

Effects of insulin changes on quality of life and glycemic control in Japanese patients with type 2 diabetes mellitus: The insulin-changing study intending to gain patients' insights into insulin treatment with patient-reported health outcomes in actual clinical treatments (INSIGHTs) study

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ABSTRACT

Aims/Introduction: Our primary objective was to assess changes in quality of life (QOL) associated with changes in insulin regimen in patients with type 2 diabetes mellitus. Secondary objectives were to assess the reasons for and patterns of changes in insulin regimen, and the effects on glycemic control.

Materials and Methods: This 12-week, observational study included patients with type 2 diabetes mellitus ($n = 625$) who planned to change insulin regimen (type of insulin, injection device and/or number of injections). The primary outcome measure was a change from baseline in QOL assessed by the Insulin Therapy-Related (ITR) QOL questionnaire. The secondary outcome measures included change from baseline in plasma glycosylated hemoglobin (HbA_{1c}) level, the reasons for and pattern of insulin regimen change, and change from baseline in QOL assessed by Diabetes Treatment Satisfaction Questionnaire (DTSQ).

Results: QOL did not worsen during the study. Improvements were seen in the ITR-QOL 'daily activities' subscale score (baseline: 12.7 ± 2.3 ; week 12: 12.9 ± 2.3 ; $P = 0.038$, $n = 568$) and the DTSQ 'perceived frequency of hyperglycemia' subscale score (baseline: 3.4 ± 1.6 ; week 12: 3.0 ± 1.7 ; $P < 0.001$, $n = 573$). Glycemic control improved, as evidenced by decreased plasma HbA_{1c} levels (baseline: $8.21 \pm 1.47\%$; week 12: $7.85 \pm 1.31\%$; $P < 0.001$, $n = 606$).

Conclusions: It was suggested that insulin regimen changes might improve glycemic control in Japanese patients with type 2 diabetes mellitus without worsening QOL. This trial was registered with ClinicalTrials.gov (no. NCT01055808). (*J Diabetes Invest*, doi: 10.1111/jdi.12086, 2013)

KEY WORDS: Glycosylated hemoglobin, Insulin therapy-related quality of life questionnaire, Type 2 diabetes mellitus

INTRODUCTION

Maintaining glycemic control is the primary goal of treatment for type 2 diabetes mellitus. Several landmark studies, including the Japanese Kumamoto study^{1,2} and the United Kingdom Prospective Diabetes Study^{3,4}, have shown that good glycemic control using intensive insulin therapy reduces the risk of microvascular complications, and might also reduce the risk of macrovascular complications in patients with type 2 diabetes

mellitus. Intensification of insulin therapy is often necessary to maintain glycemic control in patients as the disease progresses. Intensification might include switching to or adding another type of insulin and/or increasing the number of injections per day. The recent expansion of available insulin preparations allows insulin therapy to be tailored to individual patients' clinical needs and personal preferences. In Japan, the rapid-acting analogs, insulin lispro and insulin aspart, became available in 2001, and premixed combinations of each analog in 2003. The long-acting preparations, insulin glargine and insulin detemir, became available in 2003 and 2007, respectively.

Insulin therapy can have both positive and negative impacts on quality of life (QOL). Insulin therapy generally provides better glycemic control and improves health-related QOL by

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reducing diabetic complications⁵⁻⁷. However, insulin therapy can be inconvenient, painful and burdensome, and can restrict patients' daily activities⁸. Furthermore, insulin treatment sometimes induces hypoglycemic episodes, which detract from QOL, both in terms of the actual events and the fear they cause. A number of studies have compared the effects of specific insulin types and regimens on QOL in patients with type 2 diabetes mellitus^{6,9-16}. Most of these studies focused on insulin initiation or the comparison between insulin therapies, such as regular insulin vs rapid-acting insulin analogs^{13,14,17,18}, neutral protamine Hagedorn (NPH) vs long-acting insulin analogs^{9,10,12}, or multiple daily injections vs continuous subcutaneous insulin infusion (CSII)¹⁶. In contrast, few observational studies have examined the effects of changes in insulin regimen on QOL when intensifying insulin therapy in clinical practice.

The primary objective of this multicenter, observational study was to assess the changes in QOL associated with changes in insulin regimen in Japanese patients with type 2 diabetes mellitus. The secondary objectives were to assess the reasons for changing insulin regimen, the pattern of these changes and the effects on glycemic control as measured by plasma glycosylated hemoglobin (HbA_{1c}) levels.

MATERIALS AND METHODS

Study Design

The INSulin-changing study Intending to Gain patients' insights into insulin treatment with patient-reported Health outcomes in actual clinical Treatments (INSIGHTs) study was a 12-week, prospective, non-controlled observational study carried out between January and November 2010 at 68 hospital departments (including departments of endocrinology and metabolism, diabetes, and general internal medicine) in Japan. Patients with type 2 diabetes mellitus who were being treated with insulin and planned to change therapy were assessed for 12 weeks after the change in therapy (baseline). The outcomes assessed before and/or after the change in therapy included QOL, plasma levels of HbA_{1c}, reasons for the change in therapy, patterns of changes in therapy, treatment adherence and satisfaction, and concomitant oral antidiabetic medication.

