11.6 Obesity 1903

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ESSENTIALS Obesity is defined as an excess of body fat that is sufficient to affect health adversely. While the quantification of fat mass is usually only performed in the research setting, body mass index (weight in kg/ height in metres2) is a useful surrogate marker for fat mass. Using the World Health Organization definition of a body mass index more than 30 kg/m2 to define obesity, 30% of Americans, and 10 to 20% of Europeans are classified as obese, with the prevalence rising in many developing countries. As body mass index increases, so does the relative risk of type 2 diabetes, hypertension, and cardiovascular disease. As such, obesity is associated with disability, mortality, and substantial health costs. At an individual level, severe obesity can be associated with sleep disturbance and respiratory difficulties, joint and mobility disorders, as well as considerable social stigma which can affect quality of life, educational attainment, and employment opportunities. Management of patients with severe obesity is a challenge, but success is enhanced by a sympathetic approach from the physician, with realistic weight loss goals and monitoring of the effects of treat- ment. Interventions include (1) low-calorie diets which often aim to provide a 600 kcal/day (2.5 MJ/day) energy deficit, based on es- timated energy requirements; (2) motivational and behavioural ap- proaches to implement and sustain changes in eating and activity behaviour; (3) drug treatment—which should be regarded as a thera- peutic trial and stopped if weight loss is not apparent after one to two months; (4) surgery—an option for people with morbid obesity/ obesity with associated complications. Introduction Obesity is frequently considered to be a ‘modern’ disease—a re- flection of the excesses of urbanized society. However, descriptions of obese individuals in medical texts from many of the ancient civilizations, suggest that, throughout history, certain individ- uals have harboured the tendency to store excess energy as fat. Hippocrates recognized that obesity posed a threat to health when he wrote that, ‘sudden death is more common in those who are naturally fat than in the lean’. Galen elaborated upon earlier descrip- tions of the obese state, distinguishing between different degrees of obesity; ‘moderate’ or common obesity and ‘immoderate’ or morbid obesity. Many Greek and Roman physicians documented some of the clinical complications associated with obesity, including reduced frequency of menses and infertility. The first known description of obesity and sleep apnoea dates from Roman times; Dionysius, the tyrant of Heraclea of Pontius who reigned from about 360 bc, was described as ‘an enormously fat man who frequently fell asleep’. The obesity-related changes in respiratory function, which are most prominent during sleep, are now recognized as the obesity–hypoventilation or Pickwickian syndrome. Definition of obesity as a medical disorder The recognition that obesity represents a serious medical disorder at a population level came with pooled life insurance data from the United States of America, showing that increasing degrees of overweight and obesity were important predictors of decreased longevity, much of which was

attributed to cardiovascular dis- ease. Subsequently, several epidemiological studies, including the Framingham Study and the Build and Blood Pressure Study, have shown that the adverse effects of excess weight tend to be delayed, sometimes for 10 years or longer. These observations led to the rec- ognition that obesity should be defined as a disorder in which excess body fat has accumulated such that health may be adversely affected. We now recognize that obesity is associated with substantially in- creased mortality from cardiovascular and cerebrovascular disease, type 2 diabetes, and certain cancers. Obesity is also associated with increased morbidity from musculoskeletal, gastrointestinal, psychi- atric, and reproductive diseases (Table 11.6.1) and is associated with lowered quality of life, self-esteem, and socioeconomic performance. The precise measurement of body fat is challenging and accurate methods are not applicable to large populations, hence surrogate markers such as the body mass index (BMI—weight in kilograms divided by the square of the height in metres) are most often used to define obesity in population studies and in the clinic. The underlying assumption is that most variation in weight for persons of the same height is due to fat mass. A World Health Organization Expert 11.6 Obesity I. Sadaf Farooqi

SECTION 11 Nutrition 1904 Committee has proposed a classification of overweight and obesity (Table 11.6.2) using BMI. Worldwide prevalence of obesity Obesity, defined as a BMI of more than 30 kg/m2, is a common condi- tion in Europe and the United States of America—20% of American men and about 25% of American women are obese. In Southeast Asia and the Middle East a dramatic rise is being seen in all popu- lations. Figure 11.6.1 shows the prevalence of obesity in high, low, lower-middle, and upper-middle income countries. In children the relationship between BMI and body fat varies markedly with age and with pubertal maturation. BMI percentile charts using national BMI reference data facilitate the graphical plotting of serial BMI measurements in individual patients. The International Obesity Task Force (IOTF) has recommended the use of BMI data derived from six countries, which extrapolate risk from the adult experience to children. These age- and gender-specific BMI cut-offs (overweight as approximately 91st percentile or greater and obesity as approximately 99th percentile or greater) allow the com- parison of obesity prevalence in different populations. Using these criteria, it is clear that the prevalence of overweight and obesity in childhood is a global concern, and—as shown in Fig. 11.6.2—the prevalence of overweight preschool children is greatest in lower- middle- and upper-middle-income countries. Although there is no accepted definition for severe or morbid obesity in childhood, a BMI of more than 2.5 standard deviations from the mean (weight off the chart) is often used in specialist centres, and the crossing of major weight percentile lines upwards is an early indication of risk of severe obesity. Aetiology of obesity Humans, like other mammals, are able to regulate their body weight over long periods of time despite day-to-day variation in the amount of calories consumed and in levels of energy expenditure. However, this homeostatic regulation of energy balance is easily overwhelmed by external stimuli. Body weight is determined by an interaction between genetic, en- vironmental, and psychosocial factors acting through the physio- logical mediators of energy intake and expenditure. By definition, obesity results from an imbalance between energy intake and en- ergy expenditure and, in any individual, excessive caloric intake or low energy expenditure, or both, may explain the development of obesity. A third factor, nutrient partitioning, a term reflecting the propensity to store excess energy as fat rather than lean tissue, may contribute. Environmental factors The increasing prevalence of obesity worldwide (an approximate doubling in the last 30 years), the inverse relationship between obesity and socioeconomic class, and the secular trend towards increasing obesity in developing countries associated with urban-

