Liraglutide and the Preservation of Pancreatic β-Cell Function in Early Type 2 Diabetes: The LIBRA Trial

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OBJECTIVE

Clinical studies evaluating the effects of medications on β-cell function in type 2 diabetes (T2DM) are compromised by an inability to determine the actual baseline degree of β-cell dysfunction independent of the reversible dysfunction induced by hyperglycemia (glucotoxicity). Short-term intensive insulin therapy (IIT) is a strategy for eliminating glucotoxicity before randomization. This study determined whether liraglutide can preserve β-cell function over 48 weeks in early T2DM following initial elimination of glucotoxicity with IIT.

RESEARCH DESIGN AND METHODS

In this double-blind, randomized, placebo-controlled trial, 51 patients with T2DM of 2.6 ± 1.9 years' duration and an A1C of 6.8 ± 0.8% (51 ± 8.7 mmol/mol) completed 4 weeks of IIT before randomization to daily subcutaneous liraglutide or placebo injection, with serial assessment of β-cell function by Insulin Secretion-Sensitivity Index-2 (ISSI-2) on oral glucose tolerance test performed every 12 weeks.

RESULTS

The primary outcome of baseline-adjusted ISSI-2 at 48 weeks was higher in the liraglutide group than in the placebo group (339.8 ± 27.8 vs. 229.3 ± 28.4, *P* = 0.008). Baseline-adjusted HbA_{1c} at 48 weeks was lower in the liraglutide group (6.2 ± 0.1% vs. 6.6 ± 0.1%, *P* = 0.055) (44 ± 1.1 vs. 49 ± 1.1 mmol/mol). At each quarterly assessment, >50% of participants on liraglutide had an HbA_{1c} ≤6.0% (42 mmol/mol) and glucose tolerance in the nondiabetic range. Despite this level of glycemic control, no difference was found in the incidence of hypoglycemia between the liraglutide and placebo groups (*P* = 0.61). Two weeks after stopping treatment, however, the beneficial effect on ISSI-2 of liraglutide versus placebo was entirely lost (191.9 ± 24.7 vs. 238.1 ± 25.2, *P* = 0.20).

CONCLUSIONS

Liraglutide provides robust enhancement of β-cell function that is sustained over 48 weeks in early T2DM but lost upon cessation of therapy.

The natural history of type 2 diabetes mellitus (T2DM) is characterized by rising glycemia and the need for increased antidiabetic medication over time (1). This clinical course is driven by the progressive deterioration of pancreatic β-cell function, a pathologic process that precedes the diagnosis of T2DM and continues

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A slide set summarizing this article is available online.

thereafter despite antidiabetic therapy (2,3). Indeed, although antidiabetic medications differ in the durability of their glucose-lowering effects (4), none has yet been shown to definitively prevent the inexorable decline in β-cell function that occurs in T2DM (5,6). Thus, the preservation of β-cell function remains an elusive goal in the management of T2DM (5,6).

In patients with T2DM, β-cell dysfunction consists of both a presumed irreversible component (e.g., β-cell apoptosis) and a reversible element resulting from the deleterious effect of hyperglycemia on β-cell secretory capacity, a phenomenon called "glucotoxicity" (7–9). An important, often underappreciated implication of the latter component is that clinical studies evaluating the effects of antidiabetic medications on β-cell function are typically confounded by an inability to determine the actual degree of β-cell dysfunction at baseline, independent of the reversible effects of glucotoxicity (9). Moreover, the glucose-lowering activity of an antidiabetic medication can further confound such evaluation in patients with T2DM in whom improved β-cell function may be due to the elimination of glucotoxicity rather than to actual β-cell preservation (9). In this context, short-term treatment with insulin therapy has been proposed as a strategy for eliminating glucotoxicity before randomization, thereby creating a level playing field upon which to objectively evaluate the potential β-cell protective capacity of antidiabetic medications (9–11).

GLP-1 agonists comprise a novel class of antidiabetic medications with multiple beneficial metabolic effects, including glucose-dependent stimulation of insulin secretion, suppression of postprandial glucagon, inhibition of glucose production, enhanced glucose disposal, slowing of gastric emptying, and induction of weight loss (12,13). Coupled with preclinical data suggesting that GLP-1 may increase β-cell mass in animal models (14,15), these properties have fueled considerable interest in the possibility that GLP-1 agonists can preserve β-cell function in patients (13,16). However, objective evaluation of this possibility, free from the confounding elements noted previously, is lacking (16). Thus, the objective of the LIraglutide and β-cell RepAir (LIBRA) Trial was to evaluate the effect of the GLP-1 agonist liraglutide on the preservation of β-cell function over 1 year in patients with early T2DM, following the initial amelioration of glucotoxicity-induced dysfunction by using short-term intensive insulin therapy (IIT) before randomization.

RESEARCH DESIGN AND METHODS

Design and Participants

The LIBRA Trial was a double-blind, randomized, parallel-arm, placebo-controlled study that assessed the capacity of liraglutide to preserve β-cell function in patients with early T2DM (ClinicalTrials.gov; NCT01270789). Patients with early T2DM underwent 4 weeks of IIT before randomization to either liraglutide or matching placebo and were followed for 48 weeks, with serial assessment by oral glucose tolerance test (OGTT) every 12 weeks (Supplementary Fig. 1). This single-center study was approved by the Mount Sinai Hospital Research Ethics Board, and all participants provided written informed consent. All study visits took place at the Leadership Sinai Centre for Diabetes (Mount Sinai Hospital, Toronto, ON).

