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Chapter 3

Targeted Therapies in Obesity Management

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Abstract

Obesity is a well known multifactorial condition visualized as excessive fat accumulation and described by the body mass index (BMI). Since last two to three decades obesity is identified as precursor of many chronic diseases like cardiovascular, diabeties mellitus, neurological and hepatic disorders. So as obesity is also treated in many customized manner using drugs to suppress hunger, produce satiety, reduce fat products metabolism and even surgery. Though many document are available in relation to obesity treatment and management there is lack compiled information which a comprehensive information material for researching fellow. In this document we used various research and review documented to produce a ready material for obesity treatment and management. In conclusion, obesity is chronic metabolic or genetic disorder making a gateway to too many diseases, through drugs used to manage obesity still it relapse after therapy withdrawal. Different targeted therapies from lifestyle intervention to dietary modification targeting physiological appetite suppressant to gut hormones were also discussed. The all together are currently under development and may offer in the future the potential to bridge further the efficacy gap between bariatric surgery and the currently available pharmacotherapies.

1. Introduction

Obesity is referred as excessive fat accumulation and described by the body mass index (BMI), body weight (in kilograms) divided by the square of body height (in meters) [6]. Obesity is a complex, chronic, progressive and relapsing disease characterized by abnormal or excessive body fat that impairs health and result in a decreased life expectancy of 5–20 years and increased healthcare costs [7, 10]. The last several years have seen remarkable progress in understanding the mechanisms of body weight regulation [38].

A major contributor to understanding food intake was the discovery in 1994 of the adipose tissue hormone leptin [65]. Several published reviews suggest that obese individuals have higher levels of circulating leptin and insulin than lean individuals [14, 51]. Leptin is a signaling chemical secreted mainly from fat cells that has been linked to hypothalamic neuropeptide systems to control food intake and energy homeostasis. Leptin and Insulin react on specific receptors in the hypothalamus of the brain to influence food intake and energy expenditure to maintain overall system homeostatic [35, 49]. When the leptin feedback part of the system is permanently changed, there is a chronic bias to overeat and gain weight [13]. However, leptin cannot be the only critical factor many individuals gain weight as they age and lifestyle lethargy steadily increase the prevalence of obesity.

The recent upward trend in the adult obesity rate is attributable to energy imbalance, where people consume more calories than they expend [58]. The increasing prevalence of obesity throughout the world is associated with an escalating incidence of obesity-related disorders and health costs [22, 31]. Obesity has more than doubled since 1980 all over the world, and in the European perspective it seems to be blooming out every year while it is flourishing rapidly in developing countries like India as physical activity in leisure has increased slightly while physical activity in work, housework, and travel has declined steadily. Thus the exact mechanism to prevalence of obesity is uncertain due to complex interaction between diet composition, eating and physical activity behaviors, and human physiology to pinpoint [23]. Obesity-related diseases like diabetes, hypertension, coronary heart disease, stroke and hyperlipidemia are the main cause of mortality and morbidity in developed countries.

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2. Targeted Therapies in Obesity management

An Obesity control therapy is an comprehensive approach to obesity management and treatment that includes a variety of therapeutic approaches [8]. This therapy seeks to assist, attain and maintain a healthy weight while also enhancing their overall health and well-being. Lifestyle interventions are the cornerstones for the management of obesity, but even the most intensive programmes still commonly only achieve 5–10% weight loss and long-term weight maintenance remains a challenge and attributes to the loss of motivation or compliance from the patients [54].

3. Life style interventions

Lifestyle interventions usually include support for health-improving behavioral changes including diet, increasing physical activity, and reducing sedentary time [59]. A report suggest moderate intensive lifestyle manipulations such as 500–600 kcal deficit diet together with to increased physical activity to 150 min/week can lead to 2–5% weight loss. While heavy intensive lifestyle interventions, which often include partial or total meal replacements, intensive behavioral therapy, and/or structured exercise, can lead up to more than 10% of weight loss in span of few months [44]. Structured exercise programmes and dietary intervention can have multiple health benefits such as improvement in body composition, physical function, and cardio respiratory fitness.

3.1. Dietary Modifications

Patient centered nutritional modifications needed to ascertain weight loss is unique individuals [17]. Some people may benefit from eating smaller portions or snacking in between meals while some others may benefit weight loss by adjusting what they eat rather than how much they eat. Its obligatory to say that almost every individual would benefit from consuming more plants, fruits, vegetables, whole grains, and legumes which contain less fat and more fiber and minerals [37].

