

Randomized Crossover Study to Examine the Necessity of an Injection-to-Meal Interval in Patients With Type 2 Diabetes and Human Insulin

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OBJECTIVE—Patients with diabetes and insulin therapy with human insulin were usually instructed to use an interval of 20–30 min between the injection and meal. We examined the necessity of the injection-to-meal interval (IMI) in patients with type 2 diabetes mellitus (T2DM) and flexible insulin therapy with human insulin.

RESEARCH DESIGN AND METHODS—In this randomized, open crossover trial, 100 patients with T2DM (47% men, mean age = 66.7 years) were randomized to the IMI first group (phase 1, IMI 20 min; phase 2, no IMI) or IMI last group (phase 1, no IMI; phase 2, IMI 20 min). The main outcome measures were HbA_{1c}, blood glucose profile, incidence of hypoglycemia, quality of life, treatment satisfaction, and patient preference.

RESULTS—Forty-nine patients were randomized to the IMI first group and 51 patients to the IMI last group. Omitting the IMI only slightly increases HbA_{1c} (average intraindividual difference = 0.08% [95% CI 0.01–0.15]). Since the difference is not clinically relevant, a therapy without IMI is noninferior to its application ($P < 0.001$). In the secondary outcomes, the incidence of mild hypoglycemia also did not differ between no IMI and IMI significantly (mean of differences = -0.10 , $P = 0.493$). No difference in the blood glucose profile of both groups was found. Treatment satisfaction increased markedly, by 8.08, if IMI was omitted ($P < 0.001$). The total score of the quality of life measure did not show differences between applying an IMI or not. Insulin therapy without IMI was preferred by 86.5% of patients ($P < 0.001$).

CONCLUSIONS—An IMI for patients with T2DM and preprandial insulin therapy is not necessary.

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Type 2 diabetes mellitus (T2DM) affects ~5% of the German population (1). About 30% of those patients are treated with insulin (2). In the preanalog-insulin era, patients with diabetes were usually instructed to use an interval of 20–60 min between the injection and meal consumption to compensate for the process of absorbing regular insulin preparations. This recommendation has been supported by pharmacodynamic studies measuring the rate of appearance of insulin in the serum (3,4). However,

half of the patients with type 1 diabetes (T1DM) and T2DM do not use any injection-to-meal interval (IMI). The other half is using a fixed or flexible IMI. In contrast to the many recommendations to apply an optimal IMI of 20–30 min, most patients use a shorter IMI of 17–18 min (5–7).

There are some studies with considerable limitations on the IMI in patients with T1DM (9–12). However, almost no information is available for patients with T2DM, although they represent the

largest group of insulin-treated patients. The few small, short studies on T1DM were published between 1980 and 1995, a time in which animal insulins were predominantly used. It is known that animal insulins induce anti-insulin autoantibodies more frequently than human insulin. This is evident particularly for bovine insulin (8). At that time, the therapy strategy was conventional insulin therapy, with one or two injections of a mix of short- and intermediate-acting insulin per day, and patients did not regularly self-monitor their blood glucose. If reported, patients usually had insufficient metabolic control, indicated by HbA_{1c} values between 9 and 11%. None of the studies dealing with the IMI were long enough to show any differences in HbA_{1c} (9–12).

In 1996, the first short-acting insulin analog was introduced to diabetes therapy. The fact that short-acting analogs do not need an IMI at all was claimed to be a great advantage, although it is questionable, according to current data, if the IMI is really necessary (13–15). In Germany, the most commonly used diabetes teaching and treatment programs do not necessarily recommend an IMI, with either regular human insulin or short-acting analogs (16). This randomized, two-phase crossover study examines the necessity of an IMI in patients with T2DM and flexible insulin therapy with human regular insulin for metabolic control and its impact on treatment satisfaction and quality of life.

RESEARCH DESIGN AND METHODS

RESEARCH DESIGN AND METHODS—This trial was designed as a clinical, prospective, randomized, open-label, single-center crossover study. The trial was carried out in a general practice. We considered patients to be eligible if they met the following criteria: age between 40 and 80 years, have T2DM, and use insulin therapy with regular human insulin. The exclusion criteria included pregnancy or planned pregnancy in the next year, eating disorders,

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BMI <25 kg/m², severe and enduring mental health problems, cancer, and HbA_{1c} >9%.

