Learning Objectives

- To understand the principles of interdisciplinary obesity therapy;
- To know the various nutritional and behavioural interventions needed for obesity therapy in adults;
- To know about the multimodal approach to treat obesity;
- To know about the benefits and risks of formula diets for obesity therapy;
- To be familiar with post-intervention follow-up and weight maintenance strategies;
- To know about costs and reimbursement of obesity therapy.

Contents

1. Introduction: challenges in obesity therapy in adults
   1.1 Definition of obesity
   1.2 Clinical presentation
   1.3 Therapeutic principles
   1.4 Indication for specific obesity therapy
   1.5 Therapy targets and endpoints
2. Non-surgical lifestyle therapy (nutrition, exercise, behaviour)
   2.1 Nutrition
   2.2 Formula diets
   2.3 Exercise
   2.4 Motivation and behavioural therapy
3. Drugs supporting or obstructive to therapy of obesity
   3.1 Drugs for obesity therapy
   3.2 Drugs that promote weight gain
4. The multimodal approach: outcome, costs and responsibilities
   4.1 Effectiveness of multimodal weight reduction programmes
   4.2 Costs of multimodal weight reduction programmes
5. Interface with bariatric surgery
6. Weight maintenance strategies
7. Summary
8. References
Key Messages

- Primary obesity therapy should be with a non-surgical approach, but bariatric surgery may be needed if the problem cannot otherwise be solved;
- Non-surgical obesity therapy comprises nutrition, exercise and behavioural therapy ("basic therapy") with or without formula diet;
- Formula diet as initial therapy (up to 12 weeks) is indicated if more than 10 kg body weight reduction is intended;
- Successful and sustained obesity therapy needs a clear structure, a well-trained team of professionals, and coverage of costs;
- Every successful weight reduction requires a subsequent weight maintenance strategy.
1. Introduction: Challenges in Obesity Therapy in Adults

Obesity and related co-morbidities have become the most relevant diet-induced diseases. The WHO reports that, worldwide, obesity has nearly tripled since 1975.

1.1 Definition of Obesity

Obesity is defined as a pathologically increased fat mass, which is associated with an increased health risk. Obesity is not defined by a body mass index above the normal range. However, as the fat mass is not easily measurable and there is no consensus regarding normal levels of body fat mass, the above definition of obesity is not easy to use in everyday life. Therefore classifications of overweight and obesity exist. The most common is the classification according to the "Body Mass Index" (BMI). Overweight is defined as BMI 25-29.9 kg/m², obesity as BMI ≥ 30 kg/m² (Table 1). The BMI is a practical tool for the rapid, age-, size- and gender-independent estimation of the nutritional status.

A BMI ≥ 30 kg/m² does not necessarily mean that obesity is present. A significant increase in muscle mass, as observed in the bodybuilder, or a significant increase in body water, e.g. oedema associated with heart or kidney failure or ascites in hepatic insufficiency, may result in increased BMI. Based on the BMI, obesity is divided into three levels (Table 1).

A simple measure for the assessment of the visceral fat depot is the measurement of the waist circumference (WCF), which is made more difficult in the obese by the fact that no waist is recognizable. If the WCF is ≥ 88 cm in women and ≥ 102 cm in men, abdominal obesity is present (1). The measurement of WCF in the overweight, and possibly also grade I obesity, allows a better estimation of metabolic risk than BMI alone, whereas at higher obesity waist circumference and metabolic risk are almost always elevated (2). Therefore it is recommended to measure and document the BUF at BMI 25-35 kg/m² in addition to the BMI.

Table 1
Classification of overweight and obesity

<table>
<thead>
<tr>
<th>Category</th>
<th>BMI [kg/m²]</th>
<th>Risk for associated diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
<td>low</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5 – 24.9</td>
<td>low</td>
</tr>
<tr>
<td>Overweight</td>
<td>25 – 29.9</td>
<td>slightly elevated</td>
</tr>
<tr>
<td>Obesity grade I</td>
<td>30 – 34.9</td>
<td>elevated</td>
</tr>
<tr>
<td>Obesity grade II</td>
<td>35 – 39.9</td>
<td>high</td>
</tr>
<tr>
<td>Obesity grade III</td>
<td>≥ 40</td>
<td>very high</td>
</tr>
</tbody>
</table>

1.2 Clinical Presentation

Obesity is a chronic, systemic disease that requires a multidisciplinary treatment approach at both the diagnostic and the therapeutic level (3). It is rarely spontaneously reversible and is associated with increased morbidity, mortality, and reduced quality of life (4, 5).

Obese people have a higher prevalence of co-morbid mental disorders than normal-weight people. Baumeister and Harder, for example, found in their study of large samples of...
normal-weight, and people that adipose people have a much higher prevalence of mental disorders than normal-weight individuals (obese OR 2.0 and overweight OR 1.4, respectively), with depressive disorders the most common ones (6).

### 1.3 Therapeutic Principles

Treatment of obesity with its multifactorial origin needs an interdisciplinary and multimodal approach. This starts with a careful assessment of the individual patient’s history. To treat the patient appropriately and to evaluate the treatment options correctly, a phase-dependent therapy is needed (Fig. 1). Usually, this needs an interdisciplinary approach according to a “case management” (see chapter 5). For primary prevention see module Module 23.2. The present module focuses on (weight reduction) therapy and weight maintenance.

![Fig. 1. Phase-dependent therapy](image)

This means that the indication for therapy is BMI-dependent and the type of therapy varies depending on the phase of disease. If the goal is primary prevention or secondary prevention (weight maintenance) healthy food according to individual requirements, behavioural training and lifestyle modification is need. If the goal is obesity therapy in a narrower sense (weight reduction), a negative energy balance is needed.

