

Towards a multidisciplinary approach to understand and manage obesity and related diseases[☆]

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SUMMARY

Overnutrition and sedentary lifestyle result in overweight or obesity defined as abnormal or excessive fat accumulation that may impair health. According to the WHO, the worldwide prevalence of obesity nearly doubled between 1980 and 2008. In 2008, over 50% of both men and women in the WHO European Region were overweight, and approximately 23% of women and 20% of men were obese. Comprehensive diagnostic and therapeutic approaches should include nutritional treatment to favor the best metabolic and nutritional outcome, as well as to induce potential disease-specific benefits from selected nutritional regimens. Obesity is usually accompanied by an increased muscle mass. This might explain why obesity, under particular circumstances such as cancer or high age, might have protective effects, a phenomenon named the 'obesity paradox'. However, loss of muscle mass or function can also occur, which is

Abbreviations: BIA, bio-electric impedance analysis; BMI, body mass index; CBW, current body weight; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRF, cardiorespiratory fitness; CV, cardiovascular; DXA, dual X-ray absorptiometry; EBW, excess body weight; EN, enteral nutrition; ERAS, enhanced recovery after surgery; GI, gastrointestinal; HPA, hypothalamic-pituitary-adrenal; HRQoL, health-related quality of life; IBW, ideal body weight; ICU, intensive care unit; LPS, lipopolysaccharides; MHD, mental health disorders; NAFLD, non-alcoholic fatty liver disease; OA, osteoarthritis; PN, parenteral nutrition; QoL, quality of life; RWL, relative weight loss; REE, resting energy expenditure; SCFA, short-chain fatty acids; T2DM, type 2 diabetes mellitus; WHO, World Health Organization.

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associated with poor prognosis and termed 'sarcopenic obesity'. Therefore, treatment recommendations may need to be individualized and adapted to co-morbidities. Since obesity is a chronic systemic disease it requires a multidisciplinary approach, both at the level of prevention and therapy including weight loss and maintenance. In the present personal review and position paper, authors from different disciplines including endocrinology, gastroenterology, nephrology, pediatrics, surgery, geriatrics, intensive care medicine, psychology and psychiatry, sports medicine and rheumatology, both at the basic science and clinical level, present their view on the topic and underline the necessity to provide a multidisciplinary approach, to address this epidemic.

1. Introduction

1.1. Definition of obesity

Recently, the ESPEN society has published a consensus on new terminology for clinical nutrition, in which obesity and related terms as well as related diagnostic procedures have been defined [1]. According to this terminology, nutrition disorders and nutrition-related conditions are divided into malnutrition/undernutrition and overnutrition resulting in overweight or obesity (Fig. 1). Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health (WHO 2000). Apart from fat accumulation, adipocyte dysfunction may occur, leading to metabolic changes enhancing the risk of chronic diseases and cancer. Classification of overweight and obesity in adults is achieved through the use of body mass index (BMI), which is a simple index of weight-for-height (Table 1).

1.2. Sarcopenic obesity

According to the new ESPEN consensus on terminology [1] sarcopenia is a syndrome characterized by the progressive and generalized loss of skeletal muscle mass, strength and function

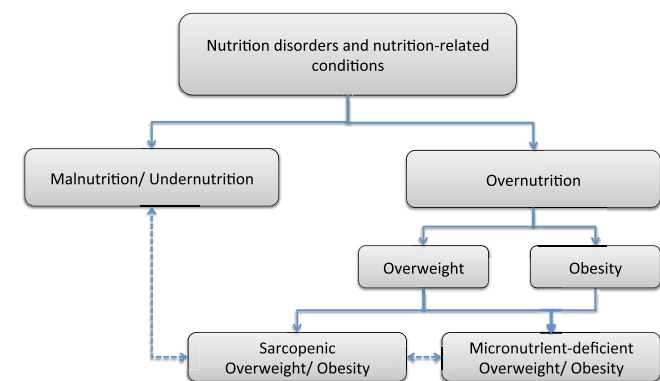


Fig. 1. Nomenclature of overnutrition, overweight and obesity. For explanations see text.

Table 1
Classification of overnutrition.

Classification	Subclassification	Criteria
Overweight		BMI 25–29.9 kg/m ²
Obesity		BMI ≥30 kg/m ²
	Obesity grade I	BMI 30–34.9 kg/m ²
	Obesity grade II	BMI 35–39.9 kg/m ²
	Obesity grade III	BMI ≥40 kg/m ²

Abbreviation: BMI, body mass index, defined as a person's weight in kilograms divided by the square of their height in meters.

(performance) with a consequent risk of adverse outcomes [2–4]. Whilst often a phenomenon of the ageing processes (primary sarcopenia) it may also result from pathogenic mechanisms (secondary sarcopenia) that are disease-related, physical activity-related (e.g. disuse) or nutrition-related (e.g. protein deficiency). Diagnostic criteria for sarcopenia have not been firmly established to date. Sarcopenic obesity is defined as obesity in combination with sarcopenia that occurs for example in older individuals, in those with type 2 diabetes mellitus (T2DM) or chronic obstructive pulmonary disease (COPD), and in weight-losing obese patients with malignant disorders. Mechanisms include inflammation and/or inactivity induced muscle catabolism in obese patients [5,6]. The condition can occur virtually at all ages.

1.3. Obesity as a chronic systemic disease

Obesity is a chronic systemic disease requiring a multidisciplinary approach (Fig. 2). This fact is not clearly pointed out in the current definitions of obesity. Data indicate that obesity is hardly reversible spontaneously and is associated with increased mortality [7,8]. Despite some genetic and epigenetic influences, obesity is an acquired disease that depends on lifestyle factors such as over-eating and low physical activity [9]. This makes – at all ages – obesity prevention as well as obesity therapy a realistic albeit difficult option. There is no critical time for the development of obesity, and previous weight history is not consistently a dominant factor in determining subsequent weight gain [10].

Obesity affects almost every organ system of the body including the endocrine, gastrointestinal (GI), cardiovascular (CV), and central nervous systems. Obesity challenges not only endocrinologists, gastroenterologists, nephrologists and cardiologists, but also pediatricians and geriatricists, surgeons and intensivists, orthopedists

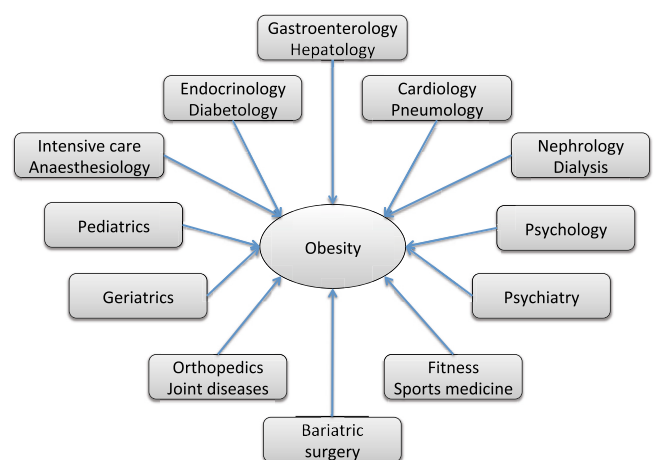


Fig. 2. Obesity is a chronic systemic disease requiring a multidisciplinary approach. For explanations see text.

and psychologists, nutritionists and sports medicine specialists. A multidisciplinary approach is therefore warranted to prevent and manage obesity; however, this is often not the reality. The lack of comprehensive and multidisciplinary approaches might be one explanation why we still fail to control the obesity epidemic.

Comprehensive diagnostic and therapeutic approaches should include nutritional treatment to favor the best metabolic and nutritional outcome, as well as to induce potential disease-specific benefits from selected nutritional regimens [11]. Disease-specific therapeutic decisions are often needed in terms of nutrient selection, interactions, timing and duration of administration. ESPEN traditionally hosts and favors interactions between nutritionists from different specialties, whose expertise can provide the best multidisciplinary approach to ensure optimal choices for nutritional assessment, treatment and follow-up. In the present position paper, experts from different specialties aim to contribute to the understanding of obesity to foster the multidisciplinary approach and to ensure optimal prevention and management of this major global health challenge.

2. Clinical challenges

2.1. Obesity from an endocrinologist's view

Obesity is often associated with several endocrine alterations. Insulin resistance is related to impaired glucose disposal in skeletal muscle and adipose tissue, as well as excess hepatic glucose production. Obesity-associated insulin resistance is at least partly initiated by excess glucose and lipid availability, which may primarily impact gut microbiota leading to unfavorable changes in gut permeability contributing to sustained systemic inflammation. Excess lipid and its deposition may lead to enhanced reactive oxygen species generation, oxidative stress and inflammation at systemic and tissue level, with activation of intracellular pathways inhibiting insulin signaling [12,13].

Insulin resistance and hyperinsulinemia also play a central role in the pathogenesis of the metabolic syndrome (MetS), as defined by at least three-out-of-five clustered abnormalities among high waist circumference, high blood pressure, high glucose and dyslipidemia with high triglycerides and low HDL-cholesterol. Although diagnostic thresholds still vary among different definitions, the MetS is unequivocally associated with strong increments in CV morbidity and mortality, thereby representing a potential useful screening tool to assess cardiometabolic risk in overweight-obese patients. The potential onset of T2DM is further associated with increased morbidity and mortality, due to its chronic complications and increased risk of CV events, surgery, infection and other common clinical conditions [14].

Additional relevant endocrine alterations in obese individuals include altered sex hormones and gonadal function. Male obese patients may present with low plasma testosterone, low sex hormone binding globulin and hypogonadism that may also directly contribute to insulin resistance [15]. Female patients may present with the polycystic ovary syndrome, including hyperandrogenism, oligo-amenorrhea and altered ovarian structure [16]. Reduction of insulin resistance and circulating insulin through lifestyle intervention and pharmacological treatment have been reported to improve hormonal patterns and fertility, and to reduce the high risk of T2DM in the polycystic ovary syndrome population [16].

Cortisol has negative metabolic effects in obese individuals but baseline cortisol and ACTH levels appear, however, to be unaltered by obesity per se. On the other hand, enhanced responses to stimulatory tests are reported, particularly in patients with MetS [17]. Thus, the role of altered cortisol production and excess availability has potential clinical relevance in selected patient groups.

Adipose tissue and the gut have been only recently appraised, or re-appraised, as endocrine tissues regulating energy homeostasis. For example, deficiency of the adipose anorexigenic hormone leptin causes familial monogenic obesity. Moreover, obesity is associated with leptin resistance and excess circulating hormone may be paradoxically involved in obesity-associated metabolic complications [18]. Several additional adipokines modulate energy balance, intermediate metabolism and blood pressure: as a relevant example, the renin-angiotensin-aldosterone system is also expressed in adipose tissue and its activation may contribute to hypertension and renal complications [19].

Gut hormones also include appetite regulators such as the duodenal anorexigenic hormone and stimulator of insulin secretion glucagon-like peptide 1 (GLP-1). GLP-1 effects and plasma levels may be impaired in obesity and T2DM, and its pharmacological activation has become a relevant option in their treatment [20]. On the other hand, the orexigenic hormone ghrelin may contribute to excess food intake in its acetylated form, and regulation of ghrelin acylation is a potential target for the treatment of complicated obesity [21].

Finally, primary endocrine diseases may cause secondary obesity, such as Cushing syndrome, insulinoma and hypopituitarism with low growth hormone. Hypothyroidism should be ruled out in initial screening of obese individuals due to its relatively high prevalence in the general population.

In conclusion, obesity is a challenging condition whose endocrinological implications remain partly underappreciated. The impact of obesity on several relevant endocrine networks should be considered.

2.2. Obesity from a gastroenterologists' view

Gastroenterologists often do not consider obesity as their field of interest and experience. Obesity and related diseases are generally assigned to general practitioners, endocrinologists and diabetologists, despite the fact that the GI tract is the site of food uptake (and thus also a potential site for intervention against obesity) and that virtually all organs the gastroenterologist concerns to such as liver, gallbladder, pancreas and intestine are afflicted by obesity. Liver develops steatosis and inflammation, gallbladder motility is reduced and risk of stone formation enhanced, endocrine pancreas functions become impaired, and intestinal microbiota changes in the course of disease. For more details on the role of the intestinal microbiota in obesity see "Obesity and the gut microbiota", a section later.

