BMJ Open Diabetes Research & Care

Predictors of sustained drug-free diabetes remission over 48 weeks following short-term intensive insulin therapy in early type 2 diabetes

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To cite: Kramer CK, Zinman B, Choi H, *et al*. Predictors of sustained drug-free diabetes remission over 48 weeks following short-term intensive insulin therapy in early type 2 diabetes. *BMJ Open Diabetes Research and Care* 2016;**4**:e000270. doi:10.1136/bmjdrc-2016-000270

Received 12 May 2016
Revised 14 June 2016
Accepted 14 July 2016

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ABSTRACT

Objective: In early type 2 diabetes (T2DM), short-term intensive insulin therapy (IIT) for 2–4 weeks can decrease insulin resistance, reduce glucagonemia, improve β-cell function, and even induce a remission of diabetes that can last up to 1 year in some patients. However, little is known about the predictors of such a sustained remission.

Methods: We evaluated data from the placebo arm of a double-blind randomized controlled trial in which patients with early T2DM (≤7 years duration) underwent 4 weeks of IIT (basal detemir, bolus aspart), followed by placebo therapy for 48 weeks (n=25). Participants underwent an oral glucose tolerance test every 12 weeks, enabling serial assessment of insulin sensitivity, α-cell response, and β-cell function. Diabetes remission was defined as A1c<6.5% on no medication for T2DM.

Results: At 48 weeks post-IIT, 56% of the participants remained in remission. Comparison of remitters to non-remitters revealed no differences in waist, body mass index, insulin sensitivity (Matsuda index), or glucagon profile, either at baseline or over 48 weeks. Compared to non-remitters, the remission group had lower baseline A1c (p=0.006) and better baseline β-cell function (Insulin Secretion-Sensitivity Index-2) (p=0.01) that was then sustained across 48 weeks post-IIT (p=0.006). On logistic regression analyses, however, shorter duration of diabetes supplanted baseline A1c (p=0.24) and β-cell function (p=0.19) as an independent predictor of remission (p=0.04). In particular, diabetes duration <2 years predicted persistence of remission (p=0.006).

Conclusions: The key determinant of the likelihood of inducing sustained drug-free diabetes remission with short-term IIT is early intervention, particularly within the first 2 years after diagnosis.

Trial registration number: ClinicalTrials.Gov NCT01270789; Post-results.

Key messages

- Participants who attain sustained drug-free remission over 48 weeks following 4 weeks of intensive insulin therapy have better baseline β-cell function that is then preserved over the year thereafter, in contrast to the deterioration that occurs in non-remitters.
- Although short-term intensive insulin therapy improves insulin sensitivity and glucagonemia, these effects do not differ between individuals who maintain remission and those who do not across the year thereafter.
- Metabolic effects notwithstanding, the key determinant of the likelihood of inducing sustained remission with short-term intensive insulin therapy is early intervention, particularly within the first 2 years after diagnosis of diabetes.

INTRODUCTION

Early in the course of type 2 diabetes (T2DM), treatment with short-term intensive insulin therapy (IIT) for 2–4 weeks can have favorable effects on metabolic function by decreasing insulin resistance, reducing hyperglucagonemia, and improving β-cell function.[1–8] Moreover, beneficial effects on glucose homeostasis can persist long after the therapy is stopped.[8 9] Indeed, short-term IIT can induce a subsequent remission of diabetes, defined as normoglycemia in the absence of any antidiabetic medication. In a meta-analysis of interventional studies applying this therapy, 58.9% of patients were in remission when assessed 6 months after the cessation of IIT and 46.3% were in remission at 12 months.[1] While these findings are encouraging, they also highlight two sobering points. First, there is clearly heterogeneity in the patient response to this therapy. Second, the long-term metabolic effects of IIT likely change over time. Taken together, it thus emerges that (1) there is a need for identification of the predictors of a sustained positive response to identify those patients who are most likely to benefit from this therapy and (2) serial assessment of metabolic function in the months after stopping IIT may provide relevant mechanistic insight in this regard. However, little is currently known about such predictors and, to date, studies in patients with T2DM of modest

duration (eg, <7 years) have not undertaken systematic assessment of metabolic function at regular intervals in the months after IIT. Thus, in this context, we sought to evaluate the predictors of sustained drug-free diabetes remission over 48 weeks post-IIT in participants undergoing serial characterization of glucose homeostasis, insulin sensitivity, α-cell response, and β-cell function every 12 weeks as part of a randomized clinical trial.

