Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 2112–2120

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

Obesity an overview: Genetic conditions and recent developments in therapeutic interventions

Vikram Rao B. Vasanth Rao [a], Mayuren Candasamy [b], Subrat Kumar Bhattamisra [b, *]

[a] School of Postgraduate Studies, International Medical University, No 126, Jalan Jalil Perkasa 19, Jalan Jalil Perkasa 19, Bukit Jalil, 57000, Kuala Lumpur, Malaysia
[b] Department of Life Sciences, School of Pharmacy, International Medical University, Bukit Jalil, 57000, Kuala Lumpur, Malaysia

ARTICLE INFO

Article history:
Received 19 April 2019
Accepted 6 May 2019

Keywords:
Obesity
Genetic conditions
Anti-obesity drugs

ABSTRACT

Obesity is a complex disorder that is linked to many coexisting disorders. Recent epidemiological data have suggested that the prevalence of obesity is at an all-time high, growing to be one of the world's biggest problems. There are several mechanisms on how individuals develop obesity which includes genetic and environmental factors. Not only does obesity contribute to other health issues but it also greatly affects the quality of life, physical ability, mental strength and imposes a huge burden in terms of healthcare costs. Along with that, obesity is associated with the risk of mortality and has been shown to reduce the median survival rate. Obesity is basically when the body is not able to balance energy intake and output. When energy intake exceeds energy expenditure, excess calories will be stored as fat leading to weight gain and eventually obesity. The therapeutic market for treating obesity is composed of many different interventions from lifestyle intervention, surgical procedures to pharmacotherapeutic approaches. All of these interventions have their respective benefits and disadvantages and are specifically prescribed to a patient based on the severity of their obesity as well as the existence of other health conditions. This review discusses the genetic and environmental causes of obesity along with the recent developments in anti-obesity therapies.

© 2019 Diabetes India. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Obesity is said to be a complex medical condition caused by excessive accumulation of fat in the body due to increased intake of energy-rich foods and lack of physical activity. This condition is associated with a myriad of non-communicable diseases and health problems such as high blood cholesterol, metabolic syndrome, atherosclerosis, type II diabetes, high blood pressure and even cancers. Obesity is commonly diagnosed by assessing an individual's body mass index (BMI), waist to hip ratio (WHR) and waist to height ratio (WtHR) [1]. Obesity is defined by having a BMI $\geq$30 kg/m^2 while individuals who are severely or morbidly obese have either a BMI $\geq$40 kg/m^2 or a BMI of 35–40 kg/m^2 and obesity-related co-morbidities [2]. Obesity is one of the biggest growing problems of the world, which is turning out to be a major issue towards health and a very costly one too. The Milken Institute estimates the healthcare costs for obesity in the US to be approximately 480.7 billion [3]. In the US, obesity is prevalent in 39.8% of adults and 18.5% of youths based on a recent survey conducted on obesity rates from 2015 to 2016 [4]. The World Health Organization (WHO) had estimated that 13% of the world's population was obese in 2016 and has tripled since 1975 [5]. Based on 57 prospective studies amounting to a total of 894,576 subjects within Western Europe and North America, severe obesity is positively correlated with mortality and that the median survival rate could be lowered by 10 years [6]. The vivid rise in obesity can be attributed to genetic factors as well as environmental factors such as the constant availability of calorie-rich foods and the increasing trend of sedentary lifestyles lacking physical activity. In addition to elevated health risks, obesity can also lead to social expulsion and emotional distress due to physical limitation. Obese children were found to be socially isolated as they could not keep up with the physical fitness of other children leading to them having reduced self-esteem [7]. Several interventions targeting obesity are readily available, from lifestyle changes, pharmacotherapeutic approaches to bariatric

* Corresponding author. Department of Life Sciences, School of Pharmacy, International Medical University, No 126, Jalan Jalil Perkasa 19, Bukit Jalil, 57000, Kuala Lumpur, Malaysia.
E-mail addresses: vikram.rao@student.imu.edu.my (V.R.B. Vasanth Rao), subratkumar@imu.edu.my, bhattamisra@yahoo.co.in (S.K. Bhattamisra).

https://doi.org/10.1016/j.dsx.2019.05.004
1871-4021/© 2019 Diabetes India. Published by Elsevier Ltd. All rights reserved.

Abbreviations

5-HT2c	5-Hydroxytryptophan 2c
ACC	American college of cardiology
AgRP	Agouti-related peptide
AHA	American heart association
ALMS1	Alstrom syndrome protein 1
BAT	Brown adipose tissue
BBS genes	Bardet-Biedl syndrome
BMI	Body mass index
CB1	Cannabinoid receptor type 1
COR I	Contrave obesity research I
COR II	Contrave obesity research II
DBP	Diastolic blood pressure
FDA	Food and drug administration
FTO	Fat mass and obesity-associated
GLP-1R	Glucagon-like peptide 1 receptor
GLUT4	Glucose transporter type 4
GPD1L	Glycerol-3 phosphate dehydrogenase 1-like
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HIF-1α	Hypoxia-inducible factor
IRS1	Insulin receptor substrate 1
IRS2	Insulin receptor substrate 2
Irx3	Iroquois homebox gene 3
JAK2	Janus kinase 2
LDL	Low-density lipoprotein
LEPR	Leptin receptor
MCR4	Melanocortin-4 receptor
mIU/L:	Milli-international units per litre
NPY	Neuropeptide Y
CART	Cocaine- and amphetamine-regulated transcript
POMC	Pro-opiomelanocortin
SBP	Systolic blood pressure
SH2B1	Src homology 2 B adapter protein 1
SNORD115	Small nucleolar RNA, C/D Box 115
SNORD116	Small nucleolar RNA, C/D Box 116
SNPs	Single nucleotide polymorphisms
T3	Triiodothyronine
T4	Thyroxine
TOS	The obesity society
TSH	Thyroid stimulating hormone
UCP1	Uncoupling protein 1
CIDEA	Cell death inducing DFFA like effector A
PGC1α	Peroxisome proliferator-activated receptor gamma coactivator 1α
VPS13B	Vacuolar protein sorting-associated protein 13B
WAT	white adipose tissue
WHO	World health organization
WHR	Waist to hip ratio
WtHR	Waist to height ratio

surgical procedures. However, major limitations in these interventional approaches have resulted in adverse side effects and relapse of weight gain. The current review discusses the causes of obesity, genetic mechanisms involved, conventional and future approaches for the treatment of obesity as well as an update on ongoing clinical trials.

2. Energy imbalance and obesity

As briefly discussed above, one of the most common causes of obesity is the increased intake of energy-dense foods coupled with the lack of physical activity. An active adult male and female require approximately 2500 and 2000 calories respectively per day however, most individuals consume half this amount of calories in just one meal [8]. When calorie intake exceeds energy output, the extra calories will be stored as fat, which leads to excess weight and obesity. Foods that contain high amounts of carbohydrates and fats are the main culprits for causing obesity along with the lack of physical activity. It has been found that only a minor surplus in overall energy balance, by 7–10 kcal above the required amounts can lead to an increase in BMI [9].

