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Insulin-Based versus Triple Oral Therapy for Newly-Diagnosed Type 2 Diabetes: Which is Better?

Running Title: Insulin vs. Oral Therapy in Early Diabetes

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Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org

Objectives: Early use of insulin following diagnosis of type 2 diabetes is met with resistance due to associated weight gain, hypoglycemia, and fear of decreased compliance and quality of life (QoL).

Research Design and Methods: Treatment naïve patients with newly-diagnosed type 2 diabetes were initiated on insulin and metformin for a 3-month lead-in period, then randomized to insulin and metformin (insulin group) or metformin, pioglitazone, and glyburide (orals group) for 36 months. Hypoglycemic events, compliance, HbA1c, weight, QoL, and treatment satisfaction were assessed.

Results: Of 29 patients randomized into each group, 83% (insulin group) and 72% (orals group) completed this 3-year study. At study completion, HbA1c was 6.1±0.6% (insulin group) versus 6.0±0.8% (orals group). Weight increased similarly in both groups (P=0.09), by 4.47kg (95% CI 0.89-8.04kg) (insulin group) and 7.15kg (95% CI 4.18-10.13kg) (orals group). Hypoglycemic events did not differ between groups, both mild (0.51 events/person-month in the insulin group vs. 0.68 events/person-month in the orals group - P=0.18) and severe (0.04 events/person-year in the insulin group vs. 0.09 events/person-year in the orals group - P=0.53). Compliance, QoL, and treatment satisfaction were similar between groups, with 100% of patients randomized to insulin willing to continue such treatment.

Conclusions: When compared with a clinically equivalent treatment regimen, insulin-based therapy is effective, 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.

Clinical Trials Registration # NCT00232583

Type 2 diabetes is characterized by a progressive loss of beta-cell function that results in deterioration of glucose control, which increases the incidence of diabetes related complications. There is 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 beta cell dysfunction and loss of insulin secretory 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 HbA1c level at goal. In the UK Prospective Diabetes Study, only 9% of patients randomized to therapy with diet alone had HbA1c level of less than 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 beta-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 even 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 when comparing insulin glargine or rosiglitazone added to a combination of sulfonylurea and metformin therapy. Insulin therapy was more cost-effective and produced greater reductions in HbA1c, when the baseline HbA1c was greater than 9.5% (13). When an insulin and metformin treatment regimen was compared to 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 following diagnosis (15) or at time of "secondary drug failure" (16) improves beta-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, QoL, effectiveness, and safety in patients with newly-diagnosed type 2 diabetes randomized to triple oral hypoglycemic therapy or an insulin-based regimen.

RESEARCH DESIGN AND METHODS

Study Population: Patients between the ages of 21 and 70 years old, diagnosed with type 2 diabetes within the previous 2 months, and treatment-naïve were recruited from Parkland Memorial Hospital inpatient and outpatient services, or by self-referral to the Clinical Diabetes Research Clinic at UT Southwestern. Patients with type 1 diabetes-related antibodies, a baseline HbA1c level <7%, an elevated serum creatinine level, clinical history of heart failure, history of lactic acidosis, untreated proliferative diabetic retinopathy, any life-threatening conditions, use of >2 alcoholic drinks/day or illicit drug use within the 6 months prior to 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 UT Southwestern, and written informed consent was obtained from all subjects preceding the start of the study.

Study Design and Intervention: This was an open label randomized trial comparing triple oral therapy with an insulin plus metformin regimen. Following enrollment, all patients were initiated on insulin and metformin 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; (2) to expose all subjects to an insulin-based treatment regimen which 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 U/kg/24 h 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 dosage of 1000 mg twice daily. Results of this study period were previously published (17).

After 3 months of treatment, patients were randomized 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 (BAH) using SAS Proc Plan software. The randomization was stratified by race (African-American, non African-American) and BMI (<35 kg/m^2, ≥ 35 kg/m^2), 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 randomized to triple oral therapy continued metformin and started glyburide 1.25 mg twice daily and pioglitazone 15 mg daily. 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 10mg 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 postpandial blood glucose 140mg/dL. All patients were asked to monitor blood glucose at least twice daily, regardless of the group assignment. Initiation and dose adjustment of anti-hypertensive and lipid-lowering agents were allowed if medically necessary. Patients were followed at the Clinical Diabetes Research Clinic at UT 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 pre-defined study end-point, was defined as HbA1c >8%, confirmed by a second reading, occurring after maximizing the glyburide dose or adequate insulin dose adjustments. Volunteers randomized to the triple oral group who reached this end-point were transitioned to insulin and metformin treatment, while those randomized to insulin remained on the same treatment. Follow-up after "treatment failure" continued as scheduled.

