Reducing Snacks When Switching from Conventional Soluble to Lispro Insulin Treatment: Effects on Glycaemic Control and Hypoglycaemia

T. Rönnemaa*, J. Viikari

Department of Medicine, University of Turku, Turku, Finland

The lack of significant improvement in HbA_{1c} during insulin lispro treatment in previous studies may have been due to inadequate dietary adjustments. We tested whether reduction of snacks and a compensatory increase in main meals results in improved metabolic control when switching to lispro treatment. One hundred and forty-one Type 1 diabetic patients, mean ± SD age 36 ± 9 years, diabetes duration 14 ± 10 years, had two daily NPH injections throughout the study. After a baseline visit, the patients used conventional soluble insulin preprandially thrice daily for 12 weeks. Thereafter they were switched to lispro insulin and advised to transfer ≥50 % of their snack carbohydrates to preceding main meals. Mean HbA_{1c} at baseline was 8.05 %. After the conventional period and the 12-week lispro period, HbA_{1c} was 7.81 and 7.70 % ($p = 0.088$), respectively. In those patients who diminished their snacks as advised ($n = 67$), HbA_{1c} decreased from 7.91 to 7.66 % ($p = 0.014$) during lispro, whereas no change was observed in patients not compliant with the dietary change. The number of hypoglycaemic episodes was lower during lispro period (blood glucose <2.5 mmol l^{-1}: 1.43 vs 2.19 episodes, $p = 0.004$; symptomatic nocturnal hypoglycaemia 1.16 vs 1.67 episodes, $p<0.001$). When switching from conventional soluble to lispro insulin, reduction of snack carbohydrates is safe and results in slightly improved HbA_{1c} in patients who are fully compliant with the dietary change. © 1998 John Wiley & Sons, Ltd.

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Introduction

The lispro insulin analogue takes a monomeric form rapidly after subcutaneous injection and its absorption into the circulation begins within 15 min.[1] Its action reaches its maximum approximately 50 min after administration.[2,3] Lispro insulin has been shown to reduce postprandial glucose excursions compared with conventional human-soluble insulin.[3–5] However, so far no significant improvements in overall glycaemic control (expressed as changes in HbA_{1c}) have been observed in studies which have not focused on adjustment of basal insulin supply.[4,5] This has been attributed to higher preprandial glucose values during lispro treatment because of its short duration of action compared with regular insulin.

Dietary guidelines for patients with Type 1 diabetes mellitus (DM) using multiple insulin injection therapy include, in addition to four main meals (breakfast, lunch, dinner, late evening meal), snacks to be taken between breakfast and lunch and between lunch and dinner.[6,7] These dietary guidelines are based on the assumption that without snacks there is a considerable risk for hypoglycaemia after meals, secondary to the prolonged action of soluble insulin. Until now, no special dietary recommendations have been given when lispro insulin is used instead, although one short-term study has shown that meal composition is an essential determinant of the glucose lowering effect of lispro.[8] Theoretically, reduction of snacks and switching calories from snacks to preceding main meals may ameliorate the late rise in preprandial glucose values and lead to improved glycaemic control. The aim of this study was to evaluate the effect of transferring snack carbohydrates to preceding meals when switching patients from conventional human soluble to lispro insulin treatment. The primary outcome measures were glycaemic control, expressed as HbA_{1c}, and the occurrence of hypoglycaemia. In addition, we analysed the primary outcome measures separately in subgroups of patients with or without complete dietary change.

