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Dr. Stephen Glazer holds certification in Internal Medicine and Intensive Care Medicine from the University of Toronto in Ontario. He is also certified as a specialist in Sleep Medicine through the College of Physicians and Surgeons of Ontario. He has a strong interest in perioperative risk assessment.

Dr. Glazer is both a provincial and a national leader in Bariatric Medicine. In 2010, Dr. Glazer became the Medical Director for both the Bariatric Surgical and Medical Program at Humber River Hospital, a dedicated center of excellence for the management of Obesity in Ontario. He is an active board member of the Ontario Bariatric Network, sitting on numerous subcommittees, including being the Vice-Chair of the OBN Medical Program Task Force. He is involved in establishing the standards of care for patients in Ontario participating in both surgical and medical approaches for weight loss. In 2012, he was among one of the first Canadian physicians who successfully completed the American Board of Obesity Medicine (ABOM) Certification examination and is a diplomat of the ABOM.

In 2019, Dr Glazer became the President of the Canadian Association of Bariatric Physicians and Surgeons (CABPS), an national organization representing Canadian specialists interested in the treatment of obesity for the purposes of maintenance and improvement for the standards of Bariatric care in Canada, supporting both primary and continuing educational programs, knowledge, research and developing policies and new ideas in the areas of clinical care, education, and research in Bariatric Medicine and Surgery.

Dr Glazer participates in multiple clinical research projects and publications. He is the author of the Pre-Operative Management for Bariatric Surgery chapter for the 2020 Canadian Obesity Clinical Practice Guidelines. His greatest enjoyment is teaching and interreacting with other health care providers via lecturing at conferences or other educational venues. His enthusiasm and passion for the field of Obesity Medicine and the care of patients living with obesity is blatantly obvious and he hopes infectious to others.

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THE MANAGEMENT OF OBESITY IN 2023: AN UPDATE

Prevalence of obesity

In 2015, obesity was declared by the Canadian Medical Association (CMA) and other global health organizations (World Health Organization [WHO], World Obesity Federation and the American Medical Association [AMA]) to be a chronic, relapsing and remitting disease caused by the deposition of adipose tissue in organ systems within the body leading to dysfunction and adverse health outcomes. Obesity should be medically addressed no differently than other chronic illnesses such as diabetes, hypertension or coronary artery disease.

The incidence of obesity has risen dramatically over the past 30 years and it is currently estimated to affect 13% or 650 million individuals greater than 18 years of age worldwide.[1-3] In 2021, there were more than 8.2 million (29.2%) adult Canadians living with obesity (BMI >30), and more than 10 million (35.5%) of Canadians were classified as overweight (BMI >25).[4] In 2017, 30% of children between ages 5 and 17 were either overweight or obese.[5] The prevalence of obesity in 2015-2016 was highest in the Atlantic provinces and lowest in Quebec and British Columbia.[6] Data from the past 10 years indicates that the prevalence of obesity in adults and children may have stabilized.[7-9] Obesity is one of the largest contributors to adverse health outcomes; additionally, it is a global public health and financial challenge, accounting for approximately $7.1 billion annual direct and indirect costs in Canada.[10,11] The World Obesity Federation has predicted that by the year 2030, 1 in 5 women and 1 in 7 men, or 1 billion individuals globally, will be living with obesity.[12]

Risk factors

There are modifiable and nonmodifiable factors involved in body weight regulation. Genetic determinants play a significant role in determining body weight, especially at higher BMIs. Genetic abnormalities in the hypothalamus leptin-melanocortin pathway, as well as single genetic mutations, can occur, as well as variations in several genes which may predispose an individual to obesity. Physiologic pathways of the neuroendocrine system involved in hunger, satiety, reward and executive function also play a significant role in weight regulation. Behavioural, environmental and other factors including the microbiome and weight-promoting medications also play a role in increased weight.[13,14]

