

β -Cell Function Preservation After 3.5 Years of Intensive Diabetes Therapy

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OBJECTIVE—To assess β -cell function preservation after 3.5 years of intensive therapy with insulin plus metformin (INS group) versus triple oral therapy (TOT group) with metformin, glyburide, and pioglitazone.

RESEARCH DESIGN AND METHODS—This was a randomized trial of 58 patients with treatment-naïve newly diagnosed type 2 diabetes. All patients were treated with insulin and metformin for a 3-month lead-in period followed by random assignment to the INS or TOT group. β -Cell function was assessed using a mixed-meal challenge test at randomization and 6, 12, 18, 30, and 42 months. Analyses were intention to treat and performed with repeated-measures models.

RESULTS—Completion rates at 3.5 years were 83% in the insulin group and 72% in the TOT group, with good compliance in both groups ($87 \pm 20\%$ in the INS group vs. $90 \pm 15\%$ in the TOT group). β -Cell function was preserved at 3.5 years after diagnosis, with no significant change from baseline or difference between the two groups as measured by area under the curve (AUC) of C-peptide ($P = 0.14$) or the ratio of C-peptide to glucose AUC ($P = 0.7$). Excellent glycemic control was maintained in both groups (end-of-study HbA_{1c} $6.35 \pm 0.84\%$ in the INS group vs. $6.59 \pm 1.94\%$ in the TOT group). Weight increased in both groups over time (from 102.2 ± 24.9 kg to 106.2 ± 31.7 kg in the INS group and from 100.9 ± 23.0 kg to 110.5 ± 31.8 kg in the TOT group), with no significant difference between groups ($P = 0.35$). Hypoglycemic events decreased significantly over time ($P = 0.01$) but did not differ between groups ($P = 0.83$).

CONCLUSIONS— β -Cell function can be preserved for at least 3.5 years with early and intensive therapy for type 2 diabetes with either insulin plus metformin or triple oral therapy after an initial 3-month insulin-based treatment period.

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Type 2 diabetes is a chronic disease marked by progressive β -cell dysfunction leading to insulin deficiency. Insulin secretion declines because of the toxic effects of hyperglycemia (glucotoxicity) and free fatty acids (lipotoxicity) on pancreatic β -cells (1); therefore, correction of these insults early and intensively might preserve endogenous pancreatic function.

Current American Diabetes Association treatment guidelines advocate starting with dietary therapy alone or monotherapy with metformin followed by a stepwise addition of further therapy after documented treatment failure (2). In the

UK Prospective Diabetes Study (UKPDS), dietary therapy achieved HbA_{1c} goals in only 25% of patients at 3 years. Although insulin and sulfonylurea monotherapy were more effective, only 47 and 50%, respectively, were at goal at 3 years (3). Such an approach does not prevent the natural decline in β -cell function and potentially exposes patients to prolonged periods of hyperglycemia, which has been associated with increased diabetes complications (4,5).

A large retrospective review showed that patients' HbA_{1c} averaged 9.4% before a therapeutic change was made, and

patients spent up to 24 months with HbA_{1c} >8% (6), a phenomenon known as clinical inertia. We believe that this stepwise approach does not alter the course of the disease and the end result is patients who are taking multiple antidiabetes drugs and still have not achieved glycemic targets. In vitro studies have shown that the shorter the period of antecedent glucose toxicity, the more likely that full recovery of β -cell function will occur (7), thus early and sustained interventions have the best chance of preserving β -cell function.

Several short-term studies have shown that intensive insulin therapy for 2–3 weeks at the time of diagnosis leads to rapid improvement in insulin secretion, which may be maintained months after therapy is stopped (8–11). However, after 1 year off therapy, remission rates were only 45–51% (11). In a longer study comparing insulin versus oral monotherapy, after 6 months both groups achieved improvement in β -cell function, but improvement was significantly greater in the insulin group (12). In A Diabetes Outcome Progression Trial (ADOPT), treatment with either glyburide, metformin, or rosiglitazone showed initial improvement in β -cell function over the first 6 months but then declined in all three groups over the following years as patients began to fail monotherapy (13). In conclusion, neither short-term intensive insulin therapy alone nor any oral monotherapy regimens have proven so far to preserve β -cell function long term, and the stepwise approach to diabetes treatment with its inherent clinical inertia leads to hyperglycemia and continued β -cell dysfunction.

