Pathophysiology and aetiology and medical consequences of obesity

Adrian Park

Abstract

The World Health Organization has classified obesity as an epidemic. Obesity (defined by body mass index) substantially increases a patient's lifetime risk of developing type 2 diabetes mellitus, as well as many other co-morbidities, including cancers and cardiovascular disease. Obesity is caused by multiple factors, which vary from patient to patient, but include obesogenic environment, genetics, medical, mental health and prescribed medications. Obesity appears to predispose patients to developing these multiple co-morbidities by interacting with metabolic and endocrinological processes, as well as exposing the body to increasing mechanical forces. The review explores the pathophysiology, aetiology and medical consequences of obesity.

Keywords Adipostat factors; aetiology; body mass index; co-morbidity; homeostasis; MRCP; obesity; waist circumference

Key points

- Obesity is diagnosed by body mass index (BMI) but metabolic risk can occur at lower BMI levels dependent on ethnicity
- The 'Western lifestyle' is an obesogenic environment
- Genetic factors, medical factors, mental health factors and prescribed medication all can significantly contribute to gain of body weight
- Obesity predisposes to multiple co-morbidities that need evaluation on assessment of a patient's obesity

Background

The World Health Organization has classified obesity as an epidemic. Being overweight or obese substantially increases the risk of type 2 diabetes mellitus, hypertension, stroke, cardiovascular disease, respiratory problems, gallbladder disease, osteoarthritis and sleep apnoea, as well as certain cancers. In the USA alone >65% of adults are currently overweight or obese, with >30% of the population obese. The USA has significant levels of obesity-related co-morbidities and mortality.[1] The increase in the prevalence of obesity worldwide is similarly alarming and is associated with major financial costs.

The aim of this review is to provide a brief account of human energy homeostasis, define obesity, and discuss causes of human obesity and the medical consequences of obesity.

Energy homeostasis

Energy homeostasis results from the balance between energy intake and energy expenditure. Energy intake is from food and drink, while energy expenditure is the sum of the energy used to maintain essential bodily processes and carry out physical activity. If energy intake exceeds energy expenditure, the surplus energy must be stored; this excess energy is principally stored as fat. Conversely, if energy expenditure exceeds energy intake, energy stores are consumed to make up the shortfall in energy requirements. Thus, maintenance of an appropriate balance between energy intake and energy expenditure is critical for survival.

Central control of appetite

The central nervous system (CNS) interprets and integrates humoral and neuronal signals arising from the periphery and inputs from the higher areas of the brain. The major humoral mechanisms arise primarily from the adipose tissue (leptin) and gut (gut hormones).[1,2] The neuronal mechanisms are predominantly vagal afferents from the gut acting via the brainstem. The major CNS areas regulating energy homeostasis are the hypothalamus and brainstem.

Energy homeostasis is thought to be regulated by discrete neuronal populations forming complex interconnected circuits within the brain. These neurones use neuropeptides as well as the classical amine neurotransmitters, and are in turn regulated by specific signals of nutritional state. As would be expected for such a vital function, there is redundancy at many levels of energy homeostasis regulation. Hence the loss of a neuronal pathway or neurotransmitter can lead to compensations that preserve normal energy balance.

Peripheral regulation of appetite

The peripheral regulation of appetite is mediated by adipostat factors and by gut hormones. Figure 1 shows a scheme for the peripheral regulatory pathways involved in body energy homeostasis.

Adipostat factors[1,2]

Leptin: this is a hormone which is a 16 kDa protein expressed and secreted by adipocytes in white adipose tissue. Leptin is an example of an adipokine (i.e. a cell signalling protein secreted by adipose tissue). Leptin is thought to 'report' the levels of body fat stores to the CNS. Circulating levels of leptin are elevated in obese rodents and obese humans, and leptin circulates in plasma at concentrations proportional to fat mass. Low circulating leptin

Adrian Park *PhD MRCP FRCPath is the Lead of the Obesity Services at Addenbrooke's Hospital, Cambridge, UK and a Consultant Clinical Biochemist. He trained in clinical biochemistry and metabolic medicine, also undertaking a PhD investigating effects of gut hormones on body weight homeostasis. Competing interests: none declared.*

