

Diets and drugs for weight loss and health in obesity – An update

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ABSTRACT

Numerous combinations of diets and pharmacological agents, including lifestyle changes, have been launched to treat obesity. There are still ambiguities regarding the efficacies of different approaches despite many clinical trials and the use of animal models to study physiological mechanisms in weight management and obesity comorbidities. Here, we present an update on promising diets and pharmacological aids. Literature published after the year 2005 was searched in PubMed, Medline and Google scholar. Among recommended diets are low-fat (LF) and low-carbohydrate (LC) diets, in addition to the Mediterranean diet and the intermittent fasting approach, all of which presumably being optimized by adequate contents of dietary fibers. A basic point for weight loss is to adopt a diet that creates a permanently negative and acceptable energy balance, and prolonged dietary adherence is a crucial factor. As for pharmacological aids, obese patients with type 2 diabetes or insulin resistance seem to benefit from LC diet combined with a GLP-1 agonist, e.g. semaglutide, which may improve glycemic control, stimulate satiety, and suppress appetite. The lipase inhibitor orlistat is still used to maintain a low-fat approach, which may be favorable e.g. in hypercholesterolemia. The bupropion-naltrexone-combination appears promising for interruption of the vicious cycle of addictive over-eating. Successful weight loss seems to improve almost all biomarkers of obesity comorbidities. Until more support for specific strategies is available, clinicians should recommend an adapted lifestyle, and when necessary, a drug combination tailored to individual needs and comorbidities. Different diets may change hormonal secretion, gut-brain signaling, and influence hunger, satiety and energy expenditure. Further research is needed to clarify mechanisms and how such knowledge can be used in weight management.

1. Introduction

Obesity is a global, multifactorial disease defined as abnormal or excessive fat accumulation that presents a risk to health. Obesity is associated with several comorbidities [1], such as cardiovascular diseases (CVDs), metabolic syndrome, type 2 diabetes mellitus (T2DM), cancer, and according to recent studies also increased risk of severe COVID-19 [2]. The world-wide prevalence of obesity doubled between 1980 and 2008 [3]. From 1980–2013 the global proportion of overweight individuals increased in both men (from 28.8% to 36.9%) and women (from 29.8% to 38%) with a trend to continued increase of the prevalence rate for both obesity and overweight [4]. Because of their increasing prevalence, significant impacts on health and medical costs,

obesity with its comorbidities has become a public health concern.

Traditionally, the cause of obesity is considered an imbalance between caloric intake and energy expended. It is now recognized that the development of obesity involves a complex interplay of biological and psychosocial factors [5]. Of especial relevance is that research has shown that a weight loss between 5% and 10% is enough to induce clinically relevant improvements in health risk factors such as raised blood glucose and other biomarkers related to augmented risk of CVD [6,7]. To achieve successful maintenance of weight loss over time, the WHO and EU [8] as well as US Academy of Nutrition and Dietetics [9] recommend changes in lifestyle including a diet that reduces excessive energy intake and improves dietary quality. However, successful treatment of obesity may in several cases require adjuvant pharmacotherapy

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[10], which is briefly reviewed in the present paper. In selected cases bariatric surgery can be chosen [11]. However, surgery is only recommended when BMI is $\geq 40 \text{ kg/m}^2$ or $\geq 35 \text{ mg/m}^2$ in the presence of weight-related comorbidities [12].

Irrespective of method for obesity treatment lifestyle advice remains a corner-stone remedy. An individually adapted diet that succeeds in achieving a state of negative energy balance is recommended. Based on calorie calculations numerous dietary approaches can result in a reduction in energy intake. Frequently prescribed diets are based on changes in different food groups to achieve a *continuous* daily energy restriction, although *intermittent* energy restriction (intermittent fasting) has lately emerged as an alternative [13,14]. The present review aims at providing updated evidence regarding the most common dietary and pharmacological strategies to promote weight loss. Literature published after the year 2005 was searched in Pubmed, Medline and Google scholar by making use of the search keyword obesity combined with drugs, diets, low-fat, low-carbohydrate, fasting, weight loss or macronutrients.