The presence of abnormal or excessive adiposity contributes to several diseases leading to increased morbidity and mortality. Obesity is a major contributor to cardiovascular disease (CVD),diabetes and metabolic syndrome. Sixty-six percent of hypertension is linked to excess body weight, and obesity accounts for 80%-85% of the overall risk of developing diabetes. Obstructive sleep apnea; musculoskeletal conditions such as osteoarthritis; venous stasis dermatitis; gout; recurrent skin infections; polycystic ovary syndrome (PCOS); menstrual irregularities; male and female infertility; and neurologic abnormalities including benign intracranial hypertension, stroke and dementia/ cognitive dysfunction are associated with obesity. In addition, depression, anxiety and eating disorders may be linked with obesity. Forty percent of all patients with nonalcoholic fatty liver disease (NAFLD) are obese, and there is a 3- to 7-fold increased risk of gallbladder disease in individuals with BMIs >32 kg/m^2 to 45 kg/m^2. Approximately 20% of all malignancies (esophageal, kidney, pancreas, colon, postmenopausal breast, endometrial) are linked to obesity unrelated to diet, and contribute to approximately 10% of all cancer deaths in non-smoking individuals.[15-22] Obesity may be responsible for decreasing life expectancy by as many as 14 years as a result of premature death from CVD or malignancy.[23,24] Minimal weight loss of 5%-10% may be associated with improvement of obesity-related comorbidities including diabetes; hypertension; hyperlipidemia; hepatic steatosis and inflammation; sleep apnea; arthritis; urinary stress incontinence; gastroesophageal reflux disease; and hormonal irregularities associated with PCOS.[25]

Pharmacologic Treatment Modalities

It is necessary for all individuals, regardless of their body size or weight, to adopt healthy eating patterns. The evidence-based approach of medical nutritional therapy should be utilized where nutritional requirements are determined which encourage overall health, promoting eating behaviours that are sustainable and realistic. This will enable the individual to achieve a risk reduction for chronic disease. Short-term weight loss over 12 months or less may be achieved through caloric restriction; however, long-term weight loss may not be sustainable due to the body's neurobiological compensatory mechanisms involved in the regulation of eating behaviours and body weight. A thorough evaluation for micronutrient deficiencies and nutritional status should be undertaken for each patient.[26] In conjunction with healthy eating, moderate to vigorous physical activity for at least 150 minutes per week is recommended. In addition, resistance training at least twice weekly

is encouraged for weight maintenance, along with a moderate increase in mobility to promote muscle mass.[27] Interventions including behaviour modification, cognitive therapy and valued-based strategies aimed at improving nutrition and activity are additional essential components for weight management.[28]

As part of a comprehensive, long-term approach to the treatment of obesity, four pharmacologic agents are approved in Canada for achieving weight loss and weight maintenance. The use of medication should be considered in conjunction with healthy behavioural changes and increased activity as described above. The use of pharmacotherapy may be indicated in individuals with a BMI ≥30 kg/m^2 or a BMI ≥27 kg/m^2 in individuals with obesity-related complications. These include hypertension, type 2 diabetes (T2D), hyperlipidemia and obstructive sleep apnea. The use of obesity medications should be considered early in the course of management. Following three months of pharmacologic therapy, if a weight loss of ≥ 5% is not achieved, the medication should be discontinued.

Orlistat 120 mg TID is a derivative of lipstatin. Its mechanism of action is inhibition of lipase, the enzyme that aids in the gastrointestinal (GI) absorption of fat contained in the human diet. This medication has no effect on appetite suppression or satiety. Published data from randomized, controlled trials has demonstrated a net weight loss (placebo subtracted) of 2.9% with orlistat vs low-fat and low-calorie control patients at one year.[29] Fifty-four percent of patients achieved ≥ 5% weight loss and 26% achieved ≥10% weight loss. Orlistat is associated with significant GI side effects including diarrhea, flatulence, and steatorrhea, and has had limited use as a therapeutic agent due to intolerance.

Liraglutide 3 mg injected subcutaneously once daily is a glucagon-like peptide-1 (GLP-1) receptor agonist. As an anti-obesity medication, its effects include central nervous system (CNS) actions resulting in increased satiety and decreased hunger while decreasing gastric emptying. In nondiabetic or prediabetic individuals, clinical trial results demonstrated that liraglutide achieved a net weight loss of 5.4% after one year with ≥ 5% net weight loss in 36.1% and ≥ 10% net weight loss in 22.5% of subjects.[30] Prediabetic patients followed for three years experienced net weight loss of 4.2% with liraglutide, and a 2.7-fold delay in the progression of prediabetes to diabetes.[31] Nausea is the most frequent side effect associated with this medication. In addition, constipation or diarrhea, vomiting, acid reflux and headache can occur. In addition, a slightly increased risk of cholelithiasis and pancreatitis may occur.[32] Liraglutide is contraindicated for patients with a history or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type II.