METHODS

Study population

The *LI*raglutide and *B*eta-cell *R*ep*A*ir (LIBRA) trial was a double-blind, randomized, parallel-arm, placebo-controlled trial that was designed to determine whether liraglutide can preserve β-cell function over 48 weeks in early T2DM, following a short course of IIT prior to randomization (ClinicalTrials.Gov NCT01270789). The current analysis describes a retrospective, nested study within this completed trial. The protocol, design, and main results of the LIBRA trial have previously been described in detail.[10 11] In brief, patients with early T2DM underwent 4 weeks of IIT before being randomized to either daily liraglutide or matching placebo injection, and then followed for 48 weeks, with serial assessment by oral glucose tolerance test (OGTT) every 12 weeks. Inclusion criteria included duration of diabetes ≤7 years, treatment with 0-2 oral antidiabetic medications, and baseline A1c <9.0% if on antidiabetic medications, or A1c <10.0% if not on antidiabetic medication. Exclusion criteria included current insulin or injectable antidiabetic therapy, renal/hepatic dysfunction, malignancy, chronic infection, and any contraindications to GLP-1 agonists, including previous pancreatitis or personal/family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2. The study protocol was approved by the Mount Sinai Hospital Research Ethics Board, and all participants provided written informed consent. For the current study, we evaluated data from the placebo arm in order to study the predictors of drug-free diabetes remission following the initial short-term IIT. The study design chart showing the derivation of the placebo arm has been previously reported.[10]

Intervention

The protocol for the IIT phase has been previously described in detail.[6 10 12] Briefly, the participants underwent a 4-week course of multiple daily insulin injection therapy consisting of basal insulin detemir and premeal insulin aspart with starting total daily doses of 0.2–0.4 U/kg (based on initial degree of hyperglycemia and dietary habits), divided as 60% bolus insulin and 40% basal insulin. Participants were asked to perform self-monitoring of capillary blood glucose (SMBG) at least four times per day and to send their SMBG records to the study nurse at least three times per week for insulin dose titration. Insulin doses were titrated to target fasting and premeal glucose between 4.0 and 6.0 mmol/L and 2-hour postprandial glucose <8 mmol/L. Hypoglycemia was defined as capillary blood glucose ≤3.9 mmol/L, and was classified as severe if it required third-party assistance and/or involved impairment of consciousness.

Participants who achieved fasting venous glucose <7.0 mmol/L 1 day after stopping IIT (reflecting the capacity of endogenous insulin secretion to maintain fasting glucose in the non-diabetic range)[13 14] were considered eligible for 1:1 randomization to either liraglutide or identical placebo. The details of the randomization protocol were described previously.[10] Participants were then assessed every 12 weeks, including OGTT and measurement of A1c. If participants had A1c ≥8.0% at any visit, metformin rescue therapy was initiated to avoid exposure to excessive hyperglycemia. If participants then had an A1c ≥8.0% while on metformin rescue therapy, the protocol was stopped and the patient returned to usual clinical care. As previously reported,[10] five participants in the placebo arm required metformin during the trial. Diabetes remission was defined as A1c <6.5% with no antidiabetic medication in the preceding 3 months.

Laboratory measurements

Participants underwent 2-hour 75 g OGTT at baseline (before IIT), 1-day post-IIT, and each of 12, 24, 36, and 48 weeks thereafter. Each OGTT was performed in the morning after overnight fast. For each OGTT, venous blood samples were drawn for measurement of insulin, C peptide, and glucose 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 Roche Modular system and electrochemiluminescence immunoassay kit (Roche Diagnostics, Laval, Canada). Serum glucagon was measured from samples at fasting and at 30, 60, 90, and 120 min on each OGTT by manual ELISA (R&D Systems, Minneapolis, Minnesota, USA), with detection limit of 14.7 pg/mL and analytical range of 31.3–2000 pg/mL.

Metabolic characterization

Participants underwent serial detailed metabolic characterization at each OGTT, including assessment of weight, waist circumference, blood pressure, liver enzymes, glucose tolerance, insulin sensitivity/resistance, α-cell function, and β-cell function. Specifically, whole-body insulin sensitivity was measured by Matsuda index[15] and hepatic insulin resistance was assessed by Homeostasis Model Assessment (HOMA-IR).[16] β-Cell function was assessed with the Insulin Secretion-Sensitivity Index-2 (ISSI-2), a validated OGTT-derived measure of β-cell function that is analogous to the disposition index obtained from the intravenous glucose tolerance test and defined as the product of (1) insulin secretion measured by the ratio of area-under-insulin-curve to area-under-glucose curve and (2) insulin sensitivity measured by the Matsuda index.[17 18]

A secondary measure of β-cell function was $\Delta ISR_{0–120}/\Delta gluc_{0–120}$×Matsuda index (where ISR is the prehepatic insulin secretion rate determined by C peptide deconvolution), as previously described.[10 19 20] α-Cell function was assessed by fasting glucagon and the glucagon response to the OGTT calculated as the area-under-the-glucagon-curve ($AUC_{glucagon}$) by trapezoidal rule.[7 11]

Statistical analyses

All analyses were conducted using SPSS V.18.0 (Chicago, Illinois, USA). Participants were stratified into two groups based on their diabetes remission status at 48 weeks: those in remission (A1c <6.5% with no use of any antidiabetic medication) and those not in remission (A1c ≥6.5% and/or use of antidiabetic medications). The clinical and metabolic characteristics of these groups were compared at baseline, during IIT, following IIT, and at 48 weeks by Student's t-test (continuous variables) or either χ^2 or Fisher exact test (categorical variables; table 1).