The trial was approved by the local ethics committee and was performed according to the principles of the Declaration of Helsinki. The trial was registered with ClinicalTrials.gov (NCT00529165).

Intervention

After obtaining written informed consent, the individual insulin dosage, carbohydrate intake, and four-point blood glucose profile (before meal and bedtime) were determined in a 4-week run-in period. One day per week, blood glucose self-monitoring was also performed 1 h after the main meals. During the run-in period, all patients kept their IMI the same as before the study recruitment.

After the run-in period, we randomized volunteers into two groups: group A (IMI first, with phase 1 IMI 20 min and phase 2 no IMI) and group B (IMI last, with phase 1 no IMI and phase 2 IMI 20 min).

We randomized participants by using a computer-generated random list. Randomization was undertaken independently at the Institute of Medical Statistics, Computer Sciences, and Documentation, Jena University Hospital. Group IMI first started with an IMI of 20 min and group IMI last without an IMI. All eight visits every 4 weeks were the same in both groups and were held in the general practice. Participants completed a 12-week study sequence until crossover at visit four. After visit

four, they completed the second 12-week study sequence. At the end of the trial, the IMI preference was investigated (Fig. 1).

Outcome measures

The primary end point was HbA_{1c}, and the secondary end points were mild and severe hypoglycemia, mean blood glucose, diabetes treatment satisfaction, quality of life, and patient preference for the IMI; all were measured 12 and 24 weeks after the run-in period.

Metabolic control and other biomedical measures

We measured HbA_{1c} at baseline and at 12 and 24 weeks after the run-in period. Samples were drawn from a venous sample and assayed in the laboratory of the local hospital. HbA_{1c} was measured using high-performance liquid chromatography (normal range, 4.3–6.1%) (Variant II Hemoglobin Testing System; Bio-Rad, München, Germany). Blood pressure and body weight were measured at baseline and each visit.

Patients recorded in their diaries the insulin dosage, hypoglycemic episodes, and four-point blood glucose profiles (before the main meal and bedtime). One day per week, blood glucose control was also performed 1 h after the main meals. Mild hypoglycemia was defined as symptomatic neuroglycopenia or blood glucose readings <3.5 mmol/L, and severe hypoglycemia as a condition that requires intravenous glucose injection.

Psychosocial data

We used the audit of diabetes-dependent quality of life (ADDQoL) questionnaire from C. Bradley (Health Psychology Research Unit, Royal Holloway, University of London, London, U.K.) to measure the impact of diabetes on the quality of life. This questionnaire included 19 potentially applicable domains of life. The weighted impact score is a composition of all of these 19 domains. The score can range from -9 (maximum negative impact of diabetes) to +3 (maximum positive impact of diabetes) (17). The ADDQoL was measured at baseline and at 12 and 24 weeks after baseline.

The treatment satisfaction was measured with the diabetes treatment satisfaction questionnaire (DTSQ) by C. Bradley. There are two versions of the DTSQ: standard and change. The standard questionnaire includes eight items, six of which measure treatment satisfaction with a scale (scored 0–36), a higher score indicating a greater treatment satisfaction. The other two items (scored 0–6) measure perceived hypoglycemia and hyperglycemia. Higher scores indicate greater perceived frequency (18,19). The DTSQ change version includes the same eight items but inquires in six items if the treatment satisfaction is better or worse than before (score -18 to +18). A higher score indicates a greater improvement of treatment satisfaction. The other two items measure the change of problems with high or low blood glucose (score -3 to +3). A higher score indicates a greater frequency. The DTSQ standard was measured at baseline, and DTSQ change was measured at 12 and 24 weeks after baseline.

Statistical analysis

The data of a pilot study were used to calculate the sample size of the noninferiority trial. Based on the preliminary data, the expected HbA_{1c} difference of no IMI and IMI was 0.15%, and the expected SD of intraindividual HbA_{1c} differences was 0.51%. The HbA_{1c} difference of no IMI and IMI should not exceed 0.30% (noninferiority margin). To show noninferiority of no IMI compared with IMI with 80% power at the 5% significance level, we calculated 37 patients per study arm. Assuming a dropout rate of 25%, 100 patients (50 in each arm) needed to be referred.

