Health-Related Quality-of-Life Results From Multinational Clinical Trials of Insulin Lispro

Assessing benefits of a new diabetes therapy

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OBJECTIVE — To compare health-related quality of life (HRQOL) in patients with diabetes receiving insulin lispro with patients receiving regular human insulin (Humulin R).

RESEARCH DESIGN AND METHODS — We performed two randomized comparative studies over a 6-month period (3 months per treatment). Primary analyses used crossover baseline to 3-month changes in HRQOL scores. Ninety-three principal investigators in Canada, France, Germany, and the U.S. participated in these studies. One HRQOL crossover study included 468 patients with type I diabetes; the other HRQOL crossover study included 474 patients with type II diabetes. In both studies, patients were taking insulin at least 2 months before enrollment. Primary outcomes included two generic HRQOL domains, energy/fatigue and health distress, and two diabetes-specific domains, treatment satisfaction and treatment flexibility. Thirty secondary outcomes included both generic and diabetes-specific measures. Secondary outcome domains were controlled for multiplicity in the analyses.

RESULTS — Primary analyses showed that treatment satisfaction scores ($P < 0.001$) and treatment flexibility scores ($P = 0.001$) were higher for insulin lispro in type I diabetic patients. No other significant treatment differences were detected using the data from these 6-month crossover studies.

CONCLUSIONS — Treatment satisfaction and treatment flexibility were significantly improved in patients with type I diabetes using insulin lispro. Other HRQOL findings were comparable for insulin lispro and regular human insulin. Insulin lispro appears to have a measurable impact on lifestyle benefits in patients with type I diabetes, as demonstrated by increased treatment satisfaction and treatment flexibility.

The assessment of drug effects on health-related quality of life (HRQOL) has become an objective of clinical trials (1), and some of these assessments have contributed to decisions about the relative merits of investigational treatments (2). HRQOL is a collective term that encompasses multiple components of a person's physical and occupational functioning, psychological status and well-being, social interaction and somatic sensation (3,4). Diabetes is a disease that impacts HRQOL. Unlike terminal diseases (e.g., certain cancers, AIDS), in which the goal is to improve HRQOL for a relatively short period of time, diabetes requires the patient to self-manage his or her disease and is often a lifetime struggle to maintain quality of life. In the past few years, there has been much discussion in the literature regarding the necessity of formulating a valid construct for measuring quality of life (5,6).

Low HRQOL and problematic psychosocial status may affect metabolic control by interfering with treatment compliance (7). Treatment plans that inherently improve or include strategies to enhance patients' HRQOL may increase compliance, thereby improving these patients' metabolic status. A working group representing the World Health Organization (WHO) and International Diabetes Federation published guidelines that recommend improving psychological well-being as an important goal of diabetes management (8). Thus, it is essential that physicians consider diabetes patients' HRQOL when establishing a treatment regimen.

Insulin lispro is an investigational product that has a more rapid onset and a shorter duration of action than regular human insulin (9). Insulin lispro can be administered immediately before the meal, whereas it is recommended that regular human insulin be administered 30–45 min before a meal. Clinical studies have been performed to examine the safety and efficacy of insulin lispro in the premeal treatment of patients with type I and type II diabetes. The results indicate that the postprandial rise in serum glucose concentration was substantially lower with insulin lispro than with regular human insulin (10). Additionally, in one trial, there were fewer total hypoglycemic events in patients with type I diabetes (11). Because of the more rapid onset of action and shorter duration of insulin lispro, its use can have a substantial impact on the relationship between time of insulin injection and meal consumption. Therefore, our hypothesis was that rapid-acting insulin lispro used in the treatment of

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ANOVA, analysis of variance; DQLCTQ, Diabetes Quality of Life Clinical Trial Questionnaire; HRQOL, health-related quality of life; PEQ, Patient Evaluation Questionnaire; WHO, World Health Organization.

patients with diabetes would lead to increased flexibility with regard to choice and timing of meals, quantity of foods consumed, and improved satisfaction in patients' daily lifestyle than patients using regular human insulin. Moreover, these benefits would result in improved HRQOL for patients with diabetes.

This article summarizes the results of two clinical studies comparing the HRQOL of diabetes patients taking insulin lispro with those taking regular human insulin. These studies were randomized open-label multinational controlled crossover studies involving patients with type I and type II diabetes.

RESEARCH DESIGN AND METHODS

Eligibility criteria and trial design

The HRQOL studies were conducted as a secondary objective of two randomized open-label crossover trials that evaluated the safety and efficacy of insulin lispro versus regular human insulin in patients with type I and type II diabetes (11,12). Patients with type I and type II diabetes who had received insulin therapy for at least 2 months before enrollment were recruited for participation in the two crossover studies. Diagnosis of diabetes was based on the classification by the WHO (13).

A total of 93 principal investigators in four countries participated in these studies (7 investigators in Canada, 16 in France, 20 in Germany, and 50 in the U.S.). Each study was conducted and informed consent was obtained according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practice, and the applicable laws and regulations of the U.S., whichever provided the greatest protection of the individual.

At baseline, the patients were placed on basal insulin therapy for a 2- to 4-week lead-in period. Patients were then randomized at the second study visit to one of two treatment sequences. One treatment sequence consisted of insulin lispro therapy for 3 months, followed by regular human insulin therapy for an additional 3 months. The other treatment sequence consisted of regular human insulin therapy for 3 months, followed by insulin lispro therapy for an additional 3 months. The patient was also administered either Humulin U or Humulin N once or twice daily as determined by the investigator to be appropriate for the patient's metabolic needs and meal pattern. Patients were administered a dose of either insulin lispro or regular human insulin before each meal (defined in the study as any consumption of food that contained >20% of their daily total caloric intake).