In the present overview currently recommended dietary approaches to obtain weight loss are classified into two main groups: Firstly, we discuss the low-fat and the low-carbohydrate concepts, as well as the Mediterranean dietary concept. Secondly, we discuss diets based either on restriction of specific food groups (“the Paleo concept”) or on intermittent calorie restriction (“the intermittent fasting concept”). Included in our overview is also the insight that any nutritional approach is counteracted by physiological defense mechanisms against weight reduction, explaining a general acceptance of pharmacological aids to obtain lowering of the body weight. The “very-low-calorie diet” concept, defined as a diet with extremely low daily food energy intake, maximally 800 kilocalories (3300 kJ) per day is not further discussed in the present overview, since this approach is only used under close medical supervision for up to 3 months [15] such as for rapid weight loss in morbid obesity before bariatric surgery.

2. Central defense mechanisms against body weight reduction

The recognition that there exist central mechanisms to resist changes in body composition, thus contributing to maintenance of the current body weight, represents an important insight within obesity research. Powerful central mechanisms triggering increased hunger and a decline in metabolic rate appear to operate *against* any dietary calorie restriction. At present, we do not fully understand the molecular mechanisms behind this defense [16]. Experiences from bariatric surgery suggest that

when surgical treatment leads to sustained weight loss it is because of changes in the defended state of obesity [17]. Therefore, understanding the mechanisms of body weight loss obtained by bariatric surgery is of importance for further development of alternative strategies. Post-operative suppression of ghrelin levels seems to explain only a minor part of the postoperative weight loss [18]. Changed gut microbiota accompanied by changed gut-brain signaling [19], i.a. by reduced endocannabinoid [20] or increased butyrate synthesis [21] in the gut, represents other possible mechanisms [22]. Furthermore, recent research has disclosed that facilitated nutrient flow after surgery to the distal gut with its concentrated occurrence of enteroendocrine L-cells enhances postprandial secretion of glucagonlike peptide-1 (GLP-1) [23]. The recently reported observation that gastric bypass is superior to sleeve gastrectomy for remission of type 2 diabetes [24] conforms with the proposed role of increased GLP-1 secretion in the distal gut. Receptors for GLP-1 expressed in hypothalamus may explain the ability of this hormone to promote satiety and thereby reduce food intake [25] (Fig. 1).

In the brain, a major candidate for body weight regulation is the middle region of hypothalamus, where appetite and perceptions of food are processed [26]. Here, GLP-1 stimulates secretion of melanocortins that act on receptors in various brain regions. Food intake and energy expenditure are to a large extent regulated through the melanocortin-4 receptors, which are widely distributed within the central nervous system, including in the hypothalamus [27]. Loss of normal melanocortin signaling leads to hyperphagia and obesity [28], whereas over-activity of the same system may lead to suppression of food intake. However, melanocortin-signaling appears not to be the only aspect of neural body weight regulation, since several cell populations in the arcuate nucleus operate on the same functions [29].

In clinical nutrition, the food palatability including smell and taste is considered to play an important role in appetite regulation and obesity pathogenesis. Diets rich in sugar and saturated fats may influence the regulations through their proinflammatory actions on microglia in hypothalamic regions [30]. Dopamine is a crucial transmitter in the reward system of the brain, although appetite stimulation also depends on other signaling substances [31]. Recent observations have shown interactions between obesity and cognitive functions related to learning and memory [32]. Strengthening of cognitive functions may thus represent an appropriate strategy to modulate food intake in obese subjects [33]. A therapeutic challenge is to convert unhealthy habits into conscious behavior [34]. Accordingly, it is important to mediate adequate lifestyle cognition. When it comes to dietary advice (Table 1), energy restriction