Inclusion criteria were age 30–75 years inclusive, physician-diagnosed T2DM of ≤7 years' duration, treatment with zero to two oral antidiabetic medications, serum negativity for anti-GAD antibodies, and screening glycated hemoglobin (HbA_{1c}) <9.0% (<75 mmol/mol) if on oral antidiabetic medications or HbA_{1c}<10.0% (<86 mmol/mol) if not on antidiabetic medications. Exclusion criteria were treatment with insulin, GLP-1 agonists, or dipeptidyl peptidase-4 inhibitors; renal dysfunction (estimated glomerular filtration rate <50 mL/min/1.73 m^2); liver disease or transaminase levels >2.5-fold above normal; malignancy; and GLP-1 agonist-specific contraindications, including history of pancreatitis, multiple endocrine neoplasia type 2, or medullary thyroid carcinoma.

Prerandomization IIT Phase

The insulin protocol and patient characteristics before and during the prerandomization IIT phase have been previously described in detail (8,17). In brief, 63 participants stopped taking all antidiabetic medications and completed an overnight fast before undergoing a 2-h 75-g OGTT the next morning. After OGTT, they began a 4-week course of multiple daily insulin injection therapy comprising basal insulin detemir and premeal insulin aspart, with starting total daily doses of 0.2–0.4 units/kg consisting of 60% bolus and 40% basal insulin. This course of IIT was extended to 5–6 weeks in 19 participants (generally due to patient scheduling issues). While on IIT, participants were asked to perform self-monitoring of capillary blood glucose levels at least four times a day, enabling titration of insulin doses to target fasting glucose between 4.0–6.0 mmol/L and 2-h postprandial glucose <8 mmol/L. On the final day of IIT, the last insulin dose was the bolus insulin before dinner, with no bedtime basal insulin. An OGTT was performed the day after cessation of IIT to determine eligibility for randomization.

Randomization and Study Intervention

We previously demonstrated that the achievement of fasting venous glucose <7.0 mmol/L 1 day after stopping IIT is indicative of reversibility of β-cell dysfunction, reflecting the capacity of endogenous insulin secretion to maintain fasting glucose levels in the nondiabetic range (10,18). Thus, in the present study, participants who achieved this target on the post-IIT OGTT were eligible for 1:1 randomization to either liraglutide or identical placebo. The computer-generated random allocation sequence was prepared by the Mount Sinai Hospital research pharmacy in blocks of four participants, and all study personnel and participants were masked to treatment allocation. Study medication was supplied to the research pharmacy by Novo Nordisk as liraglutide 6.0 mg/mL or identical placebo solution in 3-mL prefilled pen injectors.

Study medication (liraglutide or placebo) was administered by daily subcutaneous injection in the morning and titrated over a 3-week period from 0.6 mg daily (first week) to 1.2 mg daily (second week) to 1.8 mg daily (third week), with the third-week dose maintained for the 48-week treatment period. Participants underwent 2-h 75-g OGTT at 12, 24, 36, and 48 weeks. If participants had an HbA_{1c} ≥8.0% (≥64 mmol/mol) at any visit, metformin rescue therapy was initiated at 500 mg twice daily for the first 2 weeks before progressing to 1,000 mg twice daily for the duration of the trial. Metformin rescue therapy prevented exposure to excessive hyperglycemia while allowing participants to remain in the study. However,

if participants had an HbA_{1c} ≥8.0% (≥64 mmol/mol) while on metformin rescue therapy, the protocol was stopped and the patient returned to usual clinical care. At 48 weeks, all participants stopped their study medication before undergoing a washout OGTT 2 weeks later to evaluate for persistence of effects.

At each visit, participants completed questionnaires and underwent physical examination. Hypoglycemia was defined as capillary blood glucose ≤3.9 mmol/L and classified as severe if required third-party assistance and/or involved impairment of consciousness.

Laboratory Measurements and Physiologic Indices

Each OGTT was performed in the morning after overnight fast. Study medication was withheld on the morning of the OGTT such that the last dose was administered ~24 h earlier. During each OGTT, venous blood samples were drawn for measurement of glucose, C-peptide, and insulin at fasting and at 10, 20, 30, 60, 90, and 120 min following ingestion of the 75-g glucose load. Specific insulin was measured with Roche Elecsys 1010 immunoassay analyzer and electrochemiluminescence immunoassay kit, and C-peptide was measured with a Roche modular system and electrochemiluminescence immunoassay kit (Roche Diagnostics, Laval, QC, Canada).

Area under the insulin curve (AUC_{ins}) and area under the glucose curve (AUC_{gluc}) during the OGTT were calculated using the trapezoidal rule. Glucose tolerance categories on OGTT were determined according to Canadian Diabetes Association clinical practice guidelines (19). Whole-body insulin sensitivity was measured by Matsuda index (20), and insulin resistance (primarily hepatic) was assessed by HOMA-IR (21).

