New advances in the management of obesity

N Schellack, S Grobbelaar, L Wadesango, E Bronkhorst, K Kupa

Division of Clinical Pharmacy, School of Pharmacy, Faculty of Health Sciences, Sefako Makgatho Health Sciences University, South Africa

Corresponding author, email: natalie.schellack@smu.ac.za

Abstract

Being overweight or obese has become a significant global health concern, even a worldwide epidemic, and may actually be viewed as chronic disease conditions. In addition to the necessary lifestyle modifications required to effect weight-loss, which constitutes an essential healthcare intervention in this patient population, the use of adjunctive pharmacotherapeutic agents is often required. This article provides an overview of new advances in the treatment of obesity and the role of the pharmacist in promoting weight-loss in this patient population.

Keywords: overweight, obesity, weight-loss, type 2 diabetes mellitus

S Afr Pharm J 2020;87(6):17-22

Introduction

Obesity and being overweight have become a significant global health concern, even a worldwide epidemic, and may actually be seen as chronic disease conditions.[1-3] According to the World Health Organization (WHO), in 2016, just less than 40% of adults were obese, and 18% of children and adolescents aged 5–19 were overweight or obese.[4] Obesity and overweight can be calculated by using the body mass index (BMI) which is the individual's weight in kilograms divided by the square of his height in meters (kg/m^2). By using this index, overweight can be defined as a BMI ≥ 25 kg/m^2 and obesity as a BMI ≥ 30 kg/m,^{2} with morbid obesity being classified as a BMI ≥ 40 kg/m^2.[2,5,6] Mean BMI has risen in both men and women from 1975 to 2016.[4] The fundamental cause of the global rise in the prevalence of overweight and obesity can be attributed to the increased intake of energy-dense foods that are high in saturated fat, and a decrease in physical activity because of sedentary lifestyles caused by increasing urbanisation, changed modes of transportation and extended working hours. Four comorbidities associated with obesity include cardiovascular morbidity and mortality, type 2 diabetes mellitus (T2DM), various cancers and dyslipidaemia. Obesity can reduce one's overall, health-related quality of life.[1] Weight-loss is an important lifestyle modification in all of these chronic diseases, but losing weight through lifestyle intervention alone is usually difficult to maintain.[7]

The WHO defines obesity and overweight as excessive or abnormal fat accumulation usually exceeding 20% or more of an individual's ideal body weight, that may impair a person's health. As mentioned before, overweight and obesity can be classified by using a simple index of weight-for-height calculations, referred to as BMI. BMI is closely related to both body fat percentage (BFP) and total body fat composition. For both children and adults, a healthy weight varies with age and sex. More importantly, obesity in children and adolescents is defined not by an absolute number but may be related to a historical normal group – match for age and sex, and should be classified as a BMI greater than the 95th percentile. Refer to Table I for grading and classification based on BMI.

Table I: Classifying or grading of the level of obesity by utilising the body mass index[5]

Level of obesity	Corresponding BMI*
Overweight	≥ 25 kg/m^2
Obese	≥ 30 kg/m^2
Morbidly obese	≥ 40 kg/m^2

*BMI – body mass index

More recently, the tripling in the prevalence of T2DM worldwide, has been attributed to the increase in the rate of obesity.[7] The prevalence of T2DM is an increasing global public health problem, and targeted behaviours, such as physical exercise and healthy eating, are important in both the prevention and treatment of T2DM.[8] The first-line treatment of obesity is still lifestyle modifications, but the limitation is poor long-term compliance and control. Furthermore, obesity is associated with increased risk of many physical and mental disease conditions, particularly cardiovascular diseases, T2DM, obstructive sleep apnoea, immunomodulatory effects as expressed as certain types of cancer, osteoarthritis, asthma, and depression disorders.

It was once considered a problem of high-income countries but it is on the rise in countries in sub-Saharan Africa, thus now affecting both developing and developed countries.