The therapeutic principles differ significantly in the weight reduction and the weight maintenance phases. In the weight reduction phase negative energy balance is in the foreground; in the weight maintenance phase balanced energy balance and the nutritional composition predominate. Therefore, no nutritional concepts are to be expected which are suitable for successful weight loss as well as for long-term weight stabilization. But in the past exactly this was expected of many nutritional concepts in obesity therapy. Current recommendations for weight loss therapy largely follow the recommendations in selected major national and international guidelines:

1. The US guideline “Management of Overweight and Obesity in Adults” (AHA/ACC/TOS Guideline 2013) (7);
2. The UK guideline “Obesity: identification, assessment and management” (NICE 2014) (8);
3. The Scottish guideline “Management of Obesity” (SIGN 2010) (9);
4. The German guideline “Interdisciplinary guideline of quality S3 for Prevention and treatment of obesity” (DAG/DDG/DGE/DGEM 2015) (10) and comments or extensions (11-13).

1.4 Indication for Specific Obesity Therapy

The indication for the treatment of obesity and obesity is based on BMI and body fat distribution, taking into account co-morbidities, risk factors and patient preferences. According to the guidelines, the indications for the treatment of obese and obese people, are if the following criteria are met:

1. a BMI ≥ 30 kg/m² or
2. Overweight with a BMI between 25 and <30 kg/m² and simultaneous presence of
   – related health disorders (e.g. hypertension, T2DM) or
   – abdominal obesity or
   – diseases that are aggravated by obesity or
   – a high level of psychosocial distress.

Alternatively, one could say that the presence of the metabolic syndrome (MetS) justifies treatment already at BMI > 25 kg/m², whereas individuals without MetS should go for obesity treatment only at BMI > 30 kg/m².

This guideline-oriented indication for obesity therapy, which is predominantly based on BMI, can be questioned on the basis of recent findings on the pathophysiology and the risk factors for obesity. Depending on the age of the person, a BMI of 25-30 kg/m² ("overweight") may not be a risk factor, and is even associated with a better probability of survival among those over 60 years of age than those with a BMI <25 kg/m² (14).

Perhaps even more important here is the concept of the "healthy obese", who – despite a BMI > 30 kg/m² – has no cardiometabolic risks such as ectopic fat deposition in internal organs (liver, heart, muscle, kidneys), insulin resistance or increased inflammatory parameters (15). BMI and waist circumference are therefore not the only risk variables that have to be assessed according to age. Based on these considerations, the indication for therapy could be adapted to age and to individual risk.

1.5 Therapy Targets and Endpoints

The goal of obesity therapy is to reduce the body weight in the long term in combination with a change in behaviour, which aims to improve obesity-associated risk factors, reduce obesity-related illnesses, reduce the risk of premature mortality, incapacitation and early retirement, and improve quality of life. Choice of the most suitable endpoints of obesity therapy remains controversial. Lowering body weight is certainly not the only conceivable endpoint. The choice of endpoint determines the length of time after which a therapy can be assessed, and/or the design of clinical studies on obesity therapy. The choice of the endpoint also determines the effort that must be made to measure target sizes. Body weight can be reliably measured without great effort and therefore continues to be a global target parameter that correlates with many comorbidities (16).
2. Non-surgical Lifestyle Therapy (Nutrition, Exercise, Behaviour)

2.1 Nutrition

All weight management should be based on a "basic programme" that includes the components of nutrition, exercise and behavioural therapy. Depending on the individual situation, these components should primarily be used in combination and possibly also as individual components.

Eating habits and eating habits are subject to years of experience and it requires a high degree of responsibility and sensitivity when engaging in their restructuring. All changes must be carefully communicated and practiced and be practicable in the long term. As a result, a lifestyle change should result in sustained weight loss. With all sorts of crash diets, one-sided diets and total fasting, only short-term successes can usually be achieved. The long-term efficacy and safety of such measures has rarely been scientifically documented, which is why they cannot be recommended for weight reduction.

Patients with obesity and obesity should routinely be advised on ways to lose weight. For that, it is necessary to compare the patient's expectations regarding weight loss with the expected results. The patient's expectations regarding weight loss are usually twice as high as the expected result (17). In addition, in the therapy planning, it must be discussed which contributions the patient is willing and able to consider. These contributions include motivation as well as time and financial participation. The latter is necessary because health insurance often grants conservative therapy measures at best a financial subsidy, and not the full reimbursement of costs.

The nutritional history should be taken at the beginning of each nutritional therapy as well as in its course by a state-certified dietician (or nutritionist) or a qualified doctor. A structured anamnesis sheet can be used for the initial consultation. It allows a quick and effective capturing of relevant data about the patient and his life situation. The nutritional history should include eating behaviour and physical activity as well as special circumstances. Only by taking a comprehensive medical history can the nutritionist respond to the individual needs of the patient. During the course of treatment, target agreements on food selection, eating behaviour as well as physical activity should be regularly queried and checked for success. Weight history as an indicator of successful intervention should also be collected and documented regularly.