β-Cell function was assessed with the Insulin Secretion-Sensitivity Index-2 (ISSI-2). ISSI-2 is a validated OGTT-derived measure of β-cell function analogous to the disposition index obtained from the intravenous glucose tolerance test (22,23). ISSI-2 has been directly validated against the intravenous glucose tolerance test disposition index, with which it exhibits a stronger correlation than other OGTT-derived measures of β-cell function (23), and has been used to measure β-cell function in both clinical trials and observational cohort studies in subjects with and without diabetes (8,17,22–28). ISSI-2 is defined as the product of *1*) insulin secretion as measured by the ratio of AUC_{ins} to AUC_{gluc} and *2*) insulin sensitivity as measured by the Matsuda index. Secondary measures of β-cell function included *1*) $\Delta Ins_{0-120}/\Delta gluc_{0-120} \times$ Matsuda index (where $\Delta Ins_{0-120}/\Delta gluc_{0-120}$ is the mean incremental concentrations of insulin and glucose during the OGTT), *2*) $\Delta Cpep_{0-120}/\Delta gluc_{0-120} \times$ Matsuda index (where $\Delta Cpep_{0-120}/\Delta gluc_{0-120}$ is the mean incremental concentrations of C-peptide and glucose during the OGTT), and *3*) $\Delta ISR_{0-120}/\Delta gluc_{0-120} \times$ Matsuda index (where ISR is the prehepatic insulin secretion rate determined by C-peptide deconvolution); all three measures were calculated as previously described (29–31).

Outcomes

The primary outcome was β-cell function as measured by ISSI-2 at 48 weeks, adjusted for baseline (ISSI-2 at randomization). Continuous secondary outcomes were baseline-adjusted glycemic measures at 48 weeks, including HbA_{1c}, fasting glucose, 2-h glucose, and AUC_{gluc}. Categorical secondary outcomes were the prevalence of HbA_{1c} <7.0% (<53 mmol/mol) at 48 weeks, glucose tolerance status, and loss of glycemic control (defined by need for metformin rescue therapy). A sample size of 50 participants (25 per arm) was expected to provide 80% power to detect a 20.8% difference between treatment arms in the primary outcome of baseline-adjusted ISSI-2 at 48 weeks at a significance level of 0.05.

Statistical Analyses

Statistical analyses were conducted with SAS 9.2 software (SAS Institute, Cary, NC) and performed on the intention-to-treat population. Missing data were imputed using last observation carried

Table 1—Baseline characteristics of the study groups at randomization

	Placebo (*n* = 25)	Liraglutide (*n* = 26)	*P* value
Demographic			
Age (years)	57.4 ± 7.4	58.9 ± 8.7	0.50
Male sex	64.0	61.5	0.86
Ethnicity			0.69
White	68.0	73.1	
Other	32.0	26.9	
Duration of diabetes (years)	1.5 (0.75–3.0)	3.0 (2.0–5.0)	0.028
Diabetes therapy before study			0.69
Diet alone	32.0	26.9	
Metformin alone	64.0	57.7	
Sulphonylurea alone	0	7.7	
Metformin + sulphonylurea	4.0	7.7	
Metabolic status			
BMI (kg/m^2)	30.4 ± 5.8	30.0 ± 4.3	0.82
Waist circumference (cm)	103.0 ± 13.7	99.8 ± 10.3	0.35
Systolic blood pressure (mmHg)	120.0 ± 12.9	124.0 ± 11.9	0.25
Diastolic blood pressure (mmHg)	67.0 ± 10.5	70.4 ± 11.1	0.27
Heart rate (beats per min)	70 ± 11	68 ± 9	0.48
Aspartate aminotransferase (IU/L)	26 (21–34)	25 (21–30)	0.31
Alanine aminotransferase (IU/L)	26 (21–42)	26 (20–32)	0.34
γ-Glutamyl transpeptidase (IU/L)	28 (21–39)	21 (17–27)	0.17
Creatinine (μmol/L)	72 ± 10	75 ± 15	0.41
Urine microalbumin-to-creatinine ratio	0.6 (0–1.9)	1.0 (0.4–1.8)	0.38
Glycemia			
Fasting plasma glucose (mmol/L)	5.7 ± 0.5	5.9 ± 0.7	0.53
2-h glucose on OGTT (mmol/L)	13.3 ± 3.0	14.8 ± 2.8	0.07
AUC_{gluc} on OGTT	49.0 ± 4.8	50.3 ± 7.4	0.46
HbA_{1c} (%)	6.2 ± 0.4	6.4 ± 0.5	0.07
Insulin sensitivity/resistance			
Matsuda index	2.2 (1.6–3.8)	3.3 (2.1–5.5)	0.18
HOMA-IR	3.2 (1.8–4.9)	2.5 (1.3–4.1)	0.33
β-Cell function			
ISSI-2	220 (190–289)	193 (146–321)	0.34
$\Delta Ins_{0-120}/\Delta gluc_{0-120} \times$ Matsuda index	1.5 (1–1.9)	1.1 (0.6–2.2)	0.24
$\Delta Cpep_{0-120}/\Delta gluc_{0-120} \times$ Matsuda index	46 (34–81)	46 (31–85)	0.50
$\Delta ISR_{0-120}/\Delta gluc_{0-120} \times$ Matsuda index	0.29 ± 0.06	0.32 ± 0.08	0.77

Data are %; mean ± SD, if normally distributed; or median (25th–75th), if skewed.