The intestine seems to be involved in the regulation of food intake and thus in the pathophysiology of obesity. Intestinal motility, hormones and nerve signals have been identified as crucial signals that either locally in the bowels or centrally in the brain affect food intake and satiety that finally regulate body weight and body composition [22,23]. Obesity is a risk factor for a variety of GI diseases, e.g. gastro-esophageal reflux, Barrett's esophagus, and neoplastic diseases such as esophageal adenocarcinoma, colorectal carcinoma, and gallbladder cancer. Intestinal targets could be of relevance for future nutritional or pharmacological treatment of obesity and related diseases. For example, recent studies revealed that orally administered glycine- β -muricholic acid, an inhibitor of the farnesoid X receptor in the gut, improves metabolic parameters in mouse models of obesity [24]. Thus, gastroenterologists could contribute to the topic of obesity, both on the research level and the clinical level, the latter by diagnosing obesity related GI disorders and prescribing supportive therapies.

The liver plays a central role in obesity pathophysiology. Liver steatosis has been recognized as an early indicator of the obesity-

associated MetS [25]. This type of liver steatosis, also named non-alcoholic fatty liver disease (NAFLD), is a risk factor for cirrhosis and hepatocellular carcinomas for which obese patients at risk need to be screened [26]. See also “The gut-liver-axis” a section later.

The only activities that gained some interest among practicing gastroenterologists are endoscopic approaches such as placing gastric balloons into the stomach or plastic tubes into the duodenum to reduce food intake prior to a surgical intervention [27]. Gastroenterologists could do much more in the field of obesity. First, the gastroenterologists have a particular proximity to clinical nutrition – and indeed many clinical nutritionists have a GI background –, second, gastroenterologists have direct access to the intestine allowing them to study human GI pathophysiology in the obese, and third, gastroenterologists know about most relevant organs involved in obesity –related diseases such as the liver and its pathophysiology predestining them to study e.g. NAFLD. Step by step, some gastroenterologists realize this potential and started to work with great success in this field. However, much more gastroenterologists need to be involved in this field in the future.

2.3. Obesity from a nephrologist's view

Obese patients undergoing chronic dialysis present a greater survival than lean patients. In contrast, obesity is a condition associated with renal worsening and progression of renal disease towards dialysis. Obesity aggravates hypertension, a prominent kidney disease progression factor [28]. Obese patients have increased proteinuria, independent from the causal of renal disease, in response to protein and salt overload [29]. Interestingly, proteinuria improves after bariatric surgery and concomitant weight loss [30]. A high BMI is therefore deleterious with respect to metabolic disorders and progression of renal disease.

A state of glomerular hyperfiltration is present in the obese and will induce glomerular slit membrane stress, which can be monitored by microalbuminuria measurement [31]. This is later followed by a more pronounced albuminuria, consequence of irreversible glomerular hyalinosis and sclerosis. At this stage, renal function has already decreased by more than 50%, corresponding to chronic kidney disease (CKD) stage 3. High blood pressure is also frequently present and further aggravates the loss of renal function. Thus, there is a continuous spectrum from obese adults without kidney disease towards progressive renal lesions leading to severe CKD and the need for dialysis.

Links between obesity and CKD have been recently unraveled. Intestinal protein degradation products such as p-cresyl sulfate, indoxyl-sulfate and trimethylamino-oxide enter the bloodstream and will accumulate in CKD patients [32] and exert a toxic effect on adipocytes. These cells will undergo a pro-inflammatory phenotype and promote insulin resistance, an early event reported during CKD which is aggravated by overweight [33]. Other metabolic abnormalities may also worsen renal function such as dyslipidemia, which is per se a consequence of proteinuria. Thus, a number of vicious circles are present in CKD and some are directly triggered by obesity. Finally, the GI microbiota has been recently shown to be altered during CKD. Not only is the number of bacteria species reduced, but its spectrum also expresses a pro-inflammatory pattern [34].

In the course of CKD, body composition can be altered through water retention (nephrotic syndrome, cardiac insufficiency). This complicates body composition measurements during CKD while using bio-electric impedance analysis (BIA). Fat and muscle mass might also be estimated inadequately [35]. The concept of metabolically healthy overweight individuals without MetS or CV

complications, is a promising field [36], but to date no data are available in obese CKD patients.

During maintenance dialysis, death risk is markedly increased and protein/energy wasting is a greater death risk than overweight during the first years of dialysis [37]. This explains the paradox of better survival in obese dialysis patients [38]. In elderly dialysis patients, both increase and decrease in BMI are associated with an increased mortality, suggesting that weight should be kept stable over time. In overweight patients with early CKD, efforts should be done to reduce obesity that aggravates proteinuria and fastens CKD progression. A successful weight loss is able to reverse proteinuria, a well identified independent kidney disease progression factor [39]. Obesity is linked to a greater rejection rate in transplant patients and weight gain, a frequent condition after transplantation, should be avoided by adherence to a dedicated nutritional care plan [40].

2.4. Obesity from a pediatrician's view

Obesity is the most prevalent pediatric nutritional disorder worldwide [41]. From a disorder of affluent societies, obesity is increasingly recognized in developing countries and turns malnutrition, which includes both under- and over nutrition, to a disorder where both ends of the spectrum should be addressed. Recently, prevalence of overweight and obesity in children and adolescents in developed countries was estimated at 23.8% for boys and 22.6% for girls [42]. In developing countries the prevalence was estimated as 12.9% of boys and 13.4% of girls [42]. While reports indicate that obesity in children is a major public health hazard [43,44], there is no definite consensus on the definition of pediatric obesity.

In contrary to adults, BMI is dependent on age, which mandates that BMI data in children are plotted on age and sex specific charts. The WHO defines overweight as a Z score above 2 and obesity as a Z score above 3. Determination of obesity depends on the growth charts used, e.g. National growth charts or the WHO growth standards, resulting in different cut off values [45].

The rationale for treating obesity already in childhood is not limited to its relationship with obesity in adulthood, but spans to the multiple complications associated with obesity (Table 2). Thus, pediatricians should identify obese children and evaluate the presence of complications including but not limited to hypercholesterolemia, diabetes and hypertension.

Prevention and treatment of obesity focuses on life style interventions (mainly increase in physical activity and reduction of sedentary activities), on diet and behavioral programs. The conclusions of the 2009 Cochrane analysis are still valid stating that “While there is limited quality data to recommend one treatment program to be favored ... combined behavioral lifestyle interventions compared to standard care or self-help can produce a significant and clinically meaningful reduction in overweight in children and adolescents high quality research that considers psychosocial determinants for behavior change, strategies to improve clinician-family interaction, and cost-effective programs for primary and community care is required” [46].

When life style modification fails, the need for drug treatment in pediatric obesity is hampered by limited understanding of pathophysiology, lack of agreement on dosing, adherence, ethical considerations and post marketing complications that terminated the use of previously approved drugs. Currently there is only one drug, orlistat, that is approved for treatment of adolescents. It reduces fat absorption by up to 30%, and provides an additional BMI loss of 0.5–4 kg/m² over a period of 12 months, but is only suitable for adjuvant therapy that accompanies behavioral interventions targeting effective lifestyle changes [47].

As in adults, bariatric surgery is a promising treatment of morbid obesity, and is gaining popularity in morbidly obese

Table 2
Complications of overweight and obesity in children and adolescents.

Category	Complication
Psychological	Impaired body perception
	Isolation
	Aggression
	Drugs and alcohol abuse
	Bulimia
	Smoking
Cardiovascular	Atherosclerosis
	Hyperlipidemia
	Endothelial dysfunction
	Hypertension
	Left ventricular hypertrophy
Respiratory	Obstructive sleep apnea
	Asthma
	Hypoventilation
Endocrine	Metabolic syndrome (MetS)
	Type 2 diabetes mellitus (T2DM)
	Polycystic ovary syndrome
	Premature adrenarache
	Menstruation abnormalities
Orthopedic	Thyroid gland dysfunction
	Slipped capital femoral epiphysis
	Early degenerative arthritis
	Coxa Vara
	Blount disease (Adolescent tibia vara)
	Perthes disease
	Back pain
Miscellaneous	Reduced quality of life
	Non alcoholic fatty liver disease (NAFLD)
	Cholesterol gallstones
	Pseudo tumor cerebri
	Colon cancer
	Breast cancer

adolescents. Yet, a recent review [42] identified only one randomized controlled trial evaluating laparoscopic adjustable gastric banding. This trial demonstrated better weight loss, leading the authors to conclude that “Results do not provide enough data to assess efficacy across populations from different countries, socio-economic and ethnic backgrounds, who may respond differently” [42].

In summary, pediatric obesity is a research as well as clinical challenge as it constitutes a major health hazard. A better understanding of its pathophysiology, definitions, diagnosis, as well as evaluation of the effect of various treatment modalities with prolonged follow up is therefore urgently needed.

2.5. Obesity from a surgeon's view

A surgeon's focus is directed towards reduction of postoperative complications. A well-known association between preoperative functional health status and postoperative morbidity and mortality has been recently confirmed [48]. Complications prolong hospital length of stay, with delay in recovery and rehabilitation of the patient. Additionally, it will be a financial burden for the hospital and the health care system. Besides malnutrition and despite the obesity paradox, which might be true for subgroups of the population but not for the general population [49], obesity remains a significant metabolic risk factor for anastomotic leaks, surgical site infections, and poor outcome [50,51]. The risks of obesity and the MetS are enhanced by co-existing diabetes [51]. Therefore, an appropriate management of adjustable risk factors is mandatory. For any elective non-tumor surgery, especially abdominal surgery, risk minimization may be achieved by preoperative weight reduction and optimal treatment of comorbidities. In bariatric surgery, preoperative weight loss by a very low calorie diet has been shown to facilitate the procedure and to decrease the risk for

complications [52]. Aiming at ‘Enhanced Recovery After Surgery’ (ERAS) for severely obese patients, new “prehabilitation” strategies for the adjustable risk factors in elective benign and non-bariatric abdominal surgery need to be explored [53].

Benefits and risks have to be critically balanced in all surgical procedures. Nowadays, bariatric and metabolic surgery has been well established and considered the treatment of choice in morbid obesity. Although the surgical complication rate is very low and the benefits are very convincing, severe long-term complications like protein malnutrition that may even require parenteral nutrition (PN) may occur. Current guidelines mandate supplementation after all bariatric procedures, with dose stratification according to the surgical procedure [54]. The ESPEN special interest group “Chronic intestinal failure” has recently opened a chapter for bariatric surgery. According to the latest Cochrane analysis based on twenty-two trials, the long-term effects of bariatric surgery remain unclear [55].

Recently, a decision-analytic model to estimate the balance between treatment risk and benefits for severely obese patients with diabetes was developed. For a typical 45 y old woman with diabetes and a BMI of 45 kg/m², the gain-of-life-expectancy was 6.7 years. However, this decreases with increasing BMI, and in patients with a BMI of 62 kg/m² and higher the non-surgical treatment may be associated with greater life expectancy compared to the surgical intervention [56]. There has been some considerable nihilism regarding the success of conservative treatment options, and there is a shortage of programs and controlled data as well [57–59]. Promising results with comparable weight loss have been confirmed by own data (manuscript in preparation). In an intensified conservative program using very low calorie diet (VLCD) weight reductions of more than 20% of initial body weight loss, and 40% of excessive body weight loss, could be achieved within 12 months of intervention. These changes are accompanied by an improvement in hypertension, diabetes and quality of life. Therefore, even in morbid obesity conservative treatment should be not excluded per se. It may be easier to decide for surgery taking into account some risks and potential disadvantages if all available conservative options have been maximally exploited.

2.6. Obesity from a geriatrician's view

Obesity in people >70 years of age is not unambiguously negative. On the contrary, prospective population based cohort studies indicate that overweight, i.e. BMI 25–30 kg/m² in particular, but sometimes also obesity (BMI > 30 kg/m²) is associated with improved survival when compared to being “normal-weight” (BMI 18.5–25 kg/m²) [60]. This observation is usually referred to as the ‘obesity paradox’ that is also present in chronic diseases [61]. The reasons for this reversed epidemiology are not clear. Selection could be one, meaning that people with dysmetabolic obesity, mainly in the form of central obesity (i.e. enhanced waist circumference) which is linked to the MetS, die at younger age. Thus, people with a metabolically less active fat mass are left to survive into older age. In such cases, overweight/obesity may reflect absence of disease, rather than representing a healthy condition per se. An energy reserve to use in case of incident disease could be beneficial in the “geriatric” period of life when acute and chronic diseases commonly occur. Age-related osteoporotic height reduction alone may increase BMI up to one kg/m² unit and add to the obesity paradox. At old age underweight, already defined as BMI <22 kg/m², is far more deleterious than obesity. Still, severe obesity and abdominal obesity are never beneficial, not only reducing survival but also contributing to disability [60].

