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Intensive Therapy in Newly Diagnosed Type 2 Diabetes – Results of a 6-Year Randomized Trial:

Beta-Cell Preservation in Type 2 Diabetes

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Abstract

To assess the efficacy of early intensive diabetes therapy with either insulin plus metformin (INS) or triple oral therapy (TOT) with metformin, glyburide, and pioglitazone on glycemic control and beta-cell function.

Fifty-eight treatment-naïve newly-diagnosed patients with type 2 diabetes underwent a 3-month lead-in treatment period with insulin and metformin, then were randomized to INS or TOT for 6 years. Beta-cell function was measured using mixed meal challenge test.

Beta-cell function remained stable throughout the 6-year study in both groups, as measured by the c-peptide area under the curve (AUC) ($p=0.13$), the AUCc-peptide/AUCglucose ($p=0.9$) and by the Disposition Index ($p=0.8$). Excellent glycemic control was maintained in both groups (end-of-study HbA1c $7.3\pm1.7\%$ INS versus $6.4\pm1.4\%$ TOT; $p=0.4$). There were 8 treatment failures (confirmed HbA1c $>8\%$) in INS and 6 in TOT ($p=0.93$). Predictors of treatment failure included

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Disclosures

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higher fasting glucose ($p=0.008$), fasting c-peptide ($p=0.008$), and systolic blood pressure ($p=0.004$), and lower insulin sensitivity ($p=0.04$) at randomization.

Early intensive treatment at the time of type 2 diabetes diagnosis – initial short-term insulin treatment followed by either insulin-based or intensive oral hypoglycemic-based therapy – stabilizes beta-cell function for at least 6 years. Treatment failure was independent of intervention and was associated with worse disease pathology at baseline.

The natural history of type 2 diabetes is hallmarked by progressive loss of beta-cell function coupled with increased insulin resistance. This is thought to be due to the combined toxic effects of hyperglycemia and increased free fatty acids (glucolipotoxicity)¹. The shorter and less severe the glucolipotoxicity insulin, the more beta-cell preservation and/or recovery can be expected. A higher beta-cell function has been associated with improved glycemic control, less treatment burden, and fewer microvascular complications². We hypothesize that early and intensive antihyperglycemic therapy may change the natural course of disease, by preserving beta-cell function.

The Origin Trial explored whether early use of insulin glargine, compared to standard of care treatment, in patients with impaired fasting glucose, impaired glucose tolerance, or newly-diagnosed type 2 diabetes³ can prevent disease progression. In the 1456 patients without diabetes, those who were assigned to insulin glargine were 28% less likely to develop diabetes during the 6.2 years of follow-up, an effect presumed to be due to stabilization/improvement in beta-cell function. While this approach did not show an overall decrease in cardiovascular events during the study follow-up, a proactive treatment approach, very early in the course of the disease, could have longer term impact on the disease course, and thus be superior to the current reactive approach where treatment is only initiated or escalated as the disease worsens.

Short-term (2–3 weeks) intensive insulin treatment has been shown to result in disease remission in some patients, especially those with newly-diagnosed diabetes^{4–6}. Unfortunately this approach alone, without subsequent treatment, is not durable as >50% of patients required additional treatment by one year. Weng et al. compared a short course of oral therapy to insulin therapy in patients with newly diagnosed type 2 diabetes. After normoglycemia was attained, treatment was discontinued and patients followed for one year. Fewer patients reached control (83.5% vs 95–97%) or attained remission at one year (26.7% vs 45–50%) in the oral group⁷, suggesting that initial insulin treatment may have a stronger beta-cell preservation effect, yet still not sufficient to change the course of the disease long-term in the absence of subsequent therapy. Therefore short-term intensive treatment, whether with insulin or oral hypoglycemic agents, in the absence of subsequent maintenance treatment is not sufficient to preserve beta-cell function long term. Chen et al performed a study where both groups received initial insulin therapy followed by randomized to oral therapy or insulin. The insulin group preserved more beta-cell function at 6-months but it is unclear if this was due to the treatment received or the glycemic targets achieved (the oral group had significantly higher HbA1c throughout the study)⁸.

Long-term studies in patients with newly-diagnosed diabetes evaluated diet therapy, monotherapy with metformin, sulfonyureas, or glitazones, but none of these monotherapy interventions were successful in stabilizing the disease process^{9,10} beyond the initial 6–18 months. There are no long-term studies to investigate whether insulin is superior to an intensive oral therapy in preserving beta-cell function, especially when similar glycemic control is maintained between groups.

We evaluated whether short term (3-month) insulin therapy followed by either continued insulin regimen versus a multi-drug oral regimen can achieve and maintain long-term (6-year) glycemic control and preserve beta-cell function. Safety and quality of life parameters were also compared.

Research Design and Methods

We recruited newly-diagnosed treatment-naïve patients with type 2 diabetes from Parkland Memorial Hospital inpatient and outpatient services and accepted self-referrals to the University of Texas Southwestern (UTSW) Clinical Diabetes Research Clinic. The study was approved by the UTSW Institutional Review Board and all patients signed informed consent. Clinical Trials Registration Number: NCT00232583.

