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Review

Current and Emerging Pharmacotherapies for Weight Management in Prediabetes and Diabetes

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ABSTRACT

Type 2 diabetes is a serious chronic disease that is associated with increased morbidity and premature mortality. It has become the tsunami of noncommunicable diseases, with more than 400 million people worldwide currently living with diabetes. The global diabetes epidemic is driven by rising obesity rates. Excess body fat increases the risk for insulin resistance and prediabetes; obese men and women, respectively, have a 7-fold and 12-fold higher risk for developing type 2 diabetes. Obesity also predisposes to the development of a myriad of medical complications leading to increased morbidity and mortality. Each increase in body mass index of 5 kg/m^2 or higher is, on average, associated with about a 30% higher overall mortality rate. Modest weight loss through health-behaviour modification can significantly prevent or delay the onset of type 2 diabetes in people at risk. Each kg of body weight loss is associated with a 16% relative reduction in diabetes risk. Intentional weight loss is also associated with a 15% reduction in all-cause mortality. Unfortunately, health-behaviour modification alone seldom sustains adequate weight loss to achieve the desired health outcomes, especially in people with diabetes who already have greater difficulty losing weight. Pharmacotherapy is a realistic treatment option as an adjunct to diet and exercise. In addition to orlistat, the glucagon-like peptide-1 receptor agonist liraglutide has recently been approved in Canada for the treatment of obesity in doses of up to 3.0 mg daily. This review is focused on current and emerging pharmacotherapies for obesity in people with prediabetes or diabetes.

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RÉSUMÉ

Le diabète de type 2 est une maladie chronique sérieuse qui est associée à une augmentation de la morbidité et de la mortalité prématurée. Elle est devenue le tsunami des maladies non transmissibles et regroupe actuellement dans le monde entier plus de 400 millions de personnes atteintes. L'épidémie mondiale de diabète est déterminée par la hausse des taux d'obésité. L'excès de tissu adipeux augmente le risque d'insulinorésistance et de prédiabète; les hommes et les femmes obèses ont respectivement 7 et 12 fois plus de risque de développer un diabète de type 2. L'obésité prédispose également au développement d'une myriade de complications médicales qui mènent à l'augmentation de la morbidité et de la mortalité. Chaque augmentation de l'indice de masse corporelle de plus de 5 kg/m^2 est en moyenne associée à un taux global de mortalité supérieur d'environ 30%. Une perte de poids modeste liée à la modification du comportement en matière de santé peut prévenir ou retarder significativement l'apparition du diabète de type 2 chez les personnes exposées à ce risque. Chaque kilogramme de perte de poids corporel est associé à une réduction relative de 16% du risque de diabète. La perte de poids intentionnelle est également associée à une réduction de 15% de la mortalité toutes causes confondues. Malheureusement, la modification du comportement en matière de santé favorise rarement à elle seule la perte de poids appropriée pour atteindre les résultats cliniques souhaités, particulièrement chez les personnes diabétiques qui ont déjà une plus grande difficulté à perdre du poids. La pharmacothérapie en complément du régime alimentaire et de l'exercice est une option de traitement réaliste. En plus de l'orlistat, le liraglutide, un agoniste des récepteurs du GLP-1 (*glucagon-like peptide-1*) a récemment été approuvé au Canada pour

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le traitement de l'obésité à des doses allant jusqu'à 3.0 mg par jour. Cette revue porte essentiellement sur les pharmacothérapies actuelles et émergentes contre l'obésité chez les personnes prédiabétiques ou diabétiques.

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Introduction

A meta-analysis of 37 prospective studies indicated that people with type 2 diabetes have much higher rates of morbidity and premature mortality resulting from cardiovascular diseases than non-diabetic individuals (1). Type 2 diabetes exerts a significant personal, societal and economic burden and has become the tsunami of non-communicable diseases, with more than 400 million people worldwide currently living with this chronic disease (2). By 2035, the World Health Organization predicts that 592 million people globally will have diabetes, which is an alarming 70% increase (3). The dramatic rise in the prevalence of diabetes is fueled mainly by the continuing global obesity epidemic. The causal relationship between excess body fat and type 2 diabetes is well-known; the risk for type 2 diabetes increases exponentially as body mass index (BMI) rises above 25 kg/m^2, the operational definition of overweight (4). A meta-analysis of 9 prospective cohort studies from the United States and Europe reported that, when compared with individuals in the healthy weight range, overweight men have a 2-fold and women have a 4-fold higher risk for developing type 2 diabetes. Men and women who were obese (BMI ≥30 kg/m^2) had a 7-fold and a 12-fold higher risk, respectively (5). Furthermore, the lifetime risk for diabetes increases substantially and proportionally with the magnitude of overweight and obesity (6). The number of overweight or obese Canadians has continued to soar over the past several years, from 12.1 million in 2007 to 13.2 millionin 2011 (7). Based on self-reported BMIs, 67% of Canadian men and 54% of Canadian women 18 years of age and older are overweight or obese. The Canadian Diabetes Association projects that 1 in 4 Canadians lives with diabetes or prediabetes, and that includes people with impaired fasting glucose, impaired glucose tolerance or glycated hemoglobin (A1C) levels between 6.0% and 6.4% (8). If the current trend continues, 1 in 3 Canadians will be affected by prediabetes or diabetes by 2020. However, it should be emphasized that not all people with prediabetes will progress to diabetes, but the risk is 7-fold higher if they are overweight and 17-fold greater if they are obese (9).

