1

Introduction to Obesity and Obesity-Related Diseases

Iskandar Idris

The past few decades have seen an exponential rise in the prevalence of overweight and obesity, affecting approximately 1.9 billion adults who were overweight, and of these, 650 million were obese. As such, in 2016, 39% of adults were overweight and 13% were obese worldwide. Alarmingly, this global trend in the prevalence of obesity is projected to rise further with trends of weight gain also reported for children and adolescents. Recent data from the World Health Organization (WHO) have estimated that 40 million children under the age of 5 years were overweight or obese in 2018, and over 340 million children and adolescents aged 5–19 were overweight or obese in 2016. Due to the related threat to public health, the WHO declared obesity a global epidemic, which in many cases remains to be an under-recognised problem within the public health agenda.

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. Body mass index (BMI) is used as a simple index to classify overweight and obesity in adults and is defined as a person's weight in kilograms divided by the square of his height in meters ($kg\,m^{-2}$). WHO defines overweight and obesity as follows (Figure 1.1):

For adults aged (18 years or over):

- overweight is a BMI greater than or equal to 25 or >23 in Asians; and
- obesity is a BMI greater than or equal to 30.

For children under five years of age (Figure 1.2):

- overweight is weight-for-height greater than 2 standard deviations above WHO Child Growth Standards median; and
- obesity is weight-for-height greater than 3 standard deviations above the WHO Child Growth Standards median.

Overweight and obesity are defined as follows for children aged between 5 and 19 years:

- overweight is BMI-for-age greater than 1 standard deviation above the WHO Growth Reference median; and
- obesity is greater than 2 standard deviations above the WHO Growth Reference median (Figure 1.3).

While BMI is widely used to classify overweight and obesity, intra-abdominal and subcutaneous fat accumulation around the abdomen (central, abdominal and visceral) is known to be associated with higher risks for cardiometabolic diseases, independent of BMI when compared with fat accumulation in the subcutaneous regions of hips, thighs and lower trunks (gluteofemoral, peripheral, gynoid, lower body or pear-shaped obesity) – the later considered to be less harmful or even protective against cardiometabolic complications (Figure 1.4).

Obesity is therefore neither just a cosmetic consideration nor simply a risk factor, but rather needs to be considered to be a disease state in its own right. Since obesity is associated with high relapse rate (most people who lose weight regain the weight within five years), obesity should also be considered to be a chronic relapsing and progressive disease, when untreated, it can be a leading risk factor for global deaths. In the United States, approximately 112 000 deaths per year were directly related to obesity, and most of these deaths occurred in patients with a BMI of more than 30.

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Nutritional status based on the WHO and "Asian criteria" values		
Nutritional Status	**WHO criteria BMI cut-off**	**"Asian criteria" BMI cut-off**
Underweight	<18.5	<18.5
Normal	18.5–24.9	18.5–22.9
Overweight	25–29.9	23–24.9
Pre-Obese	–	25–29.9
Obese	≥30	≥30
Obese Type 1 (obese)	30–40	30–40
Obese Type Type 2 (morbid obese)	40.1–50	40.1–50
Obese type 3 (super obese)	>50	>50

Figure 1.1 Adults Aged (18 Years or over); overweight is a BMI greater than or equal to 25 or >23 in Asians; and obesity is a BMI greater than or equal to 30.

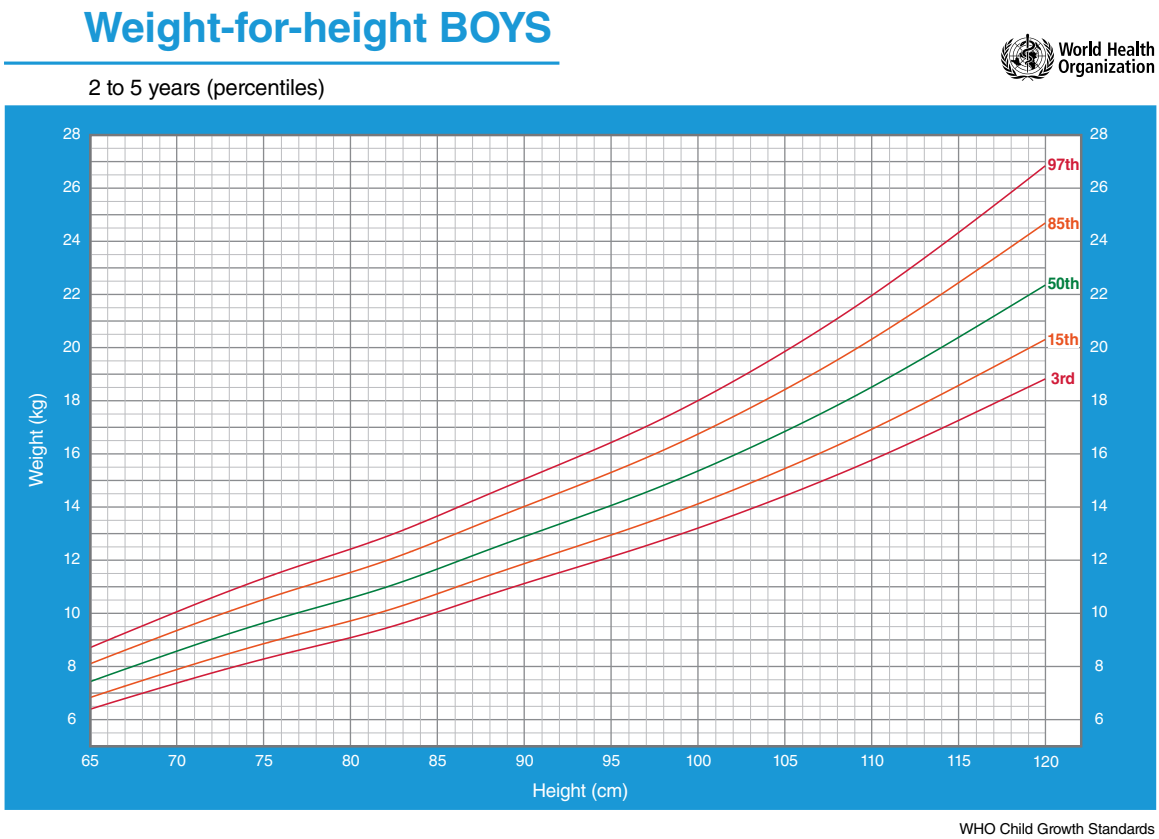


Figure 1.2 Charts and tables: WHO child growth standards for children aged under 5 years.