Our study evaluated whether early intensive therapy with either an insulin-based or a triple oral hypoglycemic regimen following an initial period of insulin therapy in treatment-naïve newly diagnosed patients with type 2 diabetes would preserve or even improve β -cell function over 3.5 years of treatment.

RESEARCH DESIGN AND METHODS

We conducted a single-center, open-label, randomized clinical trial to evaluate the progression of β -cell dysfunction over 3.5 years in patients with treatment-naïve newly diagnosed type 2

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A slide set summarizing this article is available online.

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diabetes. All patients were treated for 3 months with insulin and metformin and then randomly assigned to treatment with either insulin plus metformin (INS group) or triple oral therapy (TOT group) with metformin, pioglitazone, and glyburide. The results of the first 3-month run-in period were published previously (14) as were results of the glycemic control, adverse effects, and quality of life up to 36 months (15).

Participants and eligibility

Patients aged 21–70 years with treatment-naïve type 2 diabetes diagnosed within the previous 2 months were recruited from Parkland Hospital and the Clinical Diabetes Research Center at the University of Texas Southwestern Medical Center at Dallas (UTSW). Exclusion criteria included type 1 diabetes–related antibodies, baseline HbA_{1c} level <7%, elevated serum creatinine (>1.5 mg/dL in male and >1.4 mg/dL in female subjects), liver enzymes higher than two times the upper limit of normal, severe coronary artery disease (myocardial infarction within the past 6 months or active angina), heart failure stages III–IV, pregnancy or lack of approved contraception, untreated proliferative diabetic retinopathy, any life-threatening conditions, use of more than two alcoholic drinks per day, or illicit drug use within the 6 months before enrollment. The study was approved by the institutional review board at UTSW, and written informed consent was obtained from all subjects preceding the start of the study.

Randomization and interventions

Following enrollment, insulin and metformin were initiated in all patients for a 3-month lead-in treatment period to enable everyone to attain similar glycemic control prior to randomization. This also removed any preexisting glucotoxicity and associated temporary β -cell stunning that might have been present in different degrees at the time of diagnosis. NovoLog mix 70/30 by Flexpen and metformin were initiated and titrated based on a previously published algorithm (14). All patients received diabetes education and nutritional and lifestyle counseling at enrollment with reinforcement throughout the study.

After 3 months of treatment, patients were randomly assigned to either continue insulin and metformin or begin triple oral therapy. Treatment assignment was determined with a stratified, blocked randomization. Randomization strata were race

(African American or non–African American) and BMI (cutoff 35 kg/m²), chosen to minimize possible baseline characteristic confounders on β -cell function. The participants were enrolled and assigned (by I.L.) to interventions according to the randomization schema generated by the study statistician (B.A.-H.).

Patients randomly assigned to the TOT group discontinued insulin, continued metformin 1 g twice daily (or maximum tolerated dose), and started 1.25 mg glyburide twice daily and 15 mg daily pioglitazone. Pioglitazone was titrated monthly to a final dose of 45 mg daily. Titration of insulin and glyburide (up to the highest clinically effective dose of 10 mg daily) was performed by the study physician throughout the study, based on home blood glucose–monitoring logs to attain a fasting blood glucose level of 70–110 mg/dL and postprandial blood glucose level of <140 mg/dL. All patients were asked to monitor blood glucose at least twice daily regardless of the group assignment. Initiation and dose adjustment of antihypertensive and lipid-lowering agents were allowed if medically necessary. Patients were followed at the Clinical Diabetes Research Center at UTSW monthly for the first 4 months, at 6 months after randomization, and every 3 months thereafter for a total of 42 months. Treatment failure was a predefined study end point defined as HbA_{1c} >8% confirmed by a second reading and occurring after maximization of the glyburide dose or adequate insulin dose titration. Volunteers randomly assigned to the TOT group who reached this end point were transitioned to insulin and metformin treatment, whereas those randomly assigned to insulin continued with the same treatment. Follow-up after treatment failure continued as scheduled.

