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Impact of diabetes duration on achieved reductions in glycated haemoglobin, fasting plasma glucose and body weight with liraglutide treatment for up to 28 weeks: a meta-analysis of seven phase III trials

This meta-analysis of seven randomized, placebo-controlled studies (total 3222 patients) evaluated whether type 2 diabetes (T2D) duration affects the changes in blood glucose control and body weight that can be achieved with liraglutide and placebo. With liraglutide 1.2 mg, shorter diabetes duration was associated with a significantly greater, but clinically non-relevant, difference in glycated haemoglobin (HbA1c) reduction ($p < 0.05$), i.e. a 0.18% (1.96 mmol/mol) reduction in HbA1c per 10 years shorter diabetes duration. With liraglutide 1.8 mg, shorter diabetes duration was associated with a small but statistically significant trend for greater fasting plasma glucose (FPG) reduction ($p < 0.05$), i.e. a 0.38 mmol/l reduction in FPG per 10 years shorter diabetes duration. Neither the liraglutide 1.8 mg nor placebo results showed a significant association between HbA1c and diabetes duration and neither the liraglutide 1.2 mg nor placebo results showed a significant association between FPG and diabetes duration. Likewise, neither liraglutide nor placebo showed a significant association between change in weight and diabetes duration. These results suggest diabetes duration has a clinically negligible effect on achievable blood glucose control and weight outcomes with liraglutide and placebo in patients with T2D.

Keywords: HbA1c, FPG, weight, diabetes duration

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Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a mainstay of type 2 diabetes (T2D) therapy because of their ability to lower glucose with concomitant body weight reduction and low hypoglycaemia risk [1,2]. As endogenous insulin secretion decreases with increased T2D duration, it might be expected that GLP-1RAs would have a larger glucose-lowering effect in the early stages of the disease. A recent trial raised the question that the use of the GLP-1RA liraglutide, early in the T2D treatment paradigm, may have benefits for patients, such as preservation of β-cell function [3]. Furthermore, some studies have shown that glycated haemoglobin (HbA1c) reduction with liraglutide was significantly greater in patients with ≤4 years of diabetes duration, and the magnitude of HbA1c reduction was inversely related to diabetes duration [4,5]; however, data on the individual effect of diabetes duration *per se* on achievable blood glucose control and body weight reductions with GLP-1RA, such as liraglutide, are limited.

The available data from the prospective Liraglutide Effect and Action in Diabetes (LEAD) studies, that measured efficacy and safety of liraglutide at doses up to 1.8 mg, both as mono- and combination therapies, together with a range of antidiabetic drugs, provide an opportunity to address this question. We therefore conducted a *post hoc*, pooled analysis to evaluate how T2D duration affected the observed changes in HbA1c, fasting plasma glucose (FPG) and body weight with liraglutide 1.8 mg, liraglutide 1.2 mg and placebo.

Methods

Data from patients with T2D treated with liraglutide 1.2 mg (n = 1117), liraglutide 1.8 mg (n = 1581) or placebo (n = 524) in seven phase III trials were included in this analysis [6–12]. The 28-week data from one study [8] and 26-week data from the six other trials were assessed [6,7,9–12]. The relationships of HbA1c, FPG or body weight (change from baseline) with diabetes duration were plotted using available data from the intention-to-treat population, using a last observation carried forward approach.

Data analyses were conducted by individual trial and pooled across trials. The slope for change in HbA1c or body weight versus diabetes duration was determined using a linear regression analysis (Figures S1–S9, Supporting Information). The statistical analysis used the baseline endpoint value, diabetes duration and age as continuous covariates. Categorical covariates were previous treatment and country. Significance and non-significance in discussing results refers to statistical significance, unless otherwise specified.