Means and SDs were calculated to describe the baseline characteristics and outcomes after 12 and 24 weeks. The Student *t* test for paired samples was used

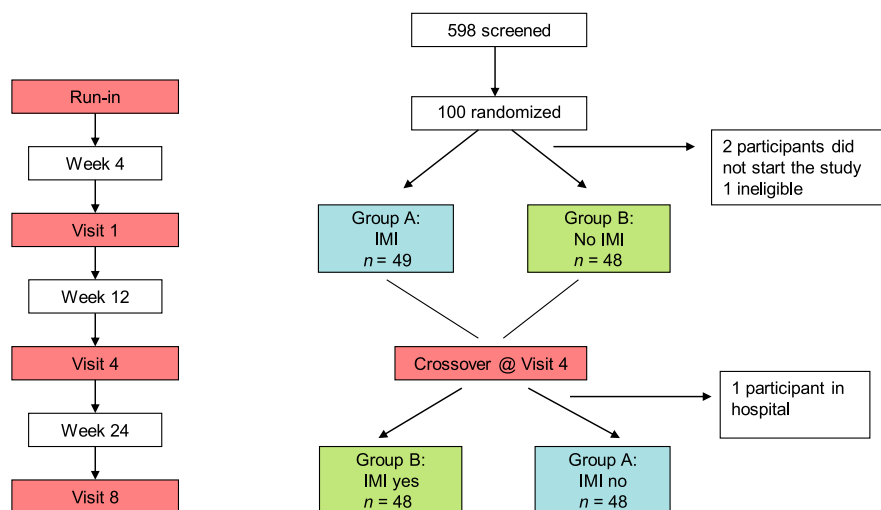


Figure 1—Study design. (A high-quality color representation of this figure is available in the online issue.)

to test for carryover, period, and treatment effects. The average intraindividual differences between both phases (no IMI/IMI) with the corresponding 95% CIs were determined to assess the effect of IMI. To compare the blood glucose profiles of both therapies, repeated-measures ANOVA was applied. A binomial test was used to test the patient preference for the IMI. A *P* value of <0.05 was considered to be statistically significant.

All data analyses were performed according to the intention-to-treat principle using IBM SPSS Statistics 19 (SPSS, Chicago, IL).

RESULTS—In total, 600 patients were screened and 100 patients were randomized. Only four patients dropped out during the study, three patients in the run-in period and one after 24 weeks. The participant mean age was 66.7 (± 7.7) years, and the mean duration of diabetes was 12.7 (± 7.3) years. Fifty-one (53%) patients were women, and all patients were using an IMI on average 17 (± 8.2) min before study recruitment. The baseline clinical data of both groups are shown in Table 1. All patients injected short-acting insulin at least three times a day (before main meals), and 90 (93.7%) patients injected an additional long-acting insulin (mean insulin dose 17.8 ± 10.9 IU) for the night. Fifty-eight patients (58%) took additional oral antihyperglycemic agents, 56 patients took metformin, 1 patient took glimepiride, and 1 patient took glinide.

Biomedical outcomes

The results of the primary and secondary end points are summarized in Table 2. HbA_{1c} only slightly increases without IMI compared with IMI (average intraindividual difference = 0.08% [95% CI 0.01–0.15]). Considering the differences

in HbA_{1c} >0.30% as clinically relevant, no IMI is noninferior to IMI (*P* < 0.001). There was no evidence of a carryover effect (*P* = 0.86) or period effect (*P* = 0.15) in the trial.

Without the IMI, the mild hypoglycemia incidence decreases by 0.10 episodes per month, on average, compared with IMI. However, the decrease was not significant (95% CI -0.41 to 0.20 , *P* = 0.49). There was no case of severe hypoglycemia in the study.

There was also no significant difference in the daily insulin dose between no IMI and IMI (average intraindividual difference in daily insulin dose = -0.49 [95% CI -1.56 to 0.59], *P* = 0.37).

Repeated-measures ANOVA revealed that blood glucose does not significantly differ between the IMI and without IMI phases (*P* = 0.33). There was also no significant interaction between the observed time and phase (IMI/without IMI) found in the model (*P* = 0.65), which indicates that both blood glucose profiles are similar (Fig. 2).

