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ORIGINAL ARTICLE

Two-year trial of intermittent insulin therapy vs metformin for the preservation of β-cell function after initial short-term intensive insulin induction in early type 2 diabetes

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Aims: To test the hypothesis that "induction" intensive insulin therapy (IIT) needs to be followed by "maintenance therapy" to preserve β-cell function, and to evaluate the impact on β-cell function over 2 years of two approaches to maintenance therapy: intermittent short-term IIT every 3 months vs daily metformin.

Materials and methods: In this trial, 24 adults with a mean type 2 diabetes mellitus (T2DM) duration of 2.0 ± 1.7 years and glycated haemoglobin (HbA1c) levels 6.4 ± 0.1% (46 ± 1.1mmol/mol) were randomized to 3 weeks of induction IIT (glargine, lispro) followed by either repeat IIT for up to 2 weeks every 3 months or daily metformin. Participants underwent serial assessment of β-cell function using the Insulin Secretion-Sensitivity Index-2 (ISSI-2) on an oral glucose tolerance test every 3 months.

Results: The primary outcome of baseline-adjusted ISSI-2 at 2 years was higher in the metformin arm compared with intermittent IIT (245.0 ± 31.7 vs 142.2 ± 18.4; P = .008). Baseline-adjusted HbA1c at 2 years (secondary outcome) was lower in the metformin arm (6.0 ± 0.2% vs 7.3 ± 0.2%; P = .0006) (42 ± 2.2 vs 56 ± 2.2mmol/mol). At study completion, 66.7% of participants randomized to metformin had an HbA1c concentration ≤ 6.0% (≤42mmol/mol), compared with 8.3% of those on intermittent IIT (P = .009). There were no differences in insulin sensitivity.

Conclusion: After induction IIT, metformin was superior to intermittent IIT for maintaining β-cell function and glycaemic control over 2 years. The strategy of induction and maintenance therapy to preserve β-cell function warrants exploration in early T2DM.

KEYWORDS

intensive insulin therapy, induction, maintenance, β-cell function, preservation

1 | INTRODUCTION

Current guidelines for the pharmacological management of type 2 diabetes (T2DM) typically start with metformin monotherapy, followed by sequential addition of other antidiabetic medications in the years thereafter, whenever glycaemic targets can no longer be achieved with the existing therapeutic regimen.[1–3] This ongoing need for treatment intensification is ultimately a reflection of the inability of current regimens to prevent the progressive deterioration of pancreatic β-cell function that characterizes the natural history of T2DM.[4] Although this deterioration has been perceived at times as an inexorable process, it has recently emerged that there is a reversible element to β-cell dysfunction early in the course of T2DM.[5,6] Interestingly, it has been known for over two decades that, when administered in early T2DM, a short course of intensive insulin therapy (IIT) for 2 to 3 weeks can have metabolic benefits that persist well after stopping the therapy that can even include the remission of diabetes.[7–11] It is now apparent that this short-term IIT improves

reversible β-cell dysfunction and is thereby able to induce a subsequent remission that can persist for up to 1 year in some patients.[11–13]

Historically, the promise of using short-term IIT in this way eventually gave way to disappointment when it was realized that the remission that it induces is ultimately temporary, as β-cell function deteriorates over time after the therapy is stopped.[11,14] In this context, we have proposed that a therapeutic strategy to consider may be the use of short-term IIT as "induction therapy" to first improve reversible β-cell dysfunction, followed by a suitable "maintenance therapy" to preserve this beneficial β-cell effect.[6] With this perspective, we undertook the present study to evaluate the impact on β-cell function over 2 years of two potential approaches to maintenance therapy: intermittent courses of short-term IIT administered every 3 months vs daily metformin.

2 | METHODS

2.1 | Design/participants

The Remission Studies Evaluating Type 2 Diabetes – Intermittent Insulin Therapy Pilot (RESET IT Pilot) was an open-label, parallel-arm, randomized controlled trial that was designed to evaluate the feasibility of administering induction therapy (short-term IIT) followed by maintenance therapy (either intermittent IIT or daily metformin) to preserve β-cell function in early T2DM (ClinicalTrials.Gov-NCT01755468). In the present pilot study, adults with T2DM of modest duration were randomized to receive induction therapy with a 3-week course of IIT, followed by maintenance therapy consisting of either intermittent IIT for up to 2 weeks administered every 3 months, or daily metformin (Figure 1). Participants underwent serial assessment of glucose homeostasis by oral glucose tolerance test (OGTT) at baseline, after induction IIT, and then every 3 months thereafter during the 2-year maintenance phase. This single-centre study was approved by the Mount Sinai Hospital Research Ethics Board and all participants provided written informed consent.

Inclusion criteria included: age 30 to 80 years inclusive; physician-diagnosed T2DM of ≤5 years' duration; treatment with either metformin or lifestyle modification only; serum negativity for anti-glutamic acid decarboxylase antibodies; and screening glycated haemoglobin (HbA1c) concentration between 6.0% and 9.5% (42 and 80 mmol/mol) inclusive if on no antidiabetic medications or between 5.5% and 9.0% (37 and 75 mmol/mol) inclusive if on metformin (recognizing the broad range of glycaemia that may occur in early T2DM because of reversible β-cell dysfunction).[6] Exclusion criteria included previous treatment with any antidiabetic medication other than metformin; renal dysfunction (estimated glomerular filtration rate < 50 mL/min); and liver disease or transaminases >2.5-fold above normal.