Weight reduction can only be achieved by negative energy balance. By reducing the energy intake by 500-1000 kcal per day with constant movement, a weight reduction of 0.5-1.0 kg body weight per week (or 2-4 kg per month) is realistic. The negative energy balance should be at least 500 kcal/d, otherwise a change in weight will initially be completely absent due to weight-retaining regulatory mechanisms. A nutritionally balanced diet, which ensures the supply of protein and micronutrients on demand, should be ensured. This is possible using commercially available foods, provided the energy intake does not fall below 1200 kcal. This means that the energy-yielding dietary substrates (fat and/or carbohydrates) need to be reduced instead of a global reduction of all nutrients. The choice of nutritional therapy depends on the degree of overweight. In pre-obesity (BMI 25-<30 kg/m²) with concomitant diseases, a permanent weight reduction of 5-10% is desirable. There are many ways of doing this, including reducing fat intake or carbohydrate intake, or energy-reduced mixed foods.
The frequently asked question of whether a predominant "low-fat diet" or "low-carb diet" should be preferred is overrated, since studies show that both strategies can be effective (18). Certainly, fat reduction in food is not the only valid strategy, as was sometimes assumed in the past (19). Individual studies even suggest that "low carb" is more effective than "low fat" in terms of weight loss, reduction of insulin resistance and quality of life improvement (20-22). This may be due to activation of the central reward system and starvation-inducing effects of sugar. The "low-carb" or "low-fat" principle should be linked to a "high protein" strategy, because protein will satisfy hunger. In contrast, sugars (mono- and disaccharides), sugar alcohols and alcohol can induce hunger, and thus need to be particularly avoided. The advantage of a "high protein diet" for the treatment of obesity or for the prevention of secondary diseases has been repeatedly demonstrated (23, 24). The underlying mechanisms are not fully understood.

- For grade I obesity (BMI 30- <35 kg / m²) the same recommendations apply as for patients with pre-obesity and comorbidities. The same therapeutic approaches can be used. In addition, the use of a formula diet for initial weight reduction may be recommended for patients with a BMI> 30 kg / m² or more.
- For obesity grade II + III (> 35 kg / m²), a permanent weight reduction of 10-20% should be the goal; from a BMI> 40 kg / m² 10% to even 30%. There are only two ways to achieve this long-term weight loss: either multimodal conservative therapy (weight reduction programmes), or bariatric surgery.
- The implementation of such dietary recommendations requires the accompanying skills of an experienced dietician.

2.2 Formula Diets

Formula diets are dietary foods for special medical purposes such as obesity treatment. They are industrially produced nutrients on a milk protein or soy protein base and serve for complete or partial replacement of meals. When meals are completely replaced, a daily ration should contain at least 800 kcal and be fully balanced. Since not all products available on the market are fully balanced, the selection must be thorough. Occasionally, a distinction is made between "very low calorie" (VLCD, <800 kcal / day) and "low-calorie diet" or "low-energy liquid-formula" (LCD or LELD, 800-1000 kcal / day).

Weight loss formula diets are successfully used for the “Modified Fasting” during the initial phase of therapy (25-27). The supply of all nutrients and micronutrients must be ensured despite low energy input (800-1000 kcal/d). This form of nutritional therapy should be accompanied by medical assistance and can be taken exclusively over a period of max. 12 weeks. A sufficient fluid intake of at least 2-3 litres per day is essential during this "fasting phase". Following this, a gradual reduction of the product must be made, with a simultaneous change in eating habits and the goal of a mixed diet that is energy-limited according to individual needs. Ideally, this approach will be part of a multimodal weight reduction programme, with formula-weighted programmes able to achieve a relative weight loss (RWL) of 15-25% and an excess weight loss (EWL) of 40-50% (27, 28). This approach is clearly superior to weight reduction programmes without formula diet that usually achieve less than 10% RWL and less than 30% EWL. This approach is, however, inferior to bariatric surgery in terms of weight loss since surgery usually achieves a RWL of 20-40% and an EWL of 50-60% (29).
Formula diets should not be used on their own, as possible dietary mistakes can have serious consequences. Self-administered formula diets usually do not have long-lasting success, as the learning effect is missing and there is no change in eating habits. Therefore, the so-called "yo-yo effect" usually occurs very quickly when the integration of the formula diets into a behavioural weight-loss programme is missing.

Meal replacement with formula products (30). For meal replacement, 1-2 meals are replaced with formula for a period of several weeks. The remaining meals should correspond to a healthy energy-reduced mixed diet. This method can lead to faster and stronger weight loss in the beginning compared to a normal energy-reduced mixed diet, which has a positive impact on patient compliance. The meal replacement can also be designed alternately from day to day. In a recent Systematic Review, which considered 28 studies, it was shown that "every other day fasting" is almost as effective as "modified fasting" (modified fasting: only 0.88 kg more weight loss than every other day fasting, 95% CI: -4.32, 2.56) (31). For individuals, "every second-day fasting" may be easier to perform and may lead to better compliance, as far as one can draw such conclusions from studies that have not directly compared the two procedures.

2.3 Exercise

An increase in muscular energy expenditure is a central pillar of obesity therapy. Meta-analyses clearly showed that combining dietary intervention with adequate physical activity is more effective than only reducing energy intake through diet (32). Movement-based therapy concepts also have the goal of improving the metabolic and cardiovascular risk profile, favourably influencing possible comorbidities and increasing physical fitness. Ultimately, a return to higher physical functionality and mobility is to be achieved and, in particular, the health-related and psychosocial quality of life to be improved. Accordingly, increased physical activity is recommended in the guidelines with high level evidence and, when combined with energy-reduced diets, is considered to be the optimal strategy to achieve weight reduction through a lifestyle change. Moreover, regular physical activity is the best one can do to avoid regain of body weight after successful weight loss, because of increased energy consumption through exercise and increased energy expenditure resulting from increased muscle mass (33). The following principles should be considered:

- To achieve weight reduction by means of exercise therapy, requires extensive endurance exercise of about 4 hours per week or an increase in energy consumption by about 2000 kcal / week. Only a few will succeed. If achieved, it is a sustainable action.
- Physical activity may be measured in practice by accelerometers, questionnaires (Baecke, IPAQ) or activity diaries (MET conversion); such measurements may be activity enhancing.
- Before starting physical training, the exercise capacity should be examined by means of exercise ECG, lactate diagnostics and / or spiroergometry.

