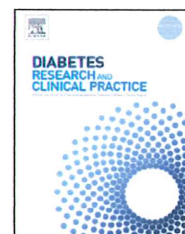


ELSEVIER

available at www.sciencedirect.comjournal homepage: www.elsevier.com/locate/diabres

Six-month multicentric, open-label, randomized trial of twice-daily injections of biphasic insulin aspart 30 versus multiple daily injections of insulin aspart in Japanese type 2 diabetic patients (JDDM 11)

Koichi Hirao^a, Keiko Arai^{b,*}, Mikio Yamauchi^a, Hirofumi Takagi^c, Masashi Kobayashi^d
for the Japan Diabetes Clinical Data Management Study Group¹

^aH.E.C. Science Clinic, Yokohama, Japan

^bArai Clinic, 1-38 Shiratoridai, Aoba-ku, Yokohama 227-0054, Japan

^cFaculty of Medicine, Toho University, Tokyo, Japan

^dDepartment of Internal Medicine, Toyama University, Toyama, Japan

ARTICLE INFO

Article history:

Received 21 June 2007

Accepted 21 August 2007

Published on line 24 October 2007

Keywords:

Biphasic insulin aspart 30

Insulin aspart

Type 2 diabetes mellitus

Randomized trial

ABSTRACT

To evaluate glycemic control using convenience-oriented biphasic insulin analog compared with intensified insulin therapy, we conducted a 6-month multicentric, open-label, randomized trial in Japanese insulin-naïve patients with type 2 diabetes mellitus. A total of 160 adult patients at 19 centers were randomized into two groups: those who received twice-daily injections of biphasic insulin aspart 30 and those on three-times-daily injections of insulin aspart with or without NPH insulin (multiple daily injections). At 6 months, mean HbA_{1c} decreased by approximately 2.5% in both groups. Reduction of HbA_{1c} on both regimens was better in patients whose prior therapy before starting the study was only diet and exercise (−5.0%) than in patients who were previously taking oral antidiabetic agents (−1.0%). No incidence of major hypoglycemia was observed in either regimen. These results suggest that convenience-oriented insulin therapy using biphasic insulin analog is as useful as intensified insulin therapy with insulin analog for the treatment of type 2 diabetes mellitus over 6 months. Furthermore, early induction of insulin therapy in individuals hitherto using only diet and exercise may provide good glycemic control. This study suggests that convenience-oriented biphasic insulin aspart 30 might be a useful option for the treatment of type 2 diabetes mellitus, especially for insulin-naïve patients over 6 months, although it should be changed to another regimen when expected efficacy is not obtained.

© 2007 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Many studies have shown that strict glycemic control is one of the most important factors in the management of diabetes

mellitus to prevent risk of death from diabetic complications and cardiovascular diseases. The Diabetes Control and Complication Trial (DCCT) [1] showed that intensified insulin therapy using a regimen consisting of three-times-daily

* Corresponding author. Tel.: +81 45 989 1707; fax: +81 45 989 1708.

E-mail address: arai-cl@n04.itscom.net (K. Arai).

¹ See Appendix A.

0168-8227/\$ – see front matter © 2007 Elsevier Ireland Ltd. All rights reserved.

doi:10.1016/j.diabres.2007.08.011

injections of regular insulin with or without NPH insulin provides better glycemic control than convenience-oriented insulin therapy using twice-daily human insulin in patients with type 1 diabetes mellitus. Furthermore, Ohkubo et al. [2] reported similar results in patients with type 2 diabetes mellitus.

The increasing incidence of type 2 diabetes mellitus in Japan is believed to reflect shifting diet and lifestyle changes among the general population. As a result, it is increasingly necessary to select therapeutic regimens that not only effectively maintain glycemic control but also allow diabetic patients to pursue many daily activities; in large numbers of insulin-requiring diabetic patients, multiple-daily injection regimens are not desirable. In this regard, in many outpatients overall glycemic control attained with twice-daily injection regimens may be as effective as that with multiple injection therapy [3,4].

