the type 1 group on the basis of positive antibody tests (including anti-GAD antibody) and in the knowledge that they would require insulin therapy in the future.

Using the hypertension guidelines of the JDS as a reference, the average systolic blood pressure of type 2 diabetics was relatively high. In contrast, the average lipid profiles when compared to existing guidelines were more acceptable. However, more evidence in the form of long-term prospective studies is required to confirm whether the existing guidelines are adequate.

In summary, this is the first study to gather and analyze data relating to the daily clinical management of diabetes in Japan. This study clearly shows that the average HbA1c in Japanese patients was superior to most of the reported results from Western and other countries [9–16]. Sixty six percent of the patients still had HbA1c levels greater than 6.5% and required improved glycemic control to reduce the rate of diabetic complications. A recent national survey in 2002 showed that there were 8.8 million IGT and 7.4 million diabetic patients in Japan. Half of the 7.4 million diabetic patients, i.e. 3.7 million diabetic patients, were under medical care and the rest were receiving no medical care for their diabetes according to the national survey. People should be screened for diabetes as part of an annual medical checkup to facilitate the early treatment of IGT and diabetes. Once diagnosed with diabetes or IGT, they should be cared by medical institutes to be adequately advised for their life style and treated by drugs if necessary. If not, unnecessary diabetic complications are potentially being incurred by 6.1 million patients, i.e. 82% of all Japanese diabetic patients because only half of diabetic patients are treated in medical institutes and 34% of these treated patients are adequately controlled to the level of HbA1c being less than 6.5% in Japan as suggested in this study. These complications could be prevented by patients' education and adequate diabetes treatment. A similar suggestion could be made for the blood pressure and lipid profile results. With the recent advent of new anti-diabetic drugs, prospective studies based on the CoDiC data are necessary for the development of new guidelines for the prevention of complications in Japanese diabetic patients.

## Acknowledgments

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## Appendix A

The following members of JDDM participated in this study: Dr. Naoki Manda (Manda Memorial Hospital); Dr. Yoshio Kurihara (Kurihara Internal Medicine); Dr. Atsushi Hasegawa (Chitose City Hospital); Dr. Takahiko Konno (Yakumo General Hospital); Dr. Shinji Taneda (Taneda Internal Medicine); Dr. Hiroki Yokoyama (Jiyugaoka Yokoyama Internal Medicine Clinic); Dr. Fumihiko Dake (Hokusei Hospital); Dr. Azuma Kanatsuka (Chiba Central Medical Center); Dr. Kenichi Kimura (Kenichi Kimura Internal Medicine Clinic); Dr. Mikihiko Kudo (Kudo Internal Medicine Clinic); Dr. Koichi Kawai (Kawai Clinic); Dr. Fuminobu Okuguchi (Okuguchi Internal Medicine Clinic); Dr. Hiroshi Fujiya (Fujiya Internal Medicine Clinic); Dr. Yasuko Chiba (Nagasaki Hospital); Dr. Yoko Notoya, Dr. Takashi Miwa (Tokyo Medical University); Dr. Osamu Tomonaga (Shinjuku Koushin Clinic); Dr. Madoka Taguchi (Toshiba Hospital); Dr. Hisako Ogawara (Akasaka Central Clinic); Dr. Hiroshi Takamura (Takamura Internal Medicine Clinic); Dr. Koichi Hirao, Dr. Hajime Maeda, Dr. Ritsuko Yamamoto (H.E.C. Science Clinic); Dr. Masahiko Takai (Takai Internal Medicine Clinic); Dr. Hiroshi Takeda (Takeda Clinic); Dr. Hiromichi Sugiyama (Sugiyama Clinic); Dr. Hideo Sasaki (Niigata Kobari Hospital); Dr. Masashi Kobayashi, Dr. Katsuya Yamazaki (Toyama Medical and Pharmaceutical University); Dr. Michiyo Takada (Shimizumachi Internal Medicine Clinic); Dr. Hiroshi Hayashi (Saiseikai Matsusaka General Hospital); Dr. Mariko Oishi (Oishi Clinic); Dr. Kunihiro Doi (Doi Internal Medicine); Dr. Yoshiyuki Hattori (Hattori Clinic); Dr. Nobuyuki Abe (Internal Medicine Abe Clinic); Dr. Hidekatsu Sugimoto (Sugimoto Clinic); Dr. Yoshifumi Yokomizo (Yokomizo Internal Medicine Clinic); Dr. Gendai Lee (Lee Internal Medicine Clinic); Dr. Hiroshi Ninomiya, Dr. Yoshio Kaku (Fukuoka University Chikushi Hospital); Dr. Yoshihide Fukumoto (Fukumoto Clinic); Dr. Noriharu Yagi (Yagi Internal Medicine Clinic); Koichi Iwasaki (Iwasaki Internal Medicine Clinic).