The lack of physical activity has been said to affect hormone levels such as insulin whereby its unstable levels are associated with weight gain [1]. Insulin sensitivity, which is described by how sensitive an individual is to the effects of insulin and research has suggested that a lack of physical activity can lead to a decrease in insulin sensitivity. Insulin sensitivity is commonly determined by measuring fasting insulin levels whereby elevated fasting insulin levels (>25 mIU/L) indicates reduced insulin sensitivity. This is because the pancreas works harder to secrete higher amounts of insulin to compensate for insulin insensitivity, which results in hyperinsulinaemia [10]. The lack of physical activity coupled with obesity causes the accumulation of intracellular lipids within the skeletal muscle and liver thus impairing insulin signaling, decreasing uptake and utilization of glucose by the skeletal muscles and the weakening of insulin-regulated prevention of hepatic glucose production [11,12]. In 2013, Roberts and colleagues reported that a single aerobic exercise session was able to acutely improve insulin sensitivity by more than 50% for up to 72 h [13]. Additionally, Damirchi and colleagues also identified that a 6-week aerobic exercise program had improved insulin sensitivity in men with metabolic syndrome therefore, proving the association between lack of physical activity and insulin insensitivity [14].

3. Genetic mutations and obesity

3.1. Prader-Willi syndrome

Research has helped us understand that underlying genetic syndromes are closely associated with obesity. One of the genetic syndromes associated with obesity is Prader-Willi syndrome, which is a rare condition known to cause a range of physical symptoms, behavioural problems and intellectual impairment. Some of the symptoms of Prader-Willi syndrome are excessive appetite and overeating, learning difficulties, short-tempered and stubborn, lack of sexual development and stunted growth [15]. This syndrome affects approximately 1 in 10,000 to 30,000 individuals globally due to faults in genomic imprinting with the loss of function of paternally expressed genes on chromosome 15. This condition occurs due to the deletion of the paternal chromosome region 15q11 − q13 and during maternal disomy 15 [16]. The genes responsible are paternally activated via genomic imprinting hence, a functional copy of the paternal genes is required to avoid this syndrome [17]. Individuals with this disorder exhibit a paternal deletion of the snoRNA of the SNORD116 and SNORD115 genes. This was also seen in mice whereby paternal deletion of these genes resulted in hyperphagia and obesity [16]. Prader-Willi syndrome is the most common genetic cause of morbid obesity in children. The reduced muscle tone in individuals suffering from Prader-Willi syndrome contributes to a decreased metabolic rate and lack of

physical activity. This along with the increased appetite causes a chronic imbalance between energy intake and output, resulting in obesity [16]. In comparison with obese subjects, those with Prader-Willi syndrome had lower energy expenditure and decreased lean body mass. Additionally, the energy expenditure of these individuals at rest was significantly suppressed by 16% compared to the obese subjects [18]. In 2006, Holsen and colleagues conducted an interesting study on post-meal brain responses to food stimulation images in subjects with Prader-Willi syndrome [19]. Results showed that there was higher brain activation primarily in the medial prefrontal cortex, insula, orbitofrontal cortex and the hippocampus towards food stimulation images post-meal for the subjects affected by Prader-Willi syndrome compared to the control group. All of these brain regions are associated with increased eating behaviour [19].

3.2. Bardet-Biedl syndrome

Another rare genetic disorder linked to obesity is the Bardet-Biedl syndrome. Characteristics of this condition include obesity, renal abnormalities, learning difficulties, polydactyl and retinopathy. In North America and Europe, the prevalence of this disorder is 1 in 140,000 to 160,000 [20]. Bardet-Biedl syndrome is an autosomal recessive disorder, which causes abnormalities in hypothalamic action of leptin, the satiety hormone. The Bardet-Biedl genes are responsible for producing Bardet-Biedl proteins, which act as essential regulators of leptin receptor trafficking. Hence the loss of function of these genes can lead to leptin resistance [21]. Leptin is a hormone expressed by adipocytes that acts within the central nervous system to reduce food intake and elevate energy expenditure in response to weight gain [22]. Population studies conducted on the French-Caucasian population identified four single nucleotide polymorphisms (SNPs) within three (BBS2, BBS4 and BBS6) of the twelve BBS genes identified up to date. It was identified that an SNP, rs4784675 within the BBS2 gene and an SNP, rs221667 within the BBS6 gene were significantly different in allele frequency between lean and obese adults. Additionally, an SNP, rs7178130 within the BBS4 gene and two SNPs, rs6108572 and rs221667 within the BBS6 gene were found to be linked with childhood obesity [23].

3.3. Alstrom syndrome

Alstrom syndrome is also an autosomal recessive genetic disorder caused by a mutation in the ALMS1 gene, located on chromosome 2p13. Characteristics of this disorder are childhood obesity, hyperinsulinemia, type 2 diabetes, hypertriglyceridemia and hearing loss, amongst others. The prevalence of this extremely rare genetic disorder has been reported as more than 900 individuals worldwide [24]. Colin and colleagues discovered that mice with an insertion mutation on the ALMS1 gene in mice led to body weight gain and early hyperinsulinemia [25]. In 2014, Favaretto and colleagues further proved this by identifying that suppression of the glucose transporter type 4 (GLUT4) via mutation of ALMS1 increased fat pad size and elevated expression of lipogenesis enzymes in mice causing adipose tissue enlargement as seen in obesity [26]. Leptin levels of individuals suffering from Alstrom syndrome are also significantly higher compared to unaffected obese controls suggesting leptin resistance [27].

3.4. Cohen syndrome

Cohen syndrome is an autosomal recessive genetic disorder that can result in abnormal fat storage, obesity, intellectual disability, microcephaly and retinal dystrophy. An accurate prevalence of this disorder has not been determined but it is speculated to occur in less than 1000 individuals globally based on diagnosis reports [28]. This disorder is caused by mutations in the VPS13B gene located on chromosome 8q22.2, which produces essential proteins that are part of the Golgi apparatus [29]. The exact mechanism on how this disorder results in obesity is not fully understood but mutations in this gene would ultimately result in glycosylation defects. Glycosylation is a process that occurs in the Golgi apparatus where carbohydrate molecules are attached to newly synthesized proteins for sorting and vesicle-mediated transport of proteins within the cell. It can be suggested that the defect in the VPS13B gene can affect proteins playing an important role in the cellular mechanism of adipogenesis [30]. In a study conducted by Limoge and colleagues in 2015, Cohen syndrome fibroblasts that are VPS13B-deficient were isolated from patients suffering from the disorder. Results showed that adipogenesis and adipocyte differentiation were more apparent in these fibroblasts compared with the control fibroblasts [31]. The supernatant of the adipocytes in the Cohen syndrome fibroblasts had long thread-like projections and was stickier when aspirated indicating adipogenic differentiation. Adipogenic differentiation is characterized by the synthesis and release of proteoglycans that provides lubrication, and help cells to obtain more space and move about as they swell with fat. Furthermore, lipogenic and adipogenic genes were found to be elevated in the Cohen syndrome cells as compared to the control cells. A similar observation was noticed for the triglyceride content. All of these indications suggest that a defective VPS13B gene is linked to abnormal fat accumulation and differentiation as seen in patients with Cohen syndrome [31].