Naltrexone/bupropion 16 mg/180 mg BID consists of an opioid receptor antagonist utilized to treat alcohol and opioid addiction, and a dopamine and norepinephrine reuptake inhibitor. Bupropion works centrally by increasing the production of alpha-melanocyte stimulating hormone (alpha-MSH) and beta endorphin in the hypothalamus. Naltrexone blocks the reuptake of alpha MSH. In addition, cravings are reduced through its influence on the mesolimbic reward system.[33] After one year, a randomized, controlled trial demonstrated a 4.8% net weight loss. Thirty two percent of patients had ≥5% net weight loss and 18% had ≥10% net weight loss.[34] Side effects include nausea, headache, constipation or diarrhea, sleep disturbances, and dizziness. Naltrexone/bupropion is contraindicated in patients with poorly controlled hypertension, opioid use, seizure disorders, and anorexia or bulimia. Caution should be used with any medications that lower seizure threshold or medications metabolized by the hepatic CYP2D6 enzyme system. Increased absorption of this medication occurs with high-fat meals; therefore, high-fat meals should be avoided while taking naltrexone/bupropion.[35]

Semaglutide 2.4 mg is administered weekly and is a newly- approved, centrally acting GLP-1 analog with similar activity as that of once-daily liraglutide: decreasing hunger and cravings, as well as promoting satiety.[36] In a clinical trial, semaglutide 2.4 mg demonstrated 12.5% net weight loss over 68 weeks of therapy. There was a ≥ 15% decrease in body weight in more than 50% of all study subjects vs 5.0 % with placebo.[37] The side effects and contraindications of semaglutide were similar to those of liraglutide. Trials demonstate that withdrawal of this or other anti-obesity medications is associated with significant weight regain, further emphasizing that obesity is a chronic and relapsing disease requiring long-term treatment.[38]

Therapeutic agents utilizing state-of-the-art knowledge of the control of weight and obesity are in development. Tirzepatide, a novel once weekly combined gastric inhibitory peptide (GIP) and GLP-1 receptor agonist, demonstrated in adults with obesity or overweight taking 5 mg, 10 mg, or 15 mg respectively, an average weight loss of 15.0%, 19.5%, and 20.9% compared to 3.1% in those taking placebo.[39] This medication presently is not available in Canada but will be an additional pharmacologic option.

Future potential therapeutic candidates may focus on targeted areas including leptin, ghrelin, mitochondrial uncouplers, and growth differentiation factor 15. A more advanced understanding of the incretin system, in particular GLP-1, gastric inhibitory peptide (GIP), and amylin activating the GLP-1 receptor and/or GIP receptor, is necessary. Leptin sensitizers and glucagon agonists also remain a focus in the development of anti-obesity medications.

Surgical treatment modalities

Bariatric/metabolic surgery remains an option for adult patients with a BMI of ≥35 kg/m^2 and obesity-related diseases (T2D; hypertension; cardiac disease; intractable gastroesophageal reflux disease; pseudotumour cerebri; and obstructive sleep apnea), or those with a BMI ≥40 kg/m2. Recent guidelines have recommended metabolic/bariatric surgery for individuals with a BMI ≥30 kg/m^2.[40] Contraindications to bariatric surgery include malignancy associated with a poor life expectancy; active and unstable psychiatric illness; alcohol and drug abuse; impaired cognitive function resulting in the inability to adhere to the behavioural changes necessary for optimization of bariatric surgery; and tobacco smoking. In the Asian population, bariatric/metabolic surgery should be considered for individuals with a BMI ≥27 kg/m^2 as diabetes and CVD occur at lower BMIs. While advanced age is not a contraindication to surgery, a thorough preoperative evaluation, including an assessment for frailty, which is independently associated with a higher occurrence of postoperative complications, should be undertaken.[41] The overall mortality rate from bariatric surgery is 0.01%.

In Canada, the most commonly performed bariatric surgery is Roux-en-Y gastric bypass (RYGB) where a small gastric pouch is created and the duodenum and proximal jejunum are bypassed. With this procedure, there is a decrease in the hunger-promoting hormone ghrelin and an increase in the satiety-promoting hormones PYY, GLP-1 and CCK. This procedure is associated with 65%-80% excess body weight reduction at 1-2 years. It is also associated with vitamin and mineral deficiencies requiring lifelong supplementation.

Vertical sleeve gastrectomy (SG) involves the removal of 75%-80% of the gastric fundus resulting in hormonal changes involving a reduction of ghrelin and leptin. It is associated with 55%-60% excess body weight reduction 1-2 years postoperatively. Vitamin and mineral absorption attributed to loss of a significant portion of the stomach may occur with this procedure, as well as reflux symptoms.