Measurements

Evaluation of β -cell response was performed at 0, 6, 12, 18, 30, and 42 months postrandomization. Patients fasted the evening before, and antidiabetes treatment was withheld for 24 h prior to testing. A mixed-meal challenge test (MMCT) was performed using high-protein Boost 1 g/kg carbohydrate equivalent (or maximum of 90 g, equivalent to 480 cc) ingested over 5 min. Glucose and C-peptide were collected at 0, 15, 30, 60, 90, 120, 150, and 180 min from the time of ingestion. β -Cell function was assessed using calculated C-peptide area under the curve (AUC_C) and glucose

AUC (AUC_G). Total insulin secretion was calculated as the ratio of AUC_C to AUC_G. Initial insulin release was calculated as C_{0–30} and C_{0–30}/G_{0–30}, and maximal insulin production was calculated as C_{0–max} and C_{0–max}/G_{0–max}. The incremental AUC_C (iAUC_C) and incremental AUC_G (iAUC_G) were calculated as the AUC above baseline (fasting) values. C-peptide was measured using radioimmunoassay (Millipore), HbA_{1c} by high-performance liquid chromatography, and glucose with Yellow Springs Instrument in the Clinical Diabetes Laboratory at UTSW. The laboratory is accredited by the National Glycohemoglobin Standardization Program.

Patients were instructed to return their unused medications at every visit for inventory and estimation of patient compliance. We report the average compliance of all study medications in each group.

Adverse events were documented throughout the study. Weight was assessed at every visit using the same scale. Mild hypoglycemic episodes were defined as symptoms indicative of low blood glucose accompanied by a documented capillary blood glucose value of <70 mg/dL. Severe hypoglycemia was defined as symptoms of hypoglycemia that required assistance from another individual for treatment, regardless of capillary blood glucose level.

Statistical analysis

The sample size was estimated to detect differences between the INS and TOT groups in AUC_C of 240 ng/mL/min, with an estimated SD of 225 ng/mL/min (16). To detect this effect size, completion of 20 patients in each group was needed for power of 90% at $\alpha = 0.05$.

The intention-to-treat analysis is reported (unless otherwise stated), which included all subjects according to their randomization treatment assignment, including those who reached the predefined treatment failure end point and were switched from the TOT to INS group.

AUC was computed using the trapezoidal rule. Biochemical measurements and AUC responses were assessed with mixed-model repeated-measures analysis. Measurements obtained throughout the 42 months of treatment were included in the analysis. The repeated-measures models consisted of a treatment group factor, study time (month) factor, and interaction between group and time, with subject modeled as a random effect. The difference in response between treatment groups was assessed via the interaction effect. Between- and within-group contrasts

were constructed from these models. AUC responses and hypoglycemic event rates were log or rank transformed, respectively, prior to analysis. Comparison of treatment failures rates was made with the log-rank test. Results are presented as mean and SD, unless otherwise specified. A two-sided *P* value <0.05 was considered statistically significant. Statistical analysis was performed with SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS—Sixty-three patients were recruited from November 2003 to June 2005, and 58 completed the 3-month run-in period (29 were randomly assigned to continue insulin plus metformin and 29 were changed to triple oral therapy (Fig. 1). Baseline characteristics of the two groups were similar (Table 1). Completion rates at 3.5 years in the study were 24 of 29 (83%) in the INS group and 21 of 29 (72%) in the TOT group. Treatment failure occurred in three (10.3%) patients in the INS group and five (17.2%) patients in the TOT group (*P* = 0.33).

β-Cell function

Results of all the calculated β-cell function indices are shown in Table 1. There

was no significant change over time in β-cell function between or within groups, as calculated by AUC_G, AUC_C, and AUC_C/AUC_G (Fig. 2A, C, and E). There also was no significant change over time or between groups in the following: iAUC_C, iAUC_C/iAUC_G (Fig. 2D and F), baseline-maximum or baseline–30 min ΔC-peptide or ΔC-peptide/Δglucose. There was a significant over-time decrease in iAUC_G (*P* < 0.001) in the TOT group when compared with the INS group, which had no significant change (*P* = 0.009 group-by-time interaction) (Fig. 2B). Likewise, the baseline–30 min and baseline-maximum glucose (*P* = 0.004) were significantly reduced over time in the TOT but not the INS group (*P* = 0.002 and *P* = 0.03, respectively, group-by-time interaction). These findings suggest an overall postprandial glyceemic benefit of triple oral therapy, yet the two groups had very similar glyceemic control and β-cell function.

Glyceemic control

HbA_{1c} was substantially improved in both groups during the 3-month lead-in period (from 10.8 ± 2.6% to 5.9 ± 0.5%) (14). At 3.5 years after randomization HbA_{1c} was

6.35 ± 0.84% INS versus 6.59 ± 1.94% TOT (*P* = 0.54 group by time interaction), and 19/24 (79%) in INS and 17/21 (81%) in TOT met ADA guidelines of HbA_{1c} <7%. The average insulin dose at the time of randomization was 0.63 ± 0.29 units/kg/day while after 42 months it increased to 0.82 ± 0.43 units/kg/day in INS.