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

# Outcome of One-year of Specialist Care of Patients with Type 2 Diabetes: A Multi-Center Prospective Survey (JDDM 2)

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## Abstract

**OBJECTIVE** Specialist care is reportedly associated with favorable therapeutic results, although detailed outcomes of recent large-scale prospective surveys of specialist care have yet to be published. The goal of this study was to elucidate the effects of one year's specialist care on the management of type 2 diabetes.

**PATIENTS AND METHODS** A multi-centered, prospective observational study was undertaken. 754 type 2 diabetes patients, who made their first visit to one of eleven participating outpatient clinics specializing in diabetes care, were enrolled. Routine structured diabetes care according to established guideline, including diabetes self-management education, was provided to all patients at each clinic visit. Parameters relating to glycemic control, serum lipids, blood pressure, patient follow-up status and others were followed for twelve months.

**RESULTS** The $HbA_{1c}$ level had improved significantly from 8.4±2.2% at baseline to 6.8±1.2% after six months and was 7.0±1.3% after twelve months (mean±SD). The higher the baseline $HbA_{1c}$ level, the greater the subsequent improvement. Moreover, the most dramatic improvements in $HbA_{1c}$ levels were seen within the first three months. The proportion of patients satisfying all of the therapeutic goals was extremely low at baseline and remained at less than 10% after twelve months of specialist care.

**CONCLUSIONS** Diabetic patients under specialist care experienced substantial improvement, especially in glycemic control, as early as a few months after the first visit. However, 35 percent of patients dropped out during the 12-month study period and this is one area that needs to be improved.

**Key words:** diabetes specialist, diabetes clinic, quality of care, diabetes self-management education (DSME), pharmacological therapy

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## Introduction

Continuing medical care, including diabetes self-management education (DSME) provided by medical professionals with expertise in diabetes, is essential to minimize the risk of long-term complications in patients with diabetes (1-3). Specialist diabetes care has been shown to deliver a better glycemic control outcome than care provided by general practitioners (4-11). However, the outcome assessment of specialist routine care needs to be regularly updated to take into account the continual changes in modern diabetes care and pharmacotherapy (12). Other than a postal survey of secondary care services (13), very few large prospective surveys regarding the outcome of recent specialist care are available.

The Japan Diabetes Clinical Data Management Study Group (JDDM) is a large network of diabetes specialists in Japan. It consists of approximately seventy clinical diabetic specialists, most of whom are board certified and have their

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own clinics. The ultimate goal of the JDDM is to acquire clinical evidence that can be used to optimize diabetes care. To achieve this goal, the JDDM is developing a cohort of diabetic patients who are receiving care at the participating clinics, and by January 2005 approximately 60,000 patients were registered. Clinical and treatment information is stored on a standardized database system and from the cohort of the registered patients, we evaluated the clinical outcomes of new patients consecutively registered on the JDDM database during a particular period. The goal of this study was to elucidate the effects of one year of specialist care on the management of type 2 diabetes. Analyses based on prior treatment history and baseline glycemic status were also made.