2.2 | Randomization and induction therapy

At baseline, participants were randomized to the two treatment arms in a 1:1 manner. The computer-generated random allocation sequence was prepared by the Applied Health Research Centre (Toronto) in variable permuted blocks of concealed size.

Induction IIT was administered in the same way in both arms for 3 weeks (using an established protocol that we have previously implemented).[15] At the outset, participants stopped metformin (if taking) the day before and completed an overnight fast before undergoing a 2-hour, 75-g OGTT the next morning. At this baseline visit, participants received instruction on healthy lifestyle modification for the management of T2DM as per Canadian Diabetes Association Clinical Practice Guidelines,[16,17] and were encouraged to continue these practices for the duration of the trial. They then began a 3-week course of multiple daily insulin injection therapy consisting of basal insulin glargine and pre-meal lispro, with starting total daily doses of 0.2 to 0.3 U/kg, apportioned as 60% bolus and 40% basal insulin. While on IIT, participants were asked to perform self-monitoring of capillary blood glucose at least 4 times/d (including fasting glucose every day; before each meal at least 4 times/wk; 2 hours after each meal at least 4 times/wk; and at bedtime at least 4 times/wk). These glucose measurements enabled the titration of insulin doses to target fasting glucose level between 4.0 and 6.0 mmol/L and 2-hour postprandial glucose level < 8 mmol/L. On the final day of induction, the last insulin dose was the lispro before dinner, with no bedtime basal insulin. Participants then fasted overnight and returned to the clinical investigation unit the next morning for their post-induction OGTT.

2.3 | Maintenance therapy

After the post-induction OGTT, participants began one of the following two maintenance therapies, to which they had been randomly assigned at baseline.

1. Intermittent IIT: Participants randomized to this arm administered short-term IIT every 3 months, while following healthy lifestyle practices for diabetes management between each course. Specifically, after the post-induction OGTT, they followed lifestyle modification and then returned for their next OGTT after 3 months. After that OGTT at 3 months, they undertook a course of short-term IIT, starting from the final doses of their preceding induction IIT and titrated to the same glycaemic targets as described above for induction. This maintenance IIT was initially administered for 1 week but this duration was changed to 2 weeks in March 2014 (before the first randomized participant reached their 12-month visit), when new analyses from an earlier study indicated that 2 weeks of IIT may be more beneficial than 1 week.[18] Between each course of maintenance IIT, participants returned to lifestyle modification only. This process was repeated every 3 months, with participants returning for an OGTT at each of 6, 9, 12, 15, 18 and 21 months, followed each time by maintenance IIT for 1 to 2 weeks (and starting from the final doses of their preceding IIT course, with titration to the targets described earlier). The final assessment was on OGTT at 24 months.
2. Daily metformin: In this arm, participants were treated with metformin monotherapy (1000 mg/d for 2 weeks, followed by 2000 mg/d or maximal tolerated dose thereafter), in addition to

