Review

Treatment Strategy for Type 2 Diabetes with Obesity: Focus on Glucagon-like Peptide-1 Receptor Agonists

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ABSTRACT

Purpose: The progressive nature of type 2 diabetes mellitus (T2DM) calls for step-wise intensification of therapy for maintaining normal glycemic levels and lowering cardiovascular (CV) risk. Because obesity is a prominent risk factor and comorbidity of T2DM, it further elevates the CV risk in T2DM. Therefore, it is vital to manage weight, obesity, and glycemic parameters for effective T2DM management. Few oral antidiabetic drugs (sulfonylureas and thiazolidinediones) and insulin are not suitable for obese patients with T2DM because these drugs cause weight gain. The present review discusses the place of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in the treatment of obese patients with T2DM and the significance of these drugs in the prevention of future CV risk in patients with T2DM.

Methods: A literature search of PubMed and EMBASE was conducted by using the search terms *T2DM*, *GLP-1RAs*, *obesity*, and *cardiovascular complication*. Randomized controlled trials measuring the effect of GLP-1RAs versus that of placebo on CV outcomes were included in the review.

Findings: GLP-1RAs have emerged as a therapeutic alternative; these drugs exert their actions by providing glycemic control, improving insulin resistance and ö-cell function, and reducing weight. The risk of hypoglycemia with GLP-1RAs is minimal; however, GLP-1RAs are associated with gastrointestinal adverse events and raise concerns regarding pancreatitis. Combining GLP-1RAs with insulin analogues results in higher efficacy, a lowered insulin dose, and reduced insulin-related hypoglycemia and weight gain. Longer acting GLP-1RAs are also associated with improvement in medication adherence. Improvement in CV risk factors such as blood pressure and lipid profile further increases their usability for improving CV outcomes.

Implications: Overall, the properties of GLP-1RAs make them suitable for combination with oral antidiabetic drugs in the early stages of T2DM and with insulins in the later stages for optimizing comprehensive management of the disease. (*Clin Ther.* 2017;39:1244–1264)

Key words: cardiovascular complications, glucagon-like peptide-1 receptor agonists, obesity, type 2 diabetes mellitus.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) has become a global concern due to drastic and rapid changes in nutritional habits, lifestyle habits, and urbanization.[1,2] According to the World Health Organization, an estimated 422 million adults worldwide (8.5%) is affected by T2DM; this number is expected to rise to 592 million by 2035.[3,4] T2DM affects 92.4 million adults in China (50.2 million men, with a greater prevalence in older age, urban areas, and patients with a higher weight), highlighting its epidemic and widespread nature.[5] Overweight and obesity (body mass index [BMI] $\geq$25 kg/m^2 and $\geq$30 kg/m^2, respectively) are common in Western countries, and the trend is on the rise in Asian countries.[2] The trend of obesity varies worldwide, with the United States,

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Canada, Europe, and Australia having the highest number of obese people.[6] Although the Asian population has a lower BMI, they have been found to have a higher percentage of central/abdominal obesity (measured by using waist circumference and waist-to-hip ratio) and visceral adiposity (measured with computed tomography scans) compared with Western populations.[2,7,8] In China, a general trend of increasing obesity has been reported over the years, and 70% of Chinese adults are either overweight or obese (classified based on BMI, waist circumference, and waist-to-hip ratio),[9–11] which is an alarming sign and possibly indicates a greater magnitude of CV events in the Chinese population with T2DM.

A majority of patients with T2DM are obese and; vice-versa, obese people are at a high risk of T2DM occurrence.[12] Obesity accentuates the metabolic and CV complications in patients with T2DM[13] by increasing insulin resistance,[12,14,15] causing a progressive decline in ö-cell function[12] and subsequently increasing the difficulty in achieving the glycemic targets. Central obesity or abdominal adiposity, particularly in men, is associated with an increased complication.[13] Studies have also shown that measures of central obesity are associated more with mortality and must be used along with BMI for risk evaluation.[16–18] Deposition of fat in visceral organs and ectopic fat depots may also contribute to adverse CV outcomes.[13] Therefore, treatment strategies for patients with T2DM who are obese should focus equally on glycemic control and lowering weight by including drugs that reduce weight and avoiding drugs that cause weight gain.

T2DM severely affects multiple organs on a microvascular level (nephropathy, neuropathy, and retinopathy) and at a macrovascular level (increased risk of hypertension, hyperlipidemia, coagulability, and CV risks by multiple folds compared with nondiabetic patients).[13,19,20] Elevated CV risk with T2DM and obesity makes management of both T2DM and weight highly critical. The American Diabetes Association discusses a number of oral and injectable treatments (used either as monotherapy or in combination) for the treatment of hyperglycemia, depending on the duration and severity of T2DM.[21] Because the available treatments have different effects on obesity and weight, a careful selection must be made by the clinician to lower weight along with hyperglycemia.

The present review discusses the treatment strategy to be followed for patients with T2DM and obesity, with an emphasis on the glucagon-like peptide 1 receptor agonists (GLP-1RAs), and describes their role in the comprehensive treatment of T2DM.

METHODS

We conducted electronic searches for articles in PubMed and Embase to retrieve articles pertaining to effects of GLP-1RAs in patients with T2DM and obesity, safety and CV complications. No time restriction was applied and articles published in English were included in the review.

TREATMENT STRATEGY FOR PATIENTS WITH T2DM AND OBESITY

Treatment of T2DM is complex and requires consideration of multiple aspects of the patient's condition and requirements before initiating drug therapy. Insulin resistance and ö-cell function are the key pathophysiologic mechanisms of T2DM,[22] and most patients with obesity also have CV comorbidities/risk factors such as hypertension, dyslipidemia, and hypercoagulability.[23,24] The treatment strategy should take into account both the roots of the disease and the comprehensive management of CV comorbidities or risk factors. Furthermore, the treatment approach for T2DM is patient centered and includes consideration of patient preferences, cost, risk of hypoglycemia, and potential side effects of each drug class. Thus, treatment may be individualized according to the condition of the disease and the needs of the patients.[21]

The pharmacologic treatments available for T2DM can be broadly classified into 3 categories based on their effect on body weight:

- Drugs lowering the glucose levels and weight: Antidiabetic drug classes causing weight loss include the biguanides, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and GLP-1RAs. These drugs may be considered the most preferred drugs for obese patients with T2DM. A representative drug from each class was selected, and their pharmacologic actions were discussed and extrapolated to other drugs in the class (**Table I**).[25–52]
- Drugs lowering blood glucose levels with minimal or no effect on weight: Antidiabetic drug classes that are either weight-neutral or cause minimal to no weight loss include ŏ-glucosidase inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors. The characteristics of these drug classes are presented in **Table II**.[53–69]
- Drugs lowering blood glucose and increasing weight: The characteristics of belonging to this