Patients were treated with insulin and metformin for three months, and then randomized to treatment with insulin plus metformin (INS) or triple oral therapy (TOT) with metformin, pioglitazone, and glyburide. The results from the first 3-month run-in period, the glycemic control and quality of life at 3 years, and the beta-cell function at 3.5 years were published previously^{11–13}. The current manuscript describes the final study results after 6 years of follow-up, including beta-cell function, glycemic control, safety parameters, quality of life, and analysis of the treatment failure predictors.

Participants/eligibility

Patients were 21 to 70 years old, were diagnosed with type 2 diabetes in the previous 2-months, and were treatment-naïve. Exclusion criteria were published previously and are notable for type 1 diabetes-related antibodies and baseline HbA1C level <7%¹¹.

Randomization/Interventions

All participants were initiated on insulin and metformin for a 3-month lead-in period to attain similar glycemic control and reverse any temporary beta-cell stunning due to glucotoxicity by the time of randomization. NovoLog mix 70/30 by Flexpen and metformin were initiated and titrated based on a previously published algorithm¹². At the end of 3 months patients were assigned (via blocked randomization stratified by African American race and BMI) to continue the same insulin-based therapy (INS group) or switch to triple oral therapy (TOT group) with metformin (1000 mg twice daily), glyburide, and pioglitazone (45 mg daily) as described previously¹³. Insulin and glyburide were titrated throughout the study based on home capillary glucose levels, targeting a fasting glucose of <100 mg/dl and pre-dinner value of <140 mg/dl.

Patients were followed at the Clinical Diabetes Research Center at UTSW monthly initially and then quarterly for a total of 72 months. Treatment failure was a predefined study end point defined as HbA1c >8% confirmed by a second reading and occurring after maximization of the glyburide dose or adequate insulin dose titration. A treatment failure in the TOT group would prompt a group switch (from TOT to INS), while a treatment failure in the INS group would lead to intensification of the insulin regimen (3–4 injections/day). Follow-up after treatment failure continued as scheduled and all analysis were performed according to the original assigned group (intention to treat) even after treatment failure.

Measurements

Glycemic control was evaluated by HbA1c (high-performance liquid chromatography at the Clinical Diabetes Laboratory at UTSW) every 3 months. Lipid profile, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, hemoglobin, hs-CRP (high-sensitivity c-reactive protein), PAI-1 (plasminogen activator inhibitor-1) and fibrinogen were measured twice a year in a commercial laboratory (Quest Diagnostics, Irving, Tx). Evaluation of beta-cell function via mixed meal challenge testing (MMCT) was performed, using high protein Boost concentrate 1gm/kg carbohydrate equivalent, at 0, 6, 12, 18, 30, 42, 54, and 72 months post-randomization. Patients fasted for 12 hrs prior to the test and all anti-diabetic agents were withheld for 24hrs prior to each testing. Glucose and c-peptide were measured at baseline (before the ingestion of the Mixed Meal) and then 7 times over the three-hour test (15, 30, 60, 90, 120, 150, 180 minutes). Glucose was measured using a Yellow Springs Instrument (Yellow Springs, CA) while C-peptide was measured using Radioimmunoassay (Millipore) in the Clinical Diabetes Laboratory at UTSW. Unfortunately the c-peptide specimens from the final (72-month visit) were compromised due to storage failure, therefore these data are missing.

Insulin secretion was estimated using the area under the curve (AUC) for glucose (G) and c-peptide (C) (total, incremental, 0–30 minutes, and 0-maximal production) and then determining ratios (C/G) to estimate insulin production. Insulin sensitivity was calculated using the c-peptide-based Matsuda Index^{14,15}. We used c-peptide instead of insulin levels to eliminate cross contamination with exogenous insulin and insulin antibodies. The calculation was done according to the following formula:

$$\text{Matsuda Index} = \frac{500,000}{\sqrt{[(C_0 \times G_0 \times 333) \times (C_{\text{mean}} \times G_{\text{mean}} \times 333)]}}$$

The disposition index (DI) was measured by multiplying the insulin secretion (AUC_C/AUC_G) by the Matsuda Index¹⁶. The DI reflects the beta-cell function adjusted for total body insulin sensitivity.

Compliance was estimated by medication inventory at each encounter. Weight was measured on the same scale at every visit. Mild hypoglycemic events (symptoms of low blood glucose accompanied by a documented capillary blood glucose value of <70 mg/dl) and severe hypoglycemic events (symptoms of hypoglycemia that required assistance from another individual for treatment, regardless of capillary blood glucose level) were recorded

at each visit. Glucose strips were provided to all patients, and they were asked to check at least 2 times daily throughout the study.

Quality of life was measured using the modified Diabetes Quality of Life Clinical Trial questionnaire at randomization, 6, 18, 42, and 72 months. The details and rationale for choosing this assessment tool were described previously¹³.

Statistical analysis

The original sample size was estimated to detect differences between the INS and TOT groups in the primary outcome of the study, the C-peptide AUC, of 240 ng/ml/min with an estimated standard deviation of 225 ng/ml/min. To detect this effect size, 20 patients in each group was needed for power of 90% at $\alpha=0.05$.