ization, provide clear evidence of the environmental influences on weight gain. The adoption of relatively sedentary lifestyles due to reduced physical activity at work and in leisure time coupled with an abundance of easily available, energy-rich, highly palatable foods represents a nutrition transition (see http://www.hsph.harvard.edu). Interestingly, some recent analyses of trends in obesity preva- lence have suggested a decline or stabilization of obesity preva- lence. However, many countries have either increasing (China) or decreasing (European countries) birth rates, so the potential global impact of these estimations is not readily predictable. Recent studies show that second generation migrants to the United States from all ethnic groups are heavier than their parents who migrated, but that people from some ethnic groups are more likely to gain weight than others on transitioning to a more obesogenic environment, sug- gesting that in addition to strong environmental drivers, genetic fac- tors play a role in influencing obesity susceptibility. The two priority areas for public health strategies aimed at preventing obesity are increasing physical activity and improving the quality of the available diet within a community. However, such strategies must address the need to improve the population's under- standing of the nature of obesity and its management and reduce exposure to an environment that promotes obesity.
Genetic factors In any environment, whether energy rich or energy lacking, there is considerable individual variation in body weight and fat mass. There is considerable evidence from family, twin, and adoption Table 11.6.1 Medical complications associated with obesity Type 2 diabetes 90% of type 2 diabetics have a BMI of >23 kg/m2 Hypertension 60–80% of hypertension is linked to excess weight Coronary artery disease (CAD) and stroke 3.6-fold risk of CAD for each unit change in BMI Respiratory effects Neck circumference of >43 cm in men and >40.5 cm in women is associated with obstructive sleep apnoea, daytime somnolence, and development of pulmonary hypertension Cancers 10% of all cancer deaths among nonsmokers are related to obesity (30% of endometrial cancers) Reproductive function 6% of primary infertility in women is attributable to obesity Impotency and infertility are frequently associated with obesity in men Osteoarthritis (OA) Frequent association in older people with increasing body weight Liver disease Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH); 40% of NASH patients are obese Gallbladder disease Threefold risk of gallbladder disease in women Table 11.6.2 Cut-off points proposed by a World Health Organization Expert Committee for the classification of overweight and obesity BMI WHO classification <18.5 Underweight 18.5–24.9 Normal weight 25–29.9 Overweight 30.0–39.9 Obesity 40.0 or greater Morbid obesity

Uruguay 26.7 United States of America 33.7 United Kingdom28.1 United Arab Emirates 37.2 Trinidad and Tobago 31.1 Switzerland 19.4 Sweden 20.5 Spain 23.7 Slovenia 25.1 Slovakia 25.7 Singapore 6.2 Saudi Arabia 34.7 Saint Kitts and Nevis 28.3 Russian Federation 24.1 Republic of Korea 5.8 Qatar 42.3 Portugal 20.1 Poland 25.2 Oman 30.9 Norway 23.1 New Zealand 29.2 Netherlands 19.8 Malta 26.6 Luxembourg 23.1 Lithuania 25.9 Latvia23.7 Kuwait 39.7 Japan 3.3 Italy 21.0 Israel 25.3 Ireland 25.6 Iceland 22.8 Greece 22.9 Germany 20.1 France 23.9 Finland 20.6 Estonia 22.6 Equatorial Guinea 17.5 Denmark 19.3 Czech Republic 26.8 Cyprus 23.8 Croatia 23.3 Chile 27.8 Canada 28.0 Brunei Darussalam 18.1 Belgium 20.2 Barbados 31.3 Bahrain 35.1 Bahamas 36.2 Austria 18.4 Australia 28.6 Antigua and Barbuda 30.9 Andorra 29.5 0% 50% 20% 10% 30% 40% Zimbabwe 10.5 United Republic of Tanzania 7.1 Uganda 4.9 Togo 7.5 Tajikistan13.6 Somalia 4.6 Sierra Leone 7.6 Rwanda 4.0 Niger 4.3 Nepal 3.3 Myanmar 2.9 Mozambique 5.3 Mali 6.8 Malawi 5.3 Madagascar 5.4 Liberia 6.6 Kenya 7.0 Haiti 11.9 Guinea-Bissau 7.2 Guinea 6.8 Gambia 10.9 Ethiopia 4.0 Eritrea 4.1 Democratic Republic of the Congo 4.4 Democratic People's Republic of Korea 2.4 Comoros 6.6 Chad 8.1 Central African Republic 5.1 Cambodia 3.2 Burundi 2.6

