

## Clinical Information

# Obesity and Type 2 Diabetes: Two Diseases with a Need for Combined Treatment Strategies – EASO Can Lead the Way

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## Keywords

Obesity · Diabetes · Diabesity

## Abstract

Obesity is a chronic metabolic disease affecting adults and children worldwide. It has become one of the leading causes of death, as obesity is known to be the main risk factor for a number of non-communicable diseases, in particular type 2 diabetes. This close relationship led to the connotation 'diabesity', highlighting the fact that the majority of individuals with diabetes are overweight or obese. Until today the BMI is still used to classify overweight and obesity. Since reduced muscle mass is highly prevalent throughout the BMI range, the measurement of body composition is strongly recommended. Moreover, it is essential for monitoring the course of weight reduction, which is part of every effective anti-obesity treatment. Weight reduction can be achieved via different weight loss strategies, including lifestyle intervention (diet and exercise), pharmacotherapy, or bariatric surgery. However, not all of these strategies are suitable for all patients, and any further needs should be considered. Besides, attention should also be drawn to concomitant therapies. These therapies may promote additional weight gain and further trigger the deterioration of blood glucose control. Thus, therapeutic strategies are warranted, which can be easily used for the management of obese patients with type 2 diabetes to achieve their glycemic and weight loss goals.

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## Introduction

Over the last century, obesity has emerged as leading global health concern through recent environmental and societal changes, favoring a positive energy balance and weight gain. The main factors are the consumption of high-calorie or high-fat foods, insufficient physical activity, and a shift towards a well-developed sedentary lifestyle [1]. Consequently, the prevalence of obesity nearly doubled worldwide since 1980. In 2014, more than 39% of the adults, who were 18 years or older, were overweight with 13% being obese. In addition, at least 41 million children under the age of 5 were overweight or obese according to the World Health Organization (WHO) [2]. Moreover, severe obesity (i.e., a BMI > 35 kg/m<sup>2</sup>) is nowadays a rapidly growing segment of the global epidemic, which is especially marked by its negative effect on health as an increase in BMI implies an elevated mortality risk, like low BMI does [3–5]. Nonetheless, overweight and obesity are killing more people today than underweight [2].

Obesity is known to be the main risk factor for a number of non-communicable diseases like cardiovascular disease, type 2 diabetes, hypertension, coronary heart disease, or certain types of cancers. Besides, it also causes diverse psychological problems or various physical disabilities. In concordance with the WHO, overweight and obesity account for 44% of the diabetes cases, 23% of the ischemic heart disease patients, and around 7–41% of certain cancers [4, 5]. Of these diseases, type 2 diabetes is most strongly associated with obesity, and the prevalence of obesity-related diabetes is expected to double to 300 million by 2025 [6]. This close relationship also led to the connotation ‘diabesity’, highlighting the fact that the majority of individuals with diabetes are overweight or obese [7, 8]. Together, they increase the individuals’ mortality risk 7-fold [9]. Consequently, obesity is today the largest global chronic health problem according to the WHO, and it is emerging as a more serious world health problem than malnutrition [5]. If this trend continues, 60% of the world’s population will be overweight or obese by the year 2030 [10, 11].

In this review, the progressive nature of ‘diabesity’ will be discussed, focusing on anti-obesity therapeutic strategies, including lifestyle management and bariatric surgery as well as pharmaceutically based strategies and their obstacles.

## Anthropometric Data

The BMI is still used to classify overweight and obesity although the individual’s body fat mass might be underestimated [12]. While a high proportion of body fat is almost regularly seen in people with a BMI of >30 kg/m<sup>2</sup>, it can be observed in almost one-third of people with normal weight, too [13]. Such inappropriate fat-muscle distribution is the result of a low muscle mass known as ‘sarcopenia’. Quite a lot of these people can be identified through their elevated waist circumference, which should not exceed 80 cm for women and 94 cm for men in the Caucasian population [14]. Since there is a difference between ethnic groups in the association between BMI, waist, percentage of body fat and health risks, different BMI and waist cut-off points for various populations have been proposed [15]. Independent of the BMI threshold in various populations, a visceral fat distribution elevates the risk of atherosclerosis and mortality. Thus, the routine medical practice should include the standardized measurement of waist circumference as well as a proper method to measure the individual’s body composition (dual energy X-ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA), BOD-POD®). Although these measurements have some drawbacks, they are essential for monitoring the course of weight reduction and the changes in the respective body compartments [16, 17]. Moreover, the routine use of a simple, rapid, and

inexpensive method to identify an early stage of sarcopenia should be discussed as the loss of muscle mass is nowadays quite common. In elderly this can be easily addressed by a questionnaire like SARC-F, which consists of 5 questions regarding strength, assistance in walking, rising from a chair, stair climbing, and falls. The global score of the SARC-F questionnaire ranges from 0 to 10 points, wherein each component is scored with 0–2 points. A score  $\geq 4$  points is reported to be predictive for sarcopenia and could be the trigger for a more detailed assessment of positively evaluated subjects [18]. The SARC-F questionnaire is so far one of the best available tools to screen for sarcopenia in routine medical practice, and its validity has already been proven in late-middle aged and elderly patients [19, 20]. In order to get more information about muscle function, hand-grip tests are frequently performed and recommended [21].

