

## Clinical Information

# European Guidelines for Obesity Management in Adults

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## Key Words

European guidelines · Obesity management · Multidisciplinary · Primary care · OMTF · COMs

## Abstract

Obesity is a chronic metabolic disease characterised by an increase of body fat stores. It is a gateway to ill health, and it has become one of the leading causes of disability and death, affecting not only adults but also children and adolescents worldwide. In clinical practice, the body fatness is estimated by BMI, and the accumulation of intra-abdominal fat (marker for higher metabolic and cardiovascular disease risk) can be assessed by waist circumference. Complex interactions between biological, behavioural, social and environmental factors are involved in regulation of energy balance and fat stores. A comprehensive history, physical examination and laboratory assessment relevant to the patient's obesity should be obtained. Appropriate goals of weight management emphasise realistic weight loss to achieve a reduction in health risks and should include promotion of weight loss, maintenance and prevention of weight regain. Management of co-morbidities and improving quality of life of obese patients are also included in treatment aims. Balanced hypocaloric diets result in clinically meaningful weight loss regardless of which macronutrients they emphasise. Aerobic training is the optimal mode of exercise for reducing fat mass while a programme including resistance train-

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ing is needed for increasing lean mass in middle-aged and overweight/obese individuals. Cognitive behavioural therapy directly addresses behaviours that require change for successful weight loss and weight loss maintenance. Pharmacotherapy can help patients to maintain compliance and ameliorate obesity-related health risks. Surgery is the most effective treatment for morbid obesity in terms of long-term weight loss. A comprehensive obesity management can only be accomplished by a multidisciplinary obesity management team. We conclude that physicians have a responsibility to recognise obesity as a disease and help obese patients with appropriate prevention and treatment. Treatment should be based on good clinical care, and evidence-based interventions; should focus on realistic goals and life-long multidisciplinary management.

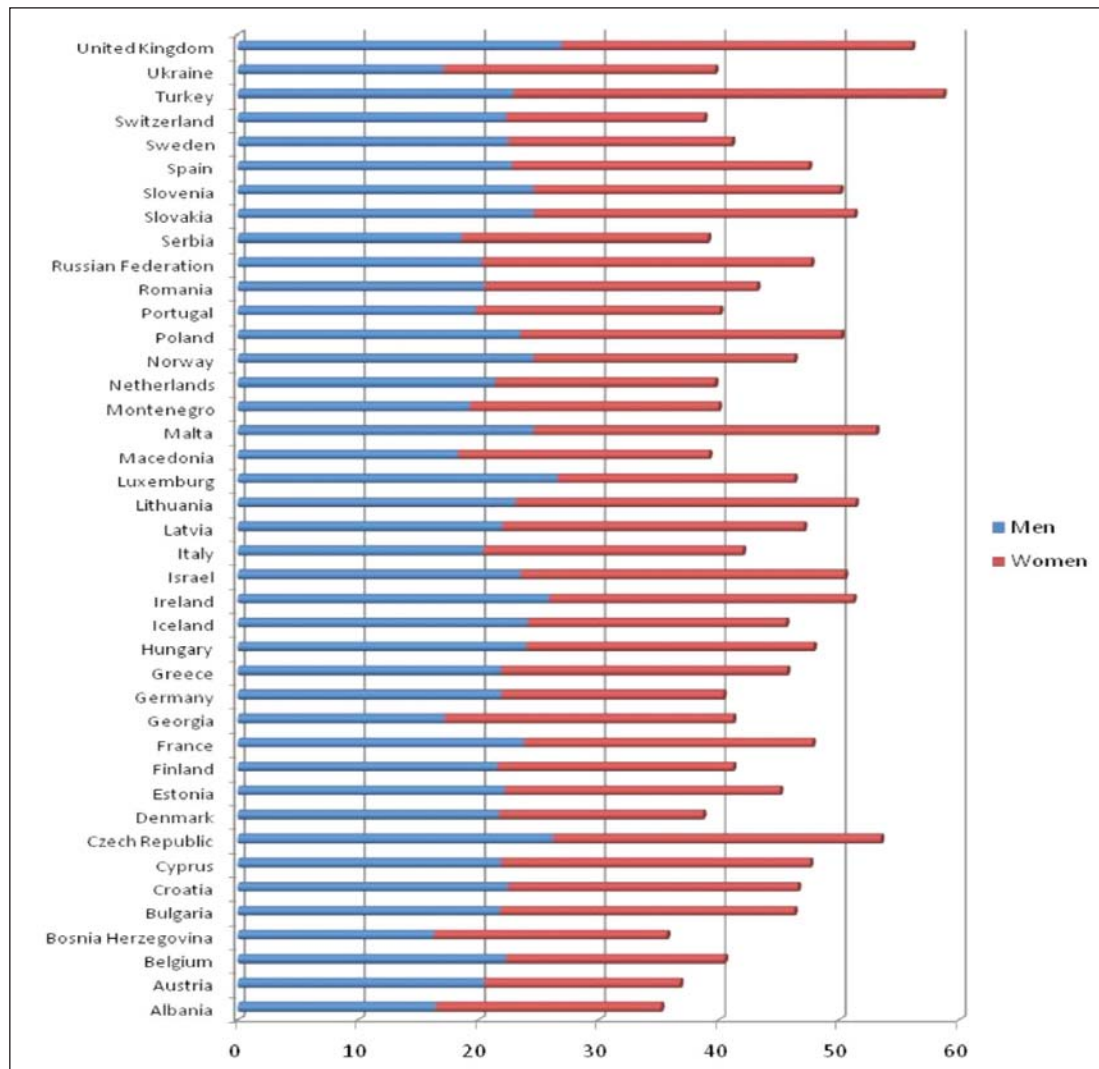
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## Introduction