The intention-to-treat analysis is reported which included all subjects according to their randomization treatment assignment, including those who reached the predefined treatment failure endpoint and were switched from TOT to INS.

The AUC from the mixed meal challenge test was computed using the trapezoidal rule. Biochemical measurements, AUC, DI, and insulin sensitivity responses were assessed with mixed linear model repeated measures analysis. Continuous variables that were positively skewed were log transformed prior to analysis. Measurements obtained throughout the 72 months (54 months for c-peptide derived variables) of treatment were included in the analysis. The primary 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. Between and within group contrasts were constructed from these models and the difference in response between treatment groups was assessed via an interaction effect. Hypoglycemic event rates were analyzed with Poisson repeated measures models. To assess longitudinal changes in subjects who reached the treatment failure endpoint, the mixed model analysis was further stratified by treatment failure status and interactions between treatment, failure, and time were assessed. Comparison of treatment failure rates was made with the logrank test. Cox proportional hazards regression models were used to compare characteristics by treatment failure status of the two treatment regimens to account for varying failure times and estimate hazard ratios for prediction of treatment failure. Results are presented as mean and standard deviation unless otherwise specified. A two-sided p-value <0.05 was considered statistically significant. Statistical analysis was performed with SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Sixty-three patients were enrolled in the study from November 2003 to June 2005 and 58 completed the 3-month run-in period: 29 were randomized to continue INS and 29 were changed to TOT (Figure 1). Baseline characteristics of the entire population were: 36% female, over 80% were minorities (43% African-American, 38% Hispanic), 44.9 ± 10.1 years old, and were similar between the two groups (Table 1). Completion rates at 6 years in the study were 19/29 (66%) in the INS group and 16/29 (55%) in the TOT group (see Figure 1 for description of drop-outs in each group).

Glycemic Control

During the initial 3-month lead-in period HbA1c was substantially improved from $10.8 \pm 2.6\%$ to $5.9 \pm 0.5\%$ ($p < 0.0001$)¹², and 100% of patients had a HbA1c $< 7\%$. HbA1c at the final visit in the study was $7.3 \pm 1.7\%$ (median 6.5%) in INS and $6.4 \pm 1.4\%$ (median 5.9%) in TOT (interaction $p = 0.42$) (Figure 2A and Table 1). At 6 years, 63.2% in INS and 68.8% in TOT ($p = 0.73$) met the ADA target of HbA1c $< 7\%$ and the average frequency of HbA1c $< 7\%$ over the entire study was 83.9% for INS and 85.5% for TOT. The total daily dose of insulin increased from 0.63 ± 0.29 units/kg/day at randomization to a final visit dose of 0.92 ± 0.55 units/kg/day in INS ($p = 0.008$ within INS group).

Beta-cell Function and Insulin Sensitivity

Beta-cell function remained stable over time in both groups, as measured by AUC_C ($p = 0.13$ – primary outcome of the study), AUC_C/AUC_G ($p = 0.9$), and DI ($p = 0.8$) (Figure 2D and 2F and Table 1), with no between groups differences. Insulin sensitivity (Matsuda index) decreased comparably in both groups over time ($p = 0.0006$ in INS and $p = 0.02$ in TOT) (Figure 2E and Table 1). The baseline-to-30 minutes ($p = 0.006$) and baseline-maximum ($p = 0.02$) C-peptide responses during MMCT increased significantly more over time in the INS compared with TOT group. There was no difference between groups in terms of glucose total AUC, 0–30 minutes, 0-max, or ratio of c-peptide to glucose (total AUC, 0–30, or 0-max) (Table 1). Fasting insulin levels decreased throughout the study in TOT while remaining stable in INS ($p = 0.0002$), yet the relevance of this measurement in the insulin-treated group is very limited.

Treatment Failure

Treatment failure occurred in 8 patients in the INS group (27.6%) and 6 in the TOT group (20.7%) (logrank $p = 0.93$) at an average of 43.1 ± 18.4 months and 29.5 ± 18.8 months, respectively (Figure 3A). Predictors of treatment failure at the time of randomization included a higher systolic blood pressure ($p = 0.004$), fasting c-peptide ($p = 0.008$), fasting glucose ($p = 0.008$), and a lower insulin sensitivity ($p = 0.04$) (Table 2 and Figure 3B). At the visit prior to failure those who failed had a higher fasting glucose ($p < 0.0001$) and a lower AUC_C/AUC_G ($p = 0.02$) and DI ($p = 0.002$) (Figure 3B). At the final visit into the study, the group who failed had significantly higher insulin doses ($p = 0.007$), HbA1c ($p < 0.0001$), and lower AUC_C/AUC_G ($p = 0.0006$) and DI ($p < 0.0001$). No other significant predictors were identified at the initial visit, randomization, or visit prior to failure, including treatment assignment, race, age, BMI, weight loss prior to diagnosis, initial insulin dose, medication compliance, inflammatory markers, and other MMCT variables not mentioned previously (Table 2).