Safety and compliance

Most participants in this study were obese at randomization (76%). Weight increased in both groups over time (from 102.2 ± 24.9 to 106.2 ± 31.7 kg in the INS group and from 100.9 ± 23.0 to 110.5 ± 31.8 kg in the TOT group), with no significant difference between groups (*P* = 0.35) (Fig. 3A).

There was a low rate of mild hypoglycemia overall, defined conservatively as any symptoms with a glucose reading <70 mg/dL. Mild hypoglycemia decreased significantly over time (*P* = 0.01) but did not differ significantly between groups (*P* = 0.5). Both groups had on average 1.3 ± 1.5 events in the month after randomization, but this fell rapidly and leveled off by month 9. At the end of the study, there were 0.5 ± 0.8 events per month in the INS group and 0.4 ± 0.5 events per month in the TOT group (Fig. 3B). Of interest, the proportion of patients having any hypoglycemic events remained stable throughout the study (48.5% in the INS group and 52.9% in the TOT group), but the number of events per person decreased over time.

Two participants in the INS group had three events of severe hypoglycemia (all within the first month postrandomization), whereas four participants in the TOT group had six such events (four in the first 2 months postrandomization).

Compliance with all medications at 3.5 years was 87 ± 20% in the INS group and 90 ± 15% in the TOT group.

CONCLUSIONS—Our data show that β-cell function can be preserved for at least 3.5 years after diagnosis of type 2 diabetes when intensive therapy is initiated early in the disease process. This was true regardless of the method used to attain intensive control (insulin-based regimen or a triple combination of oral agents, both after an initial 3-month insulin treatment period). Both treatments led to excellent glyceemic control, were well tolerated, safe, and had good compliance. Failure rate was low in both groups. This confirms previous studies that showed β-cell preservation with short-term intensive insulin

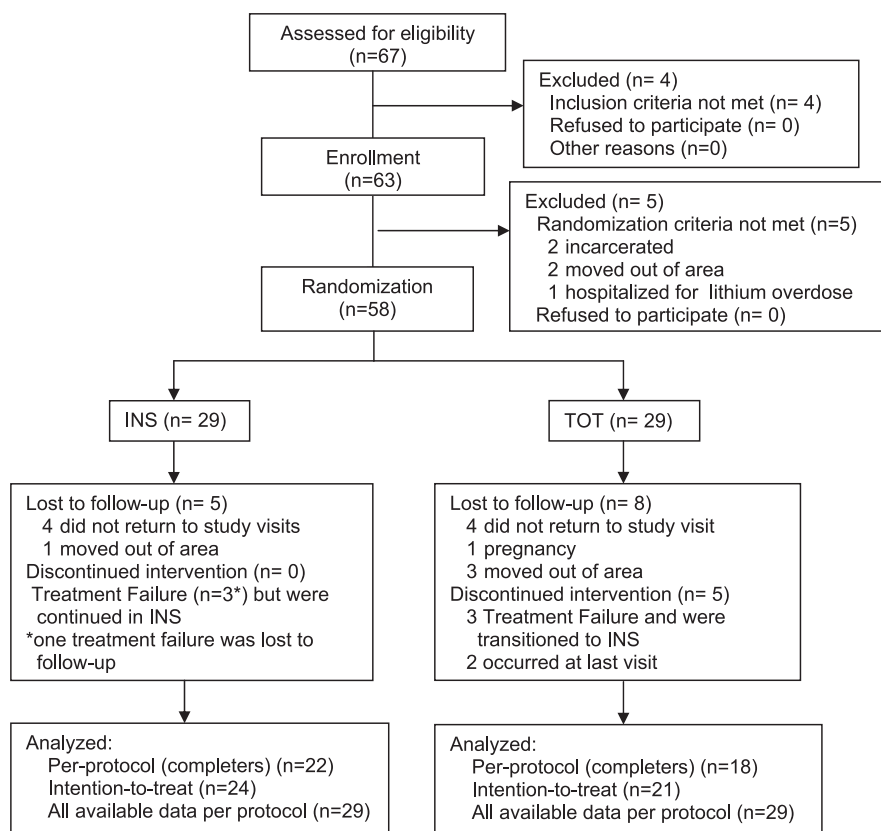


Figure 1—Patient flow chart.