The study was carried out in accordance with the Declaration of Helsinki and Good Post-Marketing Study Practice (based on the International Conference for Harmonization Good Clinical Practice) in Japan¹⁹, and in accordance with the local ethical requirements at each site. Written informed consent was obtained from all patients before any study-specific procedures were carried out. This trial was registered with ClinicalTrials.gov (no. NCT01055808).

Study Population

Patients with type 2 diabetes mellitus aged ≥ 20 years who planned to change one or more aspect of their insulin regimen (type of insulin, injecting device and/or number of injections per day) during the registration period were eligible to enter the study. Patients must have been receiving the same insulin

regimen for at least 3 months before entering. Switching insulin preparation within the same class (e.g. insulin lispro to insulin aspart) was not considered a change in insulin regimen.

Patients were excluded from participation if they planned to discontinue insulin therapy, had used or planned to use continuous subcutaneous insulin infusion, had type 1 diabetes mellitus, had obviously poor treatment adherence (determined by the investigator and based on patient history) or were incapable of completing the study questionnaires.

Insulin Treatment Regimen During the Study

Patients' individual insulin regimens during the study were determined by their treating doctors, and each insulin preparation was to be administered according to the recommended dose and frequency. The study sponsor did not provide any incentive for doctors to prescribe specific products, although individual doctors might have had personal preferences or biases. After patients changed the type of insulin, injecting device and/or number of injections per day, they could not change their insulin regimen during the study. Insulin dose adjustments, however, were allowed.

Outcome Measures

Primary Outcome Measure

The primary outcome measure was the change from baseline in Insulin Therapy-Related Quality of Life (ITR-QOL) scores^{17,18}. The ITR-QOL questionnaire is a patient-reported set of 23 questions relating to the impact of insulin therapy on aspects of daily life. Each question is rated on a five-point scale, with higher scores indicating a better QOL. The ITR-QOL consists of four subscales: social activities (five questions), physical functioning (four questions), daily activities (three questions) and feelings about insulin treatment (11 questions). The ITR-QOL questionnaire was completed at baseline and at week 12 (or discontinuation).

Secondary Outcome Measures

Change from Baseline in Plasma HbA_{1c}

Baseline plasma HbA_{1c} levels were determined within 4 weeks before or 5 days after baseline. End-of-study plasma HbA_{1c} levels were determined within 2 weeks of week 12 (i.e. between week 10 and week 14) or discontinuation. Plasma HbA_{1c} levels were measured at local laboratories using standard methods, and are expressed as National Glycohemoglobin Standardization Program equivalent values (i.e. the Japan Diabetes Society HbA_{1c} value +0.4%^{20,21}).

Reasons for Change in Insulin Regimen

At baseline, both patients and doctors chose one or more from a list of reasons (Table 2) for the change (including 'Other').

Pattern of Changes in Insulin Regimen

The details of each patient's insulin regimen were recorded before the regimen was changed, at baseline and at week 12

(or discontinuation). These details included the category of insulin: (i) rapid-acting (rapid- or ultra-rapid-acting); (ii) biphasic (biphasic/premixed); (iii) long-acting (intermediate- or long-acting/basal); (iv) the type of insulin preparation (e.g. human insulin or insulin analog); (v) the number of injections per day; (vi) the time(s) of injection (before breakfast, before lunch, before dinner, bedtime); (vii) the type of injecting device (disposable, cartridge, syringe); and (viii) the total insulin dose per day.

Treatment Adherence

Patients completed a treatment adherence questionnaire, in which they reported the extent of adherence (always, often, usually, occasionally, not at all) for each injection time, at baseline and at week 12 (or discontinuation).

Concomitant Oral Antidiabetic Medication

All concomitant oral antidiabetic medications were recorded at baseline and at week 12 (or discontinuation).

Change From Baseline in Diabetes Treatment Satisfaction Questionnaire Score

The Diabetes Treatment Satisfaction Questionnaire (DTSQ) is a patient-reported assessment of treatment satisfaction (six questions) and perceived frequency of severe hypoglycemia and hyperglycemia (two questions)²². Each question is rated on a six-point scale, with higher scores indicating either greater

treatment satisfaction or greater perceived frequency of hypoglycemic or hyperglycemic events. Patients completed a Japanese version of the DTSQ²³ at baseline and at week 12 (or discontinuation).

Questionnaire Procedures

Patients normally completed all questionnaires at the study site, but not in the presence of their doctors. All completed questionnaires (both patient and doctor) were sealed and submitted according to each institution's procedures.