Recently, rapid-acting and biphasic insulin analogs have been made available and are being widely used for the treatment of type 2 diabetes mellitus. These insulin analogs are very convenient tools for adjusting to the variety of lifestyles of today's diabetic patients. However, among modern insulin analog therapies it is not known whether rapid-acting analog plus NPH insulin or twice-daily biphasic insulin analog provides better glycemic control.

In 2001, the Japan Diabetes Clinical Data Management Study Group (JDDM) was established to promote clinical research on diabetes in Japan [5]. Data on patients at healthcare institutes across Japan are collected in the CoDiC[®] database, a data collection and diabetes management information system developed by the JDDM [5]. The CoDiC[®] system enables researchers to perform many multicentric, randomized clinical studies in Japan. Using this database, we performed a multicentric, open-label, randomized trial comparing glycemic control using twice-daily injections of biphasic insulin aspart 30 versus three-times-daily injections of insulin aspart with or without NPH insulin in insulin-naïve patients with type 2 diabetes mellitus.

2. Subjects and methods

2.1. Subjects

This was a 6-month, randomized controlled trial analyzing data on adult type 2 diabetic patients recruited at 19 centers in Japan. The definition of type 2 diabetes mellitus was based on the criteria in the "Report of the Committee of Japan Diabetes Society (JDS) on the Classification and Diagnostic Criteria of Diabetes Mellitus" [6]. These criteria are almost identical to those described by WHO [7]. Subjects had to have HbA_{1c} \geq 8.0% for \geq 3 months irrespective of using oral antidiabetic agents and indication for starting insulin therapy. Patients with soft drink ketoacidosis were excluded. Subjects were randomized to receive either twice-daily injections of biphasic insulin aspart 30 or three-times-daily injections of insulin aspart with or without NPH insulin (multiple daily injections). Oral antidiabetic agents that stimulate insulin secretion such as sulfonylureas and short-acting insulin secretagogues were discontinued and other insulin preparations disallowed during

the study. Doses of insulin analogs were adjusted to achieve target HbA_{1c} $<$ 7.0% at the discretion of each investigator.

Participating clinics and hospitals were JDDM affiliated and the clinical data of all patients were standardized and stored on personal computer using CoDiC[®] software [5]. The clinical data were collected from each institute on CD-R storage media and analyzed by SPSS[®] software (SAS Institute, Cary, NC). Data received at the central analytic center were treated on an anonymous basis. JDDM operates as an intermediate organization under the supervision of a central analytical center and ethics committee. Informed consent was obtained from all participants at each institute in accordance with the Japanese Ministry of Health, Labour and Welfare's guideline for the ethics of clinical study.

2.2. Measurement and standardization of data

HbA_{1c} was measured by HPLC method. Normal range for HbA_{1c} was defined as 4.3–5.8%. Postprandial plasma glucose was assessed after breakfast or lunch by hexokinase method. Measurement of each parameter assessed in this study was standardized at all institutions.

2.3. Statistical analyses

Statistical analyses were conducted using SPSS[®] version 13.0J for Windows software (SAS Institute). Mean intergroup values of HbA_{1c} were subjected to repeated measurement analysis of variance and non-paired t-test. The intergroup differences of the time taken until values of 7.0% or 6.5% of HbA_{1c} were achieved were analyzed by life table analysis—Wilcoxon (Gehan) test. All data are expressed as mean \pm S.D. and P-value $<$ 0.05 were considered significant.

3. Results

A total of 160 patients were equally randomized to the two treatment groups. At baseline, demographic and clinical characteristics were comparable between the two groups (Table 1). Fifty of the 80 patients (62.5%) in the multiple daily

Table 1 – Baseline characteristics of patients (mean \pm S.D.)

