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SHORT REVIEW

Do we need new treatments for type 2 diabetes?☆

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Abstract Diagnosis of type 2 diabetes mellitus encompasses multiple pathophysiological and clinical situations. Type 2 diabetes mellitus is characterized by a long and changing natural history. Personal circumstances and preferences also condition the actual effectiveness and safety of drugs used. In recent decades, modern drugs have markedly expanded and improved therapeutic options. However, their effectiveness remains limited in clinical practice. The main objective of decreasing macrovascular complications is not fully proven. Adverse events, especially hypoglycemia and weight gain, are still frequent and decrease treatment adherence. The constant loss of endogenous islet cell reserve is the main determinant of the need for intensified therapies. Current treatments have failed to improve long-term beta cell mass/function. It is desirable to move forward to obtain new drugs that offer solutions sustainable in the long term. These drugs should be able to fit the individual circumstances and preferences of patients with diabetes mellitus.

PALABRAS CLAVE
Diabetes;
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Peso

¿Necesitamos nuevos tratamientos para la diabetes tipo 2?

Resumen Dentro del diagnóstico de diabetes tipo 2 se incluyen múltiples situaciones clínicas y fisiopatológicas. La diabetes tipo 2 se caracteriza por una larga y cambiante historia natural. Las circunstancias y preferencias personales condicionan asimismo la eficacia y seguridad real de los fármacos empleados. En las últimas décadas se han ampliado y mejorado notablemente las opciones terapéuticas, sin embargo su eficacia sigue siendo limitada en la práctica clínica. El objetivo principal de reducción de las complicaciones macrovasculares no está completamente probado. Los efectos adversos, especialmente hipoglucemia y aumento de peso, son todavía frecuentes y reducen la adhesión al tratamiento. La pérdida constante de reserva insular endógena es el principal determinante de la necesidad de intensificación del tratamiento.

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Los tratamientos actuales no han demostrado mejorar la masa/función de las células beta a largo plazo. Es deseable seguir avanzando para conseguir tratamientos farmacológicos que ofrezcan soluciones sostenibles a largo plazo y adaptables a las circunstancias individuales y preferencias de los pacientes con diabetes mellitus.

Introduction

The term *diabetes mellitus* (DM) encompasses multiple diseases mainly characterized by inadequate control of carbohydrate metabolism. Most of these are chronic conditions in which impaired management of macronutrients and other associated events (inflammation, prothrombotic state...) may cause complications in any organ, although vascular complications are the most common and disabling. DM is one of the most significant causes of morbidity and mortality and is increasing worldwide.

This pathophysiological heterogeneity and complexity preclude a single and simple treatment. In addition to the indispensable and sustained approach using lifestyle measures, drug treatment is currently multifactorial almost since diagnosis.

The most common type of DM is type 2 DM (T2DM), which may account for approximately 90% of DM cases.[1] However, it is obvious that this diagnosis includes phenotypes with highly different genetic basis, pathophysiology, and clinical behavior. Moreover, different measures are required depending on the point in the natural history of disease where each patient is. Finally, but no less important, individual characteristics have a substantial impact on the potential efficacy and safety of each therapeutic option.

In recent decades, very interesting new options and modifications of already known therapeutic classes (new insulins, sulfonylureas...) have been incorporated into drug treatment for DM, and drug classes with novel mechanisms of action have been introduced. This review will try and describe currently unmet objectives in the pharmacological approach to DM in an attempt to identify new challenges for DM treatment in the future.

Efficacy of current treatments for diabetes

Antihyperglycemic efficacy

Intensive treatment aimed at achieving a level of glycosylated hemoglobin A1c (HbA1c) less than 7% markedly decreases the incidence of microvascular disease in patients with T2DM.[2] The efficacy of oral treatments for DM (measured as HbA1c decrease) is approximately 1% (Table 1).[3] Although insulin therapy has traditionally been considered to have an unlimited hypoglycemic potency, the HbA1c goal is difficult to achieve in clinical practice with the current strategies and formulations. Even when intensive strategies for T2DM control are used, such as treatment with multiple basal-bolus insulin doses, HbA1c levels < 7% are achieved in less than 60% of patients, as shown by the published meta-analyses.[4,5]

The new GLP-1 receptor agonists (GLP-1ra) may achieve greater HbA1c reductions than some oral drugs (−0.97% [95% confidence interval −1.13 to −0.81%]),[6] specially long-acting GLP1ra as compared to DPPIV inhibitors.[7] In addition, they have associated advantages in terms of weight and blood pressure reduction. However, treatment is still limited by the occurrence of gastrointestinal untoward effects, cost, and lack of experience with long-term use.

Efficacy in overall control of cardiovascular risk factors

The beneficial effect of intensive therapy on macrovascular disease is not no completely proven.[8] Two meta-analyses of clinical studies assessing standard versus intensive treatment in cardiovascular (CV) risk reduction concluded that intensive therapy significantly decreased the risk of CV events, but not CV death or all-cause mortality.[9,10]

The most recent data confirm that we are far from achieving the control goals proposed in T2DM. The results of the *National Health and Nutrition* Examination Survey for the 1999–2010 period were published in 2013 in the New England Journal of Medicine.[11] Although an improvement was seen in these years, 33.4–48.7% of patients did not meet the blood glucose (HbA1c), lipid (LDL cholesterol), weight, and blood pressure goals. In a study on data from 286.791 patients conducted in Spain (the Econtrol study), only 12.1% of adults with T2DM achieved the goals of HbA1c < 7%, LDL cholesterol <100 mg/dL, and blood pressure < 130/80 mmHg.[12]

Table 1 Hypoglycemic efficacy of drugs for type 2 diabetes mellitus.

Drug	Mean HbA1c reduction expected (%)
Alpha-glucosidase inhibitors	0.5–0.8
Metformin	1–1.5
Sulfonylureas/glinides	1.0–1.5
DPPIV inhibitors	0.7–1.0
Glitazones	0.7–1.5
GLP-1 receptor agonists	0.8–1.2
Insulin	1.0–2.0

HbA1c: glycosylated hemoglobin A1c; DPPIV: dipeptidyl peptidase IV; GLP-1: glucagon-like peptide 1.
Modified from Giugliano et al.[4]