3.2. Increase Physical Activity

Every published document states that food and exercise are vital parameter which is needed to modified and monitored for weight loss and its maintenance [11]. Walking at a moderate speed is one of the most effective forms of exercise for losing weight. Healthcare providers recommend 30 minutes, five days a week of moderated activity can attain 8-15% of weight loss in a span of 60 days. However, long-term maintenance of the recommended amount of moderate to vigorous physical activity can be challenging [9].

3.3. Challenges to maintain weight loss with lifestyle interventions

The weight regains after any lifestyle intervention programs if it is discontinued or not followed in prescribed manner and its attributes to the loss of motivation or compliance from the patients [56]. On the contrary increase in food intake, reduced energy expenditure, easy assessable high calorie foods and sedentary time causes metabolic adaptation to increased resting metabolic rate [60].

3.4. Psychological Therapies

Counseling, support groups, and techniques such as cognitive behavioral therapy may all play a role in your weight loss journey [41]. These techniques can aid in rewiring your brain to encourage positive changes towards weight loss. These therapies can also assist in managing stress and addressing emotional and psychological issues that may be interfering with patient obesity control. Obesity and its weight loss efforts have a wide range of effects on human social behavior, so having both emotional and practical support can be beneficial [64].

4. Approved pharmacotherapies for obesity over the last decade

Numerous antiobesity medications targeting appetite have been tried in the past to enhance weight loss but the many of them has been withdrawn due to safety concerns. There are not many available drugs treating obesity in the market today. On further note these drugs could be divided into three categories, the first one is the group of drugs that suppress appetite (e.g. Sibutramine, Phentermine, Amphetamine), the second is the group of drugs that interfere with digestion (e.g. Orlistat), and the third category is an inhomogeneous group of drugs that are actually used for other indications than weight loss, but with a concomitant weight loss effect. Such drugs are Incretins used in the treatment of diabetes (e.g. Exenatide, Liraglutide), antiepileptic drugs (e.g. Topiramate) and antidepressants (e.g. Fluoxetine, Sertraline).

4.1. Phentermine-Topiramate

The oral drug Phentermine-Topiramate was licensed for the treatment of obesity in the United States but is not authorized in Europe owing to worries regarding the drug's long-term cardio vascular safety. Phentermine dose range from 3.75 to 15 mg indicated for short-term use in weight management. It is a sympathomimetic amine which suppresses appetite by acting on the central nervous system [53]. Topiramate is an anticonvulsant indicated for use in the treatment of migraine and epilepsy while its other known effect is to a decrease appetite. Its dose range from 23 to 92 mg. In clinical use the Phentermine-Topiramate fixed-dose combination has been approved for use in the USA [55].

As per a study on people without diabetes, Phentermine-topiramate combination given for 56 weeks a dose of 15/92mg in extended release combination and with 500 kcal/day deficit diet resulted in 10.9% weight loss compared with 1.6% with placebo and 32.3% of participants achieved more than $\geq$15% weight loss [2]. Similar results were reported at the two year follow up of Phentermine-topiramate combination dose of 15/92mg in extended release [27]. The most commonly reported adverse events report on long term uses are upper respiratory tract infection, constipation, insomnia, paraesthesia, sinusitis, taste change and dry mouth. Phentermine-topiramate has also a warning of birth defects (cleft lip and palate) in the offspring of pregnant women taking the medication, due to the known teratogenic effect

[26].

4.2. Naltrexone-Bupropion

Naltrexone is an opioid receptor antagonist that is approved for the treatment of alcohol addiction and opioid dependence. Bupropion is a dopamine and norepinephrine reuptake inhibitor that was first approved for the treatment of depression and later for smoking cessation [4]. Although the precise mechanism by which the Naltrexone-Bupropion combination causes weight loss in obesity management is not entirely understood, it is most likely due to its effects on the hypothalamus and mesolimbic dopamine circuit, which increase satiety, decrease food intake, and potentially increase energy expenditure [45].

In a clinical trial, participants who responded to Naltrexone / Bupropion as an obesity treatment reported of feeling less hungry and more full compared with those receiving placebo and they found it easier to control their food cravings [29]. While in a study on people without diabetes, a combination dose 32/360mg of Naltrexone / Bupropion together along with 500 kcal deficit diet resulted in 6.3% weight loss after 52 weeks compared with 0.9% in the placebo group [32]. The most common adverse events with NB 32/360 are nausea, headache, constipation, dry mouth, anxiety, dizziness, hypertension, and vomiting. It is contraindicated in people with epilepsy as buproprion is associated with dose-related risk of seizures.