Statistical Analysis

The standard deviation (SD) of the change in the total ITR-QOL score was assumed to be 12.0, based on previous results¹⁷. To estimate the change from baseline in the ITR-QOL total score with sufficient precision (95% confidence interval for the estimated mean change with a width of 2.0), 554 patients were required. Allowing for 20% dropout, the study aimed to include approximately 700 patients.

Summary statistics (mean, SD) were calculated for all continuous variables (e.g. age, weight, ITR-QOL scores, HbA_{1c} levels). A one-sample *t*-test was used to compare baseline and week 12 values within patient subgroups, and a two-sample *t*-test was used to compare changes from baseline between patient subgroups. A multiple linear regression model was used to assess the relationship between independent variables (age, sex, body mass index, baseline HbA_{1c} level, duration of diabetes, number

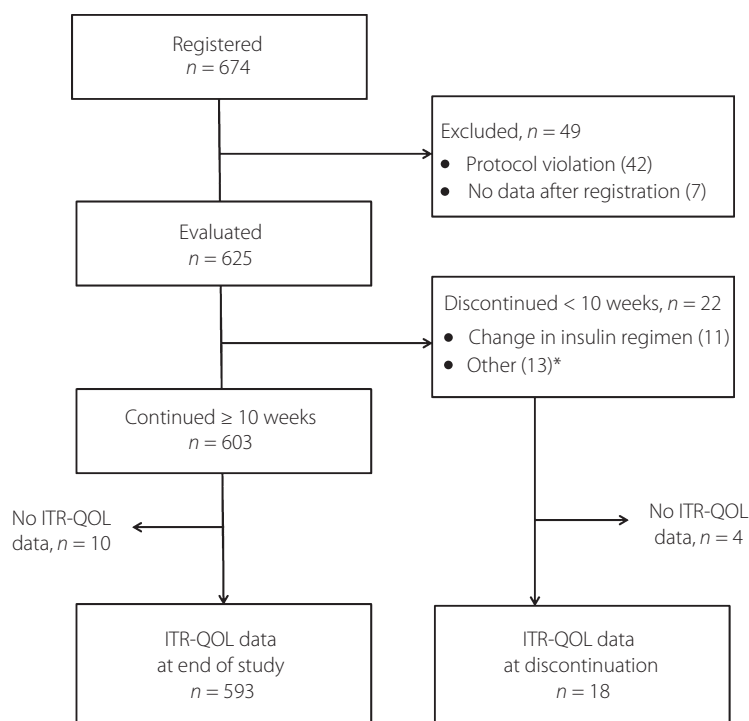


Figure 1 | Patient disposition, including number of patients with end-of-study primary outcome (ITR-QOL) data. *Includes two patients with both a change in insulin regimen plus another reason for discontinuation.

of insulin injections, type of insulin and device) and the change from baseline in plasma HbA_{1c} level. A backward, step-down method was used to further assess variables with $P < 0.05$ in the full regression model. Missing data were not imputed. All statistical analyses were carried out using SAS[®] version 9.1.3 (SAS, Cary, NC, USA), and P -values ≤ 0.05 were considered significant.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 674 patients were registered, of whom 625 were evaluated (Figure 1). The most common reason for exclusion of registered patients from evaluation was protocol violation. The most common reason for discontinuation during the study was a subsequent change in insulin regimen.

The baseline characteristics of the patients were typical of Japanese patients with type 2 diabetes mellitus (Table 1)²⁴. Among the evaluated patients, the mean age was 63.3 years, the mean BMI was 24.52 kg/m² and there were more men (54.2%) than women (45.8%). Most patients had a prolonged history of diabetes and insulin treatment (mean durations of

16.15 and 7.17 years, respectively). Approximately 60% of patients were taking oral antidiabetic medications. Most patients (86.4%) had one or more complications of diabetes.

Changes in Insulin Therapy

Most (521 of 625; 83.4%) patients changed the type of insulin as part of the change in insulin regimen (Figure 2). Approximately 20% (126 of 625; 20.2%) of patients changed the type of device and approximately 30% (183 of 625; 29.3%) of patients changed the number of injections. Among patients who changed the number of injections, most (149 of 183; 81.4%) also changed the type of insulin.

Overall, the most common reason for changing insulin regimen was 'poorly controlled glycemia' (Table 2). This was the most common doctor-reported reason and the second most common patient-reported reason. Among patients, the most common reason for regimen change was 'recommendation from the doctor', which might have been related to poorly controlled glycemia, although this cannot be determined from the questionnaires. 'Change of insulin preparation(s)' was the second most common doctor-reported reason and the third most common patient-reported reason.

The three categories of insulin type were used with similar prevalence both before and after the change in insulin therapy (Table 3). Common timings of injections were before breakfast, lunch and dinner for rapid-acting insulin, and before breakfast and dinner for biphasic insulin. Regarding long-acting insulin, the most common timing of injection was bedtime. Biphasic insulin only (i.e. without an additional insulin type) was the most commonly used insulin both before and after the change in regimen (Table 4). Changes in insulin regimen were associated with a decrease in the proportion of patients using one type of insulin (from 64.5 to 55.4%) and an increase in the proportion of patients using two types of insulin (from 34.4 to 43.0%; Table 4).