Obesity is a metabolic disease (ICD-10 code E66) that has reached epidemic proportions. The World Health Organization (WHO) has declared obesity as the largest global chronic health problem in adults which is increasingly turning into a more serious problem than malnutrition. Obesity is a gateway to ill health, and it has become one of the leading causes of disability and death, affecting not only adults but also children and adolescents worldwide [1]. In 2014, more than 1.9 billion adults (18 years and older) were overweight. Of these over 600 million were obese. 42 million children under the age of 5 were overweight or obese in 2013 [2]. The WHO world health statistics report in 2015 shows that in the European region the overall obesity rate among adults is 21.5% in males and 24.5% in females (fig. 1). The same report states that the prevalence for overweight among children under the age of 5 is 12.4% [3]. It has been further projected that 60% of the world's population, i.e. 3.3 billion people, could be overweight (2.2 billion) or obese (1.1 billion) by 2030 if recent trends continue [4]. Obesity has important consequences for morbidity, disability and quality of life and entails a higher risk of developing type 2 diabetes, cardiovascular diseases, several common forms of cancer, osteoarthritis and other health problems [5]. In 2010, overweight and obesity were estimated to cause 3.4 million deaths, 4% of years of life lost, and 4% of disability-adjusted life years (DALYs) [6].

## Definition and Classification

Obesity is a chronic disease characterised by an increase of body fat stores. In clinical practice, the body fatness is usually estimated by BMI. BMI is calculated as measured body weight (kg) divided by measured height squared ( $m^2$ ). In adults (age over 18 years) obesity is defined by a BMI  $\geq 30$   $kg/m^2$  and overweight (also termed pre-obesity) by a BMI between 25 and  $29.9$   $kg/m^2$ . Lower BMI cut-off points apply for some ethnic groups (e.g. Southeast Asians) [7, 8] (table 1) [level 1]. Accumulation of intra-abdominal fat is associated with higher metabolic and cardiovascular disease risk [7, 9] [level 1]. The amount of abdominal fat can be assessed by waist circumference (WC) which highly correlates with intra-abdominal fat content. The WC is measured in the horizontal plane midway in the distance of the superior iliac crest and the lower margin of the last rib. The most recent International Diabetes Federation (IDF) consensus defined central obesity (also known as visceral, android, apple-shaped or upper body obesity) in Europids as a WC of  $\geq 94$  cm in men and  $\geq 80$  cm in non-pregnant women. Lower cut-off points for central obesity are proposed for different ethnic groups [10] [level 4].



**Fig. 1.** Obesity prevalence in adults in Europe (Source: WHO 2014 data).

**Table 1.** BMI categories (WHO 1997)

Category	BMI, kg/m <sup>2</sup>
Underweight	<18.5
Healthy weight	18.5–24.9
Pre-obese state	25.0–29.9
Obesity grade I	30.0–34.9
Obesity grade II	35.0–39.9
Obesity grade III	≥40

### Pathogenesis of Obesity

The cause of obesity is complex and multifactorial [11, 12]. At the simplest level, obesity develops as a result of a period of chronic energy imbalance and is maintained by a continued elevated energy intake sufficient to maintain the acquired higher energy needs of the obese state. Complex interactions between biological (including genetic and epigenetic), behav-

Journal, social and environmental factors (including chronic stress) are involved in regulation of energy balance and fat stores [13, 14]. The rapid increase in the prevalence of obesity over the past 30 years is mainly a result of cultural and environmental influences. High energy density diet, increased portion size, low physical activity and adoption of a sedentary lifestyle as well as eating disorders are considered as important risk factors for the development of obesity [8, 15]. These behavioural and environmental factors lead to alterations in adipose tissue structure (hypertrophy and hyperplasia of adipocytes, inflammation) and secretion (e.g. adipokines) [16, 17]. Weight loss surgery has proven to be a convenient and proper research tool facilitating insights into the pathogenesis of obesity as well as regulation of hunger and satiation. Gut hormones communicate information from the gastrointestinal tract to the regulatory appetite centres within the CNS via the so-called 'gut-brain axis' [18, 19]. Obesity is associated with changes in the composition of the intestinal microbiota. Products of intestinal microbes may induce beneficial metabolic effects through enhancement of mitochondrial activity, prevention of metabolic endotoxaemia and activation of intestinal gluconeogenesis via different routes of gene expression and hormone regulation [20, 21]. The role of thermogenesis of brown adipose tissue and its contribution to energy expenditure is being investigated mainly to develop strategies to recruit and activate energy-dissipating brown adipose tissue as a preventive or remedial measure for weight control in obesity [22–24].

### Clinical Evaluation of the Obese Patient

A comprehensive history, physical examination and laboratory assessment relevant to the patient's obesity should be obtained [25–27] {Recommended Best Practice (RBP)}.

#### *History Taking*

- Ethnicity
- Family history
- Dietary habits
- Physical activity frequency and nature
- Eating pattern and possible presence of an eating disorder (binge eating disorder, night eating syndrome, bulimia)
- Presence of depression and other mood disorders
- Other determinants, e.g., genetic, drugs, endocrine abnormalities, psychosocial factors, chronic stress, smoking cessation etc.
- Health consequences of obesity (table 2)
- Patient expectations and motivation for change
- Previous treatments for obesity.

#### *Physical Examination*

- Measure weight and height (from which BMI is calculated), WC, blood pressure (appropriate size cuff) {grade 3}
- Assess the presence and impact of obesity-related diseases (diabetes, hypertension, dyslipidaemia; cardiovascular, respiratory and joint diseases; non-alcoholic fatty liver disease (NAFLD), sleep disorders etc.) {RBP}
- Look for the presence of acanthosis nigricans as a sign of insulin resistance {RBP}.