Sponsors: Eli Lilly Finland Company
*Correspondence to: Dr Tapani Rönnemaa, Department of Medicine, University of Turku, FIN-20520 Turku, Finland

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Patients, Design, and Methods

Patients

One hundred and fifty-one patients with Type 1 DM were recruited from the outpatient clinics of 25 hospitals in Finland. Each clinic is responsible for the care of 100 to 300 such patients. Approximately 80 % of those contacted accepted the invitation to the study. The inclusion criteria were: duration of Type 1 DM > 1 year; age 18 to 70 years; treatment with multiple, i.e. three or more short-acting insulin injections and twice daily basal (NPH) insulin for at least 1 month, before entry into the study; $HbA_{1c} \leq 10.0$ % at baseline; sufficient visual acuity for reliable self-monitoring of blood glucose. The exclusion criteria were: pregnancy or lactation; insufficient method for birth control; clinically significant coronary heart disease; constant macroproteinuria or serum creatinine > 140 μmol l^{-1}. Three patients discontinued the study during the conventional insulin period: one had taken NPH insulin only once a day by mistake, one decided to discontinue because of inability to make any changes in his dietary habits, and one was excluded because his HbA_{1c} was markedly above 10.0 % at baseline. In the final analysis, four patients did not fulfill the inclusion criteria (two had proteinuria, one was not C-peptide negative, one had only one daily basal NPH injection at baseline), two patients had switched themselves to non-study insulins before the end of the study, and in one patient a malignant mammary tumour was diagnosed and treated with anticancer drugs during the study. These 10 patients were excluded from all analyses. Three patients with baseline HbA_{1c} slightly above 10.0 % were not excluded from the study. Thus the final study population consisted of 141 Type 1 patients. Their mean (SD) age was 36.0 (9.4) years, duration of diabetes 14.3 (9.6) years, weight 73.0 (11.0) kg, height 1.72 (0.09) m, and BMI 24.5 (2.4) kg m^{-2}. The BMI of men was 0.9 kg m^{-2} higher ($p = 0.029$) than that of women; age and duration of diabetes were similar in men and women.

Protocol

This was an open sequential study. All patients had two daily NPH insulin (Humulin NPH®, Eli Lilly, Indianapolis, USA) injections (morning and bedtime) during the whole study. After the baseline examination, the patients used human soluble insulin (Humulin Regular®, Eli Lilly, Indianapolis, USA) three times daily before the main meals for 12 weeks. A dose adjustment visit took place after the first 2 weeks of the soluble insulin period. On completion, the patients were switched to lispro insulin (Eli Lilly, Indianapolis, USA) as their premeal insulin, three times daily, for 12 weeks. No systematic changes were made in either basal or short-acting insulin doses at this visit. However, simultaneously with the change in insulin preparation the patients were advised to reduce their snacks by transferring at least 50 % of their snack carbohydrate calories to the preceding main meals. After the first 2 weeks on lispro, insulin doses were adjusted by the treating physician when necessary. Patients were advised to take soluble insulin approximately 30 min before the meals and lispro insulin immediately before the meals. Patients were allowed to adjust their daily doses of short-acting insulins (soluble or lispro) throughout the study as they were accustomed to do earlier. The glycaemic targets provided for the physicians and the patients were those presented in a recent (1995) national recommendation for the treatment of Type 1 DM: premeal blood glucose 4 to 6 mmol l^{-1} and postprandial blood glucose 6 to 8 mmol l^{-1}. At both dose adjustment visits the patients were informed about their HbA_{1c} values measured 2 weeks earlier.

Dietary Assessment

At the baseline examination, diabetes nurses performed a detailed structured dietary interview, calculated the carbohydrate content of each meal and snack, and, when necessary, gave individual dietary advice according to the principles recommended for Type 1 DM patients on multiple insulin injection therapy.[6] At the end of the regular insulin period the interview was repeated. During the same visit, patients received written and verbal plans for the reduction of their morning and afternoon snacks. If the size of a snack in terms of carbohydrate content had been less than 5 % of total daily calories, all or at least 50 % of it was advised to be transferred to the preceding main meal. If the size of the snack was greater, 50 % of its carbohydrates were advised to be transferred to the preceding main meal. At the end of the lispro insulin period the structured dietary interview was performed again.