The basis of a personalized training plan and consultation tailored to the patient is the information and findings collected during the diagnosis. A clear objective of the training should be formulated, which essentially results from the severity of the overweight, the risk profile, and the comorbidities as well as physical capacity and efficiency. Other important aspects of the training and activity design are the previous sports experience, the current activity, sporting tendencies and the situation in everyday life.
2.4 Motivation and Behavioural Therapy

One way of motivating those with obesity to diet and physical activity could be to combine it with cognitive-behavioural procedures. Herpertz (34) points out that many obese patients have very high expectations of weight loss because they are more interested in looking more attractive and less so in the health benefits often associated with weight loss of 5-10%. The frustration of not achieving one's goals leads to the termination of weight reduction projects. Herpertz calls for weight loss intervention programmes against this background:

- The identification and modification of unrealistic ideas about body weight after treatment
- The treatment of dissatisfaction with one's own body image
- The naming of other important treatment goals (self-confidence, partnership, physical well-being and fitness, etc.)
- The appreciation of what has been achieved so far and the acceptance of the non-changeable (eg body proportions)

Behavioural therapy aimed at modifying diet, exercise and lifestyle is a central element of obesity therapy. Methods that aim at sustainable behaviour modification, both for weight loss and subsequent weight stabilization, are used. The effectiveness of behavioural interventions alone, but especially in combination with nutritional therapy and physical activity, has meanwhile been systematically studied and widely documented. It shows that more intensive behavioural programs also lead to greater weight loss. Whether group or individual behavioural interventions are expedient should be decided on an individual basis. Resilient data on the preference of the intervention are currently not available.

3. Drugs Supporting or Obstructive to Therapy of Obesity

3.1 Drugs for Obesity Therapy

In most international guidelines, drugs are considered as a possible adjunctive measure to obesity therapy in patients with a BMI above 27 kg/m² and co-morbidities, or at a BMI above 30 kg/m² (35). Mechanisms of action include decreased intestinal absorption of food substrates (e.g., orlistat), decreased appetite (e.g., rimonabant, liraglutide, semaglutide), or increase in energy expenditure (e.g., sibutramine).

In some countries, a drug for weight loss in patients with BMI >28 kg/m² has been approved for years: this is orlistat, whose effectiveness has been proven. However, the effectiveness is rather low, at 2.9 kg after one year at a dose of 3 x 120 mg per day (36). Orlistat inhibits lipases in the gastrointestinal area, thereby reducing the absorption of fats. Common side effects are therefore GI complaints such as diarrhoea, steatorrhoea and flatulence. This could contribute to the substance's effectiveness because sufferers can avoid such symptoms by significantly reducing fat intake. Some patients develop a deficiency of fat-soluble vitamins and vitamin levels should be monitored during orlistat therapy.

Other weight loss drugs such as sibutramine or rimonabant, which were significantly more effective than orlistat, were withdrawn from the market because of side effects such as cardiovascular side effects or increased suicide rates (which, however, are also observed
after bariatric surgery). Therefore, drug therapy within the weight reduction phase currently plays little role. In the weight stabilization phase, medication could play a more important role, but there is a lack of robust studies that would justify such recommendations.

Recently, three other drugs have been approved in the EU for the treatment of obesity, the GLP-1 analogues liraglutide 3 mg and semaglutide 0.5 mg, and the combination drug naltrexone / bupropion. Unlike in the USA, the drugs lorcaserin and phenteramine / topiramate have not been approved in the EU.

Liraglutide 3 mg can be used not only in diabetics, but also in overweight adults without diabetes - as a supportive measure for losing weight, but only in combination with a calorie-reduced diet and more exercise. The approval is based on four studies with 5358 patients. Those who lost at least 5% of their starting weight after twelve weeks lost an average of 11.2% after one year of treatment. A study showed that this drug can actually be effective in supporting weight stabilization after successful weight loss (37). The most common side effects include gastrointestinal symptoms such as nausea, vomiting, diarrhea, and constipation. Liraglutide must be administered parenterally once a day as a subcutaneous injection. The starting dose is 0.6 mg per day and increased by 0.6 mg every 3 weeks to 3.0 mg. The formulation as a 6 mg/ml solution for injection in a pre-filled pen is identical to that approved for diabetics. If the patient has not lost at least 5 percent of the original body weight after 3 weeks of 3 mg per day, treatment should be discontinued. The treatment effect has so far only been documented for one year. Following the approval of liraglutide for obesity treatment in March 2015, further studies have appeared. In a large study of 3731 patients with obesity (mean BMI 38.3 ± 6.4 kg / m²) without T2DM, after 56 weeks of treatment with liraglutide, 3 mg/d s.c. there was an additional weight reduction of 5.6 kg compared to the controls (95% confidence interval: -6.0 to -5.1; p <0.001) (38). In those allocated liraglutide + lifestyle intervention a mean weight reduction of 8.4 ± 7.3 kg was achieved, compared to 2.8 ± 6.5 kg in the control group (lifestyle-intervention only). Weight reduction of at least 10% was achieved by 33.1% in the verum group and 10.6% in the control group.