Pharmaceutical intervention should be seen as an additional therapeutic aid to such lifestyle changes.[9]

In a large survey conducted by the National Center for Health Statistics, the prevalence of diabetes mellitus in overweight individuals was above 80%. In contrast to this, the prevalence of

diabetes in the group of patients with a BMI < 25 kg/m^2 was the lowest at 8%. The findings from this study suggest that more effort should be taken to combat obesity, as obesity is a modifiable risk factor for the development of diabetes.[6] During the Look AHEAD trial, a randomised trial comparing the effects of intensive lifestyle intervention (ILI) focused on weight loss achieved through healthy eating and increased physical activity versus a control condition of diabetes support and education (DSE) in overweight and obese individuals with T2DM. Participants randomised to lifestyle intervention lost an average of 8.6% of their initial body weight, compared to 0.7% in the control group. This illustrates the importance of lifestyle modifications such as those used during the Look AHEAD trial. These included on-site treatment sessions with the goal of reducing initial body weight by at least 7%. The on-site treatment sessions were scheduled for four years in duration, with the frequency of visits reducing as time progressed. The goal of these interventions was to reduce body weight and maintain the weight-loss through dietary intervention or a reduction in calorie intake, and an increase in the intake of fruit and vegetables, whilst also increasing the level of physical activity.[6]

Furthermore, severe obesity can pose more complex health issues than just being a risk factor for comorbid diseases. The need for additional resources, such as larger imaging equipment, operating tables or wheelchairs, may place an additional burden on physician's offices and hospitals.[10]

Pathophysiology of obesity

Obesity is a complex syndrome involving an interplay of various mechanisms in not only the development but also its persistence. The majority of cases seem to be fairly simple as a combination of excessive food energy and inadequate physical activity. However, a limited number of cases are due primarily to genetic predisposition, psychiatric illness, medication and other medical reasons.[11]

The delicate interplay involved in obesity thus includes both genetic and environmental factors. A deficiency in leptin and melanocortin-4 receptors expressed in the hypothalamus seems to be mainly responsible for energy homeostasis and could explain some rare cases of obesity.[11]

A small percentage of children (2–5%) may genetically have heterozygous mutations in the melanocortin-4 receptor gene. A risk allele, the FTO gene (fat mass and obesity-associated gene) may be associated with an average increase in weight of around 3–4 kg especially in patients with two copies.[11]

Early-onset obesity (defined by an onset before 10 years of age and BMI over three standard deviations above the value for normal individual age-and-sex-match) is a major feature in several inherited syndromes such as Prader–Willi syndrome, Bardet–Biedl syndrome, Cohen syndrome, and MOMO syndrome, with less than10% genetically expressing a single point DNA mutation.[11]

Five important molecules regulate feeding (that involves appetite and satiety), energy storage, metabolism, and energy utilisation in humans. These endogenous substances include:

- leptin,
- ghrelin,
- obestatin,
- nesfatin-1, and
- endocannabinoids.

Other chemical substances influence metabolic factors related to obesity, such as insulin, glucagon, cortisol, somatostatin, growth hormone, thyroxin, gastric inhibitory polypeptide/glucose-dependent insulinotropic peptide (GIP), adiponectin, chemerin, perilipin-1, apelin, glucagon-like peptide-1 (GLP-1), cholecystokinin-pancreozymin, and catecholamines.[11]

In the predisposition and pathology of obesity, these endogenous chemical substances act on the different pathways within the central nervous system (CNS), and in some instances peripheral pathways and receptors.[11]

Some of these substances promote the development (pro-obesogenic and seemingly pro-diabetogenic) and maintenance of obesity, such as ghrelin, endocannabinoids, and perilipin-1, whilst others, such as leptin, obestatin, nesfatin-1, GIP, GLP-1, adiponectin and chemerin, are anti-obesogenic and anti-diabetogenic. This explains the various targets for pharmacotherapy.[11]