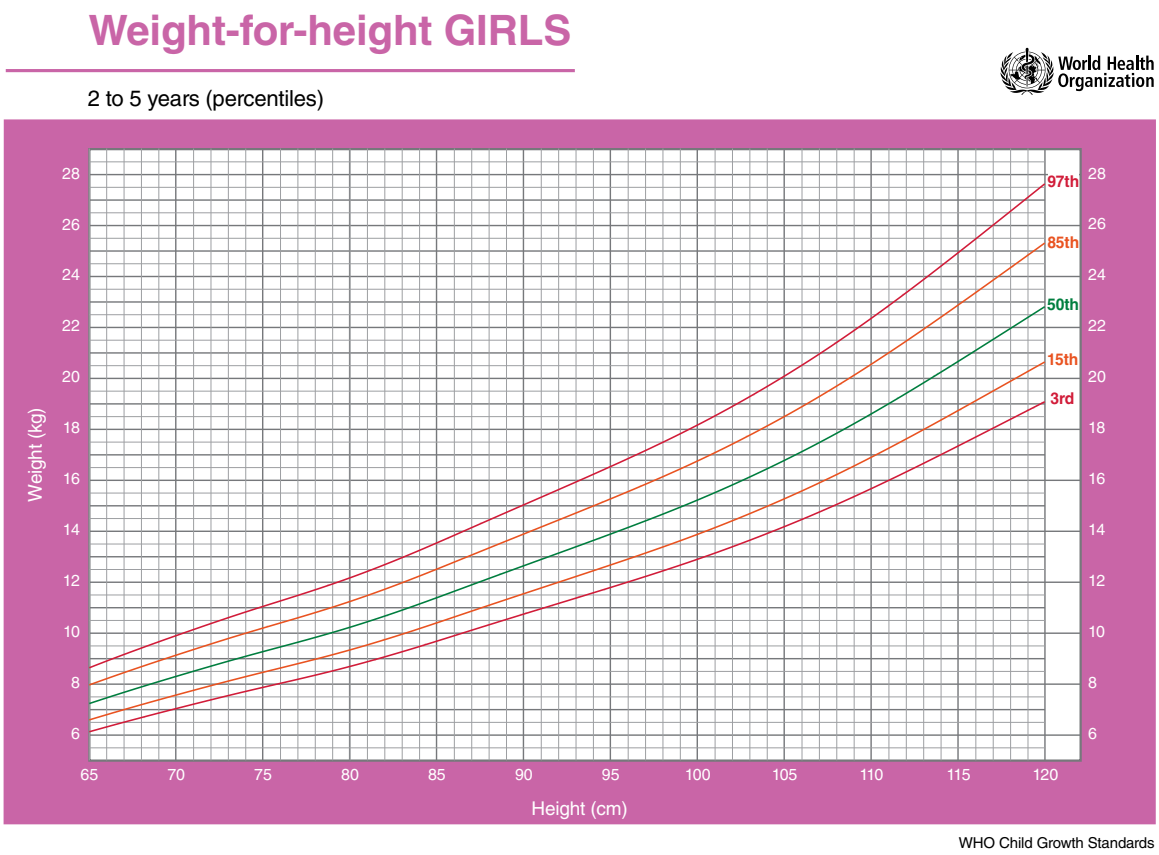


Figure 1.2 (Continued)

Once patients BMI exceed 40, their life expectancy is significantly reduced. Obesity can progressively cause and/or exacerbate a variety of co-morbidities, such as type 2 diabetes mellitus (T2D), hypertension, dyslipidaemia, cardiovascular disease (CVD), liver dysfunction, respiratory and musculoskeletal disorders, sub-fertility, psychosocial problems and certain types of cancer. The risk of developing a number of obesity-related co-morbidities rises exponentially with increasing BMI over 30 $kg\,m^{-2}$ (Figures 1.5 and 1.6).

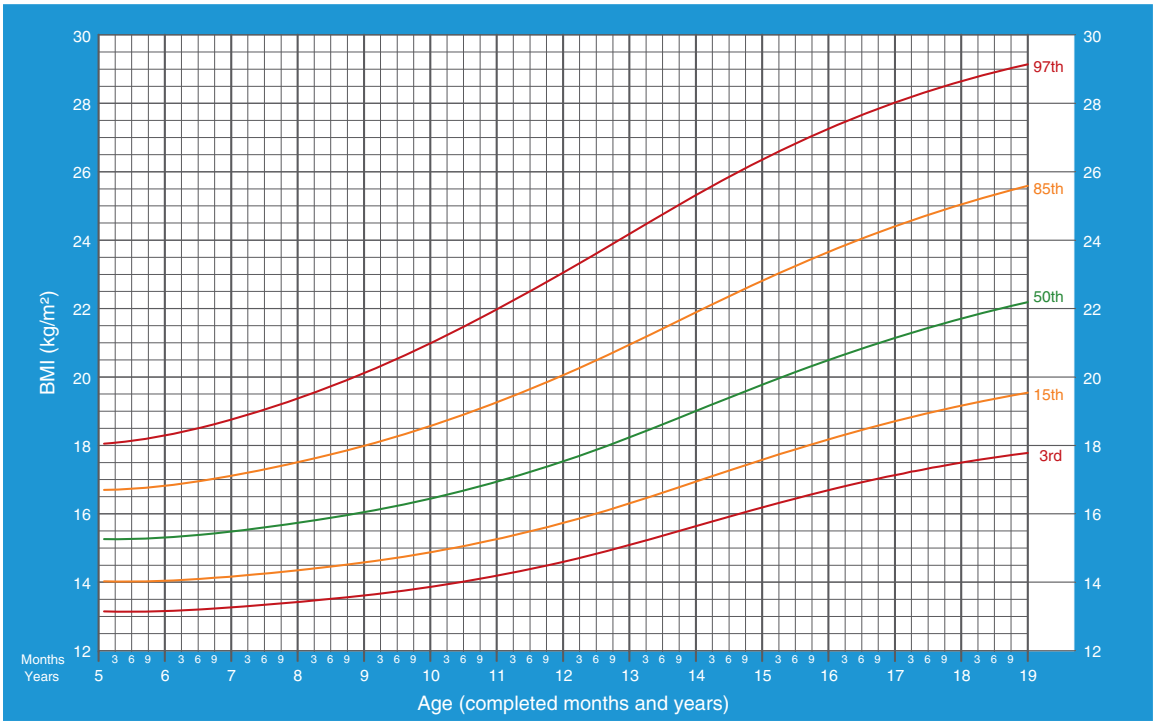
Obesity and Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2D) accounts for up to 90% of all types of diabetes cases in adults and is strongly associated with overweight and/or obesity. The parallel rise in T2D and obesity has been seen worldwide; hence, the term 'diabesity' has been introduced to describe this twin epidemic. An important pathogenic feature that links obesity and T2D is insulin resistance, thought to be driven by abnormal production of deleterious inflammatory cytokines from visceral adipose tissues. These inflammatory cytokines, such as interleukins (IL), tumour necrosis factors (TNF)-α, monocyte chemotactic protein (MCP)-1 and PAI-1, are also responsible for the increased risks of cardiovascular diseases seen in individuals who are obese or insulin resistant. Indeed, insulin resistance correlates positively to visceral fat accumulation, which constitutes an independent risk factor for T2D. Accordingly, anthropometric indices of central obesity, such as waist circumference, waist-to-height ratio and the visceral adiposity index, are better indicators of cardiovascular disease risks in people who are obese or with T2D (Figure 1.7).