Questionnaire domains

To identify the relevant HRQOL domains and their importance for persons with type I and type II diabetes, both patient and clinician focus group panels were conducted in San Francisco, CA, and Lyon, France. A total of 31 patients and 11 clinicians participated. As part of these panels, data were collected through a written questionnaire and discussions. Identical guidebooks to lead the discussions were used in both countries, although patients in France were interviewed individually rather than in a group setting. Participants rated items within physical, social, and psychological domains and emotional impact on a scale of 0 (no impact) to 10 (a great deal of impact). Qualitative information elaborating on these ratings was obtained during the discussions. Based on the identified domains of importance, a conceptual framework was developed. Existing global and diabetes-specific questionnaires dealing with social stigma, self-esteem, and symptoms did not exist in the literature, and thus original items were created.

The psychometric properties of this draft questionnaire were then evaluated in a pilot validation study conducted in 123 patients with diabetes in the U.S. (14; J.G.K., W.H., C.A., L.V., S.D.M., D.P., unpublished observations). Based on the results of the psychometric testing, the questionnaire was reduced in length to make it acceptable and practical for use in multinational trials. The questionnaire consisted primarily of a battery of questions and domains taken from validated widely used questionnaires; original domains were developed as required. Redundant questions and/or domains were eliminated, and domains with poor psychometric properties were either modified in or deleted from the final form. Thus, the final questionnaire, the Diabetes Quality of Life Clinical Trial Questionnaire (DQLCTQ), is composed of 142 questions comprising 34 domains, and contains both generic and diabetes-specific questions. Due to the inapplicability of certain questions to some patients, questions with skip patterns were used. The domains, the number of questions per domain, and the associated original scale or author for each domain included in the DQLCTQ are listed in Table 1.

Four domains were chosen as primary outcome domains based on the input from patient focus groups and expert clinician panels conducted in the U.S. and France described above (14; J.G.K., W.H., C.A., L.V., S.D.M., D.P., unpublished observations) and based on the pharmacokinetic features of insulin lispro (9). These domains, Energy/Fatigue, Health Distress, Treatment Flexibility, and Treatment Satisfaction, were expected to show treatment differences and were specified before beginning the trials. The remaining 30 domains were considered secondary outcome domains.

The questions of the primary domains are listed in the Appendix 1. As an overview, the Energy/Fatigue domain contains questions pertaining to how often a patient felt energetic or worn out. The Health Distress domain contains questions relating to patients feeling discouraged or weighed down by health problems, being frustrated about their health, being afraid because of their health, or feeling despair over their health problems. Treatment Flexibility assesses patients' choices regarding meals and physical, social, or other daily activities. The Treatment Satisfaction domain addresses issues pertaining to patients' perception of their ability to control their diabetes, their satisfaction with a particular insulin treatment, and their willingness to continue that particular insulin treatment.

DQLCTQ translation

Using modifications of translation techniques that are linguistically, technically, and culturally accurate (16), the DQLCTQ was translated from English into German and French. A certified translator and a Lilly employee translated the questionnaire from English to German concurrently and independently of each other. Then these versions of the translated questionnaires were evaluated by conducting in-depth interviews of five German patients with diabetes. An editorial board convened to review the findings and finalize the translated version. The questionnaire was translated from English into French by Lilly employees who were bilingual in English and French.

DQLCTQ reliability and validity

In addition to the pilot validation study described above, the DQLCTQ was then further validated using data from these two crossover studies. The psychometric properties, including discriminant validity, convergent validity, and responsiveness of the DQLCTQ, were very favorable, particularly

Table 1—*Domains of the DQLCTQ*

Domain	Number of questions per domain	Original scale or author
Generic		
General Health	1	SF-20 (21)
Comparative Health	1	SF-36 Modified (22)
Physical Functioning	6	SF-20
Global Role Functioning	2	MOS 6-item (23)
Social Functioning	1	SF-20
General Social Functioning	1	MOS
Energy/Fatigue	5	MOS
Health Distress	6	MOS
Mental Health	5	SF-20
Diabetes-Specific		
Diabetes Quality of Life (overall score plus four subscales: satisfaction, impact, vocational worry, and diabetes worry)	59	DQOL (24)
Hypoglycemic Fear Survey (worry subscale)	17	Cox et al. (25)
Treatment Satisfaction	3	TAG
Treatment Flexibility	10	TAG
Social Stigma (overall score plus four separate questions)	4	TAG
Symptom Frequency and Bothersomeness (overall score plus seven separate symptoms)	14	TAG
Self-Efficacy (involves three separate questions)	3	TAG
Demographics		
Background Factors (involves four factors: residence, education, employment, and injection type)	4	

MOS, Medical Outcomes Study; SF, Short Form; TAG, Technology Assessment Group.

for the Treatment Satisfaction domain (17). The internal consistency reliabilities (Cronbach alpha values) were 0.85 for Energy/Fatigue, 0.90 for Health Distress, 0.81 for Treatment Satisfaction, and 0. 90 for Treatment Flexibility.

DQLCTQ administration

The DQLCTQ was used in a subset of the countries (Canada, France, Germany, and the U.S.) in which the safety and efficacy studies were conducted. The DQLCTQ was self-administered and completed five times during the study: at baseline and at months 1 and 3 of each treatment period.