Weight-loss of as little as 5–10% has been shown to reduce complications related to obesity and significantly improve quality of life.[7] Obesity is strongly associated with obstructive sleep apnoea, and significant weight loss has been shown to reduce the severity of the disease. This includes decreased blood pressure, a decrease in the likelihood of developing T2DM with a stable haemoglobin A_{1c}. Further weight loss can also improve the level of low-density lipoprotein cholesterol and reduce the likelihood of the need for pharmacotherapy to control hypertension.[12]

New advances

Cannabinoid-1 receptor antagonists

Both cannabinoid (CB) receptors, CB_1 and CB_2, belong to the G-protein-coupled receptor family. CB_1 plays an important role in central and peripheral appetite behavioural regulation and energy metabolism.[11] Agonistic stimulation of CB_1 stimulates food consumption in both animals and humans.

The CB_1-receptors can be found in regions of the brain, such as in the hypothalamic nuclei, which is involved in maintaining energy balance and controlling body weight; neurons of the mesolimbic system, believed to contribute to the value of meal consumption; and also peripheral organs, such as the adipose tissue and the gastrointestinal tract (GIT).[11]

Genetically-induced obesity causes chronic overstimulation of the endocannabinoid system, leading to continuous overstimulation of CB_1-receptors, which may contribute to the maintenance of obesity. Peripheral stimulation of CB_1-receptors stimulates lipogenesis in adipocytes. When the CB_1-receptor is antagonised,

adiponectin production increases in adipocytes, resulting in increased fatty acid oxidation and clearance of free fatty acids.[11]

In 2006 the first CB_1-receptor antagonist, rimonabant, was approved in Europe and used as an anorectic anti-obesity drug. Due to serious psychiatric adverse effects, such as anxiety, depression and alteration in mood, rimonabant was globally withdrawn. Rimonabant is a selective CB_1 antagonist, which inhibits both short- and long-term food intake. This drug is effective in obesity treatment as it reduces appetite and body weight (Figure 1).

Four studies have been done to evaluate the effect of rimonabant alongside a restricted-calorie diet on weight loss during one year.[13] One study group received 20 mg rimonabant, the other 5 mg of rimonabant and the third group received a placebo. The first group showed a greater weight loss of 4.9 kg than the third group, who received the placebo. Individuals who received 20 mg rimonabant also showed improvements with regards to their waist circumference, high-density lipoprotein cholesterol, triglycerides and blood pressure.[13] However, individuals who received 5 mg rimonabant did not demonstrate clinically significant improvement in blood pressure and plasma lipids. When compared to the placebo, it still resulted in a greater weight loss of 1.3 kg. Although the higher rimonabant concentration resulted in better outcomes with regards to obesity, it contributed to more adverse effects.[13] The severity of psychiatric adverse effects associated with rimonabant and other drugs from the same class, lead to the development of CB_1-antagonists that target peripheral CB_1-receptors which do not cross the blood-brain barrier.[11]

Targeting brown adipose tissue

Brown adipose tissue (BAT) is specialised adipose tissue involved in metabolism and heat generation (thermogenesis). The metabolism conducted by BAT involves the oxidation of glucose and free fatty acids.[14] Natriuretic peptides stimulate growth and activation of BAT and in its turn increase thermogenesis. Furthermore, natriuretic peptides also interact with β_3-adrenoreceptors, which promote the reversing of metabolic disturbances present in obesity.[11]

Neuropeptide orexin-A, necessary for BAT development, has been shown to increase and activate BAT in studies conducted with mice. The activity and amplification of BAT are regulated by other key peptides known as irisin, metorin and fibroblast growth factor-21 (FGF-21).[11]

Sympathomimetic appetite suppressant agents

Currently available sympathomimetic appetite suppressants include the β-phenylamine derivatives. All of these derivatives have structural similarities with noradrenaline, dopamine or amphetamine. Sympathomimetic appetite suppressants reduce food intake by directly agonising adrenergic receptors and stimulating the hypothalamic satiety centre within the brain.[11]