By ageing, anabolic activities decrease and degenerative processes become more prominent. Secretion of anabolic hormones;

e.g. testosterone, estrogen and growth hormone is reduced. Mitochondrial DNA mutations enhance apoptosis, neuromuscular synaptic damages and age-induced increased inflammatory activity will further promote catabolic effects on mainly muscle cells. These processes may lead to sarcopenia, which is the combined presence of reduced muscle mass and reduced muscle strength or performance. As long as appetite is preserved and combined with reduced physical activity in older adults, there will be an accumulation of subcutaneous and ectopic fat. This muscle and fat mass disproportion may end up in a condition called 'sarcopenic obesity' [6,62].

The definition of sarcopenic obesity is pending but is obviously a combination of the two syndromes. Cohort studies in older populations have reported sarcopenic obesity prevalences ranging from 1 to 15%, the large variation is due to different settings, populations and definitions [5,63]. Sarcopenia is deleterious, whereas elevated BMI and preserved muscle mass is potentially protective at old age. The major current perception supports the assumption that sarcopenic obesity is associated with negative health outcomes at old age [64].

Under circumstances when weight loss is clinically justified, like in diabetes, MetS, joint disorders or other disabilities, weight loss programs could well be successful, but should include exercise in order to protect from loss of muscle mass and to enhance the positive metabolic effects from the weight loss [65].

2.7. Obesity from an intensivists's view

Obesity in critically ill patients is associated with increased morbidity but not increased mortality, because intensive care unit (ICU) patients are catabolic and obese therefore may use their excessive fat stores as energy source while preserving the muscle reserve [66]. A significant source of protein and lipids, enough trace elements and vitamins, and substrates that maintain the GI barrier and the immune system should be provided. However, strong evidence regarding energy and substrate requirements of obese patients fed by enteral nutrition (EN) or PN is still missing and the recommendations are at the level of expert opinion [67].

Indirect calorimetry allows the determination of individual energy requirements of obese patients. For a BMI between 40 and 80 kg/m², the required resting energy expenditure (REE) varies in mean between 1895 and 2635 kcal/day [68]. Obese critically ill cancer patients have significantly higher nutrition requirements than the current guideline recommendations indicate [67], reaching 28.7 ± 5.2 kcal/kg of ideal body weight (IBW)/day. Port and Apovian [69] recommend to measure energy needs by calorimetry and to administer 100% of these needs by EN or PN. If indirect calorimetry is not available, prediction equations such as the Penn University formula could be used providing an accuracy of around 65% [70].

Comparing the administrating of a hypocaloric diet (between 3 kcal/kg IBW/day to 14 kcal/kg current body weight (CBW)/day) versus a normo-caloric diet (25–36 kcal/kg IBW/day), both combined with a high protein intake (1.8–2.2 g/kg IBW/day), hypocaloric regimen showed slight advantages such as less insulin requirements, better wound healing and decreased ICU stay and antibiotic days [71]. Experts recommended that the goal of an EN regimen should not exceed 60–70% of target energy requirements or 11–14 kcal/kg CBW/day (or 22–25 kcal/kg IBW/day) [72]. If permissive hyponutrition (10–14 kcal/kg CBW/day) is prescribed, the enteral route should be preferred. Protein should be provided in a range >2.0 g/kg IBW/day for obesity class I and II patients (BMI 30–40 kg/m²), and >2.5 g/kg IBW/day for obesity class III patients (BMI > 40 kg/m²). A recent study showed that obese patients were fed in delay in comparison with patients with lower BMI [73]. These

findings are of importance since obese patients suffer from loss of lean body mass and need early enteral feeding to prevent negative energy balance and nitrogen balance. If the needs cannot be covered by the enteral route, the parenteral route can be used in a supplemental or exclusive manner and has been shown to be safe [74].

With the increase in bariatric surgery, related complications including anastomosis leak, narrowing lumen and too small bowel absorption surface are increasing the indication for PN. The nutritional regimen should be guided by indirect calorimetry and include a high protein intake (1.5–2 g/kg IBW/day).

In summary, the obese critically ill patients should be fed according to his requirements and if indirect calorimetry is not available, according to the Penn State equation.

2.8. Obesity from a psychologist's view: the way to long-term success

To identify and offer optimal nutritional care beyond weight-reducing calorie-restricted diets it is important to consider and be supported by psychological and behavioral strategies that offer support in the adherence of particular diets over the short and longer term. The patients' psychological and mental state such as e.g. motivational and emotional condition, as well as the social environment can determine successful behavior change [75]. On one hand, the social environment needs to be able and willing to adjust to changes in the patient's diet and lifestyle to increase the likelihood of long-term success. On the other hand, to change eating and exercise habits is difficult and practicing skills such as stress management with problem-solving techniques, cognitive restructuring to improve self-control, and self-monitoring to support lifelong changes are essential for both weight loss and weight loss maintenance [76,77].

Furthermore, psychologists and psychotherapists should be part of the multidisciplinary team approach aimed at optimal treatment and follow-up. Epidemiological studies show a positive association between obesity and mood and anxiety disorders [78]. Existing comorbidities have consequences for both pharmacological as well as psychological treatment options. Every obese patient is unique and might benefit from psychological support along the way of treatment and weight loss maintenance. Not only the body and its nutritional needs should be addressed but also the mindset and the patients' psychological well-being and quality of life.

2.9. Cognitive function and psychiatric co-morbidities in obesity

The medical consequences of obesity are well recognized since years, but the cognitive consequences have been studied only recently. Cognitive function refers to the processing, integration, storage and retrieval of information. It includes perception, attention, memory and executive function. There are no clear recommendations about the extent and type of follow-up needed to evaluate cognitive function over time in obese individuals. Whether cognitive function deficit and mental health disorders (MHD) are a cause or consequence of obesity is still a subject of debate.

In the groups of 4–18 and 19–65 years old people, obese individuals have significantly poorer cognitive indices compared with normal weight individuals. The most consistent finding is poor results in tests of executive function. Obesity may predict cognitive decline but changes in weight itself does not consistently predict changes in cognition. In the elderly age group of 66–95 years, the relation between obesity and cognition is less clear. The positive association of obesity and cognitive dysfunction is independent of socio-economic factors, depression and CV factors. Obesity by itself

can be a risk factor for cognitive dysfunction, but when associated with other CV risk factors such as hypertension, the deficit in cognitive function is more pronounced suggesting an additive effect. Since obesity is a risk factor for many components of the MetS, early treatment and prevention are mandatory to minimize the detrimental effect of the MetS on cognitive function [79,80]. The inverse relationship between low levels of executive function and motor function with increased BMI was shown in longitudinal studies [81–83].

Obesity is coincident with MHD in 45% of MDH cases. Individuals with schizophrenia, bipolar disorder, depression, anxiety, attention deficit/hyperactivity disorder (ADHD) have a higher prevalence of both obesity and MetS compared to the general population. Many of the relationships between MetS and MHDs are sex-dependent. Overweight and obese women have increased prevalence of anxiety, major depressive disorder and both childhood and adult ADHD, while obese men do not show the same trends [80]. Individuals with depression and emotional dysregulation commonly have a preference for sweets and fatty food [84]. Obesity occurring in the midlife is associated with an increased risk of dementia, such as Alzheimer's disease, in later life [85]. As for obesity and cognitive function, the bidirectional relationship between obesity and MHD may contribute to resistance against treatment.

Extremely high fat diet with 74% kcal as fat impairs cognitive function in sedentary men and is involved in mood disorders [80,83]. Weight loss, secondary to hypocaloric diet or bariatric surgery, has been shown to result in an improvement of memory performance but not executive function [83]. Neuroinflammation, genetic vulnerability, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, or neuropeptides such as dopamine, serotonin, neuropeptide Y, corticotropin-releasing factor, and disturbance of the endocannabinoid system are potential mechanisms linking obesity and obesity-associated metabolic disorders with cognitive function [80,85]. Obesity is associated with low-grade inflammation in peripheral tissues and in the circulation as well as in the brain, mainly in the hypothalamus. The systemic and central inflammation may converge to dysregulation of feeding and cognitive function.

In conclusion, obesity is associated with impaired cognition, mainly executive function, but this relationship is bidirectional since reduced cognitive function may be the cause and consequence of obesity [86]. The length of exposure to metabolic disturbances needed to induce cognitive dysfunction is not known but could explain the incomplete resolution of cognitive impairment after weight loss.

2.10. Obesity impact on physical fitness

Physical fitness refers to a state of well-being achieved by adequate nutrition, physical activity, and rest. Obesity has a major impact on health-related physical fitness, which encompasses body composition, muscle strength and endurance, cardiorespiratory fitness (CRF) and flexibility. Several methods for assessing health-related physical fitness are available (Table 3).

Obese individuals can have a different amount of muscle mass or fat distribution, which affects outcome. A high abdominal adiposity has been associated with metabolic risk factors, CV diseases, cancer, sleep apnea and mortality, and also with a low physical activity level [87]. However, a high BMI and percentage total body fat have surprisingly a protective impact in the elderly and in conditions such as CV disease, cancer, COPD, T2DM, end-stage renal diseases, and HIV [88].

The combination of a high body fat and a low skeletal muscle mass seems particularly detrimental for health. Individuals with

Table 3
Components of health-related fitness (adapted from Ref. [230]).

Component	Methods of assessment
Body composition	Body mass index, skinfold thickness, bioimpedance analysis, hydrodensitometry, dual-energy X-ray absorptiometry, computed tomography, magnetic resonance imaging
Muscular strength	One RM, ^a cable tensiometry, force platforms, dynamometry
Muscular endurance	Repetitions of lifts at a fixed percentage of RM, ^a of push-ups or abdominal curls, isokinetic dynamometry ...
Cardio- respiratory fitness	Peak oxygen consumption (peak VO ₂)
Flexibility	Sit and reach test, goniometry

^a RM: repetition maximum = maximum amount of weight lifted at one time.

this type of body composition have a higher risk of functional impairment and all-cause mortality compared to those with high body fat and normal skeletal muscle mass [89,90]. Interestingly, it has been reported that muscle mass is only a minor determinant of muscle strength, supported by the fact that, with aging, there is a more rapid loss of muscle strength than muscle mass, likely related to changes in neurological function and intrinsic properties of skeletal muscle [91].

Peripheral muscle strength adjusted for fat-free mass was shown to be at least 6% lower in obese than normal-weight individuals [92]. A few studies have evaluated the link of muscle strength and mortality in individuals with a BMI \geq 25 kg/m², without taking into account fat-free mass [93,94]. They found the worst prognosis in individuals with the lowest tertile of handgrip strength, as compared to individuals with normal weight and high handgrip strength. Consequently, poor muscle strength negatively affects outcome in obese people but the impact of fat-free mass on this relationship needs to be clarified.

A high CRF has been related with lower CV and all-cause mortality. A meta-analysis reported that a 1 km/h increased maximal running speed decreases all-cause mortality by 13% and risk of CV diseases by 15% [95]. Although the beneficial impact of high CRF may be partly related to a lower total and visceral body fat, several studies have found that CRF is a more important predictor of outcome than body composition [96,97]. A cohort study reported that mortality was similar in obese fit individuals compared with normal-weight fit individuals, but 6 times higher in overweight unfit individuals and 9 times higher in normal-weight unfit individuals [98]. Furthermore, individuals with abdominal adiposity, either fit or unfit, had an increased risk of mortality compared to fit individuals without abdominal adiposity [98]. These findings indicate that a good CRF is an essential component of health-related physical fitness.

In conclusion, health-related fitness predicts outcome of obese people, although the respective contribution of each component remains to be untangled. Obese people should thrive to a high muscle mass and strength and low visceral adiposity, a high CRF and a high flexibility.

2.11. Obesity-related joint diseases

Obesity can in some cases raise the risk for certain types of arthritis; but in all cases, obesity worsens arthritis. One in five Americans has been diagnosed with arthritis, but according to the Centers for Disease Control and Prevention, that number is higher among obese people and affects 1 out of 3 of them. The odds of arthritis and osteoarthritis (OA) are up to 7 times higher in obese people, compared with underweight or normal weight individuals [99].

