

Insulin-Based Versus Triple Oral Therapy for Newly Diagnosed Type 2 Diabetes

Which is better?

ILDIKO LINGVAY, MD, MPH, MSCS¹
JAIME L. LEGENDRE, BS¹
POLINA F. KALOYANOVA, MD¹

SONG ZHANG, PHD²
BEVERLEY ADAMS-HUET, MS^{1,2}
PHILIP RASKIN, MD¹

OBJECTIVE — Early use of insulin after diagnosis of type 2 diabetes is met with resistance because of associated weight gain, hypoglycemia, and fear of decreased compliance and quality of life (QoL).

RESEARCH DESIGN AND METHODS — In treatment-naïve patients with newly diagnosed type 2 diabetes, insulin and metformin were initiated for a 3-month lead-in period, then patients were randomly assigned to insulin and metformin (insulin group) or metformin, pioglitazone, and glyburide (oral group) for 36 months. Hypoglycemic events, compliance, A1C, weight, QoL, and treatment satisfaction were assessed.

RESULTS — Of 29 patients randomly assigned into each group, 83% (insulin group) and 72% (oral group) completed this 3-year study. At study completion, A1C was $6.1 \pm 0.6\%$ (insulin group) versus $6.0 \pm 0.8\%$ (oral group). Weight increased similarly in both groups ($P = 0.09$) by 4.47 kg (95% CI 0.89–8.04 kg) (insulin group) and 7.15 kg (95% CI 4.18–10.13 kg) (oral group). Hypoglycemic events did not differ between groups (mild 0.51 event/person-month in the insulin group vs. 0.68 event/person-month in the oral group, $P = 0.18$ and severe 0.04 event/person-year in the insulin group vs. 0.09 event/person-year in the oral group, $P = 0.53$). Compliance, QoL, and treatment satisfaction were similar between groups, with 100% of patients randomly assigned to insulin willing to continue such treatment.

CONCLUSIONS — When compared with a clinically equivalent treatment regimen, insulin-based therapy is effective and did not cause greater weight gain or hypoglycemia nor decrease compliance, treatment satisfaction, or QoL. Insulin is safe, well-accepted, and effective for ongoing treatment of patients with newly diagnosed type 2 diabetes.

Diabetes Care 32:1789–1795, 2009

Type 2 diabetes is characterized by a progressive loss of β -cell function that results in deterioration of glucose control, which increases the incidence of diabetes-related complications. There are substantial data associating chronic hyperglycemia with long-term micro- and macrovascular complications (1–4), supporting the need for stringent glycemic control. Chronic hyperglycemia is thought to contribute to pancreatic β -cell dysfunction and loss of insulin se-

cretory capacity by exerting a glucotoxic effect (5) and possibly exhaustion from the increased demand (6). This self-perpetuating cycle leads to progressive and often profound insulin deficiency, and such patients ultimately require insulin to maintain their A1C level at goal. In the UK Prospective Diabetes Study, only 9% of patients randomized to therapy with diet alone had A1C level of $<7.0\%$ at 9 years follow-up (7). In that same cohort, 53% of patients receiving sulfonylurea

therapy required insulin therapy within 6 years (8).

Insulin is the most effective hypoglycemic agent in our treatment armamentarium and is now recommended by the American Diabetes Association (ADA) guidelines (9) as the second agent added after metformin. Insulin is also thought to protect β -cell function decline (10), therefore exerting a “disease-modifying” effect. Yet there is resistance to insulin initiation among physicians and patients alike, not only as an early treatment option but also when oral hypoglycemic agents fail to control glucose levels (11). Some commonly cited barriers to insulin initiation are patient fear of disease progression and needle anxiety, as well as patient and provider fears of weight gain and hypoglycemic episodes (12). For these reasons, insulin has traditionally been viewed as a last resort for patients who fail to maintain glycemic control with diet and oral hypoglycemic drugs.