Burkina Faso 6.3 Benin 9.3 Bangladesh 3.6 Afghanistan 2.9 0% 50% 20% 10% 30% 40% High-income (a) Low-income Fig. 11.6.1 Age-standardized prevalence of obesity (percentage with BMI >30 kg/m2) in adults aged 18 years and over, by individual country and World Bank Income group, 2014. Reprinted from Global status report on noncommunicable diseases 2014, Copyright © World Health Organization 2014.

SECTION 11 Nutrition 1906 Zambia 8.9 Yemen 17.2 Viet Nam 3.6 Vanuatu 35.4 Uzbekistan 15.5 Ukraine 20.1 Timor-Leste 2.2 Syrian Arab Republic 23.5 Swaziland 17.7 Sudan 7.5 Sri Lanka 6.5 South Sudan 7.5 Solomon Islands 27.7 Senegal 9.8 Sao Tome and Principe 12.3 Samoa 43.4 Republic of Moldova 14.9 Philippines 5.1 Paraguay 16.3 Papua New Guinea 27.9 Pakistan 5.4 Nigeria 11.0 Nicaragua 17.1 Morocco 22.3 Mongolia 16.7 Micronesia (Federated States of) 37.2 Mauritania 9.7 Lesotho 14.2 Lao People's Democratic Republic 3.5 Kyrgyzstan 14.4 Kiribati 40.6 Indonesia 5.7 India 4.9 Honduras 18.2 Guyana 22.9 Guatemala 18.6 Ghana 12.2 Georgia 20.8 El Salvador 21.8 Egypt 28.9 Djibouti 9.6 Côte d'Ivoire 9.2 Congo 11.0 Cameroon 11.4 Cabo Verde 13.0 Bolivia (Plurinational State of) 17.1 Bhutan 6.7 Armenia 19.5 0% 50% (b) 20% 10% 30% 40% Venezuela (Bolivarian Republic of) 24.8 Tuvalu 40.3 Turkmenistan 20.1 Turkey 29.5 Tunisia 27.1 Tonga 43.3 the former Yugoslav Republic of Macedonia 19.6 Thailand 8.5 Suriname 26.1 South Africa 26.8 Seychelles 26.3 Serbia 19.5 Saint Vincent and the Grenadines 24.3 Saint Lucia 26.9 Romania 21.7 Peru 21.1 Panama 26.8 Palau 47.6 Niue 43.2 Nauru 45.6 Namibia 18.9 Montenegro 20.0 Mexico 28.1 Mauritius 17.9 Marshall Islands 42.8 Maldives 7.9 Malaysia 13.3 Libya 33.1 Lebanon 31.9 Kazakhstan 23.4 Jordan 30.5 Jamaica 27.2 Iraq 23.8 Iran (Islamic Republic of) 26.1 Hungary 24.0 Grenada 26.2 Gabon 17.6 Fiji 36.4 Ecuador 18.7 Dominican Republic 23.9 Dominica 25.8 Cuba 25.2% Costa Rica 24.3 Cook Islands 50.8 Colombia 21.0 China 6.9 Bulgaria 23.2 Brazil 20.0 Botswana 22.4 Bosnia and Herzegovina 17.9 Belize 22.5 Belarus 23.4 Azerbaijan 22.5 Argentina 26.3 Angola 10.2 Algeria 24.8 Albania 17.6 0% 50% 20% 10% 30% 40% Low-middle-income Upper-middle-income Fig. 11.6.1 Continued

11.6 Obesity 1907 studies that genetic factors contribute to this variability. Heritability estimates can change over time and can differ between populations. Recent studies in a UK sample of 5092 twin pairs aged 8–11 years growing up during a time of dramatic rises in obesity, confirmed substantial heritability for BMI and waist circumference (77% for both), while there was a very modest shared-environment effect, and the remaining environmental variance was unshared. Interestingly, similar heritability estimates have been found when studying mono- zygotic and dizygotic twins who were reared together and apart and in adoption studies, where adopted children were discovered to have body sizes that were more similar to those of their biological parents than their adopted parents. Recently, genome-wide association have led to the identification of multiple genomic regions/loci that are strongly associated with increased BMI and/or obesity. However, to date, the common vari- ants that have been identified explain less than 5% of the heritability of increased BMI. It is likely that rare variants that are more highly penetrant will explain more of the missing heritability of obesity. Programming and epigenetics Recent evidence suggests that undernutrition of the fetus during intrauterine development can influence the later onset of obesity, hypertension, and type 2 diabetes, independent of genetic factors. Such a phenomenon suggests the possibility of long-term program- ming of genetic expression as a consequence of altered intrauterine growth. The influence of maternal diet and other factors on the regu- lation of genes in their offspring, referred to as epigenetics, is the focus of much current research. Hypothalamic circuits regulating energy homeostasis Energy