In the dietary interview performed after the soluble and lispro insulin periods, the patients were asked to describe their average content of each main meal and each snack during the preceding 10-week period, paying special attention to the carbohydrate content of the meals. The dietary interview took approximately 15–20 min per patient on both occasions. The nurse calculated the amount of carbohydrate in each meal using standard tables on the nutrient contents of various foods. The total daily carbohydrate content was summed and the percentage share of each meal was calculated.

All diabetes nurses performed the dietary interview using the same questionnaire and the same tables on nutrient contents of various foods. A training session was arranged for all participating nurses before the study to ensure the similarity of the methodology of the dietary interviews. At each study centre the same diabetes nurse evaluated the diet at the end of both treatment periods.

In statistical analyses, a patient was considered to be fully compliant with respect to the dietary change if both morning and afternoon snacks, expressed as percentage of total daily carbohydrate calories, were at least 50 %

smaller during the lispro period compared with the soluble period.

Measurements

HbA_{1c} was determined at baseline and after both study periods with fast performance liquid chromatography (reference range in non-diabetic subjects 4.2 % to 6.0 %). HbA_{1c} values from the preceding year were obtained from patient records. The mean ± SD number of HbA_{1c} determinations per patient during the previous year was 3.0 ± 0.8. Weight was measured at every visit to nearest 0.1 kg in light clothes without shoes. Patients were asked to measure and record their blood glucose values (Accutrend®, Boehringer, Mannheim, Germany) before and 1.5 h after the main meals and at bedtime on 2 to 3 days weekly and, if possible, during each suspected hypoglycaemic episode. Prelunch and predinner glucose values from 2 consecutive days before the final visits of the soluble and lispro insulin periods were recorded by all patients. The mean values of these two prelunch and predinner glucose concentrations were used in the analyses to indicate daytime premeal glucose control.

Patients were asked to record all hypoglycaemic episodes, their severity (mild, moderate, severe) and time of occurrence in their blood glucose monitoring booklets. An episode was regarded as: mild if it did not interfere with daily activities; moderate if it interfered with daily activities; severe if the patient needed help by another person. Patients marked all blood glucose values below 3.5 mmol l^{-1} without simultaneous hypoglycaemic symptoms with a circle. Nocturnal hypoglycaemic episodes were defined as blood glucose values < 3.5 mmol l^{-1} and/or hypoglycaemic symptoms between 24.00 and 06.00 h. In the analysis of hypoglycaemic episodes, the number of episodes occurring during the last 10 weeks of each insulin treatment period was calculated.

Statistical Methods

Student's *t*-test was used to compare men and women at baseline and Mann-Whitney test to compare men and women with respect to changes in outcome variables, HbA_{1c}, and hypoglycaemia. The Wilcoxon test was used to compare values measured at the end of regular insulin and lispro insulin periods. The reason for using the Wilcoxon test was that the changes in HbA_{1c}, weight, and insulin doses were not normally distributed. Pearson correlation analysis and univariate and multivariate regression analyses were used to examine factors associated with the difference in HbA_{1c} between the two insulin treatment periods. Continuous variables are presented as means ± SD and categorical variables as percentages.

Results

Because men and women were similar with respect to the outcome variables and their changes during the study, genders were combined in all analyses. The size of both morning and afternoon snacks, expressed as the proportion of total daily carbohydrates, was reduced on average by 4.9 and 5.5 % respectively, when patients switched from conventional soluble to lispro insulin treatment (Table 1). In other words, the average size of the snacks during lispro was approximately one-third of that during regular insulin. Correspondingly, the average size of breakfast had increased by 2.5 % and the size of lunch increased by 5.2 %. Sixty-seven of the 141 patients (48 %) had reduced their snacks exactly as advised, i.e. both morning and afternoon snacks were at least 50 % smaller during the lispro treatment period compared with the regular insulin period. The reduction in especially the afternoon snack was more pronounced in the patients with complete dietary change compared with those with incomplete dietary change (Table 1).