**Table 2.** A guide to deciding the initial level of intervention to discuss with the patient

BMI, kg/m <sup>2</sup> *	WC, cm*		Co-morbidities
	men < 94, women < 80	men ≥ 94, women ≥ 80	
25.0–29.9	L	L	L ± D
30.0–34.9	L	L ± D	L ± D ± S**
35.0–39.9	L ± D	L ± D	L ± D ± S
≥40.0	L ± D ± S	L ± D ± S	L ± D ± S

L = Lifestyle intervention (diet and physical activity); D = consider drugs; S = consider surgery.

\*BMI and waist circumference cut-off points are different for some ethnic groups.

\*\*Patients with type 2 diabetes on individual basis.

### Laboratory Examinations

The minimum data set required will include {RBP}:

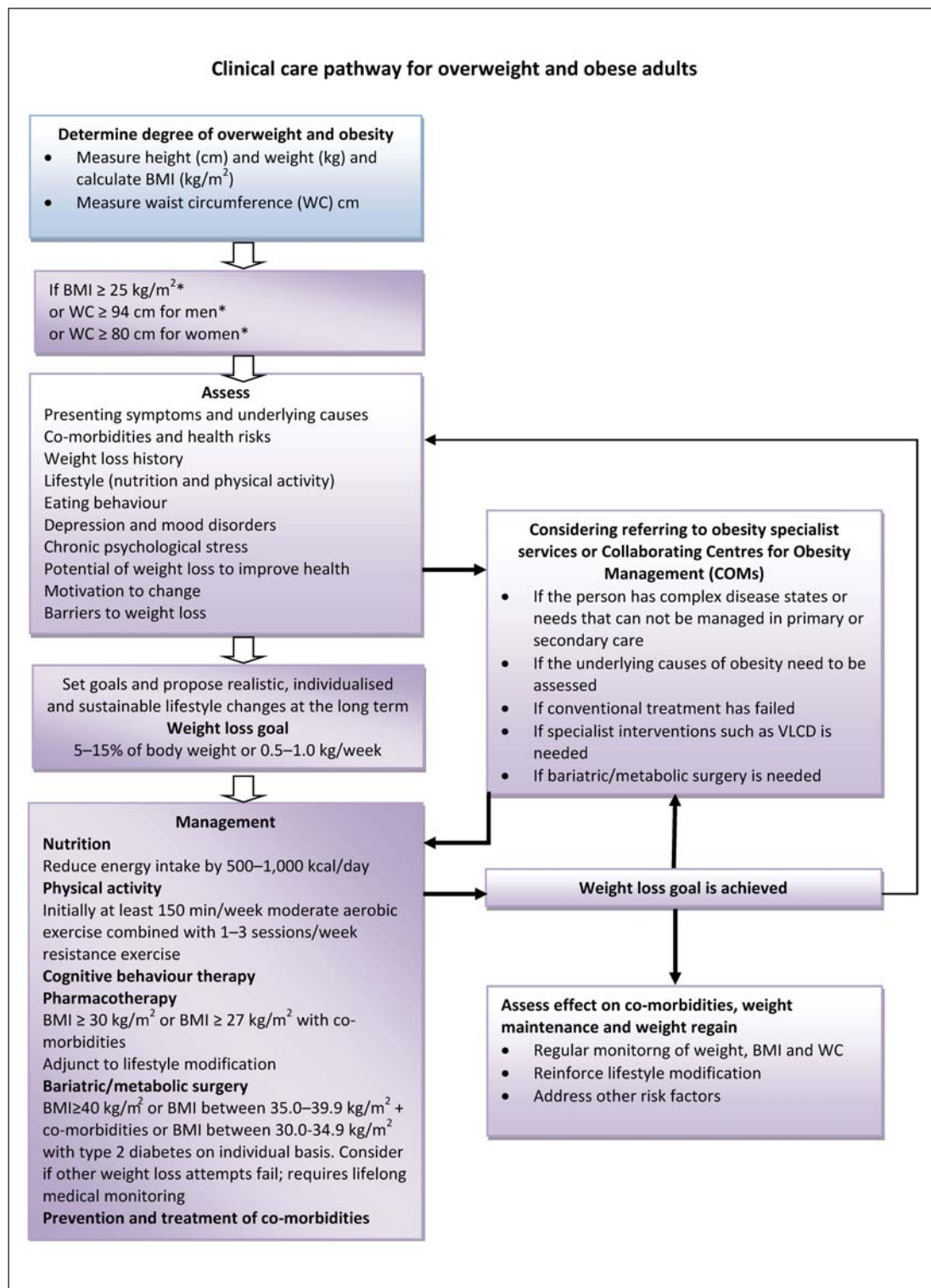
- Fasting blood glucose
- Serum lipid profile (total, HDL and LDL cholesterol, triglycerides)
- Uric acid
- Thyroid function (thyroid-stimulating hormone (TSH) level)
- Liver function (hepatic enzymes)
- Cardiovascular assessment, if indicated {RBP}
- Endocrine evaluation if Cushing's syndrome or hypothalamic disease suspected
- Liver investigation (ultrasound, biopsy) if abnormal liver function tests suggest NAFLD or other liver pathology
- Sleep laboratory investigation for sleep apnoea.

### Body Composition Analysis

WC can be used as a proxy for abdominal fat [9] {level 3; RBP}. With the development of devices and equipment to more accurately measure body fat, including dual energy X-ray absorptiometry (DEXA), air-displacement plethysmography (BodPod), bioimpedance analysis (BIA) and body scanning procedures – replacing the cumbersome underwater weighing –, it has become possible to more easily classify individuals according to the degree of body fat, independently of BMI. This approach has also drawn attention to the function of non-adipose tissue – that is, fat-free mass (FFM) or lean mass – and the contribution made by FFM to physiological functioning, pathology and well-being [28–30]. Assessment of body composition is not essential for the management of obesity in routine clinical practice, but may be a useful tool in measuring fat and FFM before and during treatment {RBP}.