OA is the most common joint disorder, affecting approximately 27 million Americans, with symptoms in the hands, knees, hips, back, and neck. It is unclear how exactly excess weight influences OA, a chronic disease that results from damage to articular cartilage induced by a complex interplay of genetic, metabolic, biochemical, and biomechanical factors (Fig. 3). In obesity-related OA, mechanical overload promotes the articular cartilage damage, but adipose tissue could also contribute to the pathogenesis by stimulating systemic low-grade inflammation and disturbed lipid metabolism leading to low synthesis/release of functional HDL cholesterol and high systemic levels of triglycerides, free fatty acids, oxidized LDL, adipokines and pro-inflammatory cytokines. Infrapatellar fat pads contribute to the high intra-articular levels of adipokines and cytokines [100].

The WHO initiative on counteracting obesity also accepts OA as a consequence of obesity [101]. Numerous large studies have shown a strong association between obesity and radiographic knee OA. The risk for osteoarthritis of the knee is increased almost fourfold in obese women and fivefold in obese men with a BMI of 30–35 kg/m² compared with lean individuals. In other terms, the risk for osteoarthritis of the knee is increased by approximately 15% for each additional kg/m² increase in BMI >27 kg/m² [101].

There seems to be also a relationship between obesity and other types of OA; however the relationship between obesity and hip OA, or hand OA, is not as strong, or could not be found at all [102,103]. It has been suggested that excessive weight may exert a greater impact on the knee joint because of particular biomechanical factors, whereas the more stable hip joint is less susceptible [104].

In conclusion, overweight and obesity have been clearly associated with OA, which substantially affects mobility and quality of life of the afflicted patients.

2.12. Obesity impact on quality of life

Numerous studies have shown a worse quality of life in obese patients. The influence of BMI on health-related quality of life (HRQoL) occurs mainly in the physical dimension of HRQoL, and in the overall assessment but not in the mental health category [105].

It has also been observed that the HRQoL of obese patients who opt for bariatric surgery is worse than that of those who choose a conventional treatment [106]. Further elements such as chronic pain, depression, or obstructive sleep apnea, have been associated with a worse HRQoL in obese patient. Therefore, the identification of these comorbidities is of great importance since they play a significant role on HRQoL [107].

HRQoL improvement is closely related to the amount of weight loss, regardless of the treatment that the patient has undergone; either the conventional treatment or bariatric surgery. Furthermore, even if there is some weight regain, as shown in several studies [106,108], the improvement is sustained. HRQoL improvement is evidenced in the scores of Physical, Psychosocial and Global dimensions of the Sickness Impact Profile (SIP). If assessed by the 36-Item Short-Form Health Survey (SF-36), it is reflected in the areas of Pain and Physical Functioning, indicating a significant impact on functional status and physical well-being, and in the perception of the patient's own health. Additionally, in patients with BMI >30 kg/m² there is also an improvement of the social functioning.

2.13. Impact of obesity for chronic diseases

Obesity rates are increasing, not only in the general population, but also in patients with chronic disease states. This supports the notion that the overall nutritional condition of patients with a chronic disease, like in cancer patients, has improved and that any weight loss because of a health issue will result in a shift from obese to overweight rather than from normal weight to underweight [109]. Chronic diseases are a group of diseases that slowly develop and need continuous chronic and acute medical care because of short periods of exacerbation of the symptoms of the disease. Examples are COPD, chronic heart failure, chronic renal failure, T2DM and the MetS, but also include cancer survivors or cancer patients in remission. While obesity is clearly related to the development of diabetes and the MetS, other pathogenetic associations are emerging suggesting that obesity may enhance the risk to develop further organ failures and related chronic diseases.

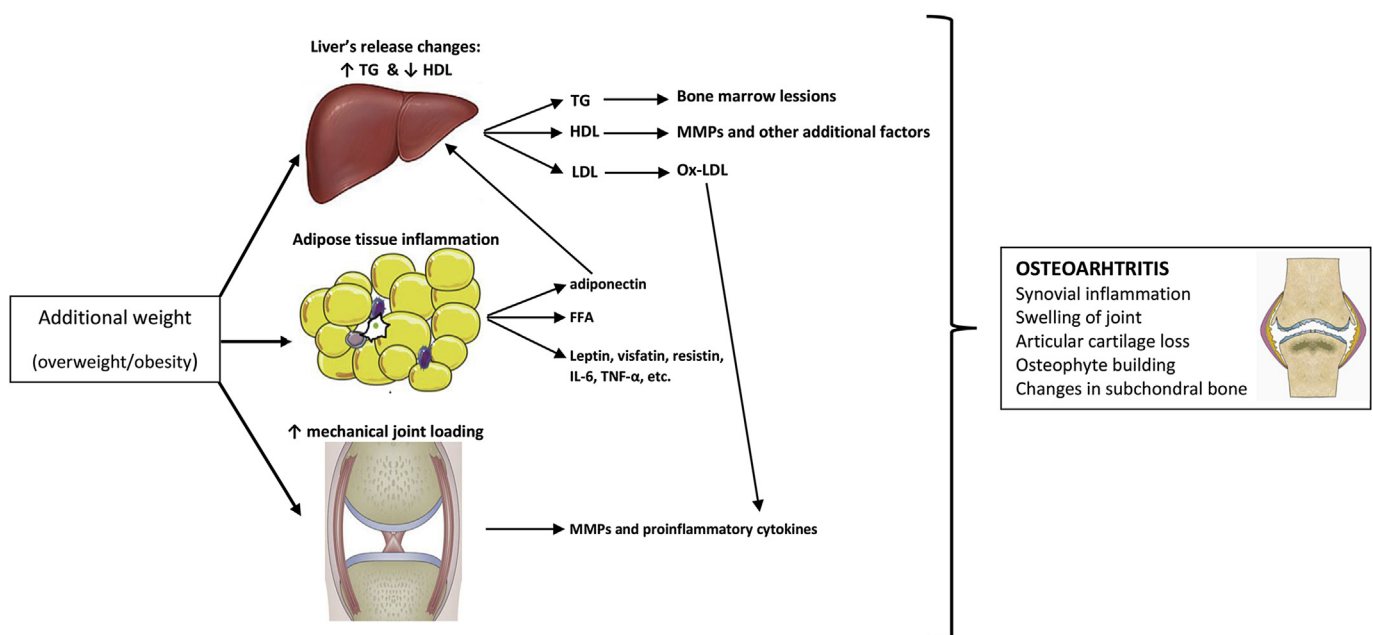


Fig. 3. Multifactorial association between obesity and osteoarthritis with central roles for loading, dyslipidemia and adipose tissue. Modified from Ref. [100].

How does obesity impact chronic diseases? Obesity can reduce the mobility and activity of an individual, e.g. by inducing orthopedic problems. On the other hand, obesity can protect people with chronic diseases from the risk of becoming underweight and losing muscle mass that will limit rehabilitation and reduce survival. This view is supported by many studies showing that a moderately high BMI is related to a lower mortality rate in chronic diseases; the obesity paradox [90,109–111]. However, this effect could be related to the fact that obese subjects usually have an increased muscle mass (Fig. 4) [112]. In other words, if somebody becomes obese, the muscle mass will increase. Therefore, it is tempting to speculate that obesity is related to better outcome, because of an increased muscle mass in the obese and thus muscle mass is related to outcome. This hypothesis is supported by the observation that in sarcopenic obesity, the benefit of obesity is not visible anymore or even turned to a reduced survival. Therefore, identifying and adequately treating patients with sarcopenic obesity is mandatory for the outcome.

3. Basic research approaches: fat tissue and beyond

3.1. Skeletal muscle and insulin resistance

Obesity is associated with structural and metabolic changes in skeletal muscle. Indeed, the accumulation of lipid metabolites and the consequential dysfunction of glucose utilization in muscle are early signs of obesity-induced insulin resistance, as the muscle mitochondrial capacity to oxidize excess fatty acids is limited [113]. Fat infiltration is also associated with muscle fiber type modifications, with a decrease in muscle mass and impairments in muscle function [114], especially in obese older individuals [115]. Interestingly, recent data support the hypothesis that intramyocellular lipids not only promote defective insulin-stimulated glucose disposal through insulin resistance, but also have detrimental consequences on muscle protein turnover through alterations in signaling pathways mostly involved in stress response [116].

The involvement of adiposity, particularly ectopic lipid deposition, in the muscle metabolic response to insulin indicates that muscle protein turnover is strongly affected [117], mostly during the chronic development of obesity [118], in relation with other metabolic disorders like lipotoxicity, inflammation, or insulin resistance (Fig. 5). Consequently and beyond metabolic impairments, these obesity-related modifications of skeletal muscle can affect mobility, morbidity and quality of life leading in fine to sarcopenic obesity with advancing age [119].

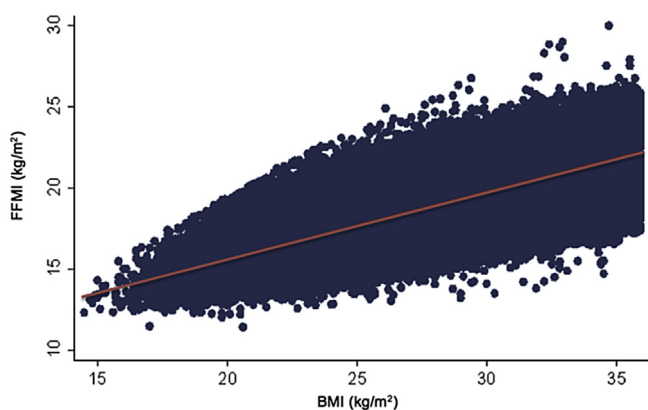


Fig. 4. Relation between BMI and FFMI (representing mainly muscle mass). From Ref. [112].

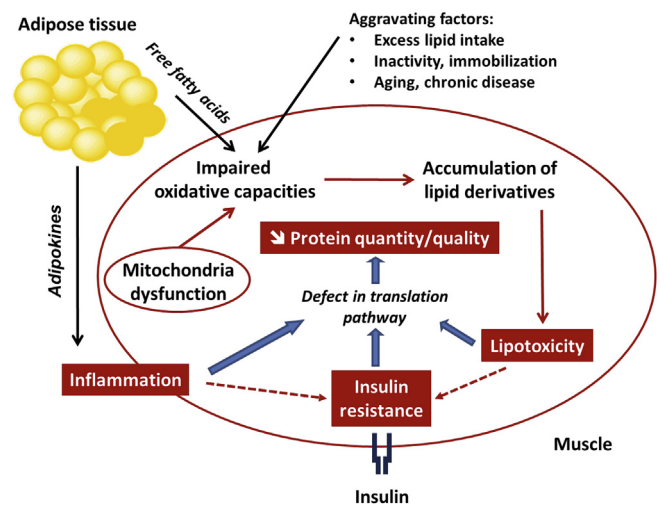


Fig. 5. Mechanisms of obesity-related insulin resistance and its links with alterations of muscle protein metabolism. For explanations see text.

As sarcopenia is defined as a reduced muscle mass and a diminished muscle function [2], it is of major importance to better phenotype muscle functionality in the obese patients in order to detect those who are prone to early sarcopenic obesity and its related deleterious effects. Interestingly, recent reports identified visceral fat as a possible link between obesity-induced insulin resistance and sarcopenia [120]. These clinical relationships suggest that the mechanisms of insulin resistance associated with lipotoxicity should be considered as a potential cause of sarcopenia in obese patients and a possible therapeutic target.

3.2. Pathophysiology of adipose tissues

Adipose tissue is a dynamic organ that actively contributes to the regulation of energy balance and nutritional status. Major breakthroughs in the definition of this concept include i) the discovery of the endocrine role of adipose tissue to produce complex patterns of adipokines and cytokines from both adipocytes and tissue macrophages; ii) the concept of adipose tissue expandability as a determinant of metabolic responses to positive energy balance; iii) the concept of differential metabolic and thermogenetic characteristics of adipocytes, with the ‘rediscovery’ of adult brown adipose tissue.

The discovery of the anorexigenic hormone leptin was probably the single most relevant finding to boost researchers’ interest in adipose tissue and its active metabolic function [121]. Since then, several adipose tissue hormones (adipocytokines or adipokines) have been described that contribute to regulate intermediate metabolism, energy metabolism, systemic inflammation, vascular function and hemostasis [121]. The unfavorable obesity-related pattern of low protective adiponectin with parallel increment of several proinflammatory and pro-atherogenic cytokines is strongly associated with the MetS [121]. Adipose tissue oxidative stress could exert a negative metabolic impact also by altering adipokine production [122]. In clinical studies, associations between plasma peroxidation markers and low adiponectin have been reported in both obese and non-obese individuals [122]. Selected nutrients or nutrition-modulated metabolites, including vitamin D, uric acid and omega-3 fatty acids, are emerging as mechanistic regulators of adipose tissue metabolism and endocrine function [123]. Regulation of adipokine production remains an exciting research area with strong potential clinical impact.