To determine whether remitters and non-remitters had differential changes in body fat, liver function, insulin resistance, α-cell function, and β-cell function over the 48 weeks post-IIT, we constructed generalized estimating equation (GEE) models to assess for an effect of response group (remitters vs non-remitters) on the pattern of change over time (figure 1). GEE models were constructed for waist circumference (figure 1A), BMI (figure 1B), alanine aminotransferase (ALT) (figure 1C), Matsuda index (figure 1D), $AUC_{glucagon}$ (figure 1E), and ISSI-2 (figure 1F). To determine the independent predictors of sustained remission, logistic regression analyses of drug-free diabetes remission at 48 weeks (dependent variable) were performed with a core model consisting of baseline HbA_{1c} and duration of diabetes (figure 2). Exploratory analyses were performed with single addition of the following covariates at baseline: waist circumference (figure 2A), Matsuda index (figure 2B), $AUC_{glucagon}$ (figure 2C), and ISSI-2 (figure 2D).

To further explore the impact of diabetes duration on the prevalence of sustained diabetes remission at 48 weeks, we determined the prevalence of diabetes remission in participants with different durations of diabetes (≤1, ≤2, and ≤3 years) (figure 3A). Finally, using log-rank test, we compared the time to loss of drug-free diabetes remission following short-term IIT between participants with diabetes duration <2 years and those with duration ≥2 years (figure 3B).

RESULTS

In the LIBRA trial, there were 25 participants randomized to daily placebo therapy, after completion of 4 weeks of IIT. At baseline (ie, before IIT), 3 participants had A1c <6.5% on no antidiabetic medication. At 48 weeks after stopping IIT, 14 participants (56%) were in drug-free diabetes remission. Table 1 shows a comparison of those in remission (n=14) and those not in remission at 48 weeks (n=11) with respect to their characteristics at baseline, during IIT, immediately post-IIT, and at 48 weeks. At baseline, the remission group had shorter duration of diabetes (1.2±1.0 vs 2.6 ±1.8 years, p=0.03), lower A1c (6.2±0.5% vs 7.1±0.9%, p=0.006), and better β-cell function, as measured by ISSI-2 (median (25th–75th)) (251 (210–341) vs 206 (145–233), p=0.01) and $\Delta ISR_{0–120}/\Delta gluc_{0–120}$×Matsuda index (0.22 (0.14–0.48) vs 0.14 (0.07–0.19), p=0.02). The two groups did not differ in other clinical characteristics, including age, gender, ethnicity, prestudy diabetes treatment, BMI, waist circumference, blood pressure, liver enzymes, insulin sensitivity, and glucagon profile. During IIT, the remission group required lower doses of basal insulin (p=0.002) and meal insulin (p=0.01). When assessed at 1-day post-IIT, the remission group continued to exhibit lower A1c and better β-cell function, although the differences in comparison to non-remitters were less pronounced than at baseline (A1c: 6.0±0.3% vs 6.4±0.4%, p=0.04; ISSI-2 median: 240 vs 189, p=0.06). At 48 weeks, however, marked differences were apparent between remitters and non-remitters in A1c (6.0±0.3% vs 7.1±0.6%, p<0.001) and ISSI-2 (median 257 vs 140, p<0.001).

We next sought to determine whether the remission and non-remission groups exhibit differential changes over time in metabolic features. As shown in figure 1, there were no differences over time between the groups in the patterns of change in waist circumference (figure 1A; p=0.91), BMI (figure 1B; p=0.65), and ALT (figure 1C; p=0.30). Insulin sensitivity (figure 1D; Matsuda index) and glucagon profile (figure 1E; $AUC_{glucagon}$) showed the expected improvement in response to IIT, but there were no differences between the remitters and non-remitters in these features over the subsequent 48 weeks (p=0.75 and p=0.43, respectively). In contrast, however, the pattern of change over time in β-cell function (figure 1F; ISSI-2) was very different between the two groups (p=0.006). Specifically, whereas the remission group had stabilization of β-cell function over time, the non-remitters experienced a decline in ISSI-2 following the initial improvement in response to IIT. Thus, β-cell function emerged as a differentiating metabolic feature between the two groups.