### Comprehensive Obesity Management

Appropriate goals of weight management emphasise realistic weight loss to achieve a reduction in health risks and should include promotion of weight loss, maintenance and prevention of weight regain (fig. 2) {RBP}. Patients should understand that, since obesity is a chronic disease, weight management will need to be continued lifelong.



**Fig. 2.** Algorithm for the assessment and stepwise management of overweight and obese adults. \*BMI and WC cut-off points are different for some ethnic groups (see text).

### *Aims of Treatment*

The management and treatment of obesity (fig. 2) have wider objectives than weight loss alone and include risk reduction and health improvement. Significant clinical benefits may be achieved even by modest weight loss (i.e. 5–10% of initial body weight), and lifestyle modification (improved nutritional content of the diet and modest increases in physical activity and fitness) [31–34] {level 1}. Obesity management cannot focus only on weight (and BMI) reduction. More attention is to be paid to WC and the improvement in body composition which is focusing on ameliorating or maintaining FFM and decreasing fat mass [35].

Management of co-morbidities, improving quality of life and well-being of obese patients are also included in treatment aims. Appropriate management of obesity complications in addition to weight management should include management of dyslipidaemia, optimising glycaemic control in type 2 diabetic patients, normalising blood pressure in hypertension, management of pulmonary disorders such as sleep apnoea syndrome (SAS), attention to pain control and mobility needs in osteoarthritis, management of psychosocial disturbances including affective disorders, eating disorders, low self-esteem and body image disturbance. Obesity management may reduce the need to treat co-morbidities by drugs [36–38] {level 1; grade A}.

### *Prevention of Further Weight Gain*

In overweight patients (BMI 25.0–29.9 kg/m<sup>2</sup>) without overt co-morbidities, prevention of further weight gain (through dietary advice and increase in physical activity) rather than weight loss per se may be an appropriate target. Weight loss objectives should be realistic, individualised and aimed at the long term (table 3) {RBP}.

### *Practical Weight Loss Objectives*

A 5–15% weight loss over a period of 6 months is realistic and of proven health benefit [39, 40] {level 1}. A greater (20% or more) weight loss may be considered for those with greater degrees of obesity (BMI ≥ 35 kg/m<sup>2</sup>) {RBP}. Maintenance of weight loss and prevention and treatment of co-morbidities are the two main criteria for success.

### *Failure to Lose and Maintain Weight*

Referral to an obesity specialist (or an obesity management team) should be considered if the patient fails to lose weight in response to the prescribed intervention (fig. 2). Weight cycling, defined by repeated loss and regain of body weight, is more frequent in women and may be linked to increased risk for hypertension, dyslipidaemia and gallbladder disease [41]. It has been associated with psychological distress and depression and may require appropriate psychological care and/or antidepressant therapy [42].

### *Patient Follow-Up*

Obesity is a chronic disease. A follow-up and continued supervision is necessary [43] to prevent weight regain {level 2}, and to monitor disease risks and treat co-morbidities (e.g. type 2 diabetes mellitus, cardiovascular disease) {RBP}.

**Table 3.** Pharmacotherapy for obesity in Europe (November 2015) [71–74, 80]

Drugs	Status	Mechanism	Dosing	Response evaluation	Warnings	Contraindications	Side-effects
Orlistat	FDA & EMA approved	pancreatic, gastric lipase inhibitor	120 mg tid 60 mg tid (OTC)	2.9–3.4% 1 year	hepatitis, liver failure (rare), concomitant multivitamin advised	pregnancy, breast feeding, chronic malabsorption syndrome, cholestasis	decreased absorption of fat soluble vitamins, steatorrhea, faecal urgency
Lorcaserin	FDA approved	5HT2c R agonist	10 bid	3.6% 1 year stop if <%5 weight loss at 12 weeks	serotonin syndrome, cognitive impairment, depression, valvulopathy hypoglycaemia, priapism	pregnancy, breast feeding, use with caution: MAOIs, SSRIs, SNRIs	headache, nausea dry mouth, dizziness fatigue, constipation
Phentermine/topiramate	FDA approved	NE release (P) GABA modulation (T)	starting dose: 3.75/23 qd recommended dose: 7.5/46 qd *high dose: 15/92 qd	6.6% (recommended dose) 1 year 8.6% (high dose) 1 year stop if <%5 weight loss at 12 weeks	fetal toxicity, acute myopia, cognitive dysfunction, metabolic acidosis, hypoglycaemia	pregnancy, breast feeding, glaucoma, hyperthyroidism, use with caution: MAOIs	insomnia, dry mouth constipation, paresthesia, dizziness, dysgeusia
Bupropione/naltrexone	FDA & EMA approved	DA/NE reuptake inhibitor(B) opioid antagonist (N)	8/90 mg tb 2 tb bid	4.8% 1 year stop if <%5 weight loss at 12 weeks	fetal toxicity, increased seizure risk, glaucoma, hepatotoxicity	uncontrolled hypertension, seizure, anorexia nervosa / bulimia, drug or alcohol withdrawal, use with caution: MAO inhibitors	nausea, constipation, headache, vomiting, dizziness
Liraglutide	FDA & EMA approved	GLP-1 agonist	3 mg sc	5.8 kg 1 year stop if <%4 weight loss at 14 wks	acute pancreatitis, acute gall bladder disease	medullary thyroid cancer history, MEN type 2 history	nausea, vomiting, pancreatitis

FDA = Food & Drug Administration; EMA = European Medicinal Agency; OTC = over the counter; 5HT2c-R = 5 hydroxytryptamine 2c receptor; MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor; NE = norepinephrine; GABA = gamma amino butyric acid; DA = dopamine; GLP-1 = glucagon-like peptide-1; MEN = multiple endocrine neoplasia.  
\*Careful observation.