## Patients and Methods

### Recruitment of patients

Eleven JDDM clinics throughout Japan (as listed in the appendix) that specialize in diabetes care voluntarily participated in this study. All type 2 diabetic patients who made their first visit to any of the participating clinics during the study period (January to June 2001) were consecutively recruited. A total of 754 patients entered the study, all of whom provided informed consent to participate. The protocol was consistent with the Japanese Government's "Ethical Guidelines Regarding Epidemiological Studies" and received ethical approval from the JDDM ethics committee. Patients were classified as having type 2 diabetes mellitus according to the Japan Diabetes Society (JDS) criteria (14) which are similar to the WHO criteria (15) in terms of glucose threshold levels. Patients with impaired glucose tolerance were not included in this study. The study follow-up period was 12 months from the patient's first visit.

### Diabetes management and care

The patients took part in a comprehensive, structured program in accordance with JDS guidelines (16) and the care package included a comprehensive diabetes self-management education (DSME) program with an emphasis on the importance of lifestyle modifications which was conducted by Certified Diabetes Educators (CDE). Topics covered included good dietary habits, physical activities, treatment adherence, and standard medication including oral hypoglycemic agents and/or insulin. The therapeutic goals, mostly based on JDS guidelines at the time of the study, for the study participants were: a stable $HbA_{1c}$ level <6.5%; a body mass index (BMI) $\leq$24 kg/m$^2$; blood pressure <130/85 mmHg; serum total cholesterol level <5.17 mmol/L (200 mg/dL); serum HDL cholesterol level $\geq$1.03 mmol/L (40 mg/dL); serum triglyceride level <1.68 mmol/L (150 mg/dL); smoking cessation; and, decreased alcohol consumption (16). Patients were requested to return to the clinic for follow-up care once a month (preferably) or at least once every two months. Changes in patient medication were made in an effort to reach the therapeutic goals outlined above on a treat to target basis. Standard JDS meal plans using diabetic food exchange lists (17) were used. Dieticians also provided individual nutritional guidance. All patients, except those with medical complications for whom a strenuous exercise regime was contraindicated, were encouraged to engage in physical exercise, for a minimum of 30 minutes at least three times a week, that was vigorous enough for them to work up a sweat. A diary to record the progress of laboratory and other data was distributed to the patients to provide feedback on the results of their therapy program.

### Clinical and laboratory parameters

Body weight, blood pressure, $HbA_{1c}$, fasting plasma glucose, serum lipids/creatinine/urea nitrogen, and urine analysis results were obtained at scheduled clinic visits during the study period. Ophthalmological and neurological examinations were done at baseline. JDS guidelines were used to assess the development of microvascular complications. Neuropathy was defined as having three or more of the following: (i) absence of ankle tendon reflex; (ii) absence of knee tendon reflex; (iii) decreased vibration sensation; (iv) abnormal results for monofilament touch test (18); or (v) abnormal subjective symptoms. Nephropathy was defined as having an albumin excretion of more than 30 mg/g creatinine in two or more consecutive urine testings. Retinopathy was defined to involve simple, non-proliferative retinopathy. $HbA_{1c}$ levels were determined by high-pressure liquid chromatography (HPLC) with 5.8% as the upper normal limit. Plasma glucose levels were determined by the glucose oxidase technique. All other laboratory tests were determined by standard methods.

### Data processing and statistical analysis

Clinical data was input to a bespoke, standardized software system "CoDiC™" (19) which was distributed to each participating clinic. Data were collected from each institute on an anonymous basis and stored centrally for statistical analysis using SPSS, version 10.05 (SPSS Inc., Chicago, IL, USA). The F-test was used to determine whether the variance of each group was equivalent. Student's paired and unpaired t-tests, one-way ANOVA and a post hoc multiple comparison test (Dunnett) were used to compare continuous variables between groups. A $P$-value of less than 0.05 was considered significant. All values are presented as means ± standard deviations unless otherwise stated.