### Weight Loss Strategies – Lifestyle Management

The treatment of obesity is always intimately linked to the reduction of body weight. This can be achieved via different weight loss strategies, including lifestyle interventions (diet and exercise), pharmaceutical interventions, or bariatric surgery. Interestingly, gender differences in these strategies exist worldwide. While men prefer to exercise, women are more likely to join weight loss programs, take prescription diet pills, and follow special diets [22, 23]. In fact, it needs a combination of both preferences, resulting in weight loss by favoring a decrease in adiposity and an increase of lean mass in both sexes.

Exercise is the key component of every lifestyle intervention. Especially aerobic exercise is the best mode to reduce fat mass. Moreover, an increase in physical activity reduces intra-abdominal fat, increases lean mass, decreases depression, and improves glucose tolerance, insulin sensitivity, and physical fitness. Thus, it is not surprising that all scientific guidelines recommend at least 150 min/week of moderate aerobic exercise combined with three weekly sessions of resistance training to increase muscle strength [1, 24–26]. However, the reality is that intensive lifestyle interventions are difficult to achieve and to maintain over a long period of time, even if the patients are included in an optimal clinical trial setting such as Look AHEAD (Action for Health in Diabetes) [27]. Although exercise is an important component of every effective weight loss strategy, several studies reported additive effects on weight loss when it is combined with an energy-restricted diet. This can be achieved either by a low-fat, low-carbohydrate, or the Mediterranean-style diet [28–30]. The latter one is characterized by its beneficial metabolic effects as well as by its delayed need for an antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes [31]. In any case, a low-fat diet should have an adequate carbohydrate source with complex carbohydrates instead of mono- or disaccharides. However, it is not the diet type that determines the success of weight loss and cardiac risk factor reduction – it is the sustained diet adherence [32]. Thus, practical techniques to increase dietary adherence rates are urgently needed. One step towards this goal can be the use of a broad spectrum of different diet options to better match the patient's individual food preferences, lifestyle, and medical conditions. Additionally, the replacement of one or two meals per day by dietary supplements (low-calorie diets) might contribute to a nutritionally well-balanced diet and maintain weight loss [33]. Under certain conditions a very-low-calorie diet might support the weight loss objectives. However, this type of diet should only be limited to specific patients and for short periods of time. It is definitely not suitable for children, adolescents, or elderly people [1].

In the case of sarcopenia, appropriate intervention strategies slightly vary as the acquisition of muscle mass is essential. Consequently, exercise alone is not sufficient and has to be combined with a high-protein diet [34]. The timing of protein intake and the optimal amino

acid composition are still controversially discussed. Besides the acquisition of muscle mass, the physical fitness as well as the overall physical activity of the patient is of great importance, especially at an advanced age [35, 36].

### **Benefit of Weight Loss in Diabetes Prevention and Therapy**

Since the majority of people with type 2 diabetes are overweight or obese, weight reduction is seen as the key therapeutic goal in the prevention and the management of type 2 diabetes. For individuals, who have already progressed to pre-diabetes, the Finnish Diabetes Prevention Study showed that an intensive dietary and exercise program decreased the overall risk of diabetes by 58% [37]. Similar results were obtained in the Diabetes Prevention Program, wherein moderate weight loss with lifestyle intervention in an obese population with impaired glucose tolerance could reduce the incidence of diabetes by 58%, while metformin alone reduced it only by 31% [38]. Unfortunately, this study has not provided data regarding a combination of both strategies. Nevertheless, the improvement of insulin sensitivity and secretion can be directly correlated with a decreased risk of diabetes. In another study, each 1 kg weight loss in the first year of diabetes diagnosis was associated with 3–4 months of prolonged survival, and a weight loss of 10 kg was associated with the restoration of 35% in life expectancy [39].