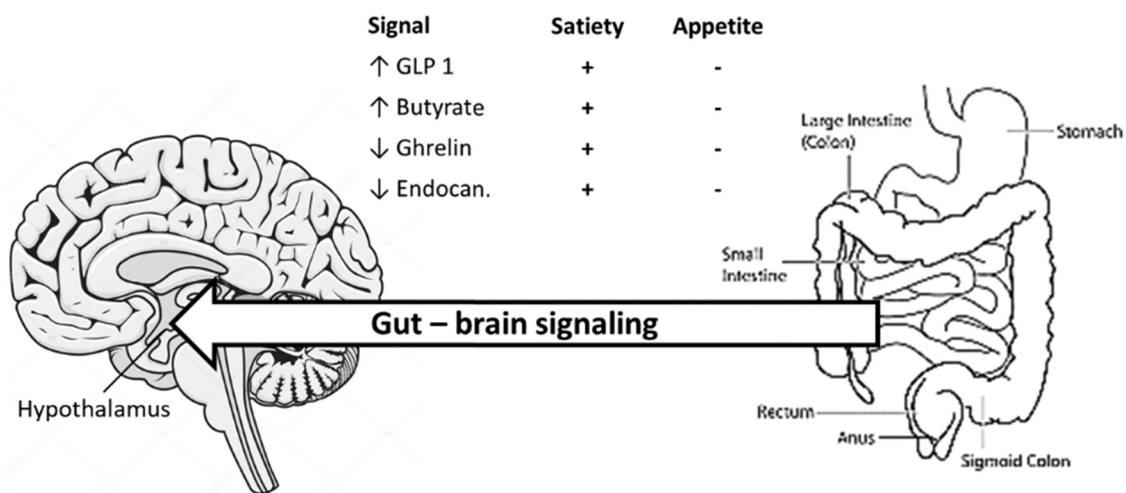


Fig. 1. Bariatric surgery is reported to lead to raised postprandial secretion of glucagon-like peptide (GLP-1) and other substances which can mediate satiety by signaling from gut to brain, particularly so to hypothalamic receptors. Increased activity of the hypothalamic melanocortin system may lead to suppressed food intake (see text).

Table 1
Commonly recommended diets for weight loss.

	Hypothesized mechanisms
Low fat diet (LFD)	Energy restriction
Low carbohydrate-high fat diet (LFD-HF)	Energy restriction (+ induction of satiety)
Low carbohydrate-high protein (LFD-HP)	Energy restriction (+ induction of satiety)
The Paleo diet(high in protein)	Energy restriction (+ induction of satiety?)
The 5:2 intermittent fasting diet	Energy restriction (+ reduced appetite?)

is considered a sine qua non in all recommended approaches [35].

3. Energy restriction based on changes in macronutrient composition

The energy distribution between the main three macronutrients in a typical Western diet, as recently determined in the mean American diet of adults [36] is shown in Fig. 2. Interestingly, energy from fat in people’s diets in USA has gone down from an average of almost 40% to about 33% during the past 30 years, while overweight and obesity rates have increased substantially [37]. Of note, the Western diet of today has a high content of refined carbohydrates and n-6 polyunsaturated fatty acids (PUFA), which represent sources of proinflammatory cytokines and endocannabinoids that can promote weight gain [38]. The acceptable macronutrient distribution range for adults (AMDR), as set by the US Food and Nutrition Board of the Institute of Medicine, advocates relative fat intake of 20–35%, protein intake of 10–35%, and carbohydrate intake of 45–65% of the total energy intake [39]. Manipulation of macronutrient content in otherwise energy-matched diets, even outside the AMDR, has been studied to determine the composition that best promotes weight loss. In this regard, it is known that changes in the macronutrient composition can affect endocrine balance and the gut microbiome that might impact fat storage [40].

3.1. Low or very-low fat intake for weight loss

Traditionally, obesity has been considered simply the result of inappropriately high intake of energy-dense food, i.e., intake of a high proportion of fat. On this background physicians have promoted decreased fat intake for weight loss since the 1950s [41,42]. As expected, low-fat diets (LFDs) (Fig. 2) containing few calories can induce significant short-term weight loss. However, the long-term efficacy of such weight loss diets has proved to be rather disappointing [43], since the effectiveness of LFDs for weight loss in long-term studies seems not

to differ significantly from that obtained by low-carbohydrate diets [44]. Here, it should be taken into account that the wide range of weight loss observed within each study complicates such comparisons. The original promotion of LFDs was based on their ability to prevent heart disease, next to the proclaimed effect on body weight. Lowering of fat intake from about 40% to about 20% of total calories was shown to decrease cholesterol by about 15%; which could be ascribed to reduced intake of saturated fat [45].

Whereas the regular LFD contain 20 – 25 E% as fat, the alternative very-low-fat variant (VLFD) contains only 10 – 20% fat [46]. To date, very few clinical trials have investigated the effect of VLFD on weight. A weight-loss study by Gardner et al. [47] did not show any significant differences in body fat reduction between VLFD (Ornish diet), low-carbohydrate (Atkins) and some other diets. However, despite the fact that the VLFD participants were assigned to a fat intake of about 10%, the actual intake progressed to above 25 E% by the end of the 12-month trial. Apparently, a targeted restriction to low or very-low fat intake is difficult to attain, especially in long-term studies, as the observed actual fat intakes typically exceed the prescribed proportions.