## Results

### Background characteristics and baseline analysis

Baseline measurements broken down according to prior or first time treatment are shown in Table 1. Of the previously treated patients, 93% were direct referrals from primary care physicians with the remainder discontinuing their previous medical care. Among the previously untreated patients, 62%

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Table 1. **Patient characteristics at baseline and 12 months later. Baseline data of the patients that completed the 12-month study period are shown in [ ]**

**(Mean±S.D., n.a.; not applicable, n.d.; not done)**

| | Total | | Newly treated patients | | Previously treated patients | |
|---|---|---|---|---|---|---|
| | Baseline[a] | 12th month[b] | Baseline[c] | 12th month[d] | Baseline[e] | 12th month[f] |
| Number of patients | 754 | 491 | 341 | 194 | 413 | 297 |
| Men/Women | 496/258 | 311/180 | 241/100 | 134/60 | 255/158** | 177/120 |
| Age (yr.) | 58.0±11.9 [58.8±11.6] | n.a. | 56.2±11.1 [57.1±10.9] | n.a. | 59.6±12.3*** [59.8±11.9] | n.a. |
| Diabetes duration (yr.) | 9.1±8.8 [9.4±8.6] | n.a. | 6.3±7.1 [6.7±7.5] | n.a. | 10.7±9.3*** [10.6±8.8] | n.a. |
| BMI (kg/m2) | 24.1±4.1 [24.2±4.4] | 24.2±3.8* | 24.7±4.2 [24.7±4.7] | 24.4(3.9 | 23.7±4.1** [23.9±4.1] | 24.1±3.7** |
| HbA1C (%) | 8.4±2.2 [8.6±2.2] | 7.0±1.3*** | 8.5±2.3 [9.0±2.4] | 6.8(1.3*** | 8.4±2.1 [8.4±2.0] | 7.2±1.3***-++ |
| Systolic blood pressure (mmHg) | 136.9±21.8 [136.9±21.3] | 131.2±17.8*** | 136.8±21.2 [136.4±20.9] | 130.4±17.1*** | 138.1±22.6 [137.2±21.7] | 131.9±18.3*** |
| Diastolic blood pressure (mmHg) | 79.6±12.9 [79.5±12.5] | 75.7±11.9*** | 81.4±12.8 [81.0±12.8] | 76.3±12.7*** | 78.7±12.5** [78.4±12.2] | 75.4±11.2*** |
| Total cholesterol (mmol/l) | 5.48±1.04 [5.37±1.00] | 5.21±0.88*** | 5.61±0.98 [5.48±0.93] | 5.23±0.80*** | 5.39±1.06 [5.31±1.05] | 5.21±0.88** |
| HDL cholesterol (mmol/l) | 1.41±0.39 [1.42±0.40] | 1.40±0.36 | 1.42±0.37 [1.44±0.38] | 1.40±0.31 | 1.41±0.39 [1.42±0.41] | 1.40±0.36 |
| Triglycerides (mmol/l) | 1.72±1.24 [1.63±1.20] | 1.73±1.63 | 1.80±1.39 [1.66±1.30] | 1.41±0.82*** | 1.66±1.13 [1.60±1.12] | 1.73±1.13++ |
| Patients with retinopathy (%) | 31.1 [34.0] | n.d. | 20.0 [23.6] | n.d. | 39.4 [40.7] | n.d. |
| Patients with nephropathy (%) | 30.6 [31.2] | n.d. | 21.1 [21.0] | n.d. | 38.1 [37.9] | n.d. |
| Patients with neuropathy (%) | 25.2 [25.8] | n.d. | 17.6 [20.0] | n.d. | 31.2 [29.7] | n.d. |
| Medication for hypertension (%) | 17.4 [19.0] | 33.8*** | 11.9 [13.8] | 28.1*** | 21.7 [22.3]* | 37.5***+ |
| Medication for hyperlipidemia (%) | 6.7 [6.9] | 18.2*** | 3.5 [3.8] | 13.8*** | 9.2 [8.8]* | 21.0***+ |
| Medications for both of the above (%) | 3.4 [3.2] | 8.7*** | 2.9 [2.9] | 6.7*** | 3.8 [3,4] | 10.1*** |
| | | *p<0.05, ***p<0.001 (a vs.b) | | ***p<0.001 (c vs.d) | *p<0.05, **p<0.01, ***p<0.001 (c vs.e) | **p<0.01, ***p<0.001 (e vs.f) +p<0.05, ++p<0.01, +++P<0.001 (d vs. f) |

visited the clinics because of elevated FPG and/or $HbA_{1c}$ levels found at a medical check-up, while 8% attended because of the development of diabetic symptoms. The remainder were referred from other speciality clinics or hospitals. Baseline $HbA_{1c}$ was similar in patients with and without a previous history of diabetes care. However, the previously untreated patients were significantly younger with a shorter duration of diabetes and a lower BMI (Table 1).