## Specific Components of Treatment

### *Nutrition and Dieting*

The use of self-recorded food diary allows a qualitative assessment of the diet. In addition, it can be used to help the patient identify meal frequency (night eating, snacking, meal skipping) perceptions and beliefs about emotional eating behaviour (cognition), eating habits (behaviour) and environmental challenges to following a healthy diet {RBP}.

Before giving dietary advice it might be useful to address motivation for change: How important is weight loss for the patients, and how confident the individual patient is to successfully and sustainably achieve body weight reduction [44, 45]? Dietary advice should encourage healthy eating and emphasise the need to increase consumption of vegetables, beans, legumes, lentils, grain, unsweetened cereals and fibre, and to substitute low-fat dairy products and meats for high-fat alternatives. It should also emphasise increased intake of seafood. It is recommended to avoid foods containing added sugars and solid fats, as well as consumption of sugary drinks and alcohol-containing beverages [37, 46–48] {level 1, 2}. An appropriate dietary regimen can be achieved in a number of ways:

#### *General Advice {level 3, 4}*

- Decrease energy density of foods and drinks
- Decrease the size of food portions
- Avoid snacking between meals
- Do not skip breakfast and avoid eating in the night time
- Manage and reduce episodes of loss of control or binge eating.

#### *Specific Advice*

Energy (calorie) restriction should be individualised and take account of nutritional habits, physical activity, co-morbidities and previous dieting attempts. Prescribing an energy-restricted diet may require the intervention of a nutritionist (dietitian) {RBP}. Balanced hypocaloric diets result in clinically meaningful weight loss regardless of which macronutrients they emphasise. An emphasis put on the macronutrient proportion in the various diets (low fat, low carbohydrate or high protein etc.) has not proved better than a balanced hypocaloric diet, except for low-glycaemic load diets (carbohydrate content of the diet × glycaemic index) in the short term [49–51] {level 1}. Despite various ranges of macronutrient composition, these diets have beneficial effects on reducing risk factors for cardiovascular disease and type 2 diabetes as well as on promoting adherence, diet acceptability and sustainability, satiety and satisfaction. Balanced hypocaloric diets can be tailored to individual patients on the basis of their personal and cultural preferences and may therefore have the best chance for long-term success (e.g. Mediterranean diet) [52, 53].

A 15–30% decrease in energy (calorie) intake from habitual intake in a weight-stable individual is sufficient and appropriate. However, underreporting of energy intake by obese patients is common. There is a great variation in energy requirements between the individuals which is dependent on the individual's gender, age, BMI and physical activity level. Tables predicting energy requirements taking into account gender, age, BMI and physical activity ratio can be used. An easy rule of thumb is a daily energy requirement of 25 kcal/kg for either gender but, for the same body weight, this creates a greater energy deficit in men. The recommended weight-reducing dietary regimen tailored to an individual's need usually provides an energy deficit of 600 kcal/day {grade A, B}. A 600 kcal (2,600 kJ) daily deficit will predict a weight loss of about 0.5 kg weekly. Thus for an obese sedentary woman with a BMI

of 32 kg/m<sup>2</sup> and with an estimated daily intake of 2,100 kcal (8,800 kJ), a diet prescribing 1,400–1,600 kcal (6,000–7,000 kJ) would be appropriate [50, 54] {level 2}.

Diets providing 1,200 kcal/day or more are classified as hypocaloric balanced diets (HBD) or balanced deficit diets [51]. Diets providing less than 1,200 kcal/day might yield micronutrient deficiencies, which could exert untoward effects not only on nutritional status but also on the weight management outcome. However in clinical practice a further reduction in caloric intake might be required. In this case the appropriate use of dietary supplements may prevent such nutritional deficits. In clinical practice low-calorie diets (LCDs) and very-low-calorie diets (VLCDs) are used. LCDs, consisting of normal meals and partial meal replacements, have an energy content between 800 and 1,200 kcal/day. VLCDs usually provide less than 800 kcal/day and may be used only as part of a comprehensive programme under the supervision of an obesity specialist or another physician trained in nutrition and dietetics. Their administration should be limited for specific patients and for short periods of time. VLCDs are unsuitable as a sole source of nutrition for children and adolescents, pregnant or lactating women and the elderly. Meal replacement diets (substitution of one or two daily meal portions by VLCD) may contribute to nutritionally well-balanced diet and weight loss maintenance [55–59] {level 2}.

### *Physical Activity*

Exercise is considered an important component of a weight reduction programme in conjunction with caloric reduction. Several studies report additive benefits of combining exercise with caloric restriction on reducing body weight and body fat and preservation of FFM as compared to diet alone. In balancing time commitments against health benefits, it appears that aerobic training is the optimal mode of exercise for reducing fat mass and body mass while a programme including resistance training is needed for increasing lean mass in middle-aged and overweight/obese individuals [60, 61] {level 1; grade B}. However, if we limit the discussion to the outcome 'weight loss' or 'fat mass loss', only aerobic exercise has solid evidence supporting its efficacy in the literature. There is enough evidence which suggests that aerobic and resistance exercises are beneficial for patients with obesity and related morbidities. For this reason, all scientific guidelines recommend that at least 150 min/week of moderate aerobic exercise (such as brisk walking) should be combined with three weekly sessions of resistance exercise to increase muscle strength [60–62] {level 2; grade B}.

