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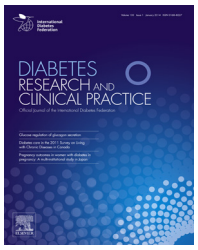

Review

Effects of three injectable antidiabetic agents on glycaemic control, weight change and drop-out in type 2 diabetes suboptimally controlled with metformin and/or a sulfonylurea: A network meta-analysis

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ABSTRACT

Aims: The objective of this review was to assess glucagon-like peptide-1 receptor agonists (GLP-1 RAs), basal insulin, and premixed insulin among participants with type 2 diabetes inadequately controlled with metformin and/or a sulfonylurea.
Methods: We searched PubMed, EmBase, and the Cochrane Library to identify eligible randomized controlled trials (RCTs) for a network meta-analysis.
Results: A total of 17 RCTs involving 5874 adult individuals were included. Compared with placebo, all three therapies showed a significant effect on achieving target glycated hemoglobin (HbA1c) (GLP-1 RAs: 31.7%, 95% CI, 24.7–38.6%; premixed insulin: 31.1%, 95% CI, 20.4–41.8%; basal insulin: 26.0%, 95% CI, 16.4–35.7%). However, there was no significant difference between the three therapies. A similar result was found in HbA1c reduction. The use of GLP-1 RAs resulted in significant body weight loss (−3.73 kg, 95% CI, −4.52 to −2.95 kg vs. basal insulin and −5.27 kg, 95% CI, −6.17 to −4.36 kg vs. premixed insulin) but there was a higher drop-out rate of participants. Premixed insulin seemed associated with more severe hypoglycemic episodes.
Conclusions: The three injectables had similar impact on glycemic control but other differentiating features relevant to the management of type 2 diabetes with GLP-1 RAs having the most favorable profile.

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Contents

1. Introduction

Type 2 diabetes (T2DM) is a very common chronic disease and usually requires sequential therapies to achieve adequate glycemic control. For the majority of patients with T2DM, metformin and/or a sulfonylurea are often the first- and second-line pharmacological treatments [1–3]. When glycemic control targets are not met with this dual combination therapy, patients are administered next-line treatments, which routinely include injectable antihyperglycemic agents.

Basal insulin, premixed insulin, and the more recently available glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are the three most common classes of injectable therapies [1–3]. To our knowledge, no head-to-head randomized controlled trials (RCTs) have compared their treatment effect. A previous network meta-analysis reports touched on this limitation [4–6]; however, there have been no specific analyses of the three injectables for patients with T2DM in whom metformin and/or a sulfonylurea provided inadequate control. This type of analysis without diverse background therapies and a varied patient population [5,6] would provide reliable findings for use in clinical practice. Due to limited data availability [4], prior reports did not provide an analysis of attainment of a glycated hemoglobin (HbA1c) goal. However, durable glycemic control is the cornerstone of the management of T2DM [7]. The American Diabetes Association recommends a treatment goal of an HbA1c level <7% to reduce the incidence of microvascular disease induced by poor glycemic control [8]. Based on this recommendation, we provide a more comprehensive efficacy assessment using both HbA1c goal and HbA1c reduction. In addition, clinical decisions for treatment selection are based on treatment tolerability and adherence—a composite consideration and so we also considered the issue of early treatment drop-out related to GLP-1 RAs [9,10].

To synthesize the available clinical trial evidence and improve the definition of the comparative benefits and risks of the three injectable antidiabetic agents for people whose T2DM was suboptimally controlled with metformin and/or a sulfonylurea, we performed a network meta-analysis to evaluate their effect on HbA1c changes, body weight changes, drop-out rate, and severe hypoglycemia episodes.

2. Material and methods

2.1. Search strategy and selection criteria

RCTs comparing GLP-1 RAs (both exenatide 10 μg bid or 2 mg QW and liraglutide), basal insulin (insulin glargine and insulin detemir), premixed insulin (Humulin 70/30, Humalog Mix 25, Humalog Mix 50; Novolin 70/30, Novo Mix 30, Novo Mix 50) or placebo were eligible for inclusion in our analysis, and no restrictions were placed on language or publication status. We electronically searched the PubMed (1965 to June 2014), EmBase (1965 to June 2014), and Cochrane Library databases using the search terms ''type 2 diabetes mellitus'' AND (''insulin'' or ''liraglutide'' or ''exenatide'') AND (''metformin'' or ''sulfonylurea compounds'') AND ''randomized controlled trial.'' We also further conducted manual searches of the reference lists from the identified relevant original and review articles.

Eligible RCTs met the following inclusion criteria: (i) published as an original article; (ii) study participants were adults aged ≥18 years with T2DM and a baseline HbA1c level >7.0% while receiving metformin and/or a sulfonylurea for at least 3 months before the screening visit; (iii) study treatment duration ≥16 weeks; (iv) comparative treatments contained two or more of the three injectables (GLP-1 RAs, basal insulin, premixed insulin) and placebo; and (v) at least mean changes in HbA1c from baseline were reported. If more than one article reported data from the same study, the most recent and complete articles were included.

2.2. Data extraction and bias risk assessment

The following information was extracted from each eligible study: (i) first author's surname; (ii) publication year; (iii) sample size; (iv) study treatment duration; (v) baseline characteristics (sex, age, HbA1c, body mass index, diabetes