Pancreatic lipase inhibitors

The pancreas secretes pancreatic lipase into the small intestine's lumen. This digestive enzyme is responsible for catalysing triglycerides to monoglycerides and free fatty acids. Pancreatic lipase inhibitors, like orlistat, block this effect and cause triglycerides to be excreted. This reduces fat absorption and increases weight loss.[11] Orlistat is efficient and relatively safe to use in obese patients with diabetes, dyslipidaemia and hypertension. However, it may inhibit vitamin A, D, E and K, the known fat-soluble vitamins.[11]

Antidiabetic drugs

Drugs normally used to treat diabetes are commonly used for weight loss in obese patients. These drugs include the biguanides (for example metformin) and GLP-1 receptor agonists (for example liraglutide). Metformin has the ability to reduce obesity alongside

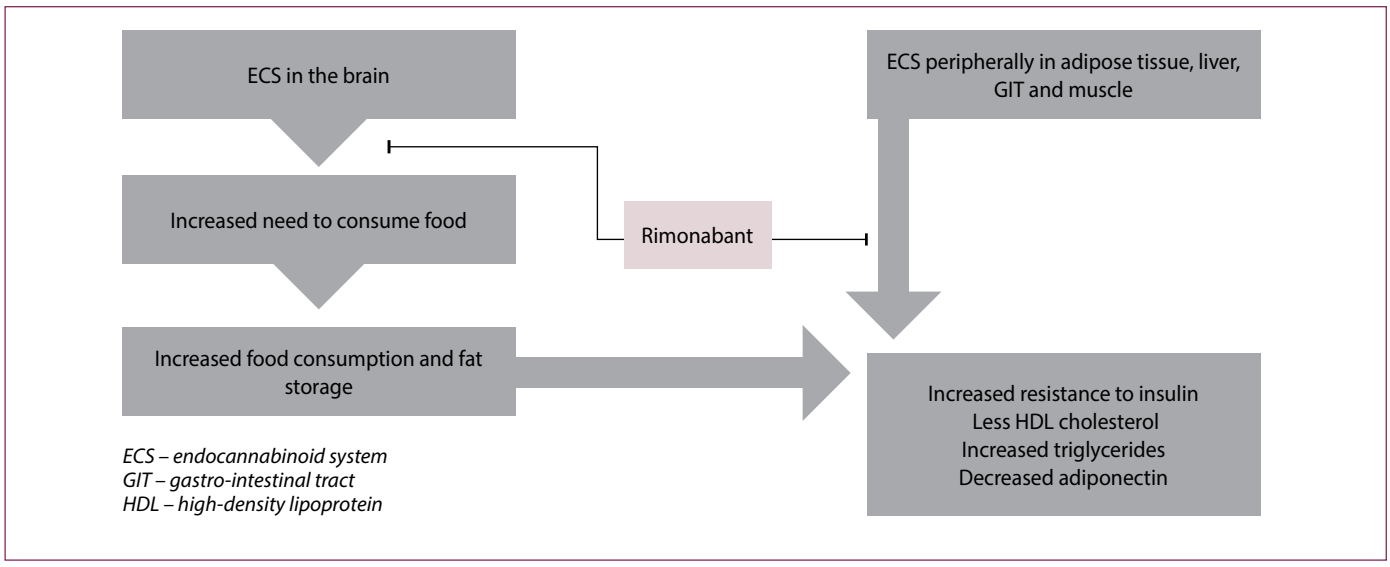

Figure 1: The mechanism of action of rimonabant when it acts on the CB_1-receptors to block the effects of an overstimulated endocannabinoid system (ENS) in the brain and peripheral tissue. The same mechanism of action applies to other CB_1-receptor antagonists.

its euglycaemic action.[11]

The GLP-1 receptor agonists

The GLP-1 receptor agonists such as liratglutide increase the synthesis and secretion of insulin from the pancreas and suppress glucagon secretion leading to decreased hepatic glucose output, on a glucose-dependent basis.[11,12] Administered subcutaneously may limit weight gain and promote weight loss.[11,12] Additionally, it decreases the tempo of gastric emptying and thus slowing the tempo of absorption and finally limiting food intake.[11]