### *Patient follow-up status and dropout*

The proportions of patients making repeat clinic visits, sub-grouped according to whether they had received prior treatment for diabetes and by baseline $HbA_{1c}$ levels, are shown in Fig. 1A and Fig. 1B, respectively. Approximately 35% of all participants defaulted from follow-up during the first year (Fig. 1A). At twelve months, patients with $HbA_{1c}$

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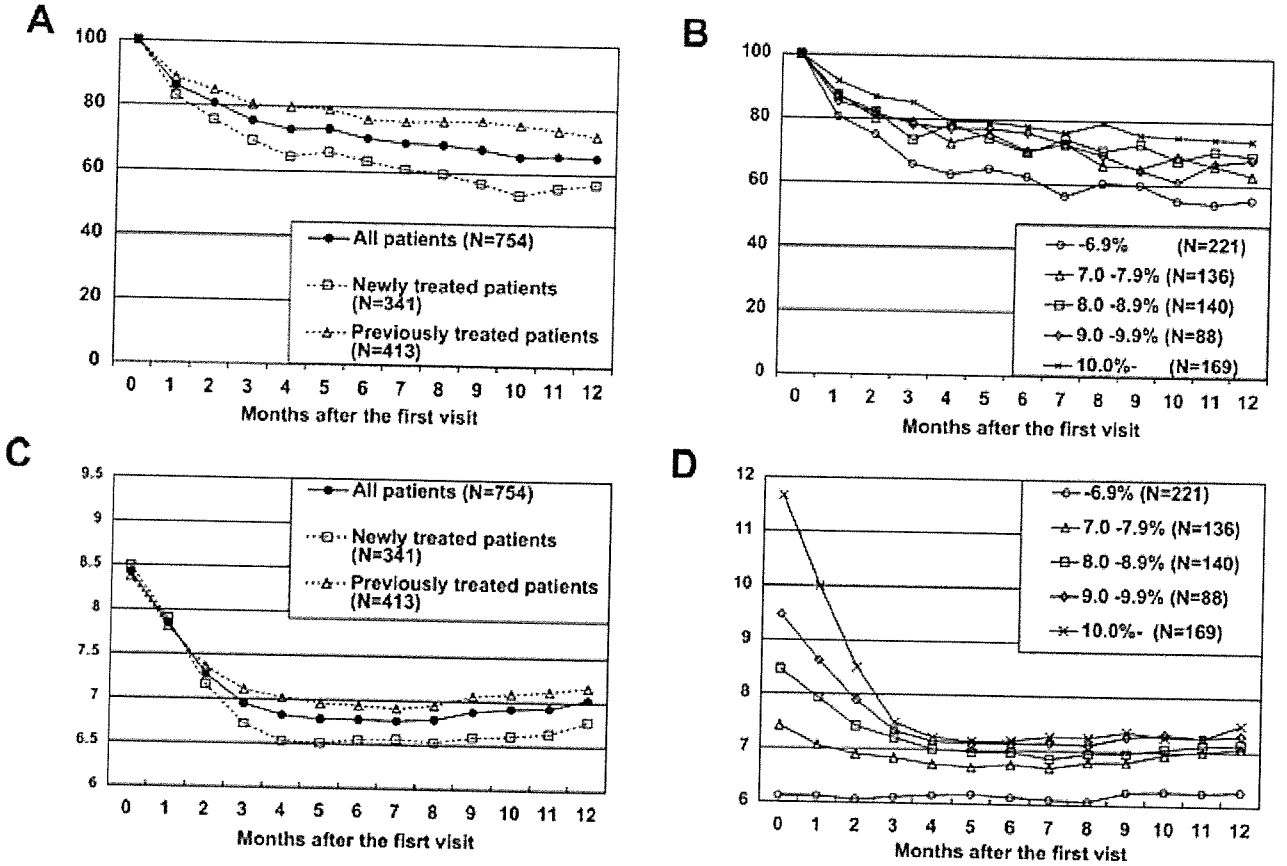