Measurements: HbA1c was performed at each visit, using high-performance liquid chromatography in the Clinical Diabetes Laboratory at UT Southwestern. Routine chemistries, hematology, and 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 indicative of low blood glucose accompanied by a documented

capillary blood glucose value of <70mg/dL. Severe hypoglycemia was defined as symptoms of hypoglycemia that required assistance from another person 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.

Quality of life (QoL) was measured using the modified Diabetes QoL Clinical Trial Questionnaire (Online Supplement #1 which is available at http://care.diabetesjournals.org) at randomization, and repeated at 6 months and 18 months after randomization. This questionnaire addresses several areas with respect to diabetes quality of life: 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 1 to 5 Likert scale, with a lower score demonstrating greater impact, worry, or satisfaction. For patients randomized 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), in order to best identify excess disease burden due to insulin treatment.

Statistical Analysis: For continuous variables, we computed means, standard deviations, and 95% confidence intervals. For categorical variables, we computed percentages. To compare weight gain and HbA1c 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. This strategy 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 between groups with Poisson regression models using a general estimating equations (GEE) approach to incorporate the repeated measurements. Responses to the quality of life 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" was not included in the per-protocol analysis described above. To confirm our results, we have also performed an intention-to-treat analysis, where all data was analyzed as randomized. All results presented below are consistent with those obtained under the intention-to-treat analysis.

RESULTS

Fifty-eight patients were randomized 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. Completion rate of this 3-year study was 83% (24/29) in the insulin-treated group and 72% (21/29) in the triple oral group (Consort study flowchart: Online Supplement #2). Reasons for drop-out were as follows: insulin group – 4 volunteers were lost to follow-up, 1 volunteer moved out of town; oral hypoglycemic group - 4 volunteers were lost to follow-up, 3 volunteers moved out of

town, 1 volunteer became pregnant (delivered a healthy infant).

Glycemic Control: HbA1c 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 (Figure 1A). Based on per-protocol analysis of the participants who finished the study, at completion, HbA1c 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 find significant difference in treatment effects between the two groups either (P=0.41). The percentage of patients meeting ADA guideline treatment target of HbA1c ≤7.0% was 100% in both groups at baseline; 92% (22/24) of patients in the insulin group and 76% (16/21) 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±0.29U/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 U/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), compared to the insulin group (at 18, 21, and 27 months after randomization).

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 events/person-month (p=0.18). The insulin group averaged 0.04 severe hypoglycemic events/person-year and the triple oral group averaged 0.09 events/person-year (p=0.53). Overall, 55/58 participants had at least one episode of hypoglycemia.

Over 76% of our study population was obese at randomization. "Completers-only" analysis found that the triple oral group had a significantly greater weight gain than the insulin group, 10.10kg (95% CI 4.46-15.74) versus 3.36kg (95% CI -0.47-7.20) (P=0.04). The linear mixed model, however, did not detect significant difference in weight gain between two groups. The estimated weight gain at study completion was 4.47kg (95% CI 0.89-8.04kg) in the insulin group and 7.15kg (95% CI 4.18-10.13kg) 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 while 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 towards baseline (Figure 1B).

Two patients experienced serious adverse reactions due 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 (approximately 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 (Figure 1C).

There were no between-group differences for any of the 12 QoL domains evaluated (Figure 2). Both groups showed improvement over time with respect to social worries, but all other domains remained constant through follow-up. All patients randomized 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 triglycerides averaged 164±43.7mg/dL, 90±39.9mg/dL, 45±13.5mg/dL and 139±59.8mg/dL in the insulin group and 172±30.4mg/dL, 98±28.6mg/dL, 48±13.1mg/dL and 135±75.7mg/dL in the triple oral group. At the end of the study, 91% of patients in the insulin group required at least 1 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±13.9mmHg and 79±6.9mmHg in the insulin group and 136±17.0mmHg and 80.8±13.1mmHg in the triple oral group. At the end of the study, 72% of patients in the insulin group required at least 1 anti-hypertensive medication, compared with 83% of patients in the oral group.