4. Association of genes and obesity

4.1. Leptin gene

Early research has identified that the hypothalamus plays an important role as a regulator of appetite and body weight but only in 1994, Zhang and colleagues had discovered that leptin was the hormone responsible for fat accumulation, appetite and energy expenditure and metabolism [32,33]. In response to nutrient depletion, leptin levels increase, which stimulates the expression of pro-opiomelanocortin (POMC) in the arcuate nucleus of neurons of the hypothalamus. The post-translational modification of POMC generates melanocortin peptides that modulate the function of the central nervous system, skin and adrenal gland through the activation of melanocortin receptors [34]. Leptin also acts to inhibit the orexigenic pathways expressing the melanocortin antagonist agouti-related peptide (AgRP) and neuropeptide Y (NPY). In brief, leptin activates POMC neurons to produce α-melanocyte-stimulating hormone that activates the melanocortin-4 receptor (MCR4) located on downstream neurons. This induces satiety and increases energy expenditure [22]. In contrast, leptin inhibits the AgRP neurons resulting in elevated feeding behaviour and decrease in energy expenditure [35]. The leptin-melanocortin pathway is essential in balancing food intake and energy expenditure. One of the mutations involved in the dysfunction of this pathway is the adapter protein Src homology 2 B adapter protein 1 (SH2B1). This gene is responsible for activating Janus kinase 2 (JAK2) and recruiting the insulin receptor substrate 1 (IRS1) and IRS2 to the leptin receptor (LEPR)-JAK2 complex [36]. Hence, SH2B1 is an important regulator of leptin sensitivity whereby the deletion of this gene can result in impaired leptin signaling and obesity [37]. Besides that, another mutation within the leptin gene known as p.N103K, which causes a change in amino acid from asparagine to lysine at position 103 of the protein. This missense mutation leads to a significant reduction in leptin activity resulting in severe

obesity [38]. Other mutations within the leptin gene that have been identified thus far are R105W and L72S which are associated with severe obesity [39].

4.2. GPD1L gene

In addition to the leptin gene, a novel gene that is linked to obesity was identified by Hao and colleagues in 2017 [40]. Glycerol-3 phosphate dehydrogenase 1-like (GPD1L) gene is negatively correlated with obesity and BMI where it is upregulated during periods of weight loss and downregulated in response to weight gain. The GPD1L gene is located on chromosome 3p22.3 and encodes for the protein, glycerol-3 phosphate dehydrogenase 1-like (GPD1L), and is said that GPD1L within adipose tissues is important in the mechanism of obesity [40]. It was found that adipose tissues are poorly oxygenated in obese individuals and the expansion of adipose tissue due to excessive calorie intake elevated oxygen consumption and developed a state of hypoxia within the adipocyte [41]. In response to low oxygen levels, the hypoxia-inducible factor (HIF)-1α is activated causing an inflammatory response within the adipose tissue. In the long-term, this state of inflammatory can progress to insulin resistance, glucose intolerance and hyperinsulinemia [41]. Similar outcomes were seen in mouse models whereby overexpression of adipocyte specific HIF-1α led to severe obesity, increased inflammation of adipose tissues, insulin resistance and greater white adipose tissue mass [42]. In contrast, HIF-1α knockout mice showed better protection against the high fat diet-induced obesity along with reduced fat formation [43]. In 2013, Kelly and colleagues discovered that GPD1L is a regulator of HIF-1α stability and a direct target of the so-called “master miRNA” of the hypoxic response, miR-210. Knockdown and overexpression studies of GPD1L further proved this as it resulted in the increase or decrease of HIF-1α activity respectively [44,45]. During a state of hypoxia, HIF-1α activity is increased thus stimulating the build-up of miR-210 which directly binds to and suppresses GPD1L protein expression. This further reduced the activity of prolyl hydroxylases which in turn, promotes HIF-1α protein expression leading to inflammation of adipose tissue, obesity and insulin resistance [44]. The GPD1L gene could possibly serve as a potential therapeutic target given that it is negatively correlated with obesity.

4.3. Irx3 gene

Recently the association of Iroquois homebox gene 3 (Irx3) and obesity was described by Smemo et al. [46]. The author has demonstrated that genetic deficiency of Irx3 expression in the full body and hypothalamus results in a 30% reduction in body weight. He has also demonstrated that promoters of Irx3 directly interacts with fat mass and obesity-associated (FTO) gene in multiple species including humans [46]. Understanding the exact role of Irx3 in energy balance and its mechanism through the involvement of regulating the POMC neurons is important [47]. It has been reported that Irx3 is depleted in fasted conditions, similar to POMC/CART, and in contrast to AgRP/NPY. This further strengthens evidence of Irx3 expression in the POMC neurons in the arcuate nucleus [47,48]. Several studies demonstrated the involvement of Irx3 genes in subcutaneous white adipose tissue (WAT) and brown adipose tissue (BAT). Zao et al. have reported that Irx3 gene expression in BAT and WAT had increased in response to β-adrenergic stimulation. Further, they have also demonstrated the knockdown of Irx3 gene resulted in the reduction in UCP1, CIDEA and PGC1α gene expression which are all involved in uncoupling heat production. This result suggests a strong association of Irx3 gene and thermogenesis [49]. However, these results are contradictory to the previously published results that reported Irx3 knockout in mice were protected against obesity [46] and overexpression of Irx3 in human adipocytes showed diminished thermogenesis [49]. The reasons for the discrepancy are totally unknown [50].

5. Endocrinal disorders and obesity

5.1. Hypothyroidism

Hypothyroidism is a disorder whereby the underactive thyroid gland is unable to produce sufficient thyroid hormone required for energy and metabolism. Thyroid hormones are essential for regulating basal metabolism, thermogenesis, food intake, and highly involved in the metabolism of lipids and glucose. Thyroid dysfunction can result in a lowered metabolic rate and resting energy expenditure and shows a strong correlation with weight gain [51]. In contrast, thyroid stimulating hormone (TSH) has also been found to be increased in obese individuals [52]. In 2001, Tagliaferri and colleagues reported that obese subjects exhibited low free T4 with a moderate increase in T3 and free T3 amongst 108 obese subjects with subclinical hypothyroidism [53]. Resting energy expenditure per kilogram of fat-free mass was also significantly lower in the patients suffering from subclinical hypothyroidism [53]. Some pediatric obese patients have also exhibited the characteristics of Hashimoto's thyroiditis, an autoimmune disorder where thyroid autoantibodies are produced by the immune system causing chronic inflammation and an underactive thyroid gland [54]. From a clinical perspective, many cases of thyroid failure go undiagnosed and these individuals will continue to gain weight. On the contrary, not all obesity cases should be deemed as caused by hypothyroidism as there are in fact lean individuals suffering from overt hypothyroidism. Hence, it is important to measure circulating plasma levels of both thyroid hormones and autoantibodies in addition to elevated serum TSH to ensure an accurate diagnosis of the patient [51].

5.2. Cushing's syndrome

Besides that, Cushing's syndrome, which is characterized by the overproduction of cortisol by the adrenal glands [55]. The high level of cortisol in the blood causes the body to feel as though it is under chronic stress. Cushing's syndrome can result from two different modes; 1) Iatrogenic Cushing's syndrome caused by the overuse of cortisol medication and, 2) Ectopic Cushing's syndrome caused by a tumour in either the adrenal gland that produces excess cortisol or the pituitary gland that secretes additional adrenocorticotropic hormone resulting in over-secretion of cortisol from the adrenal gland. Normally functioning cortisol supports the body in response to changes in the environment and stress by mobilizing nutrients such as carbohydrates, proteins and fats, and changing the body's response to inflammation as well as inducing the liver to raise blood sugar and regulating the body's water capacity [56]. Obesity is a common characteristic of Cushing's syndrome and was reported in 9.33% of subjects of 150 patients investigated based on a study conducted by Tiryakioglu and colleagues in 2010 [57]. They further reported that upon treatment for Cushing's syndrome, there was a 5.5% reduction in body weight [57]. Given that, cortisol is responsible for supporting the body during stress and inflammation or in other words, “to protect the body”, these actions increase appetite, store excess fat and breakdown quick forms of energy like collagen, skin and muscle [58].

