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Improvement in glycated haemoglobin evaluated by baseline body mass index: a meta-analysis of the liraglutide phase III clinical trial programme

In the liraglutide clinical trial programme, liraglutide 1.2 and 1.8 mg were found to effectively lower glycated haemoglobin (HbA1c) in patients with type 2 diabetes (T2D). It is unknown whether baseline body mass index (BMI) is a predictor of change in HbA1c observed during a clinical trial with liraglutide or placebo treatment. The present meta-analysis of patient-level data, using pooled data from seven phase III trials [LEAD-1–6 and the liraglutide versus sitagliptin trial (LIRA–DPP-4)] for liraglutide 1.2, 1.8 mg and placebo (n = 3222), identified no significant correlation between baseline BMI (<20 kg/m^2 up to 45 kg/m^2) and HbA1c reduction for placebo or liraglutide 1.2 mg, and a modest, clinically non-relevant, association for liraglutide 1.8 mg [−0.010 (95% confidence interval −0.020, −0.001)], whereby a 10 kg/m^2 increase in baseline BMI corresponded to 0.10%-point (1.1 mmol/mol) greater HbA1c reduction. In summary, reductions in HbA1c obtained during clinical trials with liraglutide or placebo treatment were independent of baseline BMI.
Keywords: body mass index, glycaemic control, liraglutide, meta-analysis, type 2 diabetes

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Introduction

The human glucagon-like peptide-1 analogue liraglutide is approved for the treatment of type 2 diabetes (T2D) at doses up to 1.8 mg, and its efficacy and safety have been demonstrated in seven large phase III trials (the LEAD-1–6 and Lira–DPP-4 trials) [1–7] (Table S1). In these trials, liraglutide [as monotherapy or in combination with various oral antidiabetic drug (OAD) therapies] improved glycated haemoglobin (HbA1c) to a significantly greater extent (or similar, in the case of LEAD-2) than placebo or active comparator (by a margin of 0.8–1.5% [8.7–16.4 mmol/mol] compared with placebo or active comparator).

Liraglutide also reduced body weight in most of these trials [1–7], with a mean weight loss of up to 3.4 kg [7] after 26 weeks of treatment. In the LEAD-1 study, where liraglutide was used in combination with a sulphonylurea, weight loss was relatively limited (0.2 kg) for patients receiving liraglutide 1.8 mg, while those receiving 1.2 mg experienced a small weight gain; however, this gain was significantly less than that observed for the active comparator rosiglitazone [1].

Body mass index (BMI) values in the overweight and obese ranges (25–29.9 kg/m^2 and ≥30 kg/m^2, respectively) are common in patients with T2D. It is also known that obesity may affect the distribution and elimination of some drugs; for liraglutide specifically, a population pharmacokinetic assessment showed that plasma levels may be reduced in patients with higher rather than lower body weight, because of a larger distribution volume [8]. A previous analysis of the LEAD trials has shown that higher baseline BMI is associated with greater weight reductions with liraglutide (effective only when 1.2 and 1.8 mg groups were analysed together; p = 0.04) [9].

Reduction in HbA1c is widely considered to be a benchmark of efficacy for the treatment of T2D, with improved glycaemic control translating into improved microvascular outcomes for the patient [10]. The ability to predict in advance who is likely to respond better on the basis of baseline characteristics would be of benefit to both clinicians and patients.

The aim of the present meta-analysis of patient-level data was to estimate the influence of baseline BMI on change in HbA1c during liraglutide and placebo treatment using pooled data from the liraglutide phase III clinical trials.

Methods

The primary outcome of this analysis was the association of HbA1c reduction with baseline BMI.

Study Design

We conducted a meta-analysis using pooled, patient-level data for liraglutide 1.2, 1.8 mg and placebo treatment (n = 3222) from the LEAD-1, -2, -3, -4, -5, -6 and Lira–DPP-4 trials (treatment periods: all 26 weeks, except for LEAD-3, which was 52 weeks, thus 28-week data from this trial were used; total n = 5100). All trials were randomized, parallel-group, multicentre, multinational phase III trials.

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Participants

Inclusion criteria were baseline BMI ≤45 kg/m^2, diagnosed T2D and inadequate glycaemic control [HbA1c between either 7.0 or 7.5% (53.0 or 58.5 mmol/mol) and either 10.0 or 11.0% (85.8 or 96.7 mmol/mol), depending on previous T2D treatment regimen]. All trials included in the analysis were conducted in accordance with the Declaration of Helsinki and approved by the appropriate institutional review boards. All participants provided informed consent.

Statistical Analysis

The intention to treat population from the LEAD-1–6 and Lira–DPP-4 trials was included. All HbA1c values were change from baseline to week 26 (or week 28 for LEAD-3) and missing post-baseline data were imputed using LOCF. Treatment arms with numbers of patients (n) included in the analysis are shown in Table S1.

Data from treatment arms were modelled to generate estimates of the correlation, expressed as the slope of HbA1c change from baseline per unit increase of baseline BMI [with 95% confidence intervals (CIs)], for pooled liraglutide 1.2, 1.8 mg and placebo. The correlation between baseline BMI and HbA1c change was analysed using an analysis of covariance (ANCOVA) model that accounted for age, baseline HbA1c, gender, country, trial and previous T2D treatment as covariates.