We next performed logistic regression analyses to identify independent predictors of (dependent variable) drug-free diabetes remission at 48 weeks. On these analyses, diabetes duration emerged as an independent predictor of sustained remission in all adjusted models (figure 2). Most notably, shorter duration of diabetes supplanted baseline A1c (p=0.24) and β-cell function (ISSI-2) (p=0.19) as an independent predictor of remission (OR=0.22, 95% CI 0.05 to 0.92, p=0.04) (figure 2D). In additional models with adjustments for insulin dosages (meal and basal) during IIT, post-IIT fasting glucose, post-IIT insulin resistance, and post-IIT A1c, diabetes duration remained an independent predictor of

Table 1 Characteristics of individuals with drug-free diabetes remission at 48 weeks compared to those not in remission

	Not in remission at 48 weeks (n=11)	In remission at 48 weeks (n=14)	p Value
Demographics			
Age (years)	58.5±7.4	56.5±7.6	0.52
Gender (% male)	63.6	64.3	0.97
Ethnicity			0.08
White (%)	45.5	85.7	
Other (%)	54.5	14.3	
Duration of diabetes (years)	2.6±1.8	1.2±1.0	0.03
Duration of diabetes			0.03
<1 year, n (%)	2 (18.2)	5 (35.7)	
1–2 years, n (%)	1 (9.1)	6 (42.9)	
≥2 years, n (%)	8 (72.7)	3 (21.4)	
Diabetes therapy prior to study			0.49
Diet alone (%)	27.3	35.7	
Metformin alone (%)	63.6	64.3	
Metformin+sulfonylurea (%)	9.1	0	
Baseline metabolic status (pre-IIT)			
Body mass index (kg/m^2)	30.0±4.7	31.5±6.8	0.54
Waist circumference (cm)	103.5±12.3	105.0±15.0	0.79
Systolic blood pressure (mm Hg)	126±14	122±10	0.50
Diastolic blood pressure (mm Hg)	70±9	68±8	0.60
Alanine aminotransferase (IU/L)	31±14	30±11	0.80
Aspartate aminotransferase (IU/L)	25 (17–28)	22 (20–26)	0.84
γ-Glutamyl transferase (IU/L)	36 (26–91)	24 (21–37)	0.12
Glycemia			
Fasting plasma glucose (mmol/L)	6.5±1.3	5.9±0.8	0.20
A1c (%)	7.1±0.9	6.2±0.5	0.006
Insulin sensitivity/resistance			
Matsuda index	4.9 (2.8–7.1)	5.8 (3.5–9.0)	0.70
HOMA-IR	5.0 (2.9–7.2)	3.4 (2.3–6.1)	0.36
Glucagon profile			
Fasting glucagon (pg/mL)	122±32	105±37	0.26
$AUC_{glucagon}$	535±139	470±85	0.17
β-Cell function			
ISSI-2	206 (145–233)	251 (210–341)	0.01
$\Delta ISR_{0-120}/\Delta gluc_{0-120}$×Matsuda index	0.14 (0.07–0.19)	0.22 (0.14–0.48)	0.02
IIT phase			
Final daily basal insulin dosage (U/kg)	0.36 (0.20–0.63)	0.14 (0.10–0.31)	0.002
Final daily meal insulin dosage (U/kg)	0.27 (0.17–0.56)	0.12 (0.08–0.19)	0.01
Hypoglycemia			
Any hypoglycemia (per person year)	0.20 (0–0.62)	0 (0–0.20)	0.71
Number of severe episodes	0	0	0.99
One-day post-IIT			
Body mass index (kg/m^2)	29.7±4.6	30.9±6.7	0.62
Waist circumference (cm)	102.1±12.7	103.6±14.9	0.80
Systolic blood pressure (mm Hg)	120±12	120±14	0.90
Diastolic blood pressure (mm Hg)	67±13	67±9	0.89
Alanine aminotransferase (IU/L)	39±26	28±11	0.18
Aspartate aminotransferase (IU/L)	30 (21–40)	25 (21–30)	0.17
γ-Glutamyl transferase (IU/L)	33 (21–42)	21 (16–31)	0.19
Glycemia			
Fasting plasma glucose (mmol/L)	5.8±0.6	5.7±0.4	0.66
A1c (%)	6.4±0.4	6.0±0.3	0.04
Insulin sensitivity/resistance			
Matsuda index	5.7 (4.3–11.4)	7.3 (3.5–10.4)	0.93
HOMA-IR	3.6 (2.2–4.3)	2.6 (1.7–6.5)	0.93
Glucagon profile			
Fasting glucagon (pg/mL)	80±29	93±25	0.22
$AUC_{glucagon}$	363±81	404±106	0.29

Continued

Table 1 Continued

	Not in remission at 48 weeks (n=11)	In remission at 48 weeks (n=14)	p Value
β-Cell function			
ISSI-2	189 (178–241)	240 (207–332)	0.06
$\Delta ISR_{0-120}/\Delta gluc_{0-120}$×Matsuda index	0.16 (0.12–0.24)	0.23 (0.12–0.46)	0.12
At 48 weeks			
Body mass index (kg/m^2)	29.8±4.9	30.4±6.6	0.81
Waist circumference (cm)	102.1±13.7	102.4±14.8	0.96
Systolic blood pressure (mm Hg)	118±18	123±15	0.42
Diastolic blood pressure (mm Hg)	68±9	68±11	0.81
Alanine aminotransferase (IU/L)	27±10	27±9	0.84
Aspartate aminotransferase (IU/L)	22 (19–34)	23 (19–27)	0.57
γ-Glutamyl transferase (IU/L)	30 (26–47)	27 (17–36)	0.19
Glycemia			
Fasting plasma glucose (mmol/L)	7.1±0.8	5.7±0.6	<0.001
A1c (%)	7.1±0.6	6.0±0.3	<0.001
Non-diabetic OGTT n (%)	0 (0)	7 (50)	0.006
Insulin sensitivity/resistance			
Matsuda index	4.3 (3.4–5.8)	5.8 (3.1–9.8)	0.47
HOMA-IR	5.4 (4.8–6.8)	3.5 (2.2–7.5)	0.16
Glucagon profile			
Fasting glucagon (pg/mL)	141±67	95±43	0.06
$AUC_{glucagon}$	567±293	438±162	0.19
β-Cell function			
ISSI-2	140 (100–206)	257 (206–354)	<0.001
$\Delta ISR_{0-120}/\Delta gluc_{0-120}$×Matsuda index	0.12 (0.05–0.20)	0.24 (0.14–0.54)	0.14