Despite the strong relationship between body weight and type 2 diabetes, not all individuals who are overweight or obese will develop diabetes. Although a vast majority of people with type 2 diabetes are overweight or obese, about 10% of those with type 2 diabetes are of normal weight at time of diagnosis. The relationship between body weight and individuals with diabetes has been somewhat controversial, with some studies suggesting the presence of an obesity paradox—overweight and obese people with diabetes at time of diagnosis have lower mortality than normal-weight persons (10). However, a recent analysis of the Nurses' Health Study and Health Professionals Follow-up Study has refuted this tenet. A J-shaped association was observed across BMI categories for all-cause mortality, with hazard ratios showing a linear relationship between BMIs of 22.5 to 24.9 kg/m^2 (reference group), overweight and obesity BMIs, and all-cause mortality (11).

Obesity, or excess adiposity, is the result of an imbalance between energy overconsumption and energy expenditure by an individual. The causes of obesity are complex and result from interactions among biologic, behavioural, psychosocial and environmental factors, with the latter thought to be the proximal cause of the dramatic rise in the prevalence of obesity (12). In people with type 2 diabetes who are overweight or obese, adiposity worsens the metabolic and physiologic abnormalities associated with type 2 diabetes. In addition to type 2 diabetes, obesity is associated with many chronic diseases, including cardiovascular disease, various forms of cancer, degenerative arthritis, back pain and disability. It is important to note that BMI is correlated to cause-specific mortality in 57 prospective studies with close to 900,000 participants, mostly in western Europe and North America (13). Each increase in BMI of 5 kg/m^2 was, on average, associated with about a 30% higher overall mortality (13). Research over the past 3 decades has provided compelling evidence that weight management could reap significant health benefits. Indeed, a recent meta-analysis of 15 randomized clinical trials that include data from more than 17,000 participants concluded that an intentional weight loss of 5.5 kg in obese adults may be associated with approximately a 15% reduction in all-cause mortality (14).

Although weight loss is recommended for the prevention and management of type 2 diabetes, there exist significant barriers as well as clinical inertia and therapeutic nihilism in helping patients with or at risk for type 2 diabetes to manage their body weight aggressively. People with type 2 diabetes have greater difficulty losing weight than individuals without diabetes for several reasons. In insulin-resistant states, skeletal muscle and liver are the predominant organs responsible for glucose disposal. Hyperinsulinemia promotes triglyceride synthesis and storage while inhibiting lipolysis in adipocytes, resulting in an expansion of adipose tissue. People with diabetes may live more sedentary lifestyles and are less physically active. Importantly, and as discussed in the ensuing section, some of the commonly used glucose-lowering drugs are associated with weight gain, which further complicates successful weight management. Finally, weight regain can result from the compensatory response to hormonal and metabolic changes following initial weight loss, where orexigenic mediators that stimulate appetite persist (15). These factors account partially for the reasons that weight loss through health-behaviour modification alone is challenging to sustain, and the recidivism rate is high.

The Canadian Task Force on Preventive Health Care (CTFPHC) recently updated its evidenced-based recommendations for the prevention and management of obesity in adults (16). The CTFPHC acknowledges that health-behaviour intervention reduces body weight by a modest 3.13 kg, but they have stopped short of making recommendations for pharmacologic interventions (orlistat or metformin) for weight loss because of adverse side effects that occurred when compared to controls (16). The most recent clinical practice guidelines, published by the United States Endocrine Society, are focused on the pharmacologic management of obesity and are also endorsed by the Obesity Society and the American Society for Metabolic and Bariatric Surgery. The Endocrine Society guidelines represent a paradigm shift by recommending pharmacologic and health-behaviour therapy to treat the weight first before addressing the obesity-related comorbidities (17).

Review Methods

The aim of this review is to provide an appraisal of the clinical trial evidence that supports the benefits of weight loss, with a specific focus on current and emerging pharmacotherapies for weight management in people with or at risk for type 2 diabetes. Relevant articles published between 2000 and June 2015 were identified through PubMed, Embase and Google Scholar searches using

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