For individuals with diabetes, Williamson et al. [40] could show that an intentional weight loss of 10 kg as seen in the American Cancer Society's Cancer Prevention Study I reduced the total mortality of people with diabetes about 25%. Other clinical trials as the Look AHEAD study underlined the beneficial effects of weight loss in diabetes patients. This study demonstrated that a loss of 5–10% of body weight could improve the overall fitness, reduce HbA1c levels, improve cardiovascular disease risk factors, and decrease the use of antihyperglycemic, antihypertensive, and lipid-lowering medications after 1 year [41, 42]. Furthermore, weight loss supported the reduction of depression symptoms and the remission of obstructive sleep apnea or at least reduced its severity [43, 44]. Interestingly, a weight loss of >5% appears to be necessary for these beneficial effects. Since this requires intensive interventions, including energy restriction and regular physical activity, this amount of weight loss might not be a realistic primary treatment strategy for all overweight and obese patients. Nonetheless, these patients should be encouraged to reduce their energy intake, which may – regardless of their weight loss – improve their glycemic control [45]. Besides, appropriate anti-obesity medications should be considered for those patients, who are still struggling with their weight management objectives.

### **Implications for a Combined Anti-Obesity and Anti-Diabetes Treatment**

An effective treatment of obesity has the ability to improve body weight, body composition and glycemic control simultaneously. The necessity therefor has already been demonstrated by an observational study of Eeg-Olofsson et al. [46], wherein cardiovascular disease, stroke, and total mortality were correlated with weight gain during an antidiabetic drug therapy. So far such data do not prove a direct relationship of weight gain and morbidity as many factors might influence these results, but it may be used for hypothesis generation. At least it can be argued that the observation of weight gain is an indicator of less treatment success and potentially elevates the individuals' mortality risk. Appropriate intervention studies to evaluate weight gain during an antidiabetic drug therapy are not ethical and thus not performable.

Given the strong association between the excess of weight and type 2 diabetes, the focus of a suitable antidiabetic treatment of obese patients should at least be the prevention of additional weight gain. Thus, glucose-lowering agents, which are weight neutral or support weight reduction, should be the first choice after the obligatory metformin therapy.

Currently, the options for an effective obesity pharmacotherapy vary worldwide. While several new drugs for weight management are available in the USA, only two of them – liraglutide (1.8 mg for type 2 diabetes and 3 mg for obesity treatment) and the combination of naltrexone and bupropion – have been licensed in Europe in 2015 but have not been launched so far in most European countries. These pharmacotherapies have demonstrated to assist patients with type 2 diabetes in achieving their weight loss goals and improving their HbA1c levels [47]. An overview of all licensed anti-obesity drugs in the USA and in Europe has been published in OBESITY FACTS [48]. Evidence-based recommendations on using anti-obesity drugs in the diabetes management cannot be made so far, but it seems to be most likely that they could have a place in the future. Hence, there is a need for appropriate studies to further elucidate the effect of anti-obesity agents in diabetic populations.

### Bariatric (Metabolic) Surgery

Bariatric surgery is an established and effective part of the weight loss management of morbidly obese patients. It is indicated in obese patients with a BMI  $\geq 40$  kg/m<sup>2</sup> or in individuals with a BMI  $> 35$  kg/m<sup>2</sup> in the presence of type 2 diabetes or other major comorbidities [4]. In the latter case, bariatric surgery has proven to be highly beneficial in type 2 diabetes remissions and in the reduction of cardiovascular events as demonstrated in the Swedish Obese Subjects study [49]. Today these surgeries are also conducted in patients with lower BMI. To further address the potential value or risks, the results of controlled studies with an exact benefit-risk evaluation would be needed.

In contrast to obese patients without diabetes, those with diabetes have normally access to an interdisciplinary healthcare team, which enables them to fulfill all the required examinations during the pre- and postoperative phase. Although these patients are well embedded in the required medical care system, the perfect patients' selection remains difficult as long-term nutritional and micronutrient deficiencies requiring a lifelong vitamin/mineral supplementation can occur. Moreover, the rapid and massive weight loss of muscle and fat-free mass could also lead to malnutrition and osteoporosis. Thus, attention should be drawn to the body composition (muscle-fat distribution) and the bone health. Both should be examined at least 2 years after surgery [50].

### Comparison of Drug and Bariatric (Metabolic) Therapies

Currently, bariatric therapies are more effective than drug therapies regarding weight reduction and metabolic processes – especially, when they are used to treat diabetes as demonstrated by the STAMPEDE (Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently) trial. The current 5-year follow-up analysis of this trial supports their prior findings that bariatric surgery is superior to intensive medical therapy in terms of glycemic control, weight reduction, decreasing medication use (antidiabetic, antihypertensive, and lipid-lowering agents) and improvement in quality of life. These beneficial effects were also observed among patients with mild obesity (BMI 27–34 kg/m<sup>2</sup>) [51]. Since bariatric surgery is almost excluded in this patient population, the promising results of the STAMPEDE trial raise the question if bariatric surgery should also be an approved therapeutic approach

**Table 1.** Overview of different drug types and their observed trends in weight gain; single studies and the individual response may differ in the results