However, previous studies have shown comparable weight gain, edema, and lipid changes in a comparison of insulin glargine or rosiglitazone added to a combination of sulfonylurea and metformin therapy. Insulin therapy was more cost-effective and produced greater reductions in A1C, when the baseline A1C was $>9.5\%$ (13). When an insulin and metformin treatment regimen was compared with addition of a third oral hypoglycemic agent after failure of two oral agents, patients with triple oral therapy were less likely to complete the regimen due to lack of efficacy or intolerable side effects (14). Studies suggest that short-term treatment with insulin after diagnosis (15) or at time of “secondary drug failure” (16) improves β -cell function and metabolic control. To evaluate the feasibility of an insulin-based regimen as first-line treatment for type 2 diabetes we compared compliance, satisfaction, quality of life (QoL), effectiveness, and safety in patients with newly diagnosed type 2 diabetes randomly assigned to triple oral hypoglycemic therapy or an insulin-based regimen.

From the ¹Department of Internal Medicine, Division of Endocrinology, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas; and the ²Department of Clinical Sciences, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas.

Corresponding author: Ildiko Lingvay, ildiko.lingvay@utsouthwestern.edu.

Received 3 April 2009 and accepted 29 June 2009.

Published ahead of print at <http://care.diabetesjournals.org> on 10 July 2009. DOI: 10.2337/dc09-0653.

Clinical trial reg. no. NCT00232583, clinicaltrials.gov.

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RESEARCH DESIGN AND METHODS

Patients between the ages of 21 and 70 years, with the diagnosis of type 2 diabetes within the previous 2 months and who were treatment naive were recruited from Parkland Memorial Hospital inpatient and outpatient services or by self-referral to the Clinical Diabetes Research Clinic at University of Texas Southwestern. Patients with type 1 diabetes-related antibodies, a baseline A1C level <7%, an elevated serum creatinine level, a clinical history of heart failure, a history of lactic acidosis, untreated proliferative diabetic retinopathy, any life-threatening conditions, or use of more than two alcoholic drinks/day or illicit drug use within the 6 months before enrollment were excluded. Women who were pregnant or desired to become pregnant were not enrolled. The study was approved by the institutional review board of the University of Texas Southwestern, and written informed consent was obtained from all subjects preceding the start of the study.

This was an open-label randomized trial comparing triple oral therapy with an insulin plus metformin regimen. After enrollment, insulin and metformin were initiated in all patients for a 3-month lead-in treatment period. This lead-in period had a dual purpose: 1) to homogenize the glycemic control of the study population at the time of randomization; and 2) to expose all subjects to an insulin-based treatment regimen that would serve as a real-life comparison for treatment satisfaction and lifestyle impact assessment after randomization.

Diabetes education and nutritional counseling were provided to all patients at enrollment in the study and reinforced at the time of randomization. Upon enrollment, treatment was started with 0.2 unit \cdot kg⁻¹ \cdot 24 h⁻¹ of Insulin NovoLog Mix 70/30 with Flex Pen delivery, divided into two equal doses to be injected immediately before breakfast and supper. Metformin was started at a dose of 500 mg/day and increased weekly by increments of 500 mg/day to a goal dose of 1,000 mg twice daily. Results of this study period were published previously (17).

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, block randomization scheme programmed by the biostatistician (B.A.H.) using SAS Proc Plan software. The randomization

was stratified by race (African American or non-African American) and BMI (<35 kg/m² or \geq 35 kg/m²), generating four blocked, randomized lists of treatment assignments, one for each stratum. The principal investigator assigned treatment sequentially from these randomized lists as the participant reached the randomization visit.

Patients randomly assigned to triple oral therapy continued metformin 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 targeting 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 Clinic at University of Texas Southwestern monthly for the first 4 months, at 6 months after randomization, and every 3 months thereafter for a total of 36 months. “Treatment failure,” a predefined study end point, was defined as A1C >8% and confirmed by a second reading, occurring after maximization of the glyburide dose or adequate insulin dose adjustments. Volunteers randomly assigned to the triple oral 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

A1C was performed at each visit, using high-performance liquid chromatography in the Clinical Diabetes Laboratory at University of Texas Southwestern. Routine chemistry studies, hematology, and a lipid panel were performed by a commercial laboratory (Quest Diagnostics, Irving, TX).

Weight, blood pressure, hypoglycemic events, and compliance were assessed at every visit. Mild hypoglycemic episodes were defined as symptoms indicating 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. Patients were instructed to return their unused medications at every visit for inventory and estimation of patient compliance. We reported the average compliance of all study medications in each group.