BMI-for-age BOYS

5 to 19 years (percentiles)

World Health Organization

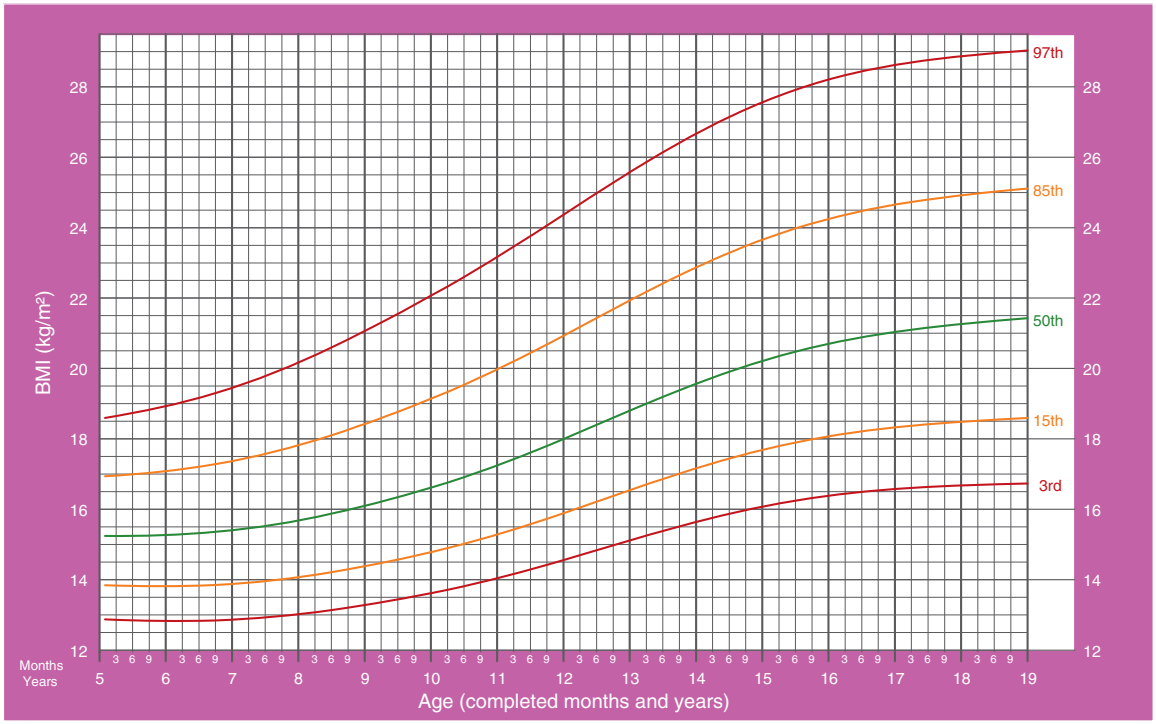


2007 WHO Reference

BMI-for-age GIRLS

5 to 19 years (percentiles)

World Health Organization



2007 WHO Reference

Figure 1.3 Charts and tables: WHO growth reference for children aged between 5–19 years.

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2. WAIST CIRCUMFERENCE

WC cut-off points for increased risk of metabolic diseases

	Men	Women
	94 cm (37 inches)	80 cm (32 inches)
WHO Asian/Indians 2000	90 cm (35 inches)	80 cm (32 inches)

(NIH: ≥102 cm and ≥88 cm respectively for Americans)

1. World Health Organisation. Obesity: Preventing and Managing the Global Epidemic. 2000. (TRS 894).
2. WHO/IOTF/IASO (2000). The Asia-Pacific perspective: Redefining Obesity and its Treatment.
3. Report of International Diabetic Federation. 2001.

Figure 1.4 Classification of waist circumference threshold that would increase risks of cardio-metabolic diseases in broad ethnic groups.