The proportion of patients using each type of injection device did not change substantially after the change in insulin regimen. Disposable devices were the most common devices used both before (471 patients; 75.4%) and after (486 patients; 77.8%) the change in regimen. Cartridges (before change: 127 patients, 20.3%; after change: 94 patients, 15.0%) were also used. A small number of patients used both disposable devices and cartridges (before change: 24 patients, 3.8%; after change: 43 patients, 6.9%). A few patients used syringes (before change: three patients, 0.5%; after change: two patients, 0.3%).

Most patients injected insulin two or three times a day both before and after the change in insulin regimen (Figure 3). However, the proportion of patients who injected insulin three or four times a day increased after the change in regimen.

Quality of Life

In the whole population, QOL did not worsen during the 12-week study. There was no statistically significant change in the ITR-QOL total score from baseline to week 12 (Table 5).

Table 1 | Patient characteristics at baseline

Variables	Value <i>n</i> = 625
Mean age, years (SD)	63.3 (12.0)
Sex, <i>n</i> (%)	
Men	339 (54.2%)
Women	286 (45.8%)
Mean height, cm (SD)	160.73 (9.47)
Mean weight, kg (SD)	63.59 (13.82)
Mean body mass index, kg/m ² (SD)	24.52 (4.32)
Mean duration of diabetes, years (SD)	16.15 (8.91)
Mean duration of insulin treatment, years (SD)	7.17 (5.53)
Concomitant oral antidiabetic medication, <i>n</i> (%)	
None	259 (41.4%)
At least one type*	366 (58.6%)
Biguanide	189 (30.2%)
α -Glucoside inhibitor	161 (25.8%)
Sulfonylurea	157 (25.1%)
Thiazolidinedione	71 (11.4%)
Glinide	18 (2.9%)
Complications of diabetes, <i>n</i> (%)	
Present	540 (86.4%)
Absent	84 (13.4%)
Unknown	1 (0.2%)
Type of complication, <i>n</i> (%)	
Hypertension	334 (53.4%)
Dyslipidemia	320 (51.2%)
Diabetic retinopathy	287 (45.9%)
Diabetic neuropathy	238 (38.1%)
Diabetic nephropathy	220 (35.2%)

*Some patients used more than one oral antidiabetic medication. SD, standard deviation.

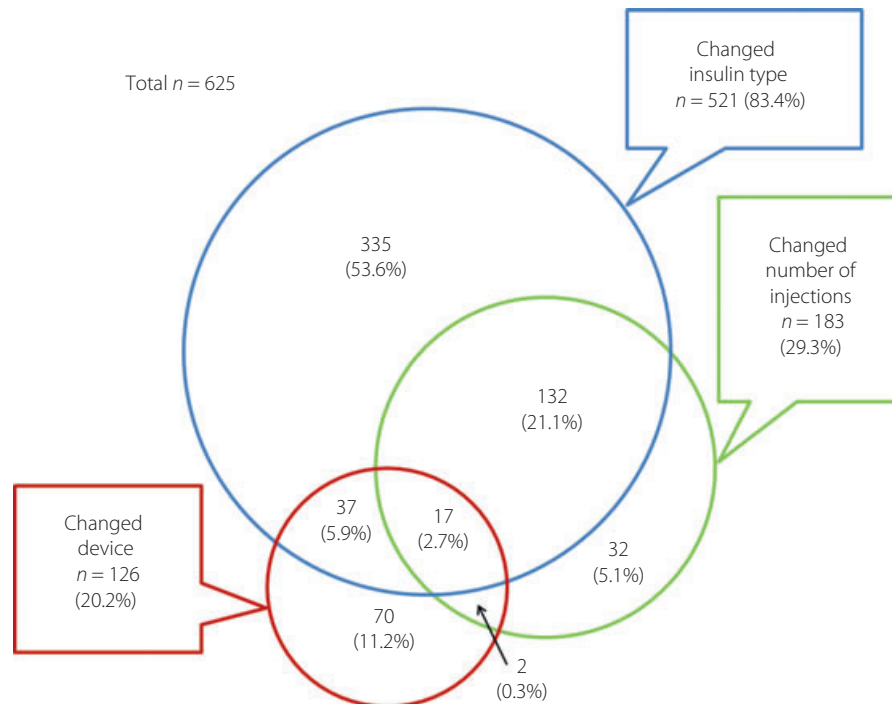


Figure 2 | Overlap of changes in insulin type, device and number of injections among patients with type 2 diabetes mellitus ($n = 625$).