A plot of change in HbA1c according to baseline BMI category was determined by stratifying pooled data according to one of five BMI categories: <20 kg/m^2; ≥20 to <25 kg/m^2; ≥25 to <30 kg/m^2; ≥30 to <35 kg/m^2 and ≥35 to <45 kg/m^2.

Results

At baseline, patient demographics were well-matched across treatment groups of liraglutide 1.2 mg (n = 1117), liraglutide 1.8 mg (n = 1581) and placebo (n = 524). The mean patient age was 55.7 years. The mean baseline HbA1c and BMI values were 8.4% (68.3 mmol/mol) and 31.9 kg/m^2 (31.8 kg/m^2 for the placebo group), respectively, for all three groups (Table S1). Previous OAD monotherapy was used in 51.3, 41.5 and 22.0%, and previous OAD combination therapy was used in 40.6, 53.0 and 78.0% of patients treated with liraglutide 1.2 mg, liraglutide 1.8 mg and placebo, respectively. These differences in OAD usage reflect the fact that not all trials had both liraglutide 1.2 mg and placebo comparison arms (LEAD-3, LEAD-5, LEAD-6 and LIRA–DPP-4).

For the liraglutide 1.2 mg and placebo groups, no significant correlation between baseline BMI and HbA1c change was observed [−0.003 (95% CI −0.014, 0.008) and −0.011 (95% CI −0.030, 0.009), respectively; Figure 1].

For the liraglutide 1.8 mg group, a weak correlation was observed between baseline BMI and HbA1c change [−0.010 (95% CI −0.020, −0.001); Figure 1]; however, the effect was small: a 10 kg/m^2 higher BMI at baseline corresponded to a greater HbA1c reduction of only 0.10%-point (1.1 mmol/mol), which was not considered clinically relevant.

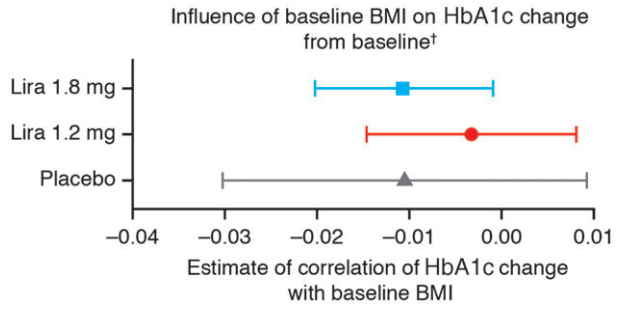

Figure 1. The relationship between baseline body mass index (BMI) and change in glycated haemoglobin (HbA1c) from baseline for liraglutide 1.8 mg, liraglutide 1.2 mg and placebo in pooled data from the LEAD-1–6 and Lira–DPP-4 trials. Data are modelled estimates (95% confidence intervals). †Pooled data were analysed using an analysis of covariance (ANCOVA) model which accounted for age, baseline HbA1c, gender, country, trial and previous type 2 diabetes treatment as covariates. Lira, liraglutide.

The mean change in HbA1c from baseline when patients were stratified according to baseline BMI category is shown in Figures 2A–C.

Discussion

This meta-analysis indicates that improvements in HbA1c observed during a clinical trial with liraglutide or placebo treatment are largely independent of baseline BMI up to 45 kg/m^2. This is the first meta-analysis testing the association between HbA1c reduction and baseline BMI with liraglutide treatment in patients with T2D. The use of a very large patient cohort, from seven randomized phase III trials, provides reliable robust estimates. Our finding that baseline BMI did not predict the HbA1c reduction with liraglutide is also supported by a recent real-world data study conducted in the USA, in which liraglutide was reported to reduce HbA1c equally well across all categories of baseline BMI in clinical practice [11].

The results also corroborate those of the HARMONY-7 trial, in which liraglutide was compared with albiglutide, where a subgroup analysis for BMI (<30 kg/m^2 and ≥30 kg/m^2) showed that differences in change from baseline in HbA1c for albiglutide versus liraglutide at week 32 were consistent with the change in HbA1c of the overall population, irrespective of BMI grouping [12].

A similar lack of association was observed between baseline BMI and HbA1c reductions with exenatide twice-daily and sitagliptin in a 30-week trial in patients with T2D. In that trial, the improved glycaemic control observed with exenatide twice-daily (added to optimized basal insulin) was independent of BMI [13]. The absense of data relating to duration of diabetes as a covariate factor might be considered a limitation of the study; however, it is worth noting that previous reports have suggested that duration of diabetes has a clinically negligible effect on HbA1c in patients with T2D treated with liraglutide, with a non-relevant trend for greater HbA1c reductions with shorter diabetes duration with 1.2 mg liraglutide [difference equated to −0.2% (2.2 mmol/mol) HbA1c per 10 years shorter diabetes duration] [14].