Table 1—Baseline and end of study (42-month) data

	INS		TOT		Interaction P*
	Baseline	42 months	Baseline	42 months	
n	29	24	29	21	
Age (years)	44.8 (9.7)		45.0 (10.7)		
Sex (male/female)	20/9		17/12		
Ethnicity (African American/Hispanic/ white/other) (%)	41/38/20/0		45/38/14/3		
Weight (kg)	102.2 (24.9)	106.2 (31.7)	100.9 (23.0)	110.5 (31.8)	0.35
BMI (kg/m ²)	35.6 (6.6)	37.4 (9.3)	36.5 (8.0)	39.7 (10.6)	0.39
HbA _{1c} (%)	6.0 (0.5)	6.4 (0.8)	5.9 (0.5)	6.6 (1.9)	0.54
Insulin dose (units/kg)	0.63 (0.29)	0.82 (0.43)	0.59 (0.21)	NA	
MMCT					
Glucose _{Fasting} (mg/dL)	111.7 (24.0)	113.3 (34.3)	103.0 (30.9)	126.9 (63.3)	0.09
C-peptide _{Fasting} (ng/mL)	3.4 (1.6)	4.8 (3.4)	2.9 (1.2)	3.7 (1.6)	0.38
AUC _G (mg/dL/min)	29,723 (6,297)	30,185 (8,748)	29,796 (6,925)	32,019 (17,164)	0.52
AUC _C (ng/mL/min)	1,624 (576)	2,084 (927)	1,646 (663)	1,700 (1,017)	0.15
Ratio (AUC _C /AUC _G)	0.058 (0.025)	0.076 (0.042)	0.058 (0.028)	0.064 (0.045)	0.75
iAUC _G (mg/dL/min)	9,619 (3,867)	9,785 (4,854)	11,250 (4,507)	9,665 (7,024)	0.009
iAUC _C (ng/mL/min)	1,016 (460)	1,301 (813)	1,115 (614)	1,160 (814)	0.55
Ratio (iAUC _C /iAUC _G)	0.125 (0.073)	0.159 (0.137)	0.109 (0.068)	0.217 (0.238)	0.10
Glucose _{30 min} (mg/dL)	157.7 (33.5)	156.5 (40.6)	160.5 (47.1)	164.2 (84.6)	0.52
C-peptide _{30 min} (ng/mL)	6.2 (2.8)	8.8 (3.9)	7.0 (3.6)	6.8 (3.6)	0.16
ΔG _{0-30 min} (mg/dL)	46.0 (20.0)	43.1 (16.9)	57.4 (31.6)	37.3 (31.6)	0.002
ΔC _{0-30 min} (ng/mL)	2.8 (2.4)	4.1 (4.0)	4.1 (3.3)	3.1 (2.8)	0.26
Ratio (ΔC/ΔG) _{0-30 min}	0.070 (0.062)	0.100 (0.125)	0.078 (0.068)	0.082 (0.105)	0.58
ΔG _{0-max} (mg/dL)	83.8 (26.8)	80.7 (37.9)	95.7 (34.6)	85.2 (62.5)	0.03
ΔC _{0-max} (ng/mL)	8.8 (4.1)	11.3 (6.8)	9.1 (4.9)	9.5 (7.3)	0.36
Ratio (ΔC/ΔG) _{0-max}	0.116 (0.067)	0.169 (0.136)	0.102 (0.060)	0.160 (0.178)	0.17

Data are means (SD). *Interaction factor (group × time) from repeated-measures analysis of all data from baseline to 42 months.

therapy or oral monotherapy, but most importantly our study shows that an insulin-based regimen or a combination of oral hypoglycemic agents has the potential to change the course of the disease for a more meaningful period of time.