Table 2 | Reasons for change in insulin therapy

Reason	Doctor-reported n (%) $n = 625$	Patient-reported n (%) $n = 625$	Agreement rate
Poorly controlled glycemia	388 (62.1%)	313 (50.1%)	0.75
Change of insulin preparation(s)	179 (28.6%)	106 (17.0%)	0.70
Dissatisfaction with device	69 (11.0%)	56 (9.0%)	0.85
Concern about hypoglycemia	53 (8.5%)	62 (9.9%)	0.86
Dissatisfaction with number of doses	32 (5.1%)	31 (5.0%)	0.94
User-friendliness	20 (3.2%)	22 (3.5%)	0.95
Patient request (for doctors) or doctor recommendation (for patients)	17 (2.7%)	407 (65.1%)	0.32
Concern about safety other than hypoglycemia	3 (0.5%)	17 (2.7%)	0.97
Other	83 (13.3%)	54 (8.6%)	0.84
No answer	2 (0.3%)	31 (5.0%)	NA

NA, not applicable.

There was a small, but statistically significant, increase only in the daily activities subscale score.

Ad hoc analysis by type of regimen changes (type of insulin, injection device and/or number of injections) in the ITR-QOL total score showed no statistically significant differences between

subgroups in each type of change (Table 6). Statistically greater increases in the ITR-QOL total score from baseline to week 12 were observed in the subgroups of patients who changed type of insulin, who did not change type of injection device and who did not change the number of injections, whereas the ITR-QOL total score did not change in the subgroups of patients who did not change type of insulin, who changed type of injection device and who changed the number of injections.

Multiple linear regression analysis was also carried out, but none of the following variables were significantly associated with the change in the ITR-QOL total score: age, sex, BMI, duration of diabetes, baseline HbA_{1c} level, the number of injections per day before regimen change, type of insulin before regimen change and device before regimen change (data not shown).

The 'perceived frequency of hyperglycemia' DTSQ subscale score (mean \pm SD) decreased significantly at 12 weeks from baseline (baseline: 3.4 ± 1.6 ; week 12: 3.0 ± 1.7 ; $n = 573$; $P \leq 0.001$), in accordance with improved glycemic control. The 'treatment satisfaction' DTSQ subscale mean improved numerically, but was not statistically significant at week 12 (baseline: 24.8 ± 6.4 ; week 12: 25.4 ± 6.4 ; $n = 552$). There was little change in the 'perceived frequency of hypoglycemia' (baseline: 1.7 ± 1.5 ; week 12: 1.8 ± 1.5 ; $n = 571$; $P = 0.106$) DTSQ subscale score.

Plasma HbA_{1c} Levels

Plasma HbA_{1c} levels decreased significantly (mean change = $-0.37 \pm 0.97\%$, $n = 606$, $P < 0.001$) from $8.21 \pm 1.47\%$ ($n = 618$) at baseline to $7.85 \pm 1.31\%$ ($n = 610$) at week 12.

Table 3 | Changes in insulin type and injection time before and during the 12-week study

Category of insulin Type of insulin	Injection time	Before change <i>n</i> (%) <i>n</i> = 625	After change* <i>n</i> (%) <i>n</i> = 625	Week 12 <i>n</i> (%) <i>n</i> = 622
Rapid-acting	Any	255 (40.8%)	268 (42.9%)	265 (42.6%)
Rapid-acting insulin	Before breakfast	228 (36.5%)	235 (37.6%)	233 (37.5%)
Ultra-rapid-acting analog	Before lunch	229 (36.6%)	235 (37.6%)	232 (37.3%)
	Before dinner	185 (29.6%)	205 (32.8%)	203 (32.6%)
	Bedtime	0 (0.0%)	0 (0.0%)	0 (0.0%)
Biphasic	Any	321 (51.4%)	364 (58.2%)	363 (58.4%)
Biphasic insulin	Before breakfast	268 (42.9%)	314 (50.2%)	313 (50.3%)
Biphasic analog	Before lunch	63 (10.1%)	120 (19.2%)	121 (19.5%)
	Before dinner	301 (48.2%)	334 (53.4%)	332 (53.4%)
	Bedtime	2 (0.3%)	1 (0.2%)	1 (0.2%)
Long-acting	Any	278 (44.5%)	282 (45.1%)	277 (44.5%)
Intermediate-acting insulin	Before breakfast	118 (18.9%)	109 (17.4%)	107 (17.2%)
Intermediate-acting analog	Before lunch	5 (0.8%)	2 (0.3%)	3 (0.5%)
Long-acting analog	Before dinner	97 (15.5%)	95 (15.2%)	92 (14.8%)
	Bedtime	137 (21.9%)	146 (23.4%)	143 (23.0%)

*Immediately after change in insulin therapy (i.e. baseline).