GLP-1 is a gut hormone which plays a role in several physiological functions: it increases the sensitivity of the pancreatic beta cells to glucose, boosting the production of insulin while suppressing glucagon. GLP-1 also decreases the intake of food through its effects on the satiety centres in the brain and exerts its effects by several hypotheses.[11] These drugs are indicated as an adjunct to a reduced-calorie diet and increased physical activity for medically supervised chronic weight management programme in adult patients with an initial BMI of:[11,12]

- ≥ 30 kg/m^2 (obese), or
- ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity such as dysglycaemia (pre-diabetes and T2DM), hypertension, dyslipidaemia, or obstructive sleep apnoea.[11]

Serotonin 5-HT$_{2c}$ receptor agonists

Pro-opiomelanocorticotropin (POMC), a protein present in the CNS, is cleaved to numerous smaller peptides, which all regulate metabolic and physiological functions of importance. When 5-HT$_{2C}$ receptors are stimulated, POMC production is increased, leading to satiety and resulting in weight loss.[11]

Anticonvulsant drugs

Topiramate, an anticonvulsant, contributes to weight loss in obesity by a mechanism not yet fully known. Studies have demonstrated a possible increased expression in noradrenaline and/or dopamine in the CNS, which results in appetite suppression.[11]

Atypical antidepressants

Bupropion inhibits dopamine and noradrenaline re-uptake. Increased dopamine centration in the nucleus accumbens, also known as the rewards or pleasure centre, contribute to antidepressive and appetite suppression effects.[11]

Hormonal agents

Numerous hormones contribute to appetite and thermogenesis homeostasis. An example includes leptin, which suppresses appetite, and increases the metabolism of energy and metabolic tempo.[11]

Selective β$_3$-adrenergic receptor agonists – mirabegron and solabegron

The β$_3$-adrenoceptors (ADRB3) are found in BAT, where they contribute to lipolysis and thermogenesis.[12] β$_3$-receptors activate adenylyl cyclase and subsequently increase cAMP production. It is vital in energy metabolism, which includes increased lipolysis, free fatty acid mobilisation in white adipose tissue (WAT) and thermogenesis in BAT. The ADRB3 is a potential target for weight loss in obesity and diabetic therapy.[12]

Health at Every Size® (HAES®) approach

Health at Every Size® (HAES®) is a registered trademark of the Association for Size Diversity and Health (ASDAH). A weight-neutral approach is followed to promote healthy lifestyles in people with different body sizes. The HAES® approach encourages the development of a positive self-esteem and acceptance of different body figures. It also focuses on promoting healthy eating habits that comply with one's nutritional needs as well as making physical activities enjoyable and sustainable.[15] Interventions made according to the HAES® approach have been shown to improve diet, eating habits, anthropometric and metabolic parameters and psychological wellbeing. However, it has not been shown to effectively promote physical activity or outcome assessment. These results concurred with a recent study, with the only exception that no changes in body weight were observed.[15]

Targeting melanocortin receptors

The leptin-melanocortin pathway is a key component of food-intake control and greatly contributes to appetite.[16] The melanocortin system, found in the brain, is an essential neural system with regards to maintaining body weight and other functions. This system contains melanocortins, a product of the pro-opiomelanocortin (POMC) gene.[16] POMC generates melanocortin peptides that antagonise melanocortin receptor 1 (MC1R) to melanocortin receptor 5 (MC5R).[15] Melanocortin peptide signalling through melanocortin receptor 4 (MC4R) plays a vital role in energy homeostasis, and mutations of this receptor remain the commonest monogenic form of obesity.[17] People with POMC deficiency develop hyperphagia and obesity. Setmelanotide, a MC4R agonist, may reduce hyperphagia and body weight in patients who are POMC-deficient.[16] This recently discovered drug exerts its effects on food intake and weight loss without modulating blood pressure, like previous MC4R agonists tended to do. Despite the beneficial outcomes achieved with setmelanotide use, significant darkening of skin pigmentation and hair colour was noted with an increased risk for the development of skin cancer.[16]