HbA1c at the time of failure was $9.4 \pm 1.8\%$ in INS and $9.5 \pm 2.1\%$ in TOT. The average HbA1c in the failure group did not improve with increasing doses of insulin in INS (final visit HbA1c $9.1 \pm 1.2\%$), and improved but did not reach goal after change to insulin treatment in TOT (final visit HbA1c $8.2 \pm 1.9\%$) (Figure 4A and 4B). Insulin sensitivity (Matsuda Index) was not different between those who failed and those who did not in INS ($p = 0.37$), but was lower in the TOT failures ($p = 0.0004$) (Figure 4E and 4F); thus failures in TOT group appear to be the non-responders to the insulin sensitizing effect of this regimen.

Absolute insulin production (AUC_c/AUC_g) and beta-cell function (DI) declined faster over the course of the study in those who failed versus those who did not fail treatment in both INS ($p=0.01$) and TOT ($p<0.0001$) (Figures 4C, 4D, 4G, and 4H), despite similar baseline values. Weight did not significantly differ by failure status in either group (Figure 4I and 4J).

At the final visit in the study, the total daily dose of insulin in the INS treatment-failures was 1.3 ± 0.3 units/kg/day ($n=8$) while in the TOT treatment-failures was 1.6 ± 1.0 units/kg/day ($n=6$), both doses being much higher than the average insulin dose at the same time-point in the entire cohort (0.9 units/kg).

Safety

Most subjects (76%) were obese at randomization with an overall average BMI of 36.1 ± 7.3 kg/m². Over the 6 years of follow-up, BMI increased significantly and comparably in both groups (INS $p=0.04$ and TOT $p=0.01$, $p=0.48$ between groups) (Figure 2B and Table 1).

ALT increased significantly in INS ($p=0.007$ between groups). Hemoglobin and creatinine did not differ significantly between study groups (Table 1).

There was an overall low rate of mild hypoglycemia. The rate of hypoglycemia (defined conservatively as a documented capillary blood glucose level <70 mg/dl in the presence of symptoms suggestive of hypoglycemia) decreased rapidly over the first 6 months into the study and remained low thereafter in both groups (from 1.2 ± 2.5 to 0.5 ± 1.0 events/month in INS ($p=0.002$) and 1.2 ± 1.5 to 0.5 ± 0.9 events/month in TOT ($p=0.006$), with no difference between groups over time (Table 1). Severe hypoglycemia was rare, with 3 patients in INS having 4 events (3 within the first month post-randomization) and 4 patients in TOT having 7 events (4 within the first two months post-randomization).

Compliance and Quality of Life

Overall compliance with medications throughout the study was $92.8\pm9.1\%$ in INS and $89.6\pm10.3\%$ in TOT ($p=0.33$) (Figure 2C). Compliance was $>80\%$ in 85.4% of INS and 74.0% of TOT participants. Compliance rate decreased significantly over the course of 6 years in TOT ($p=0.005$), while it remained stable in INS ($p=0.63$).

All 12 domains of the quality of life survey were similar between groups and stable over time, except for current health perceptions which improved more in INS ($p=0.002$). Satisfaction with insulin treatment and willingness to continue insulin injections were both very high (1.4 ± 0.7 and 1.1 ± 0.4 , respectively, on a 1–5 scale where “1=extremely satisfied, extremely willing”) and stable in the INS group throughout the 6 years (Figure 5).

Cardiovascular Risk Markers

There was no significant change over time or between groups in total cholesterol, LDL, or triglycerides (Table 1). HDL increased significantly more in INS ($p=0.002$) though it wasn't different between groups ($p=0.22$). Statin use increased over the study period from 34.5% to 79.3% in INS and from 17.2% to 75.9% in TOT.

Systolic blood pressure did not change over time in either group. Diastolic blood pressure decreased over time in TOT ($p=0.02$) but was not significantly different from INS ($p=0.3$). The number of blood pressure medications increased from 1.0 ± 1.3 to 1.8 ± 1.5 in INS and from 0.7 ± 0.9 to 1.5 ± 1.3 in TOT (Table 1).

There were no significant changes in hsCRP, fibrinogen, or PAI-1 between groups or over time (Table 1).

Conclusions

Beta-cell function, as measured by c-peptide secretion (AUC_c and AUC_C/AUC_G) and by DI, as well as good glycemic control were maintained for 6 years in patients with newly-diagnosed type 2 diabetes. These results were observed regardless of randomization to treatment with insulin and metformin or a triple oral hypoglycemic regimen with metformin, glyburide, and pioglitazone, both regimens instituted after an initial 3-month run-in period with insulin and metformin. Insulin sensitivity, measured by the Matsuda Index, decreased in both groups over the course of the study. Overall these findings suggest that early intervention in the course of the disease, with an intensive regimen which has complementary mechanisms of action, can stabilize the course of the disease and preserve the progressive decline in beta-cell function well-known to occur in this patient population.