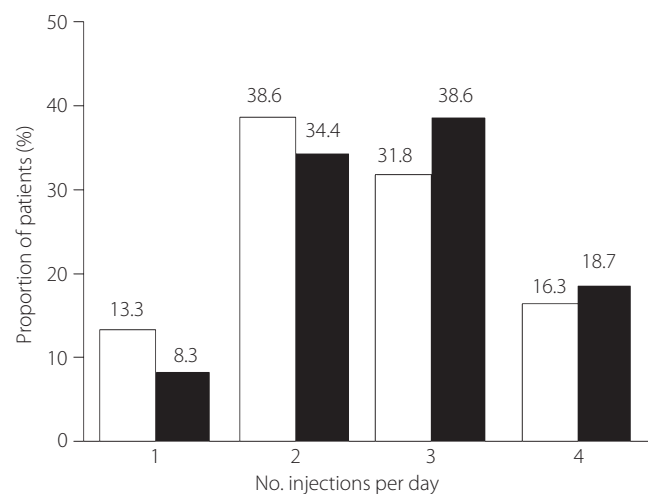
Table 4 | Changes in insulin type combinations before and during the 12-week study

Combination	Before change <i>n</i> (%) <i>n</i> = 625	After change* <i>n</i> (%) <i>n</i> = 625	Week 12 <i>n</i> (%) <i>n</i> = 622
No insulin used	0 (0.0%)	0 (0.0%)	2 (0.3%)
Rapid-acting only	49 (7.8%)	21 (3.4%)	21 (3.4%)
Biphasic only	235 (37.6%)	271 (43.4%)	271 (43.6%)
Long-acting only	119 (19.0%)	54 (8.6%)	53 (8.5%)
Rapid-acting + biphasic	63 (10.1%)	51 (8.2%)	51 (8.2%)
Rapid-acting + long-acting	136 (21.8%)	186 (29.8%)	183 (29.4%)
Biphasic + long-acting	16 (2.6%)	32 (5.1%)	31 (5.0%)
Rapid-acting + biphasic + long-acting	7 (1.1%)	10 (1.6%)	10 (1.6%)

*Immediately after change in insulin therapy (i.e. baseline).

Subgroup analysis based on the type of changes in plasma HbA_{1c} levels showed statistically significantly greater decreases in plasma HbA_{1c} levels in patients who changed the type of insulin or the number of injections compared with patients who did not make these changes (Table 7).

Multiple linear regression analysis identified a statistically significant association between the change in plasma HbA_{1c} level and the baseline HbA_{1c} level, baseline BMI, and the number of insulin injections before the regimen change (Table 8). Independent variables including age, sex, duration of diabetes, type of insulin before regimen change and device before regimen change were not significant. The decrease in plasma HbA_{1c} level was greater in patients with higher baseline HbA_{1c} levels compared with patients with lower HbA_{1c}

**Figure 3** | Number of insulin injections per day among patients with type 2 diabetes mellitus before (white columns) and after (black columns) changing insulin regimen (*n* = 625).

levels, in patients with BMI <25 kg/m² compared with patients with BMI ≥25 kg/m² and in patients with two or more insulin injections per day before the change in regimen compared with patients with one injection before the change. These associations were confirmed by backward, step-down regression analysis. However, these variables only accounted for 27% of the variance in the change in plasma HbA_{1c} levels.

There was a small, but statistically significant, increase in the total daily dose of insulin (baseline: 30.7 ± 21.8 IU; week 12: 31.5 ± 20.1 IU; change = 0.8 ± 9.0 IU; *n* = 620; *P* = 0.023)

Table 5 | Insulin therapy-related quality of life subscale and total scores during the 12-week study

Subscale (range of possible scores)	Score Mean (SD)			P-value*
	Baseline n = 625	Week 12 n = 611	Difference	
Social activities (5–25 points)	22.0 (3.7) n = 609	22.2 (3.7) n = 583	0.12 (2.99) n = 567	0.341
Physical functioning (4–20 points)	17.3 (2.5) n = 612	17.4 (2.6) n = 583	0.04 (2.17) n = 571	0.672
Daily activities (3–15 points)	12.7 (2.3) n = 614	12.9 (2.3) n = 578	0.18 (2.08) n = 568	0.038
Feeling about insulin treatment (11–55 points)	44.6 (9.0) n = 593	45.1 (9.3) n = 591	0.54 (7.06) n = 562	0.073
Total score (23–115 points)	97.0 (15.2) n = 575	97.8 (15.6) n = 560	0.86 (11.25) n = 518	0.082

*One-sample *t*-test. SD, standard deviation.

during the study; however, the increase was not considered clinically significant.

Patient-Reported Treatment Adherence

The change in insulin regimen was not associated with any apparent change in patient-reported treatment adherence. Most

patients reported adhering to treatment always or often at all injection times both before and after the change in insulin regimen.

Concomitant Oral Antidiabetic Medication

The proportion of patients who were taking concomitant oral antidiabetic medication decreased slightly after the change in insulin regimen (before change: *n* = 366; 58.6%; after change: *n* = 347; 55.5%) and was maintained at week 12 (*n* = 348; 55.7%).

