

Influence of BMI, Age and Duration of Diabetes Mellitus on Glycaemic Control with Twice-Daily Injections of Biphasic Insulin Aspart 30 versus Multiple-Daily Injections of Insulin Aspart (JDDM 18)

Retrospective Reanalysis of a 6-Month, Randomized, Open-Label, Multicentre Trial in Japan

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Abstract

Background and Objective: Good glycaemic control in patients with diabetes mellitus often requires insulin supplementation therapy. Recent developments of analogue insulin and premixed formulations have increased the therapeutic options for patients who need such therapy. This study aimed to retrospectively clarify appropriate treatment regimens according to age, body mass index (BMI) and duration of diabetes in Japanese patients with type 2 diabetes previously entered in an open-label, randomized trial that compared convenience-oriented biphasic insulin aspart 30 versus multiple injections of insulin aspart with or without NPH insulin.

Methods: Japanese insulin-naïve patients were randomized to receive either biphasic insulin aspart 30 twice daily or insulin aspart three times daily with or without multiple injections of NPH insulin for a treatment period lasting 6 months.

Results: Reduction of glycosylated haemoglobin (HbA_{1c}) at the end of 6 months was not different in the two treatment groups irrespective of BMI, age and duration of diabetes. However, the achievement rate of HbA_{1c} <7.0% was significantly higher in patients with a BMI <25 kg/m² in the multiple-injection group and tended to be higher in patients with a diabetes duration <10 years in the twice-daily injection group.

Conclusion: Twice-daily injections of biphasic insulin aspart 30 may be more suitable for obese patients whereas multiple injections of insulin aspart with

or without NPH insulin may be preferable for those with a longer duration of diabetes.

Background

Maintenance of nearly normal blood glucose levels in patients with type 2 diabetes mellitus reduces the risk of microvascular and macrovascular complications.^[1-3] Since type 2 diabetes is characterized by defects in both insulin secretion and insulin action, good glycaemic control in patients with this disease often requires insulin supplementation therapy.^[4] However, initiation of insulin therapy is not easy in many patients because of their reluctance to adhere to conventional regimens.^[5] On the other hand, the recent developments of analogue insulin and premixed formulations now allow patients to choose from a variety of therapeutic options.

We previously investigated whether twice-daily injections of biphasic insulin aspart 30 or three-times-daily injections of insulin aspart with or without NPH insulin for 6 months confer better glycaemic control, and suggested that the two regimens were equally useful for patients with type 2 diabetes.^[6] In the present study, we retrospectively analysed the influence of age, body mass index (BMI) and duration of diabetes on the suitability of these two regimens in our cohort of patients.

Patients and Methods

Patients

This was a retrospective reanalysis of JDDM (Japan Diabetes Clinical Data Management Study Group) 11, a 6-month, randomized, open-label trial conducted in adult type 2 diabetic patients recruited at 19 centres in Japan.^[6] The definition of type 2 diabetes conformed to that outlined in the 'Report of the Committee of Japan Diabetes Society (JDS) on the Classification and Diagnostic Criteria of Diabetes Mellitus'.^[7] These criteria are almost identical to those described by WHO.^[8] To be eligible for inclusion in the study, patients were required to have a gly-

cosylated haemoglobin (HbA_{1c}) level of $\geq 8.0\%$ for ≥ 3 months, irrespective of use of oral antihyperglycaemic agents, and an indication for starting insulin therapy. Patients with 'soft drink ketoacidosis', i.e. high blood levels of ketones secondary to a lack of insulin following excessive intake of sugar (typically as a result of drinking high sugar-containing carbonated soft drinks),^[9] were excluded. Patients 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) for the 6-month study period. Oral antihyperglycaemic agents that stimulate insulin secretion, such as sulfonylureas and short-acting insulin secretagogues, were discontinued and use of other insulin preparations was prohibited during the study. Doses of insulin analogues were adjusted at the discretion of each investigator to achieve a target HbA_{1c} level of $< 7.0\%$.

Participating clinics and hospitals were affiliated with the JDDM and the clinical data for all patients were standardized and stored on a personal computer using CoDiC® software (Novo Nordisk Pharma Ltd, Tokyo, Japan).^[10] The clinical data were collected from each institute on CD-R storage media and analysed by SPSS® software (SAS Institute, Cary, NC, USA). Data received at the central analytical centre were processed on an anonymous basis. JDDM operates as an intermediate organization under the supervision of a central analytical centre 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 guidelines on ethics for a clinical study.

Initially, a total of 160 patients were enrolled and equally randomized to the two treatment groups as described previously.^[6] 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 follow-up.^[6] The reasons

for discontinuation were similar in the two treatment groups. In the previous study, we obtained the same results for the protocol-compatible analysis in 117 patients and the intent-to-treat analysis, which included data for a total of 43 patients who discontinued the study early. Therefore we evaluated the 117 patients making up the protocol-compatible cohort in this study.