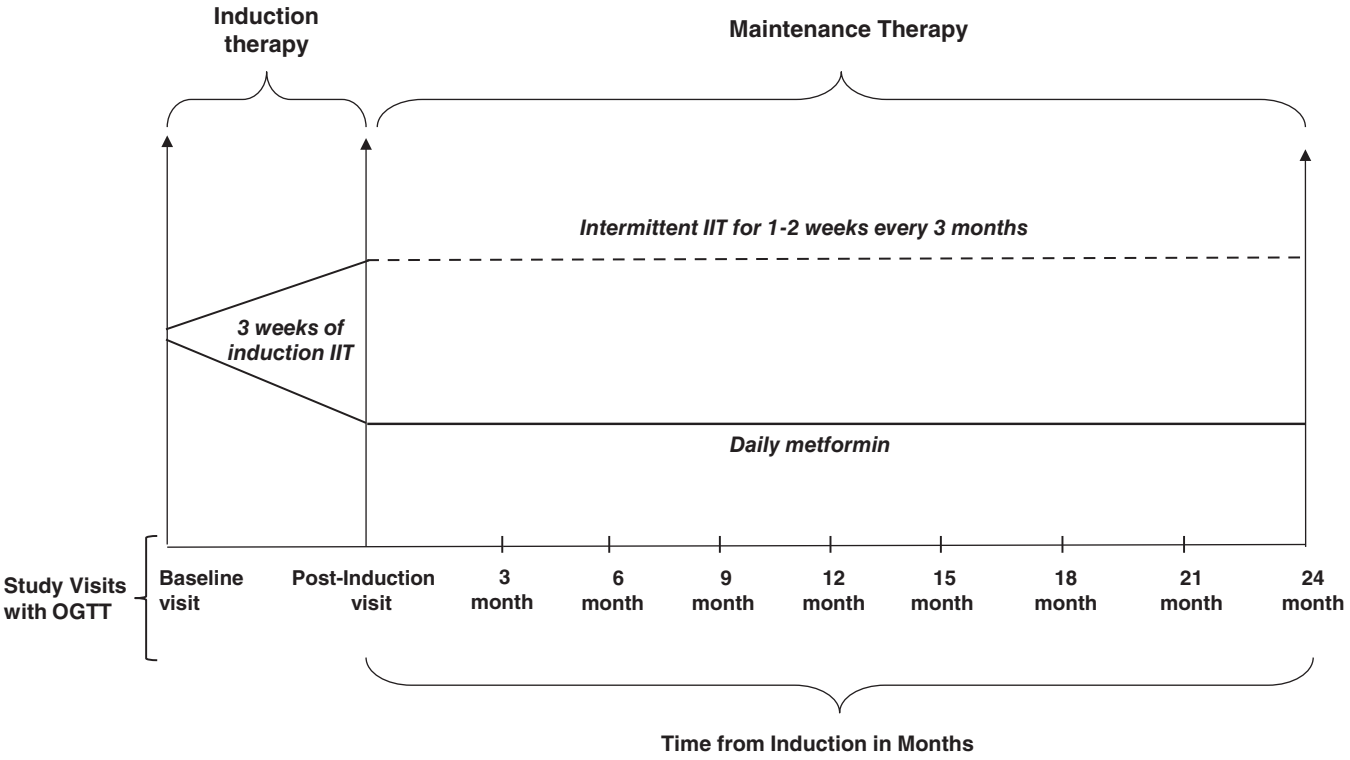


FIGURE 1 Flow diagram showing study design. OGTT, oral glucose tolerance test

their ongoing healthy lifestyle practices. Metformin was held on the morning of each OGTT at 3, 6, 9, 12, 15, 18, 21 and 24 months.

At each visit, participants in both arms completed questionnaires (medical history, comorbid conditions, medications, lifestyle and Baecke physical activity), underwent physical examination, and had standard clinical biochemistry measurements, including HbA1c. If HbA1c exceeded 8.0% on two consecutive visits (indicating loss of glycaemic control), then the protocol was stopped and the participant returned to usual clinical care.

2.4 | Physiological indices on OGTT

Each OGTT was performed in the morning after overnight fast. During each OGTT, venous blood samples were drawn for measurement of glucose, C-peptide, and insulin at fasting and at 30, 60 and 120 minutes after ingestion of the 75-g glucose load. Specific insulin was measured with a Roche Elecsys-1010 immunoassay analyser and electrochemiluminescence immunoassay kit, and C-peptide was measured with a Roche Modular system and electrochemiluminescence immunoassay kit (Roche Diagnostics, Laval, Canada).

Area under the insulin curve (AUC_{ins}) and area under the glucose curve (AUC_{gluc}) during the OGTT were calculated by trapezoidal rule. Whole-body insulin sensitivity was measured using the Matsuda index[19] and insulin resistance (IR; primarily hepatic) was assessed by homeostasis model assessment (HOMA).[20] 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 (ivGTT).[21,22] ISSI-2 has been directly validated against the ivGTT disposition index, with which it exhibits stronger correlation than do 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.[13–15,23–27] ISSI-2 is defined as the product of (1) insulin secretion measured by the ratio of AUC_{ins} to AUC_{gluc} and (2) insulin sensitivity measured by Matsuda index. Additional measures of β-cell function included (1) $\Delta Cpep_{0\text{-}120}/\Delta gluc_{0\text{-}120} \times$ Matsuda index (where $\Delta Cpep_{0\text{-}120}/\Delta gluc_{0\text{-}120}$ reflects the mean incremental concentrations of C-peptide and glucose during the OGTT) and (2) $\Delta ISR_{0\text{-}120}/\Delta gluc_{0\text{-}120} \times$ Matsuda index (where ISR is the pre-hepatic insulin secretion rate determined by C-peptide deconvolution), with both measures calculated as previously described.[15]

2.5 | Outcomes and power

The primary outcome was β-cell function measured by ISSI-2 at 2 years, adjusted for its measurement at baseline. The secondary outcome was baseline-adjusted HbA1c at 2 years. Additional outcomes were baseline-adjusted measures at 2 years for fasting glucose; $\Delta Cpep_{0\text{-}120}/\Delta gluc_{0\text{-}120} \times$ Matsuda index; $\Delta ISR_{0\text{-}120}/\Delta gluc_{0\text{-}120} \times$ Matsuda index; Matsuda index; and HOMA-IR. A sample size of 24 participants (12 in each arm) provided 80% power to detect a between-group difference of 90 in the primary outcome of baseline-adjusted ISSI-2 at 2 years at a significance level of 0.05, using analysis of covariance (ANCOVA).

2.6 | Statistical analyses

Statistical analyses were conducted with SAS 9.2 (SAS Institute, Cary, North Carolina) on an intention-to-treat basis. Missing data points