QoL was measured at randomization and also 6 and 18 months later using the modified Diabetes Quality of Life Clinical Trial Questionnaire (supplementary material available in an online appendix at <http://care.diabetesjournals.org/cgi/content/full/dc09-0653/DC1>). This questionnaire addresses several areas with respect to diabetes QoL: satisfaction with treatment, impact of treatment, worry about future effects of diabetes, and worry about social issues (18), in addition to a hypoglycemia worry scale, a lifestyle flexibility scale, and five separate questions concerning the patient's treatment satisfaction with insulin and perception of their own health (19). Answers are in the form of a Likert scale score of 1–5, with a lower score demonstrating greater impact, worry, or satisfaction. For patients randomly assigned to triple oral therapy, questions regarding treatment satisfaction with insulin were omitted. For each subscale, the mean of individual item scores was reported. This questionnaire was chosen because it addresses illness-specific issues, as well as insulin treatment issues (20) to best identify excess disease burden due to insulin treatment.

Statistical analysis

For continuous variables, we computed means \pm SD and 95% CI. For categorical variables, we computed percentages. To compare weight gain and A1C control in the presence of missing data due to loss of follow-up or treatment failure, we adopted two strategies. The first strategy was to estimate the slope of the treatment effects using a linear mixed model, with random effects accounting for the correlation among multiple observations from each subject. Then we compared treatment effects based on slope estimation. For this strategy we used all available observations. The second strategy was to use a *t* test based on complete data from subjects who finished the study (“completers” analysis). Mild and severe hypoglycemic event rates were compared among groups with Poisson regression models using a general estimating equations approach to incorporate the re-

Table 1—Baseline characteristics of the study population at randomization

	Insulin-treated group	Triple oral group
Age (years)	44.75 ± 9.7	45.00 ± 10.7
Sex (male/female)	20/9	17/12
Ethnicity		
African American	12 (41)	13 (45)
White	6 (20)	4 (14)
Hispanic	11 (38)	11 (38)
Other	0 (0)	1 (3)
Weight (kg)	102 ± 25	101 ± 23
BMI (kg/m ²)	35.6 ± 6.6	36.5 ± 7.0
Systolic blood pressure (mmHg)	125 ± 15.8	123 ± 13.6
Diastolic blood pressure (mmHg)	76 ± 10.4	78 ± 9.7
A1C (%)	6.0 ± 0.5	5.9 ± 0.5
Fasting glucose (mg/dl)	112 ± 24.7	102 ± 19.1
Fasting insulin (μU/ml)	25 ± 35.9	23 ± 22.0
Total cholesterol (mg/dl)	170 ± 38.5	171 ± 32.4
LDL cholesterol (mg/dl)	97 ± 33.7	102 ± 29.8
HDL cholesterol (mg/dl)	41 ± 9.6	42 ± 10.8
Triglycerides (mg/dl)	172 ± 159.3	136 ± 73.0

Data are means ± SD or n (%).

peated measurements. Responses to the QoL questionnaire at 0, 6, and 18 months were compared between and within groups as repeated measures using mixed models. Statistical significance was declared at 5%.

As specified a priori in the protocol, data collected after treatment failure were not included in the per-protocol analysis described above. To confirm our results, we also performed an intention-to-treat analysis, in which all data were analyzed as randomized. All results presented below are consistent with those obtained under the intention-to-treat analysis.

RESULTS— Fifty-eight patients were randomly assigned at the end of the 3-month run-in period: 29 continued insulin-based treatment and 29 began triple oral therapy. The baseline characteristics of these two groups are described in Table 1. Volunteers were recruited between November 2003 and June 2005 with follow-up through September 2008. The completion rate of this 3-year study was 83% (24 of 29) in the insulin-treated group and 72% (21 of 29) in the triple oral group (supplementary figure, available in an online appendix). Reasons for dropout were as follows: insulin group, four volunteers were lost to follow-up and one volunteer moved out of town; oral hypoglycemic group, four volunteers were lost to follow-up, three volunteers moved out of town, and one volunteer

became pregnant (delivered a healthy infant).

