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Efficacy and Safety of Dulaglutide in the Management of Type 2 Diabetes Mellitus: A Meta-analysis of Randomized Controlled Trials

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INTRODUCTION

- As many as 328 million people worldwide had diabetes in 2013; this figure is projected to rise up to 592 million, a rise of 55%, by the year 20351
- Drugs to treat type 2 diabetes mellitus (T2DM) include Insulin, Sulfonylureas, Metformin, Thiazolidinediones, Meglitinides, and the incretin- based therapeutic agents[2]
- Incretin-based therapeutic agents include DPP-4 inhibitors (sitagliptin and its congeners) and GLP-1 agonists (exenatide and its congeners)

Salient Features of GLP-1 agonists[2]

- High efficacy for HbA1c lowering
- Low risk for hypoglycemia
- Promote weight loss
- Induce gastrointestinal (GI) side effects
- Expensive compared to other antidiabetic drugs

Place in therapy

- ADA/EASD guidelines:[3]
  - 2nd and 3rd line of therapy
- AACE guidelines:[4]
  - As an alternative to metformin as 1st line therapy
  - Also preferred 2nd and 3rd line of therapy
- NICE guidelines:[5]
  - 3rd line therapy after metformin and sulfonylureas

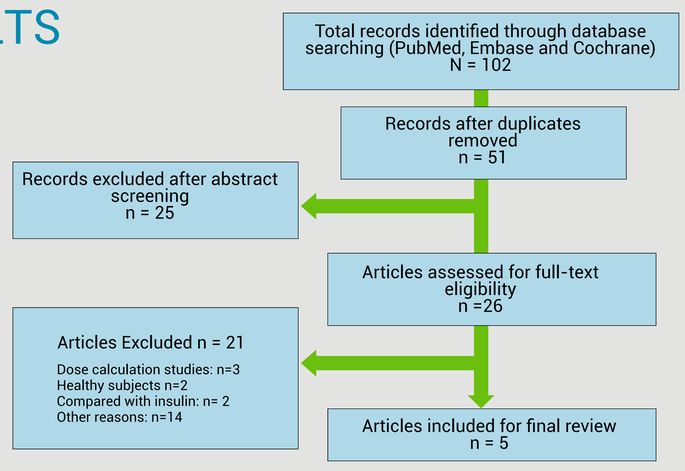
OBJECTIVE

To assess the efficacy and safety of once-weekly Dulaglutide versus other antihyperglycemic medications in T2DM.