Chen et al. (12) performed a similar study in which 50 patients with newly diagnosed type 2 diabetes were treated in-house with intensive insulin therapy for 10–14 days and then randomly assigned to continue insulin therapy (NPH only) or change to a single oral medication (metformin or a sulfonylurea based on BMI) for 6 months. The oral drugs were titrated up at clinic visits (every 2–4 weeks), and after maximum titration the other drug was added. The study showed that HbA_{1c} was significantly higher in the oral treatment group at 6 months postrandomization (7.5 ± 1.5 vs. 6.33 ± 0.70%). Both groups had improved β-cell function using oral glucose tolerance testing, but significantly more improvement was seen in the insulin therapy group. Unfortunately, the study only analyzed β-cell function in patients

with HbA_{1c} <7% (~90% of the insulin group and 45% of the oral group), which likely excluded patients in whom β-cell function actually declined below baseline, especially in the oral group. Our study showed comparable improvement in glycemic control and β-cell function in both treatment groups. This difference in results could be attributed to initial shorter treatment with insulin at diagnosis (10–14 days vs. 3 months), possibly inducing less recovery of “stunned” β-cells (17), or the stepwise treatment strategy used in the oral group. NPH insulin was titrated up every 3 days based on fasting blood glucose readings, whereas the oral agent was only titrated up or an additional pill added at office visits. This approach illustrates the pitfalls of the currently advocated stepwise titration strategy of oral medications leading to less and slower improvement in hyperglycemia and β-cell recovery.

The ADOPT trial randomly assigned recently diagnosed (<3 years) treatment-naïve patients with diabetes (baseline HbA_{1c} 7.36 ± 0.93%) to monotherapy with

either metformin, glyburide, or rosiglitazone for a median of 4 years (13). Although glycemic control improved within the first 6 months, HbA_{1c} increased over the next 3.5 years, and at 4 years only 40% of rosiglitazone, 36% of metformin, and 26% of glyburide groups had HbA_{1c} <7%. This correlated with β-cell function (assessed by homeostasis model assessment), which also increased in all groups at 6 months but then declined steadily over the remainder of the study, with a greater fall in the group with the highest failure rate (6.1% annual decline in glyburide) and lowest in the group with the lowest failure rate (2% annual decline in rosiglitazone). These results further demonstrate the lack of durability (conferred by β-cell function stabilization or improvement) of single-drug therapy even when initial glycemic control is not far from goal. Of note, rosiglitazone, a peroxisome proliferator-activated receptor-γ agonist, was most durable.

Thiazolidinediones confer a protective effect on β-cells through multiple mechanisms, as they 1) improve insulin sensitivity,