The investigators and study coordinators were instructed not to assist the patient by reading or interpreting the questions. However, they were instructed to encourage the patient to complete the DQLCTQ in its entirety to the best of his or her ability and to inform the patient that there were no right or wrong answers. The DQLCTQ was administered during the office visit after the patient had his or her blood sample taken and consumed the test meal as part of the safety and efficacy study, but before the patient was seen by the physician. The patient was not permitted to complete the DQLCTQ outside the office visit.

DQLCTQ scoring

Reverse scoring was used for selected domains so that, for all outcome measures, higher values indicate better HRQOL. The domain score for a patient was the average score for the questions answered by the patient. This method imputes the observed score for questions that were not answered. All domains, except Global Functioning-Difficulty, were converted to a 100-point scale by subtracting the low value of the range from the average, multiplying by 100, and dividing by the high minus the low value of the range. For example, for an outcome measure that has a range from 1 to 5, the transformed score would equal (average − 1) multiplied by 100 divided by (5 − 1).

Data analyses

The analysis plan specified below was followed for each crossover study separately. The change in the HRQOL domain score from baseline to the 3-month timepoint in each period was used in all analyses. Methodology suggested by Koch (18) was used to compare the change in HRQOL domain scores for insulin lispro with that of regular human insulin. For the assessment of carryover effects, the sum of treatment periods 1 and 2 scores for change was the response in an analysis of variance (ANOVA) model with sequence and country as main effects and the sequence-by-country interaction effect. For the assessment of treatment effects, the difference of treatment periods 1 and 2 scores for change was the response in a separate ANOVA model with similar effects. If the interaction with country was significant ($P < 0.10$), the results were evaluated for each country separately. Carryover and treatment-effect P values were obtained from the corresponding main-effect analysis.

When a carryover effect was present (i.e., $P < 0.10$), it was evaluated. Carryover effect can be due to either a sequence effect, where one sequence has higher scores than the other sequence at every timepoint, or a treatment-by-period interaction, where the treatment effect differs in each study period. The latter interpretation suggests a carryover of the treatment effect to the subsequent period.

Because each of the four primary HRQOL outcomes evaluated a separate prespecified hypothesis, treatment comparisons were performed at the two-tailed 0.05 level of significance. Treatment comparisons for the secondary HRQOL outcomes used the sharper Bonferroni correction proposed by Hochberg (19). According to this procedure, the largest P value is first examined. If this P value is <0.05, then all 30 treatment comparisons are declared significant. If not, then the second-largest P value is compared with 0.05/2. If smaller, then all 29 treatment comparisons are declared significant. If not, the third-largest P value is compared with 0.05/3, and so on, until the 30th P value is compared to 0.05/30 = 0.0017.

For the HRQOL domains demonstrating significant treatment differences, an evaluation of differential treatment effects in relation to patient characteristics (age, sex, BMI, duration of diabetes, type of basal insulin, living arrangements, and educational level) was undertaken using the

Table 2—*Demographic summary of patients in the HRQOL studies who completed a baseline DQLCTQ*

Studies	Study 1 (type I patients)	Study 2 (type II patients)
Sample size	468	474
Sex (% female)	44.2	42.6
Origin (%)		
African descent	1.7	7.8
Caucasian	96.6	87.1
Hispanic	1.3	3.6
Other	0.4	1.5
Mean age (years)	33.8 ± 12.1	58.2 ± 9.9*
Mean BMI (kg/m²)	24.5 ± 3.2	28.3 ± 4.0
Mean duration of diabetes (years)	12.6 ± 9.0	12.5 ± 7.5†
Mean duration of insulin treatment (years)	12.4 ± 9.0	6.5 ± 6.4
Mean duration of human insulin treatment (years)	5.2 ± 3.2	3.9 ± 3.0
Basal insulin (% using Humulin N)	78.0	85.0
Basal insulin (% using Humulin U)	22.0	15.0
Human insulin delivery system		
Cartridges	17.5	18.4
Vials	62.1	75.7
Vials and cartridges	20.2	5.9
Unspecified	0.2	0
Mean HbA_{1c} (%)	8.4 ± 1.7	8.8 ± 1.6
Nonsmoker	384 (82.7)	420 (88.6)‡
Nondrinker	285 (61.3)	331 (70.3)
Living arrangement§		
Living with others	399 (86.7)	383 (82.5)
Living alone	61 (13.3)	81 (17.5)
Educational level§		
Secondary	129 (28.3)	142 (31.9)
Undergraduate	151 (33.1)	102 (22.9)
Postgraduate	106 (23.2)	88 (19.8)
Other	70 (15.4)	113 (25.4)
Employment status§		
Full- or part-time employed	319 (69.7)	217 (47.2)
Other	139 (30.3)	243 (52.8)

Data are *n* (%) or means ± SD, unless otherwise indicated. *Insulin lispro/Humulin R sequence versus Humulin R/insulin lispro sequence, 56.73 vs. 59.50 ($P < 0.05$); †insulin lispro/Humulin R sequence versus Humulin R/insulin lispro sequence, 11.60 vs. 13.44 ($P < 0.05$); ‡insulin lispro/Humulin R sequence versus Humulin R/insulin lispro sequence, 202 vs. 218 ($P < 0.05$). §Living arrangement, educational level, and employment status are demographic and background items in the DQLCTQ.

ANOVA model as described above. Terms for treatment, patient characteristic variables, and their interactions were included. An interaction effect at $P < 0.10$ would be suggestive of a differential treatment effect.

RESULTS

Demographic characteristics

The demographic data for the patient population from the two studies are summarized in Table 2. A total of 468 patients with type I diabetes and 474 patients with type II diabetes were available for the HRQOL analyses. The mean age was 33.8 years for type I patients and 58.2 years for type II patients, reflective of the two different study populations.