Psychosocial measures

The total treatment satisfaction (DTSQc) of patients increased markedly, by 8.08 on average, if the IMI was not used (95% CI 6.16–10.00, *P* < 0.001) (Table 2). The treatment satisfaction for items 2 and 3 (perceived frequency of hyper- and hypoglycemia) was excellent. There was no significant difference of satisfaction between IMI and no IMI.

The total score of the quality of life measure (ADDQoL) did not show significant differences when applying an IMI or not (average intraindividual difference = -0.07 [95% CI -0.23 to 0.09], *P* = 0.38).

Patient preference

At the end of the trial, 86.5% of the patients decided to continue the insulin

therapy without the IMI, irrespective of having or not having used an IMI at the last study period. In group IMI first without the IMI at the end of the study, 87.5% preferred a therapy without an IMI. In group IMI last with the IMI at the end of the study, 85.4% preferred a therapy without IMI. Overall, omitting the IMI was significantly preferred by 86.5% of the patients (*P* < 0.001).

CONCLUSIONS—In this prospective, randomized, controlled crossover trial, flexible insulin therapy was noninferior to the use of the IMI regarding HbA_{1c} in patients with T2DM. Also, the blood glucose profiles, particularly with regard to the postprandial blood glucose measurements, and the incidence of hypoglycemia showed no significant or clinically relevant differences between an insulin therapy with and without the use of an IMI.

Insulin therapy without the necessity to use an IMI can improve treatment satisfaction in a clinically relevant setting. We found a significant increase in diabetes treatment satisfaction if patients stopped using an IMI and a significant decrease in treatment satisfaction if patients are obliged to restart using one. However, we did not find an influence of the IMI on quality of life. We interpret this finding as patients estimating their quality of life generally as good and their opinion that their diabetes-dependent quality of life would improve marginally without diabetes.

Insulin therapy without the IMI was preferred in 86.5% of patients, and the results of this study yield no arguments against it.

Strengths and limitations of the study

One limitation of this study is that we only looked at a 20-min IMI. The efficacy of a longer interval of 30, 45, or 60 min remains unclear.

Another limitation of this study is that the intervention could not be blinded. On the basis of the patient consent form, patients knew the rationale for the study at the time of recruitment. This may have influenced the assessment of patient treatment satisfaction. It was impossible to control the patients about the real use of the IMI of 20 min. Because all patients used an IMI before the start of the study, keeping an IMI is not an unusual intervention. We scored the bias low. The study participants were well controlled,

Table 1—Baseline characteristics of participants

Characteristics	Group A: IMI first (n = 49)	Group B: IMI last (n = 51)
Sex, % women (n)	53.1 (26)	51.0 (26)
Age (years)	66.9 (7.5)	66.6 (7.5)
Diabetes duration (years)	12.9 (7.8)	12.3 (7.5)
BMI (kg/m ²)	34.5 (6.6)	33.9 (5.2)
HbA _{1c} (%)	7.1 (0.7)	7.0 (0.7)
Systolic blood pressure (mmHg)	148.6 (20.1)	149.5 (20.0)
Diastolic blood pressure (mmHg)	78.2 (11.6)	79.2 (10.9)
Daily regular insulin dose (units)	42.9 (20.0)	42.3 (20.7)

Values are means (SD) unless stated otherwise.

Table 2—Biomedical outcomes and DTSQ and ADDQoL of both groups 12 weeks (period 1) and 24 weeks (period 2) after run-in