	Twice-daily injection group	Multiple daily injection group
Number of patients, n	80	80
Prior therapy, n		
Diet/exercise only	39	41
Oral antidiabetic agents	41	39
Sex (M/F), n	47/33	49/31
Age (years)	58.5 \pm 11.3	57.9 \pm 11.9
Duration of diabetes (years)	9.5 \pm 10.7	12.2 \pm 13.3
HbA _{1c} (%)	10.5 \pm 2.1	10.7 \pm 2.1
Postprandial plasma glucose (mg/dL)	298.6 \pm 114.2	293.3 \pm 113.6
Body weight (kg)	62.5 \pm 12.9	62.1 \pm 12.2
BMI (kg/m ²)	23.7 \pm 4.1	23.7 \pm 4.2

Table 2 – Reasons for discontinuation (number of patients)

Reasons	Twice-daily injection group	Multiple daily injection group
Defined as type 1 diabetes	1	1
Changed hospitals or clinics	11	10
Improved glycemic control	1	1
Less of an improvement in glycemic control than was expected	8	6
Worse compliance	2	1
Death of the patient	1	0
Total number	24	19

injection group used NPH insulin in addition to insulin aspart. In all, 56 of 80 patients (70.0%) in the twice-daily injection group and 61 of 80 patients (76.3%) in the multiple daily injection group completed the study. The reasons for discontinuation are summarized in Table 2 and are similar in the two treatment groups. At 6 months, in the two groups mean HbA_{1c} changed from $10.2 \pm 2.1\%$ to $7.6 \pm 1.3\%$ and from $10.4 \pm 2.0\%$ to $7.8 \pm 1.8\%$, respectively. There was no statistical difference between the two groups. Mean HbA_{1c} steadily decreased by approximately 2.5% at 6 months versus baseline in both groups (Fig. 1). At the end of the study, 32.1% and 17.9% of patients in the twice-daily injection group and 32.8% and 16.4% in the multiple daily injection group achieved HbA_{1c} < 7.0% and < 6.5%, respectively. The figures were not very different between the two groups. Besides, the times taken to achieve HbA_{1c} < 7.0% or < 6.5% at the end of the trial between the two groups were not different ($P = 0.661$, $P = 0.954$, respectively). Among patients whose therapy prior to starting the study consisted only of diet and exercise (early induction of insulin subgroup) mean HbA_{1c} changed from $12.2 \pm 1.8\%$ to $7.2 \pm 1.3\%$ in those who took twice-daily injections and from $12.0 \pm 1.8\%$ to $7.5 \pm 2.0\%$ in those who took multiple daily injections over the 6-month treatment period; no difference in

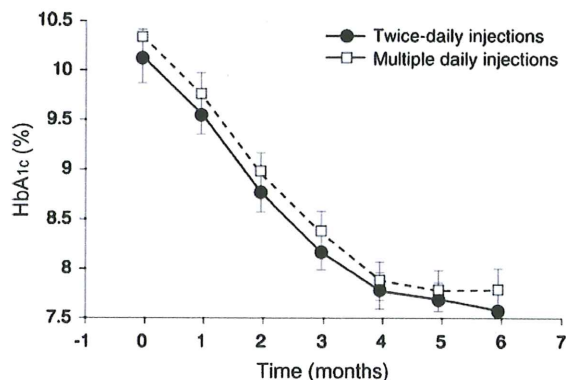


Fig. 1 – Mean (±S.E.) HbA_{1c} in patients taking twice-daily injections (●, n = 56) or multiple daily injections (□, n = 61). Mean HbA_{1c} steadily decreased to an approximately 2.5% reduction at 6 months. No statistical difference was noted between the two groups.