Adipose tissue expansion through adipocyte differentiation and proliferation is reported to be preferentially associated with metabolic benefits [124]. On the other hand, expanded fat mass through cell hypertrophy without recruitment of newly differentiated cells may lead to adipocyte damage, cell death and ultimately enhanced inflammation through macrophage activation [125]. These mechanisms may contribute to shape metabolic responses in human obesity. Hormonal and nutritional modulation of adipocyte differentiation and proliferation remain largely unknown and deserve future studies.

The management of obesity by increasing body energy dissipation through heat production appears promising. Brown adipocytes have higher thermogenic potential due to enhanced mitochondrial uncoupling that makes them less efficient ATP producers. Contrary to previous beliefs, brown adipose tissue is preserved after infancy through adult life in humans [125,126]. 'Browning' of adipose tissue, i.e. interconversion of metabolically white into brown adipocytes, has been reported following metabolic stimuli such as cold exposure and physical exercise in experimental models, but potential nutritional regulation of adipocyte browning and related changes in energy metabolism remain virtually unknown.

Visceral adipose tissue accumulation is well known to be associated with high risk of obesity-associated metabolic and CV complications, although underlying mechanisms remain only partially understood [127]. Factors regulating central adipose tissue distribution are also incompletely defined, although they include a negative impact by estrogen and stimulation by cortisol. Genetic, gender-related factors are also likely but yet poorly defined contributors.

In conclusion, excess body fat is the defining alteration in obesity. Altered adipose tissue functions in obesity likely play a key role in the development of complications.

3.3. Obesity and the gut microbiota

In the last few years, the gut microbiota has been proposed as an environmental factor that could be implicated in adiposity and related metabolic diseases. Dysbiosis, defined as changes in gut microbial composition, localization, and metabolic function, characterizes obese versus lean individuals [128]. Germ free mice, colonized with the gut microbiota from obese mice or humans, acquire an obese and/or diabetic phenotype. Those data suggest that the metabolic characteristics of the obese microbiome can increase the ability to extract energy from the diet and store this energy in the adipose tissue. Several hypotheses have been reported to explain the association between dysbiosis and metabolic disease, including increased energy harvest, changes in host gene expression, alterations in the gut barrier, and contributing to inflammation and adiposity [129].

Some components of the gut microbiota, as well as metabolites issued from microbial metabolism of nutrients of host related components, may play a role in key functions related to adiposity and metabolic disorders. Among the metabolites produced in the gut, short-chain fatty acids (SCFA) can be used as energy sources by the host, but can also act as regulators of energy intake and energy metabolism [130,131]. The tremendous variety of bile acids present in the gut reveals the important contribution of the gut microbiota for the release of steroids able to modulate the gut endocrine function and beyond, e.g. in the liver or in adipose tissue, once steroids reach the systemic circulation.

The metabolomic and metagenomic analyses of the gut microbiota allowed to explore the panel of bacterial metabolites able to act on host energy metabolism and to participate to metabolic alterations. Some bacterial components – released independent from

nutrient transformation – may also play a role in obesity and related metabolic disorders, like the lipopolysaccharides (LPS) present in gram negative bacteria, peptidoglycans, flagellins, or bacterial DNA [131–133].

Since dysbiosis has been clearly associated with obesity, there is a growing interest in evaluating changes in gut microbiota occurring following weight loss, and in developing alternative ('probiotic') therapies for weight control and prevention of obesity. The surgical approaches (gastric bypass, gastrectomy), which are effective treatments for weight reduction, lead to profound changes in gut microbiota, in favor, for example, of bacteria prone to improve the gut barrier function (*Akkermansia muciniphila*), and to changes in bacterial phyla involved in energy sparing [128,134]. These observations raise the question whether some alterations of the gut microbiota may be the consequence rather than the cause of obesity.

The transfer of the gut microbiota from apparently healthy donors to individuals presenting a MetS allowed to improve insulin resistance for several weeks, thereby opening the door to novel approaches in the management of metabolic disorders associated to obesity [128]. Future dietary advices should also consider the evolution of the knowledge in the field of microbiota-host interactions. Interesting recent papers pointed out how modeling of metagenomics and metabolomics data could help elaborating a more personalized nutrition in obese individuals, taking into account both the characteristics of the diet and the taxonomic/metabolic activity of the gut microbiota [135]. The administration of probiotics (live bacteria given orally) or prebiotics have been proposed as novel strategies to modulate the composition and activity of the microbial gut ecology. Several prebiotic dietary fibers are well characterized and their administration promotes growth of beneficial microorganisms such as *Bifidobacterium* species, *A. muciniphila*, and *Faecalibacterium prausnitzii* [132]. These microorganisms are involved in the improvement of key gut functions including endocrine function, resulting in decreased inflammation, enhanced satiety and improved health. Up to now, the number of intervention studies exploring new tools (microbiota transfer, probiotic, prebiotic approaches) in obese or overweight individuals is still low.

3.4. The gut-liver-axis

Almost all patients with obesity develop liver steatosis, also named NAFLD, which sometimes proceeds to non-alcoholic steatohepatitis' (NASH), a severe complication of obesity that may lead to acute liver failure [136,137]. Patients with NASH have an enhanced risk to develop liver fibrosis and cirrhosis, and even hepatocellular carcinoma (HCC). About 20% of the obese patients develop NASH (3) [138], and 5–10% of the NASH patients develop HCC [139].

NAFLD has been recognized now as an early indicator of obesity-associated pathologies such as insulin resistance, atherogenesis and myocardial dysfunction [25]. This association suggests that changes in the liver may not only precede such pathologies often summarized as the MetS, but trigger or at least facilitate metabolic and CV disorders. This hypothesis is supported by the observation that the 2/3 of obese individuals who develop metabolic diseases almost always show metabolic liver disease, whereas the 1/3 of obese individuals not afflicted ('the healthy obese') show a normal liver [140,141]. Obviously, the steatosis of the liver, but also of other organs such as skeletal and heart muscle and intestine, primes for metabolic and CV diseases as well as cardiac arrhythmias like atrial fibrillation [142]. Although the molecular mechanisms explaining this association are not fully understood at present, pronounced NAFLD in the obese can be regarded as an early indicator for

particular risks such as diabetes, CV diseases and hepatocellular carcinoma.

In this context, the question raises what causes liver steatosis in the obese and what are the possible pathophysiological consequences. Particular food such as high-fat diet and sugars, especially fructose, seem to promote the development of NAFLD. In animal experiments, it was shown that this triggering effect of particular food occurs independently of calorie intake suggesting that not only the energy intake but also food quality determines about obesity-associated diseases. Evidence from animal experiments [133,143,144], and to some extent also human studies [145,146], suggests that translocation of bacterial products such as endotoxin from the intestine to the liver triggers NAFLD and inflammation in the obese. Whether the above mentioned food induces NAFLD by causing intestinal barrier impairment and subsequent endotoxin translocation or also by other mechanisms, is unclear at present. On the other hand, such experiments strongly suggest that not only the amount of energy uptake by diet, but also diet composition determines about obesity and obesity-associated diseases. Therefore, the gut-liver-axis anatomically represented by the portal vein transporting food components as well as bacterial products from the intestine to the liver deserves more attention. Intestinal barrier functions may become a new determinant of obesity risk or metabolic disease risk and dietetic strategies that address such mechanisms might affect future therapeutic strategies [58].

3.5. Future research directions

Basic research on obesity relates to several aspects addressed in the previous chapters. One should not just focus on negative effects of obesity. There are clear indications that survival benefits from overweight and obesity, which is likely related to the increase in muscle mass [90,109,110,147–149]. Therefore, there are characteristics of overweight and obese subjects like individual body composition, or genetic and metabolic phenotype, that determine whether a certain characteristic will have a beneficial or harmful effect on health and the capacity to cope with a chronic disease. We clearly have only limited knowledge of the different phenotypes of overweight and obese subjects to be able to relate this to health.

Besides careful phenotyping of obese subjects, we need to introduce more advanced analytical approaches. For instance, a new state-of-the-art stable isotope approach to characterize kinetics of substrates in a large number of obese subjects was introduced. By giving one pulse of a mixture of many stable isotopes of amino acids and keto-acids, and taking blood samples at defined intervals, this technique allows to calculate the plasma and intracellular appearance and inter-conversions of substrates to better phenotype obese subjects on a metabolic level. Using other recently introduced stable isotope methods, the rates of protein digestion and amino acid absorption after consuming a defined protein meal can be assessed [150]. By the use of these metabolic kinetic approaches, together with other methods, we can link these data to the variation in muscle mass, bone mineral density, muscle function, quality of life, well-being, neuropsychological function etc. that will generate new leads to refine and individualize nutritional therapies with optimal protein and amino acid composition designed to treat the negative effects of the overweight and obesity, which will positively influence the outcome of these patients.

4. Screening and assessment

4.1. Basic examinations in obesity

In all patients, a detailed history and examination should contribute to assess obesity stage and risk level (Table 4). Recent

Table 4
Diagnostic means in patients with obesity.

Category	Examination ^a
Patient's history	Weight history Previous efforts to lose weight Physical activity Eating habits, 7-days-food-protocol Psychosocial performance Family history Drug history <i>Depression scale</i>
Physical examination and anthropometry	Actual body weight and height Waist circumference (if BMI < 35 kg/m ²) Blood pressure <i>Body impedance analysis</i> <i>Hand grip strength</i> <i>Ultrasound (liver steatosis? Gallstones?), elastography, MRI</i> <i>Calorimetry</i>
Laboratory tests	Fasting plasma glucose, HbA1c, 2-h 75-g oral glucose tolerance Lipids (triglycerides, total/HDL/LDL cholesterol, small dense LDL) Transaminases Uric acid, creatinine, micro-albuminuria Complete blood count, ferritin, transferrin saturation Micronutrients: vitamins (vitamin D, folic acid, etc.) calcium, potassium, zinc, selenium, iodine Somatic hormones (TSH, cortisol) Sex hormones
Sleep apnea diagnostic	<i>Validated questionnaires (e.g. the Epworth Sleepiness Scale and the Berlin Questionnaire)</i> <i>Polysomnography ("gold standard" method)</i> <i>Scale scores such as the Framingham Risk Score, the NCEP ATP III risk assessment or the SCORE scale</i>
Cardiovascular risk assessment	<i>Muscle mass measurement (dual X-ray absorptiometry, DXA, or bio-electric impedance analysis, BIA)</i> <i>Calculation of the FFMI (fat-free mass index = fat-free mass/height²)</i> <i>Muscle strength and/or function measurement (gait speed, chair standing test, hand grip measurement)</i> <i>Muscle power estimation by the Activities of Daily Living (ADL) score or the Short Physical Performance Battery (SPPB) instrument</i>

^a Examinations printed in italic are recommended only in the presence of clinical alterations (for details see text).

guideline recommendations [76] have more clearly introduced the concept of primary care involvement in risk stratification, by explicitly recommending measurement of waist circumference, a major marker of insulin resistance and its complications. Patients with high waist circumference should be further tested for altered blood pressure, blood glucose and lipids, and should be advised to lose even moderate amounts (<5%) of body weight.

Measurement of sex hormones is indicated in the presence of clinical alterations, such as clinical hypogonadism and-or erectile dysfunction in males or oligo-amenorrhea and hirsutism in females (Table 4). In selected cases, particularly in those resistant to dietary weight loss for unclear reasons, energy balance assessment by indirect calorimetry can be considered [151]. Indirect calorimetry may support not only individual dietetic recommendations, but may also allow a more precise calculation of metabolic equivalents (MET) in overweight to extremely obese subjects [152].

Bio-electric impedance analysis (BIA) can be used for the assessment of body composition, especially muscle mass or lean body mass, if dual X-ray absorptiometry (DXA) is not available. Although BIA might be less accurate, it is the most suitable means in a clinical setting because it is simple, inexpensive, noninvasive, and highly reproducible [153]. In particular, for follow-up analyses, e.g. during weight loss therapy, BIA seems to be appropriate to

assess loss of muscle mass [154]. At least muscle mass and total fat mass can be measured adequately, whereas measurement of visceral fat requires DXA or MRI [155]. Moreover, BIA can be helpful for motivation of obese individuals under weight loss therapy, because not only to monitor change of weight, but also prognostically relevant improvement of body composition.