6. Management of obesity

Given that obesity is an increasingly prevalent disorder having

strong associations with a number of chronic comorbidities, reduced quality of life and survival as well as increased health care costs. Patients with obesity are at a higher risk towards type 2 diabetes, cardiovascular and musculoskeletal disorders and certain cancers [59]. Both surgical and non-surgical interventions are available for patients suffering from obesity.

6.1. Lifestyle intervention

Lifestyle interventions in treating obesity could be regarded as a safer method compared to pharmacotherapy and surgical procedures. The essential components for an effective and comprehensive lifestyle intervention include; 1) appropriate counseling sessions from a trained team of practitioners, 2) reduced-calorie diet; 3) increased physical activity and, 4) behavioural strategies to ensure adherence to diet and activity programs. Jensen and colleagues had reported suitable non-surgical and non-drug strategies for weight-loss and weight maintenance based on the guidelines for the management of overweight and obesity in adults developed by the American Heart Association (AHA), American College of Cardiology (ACC) and The Obesity Society (TOS) [60]. The guidelines denote four key aspects; counseling, diet regime, physical activity and behavioural therapy. Medical practitioners and trained interventionist are responsible for prescribing a tailored diet plan and physical activity regimen based on the severity of obesity and other obesity-related coexisting diseases. Another important aspect of the program is the recording of data. Patients are encouraged to regularly record their food intake, physical activity and weight. Subsequently, patients are able to review their progress with the trained interventionist regularly, who are able to provide guidance on goal-setting, encouragement and solutions to any problems encountered [62,63]. A comprehensive program prescribed by a trained interventionist as such showed a mean weight loss of 5–8%. It was also found that 60–65% of subjects had achieved a weight loss of 5% from their initial weight [61]. The Look Ahead trial, which composed of 5145 subjects, also determined that intensive lifestyle intervention was able to improve weight loss, fitness, quality of life, glucose control as well as contributing to a reduction in healthcare costs [63]. Severely obese individuals had shown a weight loss of about 9% from their initial body weight after 1 year of the intensive lifestyle intervention. Along with that, improvements in cardiovascular risk factors were also observed. After 1 year, subjects had increased high-density lipoprotein (HDL) levels and reduced low-density lipoprotein (LDL), triglycerides, blood pressure and hemoglobin A1C (HbA1c) levels [64].

A low-calorie diet based on the guidelines of National Heart, Lung and Blood Institute provides a reduction of 500–1000 kcal per day and can contribute to a weight loss of 0.5–1 kg per week. Specific care should be taken to ensure that all recommended dietary allowances are obtained by the patient. As mentioned above, interventionists or nutritionists are essential for providing dietary education and for a successful weight loss. Patients should be taught to read nutrient labels to understand the caloric contribution of fats, proteins and carbohydrates. Additionally, patients should be advised to avoid overconsumption of high caloric foods that are high in fats and carbohydrates [65].

6.2. Surgical intervention

Weight loss surgery is also commonly known as bariatric surgery which includes a variety of procedures with the outcome of promoting weight loss. This is achieved by reducing the size of the stomach thus, restricting the amount of food that can be held by the stomach and malabsorption of nutrients [66]. Long-term studies have identified that bariatric surgeries can lead to long-term weight loss, improvements in cardiovascular risk factors and diabetes, and a reduction in mortality from 40% to 23% [67]. Bariatric surgery is prescribed mainly for individuals whose BMI is $\geq 40\ kg/m^2$ or individuals with a BMI of 35–40 kg/m^2 and a serious coexisting medical disorder such as type 2 diabetes or hypertension [66].

The common bariatric procedures include the adjustable gastric band, biliopancreatic diversion with duodenal switch, laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy. The adjustable gastric band procedure involves the placement of an inflatable band around the upper segment of the stomach that creates a small pouch as a stomach above the band. Biliopancreatic diversion with duodenal switch involves two parts, a portion of the stomach is first removed creating a tubular pouch and then a large segment of the small intestine is bypassed. The sleeve gastrectomy procedure is where 80% of the stomach is removed leaving a small tubular pouch as the stomach. As for the Roux-en-Y gastric bypass, a small stomach pouch is first created by dividing the upper and lower stomach. Then, the bottom end of the small intestine is connected to the smaller upper stomach pouch. Lastly, the top portion of the small intestine is connected to the small intestine further down the tract in order for the digestive enzymes and stomach acids from the bypassed stomach and upper portion of the small intestine to mix with the food. The adjustable gastric band and sleeve gastrectomy involve gastric restriction which reduces the volume of the stomach thus inducing early satiety. On the other hand, the biliopancreatic diversion with duodenal switch involves the bypass of various lengths of the small intestine resulting in nutrient malabsorption. The Roux-en-Y gastric bypass is known as the gold standard of bariatric surgeries. It involves both gastric restriction and a short segment bypass. Both, the biliopancreatic diversion with duodenal switch and the Roux-en-Y gastric bypass also involve the re-routing of the food stream which causes changes in the gut hormones leading to induction of satiety and hunger suppression [66,68,69].

6.3. Antiobesity drugs and its recent developments

Obesity is the central cause of the development of comorbid conditions like hypertension, cardiometabolic diseases, and type-2 diabetes mellitus. The pharmacological approach to weight loss remains an opportunity for many researchers alongside non-pharmacological management. Development of centrally acting sympathomimetics, such as phentermine and diethylpropion was initiated way back in the 1950s and 1960s [70,71]. Later in the 1970s and 1980s, fenfluramine and dexfenfluramine (serotonin (5-HT)-releasing agents) were introduced as an obesity therapy. However, 5-HT releasing agents had the potential to develop pulmonary hypertension. In the early 1990s, fenfluramine and phentermine combination results in better efficacy than monotherapy [72]. This combination results in cardiac valvulopathy [73] led to the withdrawal of fenfluramine and dexfenfluramine. These sympathomimetic agents were approved by the FDA for short-term use (up to 12 weeks). Phentermine is the most widely prescribed obesity medication in the USA between 2008 and 2011 [74]. A placebo-controlled trial of phentermine (30 mg/day) was conducted for 36 weeks in 108 women. Women took the drug continuously reported a 12.2 kg body weight loss as compared to intermittent group (13 kg) vs placebo reported 4.8 kg loss. Other sympathomimetics are less frequently prescribed than phentermine. In the late 1990s, Sibutramine, a dual monoamine (noradrenaline and serotonin)-reuptake inhibitor, was introduced to clinical practice [75,76]. It demonstrated a modest weight loss by increasing energy expenditure and decreasing energy intake. However, the serious cardiovascular risk was reported in the post-marketing clinical trial [77] leading to the suspension of marketing. Role of cannabinoid CB1 receptors in appetite was well established

[78]. In the mid-1990s, Rimonabant, a CB1 receptor antagonist was developed. It has consistently demonstrated a weight loss of 4–5 kg in four major clinical trials [79–82]. Rimonabant was approved as an anti-obesity agent in Europe in 2006. Later in 2008, it was suspended due to reports of serious psychiatric problems (such as depression, anxiety, and suicide). This led to the termination of development programmes that were involved in other CB1 antagonists such as taranabant, surinabant, otenabant and ibipinabant [83].