TABLE 1 Baseline characteristics of the study arms

	Intermittent IIT (n = 12)	Metformin (n = 12)	P
Age, years	53 (45-60)	58 (53-62)	.22
Gender, % men	58.3	41.7	.41
Ethnicity, %			.08
White	25.0	75.0	
Indo-Asian	41.7	8.3	
East Asian	16.7	8.3	
Other	16.7	8.3	
Duration of diabetes, years	2.3 (0.7-2.5)	1.3 (0.3-3.0)	.30
Metformin monotherapy prior to study, %	83.3	50.0	.19
BMI, kg/m^2	26.6 (25.0-34.8)	35.6 (28.1-40.6)	.11
Waist circumference, cm	94 (88-109)	112 (103-126)	.06
Systolic blood pressure, mm Hg	123 (105-134)	130 (119-138)	.30
Diastolic blood pressure, mm Hg	68 (66-77)	74 (69-78)	.57
Alanine aminotransferase, IU/L	27 (18-32)	32 (28-38)	.15
Creatinine, μmol/L	67 (57-72)	75 (60-81)	.35
Glycaemia			
Fasting plasma glucose, mmol/L	6.3 (5.9-7.9)	6.8 (6.3-7.7)	.48
HbA1c, %	6.4 (6.1-7.1)	6.2 (5.9-6.6)	.30
Insulin sensitivity/resistance			
Matsuda index	2.1 (1.6-2.9)	1.2 (1.0-2.8)	.14
HOMA-IR	4.5 (3.3-5.9)	7.3 (3.9-9.4)	.17
β-cell function			
ISSI-2	152 (103-269)	187 (143-308)	.19
$\Delta Cpep_{0\text{-}120}/\Delta gluc_{0\text{-}120}$ × Matsuda index	683 (476-815)	871 (601-1323)	.17
$\Delta ISR_{0\text{-}120}/\Delta gluc_{0\text{-}120}$ × Matsuda index	2.6 (1.9-2.8)	3.2 (1.8-4.6)	.21
Initial daily basal insulin dose, units/kg	0.08 (0.077-0.098)	0.08 (0.072-0.096)	.48
Initial daily meal insulin dose, units/kg	0.11 (0.107-0.118)	0.11(0.103-0.118)	.55
After induction IIT			
Final daily basal insulin dose, units/kg	0.23 (0.173-0.349)	0.22 (0.133-0.269)	.42
Final daily meal insulin dose, units/kg	0.23 (0.178-0.250)	0.19 (0.142-0.280)	.49

Abbreviations: BMI, body mass index; Cpep, C-peptide; gluc, glucose; HbA1c, glycated haemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; IIT, intensive insulin therapy; ISSI-2, Insulin Secretion-Sensitivity Index-2; ISR, insulin secretion rate. Continuous variables presented as median followed by interquartile range in parentheses. P values refer to comparison between groups by Wilcoxon 2-sample test (for continuous variables) or Fisher's exact test (for categorical variables).

post-baseline were imputed by carrying forward the last observation. Continuous variables were tested for normality of distribution, and natural log transformations of skewed variables were used where necessary. Baseline characteristics of the study arms were compared by Wilcoxon 2-sample test (continuous variables) or Fisher's exact test (categorical variables; Table 1). The primary, secondary and additional continuous outcomes at 2 years were compared between arms by ANCOVA, with adjustment for their baseline measurements (Table 2). Within each arm, the baseline-adjusted mean for each continuous outcome was calculated from the estimated regression function with the observed mean of the respective baseline measurement, and its standard error was calculated from the predicted value of the outcome. According to the delta method, we obtained the baseline-adjusted mean and its standard error in original scale from natural log scale, which was used in the ANCOVA model.

Longitudinal changes over time in outcomes of interest were evaluated using a generalized estimating equation (GEE) model. The GEE model examined the treatment effect of intermittent IIT every 3 months vs daily metformin and time effect on the outcomes (Figure 2). An appropriate correlation structure was selected for each outcome by quasi-likelihood under the independence model criterion (QIC) to optimize the goodness-of-fit. Survival analysis was performed to examine time to loss of glycaemic control (defined by HbA1c >8.0% (≤64mmol/mol), on two consecutive measurements or clinical determination by the patient's primary care physician of need for further antidiabetic therapy). Participants who did not lose glycaemic control by the end of study were censored. Kaplan–Meier estimates of the survival curves were calculated for the two arms, and compared by log-rank test (Figure 3A). Both GEE and survival analyses were based on the observed data. The proportion of participants with HbA1c ≤6.0% (≤42mmol/mol) was compared between the two arms using Fisher's exact test at baseline and at final study visit, respectively (Figure 3B). Similarly, the proportions of participants experiencing adverse events at any time during the trial (during either induction or maintenance) were compared between the two arms using Fisher's exact test.

3 | RESULTS

Recruitment took place between April 2013 and April 2014. Figure S1 shows the trial profile. The 24 individuals who met the inclusion/exclusion criteria had T2DM of 2.0 ± 1.7 years' duration, with a mean HbA1c concentration of 6.4 ± 0.1%, (46 ± 1.1mmol/mol), and two-thirds were on metformin monotherapy prior to the study. These participants were randomized to receive 3 weeks of induction IIT followed by maintenance therapy delivered as either (1) intermittent IIT every 3 months or (2) daily metformin. Table 1 shows the baseline characteristics of these two groups. Although it did not reach statistical significance, there was an imbalance in the ethnicity distribution, with more white participants in the metformin arm and more Indo- and East-Asian patients in the intermittent IIT group. These ethnicity differences probably contributed to baseline body mass index (BMI) and waist circumference being higher in the metformin group, although neither reached statistical significance. There were no baseline differences between the groups in any of the three measures of β-cell function or in glycaemic variables.