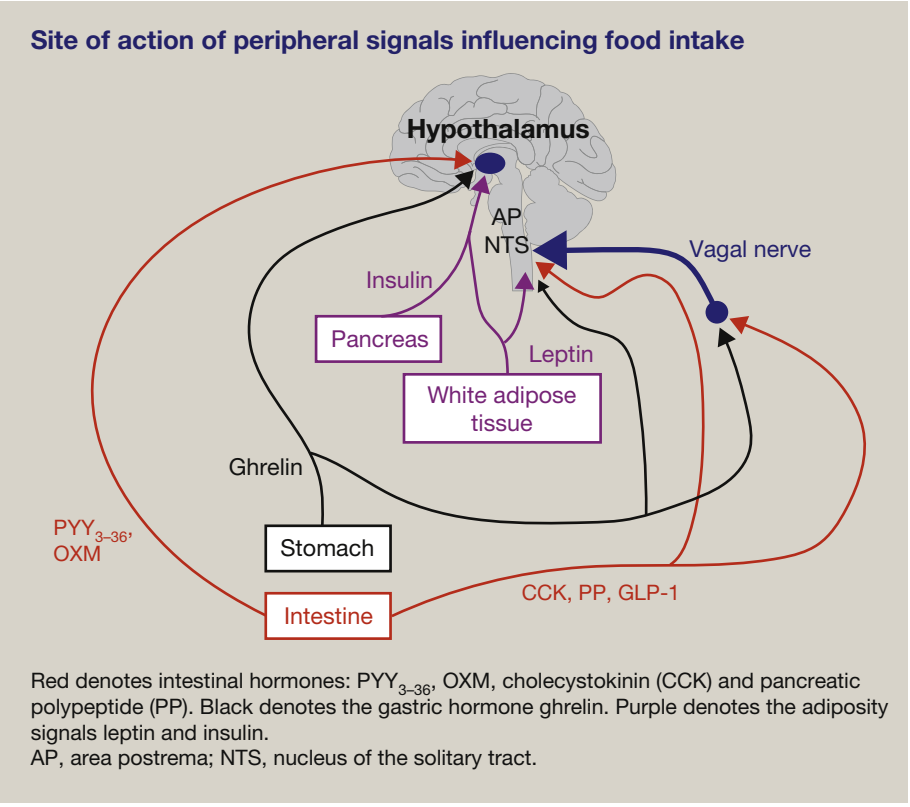

Figure 1

levels, signalling low body fat stores, initiate several neuroendocrine starvation responses.

Insulin: produced by the pancreatic β-cells, insulin is the major regulator of peripheral glucose homeostasis, modulating such processes as glucose uptake, gluconeogenesis and glycogen storage. Insulin appears to play a role similar to that of leptin as a signal of adiposity, with insulin acting in the CNS in a manner analogous to that of leptin to modulate feeding behaviour and the reproductive axis in relation to nutritional status.

Gut hormones[1,2]

Ghrelin: this is a 28-amino-acid peptide with a unique *n*-octanoic acid residue covalently acylated to the serine at position 3. Ghrelin is produced in the stomach by the X/A-like cells within the oxyntic glands of the gastric fundus mucosa. Ghrelin dose-dependently increases food intake when peripherally or centrally administered. It is the only peripherally active appetite-stimulating hormone so far discovered.

Peptide YY (PYY) and $PYY_{3–36}$: PYY is a 36-amino-acid peptide hormone found in the gastrointestinal tract. PYY mRNA is expressed in specialized endocrine L-cells present in both the upper and lower gastrointestinal tract, with PYY immunoreactivity being most highly concentrated in the large bowel and rectum.

PYY is released into the circulation after a meal, predominantly in the form $PYY_{1–36}$. In the circulation, it is converted by the enzyme dipeptidyl peptidase-IV (DPP-IV) into the major circulating form, $PYY_{3–36}$. $PYY_{3–36}$ acts as a physiological signal for appetite. When $PYY_{3–36}$ is preprandially administered intravenously to fasted healthy humans at postprandial levels, food intake is acutely decreased by 33%, and an anorectic effect is still present 24 hours after infusion. Basal $PYY_{3–36}$ plasma levels are lower in obese humans.