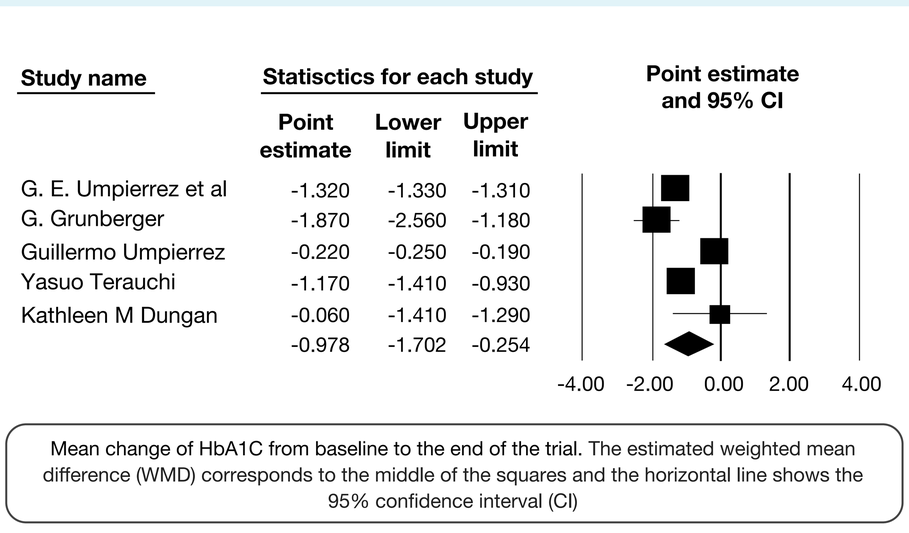
MATERIALS AND METHODS

- Literature search was conducted in MEDLINE, EMBASE, and Cochrane Library without any language or date restrictions
- All RCTs comparing Dulaglutide with other antihyperglycemic mediations (excluding insulin) or placebo in T2DM were included
- The search strategy comprised MeSH terms of "Dulaglutide" and "type 2 diabetes mellitus."
- Study quality of included trials were assessed using the Jadad scale
- Heterogeneity was assessed using the chi-square and Q test
- Two reviewers independently conducted the trial selection, data extraction, and quality assessment
- The primary outcome measure of interest was a change in glycated hemoglobin (HbA1c) levels from the baseline at the end of trial

RESULTS



- A total of 5 RCTs evaluating 1401 patients with T2DM (698 in the intervention and 703 in the control group) were selected for this meta-analysis
- Trials comparing Dulaglutide with placebo, metformin, and liraglutide varied in duration and dose of Dulaglutide (0.5–1.5 mg daily)
- Dulaglutide significantly lowered HbA1c levels compared with other antihyperglycemic medications and placebo (WMD = −0.978, 95% confidence interval = −1.702 to −0.254) in patients with T2DM.
- A decline in fasting plasma glucose levels and a reduction in body weight was observed
- Most commonly reported adverse events with Dulaglutide were nausea, diarrhea, vomiting, hpoglycemia, injection-site reaction, and abdominal distention
- All included trials demonstrated a high quality.



Mean change of HbA1C from baseline to the end of the trial. The estimated weighted mean difference (WMD) corresponds to the middle of the squares and the horizontal line shows the 95% confidence interval (CI)

DISCUSSION

- Endogenous GLP-1 is an incretin hormone that is released from the intestine in response to food intake[2]
- Effects of GLP-1 include increased insulin secretion, decreased glucagon release, increased satiety and slowed gastric emptying[2]
- Currently available GLP-1 receptor agonists include:[2]
  - Exenatide (twice-daily)
  - Liraglutide, Lixisenatide (once-daily)
  - Exenatide long-acting release (LAR), Albiglutide, Dulaglutide (once-weekly)
- On an average, GLP-1 agonists lower HbA1c by around 1% – 1.5%.[6]
- Dulaglutide reduces both fasting and postprandial plasma glucose, though its effect on fasting plasma glucose is more robust[7]
- Despite lowering both FPG and PPPG, Dulaglutide has not been associated with significant hypoglycemia[8]
- Additional benefits of GLP-1 agonists:
  - Increase in pancreatic β-cell mass has been documented both in vitro and in rodent models, leading to
  - slower progression of T2DM and a potential delay in the need for insulin therapy[9]
  - Promote weight loss (approx. 1-3 kg) compared to conventional T2DM therapies[2]
  - Cardiovascular benefits: studies show that Dulaglutide has statistically significant, but not clinically significant, reductions in Systolic and diastolic BP, total cholesterol, LDL-cholesterol, and triglycerides[2]

ADR Profile and Cost[2]

- ADR profile of Dulaglutide is similar to that of other GLP-1 agonists
- Most common ADRs are transient and mild GI side effects such as nausea, vomiting, and diarrhea
- Hypoglycemia risk is low
- Injection-site reactions are possible, but have not been reported at a high rate
- Pancreatitis is a concern for all incretin agents
- All GLP-1 receptor agonists are expensive than other conventional drugs for T2DM.

CONCLUSION

- Our results demonstrated the positive effects of Dulaglutide on HbA1c levels, weight reduction, and fasting plasma glucose levels compared with other antihyperglycemic medications
- Dulaglutide exhibited a favorable safety profile with minor adverse events
- Additional well-designed, large RCTs are necessary to further support the clinical application of Dulaglutide.

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