DISCUSSION

The psychological barriers to initiating or intensifying insulin therapy are well known and include a fear of reduced QOL. Although patients are generally more receptive to changing insulin regimen than to initiating insulin, some psychological barriers still exist, including perceived effects on daily activities, the burden of an increased number of injections and worry about weight gain^{8,25}. Most studies of QOL in relation to insulin treatment have focused on comparisons between human insulin or insulin analog initiation, rather than the effect of changing insulin regimen. However, because of the progressive nature of type 2 diabetes mellitus, most patients will eventually need intensification of insulin therapy to maintain glycemic control. The present study is the first to examine the effects of a range of insulin regimen changes on these parameters in a clinical practice setting, and contributes

Table 6 | Subgroup analysis of changes in the Insulin Therapy-Related Quality of Life total score during the 12-week study

Insulin therapy change	ITR-QOL total score Mean (SD)			Within group P-value*	Difference between group† (95% CI)	Between group P-value‡
	Baseline	Week 12	Change from baseline			
Type of insulin						
Not changed	97.3 (13.5) n = 135	97.3 (14.8) n = 125	−0.18 (10.30) n = 123	0.848		
Changed	96.9 (15.7) n = 440	97.9 (15.8) n = 435	1.18 (11.52) n = 395	0.042		
					1.36 (−0.92, 3.64)	0.241
Type of injection device						
Not changed	97.1 (15.4) n = 457	97.9 (15.9) n = 446	1.19 (11.37) n = 411	0.034		
Changed	96.5 (14.5) n = 118	97.2 (14.6) n = 114	−0.42 (10.70) n = 107	0.685		
					−1.62 (−4.01, 0.78)	0.186
No. injections						
Not changed	96.7 (15.5) n = 411	98.1 (15.6) n = 398	1.25 (10.77) n = 370	0.027		
Changed	97.7 (14.6) n = 164	97.0 (15.6) n = 162	−0.10 (12.35) n = 148	0.921		
					−1.35 (−3.50, 0.80)	0.218

*One-sample *t*-test. †Mean change from baseline in the 'Changed' group minus mean change from baseline in the 'Not changed' group.

‡Two-sample *t*-test. CI, confidence interval; ITR-QOL, Insulin Therapy-Related Quality of Life; SD, standard deviation.

Table 7 | Subgroup analysis of changes in plasma glycated hemoglobin levels during the 12-week study

Insulin therapy change	HbA _{1c} Mean% (SD)			Within group P-value*	Difference between group† (95% CI)	Between group P-value‡
	Baseline	Week 12	Change from baseline			
Type of insulin						
Not changed	8.11 (1.56) n = 135	7.87 (1.35) n = 132	-0.21 (0.80) n = 132	0.003		
Changed	8.24 (1.44) n = 483	7.85 (1.29) n = 478	-0.41 (1.01) n = 474	<0.001		
					-0.20 (-0.39, -0.01)	0.035
Type of injection device						
Not changed	8.24 (1.44) n = 493	7.87 (1.33) n = 487	-0.38 (1.00) n = 483	<0.001		
Changed	8.11 (1.55) n = 125	7.80 (1.21) n = 123	-0.31 (0.86) n = 123	<0.001		
					0.07 (-0.12, 0.26)	0.478
No. injections						
Not changed	8.01 (1.35) n = 438	7.77 (1.33) n = 431	-0.25 (0.84) n = 429	<0.001		
Changed	8.72 (1.62) n = 180	8.06 (1.22) n = 179	-0.66 (1.18) n = 177	<0.001		
					-0.42 (-0.58, -0.25)	<0.001

*One-sample *t*-test. †Mean change from baseline in the 'Changed' group minus mean change from baseline in the 'Not changed' group.

‡Two-sample *t*-test. CI, confidence interval; HbA_{1c}, glycated hemoglobin; SD, standard deviation.

much-needed data that will help patients and doctors make informed treatment choices.

In the present large observational study, changes of insulin therapy improved glycemic control in Japanese patients with type 2 diabetes mellitus without adversely affecting QOL. Patients enrolled in the present study were relatively established diabetic patients with more than 16 years' history of illness and more than 7 years of insulin treatment on average. Therefore, it was expected that the changes in insulin therapy were at the level of 'modification'. In fact, the majority of changes in insulin therapy were changes in the type of insulin, and only approximately 20 and 30% of patients changed the device and the number of injections, respectively. This would be the primary reason why the changes in insulin therapy did not significantly affect patients' QOL.

Subpopulation analyses by type of regimen changes showed that the ITR-QOL total score increased from baseline to week 12 in the subgroups of patients who changed the type of insulin, who did not change the type of injection device and who did not change the number of injections. The reason why changing the type of insulin contributed to improvements in a patients' QOL was probably because physicians chose more appropriate insulin preparations for individual patients. Regarding the influence of changes of injection device or the number of injections, improvement in glycemic control might have helped sustain patients' QOL despite any adverse emotional impact arising from regimen changes, as it was shown that better glycemic control was clearly related to better QOL

in insulin therapy¹⁷. Thus, doctors can reassure patients that modifying their insulin therapy is unlikely to detract from their QOL.

