Effectiveness of GLP-1 analogues compared to DPP-4 inhibitors for beta cell function and diabetes related complications among adults with type 2 diabetes: a systematic review and meta-analysis

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Introduction

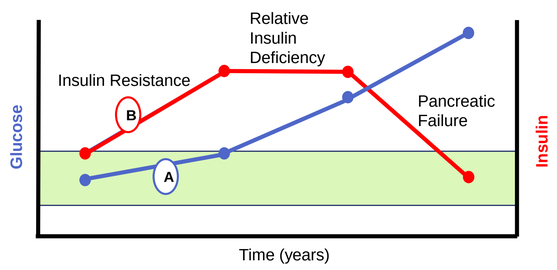
Continued loss of beta cell function is responsible for progressive deterioration of plasma glucose control, and complications characteristic of type 2 diabetes.[1] Research has indicated that a decline in beta cell function occurs early in the course of type 2 diabetes. [1] (Figure 1)

There is increasing clinical evidence that the incretin hormone glucagon-like peptide-1 (GLP-1) can improve beta cell function,[1] however clinical use of GLP-1 in its native form is hampered by its rapid, enzymatic inactivation by dipeptidyl peptidase-4 (DPP-4).[2]

Two classes of incretin-based antihyperglycaemic agents DPP-4 inhibitors and GLP-1 analogues utilise the biological potential of GLP-1 in two ways:

- GLP-1 analogues are resistant to DPP-4 inactivation and mimic the action of naturally occurring GLP-1
- DPP-4 inhibitors block enzymatic DPP-4 action and thereby prolong the activity of endogenous GLP-1[2] (Figure 2)

Figure 1. Natural history of type 2 diabetes. (A) Elevations in blood glucose level over time. (B) Progression from compensatory beta cell function to beta cell decline and failure resulting in a decrease in insulin concentration. Shaded area represents normal blood glucose range.



Aim

The aim of this systematic review was to provide a comprehensive synthesis of randomised clinical studies comparing the effectiveness of GLP-1 analogues to DPP-4 inhibitors on beta cell function and diabetes related complications.

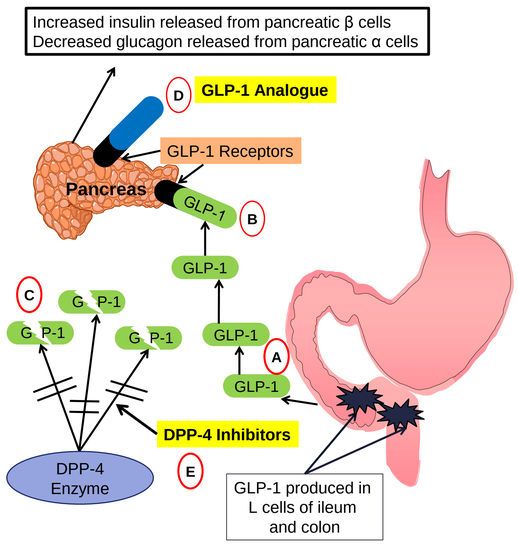
Method

A search of PubMed, EMBASE and national and international clinical trials databases was conducted. Randomised controlled trials were included that compared GLP-1 analogues to DPP-4 inhibitors, either alone or in combination with metformin, in adults with type 2 diabetes. Primary outcomes of interest were:

- beta cell function measured by hyperglycaemic clamp technique, homeostasis assessment model (HOMA), measures of C-peptide and proinsulin to insulin plasma concentration ratio
- glycated haemoglobin (HbA1c)
- fasting and postprandial plasma glucose levels.

Secondary outcomes of interest were diabetes related complications (neuropathy, nephropathy and retinopathy) adverse drug events and mortality.

Figure 2. Schematic diagram explaining: (A) physiological secretion of GLP-1 from the gut, (B) its binding to GLP-1 receptors on the pancreatic beta cells and (C) its enzymatic degradation by DPP-4. GLP-1 analogue (D) binds to and activates GLP-1 receptor, DPP-4 inhibitors (E) prevent the degradation of biological GLP-1 and thereby enhance its activity on the pancreas. (Adapted from:- Nauck M, Vilsboll T, Gallwitz B. Incretin-Based Therapies. Diabetes Care. 2009;32(Suppl):S223-S231).



Results

Figure 3. Meta-analysis of effects on beta cell function as measured by homeostasis model assessment (HOMA-B%) with GLP-1 analogue versus DPP-4 inhibitor for duration of 26 weeks.

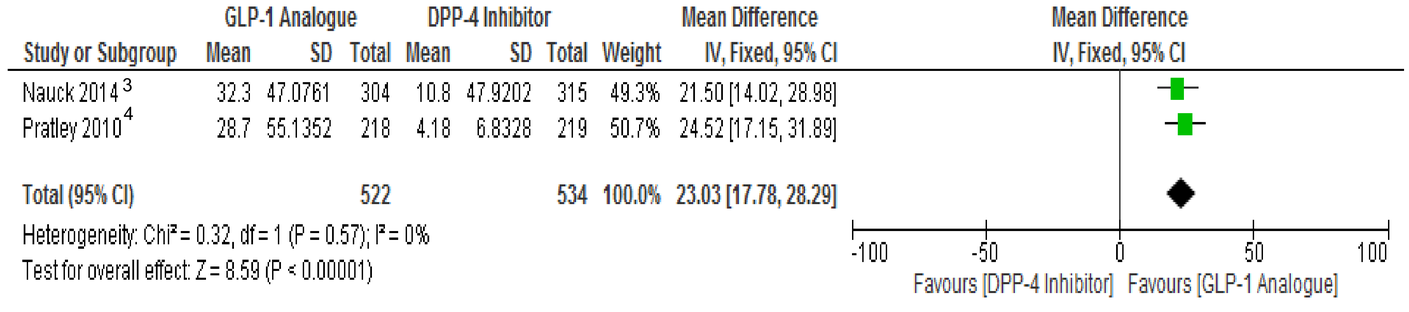


Figure 4. Meta-analysis of effects on HbA1c as measured by % with GLP-1 analogue versus DPP-4 inhibitor for duration of 26 weeks.