$AUC_{glucagon}$, area-under-the-glucagon-curve; HOMA-IR, Homeostasis Model Assessment; ISR, insulin secretion rate, ISSI-2, Insulin Secretion-Sensitivity Index-2; OGTT, oral glucose tolerance test.

remission (data not shown). In addition, this finding was unchanged when the five participants who required metformin rescue were excluded from the analyses (data not shown). Consistent with these findings, there was a stepwise decrease in the cumulative prevalence of sustained diabetes remission from individuals with the duration of diabetes ≤1 year (77.8%) than those with the duration of diabetes ≤2 years (70.6%) than those with the duration of diabetes ≤3 years (58.3%) (figure 3A). Indeed, survival analysis revealed that the time to loss of remission was significantly greater in participants with diabetes duration ≤2 years, when compared to those with longer time since diagnosis (p=0.003) (figure 3B).

DISCUSSION

In this study, the serial metabolic characterization every 12 weeks following early IIT yields three key points of insight into the long-term metabolic effects of this short-term intervention. First, although short-term IIT improves insulin sensitivity and glucagonemia, these effects do not differ between individuals who maintain remission and those who do not in the 48 weeks thereafter. Second, participants who attain sustained drug-free remission have better β-cell function at baseline that is then preserved over 48 weeks, in contrast to the post-IIT deterioration of endogenous insulin secretion over time that occurs in non-remitters. Third, the key determinant of the likelihood of inducing sustained remission is early intervention, particularly within the first 2 years after diagnosis of diabetes. Taken together, these data suggest that, early in the course of T2DM, there may be sufficient reversibility in the disease process to stabilize progressive β-cell deterioration and induce sustained drug-free remission with short-term IIT.

Several previous studies, including a meta-analysis,[1] have shown that short-term IIT can improve insulin resistance and β-cell function in early T2DM.[1–6] More recently, this therapy was also shown to reduce glucagonemia.[7] In this context, the unique element of the current study is the systematic delineation of the temporal course and longitudinal changes in metabolic function that occur over time after cessation of IIT. This approach reveals that the first 12 weeks after stopping IIT is a critical window during which those destined not to achieve sustained remission may experience a loss of the beneficial effects on insulin sensitivity, glucagon regulation, and β-cell function that were seen immediately post-IIT (see figure 1D–F, respectively). Furthermore, as shown in figure 3B, the majority of non-remitters are not in remission when first assessed at 12 weeks after IIT. It thus emerges that there is heterogeneity in the durability of the beneficial metabolic effects of short-term IIT, with non-remitters having only transient benefits, as becomes apparent just 12 weeks later.

Unlike insulin sensitivity and glucagon profile, which did not differ between remitters and non-remitters either at baseline or over the 48 weeks follow-up, β-cell