	Group A (IMI first)		Group B (IMI last)		No IMI – IMI (95% CI)†	P value (no IMI vs. IMI)
	Period 1 (I) (n = 49)	Period 2 (N) (n = 48)	Period 1 (N) (n = 48)	Period 2 (I) (n = 48)		
HbA _{1c} (%)	6.71 (0.64)	6.82 (0.60)	6.76 (0.65)	6.72 (0.65)	0.08 (0.01 to 0.15)	<0.001††
Hypoglycemia per month	0.84 (1.40)	0.73 (1.27)	0.67 (1.14)	0.79 (1.65)	–0.10 (–0.41 to 0.20)	0.493
Daily insulin dose (units)	43.8 (22.0)	44.2 (22.7)	41.5 (19.2)	43.3 (18.5)	–0.49 (–1.56 to 0.59)	0.369
DTSQ*	4.24 (6.26)	9.04 (6.28)	9.44 (6.28)	–1.90 (5.95)	8.08 (6.16 to 10.00)	<0.001
Hyperglycemia**	–0.51 (1.16)	–0.17 (1.00)	–0.52 (1.03)	–0.06 (1.00)	–0.06 (–0.38 to 0.25)	0.689
Hypoglycemia**	–0.22 (0.87)	–0.13 (0.87)	–0.27 (0.94)	–0.04 (0.65)	–0.07 (–0.32 to 0.17)	0.553
ADDQoL***	–1.25 (1.27)	–1.32 (1.58)	–1.44 (1.18)	–1.34 (1.30)	–0.07 (–0.23 to 0.09)	0.378

Values are means (SD). †Intraindividual difference. ††Alternative hypothesis: mean of intraindividual phase differences < noninferiority margin, i.e., mean of (HbA_{1c} no IMI – HbA_{1c} with IMI) < 0.30. If P < 0.05, no IMI is noninferior to IMI. *Scored from –18 to 18; a positive score indicates an improvement of satisfaction and a negative score an impairment. **Scored from –3 to 3; a positive score indicates an increment frequency of hypoglycemia or hyperglycemia and a negative score a decrement. ***Scored from –9 (maximum negative impact) to +3 (maximum positive impact).

with a mean HbA_{1c} of 7% at baseline and a low dose of regular insulin. Whether patients with worse metabolic control or a high dose of regular insulin could have an advantage by using an IMI cannot be answered by this study.

This study has several strengths. The design of the study is a randomized, controlled crossover study. All visits were held in the general practice where the patients were treated before the start

of the study; therefore, the patients trusted their doctor, and this reflects in the low dropout rate of 4%.

Other research

The first study on this topic with a sufficient duration to show differences in HbA_{1c} was conducted in Belgium but with patients with T1DM (20). Two groups of 15 patients with T1DM received insulin injections either 5 or 30

min before their three main meals in combination with bedtime NPH insulin. Similar to our results, no differences between groups were reported in relation to changes in either plasma glucose excursions or HbA_{1c}. Correspondingly, no significant difference of HbA_{1c} was reported in patients with T1DM, with or without the IMI. In a preceding survey in our center, predominately older patients with T1DM and long diabetes duration practiced IMI (5). A possible explanation could be that these patients started insulin at a time when the IMI were generally recommended by health professionals, and they did not change their habits even after the introduction of modern treatments and teaching programs after 1990, when this recommendation was abolished.

Keeping an IMI can cause hypoglycemia, especially in patients with good preprandial blood glucose values. Forgetting insulin injections could be another disadvantage in older patients who keep an IMI. Therefore, besides postprandial glucose excursions and HbA_{1c}, hypoglycemic events, quality of life, and treatment satisfaction are important to consider. No difference in the incidence of hypoglycemia in patients with or without IMIs was found. This is partially due to the lower incidence of hypoglycemia in T2DM (21).

Quality of life and treatment satisfaction with short-acting analogs were shown to be better than with regular human insulin if analogs are applied immediately (and regular human insulin 30 min) before a meal (22). If both types of insulin are applied immediately before meals, in a blinded manner, no differences in treatment satisfaction, well-being, or HbA_{1c} were found (23). These results