Weight of patients was about 0.5 kg lower at the end of the lispro period compared with the regular period (Table 2). Weight decreased similarly in patients with a complete dietary change (0.6 ± 1.5 kg, $p = 0.002$) and in patients with incomplete dietary change (0.4 ± 1.6 kg, $p = 0.046$). The mean daily dose of lispro insulin was 0.6 units lower ($p = 0.035$) than that of conventional soluble insulin. The daily dose of basal insulin was on average 1.3 units higher ($p < 0.001$) during the lispro treatment phase compared with regular period. Prelunch and predinner glucose concentrations did not differ at the end of the two treatment periods. HbA_{1c} measured at baseline and average HbA_{1c} during the preceding year were similar (Table 3). At the end of the conventional soluble period, mean HbA_{1c} was 0.24 % lower than at baseline. At the end of the lispro period mean HbA_{1c} was not significantly lower (difference 0.11 %) compared with HbA_{1c} after the soluble period.

Because less than half of the patients were fully compliant with the reduction of snacks we also analysed glycaemic control in subgroups formed according to completeness of the dietary change (Table 3). In both groups HbA_{1c} was significantly lower after the conventional soluble period compared with baseline values. After transfer to lispro insulin HbA_{1c} decreased by 0.25 % in patients with complete dietary change but was unchanged in the rest of the patients.

There was a weak inverse correlation ($r = -0.20$, $p = 0.04$) between the decrease in weight and the decrease in HbA_{1c} when the patients were transferred from soluble to lispro insulin. The change in HbA_{1c} was not associated with duration of diabetes, age, gender or change in the dose of short-acting insulin (p always > 0.10). The decrease in HbA_{1c} showed a weak positive correlation ($r = 0.18$, $p = 0.05$) to the increase in total NPH insulin dose.

Univarate and multivariate regression analyses were performed to examine whether the association between dietary change and improvement in HbA_{1c} was independent of possible confounding factors. In univariate regression analyses completeness of dietary change

Table 1. Distribution of carbohydrate calories during soluble and lispro insulin periods. Values are percentages of carbohydrate calories from total daily carbohydrates

Meal	All patients ($n = 141$)			Patients with complete dietary change ($n = 67$)			Patients with incomplete dietary change ($n = 74$)		
	Soluble	p	Lispro	Soluble	p	Lispro	Soluble	p	Lispro
Breakfast	16.0 ± 4.6	<0.001	19.4 ± 4.5	16.3 ± 4.5	<0.001	20.3 ± 4.6	15.6 ± 4.7	<0.001	18.5 ± 4.3
Morning snack	7.6 ± 3.8	<0.001	2.7 ± 3.4	7.6 ± 3.1	<0.001	1.3 ± 2.2	7.7 ± 4.3	<0.001	3.9 ± 3.9
Lunch	24.3 ± 5.0	<0.001	29.5 ± 4.8	24.3 ± 4.7	<0.001	30.2 ± 5.1	24.2 ± 5.3	<0.001	28.9 ± 4.5
Afternoon snack	9.3 ± 3.8	<0.001	3.8 ± 3.6	9.1 ± 3.3	<0.001	1.8 ± 2.5	9.6 ± 4.3	<0.001	5.6 ± 3.5

The rest of daily carbohydrate calories came from carbohydrates included in dinner, evening snack (in approximately half of the patients), and late evening meal, but no dietary advice was given to change these meals.

Table 2. Weight, insulin doses, and premeal blood glucose values during soluble and lispro insulin periods, all patients ($n = 141$)

Variable	Soluble	p	Lispro
Weight (kg)	73.4 ± 11.1	<0.001	72.9 ± 11.4
Short-acting dose (U day^{-1})	23.9 ± 10.0	0.035	23.3 ± 9.4
NPH dose (U day^{-1})	25.9 ± 9.8	<0.001	27.2 ± 10.3
Prelunch glucose (mmol l^{-1})	6.6 ± 1.9	0.95	6.6 ± 2.1
Predinner glucose (mmol l^{-1})	7.7 ± 2.7	0.31	8.0 ± 2.6

($p = 0.02$), HbA_{1c} after soluble insulin period ($p = 0.03$), and change in weight ($p = 0.02$) were associated with the change in HbA_{1c} whereas time of administration of soluble insulin ($p = 0.24$) and change in total daily NPH dose ($p = 0.11$) showed no association. In multivariate regression analyses the association between dietary change and improvement in HbA_{1c} was independent of HbA_{1c} after soluble insulin period and of the change in weight (respective standardized regression coefficients were –0.18, $p = 0.04$, and –0.19, $p = 0.02$).