Semaglutide is a successor of liraglutide and has been approved in the EU since 2017 for T2DM, but is also suitable for obesity. It is a long-acting GLP-1 analogue. The effects include the promotion of insulin secretion and the inhibition of glucagon secretion. It is injected subcutaneously only once a week, which is a clear advantage over liraglutide. In a recent multicentre trial involving 8 countries and 957 participants with a BMI> 30 kg/m², semaglutide was tested at doses 0.05-0.4 mg against placebo and liraglutide 3.0 mg. Estimated mean RWL was -2.3% for the placebo group versus -6-0% (0-05 mg), -8-6% (0-1 mg), -11-6% (0-2 mg), -11-2% (0-3 mg), and -13-8% (0-4 mg) for the semaglutide groups. Results for all semaglutide groups were significant compared to placebo (unadjusted p≤0.0010), and remained significant after adjustment for multiple testing (p≤0.0055). Mean bodyweight reductions for 0.2 mg or more of semaglutide versus liraglutide were all significant (-13-8% to -11-2% vs -7-8%). Estimated weight loss of 10% or more occurred in 10% of participants receiving placebo compared with 37-65% receiving 0.1 mg or more of semaglutide (p<0-0001 vs placebo). The most common adverse events were dose-related gastrointestinal symptoms, primarily nausea, as seen previously with GLP-1 receptor agonists (39).

The indication for the combination preparation naltrexone / bupropion is identical to that for orlistat and liraglutide. In a first controlled trial, an additional weight reduction of 4.6
kg compared to placebo was achieved (40). The most common side effect was mild nausea. In a larger follow-up study of 1742 patients with obesity (BMI 27-45 kg/m²) of the same study group, these findings could essentially be confirmed. After 56 weeks in the verum group I (Naltrexone SR 32 mg/d + Bupropion SR 360 mg/d) there was a weight reduction of 6.1% ± 0.3%, the verum group II (Naltrexone SR 16 mg/d + Bupropion SR 360 mg/d) achieved a weight reduction of 5.0% ± 0.3%, compared to 1.3% ± 0.3% in the control group (41). Treatment of obesity with naltrexone / bupropion improves quality of life, but it has not yet been demonstrated that clinical outcomes such as cardiovascular events can be reduced.

In summary, it can be stated that there are approved medications that can supportively improve weight loss. The effects, however, are moderate, ranging from about 3% additional relative weight loss (RWL) by orlistat and lorcaserin to 5-6% for naltrexone / bupropion, liraglutide and semaglutide.

3.2 Drugs that Promote Weight Gain

Many medications cause or support weight gain. Therefore, it is essential to perform a meticulous medical history for each obese person, to identify potential weight-increasing medications, and then to examine in dialogue with the relevant specialist colleague whether alternative drugs are possible that have less adipogenic effects. Also in the prevention of obesity such considerations for drug selection play a role. Before prescribing a drug that is known to be associated with weight gain, the pros and cons of this drug should be carefully considered (42, 43).

The most important drugs associated with obesity risk come from groups of psychotropic drugs, antihypertensive drugs, diabetes therapeutics, corticosteroids, protease inhibitors and antihistamines. Switching to alternative medicines is relevant because the difference in weight gain ranges from 1-5 kg after 3-6 months. Individual medications such as corticosteroids or psychotropic drugs may even have stronger effects.

In addition to medicines, there are environmental chemicals that can also cause weight gain. These so-called "endocrine disruptors" are taken up by the diet and imitate hormonal effects. They are found in pesticides (tributyltin, TBT), fire retardants (polybrominated diphenyl ether, PBDE), plasticisers (bisphenol A, BPA), non-stick coatings (perfluoroalkylsulfonate and perfluorooctanoic acid, PFOA) and organochlorine compounds (dichlorodiphenyltrichloroethane, DDT). It is not excluded that such chemicals have contributed to the increase in obesity in recent decades (44).

4. The Multimodal Approach: Outcome, Costs and Responsibilities

4.1 Effectiveness of Multimodal Weight Reduction Programmes

The individual measures described so far (nutrition, exercise, behavioural and pharmacotherapy) show effectiveness in the treatment of obesity with regard to weight reduction and reduction of cardiometabolic risk factors, in part also with regard to morbidity of secondary diseases and mortality. However, the effects are moderate and usually far below the expectations of those affected. The effectiveness can be substantially
enhanced by combining the measures into a "multimodal weight reduction programme" consisting of the so-called basic programme, which includes nutritional therapy, behavioural therapy and exercise therapy, and which can be extended by various elements such as formula diet, drug therapy or relaxation therapy (Table 2). The effectiveness of the programme is also determined by the duration of the programme (e.g. 3, 6 or 12 months), the number and length of contacts, and the qualifications of the personnel and equipment. The “multimodal weight reduction programme” is ideally implemented by a team with a physician, a dietician or a nutritionist, an exercise therapist, and a psychologist.

**Table 2**
**Effectiveness of different weight reduction measures**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Effect¹</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition, exercise and behavioural therapy as individual measures</td>
<td>1-2 kg</td>
<td>(10) and references herein</td>
</tr>
<tr>
<td>Multimodal therapy with nutritional, exercise and beha-viourial therapy in combination for at least six months (&quot;basic therapy&quot;)</td>
<td>4-5 kg</td>
<td>(10) and references herein</td>
</tr>
<tr>
<td>Multimodal therapy for at least six months combined with initial formula diet for max. 12 weeks</td>
<td>10-30 kg</td>
<td>(28)</td>
</tr>
<tr>
<td>Bariatric surgery</td>
<td>20-50 kg</td>
<td>(29)</td>
</tr>
</tbody>
</table>

¹Intention-to-treat basis; ²RWL, relative weight loss

The multimodal weight reduction programmes are predominantly carried out on an outpatient basis. Inpatient treatment can be at most an initial measure, as effective and sustainable multimodal weight reduction programmes must be carried out for 6 to 12 months. Such programmes are offered either GP-based or centre-based. In a GP-based programme, the physician is usually the coordinator who works with staff from other professions (for example, nutrition and exercise therapists, possibly also behavioural therapists). In the centre-based programme, treatment takes place in a centre that is either part of a hospital, connected to a hospital, or university-associated. Again, the programme is usually led by a physician, sometimes by a psychologist or a dietician/nutritionist and supported by a team of other professionals. Institutions offering such multimodal therapy should meet certain quality criteria.