Conclusion

Obesity has become a global health concern, for which weight loss is an intervention of ever-increasing significance. New advances in treatment have become available to reduce the burden of obesity, some with fewer success than others. Adverse effects that have become evident of some of the new advances in pharmacological treatment may mean the end of some drugs or just the beginning of others. As obesity becomes more prevalent, so our defences against it must increase. The role of the pharmacist is vital in the management of obesity by promoting lifestyle changes and referrals to other members of the healthcare team.

References

1. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patiens with type 2 diabetes. The SCALE diabetes randomized clinical trial. Journal of American Medical Association. 2015;314(7):687-99.
2. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. The New England Journal of Medicine. 2015;373:11-22.
3. Pahlajani S, Citrome L. Liragluride subcutaneous injection for weight loss: where does it fit? The International Journal of Clinical Practice. 2015;69(7):719-21.
4. World Health Organization (WHO). Obesity. 2015. Available from: https://www.who.int/topics/obesity/en/. [Accessed 20 May 2019].
5. WHO Fact sheet N 311. Obesity and overweight. 2015. Available from: http://www.who.int/mediacenter/factsheet/fs644/en/.
6. Nguyen NT, Nguyen X, Lane J, Wang P. Diabetes in a US adult population: findings from the National Health and Nutrition Examination Survey 1999-2006. Obesity Surgery. 2011;21(3):351-5.
7. Pi-Sunyer X, Astrup A, Fujioka K, et al. Liraglutide produces clinically significant weight loss in nondiabetic patients, but at what cost? Journal of Clinical Outcomes Management. 2015;22(9).
8. Hankonen N, Sutton S, Prevost AT, et al. Which behavior change techniques are associated with changes in physical activity, diet and body mass index in people with recently diagnosed diabetes? Annals of Behavioral Medicine. 2015;49(1):7-17.
9. Jensterle M, Kravos NA, Pfeifer M, Kocjan T, Janez A. A 12-week treatment with the long-acting glucagon-like peptide 1 receptor agonist liraglutide leads to significant weight loss in a subset of obese women with newly diagnosed polycystic ovary syndrome. Hormones. 2015;14(1):81-90.
10. Strum R, Hattori A. Morbid obesity rates continue to rise rapidly in the US. International Journal of Obesity. 2013;37(6):889-91.
11. Fasipe OJ. Recent advances and current trend in the pharmacotherapy of obesity. Archives of Medicine and Health Sciences. 2018;6(1):99-116.
12. Murphy JA, Doughty YA, Mangan MN. Drugs in perspective: liraglutide for the treatment of obesity. Formulary Journal: Diabetes. 2014.
13. Curiono C, Charles A. Rimonabant for overweight or obesity. Cochrane. 2006;4:CD006162. https://doi.org/10.1002/14651858.CD006162.pub2.
14. Botham KM, Mayes PA. Lipid transport and storage. In: Rodwell VW, Bender DA, Botham KM, Kennelly PJ, Weil P. editors. Harper's Illustrated Biochemistry. 31st ed. New York, NY: McGraw-Hill; 2018. Available from: http://accesspharmacy.mhmedical.com/content.aspx?bookid=2386&sectionid=187832347. [Accessed 20 May 2019].
15. Dimitrov Ulian M, Pinto JA, De Morais Sato P, et al. Effects of a new intervention based on the Health at Every Size approach for the management of obesity: The "health and wellness in obesity" study. PLoS ONE. 2018;13(7):e0198401.
16. Yeo GSH. Genetics of obesity: can an old dog teach us new tricks? Diabetologia. 2018;60:778-83. https://doi.org/10.1007/s00125-016-4187.