The mean number (SD) of blood glucose determinations performed by the patients during the two 10-week treatment periods was 117 (78) during the lispro insulin and 115 (70) during the regular insulin period ($p = 0.66$). When all 141 patients were studied together, there was no significant difference in the number of symptomatic or symptomless hypoglycaemic episodes between the two treatment periods (Table 4). However, the number of blood glucose values < 2.5 mmol l^{-1} and the number of symptomatic nocturnal hypoglycaemic episodes were significantly lower during lispro treatment compared with conventional soluble insulin treatment.

To examine whether some patient groups are particularly prone to increased risk of hypoglycaemic episodes when the transfer from soluble to lispro insulin is combined with the reduction of snacks, the occurrence of hypoglycaemia was studied separately in patients who changed (Table 5) or who did not change (Table 6) their diet as advised. Among patients with full dietary compliance, those with a HbA_{1c} value > 7.5 % at the end of the regular insulin period, i.e. the subgroup expressing a marked (0.36 %) decrease in HbA_{1c} during

Table 3. HbA_{1c} values during the preceding year, at baseline and after soluble and lispro insulin periods in the whole population and in subgroups with or without complete dietary change

	Mean of previous year	p	Baseline	p	After soluble	p	After lispro
All patients ($n = 141$)	8.06 ± 1.20	0.37	8.05 ± 1.12	<0.001	7.81 ± 1.06	0.088	7.70 ± 1.11
Patients with complete dietary change ($n = 67$)	8.14 ± 1.24	0.91	8.09 ± 1.13	0.013	7.91 ± 1.14	0.014	7.66 ± 1.07
Patients with incomplete dietary change ($n = 74$)	7.98 ± 1.18	0.13	8.01 ± 1.13	<0.001	7.71 ± 0.97	0.97	7.73 ± 1.14

The p-values refer to comparison of differences between values in adjacent columns.

Table 4. Mean number of hypoglycaemic episodes per patient during 10-week periods of soluble or lispro insulin therapy, all patients ($n = 141$)

Episode	Soluble	p	Lispro
Mild	6.15 ± 9.21	0.36	5.24 ± 6.47
Moderate	2.09 ± 3.69	0.081	1.68 ± 4.08
Severe	0.07 ± 0.35	0.84	0.07 ± 0.35
Glucose 2.5–3.4 mmol l^{-1}	7.87 ± 10.74	0.39	7.05 ± 7.46
Glucose < 2.5 mmol l^{-1}	2.19 ± 3.87	0.005	1.43 ± 2.47
Symptomless	4.56 ± 7.52	0.101	3.83 ± 6.01
Symptomatic nocturnal	1.67 ± 2.43	<0.001	1.16 ± 2.18

lispro insulin, the number of hypoglycaemic episodes was similar during both treatment periods, except that moderate episodes were less frequent during lispro treatment (Table 5). In patients whose HbA_{1c} after soluble insulin period was ≤ 7.5 % and who performed a complete dietary change, i.e. a subgroup with a potentially high risk of hypoglycaemia, the number of mild hypoglycaemic episodes and symptomatic nocturnal episodes was lower during lispro insulin period compared with soluble insulin period.

Among patients who did not change their diet as advised no difference in the occurrence of hypoglycaemia between the two treatment periods was observed in those with HbA_{1c} > 7.5 % after soluble whereas in patients with HbA_{1c} ≤ 7.5 % after soluble a significantly lower frequency was observed in blood glucose values 2.5–3.4 mmol l^{-1} and in symptomatic nocturnal hypoglycaemia (Table 6).