In the study of type II patients, statistically significant differences were found among treatment sequences for three demographic factors. Given that the primary analyses used baseline to 3-month changes such that patients serve as their own control subjects, the statistically significant factors of age, duration of diabetes, and smoking would not be expected to influence HRQOL treatment differences. To confirm this, adjustment for these factors using ANOVA did not change the inferences of the four primary HRQOL endpoints for this study.

Discontinuation

In both studies, the patient discontinuation rates were very low. Of the 468 patients with type I diabetes, 12 (2.6%) patients in the insulin lispro/Humulin R sequence and 14 (3.0%) patients in the Humulin R/insulin lispro sequence discontinued early from this study after randomization. There was no association between the treatment sequence and reason for early discontinuation.

Of the 474 randomized patients with type II diabetes included in the HRQOL analyses for this study, 16 (3.4%) patients in the insulin lispro/Humulin R sequence and 10 (2.1%) patients in the Humulin R/insulin lispro sequence discontinued early from this study after randomization. There was no association between the treatment sequence and reason for early discontinuation.

DQLCTQ completion rates

The DQLCTQ was administered in at least 91% of the patient visits in each study. Of the questionnaires administered, at least 83% were missing <10% of the 124 questions required to be completed. Of the remaining 18 questions, 14 were skip pattern HRQOL questions and 4 were background/demographic factors that were not included in this calculation.

Primary domain outcomes

The results of the analyses of the four primary domain outcomes are displayed in Tables 3–7. In each of the studies, the primary domains of Health Distress, Treatment Satisfaction, and Treatment Flexibility showed improvement over the 6-month study period. The primary domain of Energy/Fatigue showed no improvement.

Patients with type I diabetes

The baseline values of the primary HRQOL domains of the patients with type I diabetes are displayed in Table 3. There were no statistically significant differences between the treatment sequences, except for treatment satisfaction in type I patients ($P = 0.022$). All analyses of treatment satisfaction were adjusted for this baseline difference.

The baseline to 3-month changes in the primary domains are displayed in Table 4. There were no statistically significant

Table 3—*Baseline mean values of primary HRQOL domains by sequence group for patients with type I diabetes*

Domain	Insulin lispro/ Humulin R		Humulin R/ insulin lispro		Sequence	
	n	Mean ± SD	*n*	Mean ± SD	*P* value	*F* value (df)
Energy/Fatigue	239	67.2 ± 16.9	229	65.2 ± 17.5	0.178	1.82 (1, 463)
Health Distress	239	84.0 ± 16.9	229	83.8 ± 15.2	0.865	0.03 (1, 463)
Treatment Flexibility	238	70.8 ± 18.4	228	72.1 ± 17.4	0.478	0.51 (1, 461)
Treatment Satisfaction*	238	68.3 ± 17.1	228	70.8 ± 18.0	0.022*	5.31 (1, 458)

*Statistically significant sequence-by-country interaction ($P = 0.011$) with $F = 3.73$ and df = 3, 458.

Table 4—*Baseline to 3-month changes in HRQOL domain scores by treatment group for patients with type I diabetes*

Domain	Insulin lispro		Humulin R		Carryover		Treatment	
	n	Change	*n*	Change	*P* value	*F* value (df)	*P* value	*F* value (df)
Energy/Fatigue	429	−1.0 ± 16.1	421	−1.8 ± 15.0	0.911	0.01 (1, 399)	0.299	1.08 (1, 399)
Health Distress	429	1.2 ± 14.6	421	1.0 ± 14.4	0.890	0.02 (1, 399)	0.633	0.23 (1, 399)
Treatment Flexibility	425	3.1 ± 16.1	420	0.8 ± 15.8	0.862	0.03 (1, 399)	0.001	10.44 (1, 397)
Treatment Satisfaction*	426	4.7 ± 21.9	422	0.4 ± 22.0	0.389	0.74 (1, 395)	<0.001	12.07 (1, 395)

Data are *n* or means ± SD, unless otherwise indicated. *Statistically significant carryover-by-country interaction ($P = 0.051$) with $F = 2.61$ and df = 3, 395 and treatment-by-country interaction ($P = 0.015$) with $F = 3.53$ and df = 3, 395.

Table 5—*Baseline and 3-month change in Treatment Satisfaction by country for patients with type I diabetes (period 1 results)*

Country	Insulin lispro		Humulin R		Treatment	
	n	Mean ± SD	*n*	Mean ± SD	*P* value	*F* value (df)
Canada						
Baseline	13	63.7 ± 15.5	14	68.7 ± 15.5	0.412	0.70 (1, 25)
Change	12	18.1 ± 23.2	12	2.3 ± 15.4	0.169	2.03 (1, 21)
France						
Baseline	31	55.4 ± 17.5	31	71.1 ± 17.0	<0.001	12.94 (1, 60)
Change	28	13.3 ± 24.7	28	−4.4 ± 17.9	0.087	3.04 (1, 53)
Germany						
Baseline	47	72.7 ± 17.1	55	71.8 ± 17.6	0.799	0.06 (1, 100)
Change	44	−0.5 ± 25.5	51	−2.3 ± 17.3	0.560	0.34 (1, 92)
U.S.						
Baseline	147	70.0 ± 15.9	128	70.6 ± 18.8	0.773	0.08 (1, 273)
Change	138	6.3 ± 19.5	115	1.5 ± 22.7	0.047	3.97 (1, 250)
Combined						
Baseline	238	68.3 ± 17.1	228	70.9 ± 18.8	0.022*	5.31 (1, 458)
Change	222	6.5 ± 22.0	206	−0.2 ± 20.5	0.007	7.48 (1, 422)

*Statistically significant sequence-by-country interaction ($P = 0.011$) with F = 3.73 and df = 3, 458.