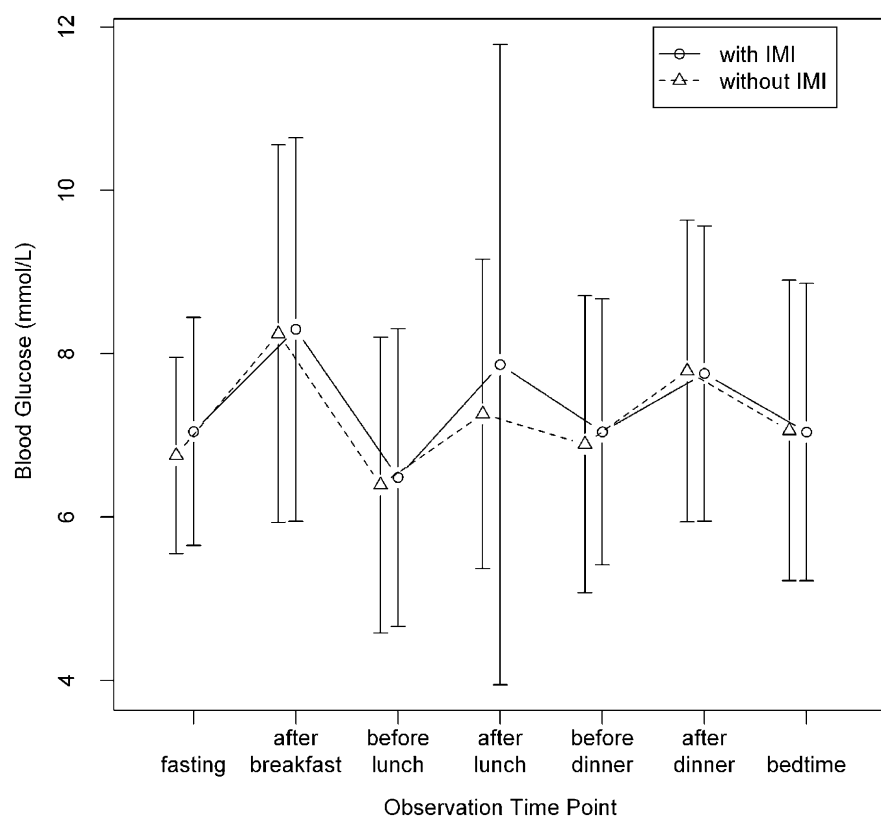


Figure 2—Blood glucose profiles (mean) of phase without IMI and phase with IMI.

are supported by the recently published Cochrane Review, which also did not show any clinical benefit of short-acting insulin analogs in comparison with regular insulin in type 2 diabetes subjects (24). This proves that in patients with T1DM, the deterioration in the quality of life and treatment satisfaction is due to an IMI but has nothing to do with the type of insulin used. Our study results support these findings in patients with T2DM because we could clearly demonstrate the impact of the IMI on treatment satisfaction. Furthermore, an IMI with its theoretical advantage of optimum overlapping insulin absorption and carbohydrate ingestion is of seemingly no importance in patients with T2DM in a real-life setting.

Conclusion

In this randomized, controlled crossover study, we found no difference in HbA_{1c}, blood glucose profile, incidence of hypoglycemia, and quality of life in patients with T2DM and insulin therapy with or without the IMI. The treatment satisfaction increased significantly and in a clinically relevant extent if patients used no IMI. Most patients preferred insulin therapy without an IMI. Insulin therapy without an IMI is not inferior to treatment with an IMI of 20 min in patients with T2DM.