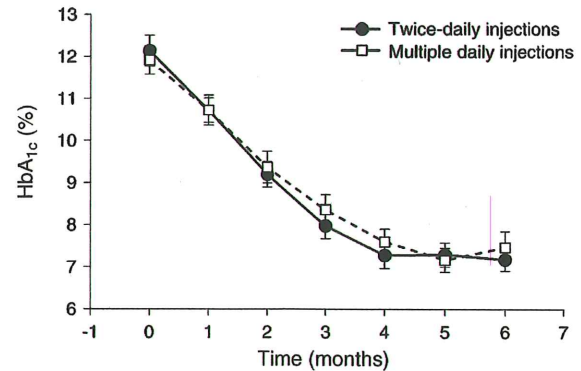


Fig. 2 – Mean (±S.E.) HbA_{1c} in patients who were not previously receiving oral antidiabetic agents before study entry. Twice-daily injections (●, n = 24); multiple daily injections (□, n = 28). HbA_{1c} decreased by approximately 5.0% at 6 months. No statistical difference was noted between the two groups.

this parameter was observed between the two treatment groups (mean reduction: $-4.9 \pm 2.4\%$ and $-4.5 \pm 2.4\%$, respectively; Figs. 2 and 3). Among patients who were previously taking oral antidiabetic agents prior to starting the study, mean HbA_{1c} changed from $8.8 \pm 0.7\%$ to $8.0 \pm 1.2\%$ in those who took twice-daily injections, and from $9.1 \pm 1.0\%$ to $8.0 \pm 1.6\%$ in those who took multiple daily injections over 6 months. Again, there was no difference noted between the two treatment groups (mean reduction: $-0.8 \pm 1.2\%$ and $-1.1 \pm 1.3\%$, respectively; Figs. 3 and 4). In the twice-daily injection group, the duration of diabetes among patients with early induction of insulin (6.58 ± 8.17 years) was significantly shorter than in patients who had been previously taking oral antidiabetic agents (10.99 ± 7.04 years) ($P = 0.034$). While in the multiple daily injection group, there was no statistical difference in the durations between the two subgroups (10.05 ± 13.59 years and 12.43 ± 8.58 years, respectively). Comparing these two prior treatment subgroups, however, the decrease of HbA_{1c} among early induction of insulin patients was significantly ($P < 0.001$) greater than that observed in patients who were previously taking oral antidiabetic agents (Fig. 3).

Statistically, the BMI in the two groups increased from 23.8 ± 4.1 kg/m² to 25.2 ± 4.0 kg/m² ($P < 0.0001$) and from 24.0 ± 4.2 kg/m² to 24.8 ± 4.5 kg/m² ($P < 0.0001$), respectively, at the end of the 6-month trial. The change in BMI during 6 months in the twice-daily injection group (1.47 ± 1.82 kg/m²) was more than that in the multiple daily injection group (0.69 ± 1.04 kg/m²) ($P = 0.013$), while, the mean BMI at the baseline and the end of the 6-month trial was not statistically different in the two treatment groups.

No major hypoglycemic episode was observed in either treatment group. Of the 24 patients in the twice-daily injection group and 19 patients in the multiple daily injection group who discontinued the study, most withdrew because of improvement or deterioration of glycemic control or were transferred to another clinic and hence lost to follow-up.

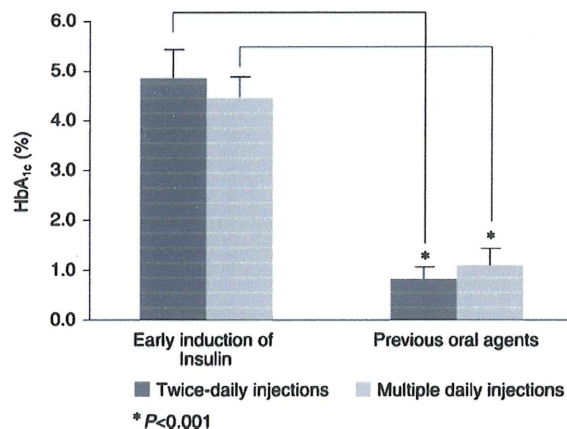


Fig. 3 – Decrease of HbA_{1c} in the two treatment groups according to whether they underwent early induction of insulin therapy or had previously received oral antidiabetic agents. Those who underwent early induction of insulin therapy exhibited significantly greater decrease of HbA_{1c} than those previously taking oral antidiabetic agents in both treatment groups irrespective of whether they were assigned twice-daily or multiple daily injections ($P < 0.001$).