Table 6—*Baseline mean values of primary HRQOL domains by sequence group for patients with type II diabetes*

Domain	Insulin lispro/ Humulin R		Humulin R/ insulin lispro		Sequence	
	n	Mean ± SD	*n*	Mean ± SD	*P* value	*F* value (df)
Energy/Fatigue	236	58.3 ± 19.4	237	60.2 ± 19.2	0.315	1.01 (1, 468)
Health Distress	236	77.8 ± 21.3	237	80.1 ± 19.2	0.230	1.44 (1, 468)
Treatment Flexibility	232	70.2 ± 18.0	237	71.3 ± 17.8	0.573	0.32 (1, 464)
Treatment Satisfaction	234	69.1 ± 20.5	237	67.4 ± 22.2	0.371	0.80 (1, 466)

Table 7—*Baseline to 3-month changes in HRQOL domain scores by treatment group for patients with type II diabetes*

Domain	Insulin lispro		Humulin R		Carryover		Treatment	
	n	Change	*n*	Change	*P* value	*F* value (df)	*P* value	*F* value (df)
Energy/Fatigue	447	−1.4 ± 16.1	445	−1.0 ± 15.9	0.116	2.48 (1, 424)	0.911	0.01 (1, 424)
Health Distress	447	1.8 ± 15.5	445	2.1 ± 14.8	0.036	4.45 (1, 424)	0.378	0.78 (1, 424)
Treatment Flexibility	440	1.0 ± 16.5	439	0.3 ± 15.7	0.553	0.35 (1, 416)	0.475	0.51 (1, 416)
Treatment Satisfaction	442	10.9 ± 22.6	443	10.0 ± 22.4	0.321	0.99 (1, 420)	0.119	2.43 (1, 420)

Data are *n* or means ± SD, unless otherwise indicated.

treatment differences for Energy/Fatigue and Health Distress. Also, there was no carryover effect for these domains.

Treatment Flexibility in patients treated with insulin lispro increased statistically significantly more ($P = 0.001$), compared with patients treated with Humulin R. Figure 1 illustrates the Treatment Flexibility scores in each time period by treatment group.

Treatment Satisfaction in patients treated with insulin lispro increased statistically significantly ($P < 0.001$), compared with patients treated with Humulin R. However, the results are complicated by significant between-country differences in the carryover ($P = 0.051$) and treatment ($P = 0.015$) effects. Because of this finding, an analysis of the first-period results was performed and is presented in Table 5. For all countries combined, Treatment Satisfaction improved significantly in patients treated with insulin lispro ($P = 0.007$). The treatment difference was 6.7 points (6.7 points = 6.5 for insulin lispro minus −0.2 for Humulin R). This effect was consistent across countries, after adjustment for baseline Treatment Satisfaction. Treatment Satisfaction was significantly improved in patients treated with insulin lispro in the U.S. ($P = 0.047$). Figure 2 shows the increase in Treatment Satisfaction with insulin lispro in the first period.

Patients with type II diabetes

The baseline values of the primary HRQOL domains of the patients with type II diabetes are displayed in Table 6. There were no statistically significant differences between the treatment sequences.

The baseline to 3-month changes in the primary domains are displayed in Table 7. There were no statistically significant treatment differences for the primary domains Energy/Fatigue, Health Distress, Treatment Flexibility, and Treatment Satisfaction. There were no statistically significant carryover effects in Energy/Fatigue, Treatment Flexibility, or Treatment Satisfaction.

There was no statistically significant treatment difference for Health Distress overall. However, there was a statistically significant carryover effect for Health Distress ($P = 0.036$). Figure 3 shows that this carryover effect is due to the difference between sequences and not between treatments. That is, Health Distress scores are higher throughout the study for the Humulin R/insulin lispro sequence, compared with the insulin lispro/Humulin R sequence.

Effect of patient characteristics on treatment response

For type I patients, there were no differential treatment effects for Treatment Satisfaction. However, for Treatment Flexibility, patients with diabetes duration <10 years had a larger treatment effect in favor of insulin lispro. In type II patients, there were no differential treatment effects for Treatment Satisfaction or Treatment Flexibility.

Secondary domains

After correcting for multiple comparisons, there were no statistically significant differences detected between treatment groups for the secondary domains in either of the two studies. Additionally, there were no significant differences between the treatment sequences at baseline, except for the study with type II patients, where we found statistically significant differences in the baseline scores between treatment sequences in Hunger Frequency. Such differences would not affect the treatment differences, since patients act as their own control subjects.

CONCLUSIONS — Diabetes management goals include improvement of psychological well-being and other HRQOL