Among the conservative options for obesity therapy, the multimodal weight reduction programmes are considered "gold standard" because they are much more effective than individual measures. The best results can be achieved with multimodal weight reduction programmes using formula diet in the initial phase. In a prospective, multicentre study of 8,296 obese patients (BMI 40.8 ± 7.2 kg/m²), multimodal therapy was evaluated for weight loss at 6 and 12 months and in a subgroup for 3 years. Body weight was reduced by an average of 19.6 kg in women and by 26.0 kg in men after PPI analysis, corresponding to a relative weight loss (RWL) of 18% and an excess weight loss (EWL) of 46% in the total collective (28). According to ITT analysis, the RWL was 16% and the EWL 36%. Of the 8,296 initial participants, 4,850 completed the programme. This corresponds to a compliance of approx. 60%. The weight loss benefits of this programme are somewhat,
but not much less, than the successes reported by surgical interventions in international studies (29).

If weight can be substantially reduced in this way, it can be expected that also cardiometabolic risk factors will improve, such as WCF (-11 cm), proportion of those with MetS (-50%), arterial hypertension (from 47% to 29%), or T2DM (from 11% to 4%) (28). In a Swedish cohort study (45), three interventions on obese adults (BMI 29-34 kg / m²) were compared directly based on different initial nutritional concepts: (i) VLCD formula diet 500 kcal / d, (ii) LCD with partial meal replacement and 1200-1500 kcal / d, (iii) energy-reduced mixed diet 1500-1800 kcal / d. After one year weight reductions of -11.4 ± 9.1 kg (i), -6.8 ± 6.4 kg (ii) and 5.1 ± 5.9 kg (iii) were achieved. Dropout rates were quite low at 18% (i), 23% (ii) and 26% (iii); they were higher in younger participants and in those with less weight-loss. This study shows that programmes with consistent initial formula diet and thus higher initial weight loss achieve better compliance and a better long-term outcome.

In another randomized prospective study, adolescent women (BMI 37.8 ± 3.9 kg / m²) underwent multimodal weight reduction therapy with 1500 versus 1000 kcal/d formulation. The low-energy group also achieved longer-term results after 6 months than the higher-energy group (-10.03 ± 0.92g vs. -6.23 ± 0.94 kg, P = 0.045). Even after 12 months, the 1000kcal group showed better results, although these patients gained more weight between month 7 and 12 than the 1500kcal group (46). These results argue for an initially strict limitation of the energy supply at the level of the LCD, which is best achieved by means of formula diet.

Although the effectiveness of such programmes with initial formula on weight reduction is clearly demonstrated, critical questions have repeatedly been asked, such as the safety and sustainability of such measures, target groups and clinical endpoints such as morbidity and mortality. According to current studies, not all but a large part of these questions can now be answered. The safety of these programmes has been repeatedly shown (28, 45). However, medical surveillance should be ensured with regular clinical and laboratory tests during the programmes. The higher efficacy and safety of rapid weight loss under formula diet was recently confirmed (47).

The repeatedly discussed potential dangers of "weight cycling" of obese people on body weight, body composition or even morbidity and mortality have not yet been scientifically proven (48). Thus, any weight reduction, even one that is limited to a few years (and which should then be repeated if necessary) is considered positive compared to "do nothing”, and sufferers should always be motivated to implement weight reduction measures when needed.

The sustainability as well as the "dropout rate" of approximately 20–40% are certainly the two most important problems of such weight reduction programmes. Although significant effectiveness could be proven even after 3 years (28), a post-programme "Weight maintenance" programme is compulsory (see chapter 6). The dropout rate, which is associated with conservative programmes along the length of the programme and is never recorded in surgical interventions, is probably due to the chronic disease.

All published data suggest that effective weight reduction of at least 5%, better still if >10%, is associated with a reduction in associated diseases such as diabetes and arterial
hypertension (28, 45). However, if long-term weight loss is <5%, positive effects on morbidity may no longer be detectable, as the "look-ahead" study has recently shown (49). In this study a higher weight loss of about 8% RWL was achieved only for a short time over about one year, then from year 2 to 10 a weight loss of only 2-3% was achieved. This study confirms that morbidity can be expected to improve with regard to obesity related complications only if a sustained weight loss of at least 5%, and preferably 10%, can be achieved over a period of years. A highly effective weight-loss therapy and a long-term successful "weight maintenance" therapy must contribute to this. Studies on the effect of multimodal weight reduction programmes on overall mortality are not yet available.

Multimodal weight reduction programmes without initial formula diet are less effective in terms of results after one year than those featuring formulas. As an example, the European multicentre study on "Weight Watchers" is cited (50). In this study, 772 overweight and obese adults were recruited and randomized into two groups: Verum ("Weight Watchers" programme for 12 months), of which 61% completed the programme and "standard care", from whom 54% participated in the last investigation. Although twice as much weight was lost in the verum group as in the control group, the effects were moderate. The mean weight loss after one year in the verum group was 5.06 +/- 0.31 kg, in the control group 2.25 +/- 0.21 kg. As expected, the results were slightly better in the PP analysis: 6.65 +/- 0.43 kg in the verum group and 3.26 +/- 0.33 in the control group. Similar results were achieved in a US study in which an ambulant multimodal weight-loss programme without formulated diet was used (51).