4. Discussion

In this study mean HbA_{1c} decreased by approximately 2.5% after patients had received either twice-daily injections of biphasic insulin aspart or multiple daily injections of insulin aspart with or without NPH insulin at 6 months. These results are comparable to those of previous studies that suggested that glycemic control using twice-daily injection regimens may be as good as that achieved with multiple daily injection therapy in certain patients [3,4]. In our study, including data on a total of 43 patients who discontinued early, we performed an intent-to-treat analysis of the results obtained in all 80 patients initially randomized to each treatment group. In this

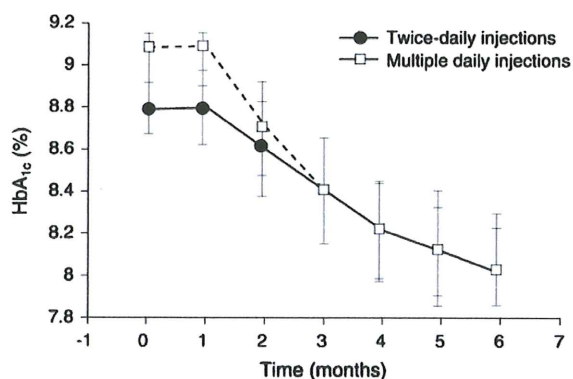


Fig. 4 – Mean (\pm S.E.) HbA_{1c} in patients who were previously receiving oral antidiabetic agents before study entry. Twice-daily injections (●, $n = 32$); multiple daily injections (□, $n = 33$). HbA_{1c} decreased by approximately 1.0% at 6 months. No statistical difference was noted between the two groups.

analysis we obtained the same results as seen in the protocol-compatible analysis. Also the reasons for discontinuation were similar in both treatment groups. The cause of death of the patient in the twice-daily injection group, which occurred within one month, was an acute myocardial infarction. In the twice-daily injection group, out of eight patients who showed less of an improvement in glycemic control than was expected, five of them added oral antidiabetic agents and three of them changed to multiple injections of insulin therapy. In the multiple daily injection group, out of six patients who showed less of an improvement in glycemic control than was expected, three added oral antidiabetic agents, two changed NPH insulin to insulin glargine and one replaced insulin aspart with NPH insulin. Therefore our results suggest that in insulin-naïve patients convenience-oriented insulin therapy using biphasic insulin analog is as effective as insulin therapy using rapid-acting insulin analog plus NPH insulin, at least over the first 6 months of treatment.

Modern rapid-acting insulin analog has been shown to elicit better reduction of HbA_{1c} than regular insulin [8,9]. Furthermore, the former exerts glucose-lowering effects more rapidly than the latter [10]. However, although it is recommended to inject regular insulin 30 min before meals, many patients inject this formulation just before meals [11]. Hence because rapid-acting insulin analog is formulated to allow injection just before meals, in the real world it may be more effective against postprandial hyperglycemia than regular insulin. It has been reported that biphasic insulin aspart 30 significantly improves postprandial hyperglycemia as compared with premixed human insulin 30/70 on a twice-daily regimen, while overall blood glucose control was similar [12]. These results suggest that not only rapid-acting insulin analog but also biphasic insulin analog effectively controls postprandial hyperglycemia.