Orlistat was approved by the FDA in 1998 for the treatment of obesity. It reduces fat absorption from the gut by ~30% by inhibiting the gastrointestinal lipase [84]. It is available in two strengths 60 mg and 120 mg. Orlistat (120 mg) is approved for use in adults and adolescents (12–16 years). In a clinical trial, orlistat (120 mg), 35%–73% of participants achieved 5% weight loss at 1 year whereas, 10% weight loss was achieved in 14%–41% of participants. The trial was continued to 2nd year with a weight-maintenance diet. Participants lost approximately 2.5 kg (≈2.5% of initial weight for 60 mg orlistat) and approximately 3.3 kg (≈3.3% of initial weight for 1120 mg orlistat) more body weight respectively as compared to placebo [85–88]. Orlistat 120 mg treatment for 1 year exhibits significant improvements in cardiovascular risks factors including reduction in SBP and DBP, fasting glucose and cholesterol [89,90]. This effects may be related to the weight reduction or independent to weight reduction [91]. The major limitation is that orlistat is associated with gastrointestinal adverse events due to its primary mechanism of action. The adverse events may be decreased by co-administering orlistat with fiber-containing supplements [92]. In Europe during 2011–2012, Orlistat was the only approved anti-obesity agent for long-term clinical use [93].

Lorcaserin, a selective 5-HT2c receptor agonist was initially rejected in 2010 due to concerns about tumour growth in preclinical studies but, the drug was approved by the FDA in June 2012 on the basis of 2 large clinical trials in nondiabetic patients along with a 3rd smaller trial in type 2 diabetes [94–97]. In these trials, participants received lorcaserin (10 mg) with low-intensity nutritional and exercise counseling. Participants with lorcaserin for 2 years had an average weight loss of 5.6 kg as compared to 2.4 kg loss in participants receiving placebo [97]. In addition to body weight loss in non-diabetic participants, it demonstrated a significant reduction in total cholesterol, LDL, triglycerides, and blood pressure [98]. Lorcaserin led to decreased body weight and HbA1c in diabetes patients [96]. Reported adverse effects in trials are dizziness, headache, fatigue, and nausea [98]. Although statistically insignificant incidences of hypertension and valvulopathy were recorded, the FDA has requested to assess the long-term cardiovascular effects in a post-approval trial [99]. In 2015, a pilot study was conducted with lorcaserin and phentermine combination. The addition of phentermine resulted as much as twice the amount of weight loss as compared to the lorcaserin alone [100].

Glucagon-like peptide 1 receptor (GLP-1R) agonists liraglutide has shown a weight loss of up to 10 kg in patients in 2-year duration [101,102]. In a double-blind, placebo-controlled trial for 20-weeks, liraglutide (1.2, 1.8, 2.4, or 3.0 mg) subcutaneously administered once daily, or orlistat (120 mg) three times a day orally. Mean weight loss with liraglutide 1.2–3.0 mg was 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg compared with 2.8 kg with placebo and 4.1 kg with orlistat. In addition to weight loss, it has reduced blood pressure in all doses and reduced the prevalence of prediabetes with 1.8–3.0 mg per day. More common and transient adverse effects are vomiting and nausea which rarely led to discontinuation of liraglutide [103].

Rosuvastatin, an HMG CoA reductase inhibitor for the cholesterol-lowering was tested for change in visceral adiposity in middle aged (40–65 years) obese participants after 26 weeks of treatment. The study, a randomized, double-blind and placebo-control phase-3 clinical trial (RIVIERA) was conducted in 54 participants [104]. The change in body weight was 0.2 and 0.5 kg in rosuvastatin (10 mg, once daily) and placebo groups respectively. Visceral adipose tissue area measured by Computed Tomography in rosuvastatin and placebo groups was $-1.5\,cm^2$ and $2.8\,cm^2$ respectively [104].

A randomized double-blind, placebo control study of zonisamide, a centrally acting drug with two different doses 200 mg and 400 mg was conducted in 225 participants. There were 134 women (59.6%) and 91 men (40.4%) without diabetes mellitus participated in the study. The change in body weight was −4.4 kg for 200 mg of zonisamide, −7.3 kg for 400 mg of zonisamide vs −4.0 kg for placebo. The proportion of patients achieved with significant weight loss (≥5%) was 23%, 26% and 41% in placebo, 200 mg, and 400 mg zonisamide respectively. However, it has reported higher incidences of the nervous system, psychiatric and gastrointestinal adverse events [105,106].

Besides monotherapy with available drugs, combination therapies are also developed for the treatment of obesity. Based on two Phase-3 clinical trials for 52 weeks EQUIP [107] and CONQUER [108], Phentermine plus topiramate-extended release (ER) was recommended for approval. The CONQUER trial, phentermine plus topiramate-ER (7.5/46 mg) combination was treated to participants with BMI of 27–45 with at least 2 obesity-associated comorbid conditions [108]. The weight loss in one year was ranged between 8.1 kg (7.8%) with the recommended dose (7.5/46 mg) and 10.2 kg (9.8%) with the higher dose (15/92 mg) of phentermine/topiramate-ER vs 1.4 kg (1.2%) with placebo [109]. In addition, improvement in cardiovascular risk factors was observed with both recommended and a higher dose [110]. The SEQUEL trial which is an extension of CONQUER trial was continued with the 78% of CONQUER participants who had completed the initial 56-weeks and they were continued for 108 weeks. Eighty-four percent of participants completed their second year of treatment with a weight loss of 9.3% and 10.5% in the recommended and highest dose respectively, vs 1.8% for placebo [111]. Further, it has demonstrated a lower incidence of progression to type-2 diabetes and reduced the cardiovascular risk factors. However, phentermine plus topiramate-ER treatment observed a small increase in resting heart rate in its top dose (56.1%) vs placebo (42.1%). This observation leads to raising concerns regarding potential cardiovascular events in long-term use of this combination [112].

Naltrexone–bupropion (sustained release- SR) combination of obesity treatment was approved by the FDA in 2014. Four phase-3 multicentre, double-blind, placebo-controlled studies were conducted for 56-weeks. Naltrexone/bupropion SR combination was tested in obese or overweight subjects with at least one weight-related comorbidity. In the Contrave Obesity Research (COR) I, COR-II trials, 36%–42% of participants achieved ≥ 5% weight loss with the combination plus lifestyle modification compared to 17%–18% with placebo plus lifestyle modification [113]. The COR-Diabetes study, participants were type-2 diabetes with anti-diabetic drugs were treated with naltrexone/bupropion SR (32/360 mg). Participants exhibited significant weight reduction (5.0% vs 1.8%) and greater proportion of patients achieving 5% or more weight loss (44.5% vs 18.9% of placebo). In addition, bupropion SR/naltrexone SR resulted in the significantly greater reduction of HbA1c (0.6%), cardiovascular risks and lipid profiles compared with placebo [113–115].

Canagliflozin (300 mg) and phentermine (15 mg) was studied for their efficacy in nondiabetic overweight and obese participants. The randomized, double-blind and placebo control phase-2b clinical trial was conducted in 335 participants for 26 weeks. Canagliflozin and phentermine were administered orally once daily. The

combination demonstrated a significant weight loss of ≥5% and a reduction in systolic blood pressure in comparison to placebo control [116,117].