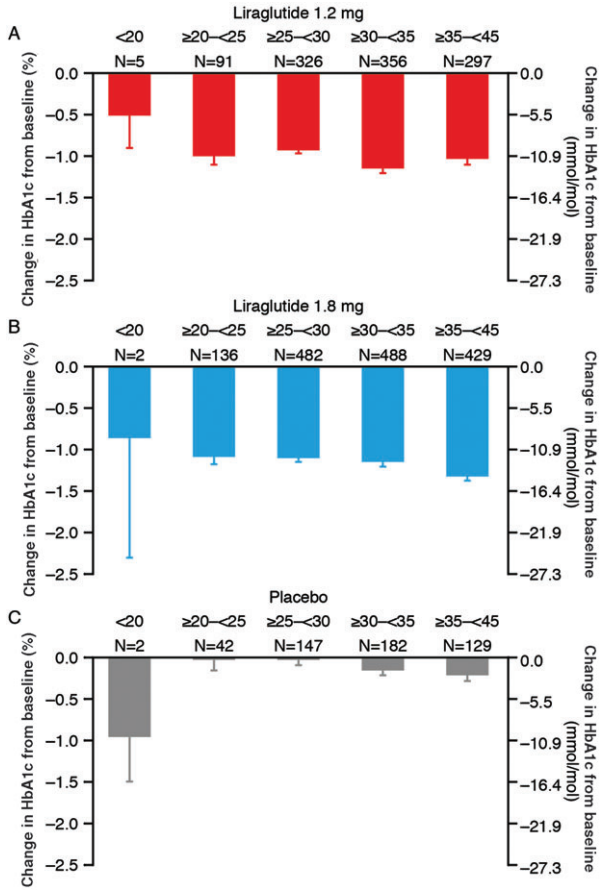

Figure 2. Change in glycated haemoglobin (HbA1c) from baseline stratified by baseline body mass index for pooled data from the LEAD 1–6 and Lira DPP-4 trials for liraglutide 1.2 mg (A), liraglutide 1.8 mg (B) and placebo (C). Data shown are mean with standard error, LOCF, based on summary statistics.

An important limitation of the present study is that it was *post hoc* in nature and therefore the results should be interpreted with caution. A prospective study would be required to confirm the initial findings reported here. Additionally, in line with the exclusion criteria of the LEAD trials, only patients with a BMI of ≤45 kg/m^2 were included, therefore, the findings should not be extended to other patient cohorts.

In summary, our results suggest that baseline BMI up to 45 kg/m^2 did not influence the change in HbA1c during liraglutide and placebo treatment using pooled data from the liraglutide phase III clinical trials; this could be important to physicians in the management of patients with T2D with a wide range of BMI values.

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Conflict of Interest

E. M. has served as an advisor for AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, GlaxoSmithKline, Intarcia Therapeutics, Inc., Jansen and Novo Nordisk. V. F. receives honoraria for consulting and lectures from Takeda, Novo Nordisk, Sanofi-Aventis, Eli Lilly, Pamlabs, Astra-Zeneca, Abbott, Amgen, Boehringer Ingelheim and Janssen, and receives investigator grant/research support to his institution from Novo Nordisk, Asahi, Eli Lilly, Abbott, Endo Barrier and Gilead Sciences. S. C. has been a member of advisory panels for Novo Nordisk, Servier, Sanofi, MSD, BMS-AZ and Takeda, and a member of speakers bureau for Novo Nordisk, Servier, Sanofi, MSD, BMS-AZ, Merck and Takeda. L. B. receives speaking honoraria from AstraZeneca, Janssen Pharmaceuticals, Inc., Merck & Co., Novo Nordisk and Sanofi, and consultant honoraria from AstraZeneca, GlaxoSmithKline, Intarcia Therapeutics, Inc., Janssen Pharmaceuticals, Inc., Merck & Co., Inc., Novo Nordisk, Quest Diagnostics, Sanofi, and receives investigator grant/research support at his institution from Eli Lilly and Company, Lexicon Pharmaceuticals, Inc., Novo Nordisk, and Sanofi. M. D. is employed by Novo Nordisk and is a shareholder of Novo Nordisk stock. M. A. N. has participated in advisory boards or was invited as speaker by Amylin Pharmaceuticals, AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Bristol Myers Squibb, Diartis Pharmaceuticals, Inc., Eli Lilly & Co, GlaxoSmithKline, Hoffmann-La Roche Ltd, Intarcia Therapeutics, Inc, Janssen Global Services, MannKind Corp, Merck Sharp & Dohme GmbH, Novo Nordisk, Novartis, Sanofi-Aventis, Takeda, Versartis, Wyeth Research. He has received research support from AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Eli Lilly & Co, GlaxoSmithKline, Merck Sharp & Dohme, MetaCure Inc, Novartis, Roche Pharma, Novo Nordisk and Tolerx Inc.

All authors contributed significantly and reviewed/approved the final version of the manuscript. E. M., V. F., S. C., L. B., M. D. and M. N. all designed and conducted the analysis and contributed to writing the manuscript.

Supporting Information

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

Table S1. Number of patients, mean baseline body mass index and mean baseline glycated haemoglobin included in different treatment arms from the liraglutide clinical programme.

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