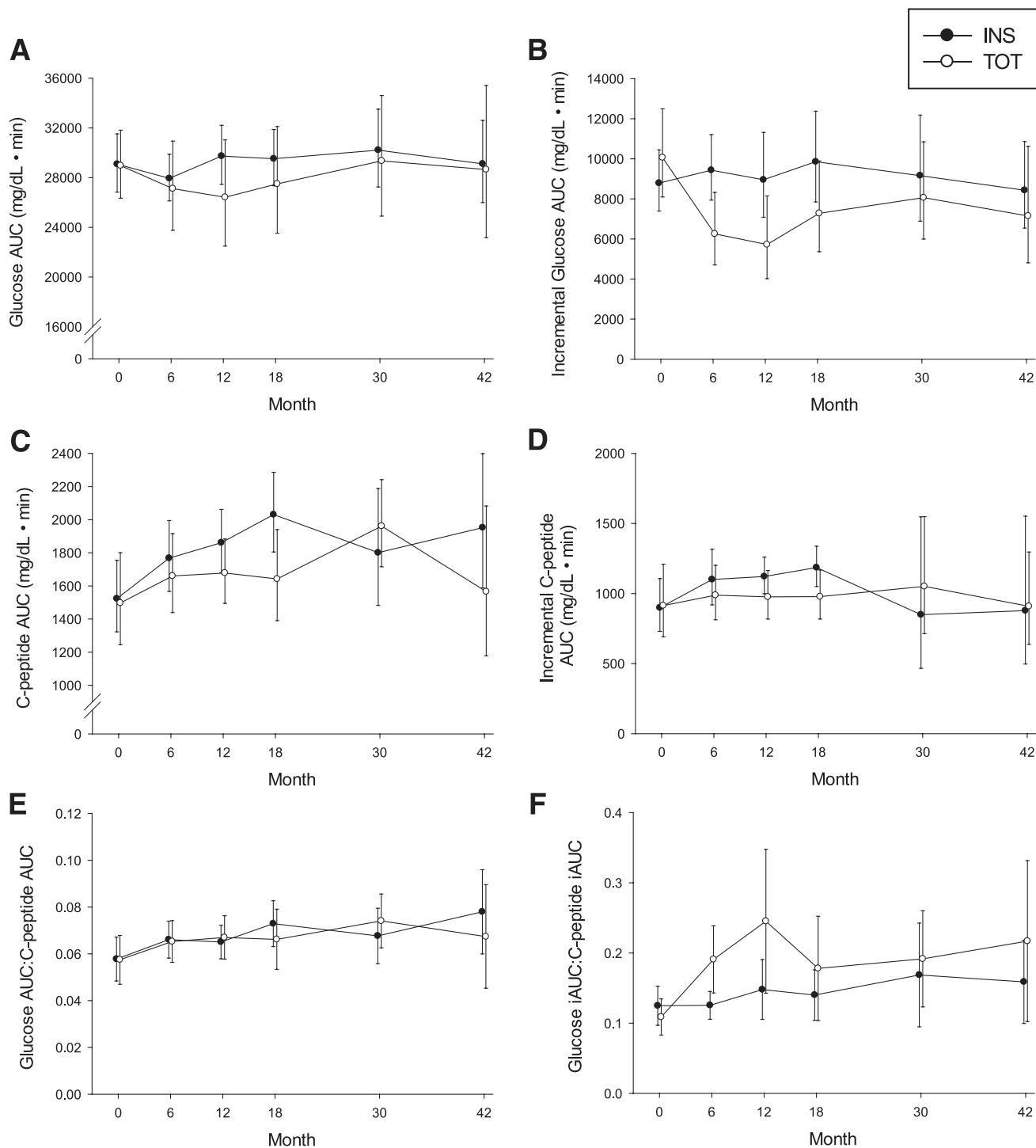


Figure 2—MMCT results. A: AUC_G . B: $iAUC_G$. C: AUC_C . D: $iAUC_C$. E: Ratio of AUC_C to AUC_G . F: Ratio of $iAUC_C$ to $iAUC_G$. Data are means and 95% CIs.

leading to reduced glucotoxicity; 2) increase insulin-sensitive adipocytes promoting fatty acid uptake and storage, leading to reduced lipotoxicity (18); and 3) directly prevent β -cell apoptosis and increase proliferation in animal models (19). They have been shown to improve β -cell function in several clinical trials (20–22)

and may have been a pivotal component in the TOT group in our study. Yet it is clear that not even thiazolidinedione monotherapy is sufficient to alter the natural course of the disease, and a multidrug approach is most appropriate.

Our study was 42 months but involved frequent clinic visits (every 3 months) with

intensive medication titration, plenty of encouragement, and regular compliance checks. This likely improved patient satisfaction and compliance. It also let us diligently collect any and all adverse events. This should not hinder applicability to outpatient clinical treatment as it is well known that type 2 diabetes is a progressive

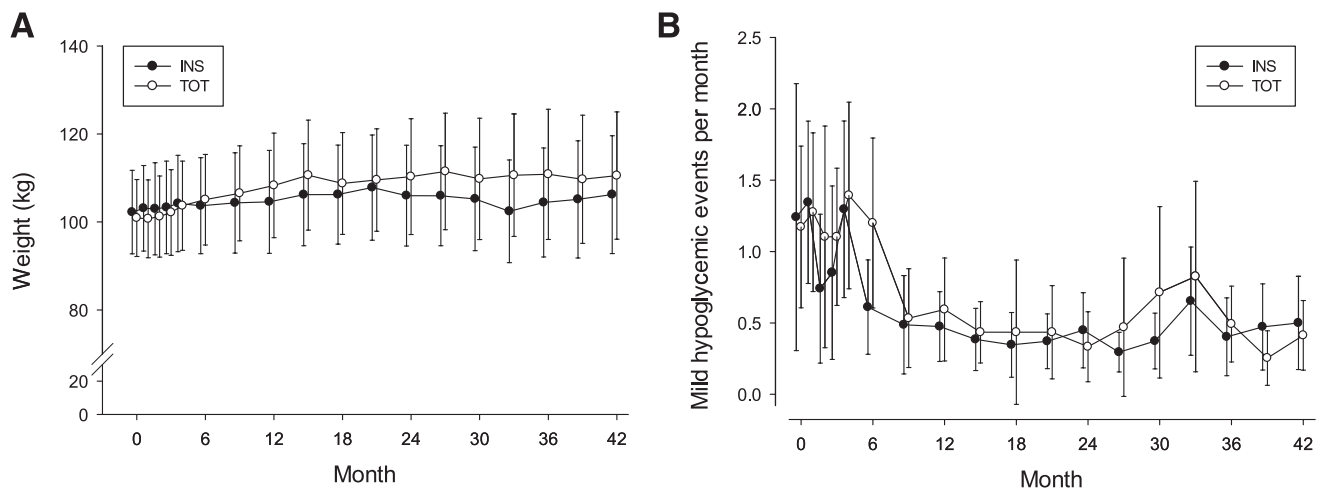


Figure 3—Safety measures. A. Weight. B. Mild hypoglycemic episodes, defined as any symptoms associated with a capillary glucose level of <70 mg/dL. Data are reported as means and 95% CIs.