4.3. Sibutramine

It is an appetite suppressant which has been discontinued in many countries which works as aserotonin–norepinephrine reuptake inhibitor-similar to atricyclic antidepressant. It was widely marketed and prescribed as an adjunct in the treatment of obesity along with diet and exercise. Sibutramine in humans reduces the reuptake of norepinephrine, serotonin, and dopamine leading to increased levels of in synaptic clefts and thus enhance satiety [30].

Sibutramine is well absorbed from the gastrointestinal tract (77%), but undergoes considerable first-pass metabolism, reducing its bioavailability. A higher number of cardiovascular events have been observed in people taking Sibutramine versus control (11.4% vs. 10.0%). Thus FDA noted the concerns that Sibutramine increases the risk of heart attacks and strokes in patients with a history of cardiovascular disease [24]. The mentioned side effects are infrequent but serious and require immediate medical attention: cardiac arrhythmias, paresthesia, mental/mood changes.

4.4. Liraglutide

Liraglutide is an Glucagon Like Peptide-1 (GLP-1) receptor agonist similar to incretin hormone secreted predominantly from L cells located in the small intestine in response to food intake. It is responsible for glucose-lowering actions such as stimulation of glucose-induced insulin secretion, delay in gastric emptying and inhibition of glucagon secretion [33].

Exogenous Liraglutide infusion in humans recurrently resulted in reduced calorie intake, reduced appetite and effects on the reward system without direct changes in energy expenditure [63]. GLP-1receptor agonists were developed initially for the treatment of type 2 diabetes, however due to their efficacy in inducing weight loss and reducing appetite, they have been repurposed in higher doses as treatments for obesity [34]. In 2014, Liraglutide 3 mg once daily became the first GLP-1 receptor agonist to be approved for the treatment of adults with obesity and in 2021 [39]. Liraglutide 3 mg in combination with a 500 kcal/day deficit diet resulted in 6.1–8% weight loss in adults without diabetes. For people with type 2 diabetes, Liraglutide 3 mg resulted in 5.8%-6% weight loss when compared with 1.5–2% with placebo. The glycated sugar HbA1c reduced by 1.6% with Liraglutide 3 mg and 0.4% compared with placebo [19].

4.5. Semaglutide

Semaglutide was approved in 2021 as a new antiobesity long-acting Glucagon Like Peptide-1 receptor agonist which was recommended as 2.4 mg once weekly [25].

When compared to a placebo, this medication is reported to reduce energy consumption in obese individuals by 35% during an uncontrolled meal. Individuals who took semaglutide reported feeling less hungry, more satisfied and full, having better control over their eating habits, and having fewer and weaker urges for food [21]. In clinical trials, 56 weeks of semaglutide 2.4 mg in combination with a 500 kcal/day deficit diet resulted in 14.9% WL vs. 2.4% with placebo in people without diabetes [62]. Weight loss with semaglutide was associated with improved quality of life and continued the semaglutide trial when compared to placebo. Some common side effects reported were mild to moderate gastrointestinal problems such as nausea, vomiting and diarrhoea [61]. Oral semaglutide is an approved treatment for Type 2 Diabetic at the doses of 7 and 14 mg once daily is currently undergoing phase 3 trials as treatment for obesity at the dose of 50 mg once daily [18].

4.6. Tirzepatide

A number of gut hormones, including glucagon, amylin, glucose-dependent insulinotropic peptide (GIP), and Peptide YY (PYY) may enhance and further complement the effects of GLP- receptor agonist, resulting in more weight reduction, increased energy expenditure, and improved metabolic outcomes [1]. Tirzepatide is the first dual co-agonist acting on GLP-1/GIP receptors) which has been approved for treatment of Type 2 Diabetes based on the findings of the clinical trials. Moreover, Tirzepatide is currently undergoing an extensive programme of phase 3 clinical trials as treatment for obesity [42].

A recently published trial study on randomized 2539 participants with obesity without diabetes to three different doses of tirzepatide of 5, 10, and 15 mg and placebo for 72 weeks showed that tirzepatide 5–15 mg results in 15–20.9% weight loss when combined with moderate intensity lifestyle interventions [47]. Nausea, diarrhea, vomiting, and constipation were the most commonly reported side effects most of them were minor to moderate in severity and temporary.

4.7. Cagrilintide

This drug is an subcutaneous amylin analogue an another gut hormones in the pipeline as potential future therapeutic candidates. Amylin is a pancreatic β-cell hormone designated to produce satiety signal that is co-secreted with insulin in response to food intake and hence contol both homeostatic and hedonic appetite regulation [20].

Cagrilintide is under development as treatment for obesity undergoing phase 2 studies. Cagrilintide led to dose-dependent weight reductions and greater weight loss at all doses compared with placebo at 26 weeks. Gastrointestinal disorders were the most common adverse events, primarily nausea [43].