Glycemic control

A1C improved from 10.8 to 5.9% during the 3-month lead-in period (17). This excellent degree of glycemic control was maintained throughout the 3-year study follow-up (Fig. 1A). Based on per-protocol analysis of the participants who finished the study, at completion, A1C in the insulin-treated group was 6.1 ± 0.6 versus 6.0 ± 0.8% in the triple oral group ($P = 0.26$). The linear mixed model did not show a significant difference in treatment effects between the two groups either ($P = 0.41$). The percentage of patients meeting the ADA guideline treatment target of A1C ≤ 7.0% was 100% in both groups at baseline; 92% (22 of 24) of patients in the insulin group and 76% (16 of 21) of patients in the triple oral group met that guideline at the end of 36 months. The average insulin dose at the time of randomization was 64 ± 31 units (0.63 ± 0.29 units/kg); at the end of the follow-up, the insulin dose in the insulin-treated group increased to 80 ± 61 units (0.75 ± 0.40 units/kg).

Three patients in each group reached the “treatment failure” end point. These failures occurred earlier in the triple oral group (at 9, 10, and 12 months after randomization) than in the insulin group (at 18, 21, and 27 months after randomization).

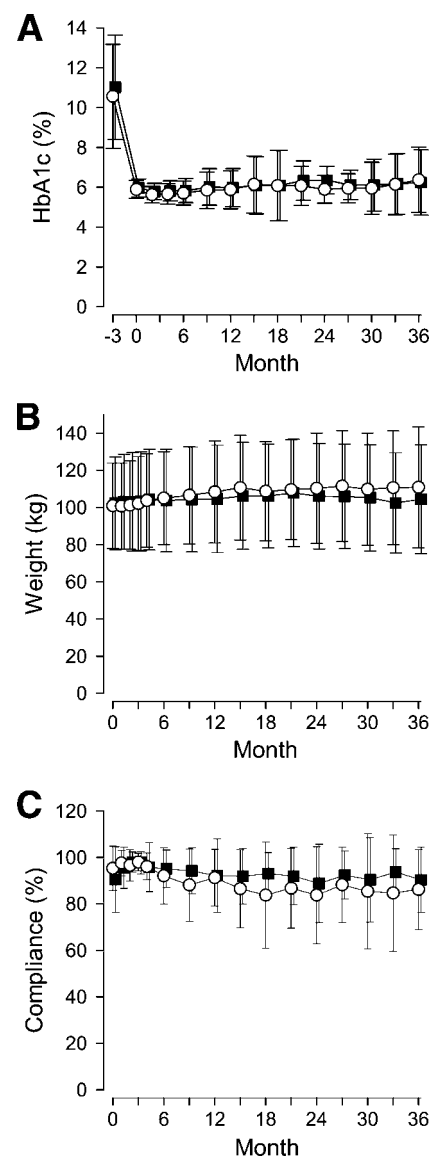


Figure 1—A1C (A), weight (B), and compliance (C) of the insulin treatment group (■) and the triple oral group (○) during the 36-month study. The results are reported as means ± SD.

Safety

The overall number of hypoglycemic events was low throughout the study, despite the use of a conservative definition for hypoglycemia. The insulin group had 0.51 mild hypoglycemia events/person-month and the triple oral group had 0.68 event/person-month ($P = 0.18$). The insulin group averaged 0.04 severe hypoglycemic event/person-year, and the triple oral group averaged 0.09 event/person-year ($P = 0.53$). Overall, 55 of 58 participants had at least one episode of hypoglycemia.

More than 76% of our study population was obese at randomization. “Com-

pleters-only” analysis showed that the triple oral group had a significantly greater weight gain than the insulin group: 10.10 kg (95% CI 4.46–15.74) versus 3.36 kg (–0.47 to 7.20) ($P = 0.04$). The linear mixed model, however, did not detect a significant difference in weight gain between two groups. The estimated weight gain at study completion was 4.47 kg (0.89–8.04 kg) in the insulin group and 7.15 kg (4.18–10.13 kg) in the triple oral group ($P = 0.09$). Neither result supports the claim that insulin therapy leads to a greater weight gain. Both groups gained weight, but although the weight gain persisted over time in the group treated with oral hypoglycemic agents, the weight gain in the insulin-treated group leveled off after 18 months and even regressed toward the baseline (Fig. 1B).