4.2. Diagnostic criteria for sarcopenic obesity

There are no commonly accepted criteria for sarcopenic obesity beyond those for sarcopenia and obesity separately. The ESPEN endorsed recommendations of the European Working Group on Sarcopenia in Older Persons [156], as well as the statement from the ESPEN Special Interests Groups of Cachexia in Chronic Disease and Nutrition in Geriatrics indicate an algorithm based on loss of muscle mass and strength and/or function [157].

Muscle mass could be measured by any validated technique, which in clinical practice would usually involve DXA or BIA. For body composition measurement in clinical practice DXA might be most accurate in obese individuals. However, such diagnosis is not always easily available. There is no clear consensus about normal ranges for FFMI (fat-free mass index = fat-free mass/height²), and the uncertainty is even larger for the obese individual, since the normal ranges might be different from the lean population [158]. For example, reduced muscle mass could be indicated by an appendicular skeletal muscle mass index <7.26 kg/m² (men) and <5.5 kg/m² (women) [2]. Using the BIA method in a large cohort of hospital patients, low FFMI and high FMI was associated with a poor outcome in terms of length of hospital stay compared with normal FFMI or FMI [159].

Muscle function may be assessed by measuring gait speed or by the chair standing test (which tests lower extremities) or by evaluating muscle strength using the hand grip measurement [160]. Practical diagnostic cut-offs for gait speed are considered to be: <0.8 m/s (2) or <1.0 m/s (3). Suggested cut-off points for reduced muscle strength measured by handgrip strength are <20 kg for women and <30 kg for men (2). Alternatively, muscle power can be estimated by the assessment of the patient autonomy using the Activities of Daily Living (ADL) score or the Short Physical Performance Battery (SPPB) instrument [161].

4.3. Assessment of co-morbidities

Obesity can progressively cause and/or exacerbate a wide spectrum of co-morbidities, including CV disease, T2DM, hypertension, dyslipidemia, liver dysfunction, respiratory and musculoskeletal disorders, sub-fertility, psychosocial problems, cognition, and certain types of cancer. Current guidelines for the management of overweight and obesity in adults recommend measuring BMI at annual visits or more frequently at 'expert opinion' level and also waist circumference (except in patients with BMI > 35 kg/m²) [162]. Blood pressure, fasting plasma glucose and lipids are further recommended for risk assessment for CVD and DM in this population [162].

The American Diabetes Association recommends testing to detect T2DM and prediabetes in asymptomatic overweight or obese adults, of any age, who have one or more additional risk factors, by means of HbA1c, fasting plasma glucose or 2-h 75-g oral glucose tolerance test (grade B) [163]. The Framingham Risk Score, the NCEP ATP III risk assessment and the SCORE scale may be used to calculate short-term (10-yr) CV risk. Recently, a new risk equation representative of different ethnic groups (non-Hispanic whites and African-American) in the US has been developed [164].

Hepatic function of obese patients may be impaired by the ectopic fat accumulated in the liver, leading to a spectrum of

abnormalities referred to NAFLD. Liver function blood tests and image tests may be used to screen the severity of the disease. Obesity is associated with a range of distinct respiratory conditions including obstructive sleep apnea, obesity hypoventilation syndrome, asthma, and COPD. Screening for obstructive sleep apnea can be performed through validated questionnaires (e.g. the Epworth Sleepiness Scale and the Berlin Questionnaire), confirmation requires polysomnography which remains the "gold standard" diagnostic method. In obese patients, the proposed Edmonton Obesity Staging System which considers the presence of co-morbidities may provide a simple framework to aid decision making in clinical practice [165].

4.4. Micronutrient deficiencies

Vitamin deficits assessed by serum or plasma levels occur more frequently in obese individuals than in the general population. This has been shown for vitamin D [166], vitamin A [167], and folic acid [168]. More recent studies in patients with advanced obesity undergoing weight reduction through multidisciplinary conservative programs or bariatric surgery revealed pre-interventional deficits mainly of vitamin D, but also of retinol, b-carotene, vitamin B6, vitamin C, vitamin E, and folic acid [169,170]. Also a number of minerals such as iron, calcium and iodine, and to a less extent potassium, magnesium, zinc, and selenium are found at lower levels in obese compared to lean individuals [169–171]. These deficiencies might become even more relevant after intervention, in particular after mal-absorptive bariatric surgery. Thus, obese individuals should be examined at least for iron status, calcium/vitamin D status, and one vegetable-associated micronutrient such as retinol, b-carotene, or folic acid once a year. Other micronutrients can be assessed in case of clinical complications or in patients at risk, e.g. pregnant women or patients undergoing surgery. There is no general recommendation suggesting micronutrient supplementation in obese people; however, proven deficits should be treated either by an adequate diet or supplements [172,173].

5. Preventive strategies against obesity

5.1. Preventive strategies in early life

Since obesity treatment strategies in adults and children remain unsatisfactory, effective primary prevention is of key priority. Prevention aims at reducing the incidence of overweight and obesity, i.e. to reduce the manifestation of new cases. The best opportunities of effective prevention exist prior to entering school age [43]. Obesity was more likely to occur in children who were already overweight when entering Kindergarten. A German representative health survey in more than 17,000 children and adolescents revealed that overweight prevalence increases from 9% among 3–6-year-olds to 15% in 7–10-year-olds, whereas in 14–17-year-olds it remained similar at 17%. Likewise, the prevalence of obesity more than doubled from 2.9% at age 3–6 years to 6.4% at 7–10 years, whereas the prevalence at 14–17 years was only slightly higher with 8.5% [174].

These data suggest that particular opportunities for prevention strategies exist in early childhood, when dietary and lifestyle preferences are learned and established, for example with setting based intervention. Key targets include at least 30 min/day of playful and fun, vigorous physical activity games at the Kindergarten setting, regular consumption of fresh fruit and vegetables, and water intake while limiting sugared beverages and juices [175]. In a cluster randomized trial, this low cost intervention achieved sustainable effects on food and drink consumption 18 months after

the start of the intervention, also in the high risk families with lower education levels. After one year, the prevalence of overweight was reduced from 18% in the control group to 13.9% in the intervention group ($p = 0.05$). An European wide day care intervention program strategy has been developed and is evaluated with financial support of the European Commission in the ‘ToyBox project’ [176]. Setting based preventive intervention should be combined with strategies to reach out and actively involve families, and efforts targeting environmental conditions, e.g. conditions encouraging regular physical activity, quality standards of school meals, and responsible marketing of foods and drinks to children.

Prevention should, however, start even earlier. High birth weight >4000 g induces a 5fold increased risk of becoming overweight by the eighth school grade (4) [175]. Early lifestyle and nutrition during the first about 1000 days of life (270 days of pregnancy and 2×365 days of the first two years of life) induces marked programming effects on long-term health until old age, including the risk of obesity and associated disorders such as diabetes [177,178]. Nutrition in early life modulates cytotogenesis, organogenesis, metabolic and endocrine response, pre- and postnatal growth trajectories, and epigenetic regulation of gene expression. Current research on early prevention of obesity focuses on three key hypotheses of early programming of later obesity and adiposity. The “Fuel mediated ‘in utero’ hypothesis” stipulates that intrauterine exposure to excessive fuels (e.g. glucose, fatty acids) resulting from maternal obesity or diabetes, enhances fetal weight and fat gain and leads to increased obesity later in life. The “Accelerated postnatal growth hypothesis” links rapid weight gain in infancy and early childhood to increased later obesity. The “Mismatch hypothesis” describes that low prenatal weight gain and low birth weight, along with high postnatal weight gain, markedly increases later disease risk.

Maternal obesity has been linked to increased infant birth weight and body fat content, increased later obesity risk, and significantly shorter life expectancy of the child (Fig. 6) [179]. Prevention is possible. In the randomized controlled ‘Limit trial’, three face to face sessions counseling overweight women during pregnancy to encourage regular physical activity and to limit intake of sugars and dietary fat achieved a significant reduction of high infant birth weight >4 kg by 19% [180]. Numerous studies also link abnormal weight gain in infancy and in the second year of life to an approximately doubled risk of obesity up to adulthood (“Accelerated postnatal growth hypothesis”) [181]. Breastfeeding reduces the likelihood of both high early weight gain and later obesity [182]. Several meta-analyses of large cohort studies reveal that breast feeding reduces the risk of later obesity by about 12–24%, compared to conventional bottle feeds [183–185]. The risk of

formula-feeding can be attenuated by improving the composition of infant formula. In a large multicenter trial funded by the European Commission, we demonstrated that feeding formulae with a lesser protein content, more similar to the protein content of human milk, normalizes early weight gain relative to breastfed infants, and it markedly reduces obesity risk at school age 2.4–2.9 fold [186,187]. Further opportunities exist during the complementary feeding period by avoiding overfeeding and excessive intakes of sugar and animal protein.

These data demonstrate the preventive potential that exists very early in life. Improvements in scientific and technical expertise on placental biology, epigenetics, and metabolomics provide great opportunities for enhancing our understanding of the relation between early life nutrition and later adiposity at the cellular and molecular level, which should help refining and improving effective preventive strategies.

5.2. Preventive strategies in adults

The development of obesity (as well as maintaining a new body weight after an initial successful body-weight loss) is caused by a combination of individual, environmental, biological and genetic factors, and, therefore, no single intervention can reasonably be expected to have a substantial impact on obesity rates. Chronic overfeeding, sedentary lifestyle and low physical activity along with shorter sleep duration seem to be major factors leading to obesity.

Prevention of overweight and obesity requires a systems-level approach that includes consistent and integrated messages for all age groups (children, adolescents and adults) [188]. Interventions should integrate behavioral and environmental approaches that focus both on dietary intake (nutrition education, dietary counseling) and on physical activity promotion. Small but consistent changes in lifestyle seem to facilitate best a long-term maintenance of the lower body weight.

Consistent self-weighing may help individuals maintaining their lower weight by allowing them to recognize body weight changes early enough to adjust behavioral changes [189,190]. Additionally, those who weight daily also report a greater adoption of diet and exercise behaviors, whereas decreasing self-weighing frequency seems to be associated with a greater weight gain [189].

Mass media campaigns – in combination with other strategies – could offer a promising means of reaching target populations with obesity prevention messages. However, careful pre-testing of these types of ads is needed to ensure avoidance of any unintended negative impacts (e.g. stigmatization of individuals and increased levels of body dissatisfaction and/or eating-disordered behavior) [191]. In an effort to find additional ways to promote more healthy choices, additional taxation for less healthy foods has come into consideration in various western countries. Such a taxation is proposed as a mechanism to reduce consumption of energy-dense food and hence reduce rates of obesity and overweight in the community [192].

In diets targeting to prevent and treat obesity by manipulating energy content, macronutrient distribution are commonly set at 15% protein, $<30\%$ lipids, and 50–55% carbohydrates, with increases in fiber favored [193]. This recommendation may be effective for decreasing energy density and promoting weight loss in the short term; however, a low level of satiety could lead to a low adherence over longer periods. Absolute protein intake seems to be more important – during weight loss and weight maintenance – than the percentage of diet’s protein. Given then high satiety level of protein, this might lead to a reduction in food intake under ad libitum conditions, resulting in successful weight loss and an increased chance of maintaining the new bodyweight [194].

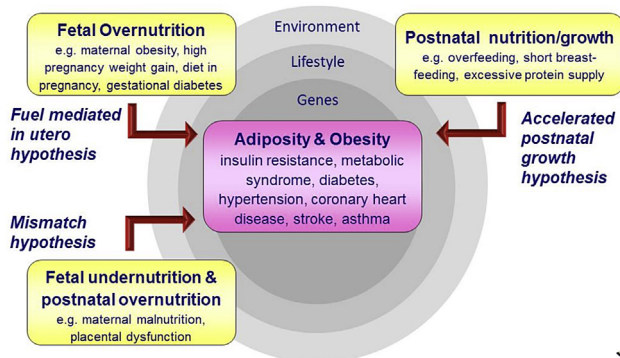


Fig. 6. Key hypotheses for pre- and postnatal modulation of later risk of obesity and related disorders. Modified from Ref. [179].

An alternative approach to calorie restriction is to lower the diet's fat content. However, fat-restricted diets have no advantage compared to calorie-restricted diets in general regarding long-term weight loss in overweight or obese people [195]. Nevertheless, diets higher in total fat seem to be associated with higher body weight, BMI, and waist circumference [196].