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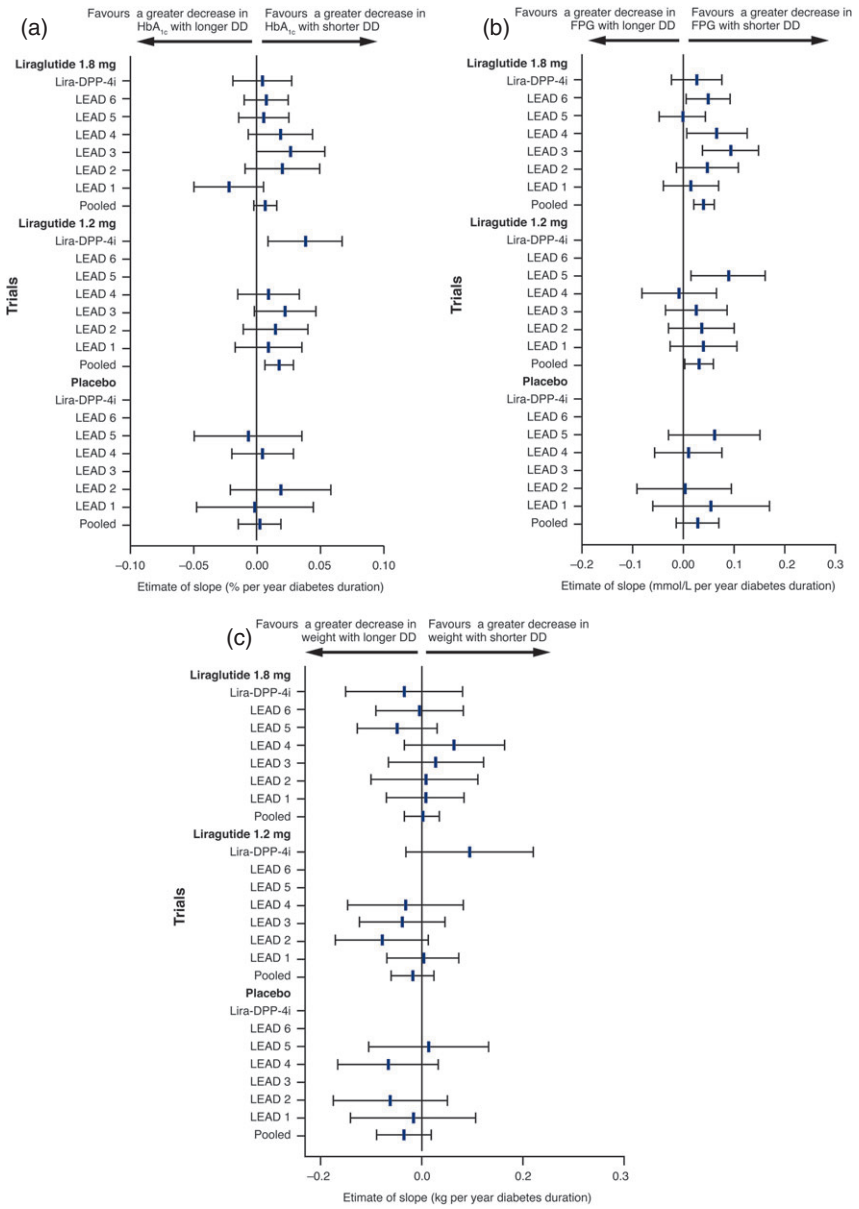

Figure 1. (a) Effect of diabetes duration on change in glycated haemoglobin (HbA1c). (b) Effect of diabetes duration (DD) on change in fasting plasma glucose (FPG). (c) Effect of DD on change in body weight. Data are modelled estimates with 95% confidence intervals. DPP-4i, dipeptidyl peptidase-4 inhibitors. (a) and (c) with permission from: The effect of liraglutide on HbA1c and body weight is largely independent of baseline diabetes duration. Diabetes July 2013;62(Suppl 1):A217–A364. Abstract 1033-P, page A266. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.

Results

Patient Demographics

Patient demographics are described in Table S1, Supporting Information. Baseline T2D duration ranged from <1 to >40 years, with a mean of ~8 years reported for the pooled groups (placebo, liraglutide 1.2 mg and liraglutide 1.8 mg).

Change in HbA1c, FPG and Body Weight from Baseline

The 26-/28-week data showed clinically relevant reductions in HbA1c, FPG and body weight from baseline in patients treated with liraglutide 1.2 and 1.8 mg compared with placebo (Tables S2 and S3, Supporting Information).

Baseline data and trial design

The baseline data and design of each trial are described in Supplementary Tables 4 and 5, respectively.

Effect of Diabetes Duration on Liraglutide Therapeutic Outcomes

With liraglutide 1.8 mg, shorter diabetes duration was associated with a non-significant trend for HbA1c reduction, i.e.

Table 1. Effect of diabetes duration on glycated haemoglobin, fasting plasma glucose and body weight (pooled estimates).