homeostasis is tightly regulated, with the hypothalamus playing a pivotal role in integrating signals from adipose tissue stores, such as leptin, and short-term meal-related signals from the gut (peptide-YY, glucagon like peptide-1 (GLP-1), cholecysto- kinin, and ghrelin; see Fig. 11.6.3). The hypothalamus integrates these sensory inputs, compares those inputs to ‘set-points’ for en- ergy homeostasis, and then initiates a set of responses by activating autonomic, endocrine, and behavioural outputs that aim to maintain these set-points (homeostasis). Leptin stimulates the expression of pro-opiomelanocortin (POMC), which is cleaved by prohormone convertases to yield the melanocortin peptides, which act as Prevalence of overweight in children aged under 5 years, by WHO region and World Bank income group, comparable estimates, 2013 14% 12% 10% 8% 6% 4% 2% 0% AFR AMR SEAR EUR EMR WPR Low- income Low- middle- income Upper- middle- income High- income Fig. 11.6.2 Prevalence of overweight in children under 5 years by World Health Organization (WHO) region and World Bank income group (estimates in 2013). AFR, African region; AMR, region of the Americas; SEAR, Southeast Asia region; EUR, European region; EMR, Eastern Mediterranean region; WPR, Western Pacific region. Reprinted from Global status report on noncommunicable diseases 2014, Copyright © World Health Organization 2014. Hypothalamus Leptin Insulin Pancreas Adipose tissue GI tract Ghrelin PYY GLP-1 CCK Vagus nerve Nutrients (glucose, fatty acids, etc.) Fig. 11.6.3 Interactions between the hypothalamus, adipose tissue, and gastrointestinal tract. CCK, cholecystokinin; GI, gastrointestinal; GLP-1, glucagon like peptide-1; PYY, peptide-YY.

SECTION 11 Nutrition 1908 suppressors of feeding through the melanocortin 4 receptor (MC4R). This is a key circuit in the regulation of body weight, but numerous other pathways involving the mesolimbic system, the hindbrain, and orbitofrontal cortex influence eating behaviour (Fig 11.6.4). Clinical history, examination, and investigation For the assessment of severely obese patients, the consultation room should be properly equipped with larger than average chairs, access for wheelchairs for patients with mobility problems, and medical equipment of appropriate size (examination couch, blood pressure cuff, weighing scales, stadiometer (for measurement of height), and tape measure). In addition to a general medical history, a specific weight his- tory should be taken, carefully establishing the age of onset (clinical photographs are helpful here), as it is useful to distinguish obesity that began in childhood (stronger genetic component) from that occurring later in life either in relation to specific physiological ‘crit- ical periods’ such as pregnancy, illness, or concomitant medications. A history of previous treatment for obesity, diet, and levels of phys- ical activity should be noted. The assessment of severely obese children and adults should include screening for potentially treatable endocrine and neuro- logical conditions and identifying genetic conditions so that ap- propriate genetic counselling and, in some cases, treatment can be instituted. In most patients, these specific causes can be excluded by a careful clinical history (Box 11.6.1), examination, and inves- tigations (Table 11.6.3), which should also address the potential hidden complications of severe obesity such as sleep apnoea, cor- onary heart disease, type 2 diabetes, gynaecological abnormalities, osteoarthritis, gallstones, and stress incontinence. Height should be measured accurately using a stadiometer and weight measured by accurate scales in light clothing. BMI does not distinguish between excess fat and lean body mass, hence waist cir- cumference (or waist-to-hip ratio), which is a predictor of metabolic complications, should be measured. Ethnicity should be taken into consideration as individuals from some groups (e.g. South Asians) have a greater metabolic risk than would be expected for their BMI and waist circumference. Waist circumference is taken as the mid- point between the lower rib margin and the iliac crest. An examination of the skin is important: thin, atrophic skin is a feature of excess