disease and does require frequent medication titration and a multidisciplinary approach with frequent visits. We also acknowledge that the 3.5 year follow-up in this study, although a lot longer than any previous intervention that achieved β -cell stabilization, is still short when the life-long burden of diabetes is considered. We are continuing to follow-up our study volunteers to assess whether these results persist.

We assessed β -cell function using oral mixed-meal testing, which gives a more comprehensive assessment of β -cell function, taking into account intestinal incretin hormone interactions. In addition, we measured C-peptide to avoid the drawbacks of using insulin concentration: 1) insulin measurement is not simply a function of pancreatic secretion but also depends on clearance, 2) insulin antibodies can develop and interfere with measurement, and 3) the insulin assays can cross-react with the exogenous insulin patients were receiving.

Given the design of the study, we are unable to differentiate whether the β -cell preservation effect was attributed to the initial insulin-based therapy that all patients received in the run-in phase or attributed to ongoing therapy received after randomization. Several studies have shown that short-term insulin treatment in patients with newly diagnosed type 2 diabetes can lead to rapid improvement in β -cell function (8–11) and even β -cell preservation up to 1 year (10,11). Although we have certainly noted a very rapid and impressive improvement in glycemia with this initial insulin treatment (14), we believe that in the absence of continuous intensive therapy this would not have been sustained.

Conversely, we believe that the results of the study might have been quite different in the absence of the run-in period, where all patients were treated with an insulin-based regimen. This study was designed to compare the progression of β -cell dysfunction in patients treated with intensive insulin-based therapy versus intensive oral therapy and had no control group receiving stepwise initiation of either therapy. However, we believe there is well-established evidence that there is progressive loss of β -cell function in patients with type 2 diabetes treated in this manner.

We did observe more variability than anticipated for the primary outcome AUC_C . This certainly limited our power to detect a between-group as well as an over-time difference in the primary outcome. Nevertheless AUC_C seems to have slightly increased overtime, especially in the INS group (Fig. 2C); therefore, our conclusions are conservative and well supported by the data.

The population in our trial is representative of minorities (43% African American and 38% Hispanic), mostly recruited from the county hospital system. This lends additional strength to these findings, as these therapeutic interventions were successfully administered and results attained in a patient population most challenging to treat.

Our study shows that it is possible to preserve β -cell function long after the initial diagnosis of type 2 diabetes if therapy is initiated in a timely and intensive manner. Instead of starting with diet and/or monotherapy followed by stepwise treatment escalation when failure is achieved, patients should be treated with an initial

period of intensive insulin therapy to maximize β -cell recovery and then either continued on an insulin-based regimen or switched to multiple hypoglycemic medications with complementary mechanisms of action. Either of these strategies will stabilize β -cell function and maintain excellent long-term glucose control, a desirable disease-modifying effect. In addition, this can be achieved safely, and we have previously shown (15) that both treatment strategies have high patient satisfaction ratings with improved quality of life.

In conclusion, intensive insulin therapy at the time of diagnosis of type 2 diabetes followed by either an insulin-based regimen or multiple oral hypoglycemic agents preserves both glycemic control and β -cell function for at least 3.5 years with no significant difference in the adverse-effect profile.

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I.L. serves on the Novo Nordisk scientific advisory board. P.R. is an advisor for Amgen and AstraZeneca and is on the Speakers Bureau for Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

L.B.H. was involved in data research and interpretation, manuscript preparation and edits, and reading and approval of the final manuscript. B.A.-H. was involved in the design of the study, data analysis, manuscript preparation and edits, and reading and approval of the final manuscript. P.R. was involved in the design of the study, manuscript edits, and reading and approval of the final manuscript. I.L. contributed to the conception and design of the study,

data collection, management, cleaning and interpretation, manuscript preparation and revision, and provided medical management and counseling to the study participants. I.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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