Dietary sugars might promote weight gain by increasing energy consumption and promoting hunger [197]. Therefore, reduction of sugar intake is an important component of any strategy to avoid overweight and obesity. In particular, a decrease in the consumption of sugar-sweetened beverages leads to a reduced prevalence of obesity and related diseases [198,199]. Recent data do not support a beneficial effect of dairy consumption for weight loss in long-term studies or studies without energy restriction [200,201].

Low glycemic index or low glycemic load diets might promote both weight gain prevention and weight loss maintenance in comparison to other diets. Lowering the glycemic load of the diet appears to be an effective method that can be easily incorporated into a person's lifestyle [202]. However, with regards to long term effects, low glycemic index diets did not show consistent effects on weight regain after 12 months [194].

In general a healthy diet regime with a regular food intake divided into 3 to 6 portions and based on the principles of the Mediterranean diet, combined with continuous physical activity, can help reducing and maintaining an individual's body weight (Table 5).

6. Multidisciplinary management of obesity

6.1. Weight reduction and maintenance by diet and lifestyle intervention

Lifestyle modification with hypocaloric diet and physical activity are the cornerstones of treating overweight and obesity, as well as

Table 5
Recommendations for prevention of overweight/obesity.

Follow a healthy eating plan	Make healthy food choices, keep your and your family's calorie needs in mind, and focus on the balance of energy
Focus on portion size	Watch the portion sizes in fast food and other restaurants. Cutting back on portion size will help balance energy intake
Be active	Find activities that you enjoy (approx. ½–1 h/day)
Reduce screen time	Limit the use of TVs, computers, DVDs, and videogames because they limit time for physical activity (<2 h/d screen time)
Keep track	Keep track of your weight, body mass index, and waist circumference.
Exercise regularly	Get 2,5–5 h/week of moderate-intensity activity to prevent weight gain. Moderately intense physical activities include fast walking and swimming.
Follow a healthy eating plan	Focus on low-calorie, nutrient-dense foods, such as fruits, vegetables and whole grains. Avoid saturated fat and limit sweets and alcohol.
Be consistent	Adhere to your healthy-weight plan as much as possible increases chances of long-term success.
Limit these foods and drinks	<ul style="list-style-type: none"> • Sugar-sweetened beverages (soda, fruit drinks, sports drinks) • Fruit juice (no more than a small amount per day) • Refined grains (white bread, white rice, white pasta) and sweets • Potatoes (baked or fried) • Red meat (beef, pork, lamb) and processed meats (salami, ham, bacon, sausage) • Other highly processed foods, such as fast food
Avoid overeating	<ul style="list-style-type: none"> • Eat breakfast • Choose small portions and eat slowly • Eat at home. • Eat mindfully

insulin resistance and T2DM. Optimal nutritional support of the obese and diabetic patient eating orally or needing artificial nutrition remains largely to be defined, particularly in the presence of nutritional deficiencies and loss of lean body mass.

Non-surgical obesity therapy comprises weight reduction and weight maintenance therapy. Weight reduction therapy is always a time-limited effort that might include a somewhat unbalanced diet in order to achieve substantial weight reduction. This requires dietetic regimen, but also physical exercise and other lifestyle actions, including behavioral education. All successful weight reduction therapy needs a subsequent weight maintenance strategy, because otherwise, weight regain must be expected independently of the means of weight reduction. The risk of weight regain is larger after weight loss by conservative means than after bariatric surgery.

The principles of weight reduction and weight maintenance therapy are quite different. Weight maintenance therapy is a non-invasive, long-term strategy which resembles to a large extent preventive strategies against obesity. In the weight reduction phase, a negative energy balance is required, whereas in the weight maintenance phase, the energy balance should be even. To achieve a negative energy balance, calorie saving is mandatory, while during the long-lasting maintenance phase, food composition and food quality becomes more relevant.

Most obesity guidelines recommend weight reduction therapy in patients with a BMI > 30 kg/m². Some guidelines indicate even lower BMI cut-offs (>25 kg/m²) for the initiation of therapy depending on the presence of metabolic or other co-morbidities or high psychological strain [162,203–205]. The goal of obesity therapy is a safe and sustained reduction of body weight in combination with a reduced risk for co-morbidities, reduced mortality and disability, and an improved quality of life.

To achieve a negative energy balance, different approaches need to be considered: (i) increase of physical activity by exercise or 'non-exercise-activity thermogenesis' (NEAT); (ii) low-calorie-diet while avoiding satiable, energy-dense food; (iii) professional behavioral therapy including personal coaching and social changes, and (iv) motivational strategies supporting adherence and acceptance. In adults, low-calorie-diet is initially the most important event, which can be made more effective by using so-called 'formula diet' for a limited time (800–1200 kcal/day usually up to 12 weeks). Increase of physical activity has usually limited effects at therapy start, because most obese individuals lack fitness and might have limitations such as joint disease. However, in the course of therapy, the ability to perform exercise usually increases, both because of better motivation and better mobility once weight reduction is achieved.

Systematic reviews of RCT showed that the combination of physical activity, dietetic means and behavioral therapy is more effective than only one of these components [206–208]. The combined approach results in an average weight loss of up to 10 kg, whereas the effects of single components are usually restricted to 5 kg at best. If more than 10 kg (or 10% of initial body weight) should be reduced, either multidisciplinary conservative intervention programs over at least 6 months using formula diet in the initial phase or bariatric surgery (if multidisciplinary programs were not sufficiently effective) should be recommended (Table 6).

Nutritional therapy of obesity can be based on fat- and/or carbohydrate-reduced diets with an energy intake reduction by at least 500 kcal/day. The type of diet seems to play a minor role in the phase of weight reduction. In contrast to previous recommendations, low-carb diets are not inferior compared to low-fat diets [209]. Physical activity (aim: ≥150 min/week) in addition to nutritional therapy leads to a higher loss of body fat, preservation or increase of muscle mass and improved muscle strength and CRF compared with dietetic energy restriction alone [210]. Like in non-

Table 6
Effectiveness of different weight reduction means.

Intervention	Effect ^a	Literature
Nutritional therapy, physical activity behavioral therapy as single interventions	1–2 kg or RWL ^b <5%	[1–4]
Nutritional therapy, physical activity behavioral therapy in combination over at least 6 month (“multidisciplinary therapy”)	4–5 kg or RWL 5–10%	[1–4]
Multidisciplinary therapy and initial usage of formula diet for 12 weeks	10–30 kg or RWL 15–26%	[5–7]
Bariatric surgery	20–50 kg or RWL 20–40%	[15,16]

^a Intention-to-treat basis.

^b RWL, relative weight loss.

obese individuals, physical activity should combine at least endurance and resistance exercise, but likely also include flexibility and balance exercises as recommended by expert societies (Table 7). Patients with BMI >35 kg/m² should preferentially perform activities avoiding high joint strain. Behavioral therapy is also mandatory for successful weight loss and should include regular self-assessments of food intake, physical activity and weight control ($\geq 1 \times$ /week) [162]. Both cognitive and motivational strategies should be considered.

Multidisciplinary conservative intervention programs that cover all these therapeutic strategies are presently the most effective conservative weight reduction means. They require surveillance by a physician and clinical evaluations on a regulatory basis [206]. Rapid weight reduction achieved by the use of formal diet is clearly beneficial as shown many years ago [211] and confirmed recently [212]. Poor sustainability and a high dropout rate are the two major limitations of presently available conservative weight reduction programs. Therefore, evidence-based ‘weight maintenance’ follow-up programs are obligatory to achieve sustainability [213]. If such well-evaluated programs performed for at least 6 month fail to reach the goals, bariatric surgery should be considered [214,215].

Table 7
Recommendations for physical activity, adapted from Ref. [231].

	Aerobic exercise	Resistance exercise	Flexibility	Neuromotor exercise ^a
Frequency	≥ 5 h/wk of moderate exercise or ≥ 3 h/wk of vigorous exercise or A combination of both	2–3 d/wk	$\geq 2-3$ d/wk	$\geq 2-3$ d/wk
Intensity	Moderate and/or vigorous intensity	To improve strength (100% = 1 RM ^b): - Novice: 60–70% - Experienced exercisers: $\geq 80\%$ - Older and previously inactive individuals: 40–50% To improve muscular endurance: < 50%	Stretching until feeling tightness	Not determined
Duration	150 min/wk with moderate intensity ^c or 75 min/wk with vigorous intensity ^c or an equivalent combination of both <20 min in previously inactive individuals	–	- Most adults: static stretch for 10–30 s - Older adults static stretch for 30–60 s 60 s of total stretching per exercise	$\geq 20-30$ min/d
Type	Involvement of the major muscle groups, continuous, rhythmic	Major muscle groups	Each major muscle-tendon unit	Exercises for training balance, coordination, agility and gait Not determined
Pattern	One session or multiple sessions with bouts of ≥ 10 min	To improve strength: 8–12 repetitions, 2–4 sets; To improve endurance: 15–20 repetitions, 1–2 sets, Rest between sets: 2–3 min	2–4 repetitions in warmed-up muscles	Not determined
Progression	Gradual increase of duration, frequency and/or intensity	Gradual increase of resistance and/or repetitions and/or frequency	Not determined	Not determined

^a Older individuals.

^b RM: one repetition maximum or maximum weight a person can lift in a single repetition.

^c Moderate intensity: 3–6 metabolic equivalents (examples: brisk walking, yoga, doubles tennis, golf); vigorous intensity: > 6 metabolic equivalents (examples: running, hiking uphill, cycling > 16 km/h, singles tennis).

Relevant criteria for a surgical intervention are summarized in Table 8. However, 2/3 of the afflicted patients have made their decision prior to any physician's consultation. Future obesity therapy should comprise an interdisciplinary ‘case management’ considering body weight, co-morbidities and patients history by the different experts.

6.2. Weight reduction by drugs

According to current guidelines, obesity drugs are indicated as adjuncts to lifestyle intervention in those patients with a BMI >27 kg/m² with comorbidity or BMI over 30 kg/m² [216]. Regarding efficacy and safety, drugs are deemed effective if they induce a weight loss $\geq 5\%$ of body weight without any significant side-effects after three months of treatment [216]. Historically, safety reasons have led to the withdrawal of many commercialized drugs due to CV and central nervous system side effects [217].

The mechanisms of action of the available medications used to lose weight consist of diminishing intestinal absorption (orlistat), decreasing appetite or increasing energy expenditure (the remaining drugs) [217].

In clinical trials obesity medications produce additional weight loss relative to placebo ranging from approximately 3% of initial weight for orlistat and lorcaserin, 3–5% for naltrexone/bupropion, 6% for liraglutide, to 9% for maximal dose (15/92 mg) phentermine/topiramate at one year (Table 9). The proportion of patients achieving >5% weight loss ranged from 37 to 47% for lorcaserin, 35–73% for orlistat, 48–50% for naltrexone/bupropion, 63% for liraglutide and 67–70% for top-dose phentermine/topiramate. All these drugs produce greater improvements in many cardiometabolic risk factors, but no obesity medication has been shown to reduce CV morbidity or mortality [218].

6.3. Drug avoidance to prevent obesity

Multiple medications can induce weight gain. In the evaluation of obese patients, health care professionals should inquire about

Table 8
Relevant criteria in favor or against bariatric surgery for obesity therapy.^a

Criteria in favor of bariatric surgery	Criteria against bariatric surgery
No or limited success of an adequate non-surgical therapy such as a validated multidisciplinary therapy program over 6–12 months based on realistic cut-offs (e.g. <15% relative weight loss or remaining BMI >40 kg/m ²)	An adequate non-surgical therapy such as a validated multidisciplinary therapy program over 6–12 months has not been performed yet
No sustained success of a adequate non-surgical therapy (e.g. return to initial body weight one year after completion of the weight loss program)	Adequate follow-up care cannot be guaranteed
An adequate non-surgical therapy program cannot be performed (e.g. because of immobility)	Severe eating disorder (validated by an psychologist), debility and other relevant restraints
Success of an adequate non-surgical therapy program cannot be expected (e.g. because of very high insulin requirements >300 IU/day)	Patient not motivated for a surgical intervention

^a Lower-ranking criteria for/against bariatric surgery are the initial BMI, the presence of co-morbidities, particular drug therapies, putative 'urgency' (e.g. prior to joint replacement surgery or cardiac surgery), and costs.

Table 9
Drugs currently approved for weight reduction.