corticosteroids; acanthosis nigricans (pigmented ‘velvety’ skin creases, especially in the axillae) suggests insulin re- sistance; severe hirsutism in women may indicate polycystic ovary syndrome. A neck circumference of more than 43 cm indicates a likelihood of obstructive sleep apnoea. Clinicians should use laboratory testing to evaluate overweight and obese patients who may be at high risk for cardiovascular dis- ease and type 2 diabetes. Some useful tests to consider are fasting plasma glucose or 2-h postprandial glucose levels and serum lipid levels. Thyroid-stimulating hormone (TSH) may be helpful in excluding hypothyroidism. Urinary free cortisol can be obtained if hypercortisolism is suspected clinically. Fig. 11.6.4 Several single-gene defects that disrupt the molecules in the leptin–melanocortin pathway cause severe obesity (indicated by *). Leptin is released from adipose tissue to act on receptors expressed on the surface of distinct populations of neurones in the arcuate nucleus of the hypothalamus. Leptin stimulates a neuropeptide called pro-opiomelanocortin (POMC), which is then cleaved by the enzyme prohormone convertase 1 (PC1) to yield the melanocortin peptides. Leptin inhibits the expression of neuropeptide Y (NPY) and agouti-related peptide (AgRP). Both sets of neurons project to synapse, with second-order neurons expressing the melanocortin 4 receptor (MC4R), ultimately leading to an inhibition of food intake.

 Other tests to consider depend on clinical assessment and include ultrasonography for hepatic steatosis, gallstones, and the polycystic ovary syndrome; electrocardiography in patients at high risk for car- diovascular disease; polysomnography for patients with possible sleep apnoea; and head CT or MRI when pituitary or hypothalamic disorders are suspected. Genetic testing is needed to confirm the diagnosis in patients with rare genetic disorders. The measurement of serum leptin is not recommended as a routine examination, but should be undertaken in cases of severe early onset obesity, since, although it is rare, congenital leptin deficiency is a potentially treat- able disorder. Genetic obesity syndromes Classically, patients affected by genetic obesity syndromes have been identified as a result of their association with developmental delay, dysmorphic features, or other developmental abnormalities. More recently, several single-gene disorders resulting from disruption of the hypothalamic leptin–melanocortin signalling pathway have been identified. In these disorders, obesity itself is the predominant presenting feature, although frequently accompanied by character- istic patterns of neuroendocrine dysfunction that will only become apparent on investigation. Mutations in several of these molecules cause severe obesity associated with specific neuroendocrine abnor- malities (Table 11.6.4). One rare genetic disorder, leptin deficiency, is entirely treatable with daily subcutaneous injections of recom- binant human leptin, and another, MC4R deficiency, is relatively common, with a population prevalence of 1 in 1000 unselected indi- viduals and 1 in 100 obese people. For the purposes of clinical assessment, it remains useful to cat- egorize the genetic obesity syndromes as those with dysmorphism and/or developmental delay, and those without these features. There are about 30 Mendelian disorders with obesity as a clinical feature but often associated with mental retardation, dysmorphic features, and organ-specific developmental abnormalities: the commonest of these are listed in Table 11.6.5. Approach to the treatment of obesity The recommendation to treat obesity is based on evidence that re- lates obesity to increased mortality and the results from randomized controlled trials, which demonstrate that weight loss reduces the risk of many metabolic complications. Professional, governmental, Box 11.6.1 History • Age of onset—use of growth charts and family photographs. Early onset (<5 years of age) suggests a genetic cause. • Duration of obesity—short history suggests endocrine or central cause. • A history of damage to the CNS (e.g. infection, trauma, haemor- rhage, radiation therapy, seizures) suggests hypothalamic obesity with or without pituitary growth hormone

deficiency or pituitary hypothyroidism. A history of morning headaches, vomiting, visual disturbances, and excessive urination or drinking also suggests that the obesity may be caused by a tumour or mass in the hypothalamus. • A history of dry skin, constipation, intolerance to cold, or fatigue sug- gests hypothyroidism. Mood disturbance and central obesity suggests Cushing's syndrome. Frequent infections and fatigue may suggest ACTH deficiency due to POMC mutations. • Hyperphagia—often denied, but a sympathetic approach is needed and responses to specific questions, such as waking at night to eat or demanding food very soon after a meal, suggest hyperphagia. If se- vere, especially in children, suggests a genetic cause for obesity. • Developmental delay—milestones, educational history, behavioural disorders. Consider craniopharyngioma or structural causes (often relatively short history) and genetic causes. • Visual impairment and deafness can suggest genetic causes. • Onset and tempo of pubertal development—onset can be early or delayed in children and adolescents. Primary hypogonadotropic hypogonadism or hypogenitalism associated with some genetic disorders. • Family history—consanguineous relationships, other children affected, family photographs useful. Severity may differ due to environmental effects. • Treatment with certain drugs or medications. Glucocorticoids, sulphonylureas, oral contraceptives, antidepressants, and antipsychotics.
Table 11.6.3 Key points in the examination and investigation of an obese patient Examination Height, weight—calculate BMI Blood pressure Waist circumference Neck circumference Acanthosis nigricans Body fat distribution Secondary sexual characteristics Any evidence of cardiac disease Signs of hyperlipidaemia Signs of thyroid disease Ophthalmic evidence of diabetes or sustained hypertension Investigations Fasting and postprandial blood glucose Fasting lipid profile Strip test for urine glucose and protein Free thyroxine and thyroid-stimulating hormone Table 11.6.4 Obesity syndromes in the absence of developmental delay Name of syndrome Clinical characteristics Alstrom Progressive nephropathy, photophobia, retinitis pigmentosa, deafness, diabetes mellitus due to marked insulin resistance Leptin Severe hyperphagia, frequent infections, hypogonadism Prohormone convertase 1 Neonatal diarrhoea, postprandial hypoglycaemia, multiple endocrine abnormalities Leptin receptor Severe hyperphagia, frequent infections, hypogonadism POMC Isolated ACTH deficiency, hypopigmentation MC4R Increased linear growth, severe hyperinsulinaemia, 'big-boned' appearance ACTH, adrenocorticotropic hormone; MC4R, melanocortin 4 receptor; POMC, pro-opiomelanocortin.