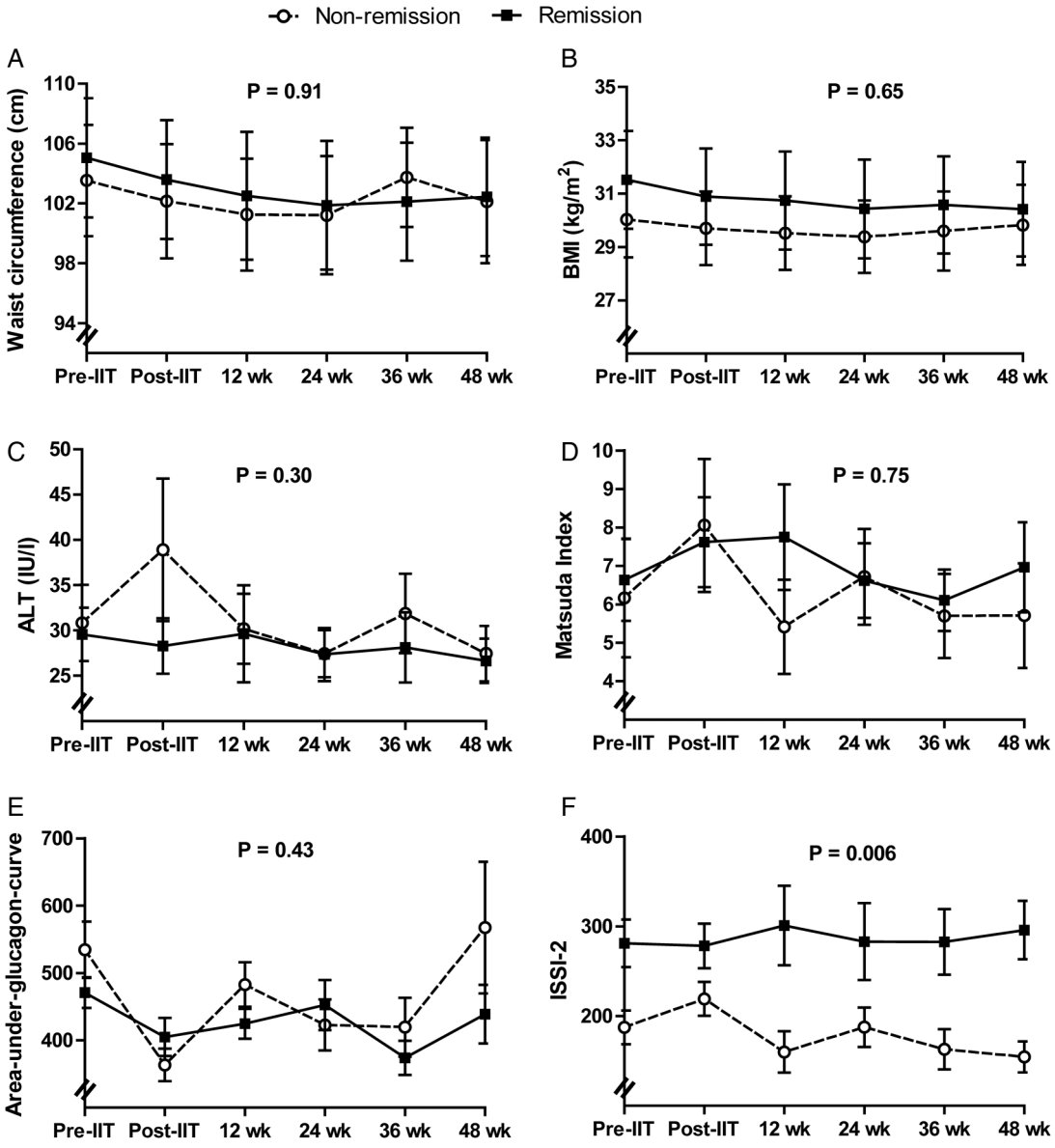

Figure 1 Changes over time in (A) waist circumference, (B) BMI, (C) ALT, (D) Matsuda index, (E) $AUC_{glucagon}$, and (F) ISSI-2, comparing patients with drug-free diabetes remission at 48 weeks and those not in remission at 48 weeks (solid square: remission; open circle: non-remission). ALT, alanine aminotransferase; $AUC_{glucagon}$, area-under-the-glucagon-curve; BMI, body mass index; ISSI-2, Insulin Secretion-Sensitivity Index-2; pre-IIT, prior to intensive insulin therapy; post-IIT, after intensive insulin therapy; p values are for differences between groups.

function was clearly different between these two groups. Specifically, those that achieved sustained drug-free remission had better β-cell function at baseline and throughout the 48 weeks post-IIT (table 1 and figure 1F). Furthermore, despite similar glycemic targets during IIT, the remitters required significantly less basal insulin (median 0.14 vs 0.36 units/kg/day, p=0.002) and meal insulin (median 0.12 vs 0.27 units/kg/day, p=0.01) than non-remitters. Figure 1F shows that remitters then had stable β-cell function across the year, whereas non-remitters had an initial improvement with IIT that was followed by ongoing deterioration thereafter. While the effect of IIT on endogenous insulin secretion has previously been described as a determinant of subsequent remission, the temporal profile of β-cell function over time in the current study offers new insight. Specifically, neither of the measures of β-cell function (ISSI-2 and $\Delta ISR_{0-120}/\Delta gluc_{0-120}\times$Matsuda index) exhibited an improvement in response to IIT in the remitters (unlike the transient benefit seen in the non-remission group). However, the stable profile of β-cell function in the 48 weeks thereafter stands in sharp contrast to the deterioration over time seen in the non-remitters, which is more characteristic of the usual natural history of T2DM.[21] One possibility is that the physiology of the remitters was such that they were destined to have stable β-cell function over the year, irrespective of the IIT, suggesting that the intervention was not responsible for