Two patients experienced serious adverse reactions to pioglitazone (diuretic-resistant severe pedal edema and heart failure), which required discontinuation of the medication. The most common treatment-related side effects were gastrointestinal in nature, occurred equally in both groups, and were related to use of metformin (~5% of patients). None were severe enough to require study drug discontinuation.

Compliance, satisfaction, and quality of life

Compliance with study medications was high throughout the trial: 93% in the insulin-treated group and 90% in the triple oral group (Fig. 1C). There were no between-group differences for any of the 12 QoL domains evaluated (Fig. 2). Both groups showed improvement over time with respect to social worries, but all other domains remained constant through follow-up. All patients randomly assigned to receive insulin reported satisfaction with insulin treatment and willingness to continue insulin at 18 months after randomization.

Metabolic comorbidities

Results of the systolic and diastolic blood pressure and lipid profile components at the time of randomization are presented in Table 1. After 30 months, total cholesterol, LDL, HDL, and triglyceride levels averaged 164 ± 43.7 , 90 ± 39.9 , 45 ± 13.5 , and 139 ± 59.8 mg/dl, respectively, in the insulin group and 172 ± 30.4 , 98 ± 28.6 , 48 ± 13.1 , and 135 ± 75.7 mg/dl, respectively, in the triple oral group. At the end of the study, 91% of

patients in the insulin group required at least one cholesterol-lowering medication, compared with 67% of patients in the triple oral group.

Systolic and diastolic blood pressures at the end of the study averaged 126 ± 13.9 and 79 ± 6.9 mmHg, respectively, in the insulin group and 136 ± 17.0 and 80.8 ± 13.1 mmHg, respectively, in the triple oral group. At the end of the study, 72% of patients in the insulin group required at least one antihypertensive medication, compared with 83% of patients in the oral group.

CONCLUSIONS— Diabetes is characterized by a progressive loss of β -cell function and glycemic control. Poor glycemic control leads to macro- and microvascular complications, identifying a need for effective, simple treatment regimens with high levels of patient compliance. It has been shown previously that an insulin plus metformin regimen is effective and safe as a short-term treatment option to gain rapid glycemic control (17). Our data show that long-term continuation of this regimen is equally effective, safe, and well accepted by patients compared with a combination of three oral hypoglycemic agents.

The progressive nature of type 2 diabetes makes the durability of a treatment regimen of utmost importance in consideration of treatment options. The traditional approach to diabetes treatment calls for addition of subsequent oral agents when A1C is $>8\%$, with insulin being considered the last resort (11). This “treat-to-failure” approach leads to long periods of hyperglycemia preceding any treatment intensification, which contribute to microvascular complications and β -cell glucotoxicity that in turn accelerates treatment failure. Insulin treatment is thought to have a beneficial effect on β -cell function through rest of the β -cell as well as prevention of the toxic effect of hyperglycemia on the β -cell. We designed our study to compare the early and long-term changes in β -cell function in patients with newly diagnosed type 2 diabetes treated with insulin and metformin versus an intensive, commonly used, oral hypoglycemic treatment regimen consisting of metformin, glyburide, and pioglitazone. The most recent ADA consensus statement (9) encourages early use of insulin, whereas commonly used agents such as thiazolidinediones are considered second tier. These guidelines were met with criticism, mostly on the basis that

insulin treatment is associated with hypoglycemia, weight gain, and low treatment satisfaction and compliance. In light of this debate, we report the rate of hypoglycemia, weight gain, treatment satisfaction, compliance, and QoL over 3 years of follow-up in this ongoing randomized clinical trial.

Patients in our study had an average A1C $>10\%$ at enrollment and achieved an A1C reduction of 5% in the 3-month lead-in phase of the study using insulin and metformin. This excellent glycemic control was maintained throughout the 3-year follow-up in both groups, showing that both treatment regimens are effective and durable in patients with newly diagnosed type 2 diabetes. We were surprised to find that after 36 months of treatment there was no difference in A1C between the insulin and triple oral group, as even with pharmacologic treatment there is known progressive deterioration in blood glucose control during the first few years of diagnosis (7,21). Most previous studies used monotherapy or a two-drug combination; thus, three drugs may be more effective than one or two. However, we suspect that the efficacy and durability of triple oral therapy in our study is related to the initial insulin treatment with subsequent reduction in glucotoxicity.