Table 2—Primary, secondary, and additional outcomes at 48 weeks (end of intervention)

	Placebo (n = 25)	Liraglutide (n = 26)	P value
Primary outcome			
Baseline-adjusted ISSI-2	229.3 ± 28.4	339.4 ± 27.8	0.008
Secondary outcomes			
Baseline-adjusted HbA_{1c} (%)	6.6 ± 0.1	6.2 ± 0.1	0.055
Baseline-adjusted fasting glucose (mmol/L)	6.3 ± 0.2	5.8 ± 0.2	0.12
Baseline-adjusted 2-h glucose (mmol/L)	12.9 ± 0.7	10.5 ± 0.7	0.01
Baseline-adjusted AUC_{gluc} on OGTT	48.5 ± 1.9	45.3 ± 1.9	0.25
Proportion of participants with HbA_{1c} <7.0%	84.0	88.5	0.70
Glucose tolerance status on OGTT*			0.04
Normal glucose tolerance	4.0	23.1	
Prediabetes	28.0	30.8	
Diabetes	68.0	46.2	
Additional outcomes			
Baseline-adjusted $\Delta Ins_{0-120}/\Delta gluc_{0-120}$ × Matsuda index§	1.4 (0.9, 2.1)	3.1 (2.0, 4.7)	0.01
Baseline-adjusted $\Delta Cpep_{0-120}/\Delta gluc_{0-120}$ × Matsuda index§	54 (36, 81)	100 (67, 149)	0.04
Baseline-adjusted $\Delta ISR_{0-120}/\Delta gluc_{0-120}$ × Matsuda index§	0.18 (0.12, 0.26)	0.37 (0.25, 0.53)	0.01
Baseline-adjusted Matsuda index	2.7 ± 0.3	2.5 ± 0.3	0.65
Baseline-adjusted HOMA-IR	5.2 ± 0.6	5.1 ± 0.6	0.87
Baseline-adjusted BMI (kg/m^2)	30.0 ± 0.3	29.3 ± 0.3	0.15
Baseline-adjusted waist circumference (cm)	100.8 ± 1.3	98.5 ± 1.3	0.20

Data are mean ± SE or %. *P for linear trend. §Data are geometric mean (95% CI).

forward. Continuous variables were tested for normality of distribution, and natural log transformations of skewed variables were used where necessary. The characteristics of the study arms were compared by Student t test (continuous variables) or either χ^2 or Fisher exact test (categorical variables) (Table 1). The primary, secondary, and additional continuous outcomes at 48 weeks were compared between arms by ANCOVA, and categorical outcomes were compared by χ^2 or Fisher exact test (Table 2). Longitudinal changes over time in the outcomes of interest were assessed with generalized estimating equation models, with interaction between treatment group and time evaluated for differential changes over time between the groups (Figs. 1 and 2). The proportions of participants achieving HbA_{1c} thresholds (<6.5%, ≤6.0%) and glucose tolerance in the nondiabetic range were compared at each visit using χ^2 test (Fig. 3). The cumulative incidence of loss of glycemic control was compared between groups by log-rank test.

RESULTS

Recruitment took place between February 2011 and November 2012. Supplementary Fig. 2 shows the trial profile. Of 63 individuals who entered the prerandomization IIT phase, 51 met the criteria for randomization to either liraglutide or placebo. Table 1 shows the characteristics of these two groups at baseline (randomization). The only significant between-group difference was longer duration of diabetes in the liraglutide group than in the placebo group (median 3.0 vs. 1.5 years, P = 0.028). Most participants were taking metformin before the study, and both groups exhibited excellent glycemic control after prerandomization IIT (mean HbA_{1c} 6.2% [44 mmol/mol] in placebo group and 6.4% [46 mmol/mol] in liraglutide group).

Final outcome status was ascertained for all patients but one; this individual withdrew at 12 weeks because he was moving away from the province. Compliance with study medication was high, with no difference in missed doses between the liraglutide and placebo groups (2.5 ± 3.5 vs. 4.2 ± 4.9 doses, P = 0.15). Six participants required metformin rescue therapy (five in placebo arm) (Supplementary Fig. 3). Of these, only one (placebo group) had subsequent HbA_{1c} ≥8.0% (≥64 mmol/mol) while on metformin. All 51 randomized participants were included in the analyses according to their assigned group.