 and other bodies have drawn up guidelines for obesity management and it is advisable to seek out the latest national and international guidelines as newer evidence is incorporated. These strategies pro- vide useful evidence-based guidance for clinical management, but it is important to remember that an individually tailored approach is often required and that any treatment programme for obese pa- tients should address weight reduction and the maintenance of the lowered weight and take account of individual circumstances. Goals of weight loss Achievement of normal or ideal body weight is not a necessary goal in the management of obesity and is rarely reached in practice. There is evidence from epidemiological studies of intentional weight loss that modest weight loss, of the order of 5 to 10% from presenta- tion weight, is associated with clinically worthwhile reductions in comorbidities, such as hypertension, dyslipidaemia, and diabetes risk (Table 11.6.6). In some patients, particularly in those with se- vere comorbidity, prevention of weight gain may be a reasonable aim of treatment. Weight loss should be approached incrementally, with new goals for weight loss negotiated with the patient once the ori- ginal target has been achieved. Dietary management Many dietary approaches have been advocated for the treatment of obesity. Recent evidence-based reviews

support the use of low- calorie diets as being most likely to be effective for modest weight loss. A review of 48 randomized control trials shows that an average weight loss of 8% of the initial body weight can be obtained over 3 to 12 months with a low-calorie diet. Such a treatment may require a period of supervision for at least 6 months. The weight-reducing dietary regimen should initially provide a 600 kcal/day (2.5 MJ/day) energy deficit, based on estimated en- ergy requirements. After 6 months, the rate of weight loss usually declines and a further adjustment of calorie intake may be indi- cated at this stage. The use of very low-calorie diets can be con- sidered, ideally under close supervision as preparations must provide a minimum of 400 kcal (1.7 MJ) per day for women and 500 kcal (2.1 MJ) per day for men. Evidence from randomized trials confirms that over the longer term (more than a year), weight loss following very low-calorie diets is no different from that obtained with low-calorie diets. Behavioural therapy and exercise Behavioural approaches aim to help people to implement and sus- tain changes to their eating and activity behaviour. There is evi- dence that combining a behavioural approach with more traditional dietary and activity advice leads to improved short-term weight loss. In general, weight loss with these approaches is modest (about 4 kg or 4% of body weight on average). Although modest physical activity has undoubted health bene- fits and can contribute to weight loss, it is not usually advocated as a sole treatment option. Many studies, however, do suggest that it can be helpful to improve weight loss maintenance once weight loss has been achieved. The results from randomized controlled trials suggest that a combination of diet and exercise generally produces more weight loss than diet alone. The optimal approach should be a high-quality diet to which patients will adhere, accompanied by an exercise prescription describing frequency and intensity of exercise with a minimum of 150 min moderate weekly activity. The type of physical activity (e.g. aerobic versus resistance) does not seem to af- fect overall weight loss. Table 11.6.5 Obesity syndromes with developmental delay Name of syndrome Gene/genetic region involved Clinical characteristics Prader–Willi Deletion or uniparental maternal disomy of chromosome 15q11.2–-q12 Hypotonia, short stature, hypogonadotropic hypogonadism, feeding difficulties <2 years of age, then hyperphagia with pica behaviour Bardet–Biedl Mutations in multiple genes affect the function of cilia Polydactyly, retinitis pigmentosa, and hypogonadism are consistent features Fragile X Unstable expansion of trinucleotide repeats in the FMR1 gene Moderate to severe developmental delay, macro-orchidism, prominent jaw, and high-pitched jocular speech Cohen COH1 mutations Microcephaly, characteristic facial features, progressive retinochoroidal dystrophy, myopia, and a cheerful disposition Albright hereditary osteodystrophy GNAS1 mutations Short stature, round facies, brachydactyly, and ectopic soft tissue ossification (osteoma cutis), variable hormone (TSH, PTH) resistance, short fourth metacarpal BDNF/TrkB deficiency Mutations/deletions in BDNF or its receptor TrKB Delayed speech and language development, impaired short-term memory, and loss of nociception BDNF, brain-derived neurotrophic factor; PTH, parathyroid hormone; TrkB, neurotrophic tyrosine kinase, receptor, type 2; TSH, thyroid-stimulating hormone. Table 11.6.6 Potential health benefits that may accrue from the loss of 10 kg from the initial body weight Mortality 20–25% fall in total mortality 30–40% fall in diabetes-related deaths 40–50% fall in obesity-related cancer deaths Blood pressure c.10 mm Hg fall in both systolic and diastolic values Diabetes