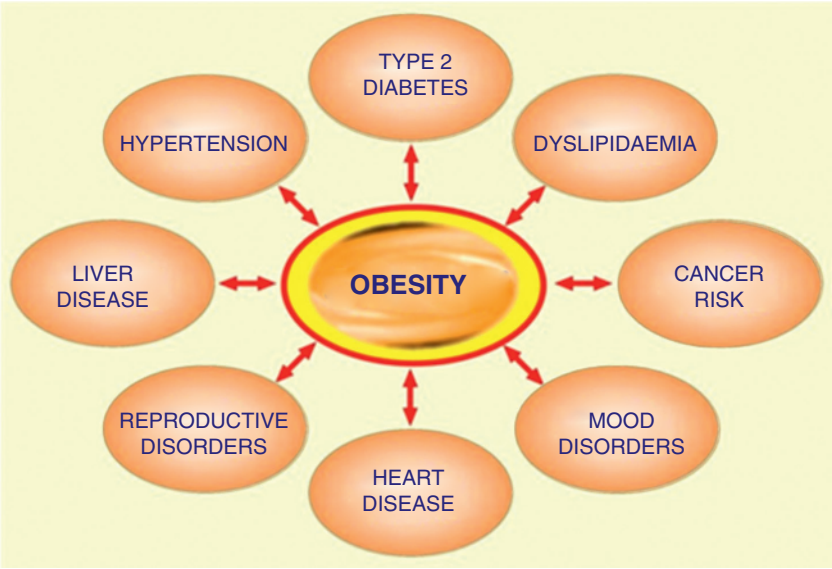

Figure 1.5 Co-morbidities associated with obesity.

Insulin resistance alone however is not sufficient for the development of T2D. This is because the pancreas has the capacity to compensate by increasing both beta-cell mass and insulin secretion to maintain normoglycaemia. Obesity contributes to premature failure of beta-cells and impaired insulin secretion through various glucotoxic and lipotoxic effects on the pancreatic beta-cells and the liver. The twin-cycle hypothesis describes the mechanism of obesity-induced T2D, where beta-cell lipotoxicity results in the impairment of insulin secretion. This induces hyperglycaemia, which in turn causes hyperinsulinemia. This, in tandem with muscle insulin resistance and calorie overload, causes increased liver and pancreatic fat accumulation, which in turn drives hepatic insulin-resistance and beta-cells lipotoxicity, respectively. This mechanism provides the basis for the role of significant calorie restriction (by means of very low calorie diet) to restore beta-cell function and potentially reverse T2D (Figure 1.8).

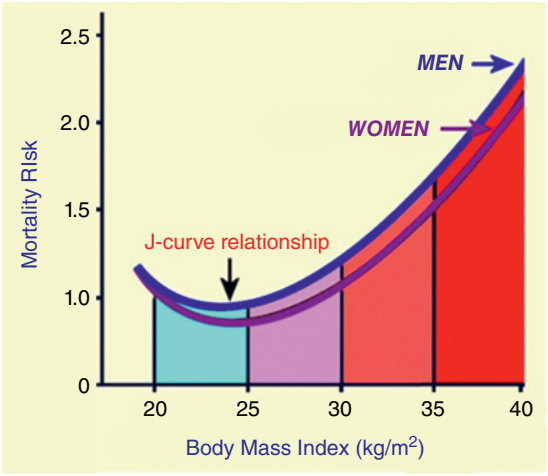

Figure 1.6 Relationship between body mass index (BMI) and mortality. *Source:* Adapted from Calle et al. (1999).

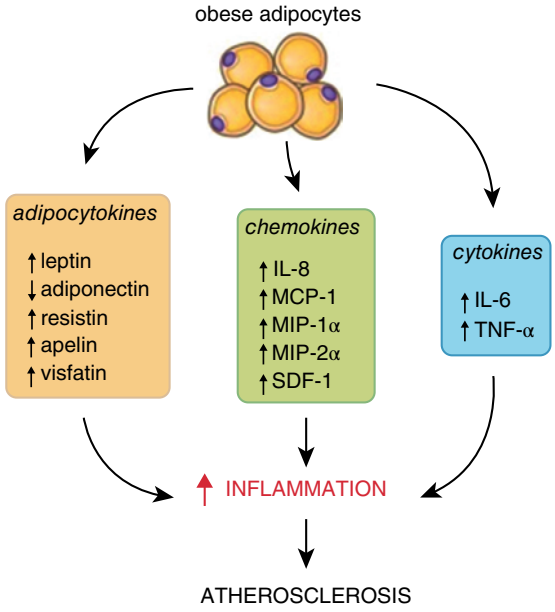

Figure 1.7 Production of cytokines which drives insulin resistance and pro-atherogenic state in obesity.

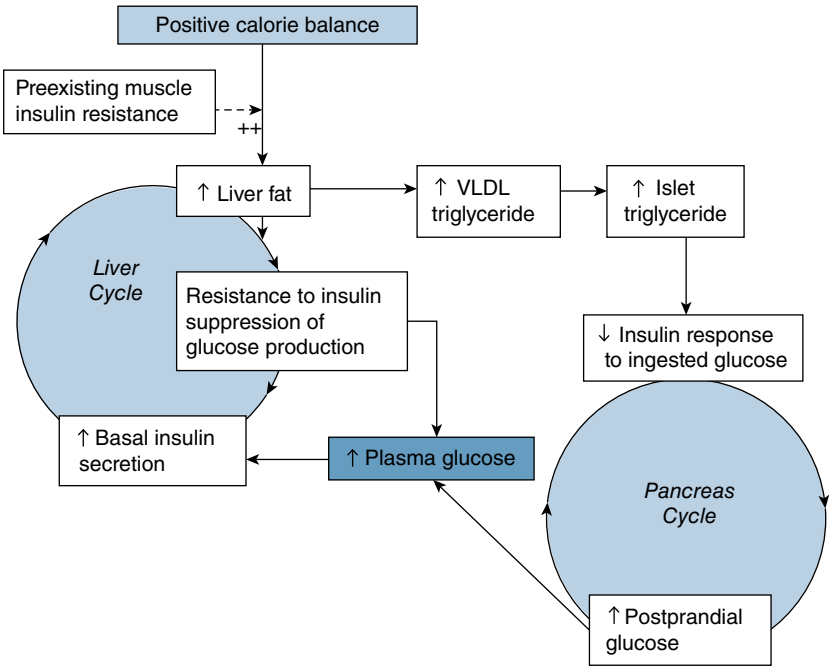

Figure 1.8 The twin cycle hypothesis of the aetiology of obesity-induced type 2 diabetes. *Source:* Adapted from Taylor (2013).