Final outcome status was ascertained for all participants. Two individuals in the intermittent IIT arm discontinued follow-up after 9 months, when HbA1c reached 8.0% (64 mmol/mol) and their primary care physician wished to add further anti-diabetic therapy. One participant in the metformin group was diagnosed with breast cancer, such that follow-up was discontinued at 18 months (with HbA1c 6.0% (42 mmol/mol) at the time) to eliminate any additional study burden on the patient. Two participants took only 1000 mg/d of metformin (rather than 2000 mg/d). All 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 2 years was significantly higher in the metformin arm compared with intermittent IIT (245.0 ± 31.7 vs 142.2 ± 18.4; P = .008). The additional measures of β-cell function at 2 years were similarly higher in the metformin arm ($\Delta Cpep_{0\text{-}120}/\Delta gluc_{0\text{-}120}$ × Matsuda index, P = .01; $\Delta ISR_{0\text{-}120}/\Delta gluc_{0\text{-}120}$ × Matsuda index, P = .02). The secondary outcome of baseline-adjusted HbA1c at 2 years was lower in the metformin arm (6.0 ± 0.2% vs 7.3 ± 0.2%; P = .0006) (42 ± 2.2 vs 56 ± 2.2mmol/mol), accompanied by lower fasting glucose (P = .0002). Baseline-adjusted Matsuda index and HOMA-IR did not differ between the groups at 2 years. Sensitivity analyses showed that the effects on β-cell function, HbA1c and fasting glucose were unchanged after adjustment for ethnicity, baseline BMI, waist circumference, pre-study metformin, and duration of diabetes, respectively (Table S1).

Figures 2A–C show the pattern of change over time in β-cell function for the primary outcome measure ISSI-2 (Figure 2A) and both additional β-cell indices (Figure 2B,C). Each measure showed the same pattern. Specifically, induction IIT improved β-cell function and there was no significant difference between the groups post-induction, but this was followed by better β-cell function across the 2 years thereafter in the metformin arm, as compared with the intermittent IIT arm. Each measure of β-cell function indicated a significant treatment effect during the maintenance phase from post-induction to 2 years (ISSI-2: P = .03; $\Delta Cpep_{0\text{-}120}/\Delta gluc_{0\text{-}120}$ × Matsuda index, P = .001; $\Delta ISR_{0\text{-}120}/\Delta gluc_{0\text{-}120}$ × Matsuda index, P = .01). Notably, with each measure, the initial beneficial effect of induction IIT on β-cell function appeared to wane in the intermittent IIT arm in the first 3 months of the maintenance phase (ie, before the first course of maintenance IIT).

TABLE 2 Primary, secondary and additional outcomes at 2 years

	Intermittent IIT	Metformin	P
(I) Primary outcome			
Baseline-adjusted ISSI-2	142.2 ± 18.4	245.0 ± 31.7	.008
(II) Secondary outcome			
Baseline-adjusted HbA1c (%)	7.3 ± 0.2	6.0 ± 0.2	.0006
(III) Additional outcomes			
Baseline-adjusted fasting glucose (mmol/L)	7.6 ± 0.3	5.7 ± 0.3	.0002
Baseline-adjusted $\Delta Cpep_{0\text{-}120}/\Delta gluc_{0\text{-}120}$ × Matsuda index	457.7 ± 89.9	993.5 ± 195.1	.01
Baseline-adjusted $\Delta ISR_{0\text{-}120}/\Delta gluc_{0\text{-}120}$ × Matsuda index	1.6 ± 0.3	3.5 ± 0.7	.02
Baseline-adjusted Matsuda index	1.7 ± 0.3	1.9 ± 0.3	.60
Baseline-adjusted HOMA-IR	6.3 ± 1.2	3.9 ± 0.8	.10

Abbreviations: Cpep, C-peptide; gluc, glucose; HbA1c, glycated haemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; IIT, intensive insulin therapy; ISSI-2, Insulin Secretion-Sensitivity Index-2; ISR, insulin secretion rate. Data shown as mean ± SE.

Figures 2D–F show the changes over time in Matsuda index, HbA1c and fasting glucose, respectively. There was no difference in insulin sensitivity (Matsuda index) between the treatment groups (P = .84). Nevertheless, mirroring the differences in β-cell function, the metformin arm had lower HbA1c (P = .0002) and fasting glucose (P = .02) than intermittent IIT across the maintenance phase. BMI did not differ over time between the groups (Figure S2).

Figure 3A shows the cumulative incidence of loss of glycaemic control during the maintenance phase (defined by HbA1c >8.0% (64 mmol/mol) on two consecutive measurements or clinical determination by the patient's primary care physician of need for further antidiabetic therapy). None of the participants randomized to metformin reached this endpoint, whereas 5 of 12 did so in the intermittent IIT arm (log-rank test, P = .01). At baseline, there was no between-group difference in the proportion of participants with HbA1c ≤ 6.0% (42 mmol/mol) (Figure 3B). By the final study visit, however, 66.7% of participants randomized to metformin had HbA1c ≤6.0% (42 mmol/mol), as compared with 8.3% of those in the intermittent IIT arm (P = .009). This level of glycaemic control was achieved without any increased incidence of hypoglycaemia or other adverse events (Table S2). Notably, short-term IIT yielded no episodes of severe hypoglycaemia at any time during either induction or maintenance therapy.

