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Efficacy and safety of incretin-based drugs in patients with type 1 diabetes mellitus: A systematic review and meta-analysis

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ABSTRACT

Aims: In patients with type 2 diabetes, incretin-based therapies can improve glucose control without increased weight gain or hypoglycemia. Incretin-based drugs added to insulin therapy in type 1 diabetes (T1DM) have also been tried in many studies. However, the results were controversial. We thus performed a meta-analysis to assess the efficacy and safety of incretin-based therapies in patients with T1DM.

Methods: We systematically searched Medline, EMBASE, and Cochrane Central Register of Controlled Trials for relevant studies published before August 25, 2016. Data was extracted by two independent reviewers. The main outcomes included glycosylated hemoglobin (HbA1c), insulin dose, weight, hypoglycemia, ketosis and ketoacidosis. All pooled data were assessed using random-effects model.

Results: Twelve randomized controlled trials with a total of 2903 individuals were finally included into the meta-analysis. Incretin-based drugs could significantly reduce HbA1c (MD −0.20, 95% CI −0.30 to −0.10), weight (MD −2.83, 95% CI −4.00 to −1.65) and insulin dose (MD −4.55, 95% CI −6.15 to −2.94). Furthermore, incretin-based drugs did not increase relative risk of severe hypoglycemia (RR 0.79, 95% CI 0.58 to 1.06), ketosis (RR 1.37, 95% CI 0.95 to 1.97) and ketoacidosis (RR 2.62, 95% CI 0.31 to 21.99).

Conclusions: Incretin-based treatment in patients with T1DM may improve glycemic control and reduce insulin dose and weight without increasing the risk of serious adverse event, such as severe hypoglycemia, ketosis or ketoacidosis. The current evidence for the aforementioned adverse effects, however, is weak. A rigorous monitoring of these adverse events should be implemented in well-designed observational studies.

1. Introduction

Individuals with type 1 diabetes mellitus (T1DM) lack endogenous insulin production and therefore need administration of exogenous insulin to promote normal glucose utilization and storage and regulate glycogen break-down, gluconeogenesis, lipolysis, and ketogenesis [1]. The long-term insulin therapy, however, leads to the presence of obesity or overweight and

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even metabolic syndrome in these patients, which drive development of insulin resistance and may lead to a more aggressive β-cell apoptosis [2,3]. The data showed that 30% of patients with T1DM were obese at the end of 12-years follow-up from Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Trial [4]. Meanwhile, primary loss of β-cell mass also results abnormal α-cell function, with excess glucagon in the fasting and postprandial state [5]. Nevertheless, administration of exogenous insulin only partly addresses the paradoxical and pathophysiological excess of glucagon [6]. Additionally, as the poor beta-cell function may be prone to episodes of hypoglycemia during intensive insulin therapy among these patients [7], they might keep away from hypoglycemic events at the cost of well glycemic control. Therefore, it seems pertinent to explore novel non-insulin adjunct therapies in patients with T1DM.

Treatment options of non-insulin hypoglycemic agents, however, are limited in T1DM. Metformin may not improve glycemic control after 6 months [8], while SGLT-2 inhibitors seem to be associated with diabetic ketoacidosis [9]. Incretin-based drugs, including DPP4 inhibitors and Glucagon-like peptide 1 (GLP-1) agonists which have been shown to improve glucose control without increased weight gain or hypoglycemia [10], are promising agents for the treatment of type 2 diabetes (T2DM). In recent years, because of a growing recognition of the similarities in insulin resistance and abnormal α-cell function among people with T1DM and T2DM [11,12], the use of incretin-based drugs in T1DM has been tried in many clinical trials, including a dozen randomized controlled trials (RCTs). Yet the effect of incretin-based treatment on glycemic control, other cardiovascular risk factors and β-cell function in patients with T1DM remains a matter of controversy. Some showed that liraglutide [13,14] or exenatide [15] added to insulin therapy reduced HbA1c level, body weight, insulin requirements and sitagliptin [16] was also effective in lowering blood glucose levels. Additionally, it was reported that liraglutide [17] or sitagliptin [16,18] would preserve or maintain β-cell function in patients with T1DM who had residual β-cell function, including recent-onset T1DM or latent autoimmune diabetes in adults (LADA). However, others suggested that liraglutide [19] or sitagliptin [11,20] has no additional effect on HbA1c and β-cell function in patients with T1DM. In term of safety, as an add-on therapy to insulin for patients with T1DM, the effect of incretin-based drugs on hypoglycemia, ketosis or ketoacidosis was also controversial. In overweight patients with T1DM, liraglutide was reported to be associated with reductions in hypoglycemic events [21]. Other study showed that the addition of exenatide or sitagliptin in new onset T1DM did not increase hypoglycemic events and ketoacidosis [15]. Another studies, however, found that liraglutide increased rates of hypoglycemia and hyperglycemia with ketosis [14].

Therefore, we conducted a systematic review and meta-analysis to provide a comprehensive assessment regarding the safety and efficacy of incretin-based drugs added to insulin treatment relative to placebo or active drugs in subjects with T1DM.

2. Methods

We followed the standards set by Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) in this systematic review [22].

2.1. Eligibility criteria

We included randomized controlled trials (RCTs), cohort studies, and case-control studies that compared GLP-1 agonists or DPP-4 inhibitors against placebo/no additional drugs or other hypoglycemic agents in type 1 diabetes. Eligible studies should report at least one of the following outcomes: glycosylated hemoglobin (HbA1c), insulin dose, weight, hypoglycemia, hyperglycemia with ketosis, ketoacidosis, gastrointestinal disorders, and other serious side effects like pancreatitis, cardiovascular events (CV events). No restrictions on type of incretin-based drugs, sample size, length of follow-up were imposed.

2.2. Literature search

We performed a systematic literature search of Medline, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to August 25, 2016. MeSH combined with free words terms about “type 1 diabetes mellitus”, “DPP-4”, “GLP-1” and “incretin” were used to identifying relevant articles (Supplement 1). We also screened ClinicalTrials.gov and reference lists of published reviews to identify additional relevant studies. Only studies published in English were included.

2.3. Study screening and data collection

Two authors (WW and YG), trained in health research methods, independently screened titles/abstracts and full-text articles to identify eligibility, assessed risk of bias, and collected data from each eligible study using standardized, pilot-tested forms, together with detailed instructions. For the included studies, we extracted data regarding study characteristics (authors’ name, year of publication, if multicenter study, number of study sites, total number of patients randomization, length of follow-up, and follow-up rate), baseline characteristics (gender, age, weight, duration of diabetes, type of diabetes, HbA1c), intervention and outcomes of interest. If a trial reported in multiple articles or multiple follow up points, we collated all data into a single study and used data with the longest follow-up. Discrepancies were resolved through discussion or, if required, adjudication by a third author (DWC).

2.4. Risk of bias assessment

We used a modified version of Cochrane Collaboration’s tool to assess the risk of bias of randomized controlled trials [23]. The items included random sequence generation, allocation concealment, blinding of participants, caregivers, and outcomes assessors, selective outcome reporting, adequate follow up.