	Placebo			Liraglutide 1.2 mg			Liraglutide 1.8 mg		
	Estimate	Lower 95% CI	Upper 95% CI	Estimate	Lower 95% CI	Upper 95% CI	Estimate	Lower 95% CI	Upper 95% CI
Body weight (kg per 10 years DD)	−0.34	−0.88	0.20	−0.18	−0.60	0.24	0.02	−0.33	0.37
HbA1c, (% [mmol/mol] per 10 years DD)	0.03 [0.28]	−0.15 [−1.59]	0.20 [2.14]	0.18* [1.96]	0.06 [0.71]	0.30 [3.21]	0.07 [0.76]	−0.02 [−0.22]	0.16 [1.74]
FPG, (mmol/l per 10 years DD)	0.27	−0.14	0.67	0.29	−0.00	0.58	0.38†	0.19	0.57

Data are modelled estimates with 95% CI, from intention-to-treat population, last observation carried forward.
CI, confidence interval; DD, diabetes duration; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin.
*Shorter DD was associated with a significantly ($P < 0.05$) greater HbA1c reduction.
†Shorter DD was associated with a significantly ($P < 0.05$) greater FPG reduction.

a 0.07% (0.76 mmol/mol) reduction in HbA1c per 10 years shorter diabetes duration (Figure 1a and Table 1/Figure S2, Supporting Information). With liraglutide 1.2 mg, shorter diabetes duration was associated with a small but significant trend of greater HbA1c reduction ($p < 0.05$), equating to a 0.18% (1.96 mmol/mol) reduction in HbA1c per 10 years shorter diabetes duration (Figure 1a, Table 1 and Figure S1, Supporting Information). No trends were observed in the corresponding placebo data (Figure 1a, Table 1 and Figure S3, Supporting Information).

With liraglutide 1.8 mg, shorter diabetes duration was associated with a small but statistically significant trend for greater FPG reduction ($p < 0.05$), equating to a 0.38 mmol/l reduction in FPG per 10 years shorter diabetes duration (Figure 1b, Figure S5, Supporting Information and Table 1). This was predominantly driven by results from two trials (LEAD 3 and LEAD 4), with liraglutide compared to glimepiride (both as monotherapy) in one trial, and used in combination with metformin and thiazolidinedione in the other [7,8]. With liraglutide 1.2 mg, there was no significant association between FPG and diabetes duration (Figure 1b, Table 1 and Figure S4, Supporting Information). No significant trends for FPG reduction were observed in the corresponding placebo data (Figure 1b, Table 1 and Figure S6, Supporting Information).

With liraglutide 1.8 and 1.2 mg, no significant associations were observed between diabetes duration and change in body weight (Figure 1c, Table 1 and Figures S8 and S7, Supporting Information, respectively), and no significant trend was seen with placebo (Figure 1c, Table 1 and Figure S9, Supporting Information).

Discussion

This assessment shows that HbA1c, FPG and body weight responses observed during a clinical trial with liraglutide or placebo treatment are not significantly influenced by T2D duration. The population represented a large spectrum of diabetes duration and, therefore, may be considered to be representative of a continuum of different stages of disease progression, as is seen in clinical practice. Of note, however, the inclusion and exclusion criteria of the different trials may have selected the patients for suitability for liraglutide treatment, hence results may not be fully representative of the likely effect in the T2D population at large. There is also the additional influence of background therapy or other systematic study differences; moreover, not all liraglutide doses were studied in all trials.

It was found that, for liraglutide 1.2 mg, shorter diabetes duration was associated with a significantly greater HbA1c reduction, although the effect was small and clinically non-relevant. With liraglutide 1.8 mg, a shorter duration was associated with significantly greater FPG reduction, but, again, the effect was small. If the effect was not spurious, statistically significantly greater reductions in HbA1c with shorter diabetes duration would have been expected at both doses, which was not the case. In addition, if the effect was not spurious, statistically significant greater reductions in both HbA1c and FPG efficacy at the same dose of liraglutide would have also been expected. Taking all these findings into consideration, our data indicate that these trends could be merely coincidental. In any case, they are of no clinical relevance for the estimation judgement of achievable outcomes with liraglutide treatment.

There was no significant association between change in body weight and diabetes duration, suggesting that the changes in body weight observed during a clinical trial with liraglutide or placebo treatment are completely independent of diabetes duration. Liraglutide influences glucose and weight reductions through different mechanisms; therefore, different trends with diabetes duration for HbA1c and FPG versus body weight could potentially be expected.

These study results suggest that the overall effects of liraglutide in patients with T2D may be less dependent on maintained endogenous insulin secretory capacity than previously thought in advanced states of diabetes, and that insulin-independent actions of liraglutide [glucagonostatic effect and central nervous system effect (reduction of appetite)] may also contribute to the therapeutic outcome [2]; however, it is worth noting that the vast majority of patients in the present study had a diabetes duration of <15 years, and that insulin secretory capacity was not formally examined against changes in HbA1c and FPG.