In our subgroup analysis, HbA_{1c} was reduced to a greater extent in patients who did not previously receive treatment with oral antidiabetic agents (early induction of insulin subgroup) versus those who did take these drugs regardless of whether they were in the intensive regimen or convenience regimen group over 6 months. The early insulin induction subgroup had a shorter duration of diabetes, though there was no statistical difference in the multiple injection group. This suggested that the shorter duration might contribute to the reserve of beta-cell function. Plasma glucose level gradually rises with progressive deterioration of beta-cell function during the natural course of diabetes [13,14]. Treatment with sulfonylureas, a widely prescribed class of oral hypoglycemic agents, has been associated with beta-cell apoptosis [15] in type 2 diabetic patients and increases postprandial secretion of beta cell-derived amylin, a component of islet amyloid characteristic of type 2 diabetes [16]. Amylin deposition in rat pancreas has also been shown to stimulate apoptosis of beta cells [17]. Treatment with insulin, on the other hand, reduces amylin concentration [16]. Moreover, UKPDS showed that insulin injections are the most powerful tool available so far to achieve satisfactory long-term metabolic control in the majority of diabetic patients who are not sufficiently controlled by diet and/or oral agents [13]. The DCCT showed that intensive insulin therapy is more effective at conserving residual beta-cell function than conventional therapy in patients with type 1 diabetes [18]. In newly diagnosed patients

with type 2 diabetes, induction of euglycemia with just 2 weeks of intensive insulin therapy was sufficient to allow long-term glycemic control without medication for a period of ≤ 3 years [19]. Therefore beta-cell rest is important for beta-cell preservation and insulin therapy given at an early stage of type 2 diabetes might be a useful option for patients who fail diet therapy alone. However, many diabetic patients resist accepting insulin therapy because of the invasiveness of injections in comparison with taking oral antidiabetic agents. In these individuals, twice-daily injections using biphasic insulin analog instead of intensive insulin therapy might be a more acceptable choice when starting insulin therapy.

Both regimens used in this study were generally safe. There was no incidence of major hypoglycemia observed in either treatment group.

In summary, the present results suggest that not only intensified insulin therapy with insulin analog but also convenience-oriented insulin therapy using biphasic insulin analog is a useful option for the treatment of type 2 diabetes mellitus, at least over 6 months. The convenience-oriented twice-daily regimen might conceivably contribute to compliance in certain patients, especially those with highly active lifestyles. Selection of therapy should be made after careful assessment of risk-benefit in each patient.

Acknowledgment

This study (JDDM 11) was supported by a grant from the Japan Diabetes Foundation.

Appendix A

The following members of JDDM participated in this study (in alphabetical order):

Dr. Nobuyuki Abe (Internal Medicine Abe Clinic)
 Dr. Kotaro Iemitsu (Konandai Iemitsu Clinic)
 Dr. Koichi Iwasaki (Iwasaki Internal Medicine Clinic)
 Dr. Koichi Kawai (Kawai Clinic)
 Dr. Shinichi Kuribayashi (Misaki Internal Medicine Clinic)
 Dr. Gendai Lee (Lee Internal Medicine Clinic)
 Dr. Hajime Maeda (HEC Science Clinic)
 Dr. Kiyokazu Matoba (Matoba Internal Medicine Clinic)
 Dr. Mariko Oishi (Oishi Clinic)
 Dr. Fuminobu Okuguchi (Okuguchi Internal Medicine Clinic)
 Dr. Takeshi Osonoi (Naka Memorial Clinic)
 Dr. Miyoko Saito (Naka Memorial Clinic)
 Dr. Hidekatsu Sugimoto (Sugimoto Clinic)
 Dr. Masato Takagi (Takagi Internal Medicine Clinic)
 Dr. Masahiko Takai (Takai Internal Medicine Clinic)
 Dr. Hiroshi Takeda (Takeda Clinic)
 Dr. Madoka Taguchi (Toshiba Hospital)
 Dr. Noriharu Yagi (Yagi Internal Medicine Clinic)
 Dr. Ritsuko Yamamoto (HEC Science Clinic)
 Dr. Hiroki Yokoyama (Jiyugaoka Yokoyama Internal Medicine Clinic)