7. Conclusion

Successful treatment of obesity requires a multimodal comprehensive approach including lifestyle and behavioural modification. Lifestyle modification of increased energy expenditure and reduced calorie consumption are the cornerstones of the treatment approach. With significant lifestyle changes, weight loss is a challenge for many patients due to a strict regulation of adaptive physiologic response to counterbalance the energy intake and expenditure [109]. Thus, successful body weight loss and weight maintenance will require multiple approaches including pharmacotherapy, lifestyle and behavioural approach. Presently, five long-term and one short-term treatment option are available by the FDA. Selection of suitable drug from the available treatments should be based on the expected benefit-to-risk balance and tailored to personalized therapy [118]. Tailoring of the treatment should also be focused on the patient's behaviour and comorbidity. The current anti-obesity drug research has not progressed to personalized therapy to obtain successful clinical outcomes [114]. Multimodal approach with personalized therapy by recognizing and targeting the phenotypes early in the treatment can get a successful clinical response.

Conflicts of interest

All authors declare no conflict of interest to disclose.

Ethics statement

This study doesn't involve animals or human subjects.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.05.004.

References

[1] Brazier Y. What is obesity and what causes it? Med News Today 2018. Available from: https://www.medicalnewstoday.com/articles/323551.php.
[2] Obesity: identification, assessment and management. National Institute for Health and Care Excellence; 2014 [cited 2019 Mar 17]. Available from: https://www.nice.org.uk/guidance/cg189/chapter/1-recommendations.
[3] Milken Institute. Economic impact of excess weight now exceeds $1.7 trillion. Science Daily; 2018 [cited 2019 Mar 17]. Available from: https://www.sciencedaily.com/releases/2018/10/181030163458.htm.
[4] Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth : United States, 2015–2016. Nat Cent Heal Stat 2017:288.
[5] World Health Organization. Obesity and overweight world health organization. 2018.
[6] Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 2009;373(9669):1083–96.
[7] Al-agha AE, Al-ghamdi RA, Halabi SA. Correlation between obesity and emotional, social, and behavioral problems associated with physical limitation among children and adolescents in Western Saudi Arabia. Saudi Med J 2016;37(2):161–5.
[8] Obesity [Internet]. National health service. 2016. Available from: https://www.nhs.uk/conditions/obesity/causes/.
[9] Farooqi SI. Genetic, molecular and physiological mechanisms involved in human obesity : Society for Endocrinology Medal Lecture 2012. Clin Endocrinol 2015;82:23–8.
[10] Bird SR, Hawley JA. Update on the effects of physical activity on insulin sensitivity in humans. BMJ Open Sport Exerc Med 2017;2(1):1–26.
[11] Kwak H. Exercise and obesity-induced insulin resistance in skeletal muscle. Integr Med Res 2013;2:131–8.
[12] Sarvas JL, Otis JS, Khaper N, Lees SJ. Voluntary physical activity prevents insulin resistance in a tissue specific manner. Phys Rep 2015;3(2):1–11.
[13] Roberts CK, Little JP, Thyfault JP. Modification of insulin sensitivity and glycemic control by activity and exercise. Med Sci Sports Exerc 2013;45(10):1868–77.
[14] Damirchi A, Tehrani BS, Alamdari KA, Babaei P. Influence of aerobic training and detraining on serum BDNF, insulin resistance, and metabolic risk factors in middle-aged men diagnosed with metabolic syndrome. Clin J Sport Med 2014;24(6):513–8.
[15] Prader-Willi syndrome. National health service. 2018 [cited 2019 Mar 17]. Available from: https://www.nhs.uk/conditions/prader-willi-syndrome/.
[16] Butler MG. Prader-Willi syndrome : obesity due to genomic imprinting. Curr Genom 2011;12:204–15.
[17] Genetics Home Reference. Prader-Willi syndrome. National Institutes of Health; 2019 [cited 2019 Mar 17]. Available from: https://ghr.nlm.nih.gov/condition/prader-willi-syndrome.
[18] Butler MG, Theodoro MF, Bittel DC, Donnelly JE. Energy expenditure and physical activity in Prader–Willi syndrome. Am J Med Genet 2017;143a(5):449–59.
[19] Holsen ML, Zarcone JR, Brooks WM, Butler MG, Thompson TI, Ahluwalia JS, et al. Neural mechanisms underlying hyperphagia in Prader-Willi syndrome. Obesity 2006;14(6):1028–37.
[20] Genetics Home Reference. Bardet-Biedl syndrome. National Institutes of Health; 2019.
[21] Guo DF, Rahmouni K. Molecular basis of the obesity associated with Bardet-Biedl syndrome. Trends Endocrinol Metabol 2012;22(7):286–93.
[22] Morton GJ, Cummings D, Baskin DG, Barsh GS, Schwartz MW. Central nervous system control of food intake and body weight. Nature 2006;443(7109):289–95.
[23] Benzinou M, Walley A, Lobbens S, Charles MA, Jouret B, Fumeron F, et al. Bardet-Biedl syndrome gene variants are associated with both childhood and adult common obesity in French Caucasians. Diabetes 2006;55(10):2876–82.
[24] Genetics Home Reference. Alström syndrome. National Institutes of Health; 2019 [cited 2019 Mar 17]. Available from: https://ghr.nlm.nih.gov/condition/alstrom-syndrome.
[25] Collin GB, Cyr E, Bronson R, Marshall JD, Gifford EJ, Hicks W, et al. Alms1-disrupted mice recapitulate human Alström syndrome. Hum Mol Genet 2010;14(16):2323–33.
[26] Favaretto F, Milan G, Collin GB, Marshall JD, Stasi F, Maffei P. GLUT4 defects in adipose tissue are early signs of metabolic alterations in Alms1 GT/GT , a mouse model for obesity and insulin resistance. PLoS One 2014;9(10):1–10.
[27] Maffei P, Boschetti M, Marshal JD, Paisey RB, Beck S, Resmini E, et al. Characterization of the IGF system in 15 patients with Alström syndrome. Clin Endocrinol 2007;66(2):269–75.
[28] Genetics Home Reference. Cohen syndrome. National Institutes of Health; 2019 [cited 2019 Mar 17]. Available from: https://ghr.nlm.nih.gov/condition/cohen-syndrome.
[29] Wang H, Falk MJ, Wensel C, Traboulsi E. Cohen syndrome. GeneReviews; 2016. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1482/.
[30] Duplomb L, Duvet S, Picot D, Aral B, Chehadeh-djebbar S El, Marle N, et al. Cohen syndrome is associated with major glycosylation defects. Hum Mol Genet 2014;23(9):2391–9.
[31] Limoge F, Faivre L, Gautier T, Petit J, Gautier E, Masson D, et al. Insulin response dysregulation explains abnormal fat storage and increased risk of diabetes mellitus type 2 in Cohen Syndrome. Hum Mol Genet 2015;24(23):6603–13.
[32] Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994;372(6505):425–32.
[33] Myers Jr MG, Leibel RL, Seeley RJ, Schwartz MW. Obesity and leptin resistance: distinguishing cause from effect. Trends Endocrinol Metabol 2010;21(11):643–51.
[34] Huszar D, Lynch CA, Fairchild-huntress V, Dunmore JH, Fang Q, Berkemeier LR, et al. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. Cell 1997;88(1):131–41.
[35] Krashes MJ, Shah BP, Koda S, Lowell BB. Rapid versus delayed stimulation of feeding by the endogenously released AgRP neuron mediators, GABA, NPY and AgRP. Cell Metabol 2013;18(4):1–17.
[36] Robertson SA, Koleva RI, Argetsinger LS, Carter-su C, Marto JA, Feener EP, et al. Regulation of Jak2 function by phosphorylation of tyr 317 and tyr 637 during cytokine signaling. Mol Cell Biol 2009;29(12):3367–78.
[37] Morris DL, Rui L. Recent advances in understanding leptin signaling and leptin resistance. Am J Physiol Endocrinol Metab 2009;297(6):E1247–59.
[38] Hasnain S. The p .N103K mutation of leptin (LEP) gene and severe early onset obesity in Pakistan. Biol Res 2016;49(23):1–5.
[39] Zhao Y, Hong N, Liu X, Wu B, Tang S, Yang J, et al. A novel mutation in leptin gene is associated with severe obesity in Chinese individuals. BioMed Res Int 2014;2014.
[40] He H, Sun D, Zeng Y, Wang R, Zhu W, Cao S, et al. A systems genetics approach identified GPD1L and its molecular mechanism for obesity in human adipose tissue. Sci Rep 2017;7(1799):1–15.
[41] Lee YS, Kim J, Osborne O, Oh DY, Sasik R, Schenk S, et al. Inflammation and insulin resistance in obesity. Cell 2014;157(6):1339–52.
[42] Zhang X, Lam KSL, Ye H, Chung SK, Zhou M, Wang Y, et al. Adipose tissue-specific inhibition of hypoxia-inducible factor 1α induces obesity and glucose intolerance by impeding energy expenditure in mice. J Biol Chem 2010;285(43):32869–77.