4 | DISCUSSION

In the present study, we showed that, after induction IIT in early T2DM, maintenance therapy with metformin was superior to

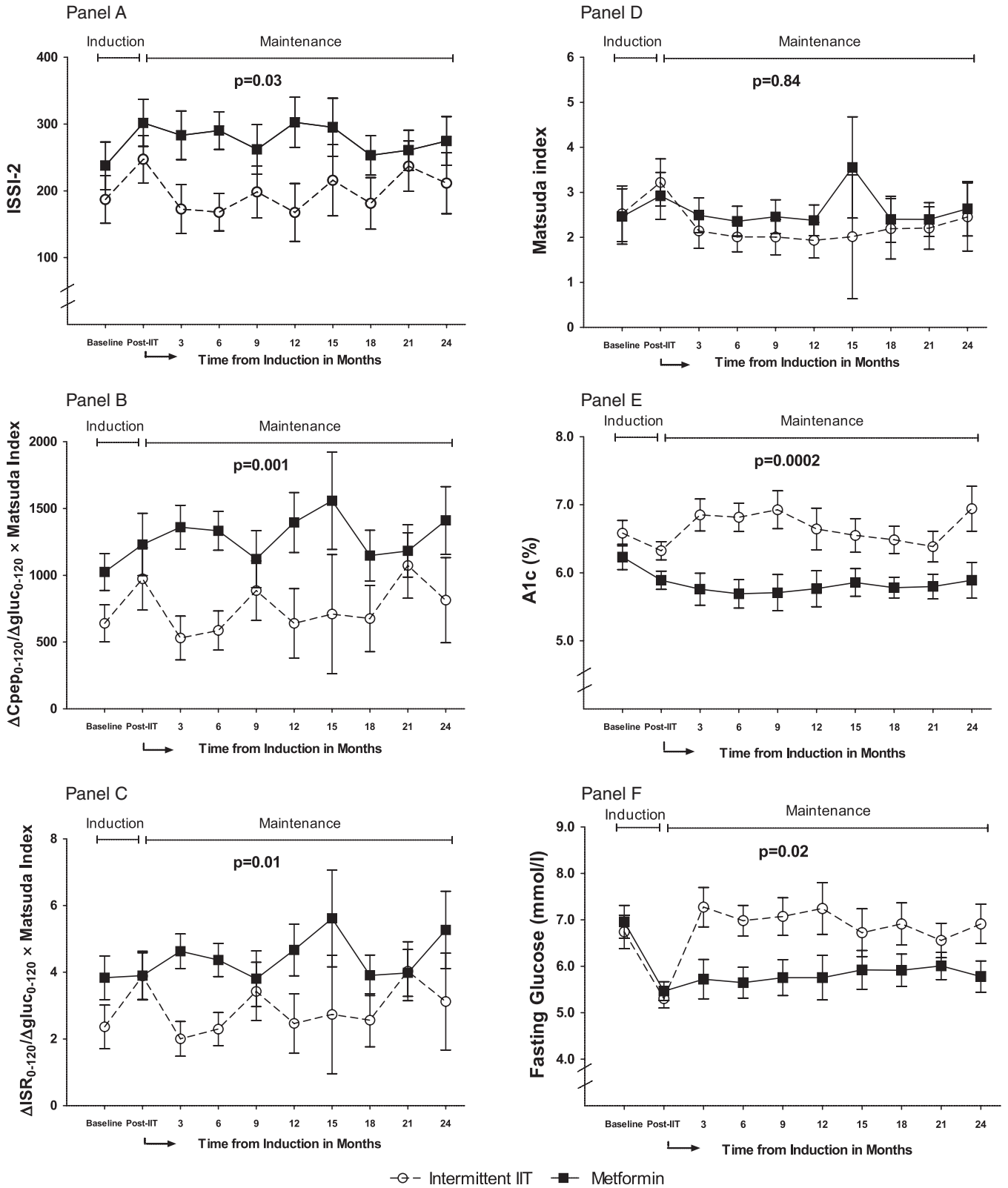
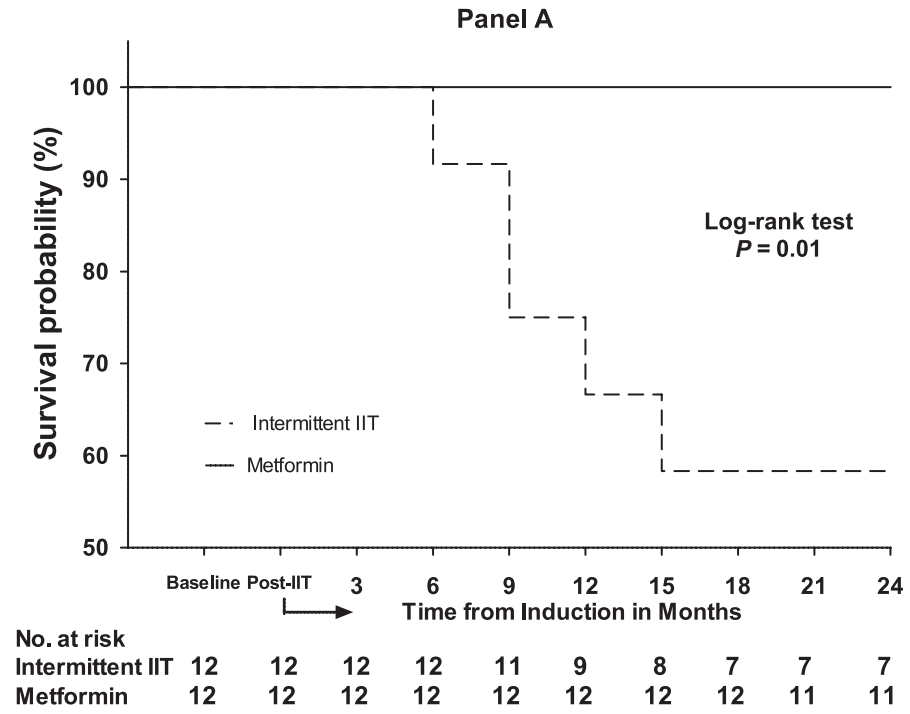