When discussing LFDs or VLFDs it is of interest to note that simultaneous use of the lipase inhibitor orlistat could inhibit fat absorption significantly and also help in maintaining a low-fat intake (Table 2), thus leading to more pronounced weight loss compared to traditional lifestyle modifications [48]. The extra weight loss obtained by orlistat treatment [49] may be accompanied by reduced development of T2DM and other risk factors for CVD [50].

3.2. The low carbohydrate concept

Low carbohydrate diets (LCDs) having a low content of easily absorbable carbohydrates, are marketed either as high-fat (HF-LCD) or high-protein (HP-LCD), with the latter involving ingestion of more than 20–25 E% from protein emerging as a particularly popular variant. Reasonably, the HF- and HP-variants of LCD, especially if combined with adequate intake of dietary fiber, will suppress secretion of ghrelin more efficiently than LFDs, and thus suppress the feeling of hunger. The LCD approach has resulted in several dietary modifications, including the Atkins diet (Fig. 2).

In contrast to LCD meals, LFD-meals with high content of refined carbohydrates elevate postprandial glucose levels accompanied by increased insulin secretion, which secondarily directs fat into adipose tissue storage, a mechanism that has been referred to as the carbohydrate-insulin model of obesity [40]. In this context, low carbohydrate diets with low glycemic load, ranging from as low as 10% to maximally 40% of energy from carbohydrates, are claimed to treat obesity by reducing insulin secretion while simultaneously maintaining adequate GLP-1-levels, a hormonal shift that should lead to increased fat oxidation [51]. Analogously, pharmaceuticals with GLP-1-like actions such as liraglutide can also increase energy expenditure [52].

Despite this captivating carbohydrate–insulin model of obesity, clinical trials comparing LCDs with low-fat diets (LFDs) in energy-

Table 2
Anti-obesity drugs^a.

	Weight loss with drug	Weight loss/ placebo	Glycemic control	Reference
Liraglutide	About 8%	About 3%	+++	[97]
Semaglutide	About 15%	About 5%	+++	[102]
Orlistat	About 8%	About 5%	++	[104]
Bupropion	About 8%	About 5%	++	[106]
Bupropion-naltrexone	About 6%	About 1%	++	[111]
Phentermine/topiramate	About 9%	About 2%		[114]

^a Note: Here, the percent of weight loss is given by whole numbers, as an approximation, due to a wide range of weight loss within each study.

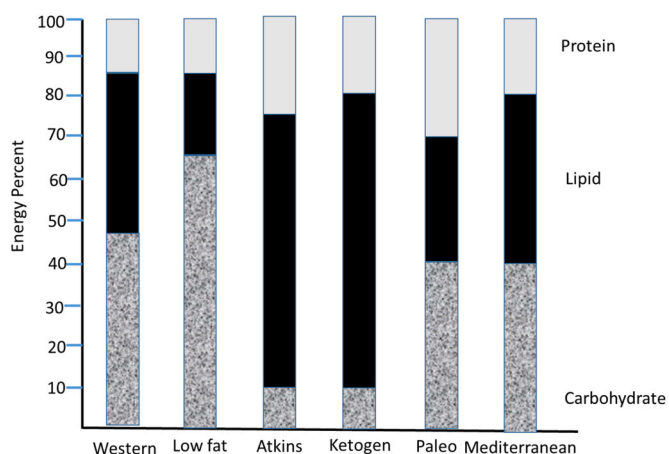


Fig. 2. Approximate macronutrient content, given in E%, of some popular diets as compared with common Western diet [35].

equivalent modifications have reported similar weight loss [53,54]. In accordance with this, a compilation of relevant studies done by an expert panel in 2013 concluded that consumption of a carbohydrate-restricted diet resulted in equivalent weight loss as a low-fat diet with comparable calorie restriction [55]. Recently, this conclusion was confirmed in a randomized clinical trial of 609 overweight and obese adults following a healthy low-fat diet or a healthy low-carbohydrate diet for 12 months showing no significant difference in weight loss [56]. A recent meta-analysis of diets where the protein intake was controlled found only a marginal benefit of keeping a low-fat rather than a low-carbohydrate diet, the difference being considered without clinical significance [57].

However, the carbohydrate-insulin model of obesity may apply to selected cases of pathological hyperinsulinemia. It is still recommended to treat obese individuals with T2DM and/or insulin resistance with appropriate kinds of LCDs [58], which in some cases is combined with a GLP-1 agonist. Thus, nutritional treatment of obesity should take into account whether the patient is insulin resistant or has a normal insulin response.