Primary, secondary, and additional outcomes are shown in Table 2. The primary outcome of baseline-adjusted ISSI-2 at 48 weeks was significantly higher in the liraglutide group than in the placebo group (339.4 ± 27.8 vs. 229.3 ± 28.4, P = 0.008). The additional measures of β-cell function were similarly higher in the liraglutide arm ($\Delta Ins_{0-120}/\Delta gluc_{0-120}$ × Matsuda index, P = 0.01; $\Delta Cpep_{0-120}/\Delta gluc_{0-120}$ × Matsuda index, P = 0.04; $\Delta ISR_{0-120}/\Delta gluc_{0-120}$ × Matsuda index, P = 0.01). Secondary outcomes of baseline-adjusted HbA_{1c} and 2-h glucose were lower in the liraglutide group (P = 0.055 and P = 0.01, respectively). In both groups, >80% of participants had HbA_{1c} <7.0% (<53 mmol/mol) at 48 weeks (P = 0.70), with the liraglutide group exhibiting better glucose tolerance (P = 0.04). Baseline-adjusted Matsuda index, HOMA-IR, BMI, and waist circumference did not differ between the groups at 48 weeks.

Figure 1 shows the pattern of change over time in β-cell function for the primary outcome ISSI-2 (Fig. 1*A*) and all three secondary β-cell measures (Fig. 1*B–D*). Each measure showed the same pattern, with IIT improving β-cell function before randomization, after which the liraglutide group experienced a marked further improvement in the first 12 weeks that was maintained for the duration of the 48-week treatment period. With each measure, there was a significant treatment effect from randomization to 48 weeks (all $P \leq 0.002$).

Figure 2 shows the changes over time in HbA_{1c}, Matsuda index, BMI, and waist circumference. Prerandomization IIT lowered HbA_{1c} in both groups, after