In summary, our analysis suggests that diabetes duration *per se* has a clinically negligible effect on achievable HbA1c, FPG and weight outcomes with liraglutide 1.8, 1.2 mg and placebo in patients with T2D. This suggests that treatment with the GLP-1RA liraglutide may be effective in the treatment of T2D regardless of its duration.

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Conflict of Interest

J. S. has attended advisory boards and/or speaker's bureaux for Takeda, Bayer, Novartis, Merck Sharp Dohme, Astra Zeneca, Bristol Myers Squibb, Novo Nordisk, Sanofi Aventis, Berlin Chemie, Eli Lilly, Boehringer Ingelheim, Merck, Roche, Ipsen, Pfizer, Janssen and Lifescan, and has received research support from Takeda, Novartis, Merck Sharp Dohme, Glaxo Smith Kline, Novo Nordisk, Sanofi Aventis, Ipsen, Pfizer, Janssen, Servier, Eli Lilly, Apitope, Intarcia and Roche. T. B. has provided research support to Abbott, ACON, Bayer, Bristol Myers Squibb, Dexcom, GlaxoSmithKline, Halozyme, Insulet, Janssen, Lexicon, Lifescan, Eli Lilly, Medtronic, Merck, Novo Nordisk, Orexigen and Sanofi, and has received consulting honoraria from Astra Zeneca, Bayer, BD, Eli Lilly, Medtronic, Novo Nordisk and Sanofi and speaking honoraria from Abbott, Insulet, Novo Nordisk and Sanofi. S.B.C is an employee of Novo Nordisk. M. A. N. has served on advisory boards for, received honoraria or consulting fees from, or received research funding from Amylin, AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Bristol Myers Squibb, Diartis Pharmaceuticals, Eli Lilly, GlaxoSmithKline, F. Hoffmann-La Roche, Intarcia Therapeutics, Janssen, MannKind, Merck, MetaCure, Novartis, Novo Nordisk, Roche Pharmaceuticals, Sanofi, Takeda, Versartis and Wyeth Research.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Relationship between glycated haemoglobin and diabetes duration: liraglutide 1.2 mg.

Figure S2. Relationship between glycated haemoglobin and diabetes duration: liraglutide 1.8 mg.

Figure S3. Relationship between glycated haemoglobin and diabetes duration: placebo.

Figure S4. Relationship between fasting plasma glucose and diabetes duration: liraglutide 1.2 mg.

Figure S5. Relationship between fasting plasma glucose and diabetes duration: liraglutide 1.8 mg.

Figure S6. Relationship between fasting plasma glucose and diabetes duration: placebo.

Figure S7. Relationship between body weight and diabetes duration: liraglutide 1.2 mg.

Figure S8. Relationship between body weight and diabetes duration: liraglutide 1.8 mg.

Figure S9. Relationship between body weight and diabetes duration: placebo.

Table S1. Baseline patient demographics.

Table S2. Change in glycated haemoglobin, fasting plasma glucose and body weight from baseline (LOCF).

Table S3. Proportion of patients with glycated haemoglobin <7%.

Table S4. Design of phase III studies included in meta-analyses.

Table S5. Baseline characteristics of liraglutide and placebo treatment groups from phase III studies.

References

1. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centred approach. Diabetes Care 2015; **38**: 140–149.
2. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 2012; **8**: 728–742.
3. Retnakaran R, Kramer CK, Choi H, Swaminathan B, Zinman B. Liraglutide and the preservation of pancreatic β-cell function in early type 2 diabetes: the LIBRA trial. Diabetes Care 2014; **37**: 3270–3278.
4. Lapolla A, Frison V, Bettio M et al. Correlation between baseline characteristics and clinical outcomes in a large population of diabetes patients treated with liraglutide in a real-world setting in Italy. Clin Ther 2015; **37**: 574–584.
5. Ponzani P. Long-term effectiveness and safety of liraglutide in clinical practice. Minerva Endocrinol 2013; **38**: 103–112.
6. Marre M, Shaw J, Brändle M et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). Diabet Med 2009; **26**: 268–278.
7. Nauck M, Frid A, Hermansen K et al. Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care 2009; **32**: 84–90.
8. Garber A, Henry R, Ratner R et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009; **373**: 473–481.
9. Zinman B, Gerich J, Buse JB et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met + TZD). Diabetes Care 2009; **32**: 1224–1230.
10. Russell-Jones D, Vaag A, Schmitz O et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met + SU): a randomised controlled trial. Diabetologia 2009; **52**: 2046–2055.
11. Buse JB, Rosenstock J, Sesti G et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009; **374**: 39–47.
12. Pratley RE, Nauck M, Bailey T 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**: 1447–1456.