Increasing physical activity reduces intra-abdominal fat and increases lean (muscle and bone) mass {level 2}, while it attenuates the weight loss-induced decline of resting energy expenditure {level 2}, reduces blood pressure, improves glucose tolerance, insulin sensitivity, lipid profile and physical fitness {level 1}, ameliorates compliance to the dietary regimen, has a positive influence on the long-term weight maintenance {level 2}, improves feeling of well-being and self-esteem {level 2}, and reduces anxiety and depression {level 2} [63–65]. Further objectives should be to reduce sedentary behaviour (e.g. television viewing and computer use) and increase daily activities (e.g. walking or cycling instead of using a car, climbing stairs instead of using elevators). Patients should be advised and helped in undertaking (or increasing) physical activity [66, 67] {level 2; grade B}. Exercise advice must be tailored to the patient's ability and health and focus on a gradual increase to levels that are safe {RBP}.

### *Cognitive Behavioural Therapy*

Cognitive Behavioural Therapy (CBT) is a blend of cognitive therapy and behavioural therapy and aims to help a patient modify his/her insight and understanding of thoughts and

beliefs concerning weight regulation, obesity and its consequences; it also directly addresses behaviours that require change for successful weight loss and weight loss maintenance. CBT includes several components such as self-monitoring (e.g. dietary record), techniques controlling the process of eating, stimulus control and re-enforcement as well as cognitive and relaxation techniques. CBT elements should form part of routine dietary management or, as a structured programme, form the basis of specialist intervention {grade B}. This care can be in part delivered in a group setting or using self-help manuals [68–70]. CBT can be provided not only by registered psychologists but also by other trained health professionals such as physicians, dieticians, exercise physiologists or psychiatrists {RBP}.

### *Psychological Support*

Physicians should recognise where psychological or psychiatric issues interfere with successful obesity management, e.g. depression. Psychological support and/or treatment will then form an integral part of management; in special cases (anxiety, depression and stress), referral to a specialist may be indicated. Self-help lay groups and the support of the obesity treatment group may all be useful in this setting {RBP}.

### *Pharmacological Treatment*

Pharmacological treatment should be considered as part of a comprehensive strategy of disease management [37, 71] {grade A}. Pharmacotherapy can help patients to maintain compliance, ameliorate obesity-related health risks and improve quality of life. It can also help to prevent the development of obesity co-morbidities (e.g. type 2 diabetes mellitus). Current drug therapy is recommended for patients with a BMI  $\geq 30$  kg/m<sup>2</sup> or a BMI  $\geq 27$  kg/m<sup>2</sup> with an obesity-related disease (e.g. hypertension, type 2 diabetes mellitus, sleep apnoea) [37] (table 2) {RBP}. Drugs should be used according to their licensed indications and restrictions {RBP}. The efficacy of pharmacotherapy should be evaluated after the first 3 months. If weight loss achieved is satisfactory (>5% weight loss in non-diabetic and >3% in diabetic patients), treatment should be continued [37, 71–74] {grade A}. Treatment should be discontinued in non-responders (table 3) {RBP}.

#### *Orlistat*

Orlistat is a potent and selective inhibitor of pancreatic lipase that reduces intestinal digestion of fat. The drug is available over the counter at a dose of 60 mg and a prescription dosage of 120 mg. Both forms are given before each meal and produce a moderate absolute and placebo-subtracted weight loss [71–74]. The efficacy and safety of the drug were assessed in the following RCTs: XENDOS [75] and X-PERT [76]. Faecal fat loss and related gastrointestinal symptoms are common. It may cause small decreases in fat-soluble vitamins; thus a multivitamin can be prescribed [77].

#### *Lorcaserin*

Lorcaserin is a serotonin type 2C receptor agonist with hypophagic effects [78]. Lorcaserin has been available in the USA since June 2013. The recommended dose is 10 mg twice daily. The product licence requires 5% weight loss after 12 weeks of treatment. If a patient does not reach this target, the drug should be discontinued [71–74, 79, 80]. The efficacy and safety of the drug were assessed in the following RCTs: BLOOM [81], BLOOM-DM [82] and BLOSSOM [83]. In the BLOOM-DM trial, both fasting blood glucose and haemoglobin A1C

(HbA1c) levels were improved. No statistically significant differences in the incidence of cardiac valvulopathy between the placebo and lorcaserin groups were found [82, 84]. The most common adverse events associated with lorcaserin included blurred vision, dizziness, somnolence, headache, gastrointestinal disturbance and nausea. The results of the ongoing cardiovascular outcomes trial CAMELLIA TIMI 61 will determine the role of lorcaserin in primary prevention of diabetes in overweight/obese individuals and its use in the high-risk population of patients with established cardiovascular disease or multiple cardiovascular risk factors [85, 86].

#### *Phentermine/Topiramate*

Phentermine and extended-release topiramate (PHEN/TPM-ER) is based on the principle of a synergistic combination of two drugs at a lower dose to obtain efficacy with less toxicity. Phentermine is an atypical amphetamine analogue that suppresses appetite by norepinephrine agonism in the CNS. Topiramate is an atypical anticonvulsant drug previously evaluated as a potential anti-obesity drug after reports of weight loss occurring in epileptic patients taking this drug. The mechanisms by which topiramate induces a weight loss are unknown and may include carbonic anhydrase inhibition of taste or influences on GABA transmission, thus reducing appetite [87]. After approval by the Food and Drug Administration (FDA), the drug was launched in the USA in September 2012. The recommended dosage is 7.5 mg phentermine / 46 mg topiramate once a day. The product licence requires 5% weight loss after 12 weeks of treatment. If a patient does not reach this target, the drug should be discontinued [71–74]. The efficacy and safety of the drug were assessed in the following RCTs: EQUIP [88], CONQUER [89], SEQUEL [90] and EQUATE [91]. Adverse events associated with PHEN/TPM-ER treatment were dry mouth, constipation, insomnia, palpitations, dizziness, paraesthesia, disturbances in attention, metabolic acidosis and renal calculi, headache, dysgeusia (distortion of sense of taste), alopecia and hypokalaemia [71–74, 92]. The combination is contraindicated during pregnancy due to its teratogenic potential. The FORTRESS (Fetal Outcome Retrospective Topiramate Exposure Study) has estimated that women taking this combination had a two times increased risk of giving birth to children with oral clefts when compared to non-users. Owing to this risk, the drug has been approved with a risk evaluation and mitigation strategy recommendation by the FDA [93].