> “ 50% reduction in risk of developing diabetes 30–50% fall in fasting glucose 15% fall in haemoglobin A1c Lipids 10% fall in total cholesterol 15% fall in LDL

> cholesterol 30% fall in triglycerides 8% increase in HDL cholesterol HDL, high-density lipoprotein; LDL, low-density lipoprotein.

11.6 Obesity 1911 Two large randomized clinical trials—the Look AHEAD and the Diabetes Prevention Programme—support the use of intensive weight loss programmes with face-to-face (group or individual) sessions. The delivery of such programmes is often expensive and a useful alternative is the use of commercial programmes to deliver advice within communities. A meta-analysis comparing named diets and several comparisons of diets with different amounts of fat/carbohydrate/protein have found that there was no significant difference between diets in terms of weight loss achieved. A key goal is identifying a diet that a particular patient finds that they can adhere to. Drug therapy General principles While intervention programmes that focus on supporting people to change their diet and/or levels of physical activity can be effective in inducing weight loss in the short to medium term in some people, they lose efficacy in the long term. In addition to the focus on pre- vention of obesity, treatment of obese patients, preferably at a stage before complications has emerged, is therefore an important priority. Previous antiobesity drugs targeted cannabinoid signalling (rimonabant), noradrenergic (phentermine), serotoninergic signalling (fenfluramine, dexfenfluramine), and reuptake (sibutramine). These compounds were moderately effective but, as with many centrally acting agents, at the expense of many off-target effects, reflecting lack of specificity of the neural targets. The use of obesity drugs should follow the same principles as for any condition and be prescribed after assessment of the potential benefits and risks with appropriately informed patients, and with medical monitoring of the results of treatment. Some healthcare providers still believe that a short course of drug treatment might ‘cure’ obesity or that efficacy is measured only by ever-continuing weight loss. These ideas are inconsistent with the known biology as people who become obese have a persistent tendency both to defend their excess weight and to continue to gain extra body fat. Effective management must be lifelong and focused on weight loss mainten- ance in a similar fashion to the effective treatment for hypertension or diabetes. Starting drug treatment should always be regarded as a therapeutic trial and stopped if weight loss is not apparent after 1 or 2 months. The initiation of drug treatment will depend on the physician’s judgement about the risks to an individual from continuing obesity. A drug should not be considered ineffective because weight loss has stopped, provided that the lowered weight is maintained. However, continuation of the drug should depend on the balance between the health benefits of maintained weight and the potential adverse ef- fects of the drug. Particular drugs Orlistat Orlistat inhibits pancreatic and gastric lipases, thereby decreasing the hydrolysis of ingested triglycerides. It produces a dose-dependent reduction in absorption of dietary fat that is near maximum at a dose of 120 mg, three times daily. It leads to 5 to 10% weight loss in 50 to 60% of patients, and in clinical trials the loss (and related clinical benefit) is largely maintained up to at least 4 years. Adverse effects of orlistat are predominantly related to malabsorption of fat. These include loose or liquid stools, faecal ur- gency, and oily discharge; they can be associated with malabsorption of fat-soluble vitamins. As the consumption of a high-fat meal will inevitably lead to severe gastrointestinal symptoms, it is possible that some of the weight loss with orlistat treatment results from an ‘Antabuse effect’, leading to behavioural change. Sibutramine Sibutramine inhibits the reuptake of noradrenaline and serotonin, promoting, and prolonging satiety. It may also have an enhancing effect on thermogenesis through the stimulation of peripheral noradrenergic receptors. Adverse effects include nausea, dry mouth, rhinitis, and