An extreme variant of LCD–HF diet, known as the ketogenic diet (KD), prescribes intake of at least 70% of energy from fat and a severe restriction of carbohydrates (maximally 10 E%) to mimic a fasting state and induce ketosis [59]. KD has been used to promote a rapid weight loss and it may also reduce appetite [60]. Clinical trials have reported significant weight reduction for individuals on this diet [61,62]. However, adverse effects of KD should be taken into account, which include headaches, muscle cramps, and general weakness [63], and some studies have demonstrated worsening of the lipid profile [64].

High and very high-protein diets (HP diets), in which >20–35% of energy is derived from protein appear to offer advantages for short-term weight loss [65]. In accordance with this, popular HP diets such as the Atkins variant, promotes significant weight loss over a short time span [66]. Upon very high intake, proteins appear to act on relevant metabolic targets, increasing satiety and also total energy expenditure [67, 68]. Proteins are thus more efficient than carbohydrates at inducing thermogenesis [69]. An important mechanism behind this appears to be activation of brown and beige adipocytes with increased uncoupled respiration including futile cycling with loss of ATP [70]. Also, the source of proteins appears to be important for its impact on dietary induced thermogenesis, with vegetarian sources seeming to be the most effective. Increased protein turnover including its promotion of increased synthesis of urea are energy-requiring metabolic processes [71].

Regarding long-term use, exceeding 6–12 months, it should be taken into account that the clinical benefits HP-diets compared with LF-diets seems to be small, and if combined with high intake of *saturated fat* HP-diets may cause undesired effects by increasing LDL cholesterol and CVD risk [72].

Altogether, in a short-term perspective, HP-LCDs, as well as ketogenic diets, are suggested to be beneficial for weight-loss. However, owing to their major effects on metabolic processes, their utilization should be restricted to the initial phase of a weight loss regimen, lasting for up to 6–12 months, and not be recommended as diets for life [73]. However, when using a LCD composition with high intakes of dietary fibers, a protein-rich variant may be preferred for weight management also after an initial weight-loss period [74].

3.3. The Mediterranean diet for weight-loss

After an initial period on a high-protein-LCD or an orlistat-LFD diet, the Mediterranean diet [75] may represent an attractive option for continued dieting, provided that it is prescribed in an energy-restricted form. Mediterranean diet is not a typical low carbohydrate diet (Fig. 2). It is rich in plant-based foods, having high levels of antioxidants and dietary fiber, and low glycemic load compared to conventional Western diets. The Mediterranean diet is characterized by high intake of

vegetables, fruits, whole-grain cereals, seafood, olive oil, and nuts. In contrast to conventional Western diets, this diet contains more adequate composition of fatty acids, as it contains less saturated fat and n-6 PUFA, and more MUFA and n-3 PUFA.

Successful weight loss with the Mediterranean diet has been reported, not only in the short term [76], but also in the long term [77], with weight losses being comparable to those obtained with other diets in overweight individuals, provided that comparable caloric restrictions are prescribed [78].

Of importance, the Mediterranean diet has been related to a variety of health benefits in addition to its effect on body weight. It has been shown that Mediterranean diet with its low glycemic load improves glycemic control in patients with T2DM [79], and it has also been associated with a reduction of inflammatory biomarkers, and reduction of other markers for CVD risk [80].

4. Concepts based on the restriction of specific foods or on intermittent fasting

Different foods and food groups have been categorized as harmful by some popular nutritionists and have been removed from specific diets, allegedly to promote weight loss. Among these specific diets are vegetarian diet, which excludes all animal products, and also the Paleo diet, which excludes several food groups including grains and dairy products. It should be noted, however, that vegetarian diets are not specifically designed for weight loss. Some people decide to go for this lifestyle simply because they cannot bear the thought of harming living creatures. Others have converted to this diet for religious reasons, or for its benefits for worldwide food sustainability. A vegetarian plan can range from the simple exclusion of meat products to a vegan plan that includes only raw vegetables, fruits, nuts, seeds, legumes, and whole grains [81]. Notably, plant-based diets vary greatly in composition and possible health effects. While plant-based diets containing high amounts of healthy foods such as fruits, vegetables, nuts, and legumes are associated with lowered risk for CVD, plant-based diets including high amounts of refined foods and beverages rich in sugar, are associated with increased risk of CVD [82].