Interestingly, 'doctor recommendation' was the main patient-reported reason for changing insulin regimen, suggesting that patients might not fully understand the clinical reasons for changing their regimen. Similar findings were reported in a substudy of the Treating to Target in Type 2 Diabetes trial, in which patients who required intensification of insulin therapy were willing to do so when recommended by their doctor²⁶. Because patients who understand the reasons for changes in therapy are more motivated to adhere to treatment²⁷, doctors should openly discuss potential changes in insulin regimen to ensure patients are actively involved in the decision.

The results of the present study are strengthened by the large number of patients from 68 medical centers. The present study provides an important 'snapshot' of the current pattern of insulin use among Japanese patients with type 2 diabetes mellitus. The patients in the present study used a wide range of insulin types, and no single type predominated. In Japan, biphasic insulin was used as frequently as rapid-acting and long-acting insulin. This is in contrast to Western countries, where guidelines from the American Diabetes Association and the European Association for the Study of Diabetes recommend long-acting basal insulin for insulin initiation²⁸. This difference in insulin type might be because intrinsic insulin secretion after meals is more impaired in patients from Japan than in patients from Western countries^{29,30}.

Table 8 | Multiple linear regression analysis of change from baseline in plasma glycosylated hemoglobin levels during the 12-week study

Variables	Full regression model		Step-down regression model	
	Regression coefficient (95% CL)	P-value	Regression coefficient (95% CL)	P-value
Intercept	1.63 (1.09, 2.17)	<0.001	1.85 (1.42, 2.28)	<0.001
Age				
<65 years	Reference	–		
≥65 years	0.02 (–0.13, 0.16)	0.815		
Sex				
Male	Reference	–		
Female	0.07 (–0.07, 0.21)	0.310		
BMI		0.051		0.022
<25 kg/m ²	Reference	–	Reference	–
≥25 kg/m ²	0.18 (0.03, 0.32)	0.016	0.20 (0.06, 0.34)	0.006
Unknown	0.20 (–0.64, 1.05)	0.640	0.19 (–0.64, 1.02)	0.653
Duration of diabetes		0.728		
<15 years	Reference	–		
≥15 years	–0.06 (–0.21, 0.09)	0.449		
Unknown	–0.07 (–0.34, 0.21)	0.634		
Baseline plasma HbA _{1c} level	–0.33 (–0.38, –0.28)	<0.001	–0.33 (–0.37, –0.28)	<0.001
No. injections per day before regimen change		0.069		0.038
1	Reference	–	Reference	–
2	0.23 (–0.02, 0.49)	0.073	0.25 (0.03, 0.47)	0.023
3	0.41 (0.09, 0.73)	0.011	0.33 (0.10, 0.55)	0.004
4	0.51 (0.09, 0.93)	0.019	0.27 (0.02, 0.53)	0.035
Type of insulin before regimen change		0.368		
Rapid-acting only	Reference	–		
Biphasic only	0.30 (0.01, 0.59)	0.044		
Long-acting only	0.24 (–0.12, 0.59)	0.188		
Rapid-acting + biphasic	0.17 (–0.15, 0.50)	0.292		
Rapid-acting + long-acting	–0.02 (–0.38, 0.33)	0.896		
Biphasic + long-acting	0.17 (–0.34, 0.67)	0.519		
Rapid-acting + biphasic + long-acting	0.05 (–0.65, 0.75)	0.887		
Device before change		0.130		
Disposable	Reference	–		
Cartridge	0.01 (–0.17, 0.19)	0.907		
Syringe	–0.88 (–1.85, 0.09)	0.076		
Disposable + cartridge	0.31 (–0.08, 0.69)	0.115		
Coefficient of determination (R ²)	0.270		0.253	

BMI, body mass index; CL, confidence limit; HbA_{1c}, glycosylated hemoglobin.

The present study had several limitations. As expected in an observational study, there was considerable heterogeneity in both the study population and insulin regimens. However, the intention of the study was to examine ‘real-life’ clinical practice in a broad range of patients with type 2 diabetes mellitus in Japan. Because the study did not include a control group, the observed improvement in glycemic control cannot be ascribed directly to the change in insulin regimen, as other factors (e.g. changes in lifestyle) might have contributed. One limitation of the QOL scales we used was the difficulty in detecting improvements if the initial ratings were relatively high (i.e. ‘ceiling effect’)¹⁰. We also cannot exclude the possibility that participation in the study itself might have affected

patients’ perception of QOL. Finally, because of the limited duration of the study, we do not know how long QOL and glycemic control are maintained during treatment with the new insulin regimen or whether they are maintained after subsequent regimen changes.

In conclusion, it was suggested that changes in insulin regimen might improve glycemic control in patients with type 2 diabetes mellitus without detracting from QOL. The range of insulin types currently available in Japan allows doctors’ flexibility in tailoring insulin therapy to optimize both the clinical and QOL needs of individual patients. This is the first publication for the INSIGHTs observational study focusing on the whole study population. Further subgroup analysis by

various aspects might provide additional information regarding glycemic control and patients' QOL.

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