Obesity and Atherosclerosis

By virtue of the various pro-inflammatory cytokines described previously, increased adiposity is associated with activation of multiple pro-inflammatory signalling pathways that are linked to atherosclerotic risks. Obesity is also characterised by increased levels of fibrinogen and plasminogen activator inhibitor-1 (PAI-1), both of which induce a pro-coagulant state that further accelerates atherogenic processes in obesity. These obesity-related pro-inflammatory pathways mediate deleterious cardiometabolic effects that can lead to various clinical manifestations of the metabolic syndrome. Metabolic syndrome refers to a constellation of metabolic abnormalities, such as glucose intolerance, dyslipidaemia and hypertension, which frequently cluster together (by more than just chance), mediated and linked together by insulin resistance. All these metabolic disorders are recognised risk factors for cardiovascular disease (Figures 1.9 and 1.10).

metabolic syndrome*

Risk Factor	Defining Level
Abdominal obesity (waist circumference)	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides†	≥150 mg/dl
HDL cholesterol‡	
Men	<40 mg/dl
Women	<50 mg/dl
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥100 mg/dl§

HDL – high-density lipoprotein.
*Diagnosis is established when ≥3 of these risk factors are present.[2]
†1 mg/dl – 0.01129 mmol/l.
‡1 mg/dl – 0.02586 mmol/l.
§Updated fasting glucose guidelines.[45] 1 mg/dl = 0.0555 mmol/l.
Adapted with permission from *JAMA*.[43]

Figure 1.9 Criteria for metabolic syndrome.

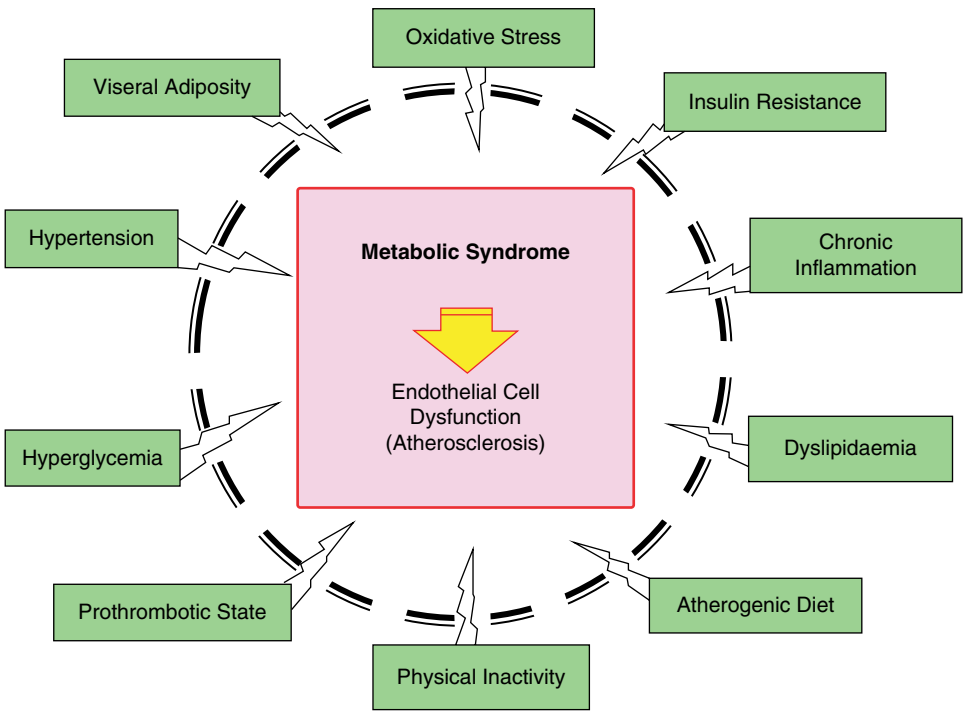

Figure 1.10 Obesity is associated with the metabolic syndrome and a chronic low-grade inflammatory state with increased risk of cardiovascular disease.

Obesity and Non-Alcoholic Fatty Liver Disease

Increased adiposity may cause hyperinsulinemia and hyperglycaemia, which generates ectopic fat accumulation and insulin resistance in the liver. Subsequent impairment of hepatic function results in a spectrum of hepatic abnormalities collectively known as non-alcoholic fatty liver disease (NAFLD). This could range from an initial modest elevation of circulating liver enzyme levels, simple local inflammation (steatosis), to more severe liver diseases, such as non-alcoholic steatohepatitis (NASH), cirrhosis, liver failure and even liver cancer. Cirrhosis represents advanced stage liver disease, where cumulative liver injury and necroinflammation result in fibrogenesis of the liver. Clinically, this correlates with the development of portal hypertension and hepatic synthetic dysfunction, where patients are at risks of bleeding varices, ascites, clotting abnormalities, encephalopathies and premature death. Today, NAFLD is the most common cause of chronic liver disease, with a prevalence of between 20 and 30% in the general population, increasing up to 90% in patients with severe obesity.

The pathogenesis of NAFLD has been the subject of intense research in recent years. Excess caloric intake increases fat accumulation in adipose tissue depots, which is typically followed by ectopic fat deposition in the liver and skeletal muscle. Insulin resistance ensues in these tissues, which results in a further net increase in the hepatic influx of circulating free fatty acids (FFAs) and lipid metabolites. Subsequently, hepatocyte-derived factors (such as cytokines/chemokines) stimulate inflammatory fibrotic response that leads to the development of inflammation and fibrosis in the liver. This is described as the 'multiple-parallel hit' model in the pathogenesis of NASH.

While bariatric surgery is associated with a significant improvement in liver outcomes in patients with early NAFLD, the safety and efficacy of bariatric surgery in patients with more advanced liver fibrosis remain unclear. Thus, screening and investigation for significant liver disease is an important component of assessment prior to bariatric surgery (see Chapter 9) (Figure 1.11).