#### *Bupropion/Naltrexone*

Bupropion/naltrexone combines two centrally acting medications that had already been approved. Bupropion is used for treating depression and to aid smoking cessation. It is a non-selective inhibitor of the dopamine and norepinephrine transporters. Naltrexone is an opioid receptor antagonist widely used to treat alcohol and opiate dependence syndromes. The anorectic effect of the bupropion/naltrexone combination is believed to result from activation of POMC neurons in the arcuate nucleus. POMC neurons release a melanocyte stimulating hormone ( $\alpha$ -MSH), which is a potent anorectic feeding neuropeptide, and these neurons project to other hypothalamic areas involved in feeding and body weight control. After approval by the FDA and the European Medicinal Agency (EMA), the drug is available in the USA since September 2012 and will be launched in Europe in approximately mid-2016. The recommended dosage is 16 mg naltrexone / 180 mg bupropion twice a day. The product licence requires 5% weight loss after 12 weeks of treatment. If a patient does not reach this target, the drug should be discontinued [71–74, 94]. The efficacy and safety of the drug were assessed in the following RCTs: COR-I [95], COR-II [96], COR-BMOD [97] and COR-DM [98]. The most common reported adverse event was nausea, which in most cases was transient for the first few weeks of treatment. Along with nausea, headache, dizziness, insomnia and

vomiting were the most common adverse events that led to discontinuation [94]. The Cardiovascular Outcomes Study of Naltrexone SR/Bupropion SR in Overweight and Obese Subjects with Cardiovascular Risk Factors (The Light Study) is still ongoing [99].

### *Liraglutide*

Liraglutide is an injectable long-acting GLP-1R agonist designed to resist rapid metabolism by dipeptidyl peptidase-IV. While glucose-induced insulin release is stimulated, the glucagon response is reduced and appetite suppressed with additional effects on gastric emptying [100]. It has already successfully been introduced in type 2 diabetic patients (1.2–1.8 mg) once daily. After approval by the FDA and EMA, the drug (in a dosage of 3 mg once daily) was launched for obesity treatment in the USA in November 2014 and in Europe in March 2015. The product licence requires 5% weight loss after 12 weeks of treatment. If a patient does not reach this target, the drug should be discontinued [71–74, 101–104]. The efficacy and safety of the drug were assessed in the following RCTs: SCALE-Maintenance [105], SCALE-Obesity [106] and LEADER [107–109]. Liraglutide is generally well tolerated. Nausea and vomiting are the main, usually transient, side-effects, but they may actively contribute to weight loss [110].

### *Bariatric and Metabolic Surgery*

Surgery is the most effective treatment for morbid obesity in terms of long-term weight loss, improvements of co-morbidities and quality of life and decreases of overall mortality [111–115]. A comprehensive overview of surgical treatment options for obesity and obesity-related co-morbidities is provided in the Interdisciplinary European Guidelines on Metabolic and Bariatric Surgery, published in 2013 by joint effort of the European Association for the Study of Obesity (EASO), and the International Federation for the Surgery of Obesity and Metabolic Disorders – European Chapter (IFSO-EC) [116]. Surgery should be considered for patients aged 18–60 years with a BMI  $\geq 40.0$  kg/m<sup>2</sup> or with BMI between 35.0 and 39.9 kg/m<sup>2</sup> and co-morbidities, in whom surgically induced weight loss is expected to improve the disorder (such as type 2 diabetes and other metabolic disorders, cardiorespiratory disease, severe joint disease and obesity-related severe psychological problems). BMI criterion may be the current BMI or a documented previous BMI of this severity [117].

Bariatric surgery is clearly confirmed to be beneficial in type 2 diabetes remission – at least in the short and medium term. Thus, patients with BMI  $>30$  and  $<35$  kg/m<sup>2</sup> with type 2 diabetes may also be considered for bariatric surgery on an individual basis, as there is evidence-based data supporting bariatric surgery benefits in regards to type 2 diabetes mellitus remission or improvement in this group [118–120] {level 1}.

Multidisciplinary skills are needed to support surgical interventions. Patients should only be referred to units able to assess patients prior to surgery, to offer a comprehensive approach to diagnosis, assessment and treatment, and to provide long-term follow-up. A decision to offer surgery should follow a comprehensive interdisciplinary assessment. The core team providing such assessment should optimally consist of the following specialists experienced in obesity management and bariatric surgery [121–123] {level 2}:

- Physician
- Surgeon
- Anaesthetist (anaesthesiologist)
- Psychologist or psychiatrist
- Nutritionist and/or dietitian, and
- Nurse practitioner/social worker.