4.8. Cotadutide

Cotadutide is other dual GLP-1/glucagon receptor agonist currently under development, were less impressive as reported phase 1 clinical studies. The mechanism of action is based on concept of GLP-1/glucagon co-agonists includes the concurrent activation of the GLP-1 receptors leading to decreased energy intake and the glucagon receptors causing increased energy expenditure and reduced energy intake [3].

In a phase 2b, randomized, double-blind study, of overweight adults or having obesity with type 2 Diabetes receiving a cotadutide dose of 100, 200 or 300 μg and placebo for 54 weeks reported body weight reduction with cotatutide 300 μg was 5.02% compared with -0.68% in placebo group and -3.33%. Cotadutide also significantly lowered HbA1c by 1.03-1.19%. Gastrointestinal disorders, including diarrhoea, nausea, and vomiting, were the most commonly reported adverse events with cotadutide at any tested dose and more patients stopped cotatutide due to side effects compared with placebo or Liraglutide [48].

4.9. Bamadutide

Another GLP-1/glucagon receptor dual agonist (SAR425899) was recently evaluated in single-ascending dose and multiple-ascending dose phase 1 trial where it was given once a day over 28 days. Bamadutide (SAR425899) improves postprandial glucose control by significantly enhancing β-cell function and slowing glucose absorption rate in vivo [57].

At the highest maintenance doses tested, there was a reduction of HbA1c by 0.54-0.59% when given to patients who were overweight or had obesity with type 2 diabetes, and mean weight loss of 2.4-5.5 kg over the 28 days. It was generally well tolerated, with treatment-emergent adverse effects of reduced appetite and nausea [36].

4.10. Orlistat

Orlistat is a drug used to treat obesity. It works largely as a lipase inhibitor, which stops the body from absorbing fats from food and reduces calorie intake [15]. Due to its greater simplicity and durability as an anti-obesity medication compared to lipstatin, orlistat is chosen as the saturated derivative of lipstatin, a strong natural inhibitor of pancreatic lipases derived from the bacterium Streptomyces toxytricini [5].

When used in conjunction with lifestyle changes like diet and exercise, orlistat is effective in promoting weight loss at its modest functionality, according to clinical trial data. Over the course of a year, those who take the medication lose roughly 2-3 kg (4-7 lb) more than those who do not. Orlistat also reportedly reduces blood pressure and prevent the onset of type 2 diabetes [28, 50]. Orlistat is noted for its gastrointestinal side effects which can include oily and or loose stools [16].

5. Bariatric surgery

The surgical management of obesity is collectively referred to as bariatric surgery [52]. Bariatric surgery was the option that consistently produced $\geq$15% weight loss and long-term weight maintenance in a research involving obese people from Sweden. This led to considerable health benefits, decreased mortality, and a better quality of life [12].

The benefits of bariatric surgery on reducing cardiovascular events, cardiovascular death, all-cause mortality and new onset heart failure compared with the non-surgical management are consistent across multiple observational, matched-cohort studies, especially in people with obesity and type 2 Diabetes. According to the report, vertical banded gastroplasty and gastric bands are the two most often used bariatric surgeries worldwide performed 85% for all kind bariatric procedures [40]. Changes in the peripheral signals of body weight control with altered gut structure are one of the possible mediators for the decreased appetite and food intake following bariatric surgery [46]. But not everyone who qualifies for bariatric surgery wants to have surgery, nor is everyone who suffers from severe and complex obesity physically capable of doing so. To try to achieve comparable weight loss, pharmacotherapies that replicate some of the post-operative physiological changes following bariatric surgery would make sense.

6. Conclusion

The World Health Organization (WHO) has recognized that obesity has more than doubled since 1980 all over the world. Obesity is associated with diabetes, hypertension, coronary heart disease, stroke, hyperlipidemia, osteoarthritis, several types of cancer, gallbladder disease, nonalcoholic steatohepatitis, sleep apnea, infertility, depression, etc. Some of these diseases are the main cause of mortality in developed countries.

Many anti-Obesity Drugs were used to treat obesity in the past. Unfortunately, there is still no ideal drug for the treatment of obesity, and the current ones are very strictly evaluated. These are the reasons for continuous search for efficient treatment of obesity. Weight loss by lifestyle changes and could help far better in weight maintenance. In this context we have discussed the most clinically used therapies in achieving weight loss in management of obesity. It included different targeted therapies from lifestyle intervention to dietary modification while medication targeting physiological appetite suppressant to gut hormones were also discussed. The all together are currently under development and may offer in the future the potential to bridge further the efficacy gap between bariatric surgery and the currently available pharmacotherapies.

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