Glucagon-like peptide-1: Glucagon-like peptide-$1_{7–36}$ amide (GLP-1) is a 30-amino-acid peptide produced in the intestine and the hypothalamus as a product of pro-glucagon processing. GLP-1 is degraded by the enzyme DPP-IV.

GLP-1 is secreted from gut L-cells in response to nutrient ingestion. It physiologically stimulates glucose-dependent insulin secretion and insulin biosynthesis, and inhibits glucagon secretion, gastric emptying and food intake. Oral glucose ingestion results in a greater increase in plasma insulin than the equivalent concentrations administered intravenously. GLP-1 is a satiety factor and regulator of energy homeostasis. GLP-1 analogues are used clinically to treat type 2 diabetes mellitus and obesity.

Oxyntomodulin (OXM): this is a 37-amino-acid peptide, comprising the entire sequence of glucagon with a C-terminal basic octapeptide extension known as spacer peptide-1 (SP-1). OXM has been found to suppress appetite and increase energy expenditure in humans, with chronic administration leading to weight loss.

$PYY_{3–36}$, GLP-1 and OXM are elevated after Roux-en-Y gastric bypass. Indeed, it is thought that the elevation of these gut hormones leads to the efficacy of this bariatric surgical procedure.

Pancreatic polypeptide and cholecystokinin: both these hormones appear to have anorectic effects and can be considered to contribute to peripheral regulation of appetite control.

Defining the degree of overweight or obesity in adults

Classification	BMI (kg/m^2)
Healthy weight	18.5–24.9
Overweight	25–29.9
Obesity class I	30–34.9
Obesity class II	35–39.9
Obesity class III	40 or more

Table 1

International guidance on BMI/waist circumference thresholds

White European populations	Asian populations	Description
<18.5 kg/m^2	<18.5 kg/m^2	Underweight
18.5–24.9 kg/m^2	18.5–23 kg/m^2	Increasing but acceptable risk
25–29.9 kg/m^2	23–27.5 kg/m^2	Increased risk
≥30 kg/m^2	≥27.5 kg/m^2	High risk

Table 3

Obesity

Definition of obesity

Body mass index (BMI) is used to determine obesity as it is not accurate to assess a patient's weight from their appearance. BMI is calculated by a mathematical formula that assesses relative body weight as weight in kilograms divided by the square of the height in metres (kg/m^2). It remains the main way of assessing how overweight or obese a patient is, and is embedded in clinical guidelines (e.g. National Institute for Health and Care Excellence (NICE) CG189[3]).

BMI is not a direct measure of adiposity (and is potentially inaccurate in highly muscular individuals). NICE CG189 therefore also advises consideration the use of waist circumference, in addition to BMI, in people with a BMI <35 kg/m^2. Some other population groups, such as people of Asian family origin and older individuals, have co-morbidity risk factors that are of concern at different BMIs (lower for adults of an Asian family origin, and higher for older people). It is thus important to use clinical judgement when considering risk factors in these groups, even in people not classified as overweight or obese.

NICE CG189[3] and NICE PH46[4] outline the following: the BMI classification used to define the degree of overweight or obesity in adults (Table 1); the base assessment of the health risks associated with being overweight or obese in adults, related to BMI and waist circumference (Table 2); and international guidance on BMI/waist circumference thresholds (Table 3).

Aetiology of obesity

It is important to remember that obesity is often not of multifactorial aetiology. In general, a patient's weight is tightly regulated, with the brain appearing central in weight regulation. There are thus a number of factors that can interfere with body weight regulation and contribute to weight gain. These factors combined with the 'Western lifestyle' appear to be driving the obesity epidemic.

The 'Western lifestyle'

Human energy intake: historically, it has been hard to determine the relationships between food intake and body weight. Understanding the role of energy intake in the aetiology of obesity is confounded by individuals' failure to report food intake accurately, with under-reporting often showing a consistent shortfall in self-reported food intake of approximately 30% of the estimated energy requirements.