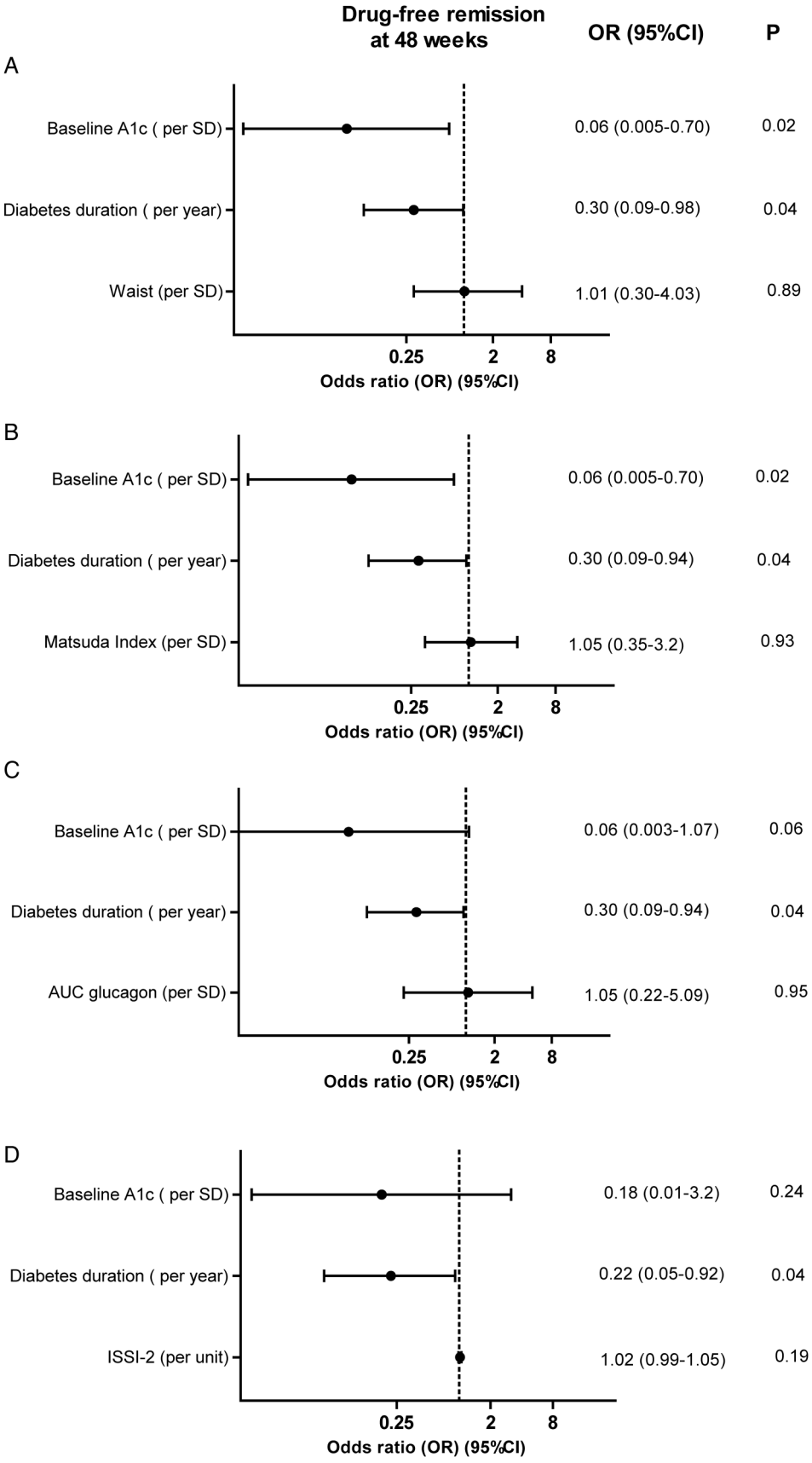

Figure 2 Adjusted OR (OR (95% CI)) of each covariate in logistic regression models of (outcome) drug-free diabetes remission at 48 weeks. $AUC_{glucagon}$, area-under-the-glucagon-curve; ISSI-2, Insulin Secretion-Sensitivity Index-2.

their superior long-term glycemic control. However, we believe that the marked increase in the prevalence of drug-free diabetes remission (from 3 participants (12%) at baseline to 14 participants (56%) at 48 weeks) argues against this possibility and suggests that the therapy did have a long-term beneficial effect in these individuals.

Previous studies have suggested that lower baseline fasting glucose, higher BMI, better early-phase insulin