Hypoglycemia and weight gain are the most common treatment-related side effects associated with insulin treatment and are an important consideration when in the choice of a treatment regimen for type 2 diabetes. Overall, the rate of hypoglycemia in this trial was very low, especially considering the level of glycemic control that was achieved. Contrary to what may have been expected, the insulin treatment group had fewer (although not statistically significant) mild and severe hypoglycemic events than the triple oral group, illustrating that an insulin-based regimen can be used to achieve tight glycemic control without fear of excess hypoglycemia. Weight gain, although present in both groups, was less in the insulin group, indicating that weight gain is not accelerated in insulin-treated patients compared with a clinically equivalent oral hypoglycemic treatment regimen.

Insulin has traditionally been viewed as a treatment of last resort because of an undesirable effect on patient QoL and decreased treatment satisfaction, leading to poor compliance. We found that patient compliance was similar in both groups ($>85\%$ compliance with study medica-

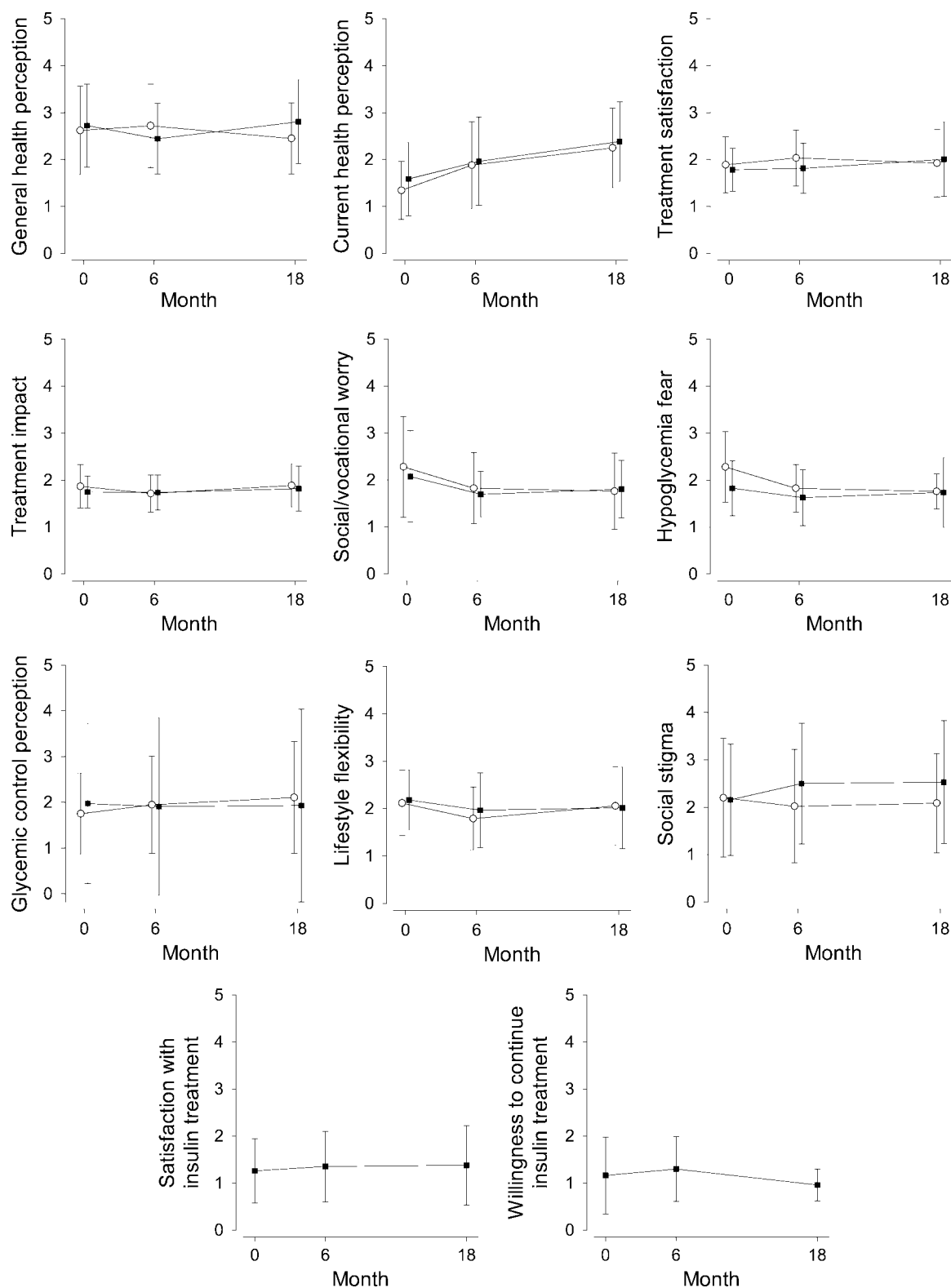


Figure 2—Results of modified Diabetes Quality of Life Questionnaire in the insulin-treated group (■) and triple oral group (○). All patients were given the questionnaire to complete at randomization and at 6 and 18 months after randomization. Patients randomly assigned to oral hypoglycemic agents did 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 improved scores with respect to social worries and a change toward stable current health perception over time. ANOVA, $P < 0.005$.

tion). The overall high compliance may be explained by the clinical study environment, but the similar (or even higher) compliance with insulin treatment compared with the oral agents is due to the use of a simple insulin regimen with an easy-to-use insulin-delivery device. In addition, QoL was not decreased by insulin treatment, and satisfaction with insulin was very high. Overall, these findings refute the myth surrounding poor acceptance of insulin treatment by patients, suggesting that “insulin resistance” lies mostly on the provider side. That is to say, physicians are resistant to the use of insulin!