Although it is often thought that obesity has increased because people are eating more, this appears to be a misconception. Indeed, there appears to be evidence from both the USA and UK that people have in fact reduced their total energy intake. However, it appears that the foods these populations are now eating are more energy-dense and eaten in bigger portions than previously. In addition, there is good evidence that individual macronutrients (protein, fat, carbohydrate) exert differing effects on eating behaviour, predominantly as a result of their effects on satiety, with fat having a weak satiating capacity compared with protein. It thus seems that affluent countries such as the USA and UK have shifted towards a pattern of food consumption that has probably made the regulation of overall energy balance more difficult in the face of a decline in energy expenditure.[1]

Human energy expenditure: resting energy expenditure has little impact on weight gain, but activity-related energy expenditure appears to be important in energy homeostasis. It has been estimated that, for Palaeolithic humans, energy expenditure in the form of physical activity probably accounted for about 5.4 MJ daily for a 57 kg individual. This is strikingly higher than the

Base assessment of health risks associated with being overweight or obese in adults in terms of BMI and waist circumference

BMI classification	Waist circumference		
	Low	High	Very high
Overweight	No increased risk	Increased risk	High risk
Obesity class I	Increased risk	High risk	Very high risk

Waist circumference in men: low, <94 cm; high, 94–102 cm, very high, >102 cm.
Waist circumference in women: low, <80 cm; high, 80–88 cm; very high, >88 cm.

Table 2

estimate of 2.3 MJ daily for a hypothetic 64 kg contemporary American. It has been calculated that for a typical 70 kg modern American to approximate the daily total energy expenditure per kilogram of his hunter/gatherer ancestor, they would need to add the equivalent of a 19 km walk to each day's activity.

This reduction in energy expenditure appears to be caused by people generally having less arduous jobs, with those in manual work having more labour-saving tools. Other factors that also contribute to this complex picture are more sedentary leisure activities and mechanized commuting (i.e. using a car or train instead of walking).[1]

Factors promoting weight gain[1,5]

In addition to the 'Western lifestyle', a number of other factors contribute to an individual's obesity. These include genetics, medical conditions, mental health factors and iatrogenic factors.

Genetics: it is estimated that obesity is 40–70% genetically determined. However, even if an individual inherited all the common polymorphisms, it is estimated that the typical weight gain would account for only a few kilograms in weight gain. Rarer genetic variants, predominantly affecting central neuronal pathways, have been demonstrated to predispose patients to *severe* early-onset obesity, with patients exhibiting hyperphagia at a very early stage (i.e. generally before 5 years of age). There has also been interest in developmental factors that affect fetal development, thereby causing obesity in later life (epigenetic factors).

Primary medical conditions causing excessive weight gain:

- **Hypothyroidism** can cause significant weight gain and is simple to screen for and treat.
- **Cushing's syndrome** can lead to significant weight gain. Generally, this condition should only be investigated if there is a clinical suspicion that it could represent the underlying aetiology.
- **Hypothalamic damage** (e.g. craniopharyngioma after neurosurgery) can lead to obesity.

Mental health factors:

- **Depression** is one of the key drivers in terms of the mental health factors leading to obesity, so it is important to treat it wherever possible. Depression invariably worsens pre-existing eating disorders and increases emotional eating. Medical conditions such as untreated hypothyroidism and obstructive sleep apnoea can also adversely contribute to a patient's low mood.
- **Binge-eating disorder** is relatively common, individuals typically presenting with two or more binges per week for several months, with no compensatory behaviours (i.e. purging). Patients generally report that they use food as a coping mechanism to cope with emotional distress.
- **Emotional eating** is generally not as severe as binge-eating disorder, but it can nevertheless have a significant impact on a patient's weight.
- **Substance abuse** in the form of excessive alcohol ingestion can lead to a significant calorie intake while contributing little in the way of nutritional benefit.
- **Abuse**, particularly sexual abuse, can lead to significant weight gain. A typical clinical scenario is a young teenage girl who is being abused and turns to food for comfort, with the subsequent weight gain allowing her to experience a sensation of protection from further abuse.

Iatrogenic causes: a number of commonly prescribed medications can cause significant weight gain (Table 4). Where possible, these should be reviewed and substituted by medications that fulfil the same purpose but are weight-neutral or weight-beneficial.