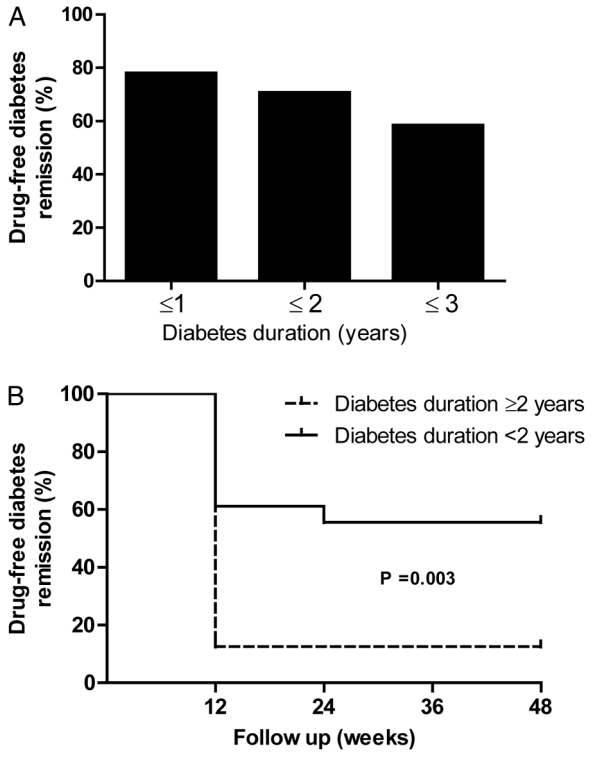

Figure 3 (A) Cumulative prevalence of drug-free diabetes remission at 48 weeks according to duration of diabetes, and (B) time to loss of drug-free diabetes remission following short-term IIT, comparing patients with duration of diabetes <2 years and those with duration ≥2 years. IIT, intensive insulin therapy.

secretion, and lower exogenous insulin requirements may be predictors of diabetes remission in newly diagnosed patients treated with short-term IIT.[1 2 4 22 23] These studies have differed from the current analysis in that they have generally not had the breadth of metabolic characterization nor the serial longitudinal assessments reported herein. In addition, they have typically been performed in patients with newly diagnosed T2DM. In this context, the current study in patients with diabetes of modest duration demonstrates that, metabolic factors notwithstanding, the most important predictor of sustained remission following short-term IIT is early intervention. Indeed, on adjusted analyses, duration of diabetes supplanted all metabolic parameters as a predictor of remission. It is particularly noteworthy that shorter duration of diabetes supplanted baseline β-cell function in predicting subsequent remission. We believe that this finding reflects that fact that current measures of β-cell function cannot differentiate between the reversible and non-reversible components of β-cell dysfunction.[8] Since the proportionate contribution of reversible dysfunction is believed to decline over time in patients with T2DM,[24] duration of diabetes likely better reflects the reversible component of β-cell dysfunction that will determine the capacity for remission in response to IIT. Overall, the current data suggest that, in the first 2 years after diagnosis of T2DM, there may be reversibility in the disease process such that short-term IIT can preserve β-cell function and enable sustained drug-free remission over 48 weeks.

This concept of a window of opportunity for reversibility early in the disease process[24] is further reinforced by studies showing that shorter duration of diabetes is an important predictor of (1) the initial β-cell response to short-term IIT,[25] (2) the rare occurrence of remission in regular clinical practice,[26] and (3) the likelihood of achieving diabetes remission in patients undergoing bariatric surgery.[27 28] The mechanism by which short-term IIT may affect long-term β-cell function remains unclear, though it has recently been suggested that early exogenous insulin may reverse the dedifferentiation of β-cells that would otherwise contribute to loss of function over time.[29] Regardless of whether an initial beneficial effect of IIT on β-cell function is detectable, however, the current study suggests that the earlier the intervention, the greater the likelihood of inducing sustained drug-free diabetes remission.

Limitations of this study are the modest sample size and the absence of a comparator group that did not receive short-term IIT. Another limitation is the use of surrogate measures of β-cell function from the OGTT, rather than clamp studies. However, the invasive and time-consuming nature of clamp studies likely would have precluded the performance of six serial assessments over 1 year as were obtained in this study. Indeed, these serial measurements have provided unique insight into the long-term metabolic effects of short-term IIT and the time course thereof over 1 year after stopping the therapy.

In summary, patients who achieve sustained drug-free diabetes remission following short-term IIT are characterized by better β-cell function at baseline that is subsequently preserved over 48 weeks after the intervention. Other metabolic benefits of IIT do not appear to differentiate remitters from non-remitters. Metabolic effects notwithstanding, however, the key determinant of the likelihood of inducing sustained remission is early intervention, particularly within the first 2 years after the diagnosis of diabetes. It thus emerges that the early years of T2DM potentially may provide a window of opportunity during which there is sufficient reversibility in the disease process such that short-term IIT may be able to stabilize the course of β-cell function and induce sustained drug-free remission.

Acknowledgements CKK holds a Banting and Best New Investigator award. BZ holds the Sam and Judy Pencer Family Chair in Diabetes Research at Mount Sinai Hospital and University of Toronto. RR is supported by a Heart and Stroke Foundation of Ontario Mid-Career Investigator Award and his research program is supported by an Ontario Ministry of Research and Innovation Early Researcher Award. RR is guarantor, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Contributors RR and BZ designed the study and protocol. CKK, HC, BZ, and RR implemented the study and acquired the data. RR and CKK contributed to the analysis plan and interpretation of the data. CKK performed the statistical analyses and wrote the first draft. All authors critically revised the manuscript for important intellectual content. All authors approved the final manuscript.

Funding This study was funded by an investigator-initiated research grant from Novo Nordisk Canada. The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interests RR and BZ have received consulting honoraria and research funding from Novo Nordisk. CKK and HC have no conflicts to disclose.

Ethics approval Mount Sinai Hospital Research Ethics Board.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data may be available on request to the corresponding author.

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