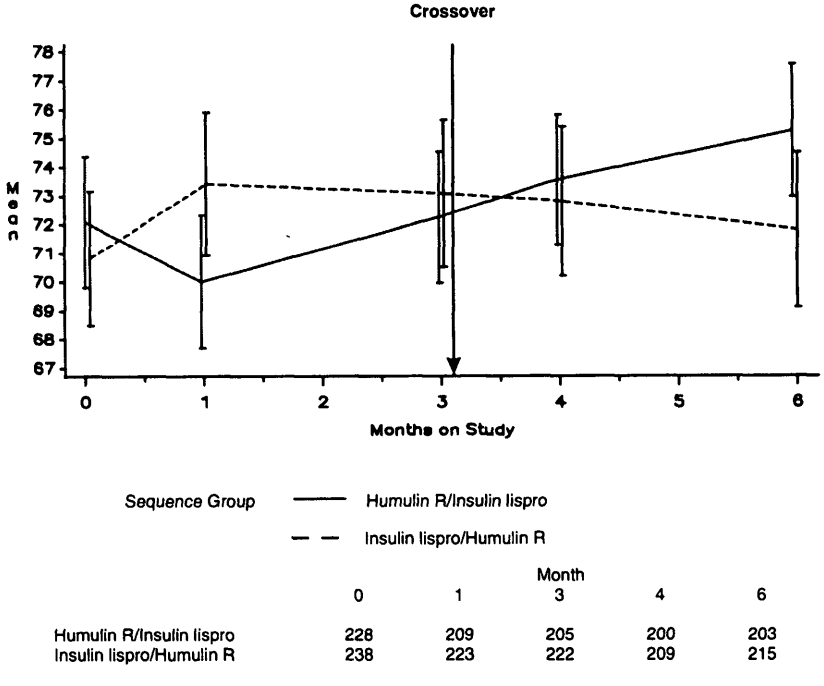

Figure 1—*Mean Treatment Flexibility scores (95% CIs shown by vertical bars) at each visit in patients with type I diabetes.*

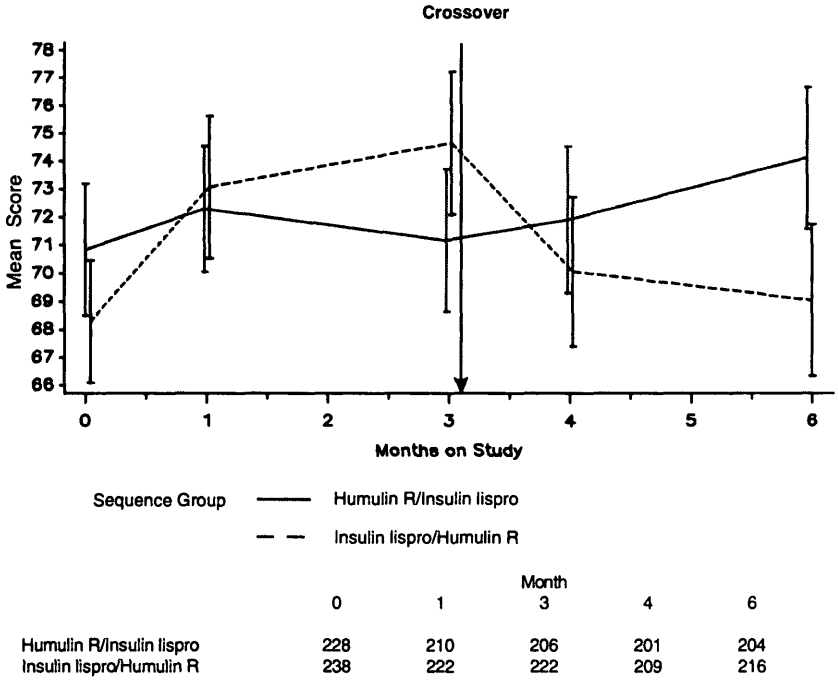

Figure 2—*Mean Treatment Satisfaction scores (95% CIs shown by vertical bars) at each visit in patients with type I diabetes.*

outcomes. HRQOL outcomes reflect lifestyles, behaviors, and treatment compliance, and these factors may in turn influence other outcomes such as metabolic control. Our primary hypothesis was that patients using insulin lispro would demonstrate better treatment satisfaction, better treatment flexibility, improved energy/fatigue, and lowered health distress versus regular human insulin. The results of these studies demonstrate better treatment satisfaction and flexibility with insulin lispro than with regular human insulin in patients with type I diabetes. Other HRQOL treatment differences were comparable.

Treatment satisfaction was significantly increased in patients with type I diabetes using insulin lispro. The improvement in Treatment Satisfaction for patients with type I diabetes treated with insulin lispro was 6.7 points. The responsiveness of the Treatment Satisfaction domain to change in HbA_{1c} was evaluated in these studies along with other psychometric properties of the DQLCTQ (17). A 5-point improvement in Treatment Satisfaction provided the optimal cutoff to discriminate improvement in metabolic control where improvement was defined as a 1%-point decrease in HbA_{1c} values.

A factor that may have contributed to the increase in Treatment Satisfaction was the decreased incidence of hypoglycemic events observed in patients with type I diabetes (11). These findings were not observed in patients with type II diabetes (12). On the other hand, the postprandial rise in serum glucose was significantly lower during insulin lispro therapy in patients with both type I (11) and type II (12) diabetes. Given these findings and the similar clinical features of lower postprandial serum glucose during insulin lispro in patients with both type I and type II diabetes, it seems reasonable to postulate that a reduction in hypoglycemic events with concomitant increase in Treatment Satisfaction may have occurred in patients with type II patients with a longer duration of treatment.