FIGURE 2 Changes over time in β-cell function, as measured by A, Insulin Secretion-Sensitivity Index-2 (ISSI-2), B, $\Delta Cpep_{0\text{-}120}/\Delta gluc_{0\text{-}120}$ × Matsuda index, and C, $\Delta ISR_{0\text{-}120}/\Delta gluc_{0\text{-}120}$ × Matsuda index; and changes over time in D, Matsuda index of insulin sensitivity, E, glycated haemoglobin (HbA1c), and F, fasting glucose. Mean and standard error are shown. *P* values are for the treatment effect during the maintenance phase. Cpep, C-peptide; gluc, glucose; IIT, intensive insulin therapy; ISR, insulin secretion rate

intermittent IIT for preserving β-cell function and glycaemic control over 2 years. These beneficial effects were achieved in the absence of differences between the groups in insulin sensitivity. Moreover, treatment with induction IIT followed by metformin maintenance yielded stable β-cell function and metabolic control across the 2-year follow-up, with mean HbA1c and fasting glucose maintained within their respective laboratory normal ranges. These data suggest that the strategy of induction and maintenance therapy to preserve β-cell



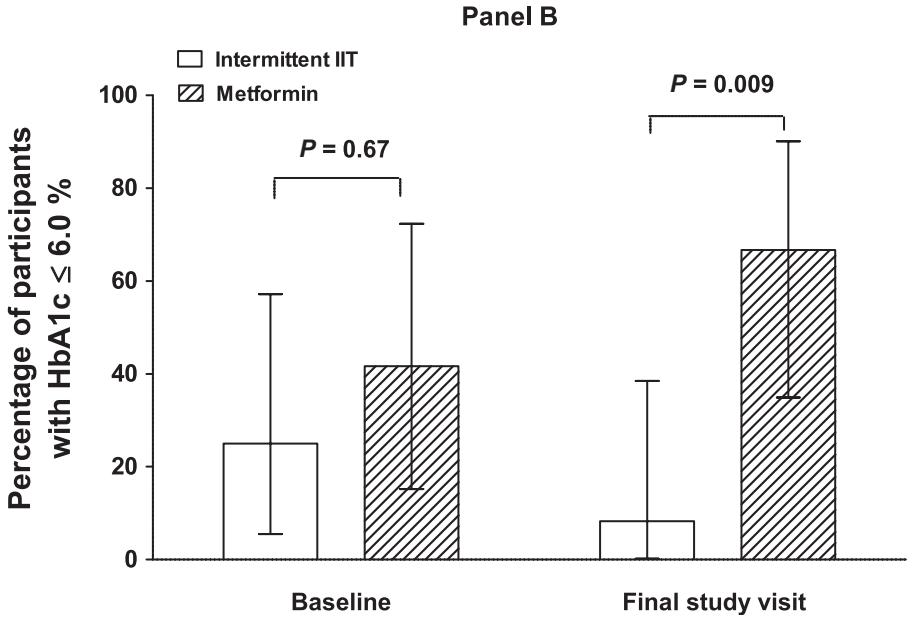


FIGURE 3 A, Survival curves showing the probability of loss of glycaemic control over time (defined by glycated haemoglobin [HbA1c] > 8.0% on 2 consecutive measurements or clinical determination by patient's primary care physician of need for further antidiabetic therapy) by treatment group. B, Proportion of participants in each treatment group with HbA1c ≤6.0% at baseline and at final study visit. IIT, intensive insulin therapy

function warrants consideration and further evaluation in early T2DM.

The strategy of induction and maintenance therapy tested in the present study is fundamentally different from current algorithms for the management of T2DM. First, whereas current approaches focus on limiting glycaemic exposure, the induction/maintenance paradigm targets the reversibility of β-cell dysfunction (with glycaemic control envisioned as a downstream consequence thereof).[6] Notably, this study was conducted in a population whose glycaemic control at baseline (mean HbA1c 6.4%) (46 mmol/mol) would not typically precipitate immediate intervention in practice. Secondly, this therapy was initiated in patients who were early in the course of T2DM (mean duration 2.0 years) because the capacity for reversibility of β-cell dysfunction is believed to wane with longer duration of diabetes. Indeed, the likelihood of maintaining remission of diabetes for 1 year after short-term IIT progressively falls when the timing of the intervention is shifted from the first year after diagnosis to the second year to the third year.[14] However, even when IIT is undertaken within this early window, the remission that it induces is ultimately temporary. This recognition led us to the strategy of coupling induction IIT with a suitable maintenance therapy, the feasibility of which was evaluated in this pilot study.

Although designed to assess the feasibility of this approach, the present study showed that daily metformin was superior to

intermittent IIT as maintenance therapy with respect to both the primary (β-cell function) and secondary (glycaemic control) outcome at 2 years. It is notable that metformin yielded lower HbA1c and fasting glucose across the 2 years (Figure 2E,F) in the absence of detectable differences in insulin sensitivity (Figure 2D), suggesting that this glycaemic benefit was probably attributable to the better β-cell function that was consistently observed with three distinct measures thereof (Figure 2A–C). Indeed, all three measures indicated that metformin achieved the desired goal of maintaining the beneficial β-cell effect of induction IIT for 2 years thereafter. The resultant stabilization of mean HbA1c in the normal range of the assay (<6.0%) across the 2 years of follow-up (Figure 2E) stands in marked contrast to both (1) the loss of glycaemic control observed in 5 of 12 participants in the intermittent IIT arm (Figure 3A) and (2) the reported 17% annual rate of failure of metformin monotherapy in clinical practice.[28] Accordingly, these data raise the possibility that the durability of metformin monotherapy potentially may be enhanced when the medication is administered after initial induction IIT, a question that warrants more definitive evaluation in a larger study population.