Measurement and Standardization of Data

HbA_{1c} was measured by a high-performance liquid chromatography (HPLC) method. The normal range for HbA_{1c} was defined as 4.3–5.8%. Postprandial plasma glucose was assessed after breakfast or lunch using the hexokinase method. Measurement of each parameter assessed in this study was standardized at all participating institutions.

Statistical Analyses

Statistical analyses were conducted using SPSS® version 13.0J for Windows software (SAS Institute, Cary, NC, USA). Mean intergroup values for HbA_{1c} level were subjected to repeated ANOVA measurement and the non-paired t-test. Patients in each treatment group were divided into subgroups according to BMI <25 and ≥25 kg/m², age <60 and ≥60 years, and duration of diabetes <10 and ≥10 years. The success rate for achieving the target HbA_{1c} level of <7.0% at the end of the trial was compared among subgroups using the chi-squared (χ^2) test. All data are expressed as mean ± SD. A p-value <0.05 was considered significant.

Results

Influence of Body Mass Index

Because BMI data were missing for two patients, a total of 115 patients were analysed for effect of BMI. In the twice-daily and multiple-daily injection groups, 33 and 41 patients, respectively, had a BMI <25 kg/m², and 21 and 20, respectively, a BMI ≥25 kg/m². No statistically significant difference in mean HbA_{1c} level was observed between subgroups of patients with a

BMI <25 kg/m² and those with a BMI ≥25 kg/m² at each month over the 6-month study period (figure 1a). At the end of the study, in patients with a BMI <25 kg/m², 33.3% in the twice-daily injection group and 43.9% in the multiple-daily injection group achieved an HbA_{1c} level of <7.0%. In patients with a BMI ≥25 kg/m², the proportions achieving this target were 33.3% and 15.0% in the twice-daily and multiple-daily injection groups, respectively. In the multiple-daily injection group the proportion of patients who achieved an HbA_{1c} level of <7.0% was significantly ($p=0.023$) higher in patients with a BMI <25 kg/m² than in those with a BMI ≥25 kg/m².

Influence of Age

A total of 117 patients were analysed for effect of age. In the twice-daily and multiple-daily injection groups, 30 and 35 patients, respectively, were aged <60 years, and 26 and 26, respectively, ≥60 years. No statistical difference in mean HbA_{1c} level in patients aged <60 or ≥60 years was observed between the two treatment groups at each month over the 6-month study period (figure 1b). At the end of the study, in patients aged <60 years, 30.0% in the twice-daily injection group and 40.0% in the multiple-daily injection group achieved an HbA_{1c} level of <7.0%. In patients aged ≥60 years the proportions in the twice-daily and multiple-daily injection groups were 38.5% and 26.9%, respectively.

Influence of Diabetes Duration

A total of 117 patients were analysed for effect of diabetes duration. In the twice-daily and multiple-daily injection groups, 32 and 34 patients, respectively, had a duration of diabetes of <10 years, and 24 and 27, respectively, of ≥10 years. No difference in mean HbA_{1c} level was observed between the two treatment groups in either subgroup at each month over the 6-month study period (figure 1c). At the end of the study, in patients whose duration of diabetes was <10 years, 43.8% in the twice-daily injection group and 38.2% in the multiple-daily injection group achieved an HbA_{1c} level of <7.0%. In patients whose duration