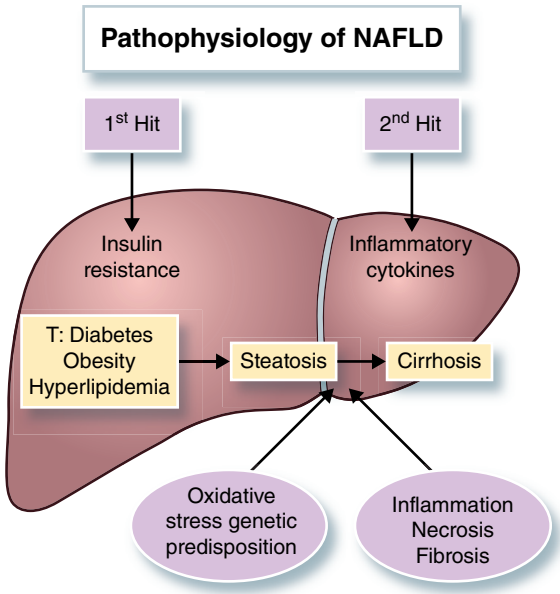

Figure 1.11 Multiple hit model in the pathogenesis of NAFD, NASH and cirrhosis.

Obesity and Gallbladder Disease

Gallbladder disease is a common gastrointestinal disorder in Western countries and is strongly associated with being overweight and obese. In the Nurses' Health Study, women with BMI over 30 $kg\,m^{-2}$ had twice the risk of gallstones compared to non-obese women, while a sevenfold excess risk was observed in women with BMI over 45 $kg\,m^{-2}$. Obesity is characterised by a high daily cholesterol turnover, resulting in an elevated biliary cholesterol secretion. This leads to supersaturation of the bile, which becomes more lithogenic with high cholesterol concentrations relative to bile acids and phospholipids. In addition, obesity is also associated with gallbladder hypomotility and stasis, which predispose to gallstones formation. Rapid weight loss in patients with obesity is also associated with increased risk of gallstone formation due to an enhanced flux of cholesterol through the biliary system. The increased risk of gallstone formation with rapid weight loss is of particular significance following bariatric surgery. Thus, the assessment of gallbladder pathology is a crucial assessment prior to surgery.

Obesity and Reproduction

Reproductive disorders are more frequent in obese men and women. The pathogenesis linking obesity and disorders of reproduction is multifactorial, and includes abnormal interactions between adipokines and the hypothalamic–pituitary–gonadal axis, increased metabolism of sex steroids within adipose tissue depots, reduced sex hormone binding globulin (SHBG) as well as psychological problems, which may manifest as decreased libido, lack of sexual activity enjoyment, difficulties in sexual performance and avoidance of sexual encounters. The adipokine leptin for example plays a crucial role in the regulation of gonadotropin secretion and ovulation. Abnormal menstrual patterns in women with obesity are primarily due to abnormalities in androgen, oestrogen and progesterone levels, whilst weight loss can restore menstrual regularity, partly by decreasing androgen aromatisation to oestrogens in adipose tissue depots. Polycystic ovary syndrome (PCOS) is the most common cause of anovulation linked with obesity and is characterised by (i) polycystic ovaries, (ii) oligo- or anovulation and (iii) clinical and/or biochemical signs of hyperandrogenism (two out of three criteria according to the Rotterdam consensus for PCOS).

Assisted conception such as *in vitro* fertilisation (IVF) maybe required for women who cannot conceive naturally. The success of such procedures however is significantly reduced in obese individuals. Women with obesity requires higher doses of ovarian stimulation drugs and have increased risk of cycle cancellation and fewer oocytes collected, as well as lower pregnancy and live birth rates compared to normal-weight women. Thus, a significant weight loss is required for women with obesity who seek fertility treatment in order to increase the chances of a favourable outcome.

Obesity and Lung Disease

Detrimental effects of respiratory function become significant when BMI exceeds 40 $kg\,m^{-2}$ due to increased mechanical pressure exerted on thoracic cage and truck. Patients with obesity therefore exhibit reductions in lung volumes and respiratory compliance, manifesting as decreased total lung capacity (TLC), expiratory reserve volume (ERV) and functional residual capacity (FRC) due to mass loading, splinting and restricted diaphragmatic descent during inspiration. In addition, forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) are also modestly affected in obesity. Previous data have shown that an increase in waist circumference of 1 cm is associated with mean reductions of 13 and 11 ml in FVC and FEV1, respectively, after adjustment for gender, age, height, weight and pack-years of smoking. Thus, obesity is associated with a spectrum of respiratory disorders, such as obstructive sleep apnoea, obesity hypoventilation syndrome, asthma and chronic obstructive pulmonary disease.

Obstructive sleep apnoea is highly prevalent amongst individuals who are obese. It is characterised by periodic reduction or cessation of breathing because of a narrowing or complete closure of the upper airway during sleep. Recurrent apnoeas (interruption in airflow by at least 50% for at least 10 s) and hypopnoeas (decrease in airflow for at least 10 s) lead to recurrent oxyhaemoglobin desaturation and arousal from sleep. An apnoea–hypopnoea index (AHI) (mean number of apnoea and hypopnoea episodes per hour of sleep) or oxygen desaturation index (ODI) (mean number of 3–4% oxygen desaturations per hour of sleep) score of more than 5/h is taken as threshold for a diagnosis of OSA, while an AHI or ODI score of >30/h is considered to be severe OSA as it is associated with heavy snoring, breath holding episodes during sleep, nocturia, unrefreshed sleep, excess daytime fatigue and hypersomnolence. Studies have shown that OSA is also associated with increased risk of cardio-metabolic diseases, hypertension, irritability, impaired concentrations as well as increased incidence of motor vehicle accidents. Screening for OSA is performed using various validated questionnaires (see Chapter 9), while the diagnosis of OSA relies on polysomnography. The mainstay treatment of OSA is continuous positive airways pressure (CPAP). Promising results have also been reported from studies exploring the impact of bariatric surgery on OSA, with meta-analysis data showing that up to 85% of OSA patients may exhibit remission and complete resolution of sleep-disordered breathing. A further systematic review reported that all types of bariatric surgical procedures

had significant beneficial effects on OSA, although recurrence of OSA has also been reported following initial improvements with weight loss even without concomitant weight regain (Figure 1.12).