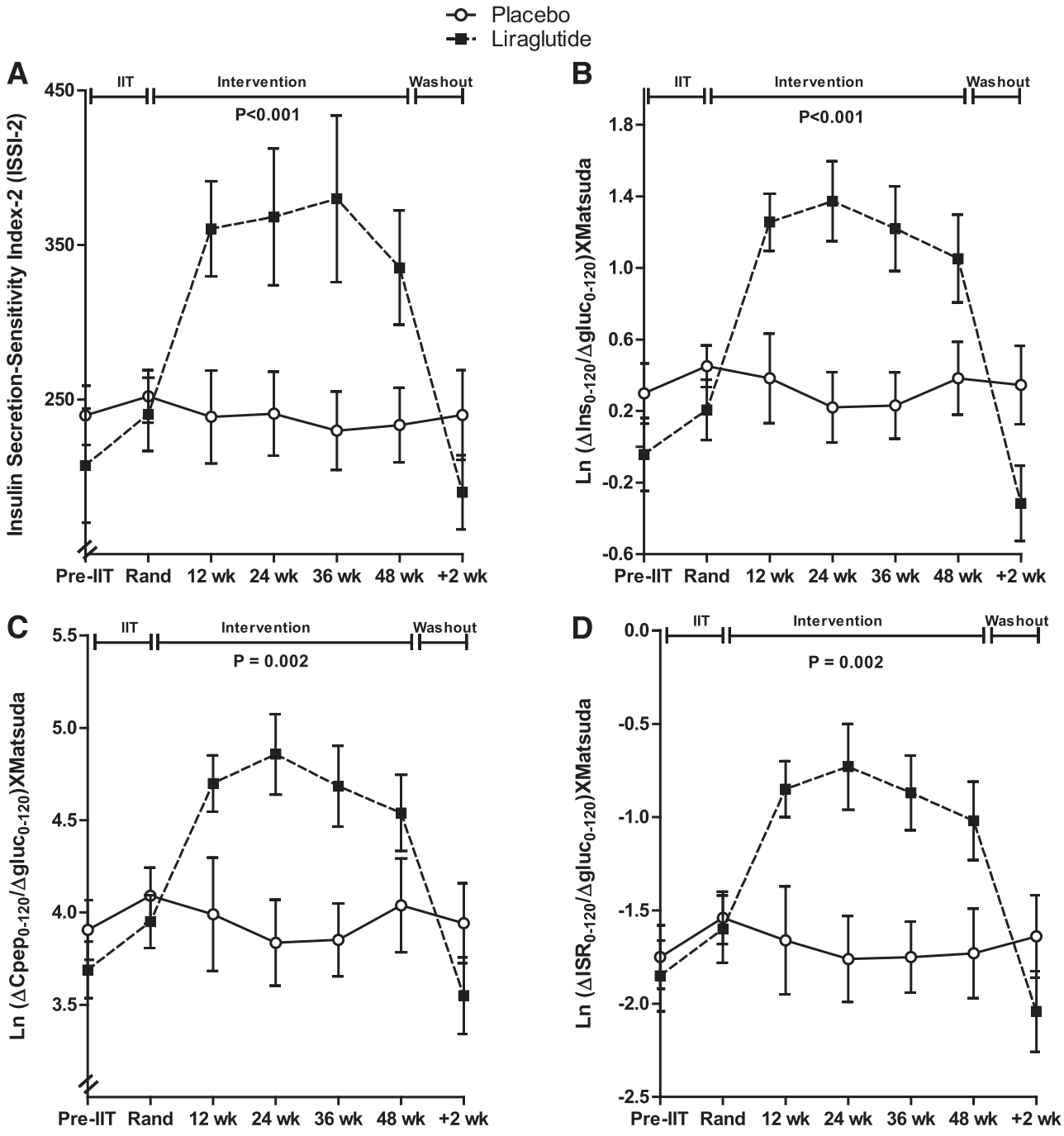

Figure 1—Changes over time in β-cell function, measured by ISSI-2 (*A*), $\Delta Ins_{0–120}/\Delta gluc_{0120} \times$ Matsuda index (*B*); $\Delta Cpep_{0–120}/\Delta gluc_{0–120} \times$ Matsuda index (*C*); and $\Delta ISR_{0–120}/\Delta gluc_{0–120} \times$ Matsuda index (*D*). *P* values are for interaction between treatment group and time during the intervention. Due to single negative or missing values precluding use of the index, the respective sample sizes analyzed in the placebo and liraglutide groups in *B–D* were as follows: 24 and 21 for $\Delta Ins_{0–120}/\Delta gluc_{0–120} \times$ Matsuda index; 24 and 23 for $\Delta Cpep_{0–120}/\Delta gluc_{0–120} \times$ Matsuda index; and 24 and 23 for $\Delta ISR_{0–120}/\Delta gluc_{0–120} \times$ Matsuda index. Pre-IIT, before IIT; Rand, randomization visit.

which HbA_{1c} decreased further in the liraglutide arm (to mean 6.0% [42 mmol/mol]) and increased in the placebo arm in the first 12 weeks (to mean 6.6% [49 mmol/mol]), with a between-group difference maintained for the rest of the trial ($P < 0.001$). There was no difference in Matsuda index ($P = 0.17$), with both groups showing a pattern of improved insulin sensitivity following IIT that was lost in the first 12 weeks after randomization. The liraglutide group experienced a greater decline in BMI in the first 12 weeks and maintained this difference for the rest of the trial ($P = 0.03$). Waist circumference showed a similar pattern, but treatment effect did not achieve significance ($P = 0.40$).

At each quarterly assessment, >70% of participants in the liraglutide group had an HbA_{1c} <6.5% (<48 mmol/mol) (Fig. 3*A*), and >50% of the liraglutide group had an HbA_{1c} ≤6.0% (≤42 mmol/mol) (Fig. 3*B*). Similarly, at each OGTT, >50% of the liraglutide group exhibited glucose tolerance in the nondiabetic range (Fig. 3*C*). This level of glycemic control was achieved