4.2 Costs of Multimodal Weight Reduction Programmes

In a 2013 study in the USA (52), several general practitioner-based obesity therapies, including a multimodal programme, were studied over 2 years, and costs were related to weight loss achieved, quality of life and mortality. The following costs were determined:

- $ 292 per kilogram of weight loss per year
- $ 115,397 per QALY (Quality adjusted life year: a measure of sustained improvement in quality of life)

The authors of the study concluded that the multimodal programme is efficient and cost-effective over a period of more than 10 years. In a similar analysis, the cost was determined based on data from various commercial weight-loss programmes in US pharmacological weight-loss therapies (53):

- $ 155-546 per kilogram of weight loss per year
- $ 34,630-54,130 per QALY

The calculated costs are of the same order of magnitude as in the first study. The majority of the costs are not needed for the products (formula diet or pharmaceuticals), but for the necessary staff to carry out the programmes.

In addition to the costs, availability is also an important factor in the performance of nationwide effective obesity therapy. It is indispensable that multimodal programmes are offered not only in specialist centres, which are usually found only in larger cities, but also in the private sector, even if it cannot be ruled out that such offers are less effective than centre-based programmes. Without a "community-based approach", nationwide obesity therapy cannot be offered.
5. Interface with Bariatric Surgery

Obesity therapy should be always an interdisciplinary therapy involving physicians including general practitioners (GPs) and specialists with non-surgical and surgical backgrounds, dieticians and nutritionist, exercise trainer and psychologists. The group of experts should provide individual Case Management according to the individual needs and preferences of the obese patient.

A matter of debate is the interface with bariatric surgery. All major guidelines (7-10) state that non-surgical options should first be preferred, but if these are “exhausted”, then surgical intervention should be considered. The question is, what “exhausted” means exactly in this context. What are good criteria to terminate non-surgical interventions and propose bariatric surgery? This question is not easy to answer, since it is clear that both approaches are effective and both have advantages and disadvantages. Surgical therapy is highly effective, even more effective than the multimodal weight reduction programmes, but surgery is not the only effective measure, as shown before. The problem of long-term outcome need to be evaluated not only at the level of weight and disease reduction, but also regarding recurrence rates, nutritional deficiencies, sarcopenia, rates of depression, suicide risk and other safety issues. For example, surgery, especially gastric bypass is more effective than lifestyle-medical management intervention in achieving e.g. diabetes treatment goals, mainly by improved glycaemic control. However, also the effect of surgery diminishes with time and is associated with more adverse events (54).

Another fact is that a majority (of about two thirds) of patients has already decided on their treatment preferences prior to any medical consultation. Even though the experts are still struggling to find a definition of "treatment failure", which defines the interface between conservative and surgical therapy, most patients have already opted for one or the other therapy before they seek advice from the doctor. Using a "shared decision making (SDM) approach", population-based patient requests were recorded in order to plan a study that envisaged a randomization between conservative and surgical obesity therapy (55). This approach produced amazing results: of the 277 participants who underwent the SDM process, 183 (66%) patients had already decided on their choice of therapy and were not available for consultation or randomization. This study shows that most of those affected make their decisions without guidelines and medical advice, but on their own or after exchanges with affected others or self-help groups.

What to do with patients who refuse surgery? A surgical unit stated "Our goal was to take advantage of non-surgical modalities and investigate an intensified treatment alternative" consisting of a 12 month weight reduction programme with LCD, gastric balloon placement, nutritional and behavioural therapy, and exercise, in small groups. The primary endpoint was RWL, the observation time three years. 166 Patients (81%) completed treatment. Mean (±SD) weight losses after 12 months for women and men were 28.8 kg (±14.7) and 33.7 kg (±19.5), respectively, among completers. RWL was 21.9% (±10.0) and excess weight loss (EWL) was 46.9% (±22.2). Weight loss was accompanied by improved quality of life, lowered HbA1c values, and a significantly reduced need for antihypertensive and diabetes medications over the study period. Three year follow-up data from the first 78 patients (76% follow-up rate) revealed a RWL of 13% (±13.1) and an EWL of 27.2%
(±28.8). The majority of patients (51%) maintained a RWL of 10% or more, and 44% had an EWL > 30% (56).

In conclusion, the advantages and disadvantages of both approaches should be considered carefully on an individual level (Table 3). In particular, realistic cutoffs should be agreed upon that define "treatment failure" (e.g. <10-15% RWL or < 30% EWL). Solution-oriented, regional partnerships are needed that allow effective working together to create interdisciplinary therapy concepts which help our obese patients.

**Table 3**

<table>
<thead>
<tr>
<th>Conservative versus surgical obesity therapy</th>
<th>Bariatric surgery</th>
<th>Non-surgical therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>More weight reduction (EWL 50% vs 30-40%)</td>
<td>Less muscle mass loss (sarcopenia)</td>
<td></td>
</tr>
<tr>
<td>More reduction of diabetes-related and cardiometabolic disorders</td>
<td>Fewer complications from malnutrition (macro- and micronutrients)</td>
<td></td>
</tr>
<tr>
<td>Faster success</td>
<td>Less restriction in eating habits</td>
<td></td>
</tr>
<tr>
<td>No drop-off rate</td>
<td>More acceptance</td>
<td></td>
</tr>
<tr>
<td>Less weight gain after intervention</td>
<td>Lower costs</td>
<td></td>
</tr>
</tbody>
</table>

**6. Weight Maintenance Strategies**

As difficult as it is for the obese patient to lose weight, it seems even more difficult to keep the new reduced weight for the long term. The problem of many successful weight reduction programmes, especially on a non-surgical basis, is the gradual increase in weight after the end of the intervention over years, and not the so-called "yo-yo effect", which is the rapid increase within weeks or months after reduction. In the past decade, the focus in practice and research has increasingly shifted to the topic of weight stabilization and its determinants.