The most aggressive weight loss procedure is the biliopancreatic diversion with duodenal switch (BPD/DS) involving a sleeve gastrectomy along with a biliary pancreatic limb which joins the alimentary limb in a common channel approximately 75 -150 cm proximal to the ileocecal valve. The average weight loss with a BPD/DS is approximately 80% of excess body weight at 2 years and has a more sustained weight loss of 71% over 20 years. The 20-year rate of remission of diabetes after BPD/DS is 93.4%.[42] In diabetic patients specifically requiring insulin preoperatively, there is complete remission of diabetes 10 years postoperatively in 68.1% with 97% discontinuing insulin.[43] Another option for more aggressive weight loss is the single anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S) where the ileum is attached to the duodenum 250-300 cm proximal to the ileocecal valve. SADI-S is associated with less fat and nutrient deficiencies compared with BPD/DS. Weight loss and resolution of diabetes was superior with SADI-S compared with RYGB and SG.[44]

The adjustable gastric band has been associated with significant postoperative complications and has a high failure rate. Therefore, it is not recommended as a weight loss surgical intervention.[45]

Bariatric surgery is associated with improvement in quality of life; 40% decreased all-cause mortality; a 56% decrease in death rates from coronary artery disease (CAD); a 60% lower cancer mortality rate; and a 92% decrease in death rates associated with diabetes. In addition, obesity-related conditions such as hyperlipidemia; hypertension; adiposity-related liver disease; musculoskeletal pain; and sleep apnea significantly improve following bariatric surgery.[46] Remission of diabetes at 3 and 5 years respectively occurs in 75% and 37% following RYGB and 37% and 23% following SG.[47-48] In the prospective, controlled Swedish Obese Subjects study examining 4,000 patients who underwent bariatric surgery, weight loss after 10 years decreased by 25% following gastric bypass and 16% following SG vs their presurgical baseline weight.[49]

Conclusion

Obesity is a complex, chronic, relapsing disease. Many modifiable and nonmodifiable factors are involved in body weight regulation. The presence of abnormal or excessive adiposity contributes to organ dysfunction resulting in significant morbidity and mortality. In conjunction with assessment and modifications to nutrition and physical activity, behavioural interventions, pharmacotherapy and surgical interventions may be considered.

	Orlistat	Liraglutide	Naltrexone/Bupropion	Semaglutide
Mode of administration	Oral	Subcutaneous	Oral	Subcutaneous
Dose/frequency	120 mg TID	3.0 mg daily	16/180 mg BID	2.4 mg weekly
Effect on % weight loss at 1 year, placebo subtracted	-2.9%[28]	-5.4%[2]	-4.8%[5]	-12.5%[1]
Effect on weight over longer term, placebo subtracted	-2.8 kg at 4 years[8]	-4.2% at 3 years[3]	Not studied	Not available
% of patients achieving ≥ 5% weight loss at 1 year	54% (vs. 33% in placebo)[28]	63.2% (vs. 27.1% in placebo)[2]	48% (vs. 16% in placebo)[5]	86.4% (vs. 31.5% in placebo)[1]
% of patients achieving ≥ 10% weight loss at 1 year	26% (vs. 14% in placebo)[28]	33.1% (vs. 10.6% in placebo)[2]	25% (vs. 7% in placebo)[5]	69.1% (vs. 12% in placebo)[1]
% of patients achieving ≥ 15% weight loss at 1 year	Not studied	14.4% (vs. 3.5% with placebo)[3]	13.5% (vs. 2.4% with placebo)[36]	50.5% (vs. 4.9% with placebo)[1]
Effect on maintenance of previous lifestyle-induced weight loss	2.4 kg less weight regain vs. placebo over 3 years[7]	-6.0% additional placebo-subtracted weight loss at 1 year[4]	Not studied	Not studied
Contraindications	• Cholestasis • Chronic malabsorption syndrome • Pregnancy, attempting conception, breastfeeding	Personal or family history of medullary thyroid cancer Personal history of MEN2 syndrome Pregnancy, attempting conception, breastfeeding	Uncontrolled hypertension Any opioid use History of, or risk factors for, seizure Abrupt discontinuation of alcohol Concomitant administration of monoamine oxidase inhibitors Severe hepatic impairment End-stage renal failure Pregnancy, attempting conception, breastfeeding	Personal or family history of medullary thyroid cancer Personal history of MEN2 syndrome Pregnancy, attempting conception, breastfeeding
Common side effects	Loose, oily stools, flatus	Nausea, constipation, diarrhea, vomiting	Nausea, constipation, headache, dry mouth, dizziness, diarrhea	Nausea, diarrhea, constipation, vomiting
Medication interactions	• Fat-soluble vitamins • Levothyroxine • Cyclosporine • Oral anti-coagulants • Anti-convulsants	May affect absorption of medications due to slowing of gastric emptying	Yes: See chapter text	May affect absorption of medications due to possible slowing of gastric emptying

Table 1. Pharmacotherapy for Obesity; adapted from Canadian Adult Obesity Clinical Practice Guidelines: Pharmacotherapy for Obesity Management, 2022

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