CONCLUSIONS

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

The progressive nature of type 2 diabetes makes the durability of a treatment regimen of utmost importance when considering treatment options. The traditional approach to diabetes treatment calls for addition of subsequent oral agents when HbA1c is above 8%, with insulin being considered last resort (11). This "treat-to-failure" approach leads to long periods of hyperglycemia preceding any treatment intensification, which contributes to microvascular complications and beta-cell glucotoxicity, which in turn accelerates treatment failure. Insulin treatment is thought to have a beneficial effect on beta-cell function through rest as well as prevention of the toxic effect of hyperglycemia on the beta-cell. We designed our study to compare the early and long-term changes in beta-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, while commonly used agents like 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 HbA1c >10% at enrollment and achieved a 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 HbA1c 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 of important consideration when choosing 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 might have been expected, the insulin treatment group had fewer (though 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, while 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 were found that patient compliance was similar in both groups (>85% compliance with study medication). 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. Additionally, 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 beta-cell function that is seen in type 2 diabetes, a treatment option that has the potential to preserve beta-cell function is optimal. There is mounting evidence that early treatment with insulin may preserve beta-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 newly-diagnosed type 2 diabetes. We continue to follow our volunteers to assess their long-term change in beta-cell function, results that we expect within the next two 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 utilized to obtain tight glycemic control in 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.

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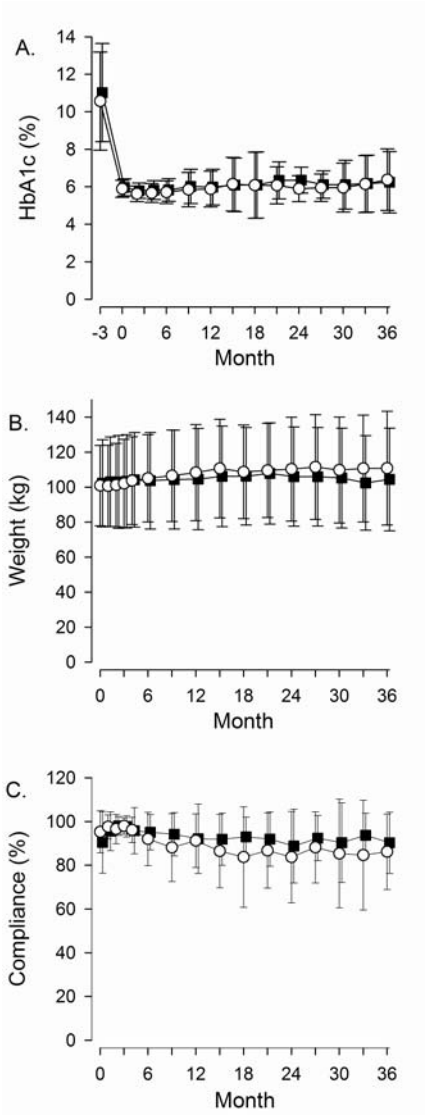
Table 1: Baseline characteristics of the study population at randomization. Results are mean and standard deviation.

Characteristic	**Insulin-Treated Group (Mean±SD)**	**Triple Oral Group (Mean±SD)**
Age (years)	44.75±9.7	45.00±10.7
Male/Female	20/9	17/12
Ethnicity (N/%)		
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
SBP (mmHg)	125±15.8	123±13.6
DBP(mmHg)	76±10.4	78±9.7
HbA1c (%)	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

Figure 1. HbA1c (A), Weight (B), and Compliance (C) of the insulin treatment group (black squares) and the triple oral group (open circles) during the 36 month study. The results are reported as mean and standard deviation.