Obesity and Cancer Risk

Compelling evidence over the past years indicates that obesity and obesity-related diabetes are associated with higher incidence of certain types of cancer. The strength of this association shows that obesity and physical inactivity are now recognised amongst the most important modifiable risk factors for primary cancer prevention, together with tobacco use. In line with other obesity-related co-morbidities, central obesity is identified as an independent predictor of increased cancer risk. Waist circumference primarily correlates with cancer of the endometrium, breast, colon, pancreas and liver, suggesting a pathogenetic link between visceral adiposity and carcinogenesis at these sites/organs. Crucially, there is also increasing evidence to support the impact of weight loss in reducing the obesity-related cancer risk. Indeed, the prospective, controlled Swedish Obese Subjects (SOS) study showed that bariatric surgery was associated with a reduction in the cancer incidence amongst women by 42%, while there was no effect on the cancer incidence amongst men (Figure 1.13).

In addition to environmental factors and genetic predisposition, multiple mechanisms have been proposed to explain the epidemiologic associations between obesity and cancer. Insulin resistance and chronic compensatory hyperinsulinemia is thought to play a crucial role

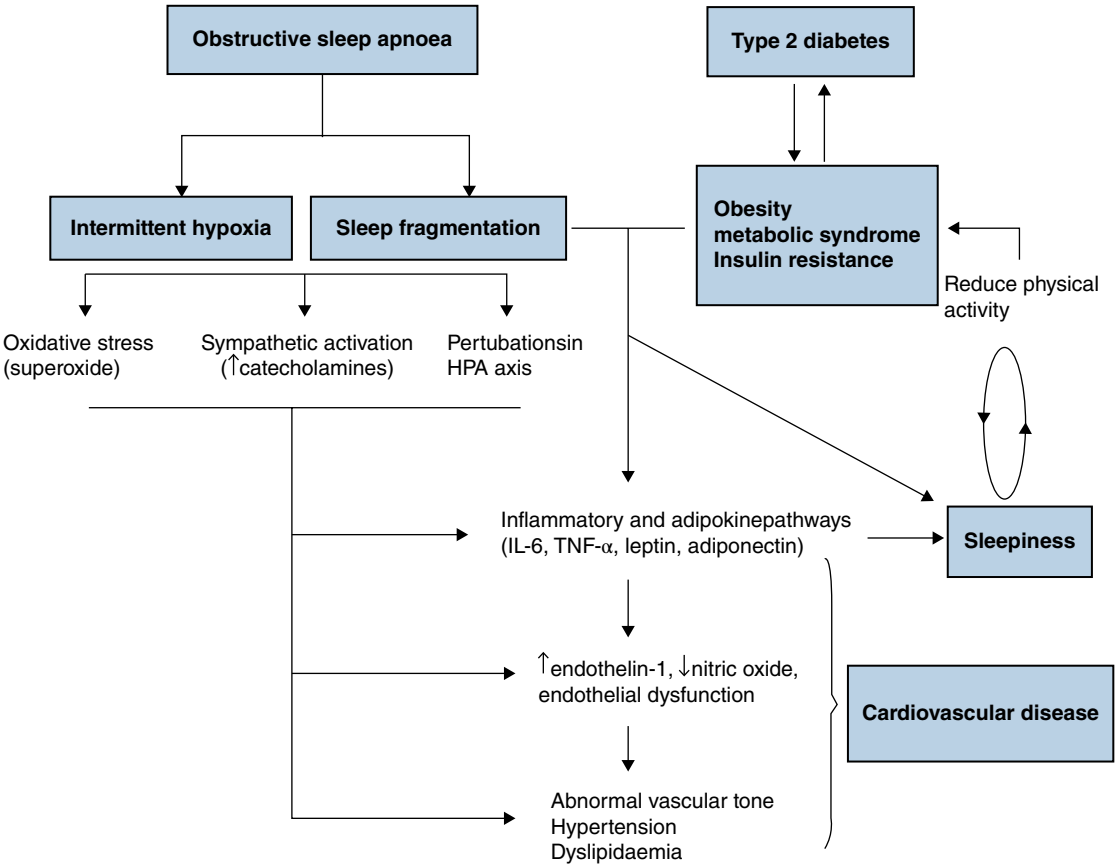

Figure 1.12 Inter-related pathways linking the pathogenesis of sleep apnoea, diabetes, excess daytime sleepiness and cardiovascular. *Source:* Adapted from Idris et al. (2009).

