortality.



obesity is a consequence of increased energy substrate flow through mitochondria as a result of excessive calorie intake and increased circulating levels of free fatty acids; decreased and dysfunctional high-density lipoprotein also contributes to oxidative stress because of high-density lipoprotein's antioxidant properties.

A vicious cycle can be established as oxidative stress can both lead to and be caused by dysfunctional high-density lipoprotein. Apart from favouring oxidation of low-density lipoprotein, oxidative stress also accelerates atherosclerosis by causing endothelial dysfunction as well as vascular smooth muscle proliferation and transformation into foam cells (Kattoor et al, 2017). Furthermore, it induces the release of metalloproteinases which degrade the fibrous wall of atheromatous plaque and endothelial basement membrane thereby favouring plaque rupture (Kattoor et al, 2017).

Apolipoprotein B is the main apoprotein found in non-high-density lipoproteins (including low-density lipoprotein, chlyomicrons, very low density lipoprotein and intermediate density lipoprotein), so is a good marker of the sum of all atherogenic lipoprotein fractions. It is important to note there is one apolipoprotein B molecule in every low-density lipoprotein particle, irrespective of its size. Therefore for any concentration of low-density lipoprotein cholesterol, there is more apolipoprotein B when low-density lipoprotein particle size is small. Consequently, apolipoprotein B also serves as a marker of small dense low-density lipoprotein.

The co-existence of a number of these adverse factors is referred to as the metabolic syndrome. There are varying definitions of the metabolic syndrome (*Table 1*). Many use a measure of adiposity as a surrogate marker of hyperinsulinaemia and insulin resistance, as these are not easy to measure in clinical practice. Waist index accurately predicts insulin resistance (Magri et al, 2016).

Metabolic health

Some obese individuals have a healthy metabolic profile, and are referred to as being metabolically healthy obese to distinguish them from the more common metabolically unhealthy obese. Conversely there are non-obese individuals who have adverse metabolic profiles. These are referred to as being metabolically unhealthy normal weight, to distinguish them from the more common metabolically healthy normal weight. For the purpose of this classification, normal weight is defined as having a body mass index <25.0 kg/m^2 and obese as having a body mass index of ≥25.0 kg/m^2 (i.e. it includes both the overweight and obese categories). Various criteria have been used to define metabolic health. The most commonly used definition of metabolic health is having two or less of the criteria of the metabolic syndrome as defined by the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (2002) (*Table 1*).

KEY POINTS

- Obesity is a major and growing global public health problem.
- Body mass index and waist circumference are the most commonly used measures of adiposity.
- Metabolic abnormalities contribute to the increased incidence of cardiovascular disease and mortality associated with obesity.
- Insulin resistance is strongly associated with obesity as a result of increased circulating free fatty acids and an abnormal adipokine profile; this explains the increased risk of developing type 2 diabetes.
- An atherogenic lipid profile occurs in obese individuals.
- Central obesity is more strongly associated with an adverse cardio-metabolic profile than body mass index.
- A small minority of persons with high body mass index maintain a normal metabolic profile while a few non-obese individuals have an abnormal metabolic profile.

Metabolically unhealthy normal weight individuals have a higher risk of cardiovascular disease than those who are metabolically healthy normal weight (Lee et al, 2018). On the other hand, the risk associated with being metabolically healthy obese is less clear and the condition may not be as benign as previously thought. For example, the risk of microvascular dysfunction and left ventricular hypertrophy in people who are metabolically healthy obese may be intermediate to that of those who are metabolically healthy normal weight and metabolically unhealthy obese (Lee et al, 2018).

A large study in Norway found people who were metabolically healthy obese to be at increased risk of heart failure but not of myocardial infarction (Mørkedal et al, 2014). In a meta-analysis by Eckel et al (2016), metabolically healthy obese people were at increased risk of cardiovascular events compared with those who were metabolically healthy normal weight, but at lower risk compared to those who were metabolically unhealthy obese and or metabolically unhealthy normal weight. An earlier meta-analysis found that metabolically healthy obese subjects are only at increased cardiovascular risk when studies with follow-up periods longer than 10 years were included in the analysis (Kramer et al, 2013). This may be because some metabolically healthy obese people move to the category of metabolically unhealthy obese when longer studies are considered. Indeed, up to a third of metabolically healthy obese people may progress to become metabolically unhealthy obese (Appleton et al, 2013). This may explain the intermediate risk associated with people who are metabolically unhealthy obese. The increased risk of diabetes in people who are metabolically healthy obese has been attributed to the progression to an unhealthy state (Navarro-González et al, 2016).

Conclusions

Increasing adiposity is associated with a number of metabolic derangements. The most central of these are insulin resistance and the resulting hyperinsulinaemia, as well as dysglycaemia, oxidative stress and an atherogenic lipid profile, all of which increase cardiovascular risk. A small proportion of individuals who are overweight or obese are metabolically healthy and are at an intermediate risk for future development of type 2 diabetes and cardiovascular disease. This may be explained by the fact that a substantial proportion becoming metabolically unhealthy over time. Increased adiposity may be regarded as a potent risk factor for current or future metabolic unhealthiness and therefore of cardiovascular disease.

Important areas for future research include investigating why some obese individuals remain metabolically healthy and why some non-obese individuals have an adverse metabolic profile. Another area which warrants further research is determining which factors affect the risk of progression from being metabolically healthy to metabolically unhealthy in obese individuals. BJHM

Conflict of interest: none.

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