Discussion

We did not find significantly better metabolic control in a population of Type 1 DM patients transferred from soluble to lispro insulin treatment and given advice to reduce the size of snacks and to increase correspondingly the size of the preceding main meals. However, a significant improvement in HbA_{1c} was observed in those patients who were fully compliant with the dietary advice and no decrease in HbA_{1c} was observed in the rest. This suggests that it is possible to achieve improved metabolic control with proper dietary adjustments when switching

Table 5. Mean number of hypoglycaemic episodes per patient during 10 week periods of soluble and lispro insulin therapy in patients who changed their diet as advised

Episode	HbA_{1c} > 7.5 % after regular ($n = 46$)			HbA_{1c} ≤ 7.5 % after regular ($n = 21$)		
	Soluble	p	Lispro	Soluble	p	Lispro
Mild	6.29 ± 10.6	0.64	5.99 ± 6.63	7.24 ± 10.35	0.040	4.06 ± 7.10
Moderate	1.92 ± 2.99	0.033	1.31 ± 2.76	1.04 ± 2.24	0.65	1.12 ± 2.59
Severe	0.05 ± 0.23	0.50	0.02 ± 0.15	0.00	1.0	0.00
Glucose 2.5–3.4 mmol l^{-1}	6.56 ± 12.18	0.26	6.54 ± 7.14	8.21 ± 8.27	0.31	6.53 ± 7.72
Glucose < 2.5 mmol l^{-1}	0.99 ± 1.53	0.17	0.73 ± 1.42	2.81 ± 6.34	0.14	0.92 ± 1.54
Symptomless	2.69 ± 4.69	0.66	2.68 ± 4.03	6.80 ± 10.81	0.063	3.86 ± 5.84
Symptomatic nocturnal	1.32 ± 2.07	0.20	1.06 ± 2.60	2.07 ± 2.92	0.010	1.31 ± 2.51

Table 6. Mean number of hypoglycemic episodes per patient during 10-week periods of soluble and lispro insulin therapy in patients who did not change their diet as advised

Episode	HbA_{1c} > 7.5 % after regular ($n = 42$)			HbA_{1c} ≤ 7.5 % after regular ($n = 32$)		
	Soluble	p	Lispro	Soluble	p	Lispro
Mild	5.22 ± 6.92	0.90	4.68 ± 5.80	6.44 ± 9.24	0.53	5.66 ± 6.76
Moderate	1.74 ± 3.29	0.85	1.49 ± 2.32	3.47 ± 5.30	0.35	2.81 ± 7.15
Severe	0.05 ± 0.23	0.63	0.10 ± 0.40	0.16 ± 0.63	0.88	0.12 ± 0.54
Glucose 2.5–3.4 mmol l^{-1}	6.15 ± 6.40	0.69	6.75 ± 7.12	11.80 ± 13.59	0.020	8.51 ± 8.23
Glucose <2.5 mmol l^{-1}	2.24 ± 3.94	0.45	1.77 ± 2.78	3.43 ± 3.70	0.055	2.34 ± 3.31
Symptomless	2.93 ± 3.76	0.39	3.03 ± 4.63	7.90 ± 10.29	0.26	6.53 ± 8.87
Symptomatic nocturnal	1.35 ± 2.18	0.13	1.02 ± 1.80	2.35 ± 2.79	0.019	1.38 ± 1.79

to lispro insulin therapy. Previous studies that have not focused on adjustment of basal insulin supply have shown that although lispro insulin effectively decreases postprandial glucose excursions compared with conventional soluble insulin, no significant improvement in HbA_{1c} is observed.[4,5] In contrast, we observed a 0.25 % reduction in HbA_{1c} in patients who were fully compliant with the dietary advice. The lack of effect of lispro on HbA_{1c} levels in previous studies may have been due to higher preprandial glucose levels during lispro treatment secondary to the very short action of lispro. Our results fit well with this hypothesis, because transferring carbohydrate calories from snacks to the main meals could theoretically diminish the need for higher insulin concentrations between the main meals.