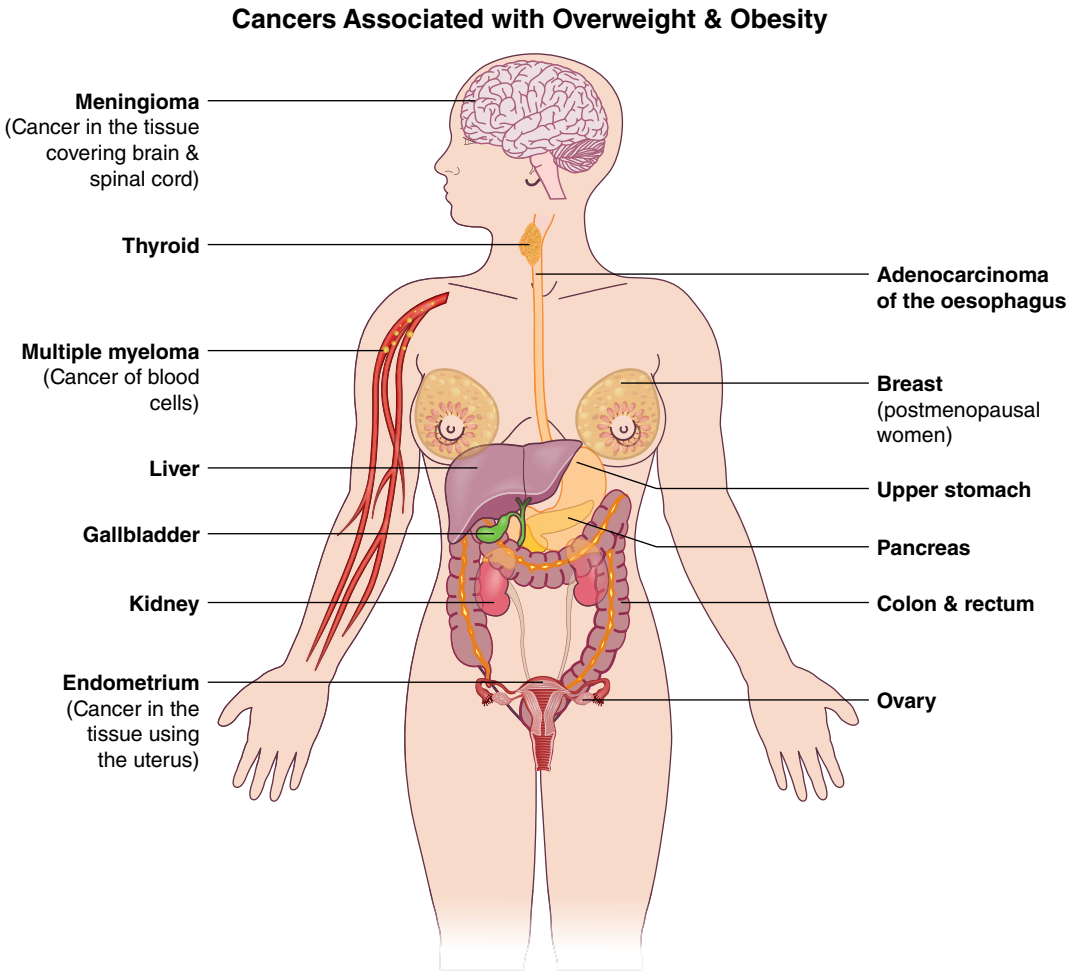

Figure 1.13 Cancers associated with overweight and obesity. *Source:* Taken from NIH National Cancer Institute. https://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/overweight-cancers-infographic.

in the pathophysiology of obesity-related carcinogenesis. Increased insulin levels have been shown to induce mitogenic effects through activation of both the insulin receptor and the insulin-like growth factor 1 (IGF-1) receptor. Hyperinsulinemia also suppressed the synthesis of insulin-like growth factor binding protein 1 (IGFBP-1) and IGFBP-2, which further increase the bio-availability of IGF-1, which promotes cellular proliferation and inhibits apoptosis through its receptor in several tissues. Increased levels of oestrogens and androgens in conjunction with suppressed SHBG levels also play an important role in mediating the carcinogenic effect, particularly for endometrial and postmenopausal breast cancers. Finally, circulating adipokines (e.g. hypoadiponectinemia and hyperleptinemia) and the chronic low-grade inflammatory state in obesity may also directly promote carcinogenesis.

Obesity and Bio-Mechanical Stress

Obesity increases the physical burden exerted on the joints, which causes and/or exacerbates several comorbidities such as knee or hip osteoarthritis and back pain, primarily due to repetitive overloading during daily activities, which progressively causes cartilage destruction and damage to ligaments and other support structures. Obesity is also associated

with higher injury rates, such as falls, sprains/strains, joint dislocations, ligament tears and lower extremity fractures. Osteoarthritis (OA) is the most frequent joint disorder worldwide and one of the leading causes of chronic pain and disability in the adult population of Western societies. Obesity is a major risk factor for knee OA. The lifetime risk of symptomatic knee OA increases with increasing BMI – i.e. each additional BMI unit above 27 $kg\,m^{-2}$ is associated with a 15% increase of knee OA. Interestingly, obesity also increases the risk of OA in non-weight bearing joints, which indicates a potential role of metabolic/inflammatory hormones in mediating obesity-related OA. Current evidence suggests that adverse hormonal and metabolic profiles in obesity, due to changes in leptin, adiponectin, TNF-α and IL-6, as well as hyperglycaemia, dyslipidaemia and chronic inflammation, can play a role in the pathogenesis of obesity-related OA. Importantly, the weight loss of approximately 5.1 kg over a 10-year period has been shown to reduce the odds of developing symptomatic knee OA by more than 50%, whilst functional disability caused by obesity-related knee OA may also be improved with weight loss over 5%. There is also a growing body of evidence, which indicates that bariatric surgery may benefit patients with obesity and knee or hip OA, although further high-quality randomised studies assessing the impact of bariatric surgery on these conditions are still required.

Case History

A 56-year old businessman attends his family doctor for a routine diabetes review and BP check. His BMI is 49.8, blood pressure is 194/104 and HbA1c of 9.3% indicating poor glucose and blood pressure control. He complains of overwhelming daytime lethargy and sleepiness, poor concentration as well as exertional shortness of breaths. He is a non-smoker and drinks 15 units of alcohol per week. His only exercise is golf, twice per week. He takes an ACE inhibitor, lisinopril 10 mg, for hypertension and diabetic kidney disease, and atorvastatin 20 mg for high cholesterol and metformin/liraglutide/empagliflozin for his diabetes and obesity. His protein creatinine ratio is raised at 94, indicating significant proteinuria – likely due to a combination of his diabetic kidney disease and obesity. Further blood tests show a normal haemoglobin level, normal electrolytes and renal function, and fasting lipids show total cholesterol 4.6 mmol/l, LDL-cholesterol 3.1 mmol/l, triglycerides 3.9 mmol/l and HDL-cholesterol 0.6 mmol/l. Liver enzyme test showed an ALT of 49, AST 61, platelet of 91 and albumin of 33 – which indicates significant NAFLD, a possible underlying liver fibrosis. Clinical examination revealed raised jugular venous pressure, bilateral crackles at lung bases, leg oedema (although difficult to assess due to obesity) and fast irregularly irregular heart rate consistent with atrial fibrillation.

Comment

This man presents with a plethora of symptoms of obesity-related co-morbidities. In addition to his diabetes and hypertension, he has significant proteinuria. Proteinuria is a risk marker for cardiovascular disease and progression of diabetic kidney disease. Proteinuria is also closely linked with obesity, and evidence suggests that weight loss can induce regression of proteinuria. He also described symptoms of obstructive sleep apnoea for which he will require a sleep study to confirm this diagnosis. Treatment of OSA with CPAP therapy has been shown to not only improve his symptoms of daytime sleepiness, but also help to reduce his blood pressure, cardiovascular risks and potentially improve his glucose control. His liver profile indicates that he is at high risk of liver fibrosis, and his lipid profile showed typical features of metabolic syndrome and insulin resistant state (raised triglyceride and reduce HDL-cholesterol). Clinical examination revealed heart failure and atrial fibrillation, both of which are significantly more prevalent in people with obesity. Extensive investigations are therefore required for his obesity-related co-morbidities.

Further Reading

Landmark Studies

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