Drug	Dosage	Mechanism of action	Efficacy ^a	Status	Side effects
Phentermine	30–37.5 mg/d	Norepinephrine-releasing agent	3.6 kg; 2–24 wk	Approved in 1960s for STU (3 mo)	Headache, elevated BP, elevated HR, insomnia, dry mouth, anxiety, constipation
Diethylpropion	75 mg/d	Norepinephrine-releasing agent	3 kg; 6–52 wk	FDA approved in 1960s for STU (3 mo)	Headache, elevated BP, elevated HR, insomnia, dry mouth, anxiety, constipation
Orlistat	120 mg TID	Pancreatic and gastric lipase inhibitor	2.9–3.4 kg, 2.9–3.4%; 1 y	FDA approved in 1999 for CWM, EMA approved in 1998	Decreased absorption of fat-soluble vitamins, steatorrhea, oily spotting, fecal incontinence, liver failure (rare)
Orlistat over-the-counter	60–120 mg TID	Pancreatic and gastric lipase inhibitor	2.9–3.4 kg, 2.9–3.4%; 1 y	FDA approved in 2007 for CWM	Malabsorption, fecal incontinence, liver failure (rare)
Lorcaserin	10 mg BID	5HT _{2c} receptor agonist	3.6 kg, 3.6%; 1 y	FDA approved in 2012 for CWM	Headache, nausea, dry mouth, dizziness, fatigue, constipation
Phentermine (P)/ Topiramate (T)	7.5–15 mg/d (P), 46–92 mg/d (T)	GABA receptor modulation (T) plus Norepinephrine-releasing agent	6.6–8.6 kg, 6.6–8.6%; 1 y	FDA approved in 2012 for CWM	Insomnia, dry mouth, dizziness, constipation, paresthesia, dysgeusia
Naltrexone (N)/ Bupropion (B)	32 mg/d (N), 360 mg/d (B)	Catecholamines reuptake inhibitor (B)opioid antagonist (N)	4.8%; 1 y	FDA approved in 2014 for CWM, EMA approved on 2015	Nausea, constipation, headache, vomiting, dizziness
Liraglutide	3.0 mg injectable	GLP-1 agonist	5.8 kg, 6%; 1 y	FDA approved in 2014 for CWM, EMA approved in 2015	Nausea, vomiting, pancreatitis

^a Weight loss above diet alone, mean weight loss in % or kg; duration of trials; Abbreviations: STU, short-term use; CWM, chronic weight management; BP, blood pressure; EMA, European Medicines Agency; FDA, Food and Drug Administration; HR, heart rate; BID: twice daily; TID: three times daily.

medications they may be receiving, obtained either over-the-counter or by prescription. When considering prescription of drugs known to be associated with weight gain, prescribers should balance its positive effects versus the risk of causing obesity [216,219–221].

It is important to be familiar with the potential mechanisms of drugs causing weight gain. This information will help to identify alternative medications that result in neutral or negative weight outcomes. In case there are no feasible alternatives, prescribers should anticipate the adverse effect of promoting obesity, recommend the lowest effective dose and emphasize lifestyle interventions that could prevent weight increase.

The main therapeutic groups that include drugs with potential risk of obesity are psychotropics, antihypertensives, antidiabetics, steroid hormones, protease inhibitors, and antihistamines (Table 10). The difference between drugs promoting weight increase and alternative drugs that are neutral or decrease weight, usually ranges from one to five kg of body weight after being administered for 3–6 months. Therefore, the consequences regarding the development of obesity are modest, but not neglectable.

Apart from drugs, there are other environmental chemicals that may influence body weight. After absorption, endocrine disruptors imitate the effect of hormones. These substances are found in pesticides (tributyltin, TBT), flame retardants (polybrominated diphenyl ether, PBDE), plasticizers (bisphenol A, BPA), non-stick coatings (perfluoroalkyl sulfonate and perfluorooctanoic acid, PFOA), and organochloride containing compounds (dichlorodiphenyltrichloroethane, DDT). This is a relatively new research

area and further investigation is needed for understanding their role in the current increase in the prevalence of obesity.

6.4. Weight reduction by surgical intervention

Due to its well documented effects in terms of not only sustained weight loss, but also on obesity-associated morbidity and mortality over time, bariatric surgery is today an established and integral part of treating morbid obesity. The estimated number of bariatric surgical procedures performed worldwide increased from 146,000 to 340,000 between 2003 and 2011, the most frequent techniques being Roux-en Y gastric bypass and sleeve gastrectomy which together constitute approximately 75% of all procedures performed [222].

Indications for surgery might vary between and within countries. In most recommendations and guidelines indications for surgery include a BMI >40 kg/m², or >35 kg/m² in the presence of obesity-associated comorbidities expected to improve after weight loss, provided that appropriate non-surgical therapy did not reach the goals. Moreover, expected compliance with postoperative dietary instructions and medical follow-up should be required. Most important contraindications include medical conditions that make the expected benefits unlikely to outweigh the risks associated with the procedure, alcohol or drug abuse/dependence and unstable psychiatric disorders including severe eating disorders.

While unsatisfactory weight loss and/or weight regain over time is seen in a limited number of patients after bariatric surgery, a

Table 10
Medications associated with weight gain and alternative drugs.

Therapeutic group	Drugs promoting weight gain	Alternative Drugs	Comments
Antidepressants	Paroxetine Mirtazapine Amitriptyline Escitalopram Lithium	Fluoxetine Sertraline Citalopram Escitalopram Bupropion Venlafaxine	Fluoxetine and Bupropion more consistently cause weight loss
Antipsychotics	Olanzapine Quetiapine Risperidone Perphenazine	Ziprasidone Aripiprazole Haloperidol	Alternative drugs produce less weight gain
Antihypertensives	β -blockers w/o a vasodilating component (Atenolol, Metoprolol, Propranolol)	ACE inhibitors ARB blockers Calcium channel blockers	
Antidiabetics	Sulfonylureas Glitinides Thiazolidinediones Insulin	Metformin GLP 1 agonists Pramlintide DPP-4 inhibitors SGLT-2 inhibitors α -glucosidase inhibitors	Weight sparing diabetes medications do not cause hypoglycemia and do not need adjustment for physical exercise. They can be preferred for T2DM patients requiring insulin Basal Insulin is associated to less weight gain than prandial ultrarapid or biphasic insulin
Steroid hormones	Prednisone Prednisolone	Nonsteroidal anti-inflammatory drugs	
Contraceptive Drugs	Oral contraceptives	Injectable contraceptives	Conflicting results. Limited evidence of weight gain when using progestin-only contraceptives.
Antiepileptic Drugs	Valproic acid Gabapentin Carbamazepine	1) Felbamate Topiramate Zonisamide 2) Lamotrigine Levetiracetam Phenytoin	Alternative drugs may cause weight loss (1) or weight neutral (2)
Antiretroviral Drugs	Protease Inhibitors		Frequent weight gain, increased deposition of visceral adipose tissue and lipodystrophy

Abbreviations: ACE, angiotensin-converting enzyme; ARB: angiotensin receptor blockers; DPP-4, Dipeptidyl peptidase IV; GLP-1, glucagon-like peptide-1; SGLT, sodium-glucose-linked transporter.

sustained weight loss in the range of 20–30% of total body weight in usually reported in most series [215]. For many patients, loss of weight per se might be the most important expected result following bariatric surgery. However, from a health perspective the beneficial effects on comorbidities such as T2DM, CV disease and kidney function are considered as more relevant. Meta analyses as well as RCT's demonstrate that in patients with T2DM, bariatric surgery is superior compared to conventional medical treatment in terms of weight loss, improvement of HbA1c and fasting plasma glucose as well as diabetes remission [223,224]. The precise mechanisms by which bariatric surgery improves or “cures” T2DM are not fully defined. Although recurrence of T2DM is seen in up to 40% of patients in long-term follow up, glucose control is still improved and risk of macrovascular complications reduced compared to medical treated controls [225,226].

In studies with long-term follow up, such as the Swedish SOS study [215], bariatric surgery was associated with a reduced CV mortality and morbidity by about 50% over time compared to controls matched for initial BMI and age. Cardiac function was also improved up to 3 years after surgery [227]. Bariatric surgery might also improve kidney damage as well as kidney function in patients with CKD. Mingrone et al. showed in a prospective study that kidney function as measured by GFR was preserved in comparison to the progressive deterioration in both kidney damage and kidney function in a matched cohort of obese patients receiving best medical care without surgery [228]. After bariatric surgery, QoL scores at one year are improved for physical as well as mental domains, with effects lasting up to ten years postoperatively in both males and females [229]. The improvement has been reported to be related to degree of weight loss and might differ between various surgical techniques [229].

It should be acknowledged that although bariatric surgery results in long-lasting beneficial effects on obesity and comorbidities, it represents a major abdominal surgical procedure with risk of

serious complications such as anastomotic leaks, bleeding, thromboembolism, and infection. Although morbidity and mortality rates are usually low, patient selection as well as preoperative medical assessment is crucial in order to further improve results after bariatric surgery. In particular, to identify the patients that are likely to benefit the most from surgery constitutes an important challenge in the future. A multidisciplinary team should collaborate in the pre-as well as postoperative setting with emphasis on information and medical assessment. Risk factors for poor postoperative outcome such as undetected hypertension, cardiac disease, sub-optimal glucose control or sleep apnea should be identified and controlled/optimized prior to surgery. Bariatric surgical patients should be submitted to life-long follow up programs in order to enable detection of complications such as macro- or micronutrient deficiencies or unsatisfactory weight loss. Ultimately, the outcome after bariatric surgery in terms of sustained weight loss and the resolution of comorbidities is dependent on the patient's strict adherence to a life-long follow up program.

7. Outlook

7.1. Rationale and aims of the ESPEN approach to manage obesity

This paper shows the widespread implications of obesity affecting almost all medical disciplines. The WHO has recognized that obesity is the largest global chronic health problem in adults. Consequently, there is strong interest in studying the myriad of aspects related to obesity, with basic researchers and practitioners of all sorts and allied health care professions integrated in scientific and clinical societies such as ESPEN devoted to this metabolic disease.

The role of nutrition in the management of obesity should be emphasized, beyond design and prescription of low-calorie dietary treatment. This includes nutritional strategies to maintain body

Table 11
Internationally reputed societies for the study of obesity.

Association	Web address	Based in	Guidelines and other resources
World Obesity (Formerly IASO, International Association for the Study of Obesity)	http://www.worldobesity.org/	United Kingdom	http://www.worldobesity.org/resources/
The European Association for the Study of Obesity	http://easo.org/	United Kingdom	http://easo.org/education-portal/guidelines/
International Federation for the Surgery of Obesity (IFSO)	http://www.ifso.com/	Italy	http://www.ifso.com/wp-content/themes/ypo-theme/pdfs/obesity-bariatric-and-metabolic-surgery.pdf
The Obese Society	http://www.obesity.org/home	USA	http://www.obesity.org/publications/position-and-policies
Obesity Medical Association (Formerly ASBP, American Society of Bariatric Physicians)	http://obesitymedicine.org/	USA	http://obesitymedicine.org/obesity-algorithm/
Canadian Obesity Network	http://www.obesitynetwork.ca/	Canada	http://www.obesitynetwork.ca/resources-pro

composition and muscle mass and to manage selected deficiencies. In addition, nutritional care represents an important tool to optimize outcome by modulating metabolism and function in many obesity-associated health conditions, thereby becoming an important means to foster multidisciplinary in this field.

7.2. Collaboration between ESPEN and other societies and initiatives

There are numerous European and international associations dedicated to the study and management of obesity from different perspectives. Three examples will be presented in brief. “World Obesity” is a federation of national obesity associations from over 50 countries around the world, the strength of which lies in uniting and connecting professionals through international congress events and the SCOPE online obesity education facility. The “European Association for the Study of Obesity” (EASO) is a membership association comprising 31 national association members, which represent more than 4000 individuals across Europe. The “International Federation for the Surgery of Obesity and Metabolic Disorders” (IFSO), formed in 1995, is a federation composed of 58 national associations of bariatric surgeons. These and other societies listed in Table 11 have produced an impressive amount of resources available to professionals and patients that describe the state of the art of the evaluation and treatment of obesity. Recommendations endorsed by these societies are consistent with those included in this position paper. ESPEN aims to collaborate with these institutions and to extend the spectrum of scientific societies engaged in obesity by adding an international society primarily engaged in interdisciplinary nutrition and nutritional medicine.

Conflict of interest

None.

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