Co-morbidities of obesity

Excess energy ingestion leads to increased adiposity, and once the peripheral adipose stores are full, excessive visceral adiposity occurs. Adipose tissue secretes adipokines, of which the most well-known is leptin. Visceral adiposity, with associated adipokine release, appears to underline the metabolic consequences of obesity (i.e. insulin resistance, type 2 diabetes mellitus, dyslipidaemia), as well as the hepatic consequences (non-alcoholic fatty

Medications that can promote weight gain and suggested treatment alternatives

Drugs that can promote weight gain	Alternative drugs that can promote weight loss or are weight-neutral
Psychiatric/neurological treatments	
Antipsychotics: olanzapine, clozapine, risperidone	Antipsychotics: ziprasidone, aripiprazole
Antidepressants: selective serotonin reuptake inhibitors, tricyclic antidepressants	Antidepressants: bupropion, nefazodone
Lithium	Antiepileptic drugs: topiramate, lamotrigine, zonisamide
Antiepileptic drugs: valproate, gabapentin, carbamazepine	
Diabetes treatments	
Insulin	Weight-neutral
Sulfonylureas	• Metformin
Thiazolidinediones	• Acarbose
	• DPP-IV inhibitors
	Weight-beneficial
	• SGLT-2 inhibitors
	• GLP-1 analogues
Corticosteroid hormones and miscellaneous agents	
Hormonal contraceptives	Barrier contraceptive methods
Corticosteroids	Non-steroidal anti-inflammatory drugs
Pro-gestational corticosteroids	Decongestants, inhalers
Antihistamines	Angiotensin-converting enzyme inhibitors, calcium channel blockers
α-Adrenoceptor blockers, β-adrenoceptor blockers	

Source: modified from Aronne.[5]

Table 4

Obesity-related co-morbidities

Neurological: benign intracranial hypertension, cerebrovascular disease, meralgia paraesthetica
Cardiovascular: ischaemic heart disease, hypertension, peripheral vascular disease, varicose veins
Respiratory: obstructive sleep apnoea, central apnoeic syndromes, pulmonary embolism
Metabolic: insulin resistance, type 2 diabetes mellitus, dyslipidaemia
Gastrointestinal:

- Hepatic: non-alcoholic fatty liver disease, non-alcoholic steatohepatitis (NASH), NASH—cirrhosis, hepatocellular carcinoma
- Gallbladder disease: including gallstone formation
- Gastro-oesophageal reflux disease
- Colon cancer
- Hernias

Renal: Obesity-related glomerulopathies
Gynaecological: menstrual irregularities, exacerbation of polycystic ovary syndrome, endometrial carcinoma, reduced fertility, urinary stress incontinence
Urological: hypogonadism, prostate cancer
Breast: breast cancer
Musculoskeletal: osteoarthritis, lower back pain, gout
Skin: lymphoedema, cellulitis, venous stasis of legs, intertrigo
Psychological: association with mental health disease, particularly depression

Table 5

liver disease, non-alcoholic steatohepatitis, non-alcoholic steatohepatitis—cirrhosis, hepatocellular carcinoma) (Table 5).[1,5]

It is likely that the adipose tissue also interferes with sex hormone levels (probably in part by increased adipose aromatase activity), which contributes to the urological, gynaecological and breast co-morbidities. Furthermore, excess adiposity leads to excessive mechanical loads and causes related disease (i.e. osteoarthritis). Finally, obesity is associated with mental health disease, in particular depression. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 44-year-old man presented to a 'well man' clinic. He had a BMI of 44 kg/m^2 and a weight of 130 kg.

An important question in the history to ascertain a likely co-morbidity in this patient relates to what?

A Daytime sleepiness
B Headache on coughing and straining
C Early morning vomiting
D Urinary retention
E Bowel habits

Question 2

A 48-year-old man presented for an employment medical examination. He was asymptomatic. He worked as an insurance loss adjuster. He smoked the occasional cigar but did not drink alcohol. On clinical examination his weight was 135 kg BMI 47 kg/m^2 and his blood pressure was 138/88 mmHg.

Which investigation should be carried out in relation to these findings?

A Full blood count
B Thyroid function tests
C Serum calcium and bone profile
D Urea and electrolytes
E Liver function tests

Question 3

Appetite is under the control of a number of hormones, which provides possible targets for the control of weight disorders.

Which one of the following stimulates appetite?

A Leptin
B Peptide YY
C Glucagon-like peptide-1
D Ghrelin
E Oxyntomodulin