Follow-up data from patients who took part in the non-surgical, multimodal weight reduction programme “Optifast®52” showed that most participants would not be able to sustain their weight without help in the long term after successful weight loss. Although three years after the start of the intervention, mean body weight was still significantly lower than baseline, only 7% of participants manage to maintain their weight stable until the end of the third year after intervention (+/- 5%) and 22% of participants are largely stable in their weight (increase <10%), but 71% report a significant increase in weight during the observation period without further support (28). The annual weight gain after cessation of non-surgical intervention is approximately 7%. Even after surgical intervention, some of the patients are expected to gain weight if no weight loss maintenance measures are taken (57). However, the annual weight gain after surgical intervention is lower than after non-surgical intervention and is around 2% on average.

Since obesity is considered to be a chronic disease with a high recurrence tendency, suitable measures for long-term weight stabilization should be recommended to the patient beyond the phase of weight loss (10). This recommendation from the current German guideline on obesity is only partially implemented in practice, for the time being for lack of validated concepts, but also because of inadequate infrastructure, unclear responsibilities and lack of funding for such measures.
Weight stabilization can be improved by long-term care (extended care) as shown by meta-analyses (57). Weight-stabilization measures partly contain elements of obesity prevention. They include nutritional, exercise, and behavioural measures, and possibly also pharmacotherapy. In particular, cognitive-behavioural approaches have proven to be effective. The following factors are associated with successful long-term weight stabilization:

- Reduction of dichotomous thinking patterns
- Reduction of emotional eating behaviour
- Restrained eating behaviour
- Lowered depression
- Less disturbed body image
- Self-efficacy
- Existing problem-solving skills

For successful weight maintenance a comprehensive lifestyle modification is needed (Table 4). Regarding weight-loss diets, there is a paradigm shift: for a long time, the low-fat diet alone was recommended, while the current recommendations are more differentiated and less focused on fat or energy. Instead, studies have shown that high-protein, low-sugar foods and plenty of vegetables and fibre are good (58).

The underlying mechanisms are not fully understood. Perhaps the intestinal microbiome plays a role, whose composition may allow prediction of the success of weight-reducing measures. Angiotensin-converting enzyme (ACE) has also been described as a predictor of the success of weight-loss measures. Genetic factors such as the FTO genotype may also be relevant. Particularly noteworthy is the effect of macronutrients on energy expenditure. It has been shown that a low-fat diet not only reduces weight but also resting energy expenditure (REE), which could reduce the long-term success of a low-fat diet, while 'low glycaemic index' diets and 'low carb' diets do not have this unfavourable effect.

Many of the nutritional concepts recommended for weight stabilization are bundled in the 'Mediterranean Diet'. This diet has proven value and not only for long-term obesity therapy and prevention of metabolic syndrome. It also appears to lower the risk of different tumours. The success of this therapy is based on the one hand on an anti-inflammatory effect, which is observable even without significant weight reduction (59), on the other hand on a long-term acceptance of this diet in many people, not least because it leaves little appetite. The advantage of the Mediterranean diet in the phase of weight stabilization is based, on the one hand, on the composition (low carb, much MUFA, abundant fibre) that largely complies with the current recommendations, and on the other hand on its anti-inflammatory effects preventing inflammation-associated cardiometabolic and malignant disease (60). Furthermore, this diet has good compliance.

In conclusion, any successful weight loss should be subject to a "weight maintenance" measure, which is usually needed throughout life to permanently stabilize body weight.
### Table 4
Current concepts for 'Weight loss maintenance'

<table>
<thead>
<tr>
<th>Category</th>
<th>Previous Recommendations</th>
<th>New Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition</td>
<td>Energy reduction</td>
<td>High-protein, low-sugar diet</td>
</tr>
<tr>
<td></td>
<td>Low-fat diet</td>
<td>Prefer MUFA and PUFA; avoidance of SFA</td>
</tr>
<tr>
<td></td>
<td>Probiotics? Drugs?</td>
<td>Mediterranean diet</td>
</tr>
<tr>
<td>Exercise</td>
<td>Sports activity</td>
<td>Everyday movement (NEAT)</td>
</tr>
<tr>
<td></td>
<td>Fitness</td>
<td>Power training</td>
</tr>
<tr>
<td>Others</td>
<td>Moderate alcohol consumption</td>
<td>Sleep 6-8h per 24h</td>
</tr>
<tr>
<td></td>
<td>Nicotine abstinence</td>
<td>Change of social environment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Regular weighing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coach partner</td>
</tr>
</tbody>
</table>

Sources: see text. Abbreviations: MUFA, mono-unsaturated fatty acids (olive oil, rapeseed oil, nuts); PUFA, poly-unsaturated fatty acids (fish oil, linseed oil); SFA, saturated fatty acids; NEAT, non-exercise activity thermogenesis.

### 7. Summary

Obesity is a chronic, systemic disease defined as a pathologically increased fat mass, which is associated with an increased health risk. A BMI > 30 kg/m² is usually considered as a sign of obesity. Obesity requires a multidisciplinary and multimodal treatment, which varies depending on the phase of disease and the purpose (e.g. weight loss, weight maintenance). The treatment should be based on evidence. The goal of obesity therapy is to reduce the body weight in the long term in combination with a change in behaviour, which aims to improve obesity-associated risk factors, reduce obesity-related illnesses, reduce the risk of premature mortality, incapacitation and early retirement, and improve quality of life. Non-surgical lifestyle therapy comprises nutrition, exercise, behaviour change (“Basic therapy”) which becomes more effective when combined with initial formula diet. Drugs can support obesity therapy, while other drugs can promote weight gain. The multimodal approach is the most effective non-surgical therapy resulting in a relative weight loss of 15-25%. A clear and realistic interface to bariatric surgery needs to be defined. Weight maintenance strategies including and beyond dietetic concepts are usually needed throughout life for long-term stabilization of body weight.
8. References


Copyright © by ESPEN LLL Programme 2019