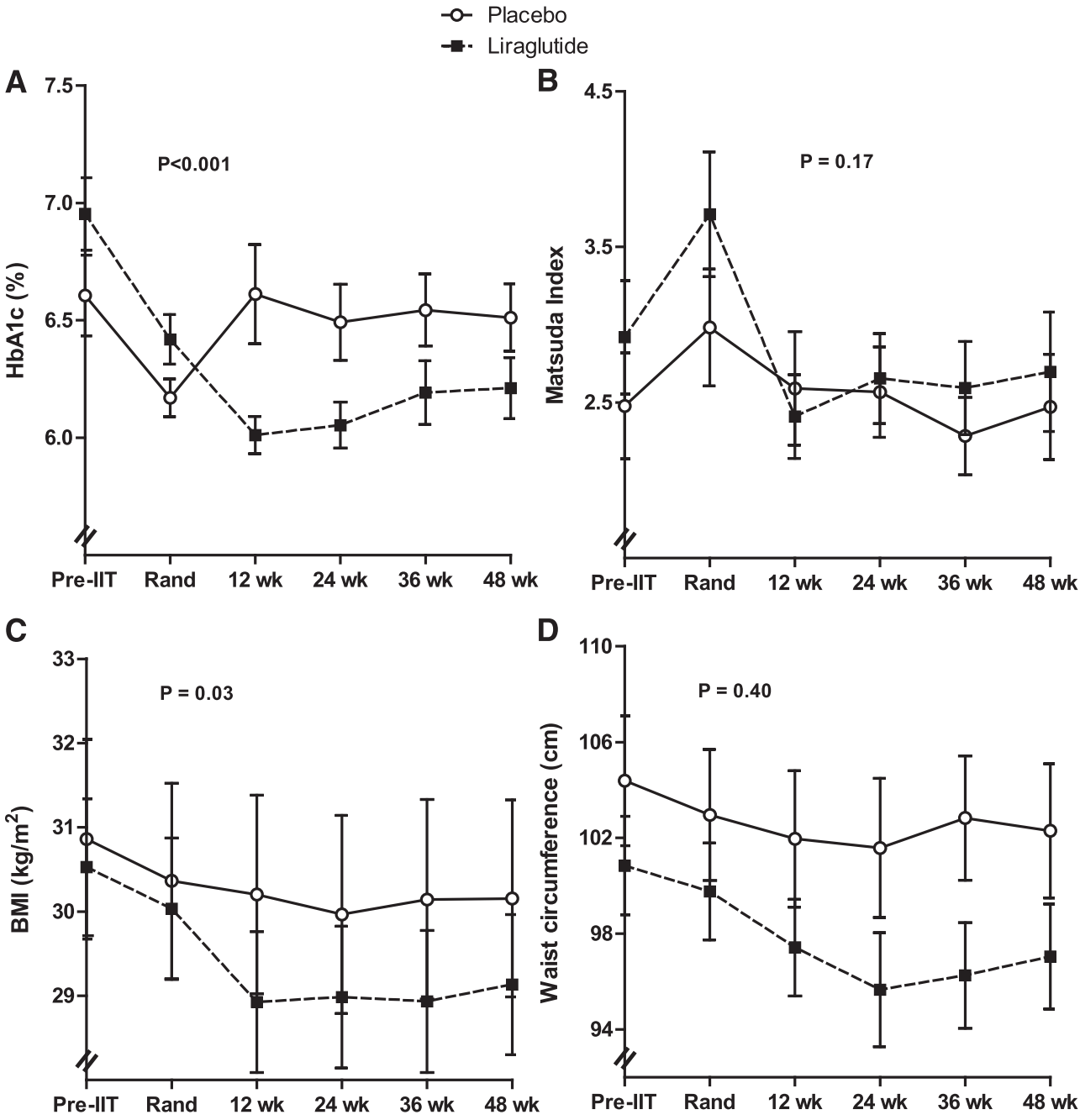

Figure 2—Changes over time in HbA_{1c} (*A*), Matsuda index of insulin sensitivity (*B*), BMI (*C*), and waist circumference (*D*). *P* values are for interaction between treatment group and time during the intervention. Pre-IIT, before IIT; Rand, randomization visit.

without any increased incidence of hypoglycemia or other adverse events (Supplementary Table 1).

Of note, when participants were reassessed by OGTT 2 weeks after stopping the study medication, baseline-adjusted ISSI-2 was no longer different between the former liraglutide and placebo groups (191.9 ± 24.7 vs. 238.1 ± 25.2, *P* = 0.20). Indeed, this loss of the beneficial effect of liraglutide after a 2-week washout was evident for each of the four measures of β-cell function shown in Fig. 1.

CONCLUSIONS

This study demonstrates that after the initial improvement in β-cell function achieved with prerandomization IIT, liraglutide induced a robust further enhancement of β-cell function that was sustained for 48 weeks in early T2DM. This effect was accompanied by near-normal glycemic control in the absence of a significant impact on insulin sensitivity. However, the marked enhancement of β-cell function induced by liraglutide was completely lost within 2 weeks of stopping the medication. Thus, despite the improvement of β-cell function while on liraglutide, the underlying pathology driving β-cell deterioration was not reversed by this therapy.