REFERENCES

- [1] The Diabetes Control Complication Trial Research Group, The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus, *N. Engl. J. Med.* 329 (1993) 977–986.
- [2] Y. Ohkubo, H. Kishikawa, E. Araki, T. Miyata, S. Isami, S. Motoyoshi, et al., Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study, *Diabetes Res. Clin. Pract.* 28 (1995) 103–117.
- [3] M. Small, S. MacRury, A. Boal, K.R. Paterson, A.C. MacCuish, Comparison of conventional twice-daily subcutaneous insulin administration and a multiple injection regimen (using the NovoPen™) in insulin-dependent diabetes mellitus, *Diabetes Res.* 8 (1988) 85–89.
- [4] H. Yki-Jarvinen, M. Kauppila, E. Kujansuu, K. Lahti, T. Marjanen, L. Niskanen, et al., Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus, *N. Engl. J. Med.* 327 (1998) 1426–1433.
- [5] M. Kobayashi, K. Yamazaki, K. Hirao, M. Oishi, A. Kanatsuka, M. Yamauchi, et al., The status of diabetes control and antidiabetic drug therapy in Japan—A cross-sectional survey of 17,000 patients with diabetes mellitus (JDDM 1), *Diabetes Res. Clin. Pract.* 73 (2006) 198–204.
- [6] T. Kuzuya, S. Nakagawa, J. Satoh, Y. Kanazawa, Y. Iwamoto, T. Kobayashi, et al., The Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus. Report of the committee on the classification and diagnostic criteria of diabetes mellitus, *Diabetes Res. Clin. Pract.* 55 (2002) 65–85.
- [7] K.G. Alberti, P.Z. Zimmet, Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1. Diagnosis and classification of diabetes provisional report of a WHO consultation, *Diabetic Med.* 15 (1998) 539–553.
- [8] P.D. Home, A. Lindholm, A. Riist, European Insulin Aspart Study Group, Insulin aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial, *Diabetic Med.* 17 (2000) 762–770.
- [9] P. Raskin, A. Riis, R.A. Guthrie, L. Jovanovic, L. Leiter, Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes, *Diabetes Care* 23 (2000) 583–588.
- [10] J. Brange, A. Volund, Insulin analogs with improved pharmacokinetic profiles, *Adv. Drug Deliv. Rev.* 35 (1999) 307–335.
- [11] L.N. Jorgensen, F.S. Nielsen, Timing of pre-meal insulin in diabetic patients on a multiple daily injection regimen. A questionnaire study, *Diabetologia* 33 (1990) A116.
- [12] B.O. Boehm, O.D. Home, C. Behrend, N.M. Kamp, A. Lindholm, Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in type 1 and type 2 diabetic patients, *Diabetic Med.* 19 (2002) 393–399.
- [13] UKPDS 33, Intensive blood glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes, *Lancet* 352 (1998) 837–853.
- [14] J. Levy, A.B. Atkinson, P.M. Bell, D.R. McCance, D.R. Hadden, Beta-cell deterioration determines the onset and rate of progression of secondary dietary failure in type 2 diabetes mellitus: the 10-year follow-up of the Belfast Diet Study, *Diabetic Med.* 15 (1998) 290–296.

-
- [15] T. Mandrup-Poulsen, Beta-cell apoptosis, stimuli and signaling, *Diabetes* 50 (Suppl. 1) (2001) S58–S63.
- [16] J. Rachman, M.J. Payne, J.C. Levy, B.A. Barrow, R.R. Holman, R.C. Turner, Changes in amylin and amylin-like peptide concentrations and beta-cell function in response to sulfonylurea or insulin therapy in NIDDM, *Diabetes Care* 21 (1998) 810–816.
- [17] S.E. Kahn, D.A. D'Alessio, M.W. Schwartz, M.W. Fujimoto, J.W. Ensink, G.J. Tarborsky Jr., et al., Evidence of cosecretion of islet amyloid polypeptide and insulin by beta-cell, *Diabetes* 39 (1990) 634–638.
- [18] The Diabetes Control and Complication Trial Research Group, Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the Diabetes Control and Complication Trial. A randomized, controlled trial, *Ann. Intern. Med.* 128 (1998) 517–523.
- [19] H. Ilkova, B. Glaser, A. Tunckale, N. Bagriacik, E. Cerasi, Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients by intensive insulin treatment, *Diabetes Care* 9 (1997) 1353–1356.