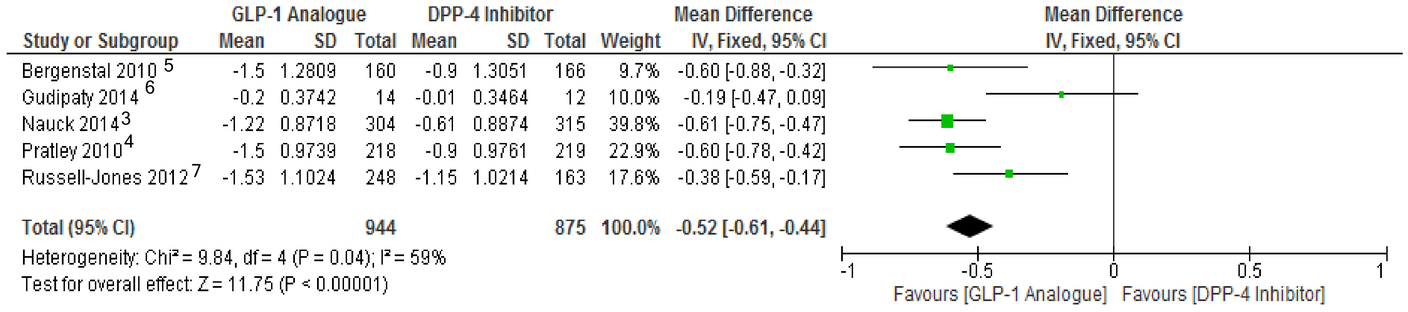
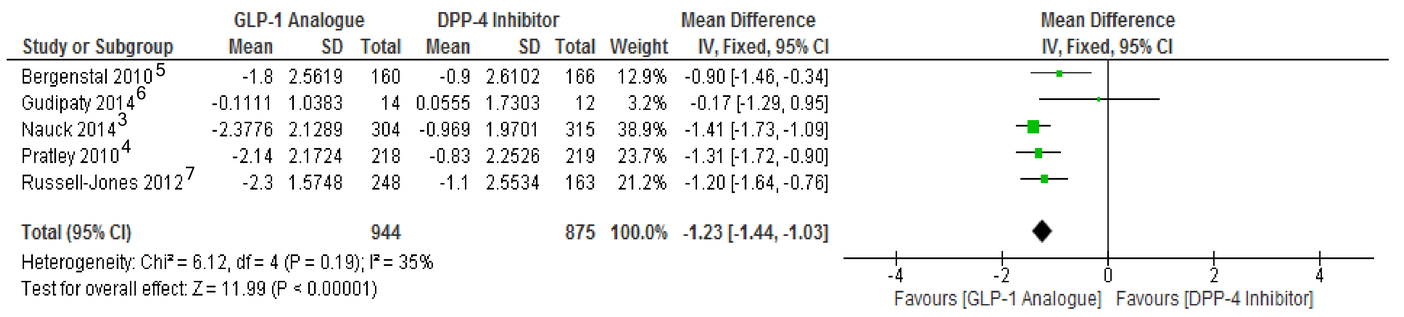


Figure 5. Meta-analysis of effects on fasting plasma glucose levels as measured by mmol/L with GLP-1 analogue versus DPP-4 inhibitos for duration of 26 weeks.



A total of eight randomised controlled trials were included in the systematic review, including two unpublished studies and three multi-arm studies. Treatment duration ranged from eight weeks to 52 weeks. Four different GLP-1 analogues were used in the retrieved studies (lixisenatide, liraglutide, dulaglutide and exenatide) while the same DPP-4 inhibitor (sitagliptin) was used as the active comparator throughout all included studies.

Meta-analysis results showed that, at 26 weeks, GLP-1 analogue compared to DPP-4 inhibitor was associated with:

- more favourable improvements in beta cell function as measured by HOMA (Figure 3)
- Greater reduction in HbA1c (Figure 4)
- Greater reduction in fasting plasma glucose (Figure 5)

No comparative outcome data were obtained for postprandial plasma glucose levels, or diabetes related complications. DPP-4 inhibitors had fewer gastrointestinal adverse events compared to GLP-1 analogues. There were no difference in headache and infection adverse events.

Conclusion

The findings showed that GLP-1 analogues had greater beneficial effects on pancreatic beta cell function, HbA1c and fasting plasma glucose levels than DPP-4 inhibitors, however caused more gastrointestinal adverse events.

References

1. Mudaliar S. Choice of early treatment regimen and impact on β-cell preservation in type 2 diabetes. Int J Clin Pract. 2013 Sep; 67(9):876-887
2. Brunton S. GLP-1 receptor agonists vs. DPP-4 inhibitors for type 2 diabetes: is one approach more successful or preferable than the other? Int J Clin Pract. 2014:1-11
3. Nauck et al. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial. Diabetes Care. 2014 Apr: 1-10
4. Pratley et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet. 2010; 375:1447-56
5. Bergenstal et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet. 2010; 376:431-39
6. Gudipaty et al. Effect of exenatide, sitagliptin or glimepiride on β-cell secretory capacity in early type 2 diabetes. Diabetes Care. 2014:1-8
7. Russell-Jones et al. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone and sitagliptin used as monotherapy in drug-naïve patients with type 2 diabetes (DURATION-4). Diabetes Care 2012; 35: 252-258

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