[43] Jiang C, Qu A, Matsubara T, Chanturiya T, Jou W, Gavrilova O, et al. Disruption of hypoxia-inducible factor 1 in adipocytes improves insulin sensitivity and decreases adiposity in high-fat diet fed mice. Diabetes 2011;60:2484–95.
[44] Kelly TJ, Souza AL, Clish CB, Puigserver P. A hypoxia-induced positive feedback loop promotes hypoxia-inducible factor 1α stability through miR-210 suppression of Glycerol-3-Phosphate Dehydrogenase 1-Like. Mol Cell Biol 2011;31(13):2696–706.
[45] Magenta A, Greco S, Gaetano C, Martelli F. Oxidative stress and microRNAs in vascular diseases. Int J Mol Sci 2013;14:17319–46.
[46] Smemo S, Tena JJ, Kim KH, Gamazon ER, Sakabe NJ, Gómez-Marín C, et al. Obesity-associated variants within FTO form long-range functional connections with IRX3. Nature 2014;507(7492):371.
[47] de Araujo TM, Razolli DS, Correa-da-Silva F, de Lima-Junior JC, Gaspar RS, Sidarta-Oliveira D, et al. The partial inhibition of hypothalamic IRX3 exacerbates obesity. EBioMedicine 2019;39:448–60.
[48] Schneeberger M. Irx3, a new leader on obesity genetics. EBioMedicine 2019;39:19–20.
[49] Claussnitzer M, Dankel SN, Kim KH, Quon G, Meuleman W, Haugen C, et al. FTO obesity variant circuitry and adipocyte browning in humans. N Engl J Med 2015;373(10):895–907.
[50] Inagaki T. Regulations of adipocyte phenotype and obesity by IRX3. positive or negative? EBioMedicine 2017;24:7–8.
[51] Sanyal D, Raychaudhuri M. Hypothyroidism and obesity: an intriguing link. Indian J Endocrinol Metab 2016;20(4):554–7.
[52] Biondi B. Thyroid and obesity: an intriguing relationship. J Clin Endocrinol Metab 2010;95(8):3614–7.
[53] Tagliaferri M, Berselli ME, Calo G, Minocci A, Savia G, Petroni ML, et al. Subclinical hypothyroidism in obese patients: relation to resting energy expenditure, serum leptin, body composition, and lipid profile. Obes Res 2001;9(3):196–201.
[54] Longhi S, Radetti G. Thyroid function and obesity. J Clin Res Pediatr Endocrinol 2013;5(Suppl 1):40–4.
[55] Norman J. Diseases of the adrenal cortex: Cushing's syndrome. Endocrine 2018. Available from: https://www.endocrineweb.com/conditions/cushings-syndrome/diseases-adrenal-cortex-cushings-syndrome.
[56] Cushing's Syndrome/Disease. America association of neurological surgeons. 2019. Available from: https://www.aans.org/Patients/Neurosurgical-Conditions-and-Treatments/Cushings-Disease.
[57] Tiryakioglu O, Ugurlu S, Yalin S, Yirmibescik S, Caglar E, Yetkin DO, et al. Screening for Cushing's syndrome in obese patients. Clinics 2010;65(1):9–13.
[58] Lee MJ, Pramyothin P, Karastergiou K, Fried SK. Deconstructing the roles of glucocorticoids in adipose tissue biology and the development of central obesity. Biochim Biophys Acta 2014;1842(3):473–81.
[59] Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham L, Anis AH. The incidence of co-morbidities related to obesity and overweight : a systematic review and meta-analysis. BioMed Cent Public Heal 2009;9(1):88.
[60] Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American heart association task force on practice guidelines and the obesity society. J Am Coll Cardiol 2013;63(25 Part B):2985–3023. 2014.
[61] American College of Cardiology. American heart association task force on practice guidelines. Expert panel report: guidelines (2013) for the management of overweight and obesity in adults. Obesity 2014;22:S41.
[62] Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. N Engl J Med 2017;376:254–66.
[63] Dutton GR, Lewis CE. The Look AHEAD trial: implications for lifestyle intervention in type 2 diabetes mellitus. Prog Cardiovasc Dis 2015;58(1):69–75.
[64] Unick JL, Beavers D, Jakicic JM, Kitabchi AE, Knowler WC, Wadden TA, et al. Effectiveness of lifestyle interventions for individuals with severe obesity results from the Look AHEAD trial. Diabetes Care 2011;34(10):2152–7.
[65] Overweight and Obesity. National heart, Lung and blood Institute. 2019 [cited 2019 Mar 18]. Available from: https://www.nhlbi.nih.gov/health-topics/overweight-and-obesity.
[66] Kissler HJ, Settmacher U. Bariatric surgery to treat obesity. Semin Nephrol 2013;33(1):75–89.
[67] Robinson MK. Surgical treatment of obesity — weighing the facts. N Engl J Med 2009;361:520–1.
[68] Bariatric Surgery Procedures. American society for metabolic and bariatric surgery. 2019. Available from: https://asmbs.org/patients/bariatric-surgery-procedures.
[69] Madura JA, Dibaise JK. Quick fix or long-term cure ? Pros and cons of bariatric surgery. F1000 Med Rep 2012;4(19).
[70] Colman E. Anorectics on trial: a half century of federal regulation of prescription appetite suppressants. Ann Intern Med 2005;143(5):380–5.
[71] Wilding J. Clinical investigations of antiobesity drugs. Appetite and body weight. Academic press; 2007. p. 337–55.
[72] Weintraub M, Sundaresan PR, Madan M, Schuster B, Balder A, Lasagna L, et al. Long-term weight control study I (weeks 0 to 34): the enhancement of behavior modification, caloric restriction, and exercise by fenfluramine plus phentermine versus placebo. Clin Pharmacol Ther 1992;51(5):586–94.
[73] Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, et al. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 1997;337(9):581–8.
[74] Hampp C, Kang EM, Borders-Hemphill V. Use of prescription antiobesity drugs in the United States. Pharmacotherapy 2013;33(12):1299–307.
[75] McNeely W, Goa KL, Sibutramine. A review of its contribution to the management of obesity. Drugs 1998;56(6):1093–124.
[76] Luque CA, Rey JA. The discovery and status of sibutramine as an anti-obesity drug. Eur J Pharmacol 2002;440(2–3):119–28.
[77] James WPT, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP, et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med 2010;363(10):905–17.
[78] Kirkham TC. Cannabinoids and appetite: food craving and food pleasure. Int Rev Psychiatry 2009;21:163–71.
[79] Després J-P, Golay A, Sjöström L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N Engl J Med 2005;353(20):2121–34.
[80] Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rössner S. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-Year experience from the RIO-Europe study. Lancet 2005;365(9468):1389–97.
[81] Pi-Synyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factros in overweight or obese patients: RIO-North American: a randomized controlled trial. JAMA, J Am Med Assoc 2006;295(7):761–75.
[82] Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. Lancet 2006;368(9548):1660–72.
[83] Plieth J. Obesity: what next after the CB1 antagonists' failure. Scrip 2008;2008:44–7.
[84] Borgström B. Mode of action of tetrahydrolipstatin: a derivative of the naturally occurring lipase inhibitor lipstatin. Biochim Biophys Acta Lipids Lipid Metab 1988;962(3):308–16.
[85] Sjostrom L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HP, et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. Lancet 1998;352(9123):167–72.
[86] Davidson MH, Hauptman J, DiGirolamo M, Foreyt JP, Halsted CH, Heber D, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. JAMA, J Am Med Assoc 1999;281(3):235–42.
[87] Finer N, James WP, Kopelman PG, Lean ME, Williams G. One-year treatment of obesity: a randomized, double-blind, placebo-controlled, multicentre study of orlistat, a gastrointestinal lipase inhibitor. Int J Obes Relat Metab Disord 2000;24(3):306–13.
[88] Rössner S, Sjöström L, Noack R, Meinders a E, Noseda G. Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity. European Orlistat Obesity Study Group. Obes Res 2000;8(1):49–61.
[89] Johansson K, Sundström J, Neovius K, Rössner S, Neovius M. Long-term changes in blood pressure following orlistat and sibutramine treatment: a meta-analysis. Obes Rev 2010;11(11):777–91.
[90] Zhou Y-H, Ma X-Q, Wu C, Lu J, Zhang S-S, Guo J, et al. Effect of anti-obesity drug on cardiovascular risk factors: a systematic review and meta-analysis of randomized controlled trials. PLoS One 2012;7(6):e39062.
[91] Erdmann J, Lippl F, Klose G, Schusdziarra V. Cholesterol lowering effect of dietary weight loss and orlistat treatment - efficacy and limitations. Aliment Pharmacol Ther 2004;19(11):1173–9.
[92] Cavaliere H, Floriano I, Medeiros-Neto G. Gastrointestinal side effects of orlistat may be prevented by concomitant prescription of natural fibers (psyllium mucilloid). Int J Obes 2001;25(7):1095–9.
[93] Rodgers RJ, Tschop MH, Wilding JPH. Anti-obesity drugs: past, present and future. Dis Model Mech 2012;5(5):621–6.
[94] Smith SR, Weissman NJ, Anderson CM, Sanchez M, Chuang E, Stubbe S, et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. N Engl J Med 2010;363(3):245–56.
[95] Fidler MC, Sanchez M, Raether B, Weissman NJ, Smith SR, Shanahan WR, et al. A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM Trial. J Clin Endocrinol Metab 2011;96(10):3067–77.
[96] O'Neil PM, Smith SR, Weissman NJ, Fidler MC, Sanchez M, Zhang J, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity 2012;20(7):1426–36.
[97] Chan EW, He Y, Chui CSL, Wong AYS, Lau WCY, Wong ICK. Efficacy and safety of lorcaserin in obese adults: a meta-analysis of 1-year randomized controlled trials (RCTs) and narrative review on short-term RCTs. Obes Rev 2013;14:383–92.
[98] Eisai Inc. BELVIQ (lorcaserin hydrochloride) tablets, for oral use. 2013. Available from: https://www.eisai.com/news/news201238.html.
[99] Colman E, Golden J, Roberts M, Egan A, Weaver J, Rosebraugh C. The FDA's assessment of two drugs for chronic weight management. N Engl J Med 2012;367(17):1577–9.
[100] Smith SR, Garvey WT, Greenway FL, Soliman W, Zhou S, Fain R, et al. Combination weight management pharmacotherapy with lorcaserin and immediate release phentermine. J Gen Intern Med 2015;30:S124.
[101] Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, et al.

Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet 2009;374(9701):1606–16.
[102] Astrup A, Carraro R, Finer N, Harper A, Kunesova M, Lean MEJ, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. Int J Obes 2012;36(6):843–54.
[103] Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. Lancet 2009;374(9701):1606–16.
[104] Rosuvastatin in visceral adiposity. Full text view - ClinicalTrials.gov. Available from: https://clinicaltrials.gov/ct2/show/NCT01068626.
[105] Gadde KM, Kopping MF, Wagner HR, Yonish GM, Allison DB, Bray GA. Zonisamide for weight reduction in obese adults. Arch Intern Med 2012;172(20):1557.
[106] Zonisamide for weight reduction in obese adults [Internet]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT00275834?sect=X01256
[107] Allison DB, Gadde KM, Garvey WT, Peterson CA, Schwiers ML, Najarian T, et al. Controlled-release phentermine/topiramate in severely obese adults: a randomized controlled trial (EQUIP). Obesity 2012;20(2):330–42.
[108] Gadde KM, Allison DB, Ryan DH, Peterson CA, Troupin B, Schwiers ML, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. Lancet 2011;377(9774):1341–52.
[109] Saunders KH, Shukla AP, Igel LI, Kumar RB, Aronne LJ. Pharmacotherapy for obesity. Endocrinol Metab Clin N Am 2016;45(3):521–38.
[110] Davidson MH, Tonstad S, Oparil S, Schwiers M, Day WW, Bowden CH. Changes in cardiovascular risk associated with phentermine and topiramate extended-release in participants with comorbidities and a body mass index $\geq$27 kg/m^2. Am J Cardiol 2013;111(8):1131–8.
[111] Garvey WT, Ryan DH, Look M, Gadde KM, Allison DB, Peterson CA, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. Am J Clin Nutr 2012;95(2):297–308.
[112] Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. JAMA, J Am Med Assoc 2014;311(1):74–86.
[113] Greenway FL, Fujioka K, Plodkowski RA, Mudaliar S, Guttadauria M, Erickson J, et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2010;376(9741):595–605.
[114] Gadde KM, Pritham Raj Y. Pharmacotherapy of obesity: clinical trials to clinical practice. Curr Diabetes Rep 2017;17:34.
[115] Srivastava G, Apovian CM. Current pharmacotherapy for obesity. Nat Rev Endocrinol 2018;14(1):12–24.
[116] Hollander P, Bays HE, Rosenstock J, Frustaci ME, Fung A, Vercruysse F, et al. Coadministration of canagliflozin and phentermine for weight management in overweight and obese individuals without diabetes: a randomized clinical trial. Diabetes Care 2017;40(5):632–9.
[117] Effects of co-administration of canagliflozin 300 mg and phentermine 15 mg with placebo in the treatment of non-diabetic overweight and obese participants - Full Text View - ClinicalTrials.gov [Internet]. Available from: clinicaltrials.gov/ct2/show/study/NCT02243202.
[118] Fruh SM. Obesity: risk factors, complications, and strategies for sustainable long-term weight management. J Am Assoc Nurse Pract 2017;29. S3–14.