Drug class	Weight effect <sup>1</sup>
<i>Antidiabetic treatments [59]</i>	
Metformin	neutral
Alpha-glucosidase inhibitors	neutral
Glinides	neutral to +
Sulfonylureas	(+) to ++
Pioglitazone	neutral to ++
DDP-IV inhibitors	neutral
SGLT-2 inhibitors	neutral to --
GLP-agonists	neutral to ---
Insulin	+ to +++
<i>Antidepressant agents [60]</i>	
Tricyclic antidepressants	
Amitriptyline, nortriptyline	+/-
MAO inhibitors	
Phenelzine, tranylcypromine	+++
Moclobemide	0/-
SSRI	
Citalopram, fluoxetine, paroxetine, sertraline	+/-
SNRI	
Duloxetine, venlafaxine, milnacipran	0/-
Others	
Bupropion	0/-
Mirtazapine	++
Lithium	+++ [61]
<i>Antipsychotic agents [60]</i>	
Clozapine	+++
Olanzapine	+++
Risperidone	++
Quetiapine	++
Aripiprazole	0/+
Ziprasidone	0/+
Haloperidol	+++ [62]
Pherphenazine	+/- [63]
<i>Antiepileptics</i>	
Valproic acid	++ to +++ [53, 64–66]
Carbamazepine	+ to ++(+) [65–68]
Gabapentin	+ to +++ [69, 70]
<i>Steroid hormones</i>	
Oral corticosteroids (prednisone)	+ to ++(+) [71, 72]
Hormone therapy-contraception (DMPA)	+ to ++ [73]
<i>Miscellaneous agents</i>	
Beta-adrenergic blockers (propranolol, metoprolol, atenolol)	+ to ++ [52]

<sup>1</sup>++++ Significant; ++ moderate; + slight weight gain; 0/+ slightly increasing effect; +/- inconsistent data; 0/- minimal to no weight reduction; -- moderate; --- significantly weight loss.

for patients with a BMI less than 35 kg/m<sup>2</sup>. However, further long-time cohort studies are needed.

Unfortunately, anti-obesity agents have not been evaluated so far in patients who received bariatric surgery. Nonetheless, mono- or combination therapies using these weight loss drugs could have the potential to improve the long-term success in weight loss and maintenance.

### Concomitant Therapies

Suitable anti-obesity treatments should consider concomitant therapies, which are not associated with weight gain. Unfortunately, this turned out to be a complex therapeutic challenge, as a number of pharmaceuticals tend to increase the patients' body weight. For many of them, the exact mechanism that causes weight gain is so far not known. Some affect the metabolism and lead to an increased appetite (antidepressants, antipsychotics, anti-epileptics, diabetes medications), cause fluid retention (diabetes medication), or slowly induce weight gain over a period of time due to fatigue and lower activity (beta blocker) [52–58]. Among them, antipsychotics represent the most important ones. However, the net weight gain varies from person to person and from drug to drug. Consequently, it can vary between a few kilograms in 1 year, to 10 or even more kilograms in just a few months. Since these medications are quite often used during chronic conditions, they significantly contribute to the individuals' weight gain over time (for an overview see table 1). Thus, attention has to be drawn to distinguish between weight gain, which is related to a specific treatment, and weight gain due to other factors like an inappropriate diet or lack of exercise. Although this is quite difficult, it will be the only option to elucidate a suitable therapy for each patient, especially when weight loss should be promoted.

Furthermore, the potential of weight gain is also discussed for several other therapeutic drugs, e.g. antihistamines like loratadine, fexofenadine, cycloheptadine, diphenhydramine, and doxepine. Although a number of drugs tend to increase body weight like psychotropic drugs, there are some, which have the potential to be either weight-neutral (e.g. the anti-epileptic drug lamotrigine) or may induce weight loss (e.g. the anti-epileptic drugs topiramate and zonisamide) [74]. Consequently, these drugs should be considered as alternatives, especially when weight loss is an objective.

### Conclusion

As obesity is an emerging epidemic of modern societies, the co-incidence with diabetes is also emerging. The resulting 'diabesity' raises the question whether weight management and diabetes should be targeted with combined treatment strategies. Data from registries show a tendency to decreased treatment success in diabetes whenever weight gain is observed. Additionally, concomitant therapies may increase body weight further with a deterioration of blood glucose control. Taken together, these observations should be the basis for a combined view of anti-obesity and antidiabetic treatment strategies. Studies based on that are warranted.

### Disclosure Statement

DRL, KS and EW reported no conflict of interest. GF has participated in a Novo Nordisk Obesity Scientific Communication Global Advisory Board Meeting. VY is on the national obesity advisory board of Novo Nordisk. DM has served as advisor and speaker for Novo Nordisk and Astra Zeneca. HT has served as advisor and speaker for Novo Nordisk, Vivus and Oregigen.

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