Figure 1. Sequential changes in the proportion of patients under follow-up (A, B), and $HbA_{1c}$ levels (C, D) during the twelve months following the first visit to a specialist clinic. The results were stratified according to the patients' previous follow-up status (A, C) or $HbA_{1c}$ levels at baseline (B, D).

levels of 6.9% or less had the greatest dropout rate (44.3%) while patients with levels of 10% or more had the lowest rate (26.0%) ($P<0.001$ between the two subgroups; Fig. 1B). A comparison of patient backgrounds at baseline between those who completed (N=491) and those who were lost to follow-up (N=263) showed that baseline $HbA_{1c}$ levels were significantly lower ($P=0.039$) in those who dropped out (8.1±2.2%) than in those who completed treatment (8.6± 2.2%). However, there were no significant differences in age, gender, diabetes duration or baseline BMI between these two groups (data not shown). Patients being treated for diabetes for the first time had a significantly higher dropout rate (43%) than previously treated patients (28%) (Table 1 and Fig. 1A) ($P<0.001$). The reasons given for patient dropout included the pressure of official (28%) or private business (11%), misunderstanding regarding diabetes therapy (13%), moving out of town (11%), and economic reasons (6%).

### Changes in glycemic and other control

The mean $HbA_{1c}$ levels of all patients who completed 12-month follow-up improved significantly from 8.4±2.2% at baseline to 6.8±1.2% after six months, and 7.0±1.3% after twelve months (Fig. 1C). Newly treated patients showed significantly greater improvements in $HbA_{1c}$ levels during the first year than the previously treated patients ($P<0.001$; Fig. 1C). As shown in Fig. 1D, the higher the initial $HbA_{1c}$ level the greater the improvement that was seen. For patients with the highest baseline $HbA_{1c}$ (10% or more), mean $HbA_{1c}$ levels fell dramatically from 11.7±1.3% to 7.5±1.6% in the first three months and remained stable thereafter. Conversely, only very limited improvement was found in patients with $HbA_{1c}$ levels of 7.9% or less. In general, decreases in $HbA_{1c}$ levels were almost exclusively observed in the three months following the first visit. There was no significant correlation between the final $HbA_{1c}$ levels and the frequency of DSME (data not shown). Total cholesterol and systolic/diastolic blood pressure significantly decreased regardless of treatment history, while HDL cholesterol did not show any significant changes during the 12-month study period. Significant improvement in triglycerides was seen only in newly treated patients (Table 1).