Given the progressive decline in β -cell function seen in type 2 diabetes, a treatment option that has the potential to preserve β -cell function is optimal. There is mounting evidence that early treatment with insulin may preserve β -cell function in these patients (10,16,22). In light of these findings, in addition to the effectiveness, safety, and acceptability shown in our study, we propose that an insulin-metformin regimen be considered as an initial treatment option in patients with newly diagnosed type 2 diabetes. We continue to follow our volunteers to assess their long-term changes in β -cell function, results that we expect within the next 2 years.

Commonly cited reasons for avoiding insulin treatment in type 2 diabetes include fear of hypoglycemia, weight gain, and a lack of patient acceptance. Our study demonstrated that treatment with insulin and metformin can be used to obtain tight glycemic control in patients with newly diagnosed type 2 diabetes without side effects in excess of those seen with traditional triple oral hypoglycemic therapy. This study provides increasing evidence to persuade physicians that insulin is a viable medical option for patients with type 2 diabetes and should not be viewed as a treatment of last resort.

Acknowledgments—I.L., B.A.H., and S.Z. have received support from National Institutes of Health (NIH) Grant IUL1RR024982. I.L. also received funds from NIH Grant K23RR02447001. J.L.L. was supported by a Doris Duke Charitable Foundation clinical research grant. P.F.K. was supported by T32 DK007307.

I.L., J.L.L., P.F.K., S.Z., and B.A.H. have disclosed no conflict of interest.

P.R. has received investigator-initiated trial grants from Novo Nordisk, research support

from Amylin Pharmaceuticals, Bayhill Therapeutics, Biodel, Boehringer Ingelheim Pharmaceuticals, Elixer Pharmaceuticals, Genex Biotechnology, Hoffmann-La Roche, Johnson & Johnson Pharmaceutical Research & Development, Keryx Biopharmaceuticals, MannKind Corporation, Osiris Therapeutics, Pfizer, Sanofi-aventis, and Tolorex; is an adviser for AstraZeneca, MannKind Corporation, Novo Nordisk, and Quigley Pharma; and is a member of the speaker's bureau for Genex Biotechnology, Merck, and Novo Nordisk. No other potential conflicts of interest relevant to this article were reported.

Parts of this study were presented in abstract form at the 69th Scientific Sessions of the American Diabetes Association, New Orleans, Louisiana, 5–9 June 2009.