Treatment flexibility was significantly increased in patients with type I diabetes using insulin lispro. This finding may be due to the features of insulin lispro in that it introduces new approaches with respect to timing of insulin injection and meal consumption. It has a more rapid onset of action and shorter duration than regular insulin. However, differences in Treatment Flexibility were not detected in the trial of patients with type II diabetes. Although this finding could be due to the study requirements whereby the time of injection for insulin lispro was specified, as was the time of injection for regular human insulin, it may be that flexible treatment regimens may not be as major a factor in patients with type II diabetes as in patients with type I diabetes. The concept of Treatment Satisfaction was also measured using the Patient Evaluation Questionnaire (PEQ) in another similarly designed study conducted in Belgium and the Netherlands (20). The Treatment Satisfaction results using the PEQ

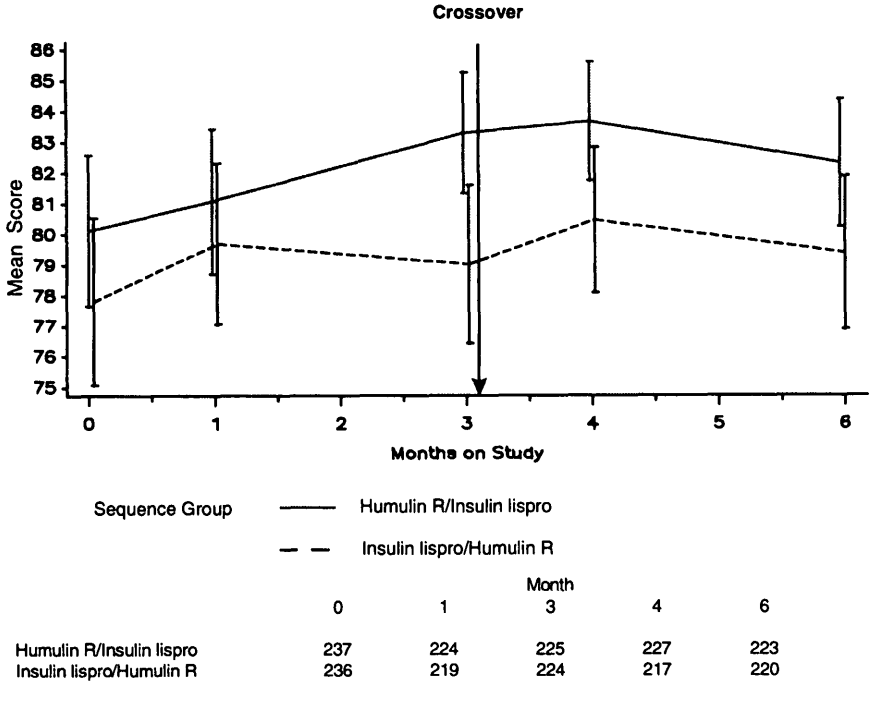

Figure 3—*Mean Health Distress scores (95% CIs shown by vertical bars) at each visit in patients with type II diabetes.*

were similar to the results presented in this paper and were significantly improved in a total of 110 patients with both type I and type II diabetes using insulin lispro versus regular human insulin. Additionally, in the Belgium and the Netherlands study, improved Treatment Flexibility with insulin lispro versus regular human insulin was observed. The PEQ contained comparative questions that may have been more sensitive to detect treatment differences than the questions used in the DQLCTQ. Although the DQLCTQ demonstrated favorable psychometric properties, including sensitivity to change with respect to clinical changes, it could be that comparative questions may be better able to detect differences in lifestyle conferred by a treatment such as insulin lispro. These comparative questions should be considered for use in comparative studies. Gill and Feinstein (5) also recommend that patient opinions be assessed.

Treatment differences, other than Treatment Satisfaction and Treatment Flexibility in patients with type I diabetes, may not have been detected in this study comparing two insulins, because numerous factors impact diabetes, including diet, exercise, self-monitoring of blood glucose levels, interpersonal relations, social support, and many others. There were no significant differences in HbA_{1c} between treatment groups in either study of patients with type I or type II diabetes (11,12). This finding may explain the lack of differences between treatment groups with respect to Energy/Fatigue, since fatigue is a common symptom associated with poor metabolic control. Finally, no overall differences were detected in Health Distress between treatment groups. These results may be related to the effect of patients participating in a study in which they experience no worsening in, or perhaps even reduced, concern about their health.

These studies were open-label and involved knowledge by both the patients and the investigators about the treatments that the patients were receiving, thus potentially influencing the results. Regarding the potential influence of the investigator's knowledge of the treatment on the HRQOL results, we took great care to design the studies to minimize the impact of the investigator on the HRQOL treatment effect (i.e., the investigators and study coordinators were instructed not to assist the patients by reading or interpreting the questions). Also, the questionnaire was administered during the office visit but before the patient saw the physician.

Co-interventions, such as diet and exercise, could potentially affect HRQOL treatment differences. Since these studies were randomized and each patient served as his or her own control subject, we anticipate that these factors remained constant; however, it is very possible that patients' HRQOL was impacted by knowledge of their treatment groups, which we are not able to measure in these studies.

Based on the post hoc analyses of relevant patient characteristics, the results of these trials are applicable to a broader patient population for Treatment Satisfaction in type I patients. However, it is possible that patients with shorter duration of diabetes may benefit more with respect to Treatment Flexibility.

The shorter duration of action of insulin lispro should allow patients to vary lifestyle patterns of timing of meals and of exercise routines. Therefore, it is clear that with all treatment regimens in which patients self-manage their disease, the perceptions of the individual patient with regard to lifestyle benefits should be incorporated into any assessment of treatment benefits. Given that improved Treatment Satisfaction and Treatment Flexibility may lead to better compliance, further exploration is needed to analyze the consequences of treatments that improve Treatment Satisfaction, Treatment Flexibility, and other HRQOL outcomes in a real-world (effectiveness) setting.

Acknowledgments — The authors wish to acknowledge the investigators (listed in APPENDIX 2) who participated in the HRQOL studies.

APPENDIX 1: PRIMARY DOMAINS OF THE DQLCTQ

Energy/fatigue

How often during the past 4 weeks . . . (responses range from 1 ["all of the time"] to 6 ["none of the time"])

- did you feel worn out?
- did you have a lot of energy?
- did you feel full of pep?
- did you have enough energy to do the things you wanted to do?
- did you feel tired?