Despite the overall beta-cell preservation in both groups, nearly 24% of the cohort experienced treatment failure even in the setting of early and intensive treatment. Since the study was designed to compare two intensive treatment interventions and it did not have a conventionally treated control group (using the traditional step-wise treatment algorithm), it is not possible to conclude whether intensive treatment improves failure rate over the traditional step-wise treatment algorithm. Furthermore, we cannot compare failure rate across different studies as failure criteria vary widely, as is the length of follow-up and the study population. The ADOPT study compared three different monotherapy agents in newly-diagnosed patients with type 2 diabetes⁹. The reported failure rates at 5 years of treatment were 15% with rosiglitazone, 21% with metformin, and 34% with glyburide monotherapy. While these failure rates seem comparable with those seen in our study, the failure definition used in ADOPT was more conservative than ours, defined as fasting plasma glucose of >180 mg/dl on two occasions. Additionally, all treatment groups in this study experienced a gradual decline in beta-cell function, while we observed a stable beta-cell function throughout our follow-up. The TODAY study, which enrolled children with type 2 diabetes (average age 14.0 ± 2.0 years¹⁷), defined treatment failure the same as our study ($HbA1c>8\%$). This endpoint was achieved by 51.7% of patients treated with metformin alone and 38.6% with rosiglitazone plus metformin¹⁸. While our failure rates were lower than those seen in the TODAY study, we cannot infer whether the improved results are due to the more intensive treatment regimen we employed, or due to a more severe disease state in the young patients with type 2 diabetes enrolled in the TODAY study.

We found several patient characteristics that predicted treatment failure. Interestingly, at the initial visit, when patients were universally hyperglycemic and metabolically decompensated, there were no failure predictors. However, after 3-months of intensive

insulin and metformin therapy, when average HbA1c declined from >10% to <6%, there were several predictive variables. The patients who eventually failed had higher systolic blood pressure, fasting glucose (albeit within near-normal range), fasting c-peptide, and lower insulin sensitivity. Therefore these patients, while still well compensated at this time-point, had features of more advanced insulin resistance, which explains the propensity to treatment failure. Patients who failed after randomization to TOT treatment had significantly lower insulin sensitivity compared to those who did not fail (Figure 4F), suggesting that perhaps those who did not respond to the insulin sensitizing effect of pioglitazone were those who failed treatment. This is in contrast to both the TODAY and ADOPT analyses that found lower baseline beta-cell function and higher HbA1c in the patients who failed^{19,20}. The difference in our findings could be explained by the fact that in both ADOPT and TODAY studies baseline beta-cell function was evaluated prior to treatment initiation, while in our study we measured baseline beta-cell function after a 3-months initial treatment with insulin and metformin during which maximal beta-cell recovery occurred. Our patients had much worse metabolic derangements at baseline but any glucolipotoxicity was reversed prior to the randomization, when the first beta-cell function analysis occurred, and perhaps that is why we did not observe lower initial beta-cell function in those who would eventually fail. Furthermore, we believe that the Matsuda index provides a better estimate of insulin sensitivity than the HOMA-IR used in either of these studies, and perhaps a reason why we were able to note insulin resistance as a predictor of treatment failure. At the visit prior (3–6 months) to failure the group who failed had worse fasting glucose, HbA1c, and beta-cell function, these being warnings signs that a failure is impending. The slope of beta-cell function decline in the treatment failure group was much higher compared with the group that did not fail treatment (who had preserved beta-cell throughout the study follow-up) (Figure 4G and H), suggesting that beta-cell decompensation is the event closely preceding the failure event. In summary, our findings suggest that treatment failure occurs in patients who have worse insulin resistance at baseline, which is the first noticeable abnormality occurring months to years prior to failure. Beta-cell decompensation on the other hand occurs in closer proximity to the time of failure and is the final pathophysiologic event leading to the failure.

After failure, despite switch to insulin therapy (in TOT group) or intensification of therapy (in INS group), at the final study visit patients continued to have worse HbA1c, beta-cell function, and insulin sensitivity despite significantly higher doses of insulin. Thus, once patients experience worsening of glycemic control they are unlikely to regain glycemic control and improve beta-cell function. This finding further supports the need to employ all available tools to prevent treatment failure in the first place, as once failure ensues subsequent rescue of glycemic control is unlikely.

Importantly, neither treatment regimen was superior at preserving beta-cell function, preventing decline in insulin sensitivity, or preventing treatment failure. Since the initiation of this study in 2003, the paradigm for diabetes management has shifted with the rise in popularity of glucagon-like peptide-1 (GLP-1) based therapy and the fall from favor of thiazolidinediones (TZDs)²¹. The TZD component of our TOT regimen likely contributed to its success in maintaining glycemic control through its pleiotropic effects on beta-cell function, peripheral insulin sensitivity, and possibly preservation of beta-cell mass²².

Though the insulin sensitivity fell in the TOT group over time, this appears to be primarily occurring in participants who failed therapy (treatment non-responders) (Figure 4F). GLP-1 drugs have been shown to primarily improve beta-cell function (with indirect effects on insulin sensitivity) and are more effective in this regard than TZDs^{23,24}. Incorporating these newer drugs early in treatment could potentially have equal or greater effects in stabilizing the disease process²⁵.