The present study also confirmed the safety and feasibility of repeated administration of short-term courses of IIT, albeit in an academic clinical trial setting that may not extend to general practice. In this patient population, with mean HbA1c 6.4% (46 mmol/mol) at baseline, there was no significant difference in the incidence of hypoglycaemia between participants who were randomized to intermittent IIT and those who received metformin. This low risk of hypoglycaemia is consistent with previous studies of short-term IIT in early T2DM,[8–10] but has been extended herein to repeat courses every 3 months. While it was safe, however, intermittent IIT could not match daily metformin in preserving β-cell function and glycaemic control after induction. The longitudinal changes over time shown in Figure 2 may provide insight in this regard. Specifically, as seen with all three measures of β-cell function (Figure 2A–C), the beneficial effect that was achieved with induction IIT was lost by the 3-month visit, which was just prior to the first course of maintenance IIT. This post-induction deterioration of β-cell function is precisely the basis for the temporary nature of remission following short-term IIT (which prompted our hypothesis of the need for maintenance therapy in the first place). As such, these data suggest that, on its own, intermittent IIT beginning 3 months later is insufficient to overcome the loss of β-cell function that occurs after the cessation of initial induction. Instead, it may be that ongoing maintenance therapy (such as metformin) is needed to prevent this deterioration after induction IIT.

A limitation of the present study is the open-label design, as masking of intermittent IIT was not practical. As some protection against bias, the primary outcome of β-cell function is a physiological measure that is not readily accessible to manipulation by either participants or providers, and all biochemical analyses were performed by personnel who were unaware of treatment allocation. Another factor to consider is the impact of lifestyle habits. Although diet was not measured, there were no differences between the groups in physical activity according to the Baecke questionnaire at baseline, 1 year or 2 years (data not shown). Although not statistically significant (Figure S2), changes over time in BMI could potentially have impacted the study findings. Another limitation is that the sample size was modest, owing to the pilot nature of the study. In this setting, it is possible that small differences between the treatment arms could disproportionately impact the findings and their generalizability. In this regard, it should be noted that (1) the primary/secondary/additional outcomes in Table 2 were all adjusted for their baseline measurements and (2) their findings were unchanged after adjustment for ethnicity, baseline BMI, waist, pre-study metformin, and duration of diabetes (Table S1). Indeed, the consistent demonstration of significant differences in β-cell function and glycaemic control with this modest sample is suggestive of robust treatment effects in this population. Moreover, the consistency of the findings on serial measurements over 2 years and across different indices of β-cell function and glycaemia is reassuring. Lastly, recognizing that this study population had mean HbA1c 6.4% (46 mmol/mol) at baseline, it may be of interest to evaluate intermittent IIT in patients with poorer glycaemic control.

Overall, on consideration of both its strengths and limitations, this study offers certain key messages for future directions. First, although the sample size was modest, the stabilization of β-cell function over 2 years with metformin monotherapy after initial IIT, coupled with mean HbA1c <6.0% (42 mmol/mol) throughout, supports the concept of induction/maintenance therapy targeting β-cell preservation in early T2DM. This therapeutic paradigm focusing on disease modification, rather than solely on glycaemia per se, warrants further study. Accordingly, to determine whether repeated courses of IIT can modify the natural history of β-cell dysfunction, we are now conducting a trial evaluating maintenance therapy of intermittent IIT on a background of ongoing metformin (ClinicalTrials.Gov NCT02192424). Furthermore, the expanding repertoire of new antidiabetic therapies may offer other options for both induction and maintenance. Finally, a sobering reality to recognize is that, despite maintaining near-normal glycaemic control for 2 years, participants in the metformin arm had mean ISSI-2 values in the range of 250 to 300, well below that which would typically be seen in individuals with normal glucose tolerance (e.g. >800).[27] Thus, even with intervention as early as the first few years of T2DM, the degree of reversibility of β-cell dysfunction may be limited, such that reversion to normal physiological function potentially might not be possible. For greater preservation of β-cell function, it may be necessary to target reversibility prior to the diagnosis of diabetes in at-risk individuals.

In conclusion, this pilot study shows that, after induction IIT in early T2DM, maintenance therapy with metformin was superior to intermittent IIT for preserving β-cell function and glycaemic control. This therapeutic strategy stabilized β-cell function and metabolic control across 2 years of follow-up. The novel paradigm of induction and maintenance therapy to preserve β-cell function thus warrants further study and consideration in early T2DM.

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Research at Mount Sinai Hospital and University of Toronto. R.R. 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. The protocol is available from R.R. on request.

Conflict of interest

None declared.

Author contributions

R.R. designed the study and protocol. R.R., H.C., C.K.K. and B.Z. implemented the study and acquired the data. C.Y. performed the statistical analyses. R.R. wrote the manuscript. All authors contributed to interpretation of the data and critical revision of the manuscript. All authors approved the manuscript.

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SUPPORTING INFORMATION

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