The National Institute of Diabetes and Digestive and Kidney Diseases recently

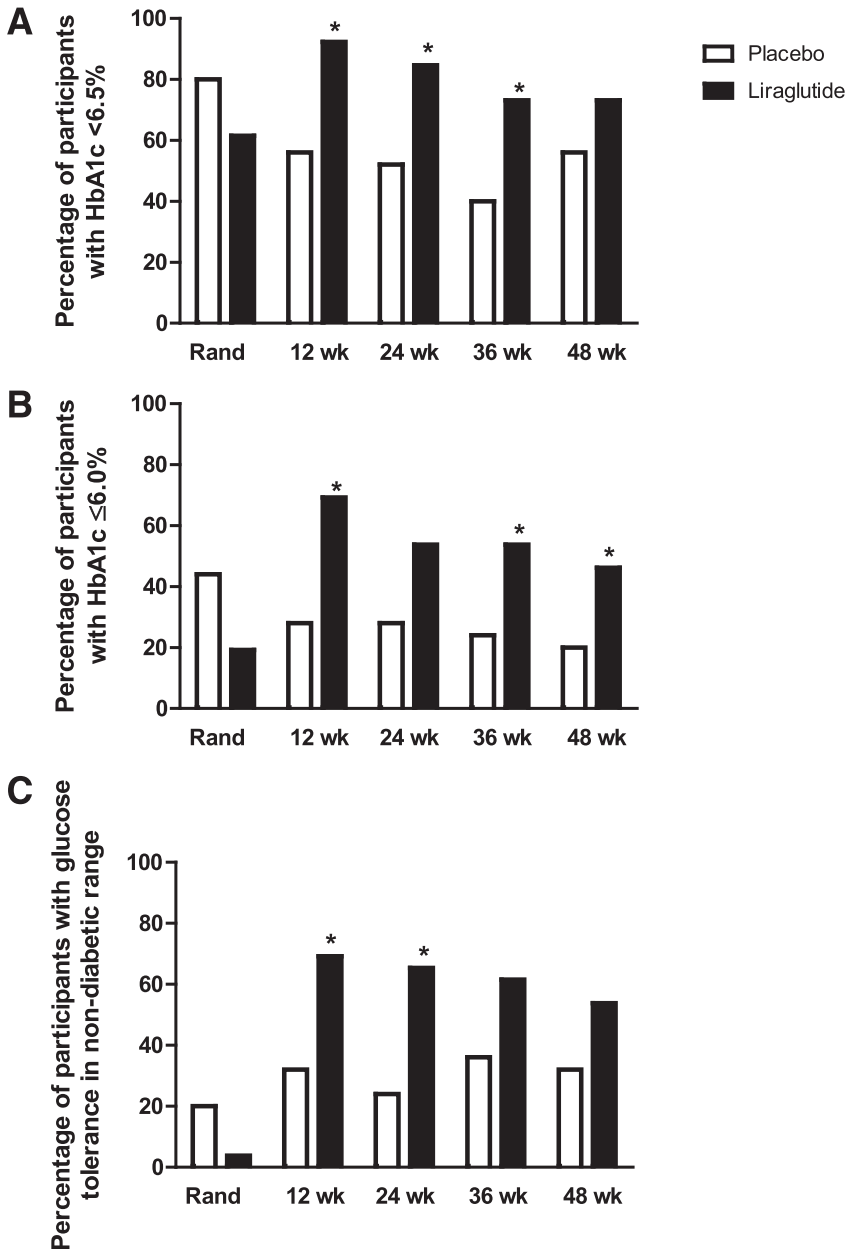

Figure 3—Proportion of participants in each treatment group with HbA_{1c} <6.5% (<48 mmol/mol) (*A*), HbA_{1c} ≤6.0% (≤42 mmol/mol) (*B*), and glucose tolerance status in the nondiabetic range on OGTT (*C*). *$P < 0.05$ for comparison between groups. Rand, randomization visit.

called for studies to investigate strategies for preserving β-cell function in early T2DM (RFA-DK-10-013), highlighting the fundamental importance of this therapeutic goal (32). In designing trials for this purpose, the reversible β-cell dysfunction induced by glucotoxicity is a potential confounder to be reconciled (9). In this context, prerandomization short-term IIT has emerged as a design strategy that can abrogate this concern. Thus, although other studies have shown that GLP-1 agonists can improve β-cell function (12,13), the current study is (to our knowledge) the first to isolate this effect after eliminating the confounding influence of glucotoxicity.

In this setting, the effect of liraglutide on β-cell function over 48 weeks yielded a very different pattern of response than that which has been previously observed with other therapies. Harrison et al. (11) found that after an initial 3-month therapy with biphasic insulin and metformin, treatment of 58 newly diagnosed patients on either continued insulin/metformin or triple oral therapy (metformin/glyburide/pioglitazone) had stabilized measures of insulin secretion such that they neither differed from baseline nor differed between treatment arms. In patients with established T2DM, we previously showed that the improved β-cell function achieved with 4–8 weeks of prerandomization IIT was completely lost during the 48 weeks of subsequent treatment with either metformin/sitagliptin combination therapy or metformin alone (10). In contrast, in LIBRA, the effect of liraglutide on β-cell function was markedly different, yielding two key messages. First, rather than merely maintaining the beneficial β-cell effect of prerandomization IIT, liraglutide induced an ~50% enhancement of β-cell function, suggesting that further reversibility of β-cell dysfunction exists beyond that achieved with insulin therapy (although the ISSI-2 levels attained on liraglutide [i.e., ~350] were still much lower than those observed in patients without diabetes [i.e., generally >800]). Second, this enhancement was maintained for 48 weeks in patients with T2DM of a mean 3-year duration (73.1% were on antidiabetic medication before the study), suggesting that robust improvement of β-cell function can be both achieved and sustained early in the course of established T2DM.

Of note, this benefit was completely lost after the 2-week washout. This finding is consistent with an earlier observation by Bunck et al. (33) where the effect of exenatide on β-cell function was lost after 4-week washout. The authors subsequently reported that when 52% of the original study population (n = 36) continued therapy for 3 years, there was a small, but statistically significant effect on β-cell function 4 weeks after stopping exenatide (34). Thus, longer treatment with liraglutide could possibly have effects that persist after stopping the medication. At present, however, the findings from LIBRA strongly suggest that ongoing treatment is needed to maintain the beneficial effect of liraglutide on β-cell function.

Strengths of this study include serial assessments over 48 weeks, with subsequent washout, and the unique design of prerandomization IIT, enabling isolation of the longitudinal effects of liraglutide on β-cell function free from initial glucotoxicity. A limitation is that β-cell function and insulin sensitivity/resistance were assessed with OGTT-based

surrogate indices rather than with clamp studies. However, the OGTT-based indices are validated measures that have been widely used in previous studies (8,20–31).

Clinically, the liraglutide group achieved outstanding glycemic control (>50% of participants had an HbA_{1c} ≤6.0% [≤42 mmol/mol] and nondiabetic OGTT at each assessment) with no increased hypoglycemia. Coupled with the β-cell response while on therapy, these clinical effects raise the question of whether ongoing liraglutide treatment in early T2DM could change the long-term natural history of β-cell decline, glycemic exposure, and ultimately, complication risks. Of note, the beneficial effect of IIT was also apparent in the placebo group (e.g., 56% had an HbA_{1c} <6.5% [<48 mmol/mol] at 48 weeks in the placebo group despite that 68% were on antidiabetic therapy before the study), consistent with existing literature showing that early short-term IIT can induce (transient) remission/improvement in diabetes for up to 1–2 years (35,36).

In conclusion, liraglutide induces robust enhancement of β-cell function that is sustained over 48 weeks in early T2DM but lost upon cessation of the medication. This on-therapy beneficial effect was achieved after initial elimination of glucotoxicity and in the absence of a significant impact on insulin sensitivity. Coupled with its effect on glycemic control, these data suggest that the early institution of liraglutide therapy warrants further study for its long-term effects on the clinical course and natural history of T2DM.

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