4.1. Paleolithic diet and weight-loss

The Paleo diet is based on adoption of food intakes that mimic the food groups of our pre-agricultural hunting and gathering ancestors [83]. This diet is proclaimed to optimize health, and also to result in weight loss. These statements are supported by the knowledge that a hunter–gatherer lifestyle has characterized humanity and its ancestors for hundred-thousands of years, causing the human genome to be adapted to it. According to advocates of the Paleo diet, the human genome has not been adapted to the radical lifestyle changes accompanying modern civilization [84].

Only foods that were available in the hunting-gathering stage of the development of mankind can be included in this diet, such as meat, nuts, eggs, fruits, berries and vegetables, whereas sugar, cereals, dairy products, and other refined products are excluded. Characteristics of the Paleo diet include a low ratio of n-6 to n-3 fatty acids along with a high content of phytochemicals that might promote health benefits. The diet is high in protein (25–35% of energy) and moderate in fat and carbohydrates including low in glycemic ones [85]. Possible benefits of the Paleo diet include ameliorations in insulin resistance and T2DM, reduction of CVD risk factors [86] and also beneficial modulation of intestinal microbiota [87]. Reductions of body weight and body fat mass in those who follow Paleo diet have been reported, both from short- and long-term studies [88,89]. However, concerns have been raised regarding problems with long-term adherence and high costs of this diet.

Taken together, available evidence suggests health benefits of Paleo diet, although it has not proven more efficient than more conventional diets for weight loss. The hypothesis of the Paleo advocates regarding

the immutability of the Paleolithic human genome is not necessarily correct.

4.2. Weight reduction diets based on intermittent energy restriction

Traditional guidelines for weight reduction recommend *continuous* energy restriction along with lifestyle intervention. However, more recently, *intermittent* energy restriction involving restricted energy intake allocated to certain periods of the day or to certain days during the week, has received considerable attention as an alternative strategy. The term intermittent fasting (IF) refers to regular periods with very low or no caloric intake. The IF approach may include various modifications, such as a 24-hour fasting on alternate days, or fasting for two non-consecutive days per week, the latter modification being referred to as the 5:2 diet [14]. The aim of modern IF is to reduce the average caloric intake over time. In addition, IF appears to promote remodeling of the gut microbiome with upregulation of intestinal butyrate production [90], which might contribute to the observed improved insulin sensitivity and reduction of inflammatory biomarkers [91,92]. Most of the human studies on IF have been limited to short term interventions, and the results are somewhat inconsistent. An updated meta-analysis of RCT trials summarizing recent evidence has concluded that intermittent energy restriction is comparable with continuous energy restriction for promoting weight loss [93]. Although appropriate control groups are lacking in some studies, it has been suggested that the beneficial effects of IF are comparable to those of other types of caloric restriction [13]. However, the long-term adherence of IF is unclear. In some cases, adequate compliance with the fasting intervals may turn out to require pharmacological support (Table 2).

5. Pharmacological aids

Commonly used drugs for weight reduction are listed in Table 2. If for some reason lifestyle measures have not led to an acceptable result after about 12 months, adjuvant drug treatment may be considered. According to current guidelines, drugs approved for weight management should then be considered for patients with a BMI of ≥ 30 kg/m² or a BMI ≥ 27 kg/m² in the presence of weight-related comorbidities [12]. The initial choices in such cases may be the GLP-1 agonist liraglutide or the lipase inhibitor orlistat. The bupropion/naltrexone combination might be preferred in selected cases. Regarding phentermine and its combination with topiramate, which are approved in USA, these agents have not been approved in Europe and are only briefly discussed here.

5.1. Liraglutide and semaglutide

Liraglutide is a GLP-1 agonist initially approved in 2010 for treatment of T2DM at doses of 1.8 mg s.c. daily. Early observations indicated that liraglutide could also decrease appetite and enhance satiety, presumably through effects on the central nervous system [94]. Early experimental studies indicated that liraglutide exerted its impact on the arcuate nucleus in hypothalamus [95], mimicking the effects of natural GLP-1. These findings led to the development of liraglutide for treatment of obesity. A 20-week trial in patients with obesity demonstrated that liraglutide treatment led to a dose-dependent weight loss of up to 4.4 kg, compared with 3.0 kg, for placebo [96]. One of the subsequent phase-3 trials, randomized overweight/obese patients to receive daily liraglutide (3.0 mg s.c.) or placebo for one year [97]. The weight loss in the liraglutide group was in average 8.0% compared with 2.6% in the placebo-treated group. Also in patients with prediabetes, the liraglutide treatment was associated with greater weight loss than placebo, with an estimated treatment difference of - 4.3% as monitored after 3 years [98]. Furthermore, the time-to-onset of T2DM in prediabetic patients was substantially prolonged with liraglutide. In order to compare *weight maintenance* in overweight patients *without* diabetes after an average of 6% weight loss with energy-restricted dieting, the studied subjects were