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N.M. researched data and wrote the manuscript. T.F. researched data and contributed to the discussion. C.K. and G.W. reviewed and edited the manuscript. T.L. researched data. U.A.M. contributed to the discussion and reviewed and edited the manuscript. U.A.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Statistisches Bundesamt, Robert-Koch-Institut: Gesundheitsberichterstattung des Bundes: Germany [Internet], 2006. Available from https://www.gbebund.de/gbe10/owards.prc_show_pdf?p_id=9965&rp_sprache=d&rp_uid=gast&rp_aid=11536177&rp_lfd_nr=1. Accessed 28 March 2012
2. Hansen B, Altenhofen L, Haß W, Blaschy S, Kretschmann J. Report of the Disease Management Programmes 2007 in North Rhine: breast cancer, diabetes mellitus type 2, coronary artery disease, asthma, and COPD [Internet], 2008. KV North Rhine. Available from http://www.kvno.de/downloads/quali/qualbe_dmp08.pdf. Accessed 28 March 2012
3. Galloway JA, Spradlin CT, Nelson RL, Wentworth SM, Davidson JA, Swarner JL. Factors influencing the absorption, serum insulin concentration, and blood glucose responses after injections of regular insulin and various insulin mixtures. *Diabetes Care* 1981;4:366–376
4. Berger M, Cüppers HJ, Hegner H, Jörgens V, Berchtold P. Absorption kinetics and biologic effects of subcutaneously injected insulin preparations. *Diabetes Care* 1982;5:77–91
5. Müller N, Kloos C, Frank T, Ristow M, Wolf G, Müller UA. Prevalence of injection-meal interval usage and its association with variables of metabolic control in patients with type 1 and type 2 diabetes. *Diabet Med* 2011;28:223–226
6. Overmann H, Heinemann L. Injection-meal interval: recommendations of diabetologists and how patients handle it. *Diabetes Res Clin Pract* 1999;43:137–142
7. Ahmad ABE, Badgandi M, Home PD. Interval between insulin injection and meal in relation to glycated haemoglobin. *Pract Diabetes Int* 2001;18:51–56
8. Davidson JK, Fineberg SE, De Meyts P, Fineberg NS, Galloway JA. Immunological and metabolic responses of patients with history of antibody-induced beef insulin resistance to treatment with beef, pork, human, and sulfated beef insulin. *Diabetes Care* 1992;15:702–704
9. Kinmonth AL, Baum JD. Timing of pre-breakfast insulin injection and post-prandial metabolic control in diabetic children. *BMJ* 1980;280:604–606
10. Witt MF, White NH, Santiago JV. Roles of site and timing of the morning insulin injection in type 1 diabetes. *J Pediatr* 1983;103:528–533
11. Dimitriadis GD, Gerich JE. Importance of timing of preprandial subcutaneous insulin administration in the management of diabetes mellitus. *Diabetes Care* 1983;6:374–377
12. Lean ME, Ng LL, Tennison BR. Interval between insulin injection and eating in relation to blood glucose control in adult diabetics. *Br Med J (Clin Res Ed)* 1985;290:105–108
13. Bolli GB. Clinical strategies for controlling peaks and valleys: type 1 diabetes. *Int J Clin Pract Suppl* 2002;129:65–74
14. Kautzky-Willer A. Are “designer” insulins the “best” insulins? *Wien Klin Wochenschr* 2005;117:571–575 [in German]
15. Brunton S. Initiating insulin therapy in type 2 diabetes: benefits of insulin analogs and insulin pens. *Diabetes Technol Ther* 2008;10:247–256
16. Müller UA, Femerling M, Reinauer KM, et al.; ASD (the Working Group on Structured Diabetes Therapy of the German Diabetes Association). Intensified treatment and education of type 1 diabetes as clinical routine. A nationwide quality-circle experience in Germany (Abstract). *Diabetes Care* 1999;22(Suppl. 2):B29–B34
17. Bradley C, Todd C, Gorton T, Symonds E, Martin A, Plowright R. The development of an individualized questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL. *Qual Life Res* 1999;8:79–91
18. Bradley C. The diabetes treatment satisfaction questionnaire: DTSQ. In *Handbook of Psychology and Diabetes: A Guide to Psychological Measurements in Diabetes Research and Practice*. Bradley C, Ed. Chur, Switzerland, Harwood Academic Publishers, 1994
19. Bradley C. Diabetes treatment satisfaction questionnaire. Change version for use alongside status version provides appropriate solution where ceiling effects occur. *Diabetes Care* 1999;22:530–532
20. Scheen AJ, Letiexhe MR, Lefèbvre PJ. Minimal influence of the time interval between injection of regular insulin and food intake on blood glucose control of type 1 diabetic patients on a basal-bolus insulin scheme. *Diabetes Metab* 1999;25:157–162
21. Reise K, Hartung V, Lehmann T, et al. Frequency of severe and nonsevere hypoglycaemia and difficulties at workplace in patients with insulin-treated diabetes mellitus (Abstract). *Diabetologia* 2011;54 (Suppl. 1):654
22. Ashwell SG, Bradley C, Stephens JW, Witthaus EG, Home PD. Treatment satisfaction and quality of life with insulin glargine plus insulin lispro compared with NPH insulin plus unmodified human insulin in individuals with type 1 diabetes. *Diabetes Care* 2008;31:1112–1117
23. Gale EAM; The UK Trial Group. A randomized, controlled trial comparing insulin lispro with human soluble insulin in patients with type 1 diabetes on intensified insulin therapy. *Diabet Med* 2000;17:209–214
24. Siebenhofer A, Plank J, Berghold A, et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. In *The Cochrane Library*. Issue 1. Chichester, U.K., John Wiley & Sons Ltd., 2010