We thank Lourdes Pruneda, Christina Garza, and the Clinical Diabetes Research Clinic staff at University of Texas Southwestern Medical Center at Dallas for their extraordinary expertise and dedication to clinical diabetes research.

References

1. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:837–853
2. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto study on optimal diabetes control in type 2 diabetic patients. *Diabetes Care* 2000;23(Suppl. 2):B21–B29
3. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 2003;290:2159–2167
4. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus: the Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993;329:977–986
5. Leahy JL, Bonner-Weir S, Weir GC. β -Cell dysfunction induced by chronic hyperglycemia: current ideas on mechanism of impaired glucose-induced insulin secretion. *Diabetes Care* 1992;15:442–455
6. LeRoith D. β -Cell dysfunction and insulin resistance in type 2 diabetes: role of metabolic and genetic abnormalities. *Am J Med* 2002;113(Suppl. 6A):3S–11S
7. UK Prospective Diabetes Study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. UK Prospective Diabetes Study Group. *Diabetes* 1995;44:1249–1258
8. Wright A, Burden AC, Paisey RB, Cull CA, Holman RR. Sulphonylurea inadequacy: ef-

ficacy of addition of insulin over 6 years in patients with type 2 diabetes in the UK Prospective Diabetes Study (UKPDS 57). *Diabetes Care* 2002;25:330–336

9. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009;32:193–203
10. Alvarsson M, Sundkvist G, Lager I, Hennricsson M, Berntorp K, Fernqvist-Forbes E, Steen L, Westermark G, Westermark P, Orn T, Grill V. Beneficial effects of insulin versus sulphonylurea on insulin secretion and metabolic control in recently diagnosed type 2 diabetic patients. *Diabetes Care* 2003;26:2231–2237
11. Peyrot M, Rubin RR, Lauritzen T, Skovlund SE, Snoek FJ, Matthews DR, Landgraf R, Kleinebreil L. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. *Diabetes Care* 2005;28:2673–2679
12. Korytkowski M. When oral agents fail: practical barriers to starting insulin. *Int J Obes Relat Metab Disord* 2002;26(Suppl. 3):S18–S24
13. Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltis-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulphonylurea plus metformin in insulin-naïve patients. *Diabetes Care* 2006;29:554–559
14. Schwartz S, Sievers R, Strange P, Lyness WH, Hollander P. Insulin 70/30 mix plus metformin versus triple oral therapy in the treatment of type 2 diabetes after failure of two oral drugs: efficacy, safety, and cost analysis. *Diabetes Care* 2003;26:2238–2243
15. Ilkova H, Glaser B, Tunckale A, Bagriacik N, Cerasi E. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. *Diabetes Care* 1997;20:1353–1356
16. Karvestedt L, Andersson G, Efendic S, Grill V. A rapid increase in β -cell function by multiple insulin injections in type 2 diabetic patients is not further enhanced by prolonging treatment. *J Intern Med* 2002;251:307–316
17. Lingvay I, Kaloyanova PF, Adams-Huet B, Salinas K, Raskin P. Insulin as initial therapy in type 2 diabetes: effective, safe, and well accepted. *J Investig Med* 2007;55:62–68
18. Jacobson A. Diabetes quality of life measure. In *Handbook of Psychology and Diabetes: A Guide to Psychological Measurement in Diabetes Research and Practice*. Bradley

- E, Ed. Chur, Switzerland, Harwood Academic Publishers, 1994, p. 65–87
19. Shen W, Kotsanos JG, Huster WJ, Mathias SD, Andrejasich CM, Patrick DL. Development and validation of the Diabetes Quality of Life Clinical Trial Questionnaire. *Med Care* 1999;37:AS45–AS66
 20. Herman WH, Ilag LL, Johnson SL, Martin CL, Sinding J, Al Harthi A, Plunkett CD, LaPorte FB, Burke R, Brown MB, Halter JB, Raskin P. A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. *Diabetes Care* 2005; 28:1568–1573
 21. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, Kravitz BG, Lachin JM, O'Neill MC, Zinman B, Viberti G. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006;355:2427–2443
 22. Li Y, Xu W, Liao Z, Yao B, Chen X, Huang Z, Hu G, Weng J. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of β -cell function. *Diabetes Care* 2004;27:2597–2602