randomized either to liraglutide (3.0 mg daily) or to placebo [99]. During this maintenance period, the weight loss with liraglutide was 6.2% and with placebo 0.2%. Nausea, vomiting, and diarrhea may occur as side effects of liraglutide. A drawback with this drug is that it has to be given by daily subcutaneous injections. A recently developed drug with similar effect profile, semaglutide, can be administered by weekly injections [100]. A recent 68-week placebo-controlled trial in patients with obesity found that semaglutide treatment (2.8 mg weekly) led to a weight loss of 14.9% compared with 2.4% with placebo [101], while another study with similar design and follow-up period found a weight-loss of 16% with semaglutide and 5.7% with placebo [102]. Oral administration of semaglutide is under investigation [103]. The latter drug has yet not been approved for clinical use against obesity, but is used in the treatment of T2DM.

5.2. Orlistat

Orlistat is a pancreatic lipase inhibitor that reduces intestinal absorption of fat by about one-third. At doses of 120 mg x 3 p.o. for 12 months, it results in a weight loss of about 8% compared with about 5% with placebo [104]. Low-dose orlistat (60 mg x 3) which is approved for use without prescription results in a somewhat less weight loss. The mechanisms of action of orlistat may involve not only reduced fat absorption, but secondarily also raised postprandial secretion of GLP-1, thus mediating satiety by gut-to-brain signaling. As such, orlistat facilitates the flow of non-absorbed fat to the distal gut, with its rich occurrence of GLP-1-producing enteroendocrine L-cells. Orlistat has been approved for weight management of obese adolescents of age 12 years and above. Adverse effects of orlistat are diarrhea, frequent defecation and fecal incontinence. Supplements with fat-soluble vitamins, in particular with vitamin D₃, are recommended to subjects on LFDs when used in combination with orlistat treatment [105].

5.3. Bupropion and the bupropion-naltrexone combination

Bupropion is a norepinephrine and dopamine reuptake inhibitor that is used for treatment of depression [106]. It activates pro-opiomelanocortin (POMC), a neuropeptide that appears to decrease appetite by affecting hypothalamic functions. It is probably the alpha-melanocyte-stimulating hormone produced by enzymatic cleaving of POMC that has the effects on food intake, presumably by acting on the melanocortin-4 receptor. Bupropion has been shown to promote clinically significant weight loss in obese individuals [107]. Upon combination with the opioid antagonist naltrexone, it has been shown to alleviate *addictive* over-eating [108]. Naltrexone monotherapy has been used for the treatment of opioid- and alcohol-dependence. Naltrexone inhibits the appetite-enhancing effects of beta-endorphin caused by cannabinoid-1 receptor activation, and it has been observed to decrease food cravings in obese and binge-eating humans [109]. The combined use of bupropion and naltrexone has a synergistic effect on appetite suppression [110]. This may be because the addition of naltrexone can enhance the bupropion-induced POMC activation and thus strengthen its appetite-suppressing effects.

Combination of bupropion with a low dose of naltrexone resulted in more pronounced weight loss compared to bupropion monotherapy in a 24-week trial [110]. In a phase-3 study, bupropion (360 mg/day) combined with naltrexone (32 mg/day) resulted in a weight loss of about 6%, compared with about 1% for placebo [111]. Some concern was expressed because this treatment was associated with a mean increase in systolic and diastolic blood pressure of about 3 mmHg, relative to a placebo. However, in a follow-up study there was no difference in major cardiovascular events between patients given active treatment vs. those on placebo [112], though the study was performed within a rather short time frame, precluding analyses of long-term effects. Adverse effects of the naltrexone/bupropion combination include constipation and dry mouths in addition to headache, insomnia, and anxiety.

5.4. Phentermine and phentermine-topiramate combination

Phentermine is an amphetamine analogue. It is approved for medical use in USA, though restricted to short-term use for up to 12 weeks. It is not approved in Europe due to its pharmacological similarities with amphetamine. A meta-analysis has estimated that treatment with phentermine (30 mg/day) for about 3 months results in a mean weight loss of about 3 kg relative to a placebo [113]. Among the side effects of phentermine are dry mouth and constipation, in addition to agitation and insomnia in some cases.