constipation. It produces 5 to 10% weight loss in 60 to 70% of patients, which in clinical trials is well maintained for at least 2 years. The noradrenergic action increases heart rate by 1 to 2 beats/min and attenuates the fall in blood pressure expected with weight loss. Some patients, especially if they fail to lose weight, may record a rise in their blood pressure; it is therefore essential to monitor blood pressure during treatment. Recent concerns about increased cardiovascular morbidity as- sociated with Sibutramine have led to prescribing restrictions, par- ticularly relevant to those patients with established cardiovascular disease. Current guidelines in Europe and the United States vary and physicians should consult local guidelines where available. Newer centrally acting antiobesity drugs Over the last few years, certain weight loss drugs have been ap- proved by the US Food and Drug Administration (FDA) and other regulators, expanding the number of options available to physicians seeking to treat patients with severe obesity and/or obesity with complications. Lorcaserin, a selective 5HT2cR agonist with limited activity at the other serotonin receptors, leads to weight loss, lowers blood pres- sure, total cholesterol, low-density lipoprotein cholesterol, and tri- glycerides, although concerns about potential cardiac valvulopathy and cancer risk remain. Adverse effects include headache, nausea, fatigue, and dizziness. An extended release combination of the anticonvulsant topiramate (which modulates GABA-ergic transmission and inhibits carbonic anhydrase) and phentermine, which increases central noradren- aline levels, is also approved in some countries. Topiramate is asso- ciated with fetal toxic effects and a pregnancy test before and during therapy is recommended. Bupropion, a dopamine and noradrenaline reuptake in- hibitor, has anorexigenic properties resulting in modest weight loss. The effectiveness of bupropion is increased (and thus the dose can be reduced) when combined with the opioid receptor antagonist naltrexone, resulting in the combination product, naltrexone-bupropion. The synthetic GLP-I receptor agonist liraglutide, effective in the treatment of type 2 diabetes, has been approved for the treatment of obesity alone by the FDA. Nausea remains a significant problem in many, but those who can tolerate the dug do well. Several other gut peptide analogues, gut hormone receptor agonists, and cen- trally active compounds are currently being studied in clinical trials.

SECTION 11 Nutrition 1912 More recently a potent melanocortin receptor agonist, RM-493, has been administered as part of a phase 1b proof-of-concept clinical trial in obese patients, including one cohort with heterozygous loss of function mutations in MC4R where there was promising weight loss after four-weeks. If this compound moves forward, this may be one of the first examples of a personalized medicine approach for treating obesity in people with a genetically characterized subtype of obesity. Surgical treatment of obesity Randomized controlled trials confirm that surgery for obesity is an effective option for carefully selected patients with severe obesity (BMI >40 kg/m2 or BMI >35 kg/m2 with comorbid conditions). The nature of the surgical procedures necessitates long-term hospital follow-up for such patients. The initial findings from the Swedish Obese Subjects study of severely obese subjects (those with a BMI

> 40. indicate that weight loss of approximately 30 kg over 2 years is associated with a 60% reduction in plasma insulin, a 25% decrease in plasma glucose and triglycerides, and a 10% reduction in blood pressure with associated effects on the risk of cardiovascular disease. Poor health-related quality of life was dramatically improved after

gastric restriction surgery, while only minor fluctuations in health-related quality of life were observed in people treated by conven- tional dietary methods. Most surgical treatment is now carried out laparoscopically. Some procedures are commonly used, each having its own risks and benefits which need to be considered carefully on an individual basis. Laparoscopic gastric banding This operation involves gastric restriction with the creation of a small compartment (<20 ml) by either a combination of vertical stapling and a constrictive band opening, or a gastric band pinching off a small proximal pouch.
A modification of the latter procedure is an inflatable gastric band attached to a subcutaneous reservoir which allows access by a hypodermic syringe to inject or withdraw fluid, thereby tightening or enlarging the band width. This method mainly works by restricting how much food patients can eat. The average weight loss is around 15 to 20% of body weight, although some weight regain occurs over time. Morbidity and mortality are relatively low (mortality <0.2%), but patients do need to return for band adjustments. Gastric bypass This involves creating a small-volume gastric pouch and produ- cing a Roux-en-Y diversion so that food bypasses the duodenum and upper jejunum. This works by both restricting food intake and causing a modest degree of malabsorption. Weight loss is generally greater than with the band. Operative mortality is less than 0.2% for laparoscopic procedures and 0.5% for open procedures. Duodenal switch and sleeve gastrectomy A variant of the older biliopancreatic diversion, this involves a partial (sleeve gastrectomy) and bypass of a long loop of jejunum. Weight loss is greatest with this procedure, but malabsorption is more likely and patients need careful follow-up and attention to their diet, vitamin, and mineral supplementation. Concluding remarks As the prevalence of obesity is rising, we are seeing more and more patients with severe obesity. It is important to have a practical ap- proach to the investigation and management of these patients who have considerably increased morbidity and mortality. The clinical evaluation of severely obese patients will become increasingly so- phisticated, and novel biochemical and molecular genetic diagnos- tics will need to be combined with the more traditional nutritional and behavioural approaches to optimize treatment for individual patients. FURTHER READING Allison DB, et al. (1996). The heritability of body mass index among an international sample of monozygotic twins reared apart. Int J Obes Relat Metab Disord, 20, 501–6. Berrington de Gonzalez A, et al. (2010). Body-mass index and mor- tality among 1.46 million white adults. N Engl J Med, 363, 2211–19. Bray GA, et al. (2016). Management of obesity. Lancet, 387, 1947–56. Feinleib M (1985). Epidemiology of obesity in relation to health haz- ards. Ann Intern Med, 103, 1019–24. Gadde KM, et al. (2011). Effects of low-dose, controlled-

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