It is also important to note the high acceptance rate of insulin therapy, and the fact that all quality of life parameters were similar regardless of the treatment regimen. These findings confirm that insulin treatment is well accepted by patients even in the very early stages of the disease and does not alter quality of life, therefore it can be safely considered as a viable treatment option at any stage of the disease.

Overall, this study shows that beta-cell function and glycemic control can be maintained at a stable level for at least 6 years after diagnosis if an intensive treatment algorithm is initiated at the time of diagnosis of type 2 diabetes. Treatment failures occurred in patients with lower insulin sensitivity at baseline, and those who experienced greater beta-cell decline over the course of the study. Identification of patients at high risk of treatment failure is important, as rescue therapy is unlikely to be successful once treatment failure ensues.

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Figure 1.

Participant Flowchart. INS- insulin group (treated with insulin+metformin); TOT – triple oral therapy group (treated with metformin+glyburide+pioglitazone); w/o – without.

Figure 2.

Major study outcomes, by treatment group, as measured over the 6-year study follow-up. A: HbA1c. B: BMI. C: Treatment compliance. D: AUC_C/AUC_G from mixed meal challenge test. E: Matsuda Index (measure of insulin sensitivity) derived from mixed meal challenge test. F: Disposition Index (DI) from mixed meal challenge test.

Figure 3.

Assessment of treatment failure over the 6-year study period in the insulin (INS) and triple oral therapy (TOT) groups. A: Kaplan-Meier curve depicting time of treatment regimen failure by group. The numbers represent the number of patients at risk at each timepoint by treatment group. B: Hazard ratios from Cox proportional hazards models for prediction of treatment failure. Hazard ratios represent per 1 unit change in the predictor variable except for age, fasting glucose, and systolic blood pressure (per 10 unit change), HbA1c and DI (per 0.1 unit change), and AUCC/AUCG ratio (per 0.01 unit change).

Figure 4.

Comparison of the changes in HbA1c, AUCc/AUCG, Matsuda index, Disposition Index (DI), and weight over time in the INS group (panels A, C, E, G, I) and TOT group (panels B, D, F, H, J) by failure status,

Figure 5.

Results of modified Diabetes Quality of Life Questionnaire in the insulin treated (INS) and triple oral therapy (TOT) groups. All patients were given the questionnaire to complete at randomization and at 6, 18, 42, and 72 months after randomization. Patients randomly assigned to TOT did not complete the two questions regarding insulin. The results are reported as means $\pm$ SD of the Likert scale score of 1–5. Both groups had similar responses

at month 72 except for current health perception which was better at month 72 in the INS group compared to the TOT group (Group×Month 72 interaction, $p=0.002$).

Table 1

Demographic and biochemical characteristics at randomization and final visit in the study.

	Randomization		Final Visit	
	INS (n=29)	TOT (n=29)	INS (n=29)	TOT (n=29)
Age (years)	44.8 (9.7)	45.0 (10.7)	---	---
Gender (male/female)	20/9	17/12	---	---
Ethnicity (AA/H/W/O)				
(%)	41 / 38 / 21 / 0	45 / 38 / 14 / 3	---	---
Compliance (%) *	90.5 (14.1)	95.3 (9.5)	89 (19.4)	86.1 (15.5) ‡
Weight (kg)	102.2 (24.9)	100.9 (23.0)	107.7 (31.3) †	107.9 (31.4) ‡
BMI (kg/m ²)	35.6 (6.6)	36.5 (8.0)	37.5 (9.2) †	39 (10.8) ‡
HbA1c (%)	6.0 (0.5)	5.9 (0.5)	7.3 (1.7) †	6.4 (1.4) ‡
Insulin Dose (units/kg)	0.63 (0.29)	0.59 (0.21)	0.92 (0.55) †	NA
Mild Hypoglycemia (events/month)	1.2 (2.5)	1.2 (1.5)	0.5 (1.0) †	0.5 (0.9) ‡
Total Cholesterol (mg/dl)	169.6 (38.5)	171.2 (32.4)	163 (36.5)	184.1 (55)
LDL (mg/dl)	96.9 (33.7)	101.6 (29.8)	87.2 (34.1)	98.6 (35.6)
HDL (mg/dl)	41.3 (9.6)	42.3 (10.8)	46.7 (15.7) †	45.3 (9.7)
Triglycerides (mg/dl)	120 (97)	112 (65)	128 (78)	127 (88)
Lipid Medication (%)	34.5	17.2	79.3	75.9
SBP (mmHg)	125.6 (15.8)	122.5 (13.6)	128 (19.5)	125.9 (16.9)
DBP (mmHg)	76.7 (10.4)	78.3 (9.7)	78 (14.5)	75.9 (9.1) ‡
Number of BP meds	1.0 (1.3)	0.7 (0.9)	1.8 (1.5)	1.5 (1.3)
Creatinine (mg/dl)	0.92 (0.23)	0.91 (0.24)	0.89 (0.21)	0.98 (0.52)
Hemoglobin (g/dl)	14.0 (1.3)	14.2 (1.8)	14.1 (1.3)	13.7 (2.0)
ALT (U/L) *	21.8 (9.0)	21.0 (10.1)	33.8 (28.9) †	17.4 (9.9)
AST (U/L)	19.0 (8.3)	18.8 (9.5)	29.3 (28.4) †	17.2 (5.2)
hsCRP (mg/L)	6.3 (8.8)	6.9 (7.7)	5.4 (8.2)	6.1 (8.9)
Fibrinogen (mg/dl)	384.0 (80.2)	399.0 (82.6)	350.6 (75.2)	395.4 (98.5)
PAI-1 (IU/L)	18.8 (14.8)	13.9 (11.7)	20 (15.1)	16.7 (18)
MMCT:				
Fasting Glucose (mg/dl)	111.6 (24.7)	101.8 (19.1)	154.7 (84.9) †	118.7 (59.9)
Fasting Insulin (uIU/ml) *	19.4 (17.2)	22.8 (22.0)	27.3 (20.9)	14.5 (21.0) ‡
AUC _G (mg/dl/min)	29723 (6297)	29819 (6905)	32596 (8411)	30414 (14119)
AUC _C (ng/ml/min)	1624 (576)	1646 (663)	2096 (795) †	1725 (618)
Ratio (AUC _C /AUC _G)	0.058 (0.025)	0.057 (0.028)	0.066 (0.025)	0.066 (0.029)
G _{30-0 minutes} (mg/dl)	46.0 (20.0)	54.3 (30.5)	47.6 (17.6)	48.3 (26.3)
C _{30-0 minutes} (ng/ml) *	2.8 (2.4)	4.1 (3.3)	4.9 (3.1) †	4.0 (3.3)
Ratio (C / G) _{30-0 minutes}	0.070 (0.061)	0.080 (0.067)	0.125 (0.132) †	0.112 (0.108)