The combination of low-dosed phentermine with low-dosed topiramate has been investigated for treatment of obesity, with most of the studies being done in USA. Monotherapy with topiramate was initially reported to lead to significant weight loss [114], but the risk associated with its use in efficient doses, including severe psychiatric adverse effects, did not allow further development of this monotherapy for clinical use. However, when combining low-dosed topiramate (100 mg/day) with a low dose of phentermine (15 mg/day) it was observed that a 6-month treatment led to reduced energy intake and a substantial weight loss compared to placebo [115]. However, also this combination gave rise to frequently occurring adverse effects such as paresthesia, and less frequently cognitive dysfunction and psychiatric events, explaining the refusal by European Medicines Agency as regards marketing authorization in the EU countries.

6. Diet-drug combinations

For any dietary regimen, research has indicated that a high level of adherence is crucial for successful achievement of weight loss [116, 117]. To obtain desired degrees of adherence and weight loss, the importance of integrating dietary modifications into a regimen of adapted physical activity has been emphasized [118]. In some subjects, pharmacotherapy is also indicated. Diet-drug combinations should be considered a valuable tool for patients who have not experienced adequate benefit from lifestyle interventions during a 12-month period or who have difficulties in adhering to dietary protocols [119]. Although we do not have substantial information about diet-drug combinations from available research, there are known factors clinicians should consider, based on the actions of the various drugs. Thus, for patients who report intense food cravings, naltrexone/bupropion may represent a beneficial option [120], which is also true for patients who struggle with addiction or reduced impulse control. Moreover, the drug liraglutide combined with LCD (low carbohydrate diet) appears to be recommendable for weight loss in obese patients with prediabetes or T2DM [121], an approach that can be combined with metformin which has been claimed to act as a GLP-1 enhancer [122]. A diet rich in dietary fibers [123], e.g. a plant-based food with high levels of antioxidants and essential trace element may be appropriate for patients with BMI > 25 kg/m² and fluctuating blood glucose values. Here, it should be noted that in Western populations the average intake of dietary fiber (about 15 g/day) [124] is less than half of the health-based recommended levels (28–36 g/day), and it is even lower in subjects with T2DM or high blood pressure [125]. Finally, the lipase inhibitor orlistat in combination with dietary modifications appears to be the drug of choice for obese individuals who need to reduce their fat intake, i.a. as a therapeutic measure for the management of hypercholesterolemia [126].

7. Conclusion

To conclude, it should be admitted that the current evidence for recommending specific diets and diet-drug combinations for weight loss remains weak, which in part can be attributed to differences in dietary protocols and different follow-up times in available trials. In the initial phase of a dietary intervention several diets promote obvious degrees of success, such as for instance the LFD-orlistat combination or the high

protein-LCD combination. However, in the longer term, there are only minimal differences between various approaches, precluding prescription of one diet over another to anyone.

Present knowledge indicates that obese individuals with T2DM or metabolic syndrome can profit from using the LCD/low glycemic-liraglutide drug-diet combination, whereas some non-diabetics might profit from the LFD-orlistat combination, with the drugs typically being prescribed after an initial period of lifestyle modifications. At present, it is not possible to conclude that there is an optimal long-term diet-drug combination for procuring weight loss or weight maintenance for anyone. Furthermore, due to the possible adverse effects of the prescribed drugs, caution is warranted. For example, when using pharmacological agents such as the bupropion-naltrexone combination to increase adherence to a calorie-restricted diet, the risk of side effects is significant, requiring adequate medical surveillance. The future might also bring new therapeutic agents that might help in medical treatment of obesity and its complications. At present, inhibitors of the sodium-glucose transporter 2 are under investigation for clinical use in obesity treatment. Regardless of the chosen therapeutic approach, a fundamental point for weight loss is to adopt a diet that creates a permanently negative and acceptable energy balance. At the same time diets prescribing high-quality and health-promoting foods should be encouraged. Among questions for further research are: How do different diets change hormonal secretion, gut microbiome composition, and gene expression? How do these changes influence hunger, satiety and appetite, and energy expenditure?

Author contributions

Jan Alexander, Jan Aaseth, Urban Alehagen, Stian Ellefsen and Tine M. SundfØr have written the paper draft. Jan Alexander and Jan Aaseth have a final responsibility for the content. All authors have read and approved the final manuscript.

Conflicts of interest statement

The authors declare no conflict of interest.

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