Figure 2. Results of modified Diabetes Quality of Life Questionnaire in the insulin-treated group (black squares) and triple oral group (open circles). All patients were given the questionnaire to complete at randomization, and at 6 and 18 months post-randomization. Patients randomized to oral hypoglycemic agents did not complete the two questions regarding insulin. The results are reported as mean and standard deviation of the 1 to 5 Likert scale. Both groups had improved scores with respect to social worries, and a change toward stable current health perception overtime. ANOVA $p<0.005$


A.
HbA1c (%)
14
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10
8
6
4
2
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-3 0 6 12 18 24 30 36
Month
B.
Weight (kg)
140
120
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C.
Compliance (%)
120
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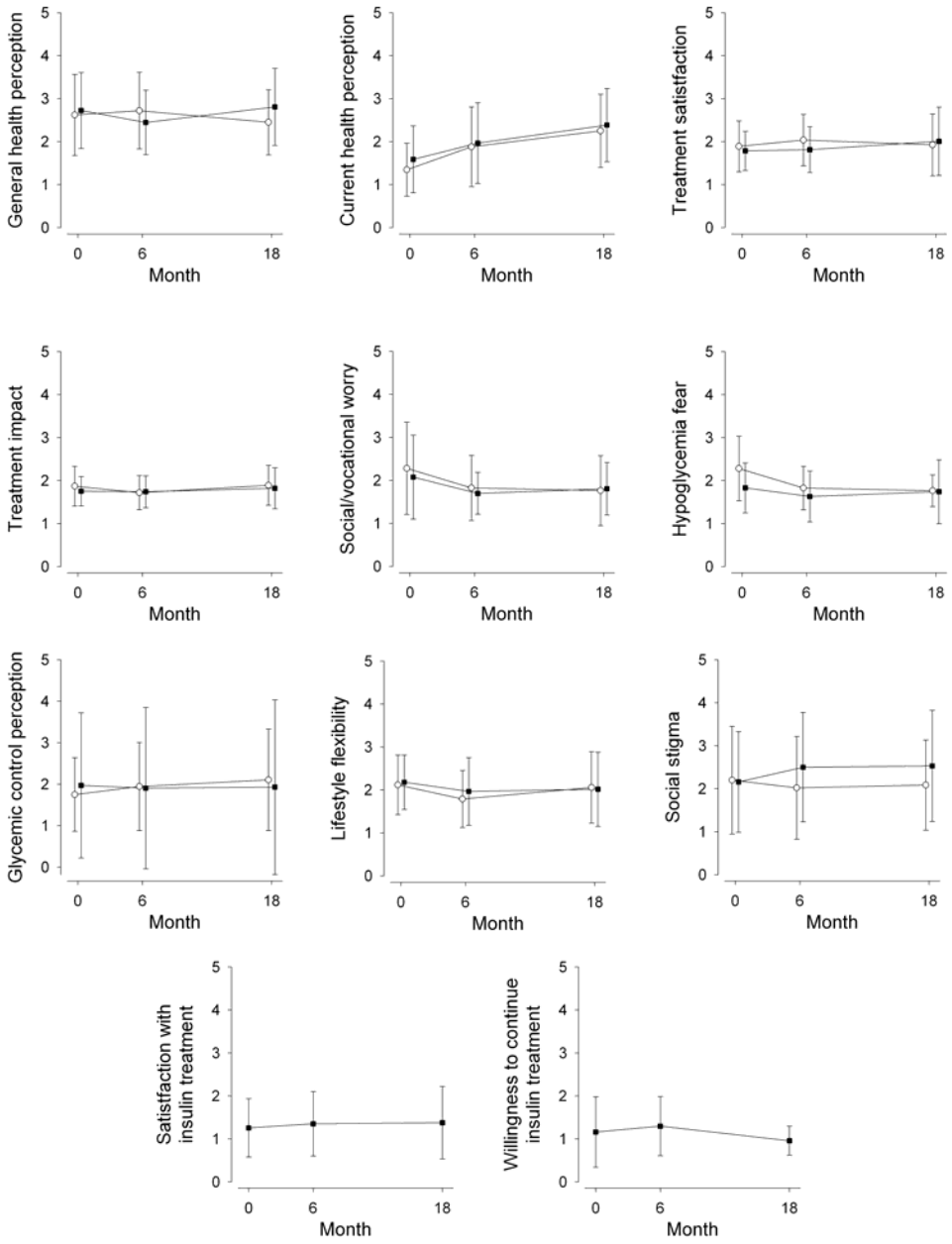
General health perception
Current health perception
Treatment satisfaction
Treatment impact
Social/vocational worry
Hypoglycemia fear
Glycemic control perception
Lifestyle flexibility
Social stigma
Satisfaction with insulin treatment
Willingness to continue insulin treatment
Month
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18
1
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