	Randomization		Final Visit	
	INS (n=29)	TOT (n=29)	INS (n=29)	TOT (n=29)
G max (mg/dl)	195.5 (37.8)	198.8 (50.1)	211.3 (50.6)	200.6 (91.1)
C max (ng/ml) *	12.1 (4.7)	12.1 (5.1)	15.7 (6.7) †	12.5 (4.3)
G _{0-max} (mg/dl)	83.8 (26.8)	92.6 (35.2)	88.4 (33.9)	84.0 (48.3)
C _{0-max} (ng/ml) *	8.8 (4.1)	9.1 (4.9)	11.0 (6.1) †	8.8 (2.9)
Ratio (C/ G) _{0-max}	0.116 (0.067)	0.105 (0.060)	0.142 (0.085)	0.173 (0.193) ‡
Matsuda Index	2.73 (1.40)	3.12 (2.62)	2.11 (1.47) †	2.45 (1.09) ‡
DI (AUC _C /AUC _G)	0.15 (0.07)	0.16 (0.09)	0.12 (0.07)	0.16 (0.09)

Data are mean (SD) except TG is median (IQR).

INS= insulin group, TOT=triple oral therapy group, AA= African American, H= Hispanic, W= White, O= Other, ALT= alanine aminotransferase, AST= aspartate aminotransferase, hsCRP= high-sensitivity C-reactive protein, PAI-1=plasminogen activator inhibitor-1, MMCT= mixed meal challenge test, AUC= area under the curve, G= glucose, C= c-peptide, max= maximum,

* Interaction factor (Group × Time) from repeated measures analysis of all measurements from randomization to year 6, p<0.05.

† Change in INS group over time p<0.05.

‡ Change in TOT group over time p<0.05.

Table 2

Study participant characteristics by treatment regimen and failure status at A. initial visit, B. randomization visit, C. visit prior to failure; D. last visit in the study.