Health distress

How often during the past 4 weeks . . . (responses range from 1 ["all of the time"] to 6 ["none of the time"])

- were you discouraged by your health problems?
- did you feel weighed down by your health problems?
- were you afraid because of your health?
- was your health a worry in your life?
- were you frustrated about your health?
- did you feel despair over your health problems?

Treatment flexibility

During the past 4 weeks, how much choice did you have in . . . (responses range from 1 ["a great deal of choice"] to 5 ["no choice"])

- how often you had to eat your meals or snacks?
- eating your meals or snacks away from home?
- the timing of your meals or snacks?
- the kinds of food you eat?
- the amounts of food you eat?
- planning your physical activities (e.g., walking, sports)?
- planning your social activities (e.g., parties, visiting with family and friends)?
- planning your daily activities (e.g., work, school, taking care of the house)?
- participating in activities at the spur of the moment?
- changing your plans at the spur of the moment?

Treatment satisfaction

How controlled do you feel your diabetes has been in the past 4 weeks? (responses range from 1 ["extremely controlled"] to 7 ["not at all controlled"])

How satisfied have you been in the past 4 weeks with your insulin treatment? (responses range from 1 ["extremely satisfied"] to 7 ["not at all satisfied"])

How willing would you be to continue with your present insulin treatment? (responses range from 1 ["extremely willing"] to 7 ["not at all willing"])

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APPENDIX 3: INCLUSION AND EXCLUSION CRITERIA FOR TYPE I AND TYPE II DIABETES TRIALS

Type I Diabetes Trial

Inclusion criteria. Patients were included in this study if they . .

- had type I diabetes (according to WHO criteria) and were between 12 and 70 years of age, inclusive, for both men and women.
- were on commercially available human insulin for at least 2 months (62 days) before enrollment in the study.
- had achieved optimum compliance with their diabetic diet and insulin therapy, as determined by the investigator.

- gave informed consent in accordance with local regulations.

Exclusion criteria. Patients were excluded from the study if they . .

- had received <2 months (62 days) of human insulin therapy.
- had a history of cancer of any type.
- had cerebrovascular or symptomatic peripheral vascular disease that would prevent participation in the study.
- were in cardiac class III or IV.
- had renal transplants or were currently receiving renal dialysis.
- had significant clinical signs or symptoms of liver disease, acute or chronic hepatitis, or aspartate transaminase (AST or SGOT) greater than twice the upper reference range limit.
- had clinical signs or symptoms of drug or alcohol abuse.
- had a life expectancy of <3 years.
- had a known allergy to insulin or excipients contained in insulin products.
- were pregnant or intended to become pregnant during the time of the study.
- were sexually active women of child-bearing age who were not actively practicing birth control by using oral contraceptives, an intrauterine device (IUD), or a barrier method plus a spermicide.
- were lactating.
- had a serum creatinine level >264 μmol/l (3 mg/dl).
- exhibited serious noncompliance with prescribed diet or drug therapy.
- were currently receiving therapy by a continuous subcutaneous insulin-infusion pump.
- were currently participating or had participated in a medical, surgical, or pharmaceutical investigation in which an investigational new drug was dispensed to the patient within the past 6 months.
- were receiving a total daily dose of insulin >2.0 U/kg.
- had a BMI >35 kg/m^2.
- had anything that would preclude them from following and completing the protocol.
- had a history of clinically significant hypoglycemia unawareness.
- had more than two hospitalizations for symptomatic or asymptomatic hypoglycemia in the past year.
- had adrenal insufficiency.
- had known hemoglobinopathy or chronic anemias.

Type II Diabetes Trial

Inclusion criteria. Patients were included in this study if they . .

- had type II diabetes (according to WHO criteria) and were between 35 and 85 years of age, inclusive, for both men and women.
- were on commercially available human insulin for at least 2 months (62 days) before enrollment in the study.
- had achieved optimum compliance with their diabetic diet and insulin therapy, as determined by the investigator.
- gave informed consent in accordance with local regulations.

Exclusion criteria. Patients were excluded from the study if they . . .

- had received <2 months (62 days) of human insulin therapy.
- had a history of cancer of any type.
- had cerebrovascular or symptomatic peripheral vascular disease that would prevent participation in the study.
- were in cardiac class III or IV.
- had renal transplants or were currently receiving renal dialysis.
- had significant clinical signs or symptoms of liver disease, acute or chronic hepatitis, or aspartate transaminase (AST or SGOT) greater than twice the upper reference range limit.
- had clinical signs or symptoms of drug or alcohol abuse.
- had a life expectancy of <3 years.
- had known allergy to insulin or excipients contained in insulin products.
- were pregnant or intended to become pregnant during the time of the study.
- were sexually active women of child-bearing age who were not actively practicing birth control by using oral contraceptives, an intrauterine device (IUD), or a barrier method plus a spermicide.
- were lactating.
- had a serum creatinine level >264 μmol/l (3 mg/dl).
- exhibited serious noncompliance with prescribed diet or drug therapy.
- were receiving therapy by a continuous subcutaneous insulin infusion pump.
- were currently participating or had participated in a medical, surgical, or pharmaceutical investigation in which an investigational new drug was dispensed to the patient within the past 6 months.
- were receiving a total daily dose of insulin >2.0 U/kg.
- had a BMI >35 kg/m^2.
- had anything that would preclude them from following and completing the protocol.
- had a history of clinically significant hypoglycemia unawareness.
- had more than two hospitalizations for symptomatic or asymptomatic hypoglycemia in the past year.
- had adrenal insufficiency.
- had known hemoglobinopathy or chronic anemias.

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