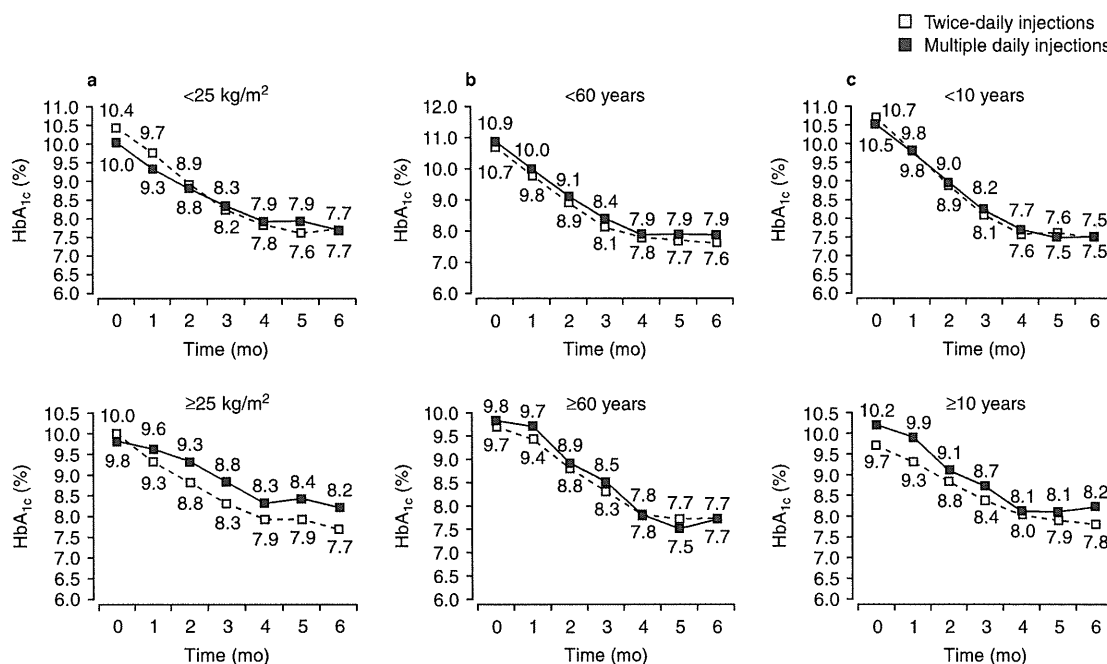


Fig. 1. Time-course of mean glycosylated haemoglobin (HbA_{1c}) level in patients with diabetes mellitus randomly assigned to receive either twice-daily biphasic insulin aspart 30 or multiple-daily injections of insulin aspart with or without NPH insulin for 6 months stratified by (a) body mass index (BMI) <25 or ≥25 kg/m², (b) age <60 or ≥60 years, and (c) duration of diabetes <10 or ≥10 years. The reduction in HbA_{1c} level at 6 months was similar in the two treatment groups regardless of BMI, age and duration of diabetes.

of diabetes was ≥10 years, the proportions in the twice-daily and multiple-daily injection groups were 20.8% and 29.6%, respectively. In the twice-daily injection group, the proportion of patients who achieved an HbA_{1c} level of <7.0% tended to be higher among those whose duration of diabetes was <10 years compared with those whose duration of diabetes was ≥10 years, although the difference was not statistically significant ($p=0.065$).

Discussion

We previously reported that twice-daily injections of biphasic insulin aspart 30 or three-times-daily injections of insulin aspart with or without NPH insulin elicited similar reductions in HbA_{1c} level following 6 months of randomized treatment.^[6] In the present retrospective subanalysis of our data, the reduction in HbA_{1c} level at the end of 6 months was not different in patients on these two regimens regardless of BMI, age and duration of diabetes. However, in the group as-

signed three-times-daily injections of insulin aspart with or without NPH insulin, patients with a BMI <25 kg/m² had a significantly higher rate of achieving an HbA_{1c} level of <7.0% than those with a BMI ≥25 kg/m². On the other hand, among patients who were assigned to receive twice-daily injections, those whose duration of diabetes was <10 years were more likely to achieve an HbA_{1c} level of <7.0% compared with those whose duration of diabetes was ≥10 years, although the difference was not statistically significant. These results suggest that twice-daily injections of biphasic insulin aspart 30 may be a better regimen for obese patients, whereas three-times-daily injections of insulin aspart with or without NPH insulin may be more suitable for those with longer duration of diabetes.

In patients with type 2 diabetes, basal insulin secretion usually gradually declines along with the duration of illness.^[11] Hence, in individuals with diabetes of longer duration, twice-daily injections of biphasic insulin aspart 30 may not be

sufficient for prandial requirements after mid-day lunch. Our results suggest that for these individuals, three-times-daily injections of insulin aspart with or without NPH insulin may be more suitable than twice-daily injections. On the other hand, although in many obese patients the capacity for secreting insulin remains intact, the action of insulin is often not sufficient to maintain good glycaemic control because of peripheral insulin resistance; in obese individuals, the level of insulin resistance is typically greater than in lean patients.^[12] Furthermore, excessive insulin secretion may accelerate weight gain and cause worsening insulin resistance. Multiple insulin injection regimens may therefore exacerbate the hazards of excessive insulin administration in obese patients.

Conclusion

In terms of reducing HbA_{1c} level, both twice-daily and thrice-daily regimens exerted similar effects regardless of BMI, age and duration of diabetes in this study. Although this study has some limitations, such as being a retrospective reanalysis and lacking a protocol-specified algorithm for insulin titration, clear differences were nonetheless observed concerning the proportion of patients who achieved a target HbA_{1c} level of <7.0% in each treatment group. Our results suggest that twice-daily injection of biphasic insulin aspart 30 may be more suitable for obese patients, whereas multiple injections of insulin aspart with or without NPH insulin may be preferable for those with longer duration of diabetes, at least over the first 6 months of treatment.

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Appendix

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).

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