	Insulin-Based Regimen (INS)		Triple Oral Therapy Regimen (TOT)		* p-value Non-Failure versus Failure
	Non-Failure (n=21)	Failure (n=8)	Non-Failure (n=23)	Failure (n=6)	
A. Initial visit (enrollment):					
Age at diagnosis (years)	45.9 (10.1)	41.8 (8.4)	45.0 (11.3)	45.2 (8.8)	0.11
Gender (male/female)	13/8	7/1	13/10	4/2	0.35
Ethnicity (AA/H/W/O) %	43/33/24/0	37.5/50/12.5/0	52/35/9/4	17/50/33/0	0.25
BMI (kg/m2)	34.8 (4.1)	36.5 (10.4)	36.0 (8.1)	36.8 (9.3)	0.25
Weight loss prior (kg)	7.6 (8.5)	7.1 (7.5)	5.2 (6.2)	13.2 (16.4)	0.18
SBP (mmHg)	125.4 (18.1)	119.9 (23.4)	120.6 (16.9)	132.3 (27.9)	0.42
HbA1c (%)	11.1 (2.7)	10.9 (2.2)	10.6 (2.5)	10.5 (3.3)	0.72
Fasting Glucose (mg/dl)	152.1 (69.2)	142.9 (79.2)	127.8 (49.9)	227.7 (128.5)	0.07
hsCRP (mg/L)	8.4 (9.9)	5.2 (7.0)	10.2 (15.5)	12.9 (12.2)	0.94
B. Randomization Visit:					
Insulin Dose (units/kg)	0.65 (0.32)	0.59 (0.19)	0.60 (0.19)	0.55 (0.28)	0.82
Treatment Compliance (%)	92.6 (12.5)	85.1 (17.3)	95.3 (10.0)	95.0 (8.5)	0.11
SBP (mmHg)	122.1 (14.0)	134.6 (17.6)	120.2 (11.0)	131.0 (19.4)	0.004
HbA1c (%)	5.9 (0.5)	6.2 (0.5)	5.9 (0.5)	5.9 (0.5)	0.30
Fasting Glucose (mg/dl)	109.0 (24.2)	118.4 (26.6)	97.0 (15.0)	120.0 (23.6)	0.008
Fasting C-peptide (ng/ml)	3.0 (1.5)	4.3 (1.6)	2.8 (1.1)	3.5 (1.1)	0.008
Matsuda Index	2.95 (1.48)	2.17 (1.04)	3.37 (2.87)	2.15 (0.85)	0.04
Ratio (C/ G) _{30-0 minutes}	0.074 (0.061)	0.060 (0.066)	0.093 (0.067)	0.029 (0.034)	0.07
Ratio (AUC _C /AUC _G)	0.054 (0.023)	0.067 (0.028)	0.061 (0.028)	0.045 (0.022)	0.95
DI (AUC _C /AUC _G)	0.15 (0.08)	0.14 (0.06)	0.18 (0.09)	0.10 (0.08)	0.08
C. Study visit prior to failure:					
Insulin Dose (units/kg)	0.8 (0.5)	0.9 (0.2)			0.30
Treatment Compliance (%)	85.5 (21.6)	90.6 (13.7)	87.9 (21.3)	72.0 (25.7)	0.33
SBP (mmHg)	129.6 (14.9)	121.1 (12.9)	123.0 (14.1)	135.7 (15.1)	0.68

	Insulin-Based Regimen (INS)		Triple Oral Therapy Regimen (TOT)		p-value [*] Non-Failure versus Failure
	Non-Failure (n=21)	Failure (n=8)	Non-Failure (n=23)	Failure (n=6)	
HbA1c (%)	6.3 (0.6)	8.3 (0.5)	5.9 (0.7)	7.9 (1.0)	<0.0001
Fasting glucose (mg/dl)	121.1 (39.1)	157.6 (65.3)	97.9 (21.0)	248.0 (107.5)	<0.0001
Fasting C-peptide (ng/ml)	4.6 (2.7)	4.8 (3.1)	3.8 (1.7)	5.4 (2.5)	0.31
Matsuda Index	2.25 (1.31)	1.99 (1.26)	2.61 (1.12)	1.39 (0.69)	0.08
Ratio (C/ G) _{30-0 minutes}	0.141 (0.145)	0.059 (0.034)	0.125 (0.114)	0.074 (0.044)	0.11
Ratio (AUC _C /AUC _G)	0.076 (0.027)	0.052 (0.017)	0.073 (0.026)	0.054 (0.036)	0.02
DI (AUC _C /AUC _G)	0.15 (0.06)	0.10 (0.07)	0.18 (0.08)	0.06 (0.04)	0.002
D. At Final Visit:					
					p-value [†] Failure as Main Effect
BMI (kg/m ²)	36.0 (5.3)	41.4 (15.3)	38.7 (11.1)	40.2 (10.4)	0.19
Insulin Dose (units/kg)	0.8 (0.5)	1.3 (0.3)	NA	1.6 (1.0)	0.007
HbA1c (%)	6.5 (1.3)	9.2 (1.2)	5.9 (0.6)	8.2 (1.9)	<0.0001
Fasting glucose (mg/dl)	142.7 (92.2)	186.3 (54.4)	101.5 (23.9)	184.5 (104.8)	0.0003
Fasting C-peptide (ng/ml)	4.7 (2.7)	4.7 (3.0)	3.6 (1.6)	4.1 (3.6)	0.78
Matsuda Index	2.13 (1.31)	2.05 (1.91)	2.67 (1.11)	1.61 (0.47)	0.05
Ratio (C/ G) _{0-30 minutes}	0.143 (0.143)	0.076 (0.068)	0.125 (0.114)	0.049 (0.040)	0.07
Ratio (AUC _C /AUC _G)	0.075 (0.023)	0.048 (0.023)	0.071 (0.025)	0.037 (0.031)	0.0006
DI (AUC _C /AUC _G)	0.14 (0.06)	0.08 (0.07)	0.18 (0.08)	0.05 (0.02)	<0.0001

All values reported as mean (SD).

AA= African American, H= Hispanic, W= White, O= Other, MMCT= mixed meal challenge test, AUC= area under the curve, G= glucose, C= c-peptide, I= incremental, DI=Disposition Index.

^{*} p-values are from Cox regression models to account for varying failure times;

[†] p-values are for mixed model repeated measures with failure as main effect.