Another possibility when striving for improved metabolic control when starting lispro treatment is to increase the proportion and number of injections of basal NPH insulin.[9] This strategy has led to a significant decrease in HbA_{1c} compared with soluble-insulin.[10] This and our results are in favour of the hypothesis that either the demand for basal insulin has to be reduced or basal insulin supply has to be increased in order to achieve improved metabolic control, when postprandial glucose excursions are effectively controlled by lispro insulin. In our study, changes in the proportions of short-acting and basal insulins were marginal but no dietary changes were made in the study by Ebeling and coworkers.[10] This suggests that both principles can act independently. Another way to increase insulin supply between meals is to deliver lispro insulin with CSII. The improvement in HbA_{1c} when using lispro in CSII was 0.4 % compared with soluble insulin in CSII,[11] i.e. a slightly greater difference between the two insulin preparations than was observed in our study in patients who were fully compliant with the dietary advice.

Because our main emphasis was laid on the effect of dietary change on metabolic control when patients are transferred from soluble to lispro insulin, we also examined possible confounding factors associated with the change in HbA_{1c}. The association between completeness of the dietary change and improvement in HbA_{1c} was independent of glycaemic control after the soluble period and change in weight.

We observed that the number of hypoglycaemic episodes expressed as blood glucose values below 2.5 mmol l^{-1} or nocturnal episodes was lower during lispro treatment. This is in accordance with previous studies.[5,12] We analysed the occurrence of hypoglycaemia in subgroups to identify possible high-risk individuals when insulin preparation and diet were changed at the same time. However, no subgroup demonstrated an increased number of hypoglycaemic episodes. Even in the patient group with the greatest decrease in HbA_{1c} (i.e. $HbA_{1c} > 7.5$ % after soluble and complete dietary change, reduction in HbA_{1c} 0.36 %), the number of moderate hypoglycaemic episodes decreased. Thus, the properly advised reduction of snacks appears to be safe in all patient groups when changing from conventional soluble insulin to lispro insulin. Although our study was not aimed at weight reduction, we may speculate that reduction of snacks without a corresponding increase of the preceding main meals and combined with slightly decreased lispro insulin doses might be an effective and safe mode of weight reduction in overweight Type 1 DM patients.

Our patients were not randomized to one of the two treatment regimens at baseline and then switched over. There were two practical reasons for our study design. First, it was known that lispro insulin would be commonly available at the end of the study. The participating physicians were afraid that patients preferring lispro would drop out from the study by refusing to change back to soluble insulin in a crossover design. Second, the multiple dietary changes required by a crossover study were considered to be very difficult to put into practice. However, with the present study design we cannot totally exclude the possibility that non-specific factors such as seasonal variation in exercise habits could have contributed to the results. There was a greater fall in HbA_{1c} between baseline values and the end of the initial soluble period than there was between the soluble and lispro periods. This suggests a significant study effect during the soluble period which might have extended to the lispro period. On the other hand, only those patients changing their diet as advised benefited from the switch from soluble to lispro insulin suggesting that non-specific factors or the study effect are unlikely to explain the advantageous effect of proper reduction of snacks when starting lispro insulin treatment.

Only approximately half of our patients were fully compliant with respect to the dietary change. Theoretically this could have been due to experience of hypoglycaemia shortly after the change in insulin preparation and the advised dietary change. However, this is not probable. Many patients informed us that they were unwilling to reduce their snacks as suggested, e.g. for social reasons (coffee breaks with colleagues, etc.). Reduction of snacks seems not to be acceptable for all Type 1 DM patients.

In conclusion, our results show that when patients are switched from soluble to lispro insulin treatment and advised to transfer 50 % or more of snack carbohydrates to preceding main meals, slightly improved metabolic control can be achieved in those patients who are fully compliant with the dietary change. This can be performed safely in outpatient clinics without an increased risk for hypoglycaemia.

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