**Table 4.** Obesity-related health risks and complications

*I. Metabolic complications*

Diabetes  
insulin resistance  
Dyslipidaemia  
Metabolic syndrome  
Hyperuricaemia  
Gout  
Low-grade inflammation

*II. Cardiovascular disorders*

Hypertension  
Coronary heart disease  
Congestive heart failure  
Stroke  
Venous thromboembolism

*III. Respiratory disease*

Asthma  
Hypoxemia  
Sleep apnoea syndrome  
Obesity hypoventilation syndrome

*IV. Cancers*

Oesophagus, small intestine, colon, rectum, liver, gallbladder, pancreas, kidney, leukaemia, multiple myeloma, and lymphoma

In women: endometrial, cervix uteri, ovary, breast cancer after menopause

In men: prostate

*V. Osteoarthritis*

Knee and an increase in pain in the weight bearing joints

*VI. Gastrointestinal*

Gallbladder disease  
Non-alcoholic fatty liver disease  
Non-alcoholic steatohepatitis  
Gastro-esophageal reflux  
Hernia

*Table 4 continued on next page*

A laparoscopic technique should be considered as the first treatment choice in bariatric surgery. In all situations the bariatric surgeon's experience is a key issue for an immediate successful outcome. It is not advisable to perform bariatric techniques on an occasional basis [124] {level 1}. Morbid obesity is a lifelong disease. The treating physician and surgeon are responsible for the treatment of co-morbidities before the operation and for the follow-up after the operation. However, the patient takes lifelong responsibility for adhering to the follow-up rules {RBP}.

In the past several years, better understanding of substantial metabolic changes induced by different surgical interventions to the alimentary tract was achieved. Therefore, the former classification of operations according to their influence on food ingestion, defined as limiting stomach capacity (restrictive), limiting absorption of nutrients (malabsorptive) or combined procedures does not appropriately reflect the current level of knowledge about early and weight-independent metabolic effects of these operations. Nowadays, most of the standard surgical interventions are being mostly referred to as metabolic operations. The focus when treating obese patients is gradually shifting from the primary goal of weight loss outcomes to the metabolic effects of the operations [125–137] {levels 1, 2}.

**Table 4** (continued)

*VII. Genitourinary system /reproductive health*

Urinary incontinence  
Menstrual irregularity  
Infertility  
Hirsutism  
Polycystic ovary disease  
Miscarriage  
Gestational diabetes  
Hypertension  
Preeclampsia  
Macrosomia  
Foetal distress  
Malformation (i.e. neural tube defect)  
Dystocia and primary caesarean section

*VIII. Psychological and social consequences*

Low self-esteem  
Anxiety and depression  
Stigmatisation  
Discrimination in employment, college acceptance, job earning etc.

*IX. Miscellaneous*

Idiopathic intracranial hypertension  
Proteinuria  
Nephrotic syndrome  
Skin infection  
Lymphoedema  
Complications from anaesthesia  
Periodontal disease

**Treatment of Co-Morbidities**

Active treatment of obesity-related co-morbidities (table 4) should be integral part of the comprehensive management of the obese patients. Appropriate management of obesity complications in addition to weight management should include [37, 138] {level 1, 2}:

- Management of dyslipidaemia
- Optimising glycaemic control in type 2 diabetics
- Normalising blood pressure in hypertension
- Management of pulmonary disorders, such as SAS
- Attention to pain control and mobility needs in osteoarthritis
- Management of psychosocial disturbances, including affective disorders, eating disorders, low self-esteem and body image disturbance.

The presence of obesity and the effects that treatments have on body weight, body composition or metabolic status should be taken into account in the selection of the drugs used to treat obesity-related co-morbidities or even non-obesity-related diseases occurring in a patient with obesity. Drugs increasing body weight and/or with negative metabolic effects should be possibly avoided or substituted. Weight-losing and weight-neutral medications should be preferred [73]. Specific guidelines for the management of hypertension in obese patients [139] have been released by the EASO in conjunction with the European Society of Hypertension.

## Alternative Therapies

Obesity treatment has often been unsuccessful. As a result, unorthodox and unproven treatments flourish and are often offered. There is insufficient evidence to recommend in favour of herbal medicines, dietary supplements or homoeopathy for obesity management in the obese person. Physicians should advise patients to follow evidence-based treatments and recommend treatments only where evidence of safety and efficacy has been established {RBP}.

### *Collaborating Centre for Obesity Management*

A comprehensive obesity management can only be accomplished by an appropriate obesity management team which is multidisciplinary and comprises different professionals who are able to tackle the different aspects of obesity and its related disorders. In accordance with this vision the EASO has developed a network of Collaborating Centres for Obesity Management. This European networking comprises education and training, research initiatives and contemporary obesity care [140].

## Conclusion

Physicians have a responsibility to recognise obesity as a gateway disease and help patients with appropriate prevention and treatment schemes for obesity and its co-morbidities. Along with physicians all care givers have the same responsibility. Obesity care needs to be delivered by certified obesity experts in specialised and accredited obesity centres. Treatment should be based on good clinical care and evidence-based interventions and it should be individualised and multidisciplinary, focus on realistic goals, weight maintenance and prevention of weight regain. Everybody in the field, including the patients, should understand that, since obesity is a chronic disease, weight management will need to be lifelong.

## Appendix

### *Levels of Evidence and Grades of Recommendation*

The evidence for the guidance given is drawn from a number of systematic reviews listed in the references. The grading system is based upon the Scottish Intercollegiate Guidelines Network (SIGN), but has been simplified by amalgamating sub-categories of each level into a single criterion. No health-care system can provide treatment for all who are obese and overweight. Support groups, commercial and lay organisations, books and other media can provide useful help and support; the advice they give should conform to the principles of these guidelines (table 5) [141] {RBP}.



**Table 5.** Levels of evidence, grades of recommendation and good practice points

<i>Levels of evidence</i>	
1	1++ high-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
	1+ well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
	1– Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2	2++ high-quality systematic reviews of case-control or cohort or studies
	2+ high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is casual
	2– well-conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is casual
3	non-analytic studies, e.g. case reports, case series
4	expert opinion
<i>Grades of recommendation</i>	
A	at least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	a body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++, or 1+
C	a body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	evidence level 3 or 4; or extrapolated evidence from studies rated as 2+
<i>Good practice points</i>	
RBP	recommended best practice based on the clinical experience of the guideline development group

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