### Pharmacological therapy and adherence to guidelines

The pharmacological therapy of patients is shown in

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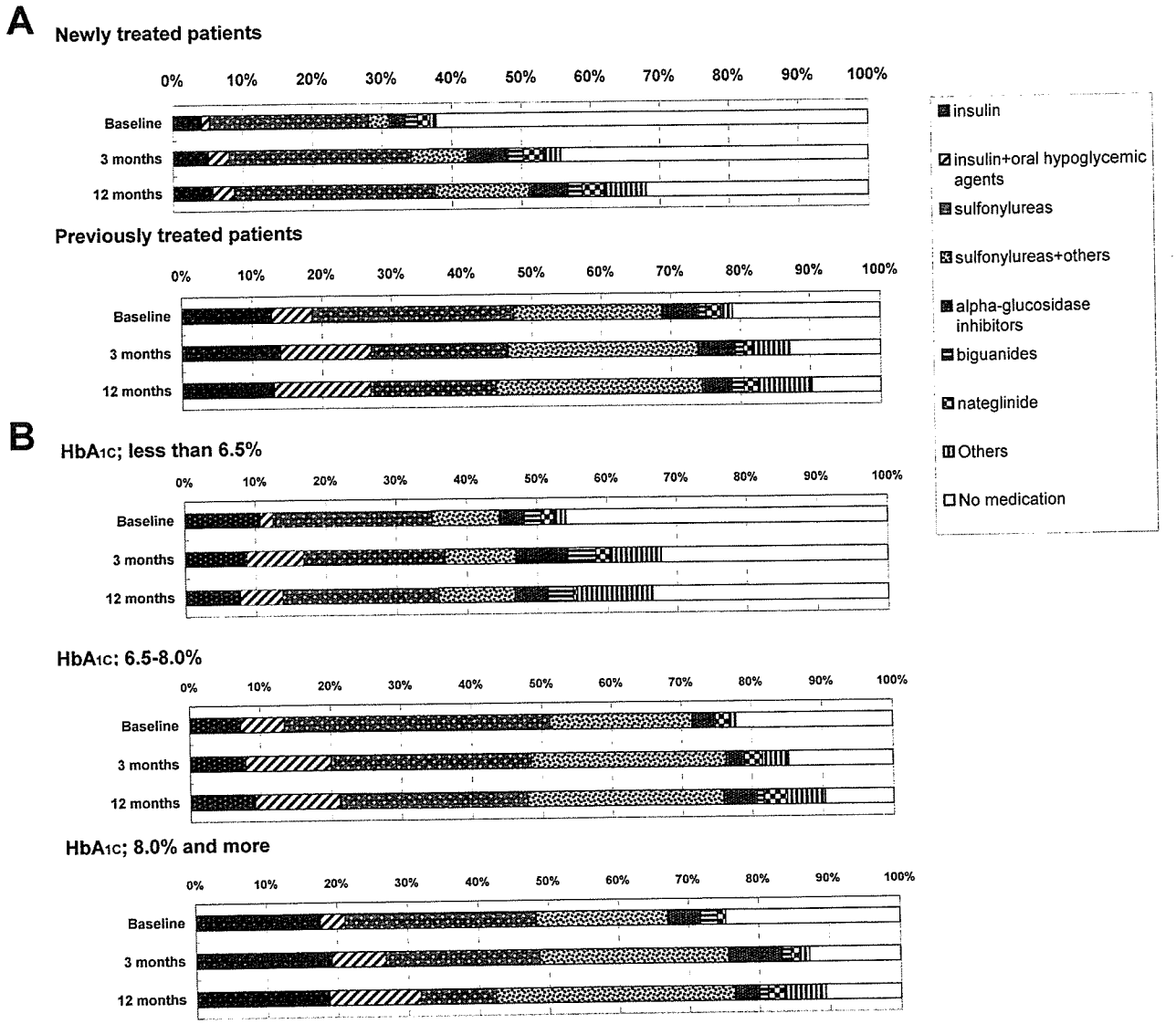


Figure 2. **Pharmacotherapeutic status of the patients at baseline, three months and twelve months after start of the study, stratified according to previous follow-up status (A) or $HbA_{1c}$ levels at baseline (B).**

Fig. 2A and Fig. 2B, broken down according to previous treatment status or baseline $HbA_{1c}$ level, respectively. The use of hypoglycemic agent, including insulin differ, according to a patient's prior treatment history. Patients who had been previously treated used more insulin than previously untreated patients and the proportion of patients using two or more agents was higher in previously treated patients (Fig. 2A). The proportion of patients using sulfonylureas was increased in patients with baseline $HbA_{1c}$ levels of 6.5% or higher and insulin usage was higher in patients with initial $HbA_{1c}$ levels of 8.0% and more than in the other subgroups (Fig. 2B). The proportion of patients taking medications for hypertension, hyperlipidemia, or both significantly increased two- or three-fold during the twelve months of study regardless of prior treatment history (Table 1). To investigate the adherence of each clinic to the guidelines, the $HbA_{1c}$ levels used by clinics to trigger the start of medication were surveyed. The medication thresholds were as follows: 6.5% or more (2 clinics), 7.0% or more (2), 8.0% or more (3), 9.0% or more (1), and patient-by-patient assessment (3). The survey also revealed that clinic $HbA_{1c}$ target levels were as follows: 5.8% or less (1 clinic), 6.5% or less (7) and 7.0% or less (3).

### *Therapeutic goal achievement rates*

In assessing the proportions of patients who achieved either the individual or all of the therapeutic goals, comparisons were made at 12 months with two baseline groups; one containing all the patients who participated in the study, and the other containing only those patients who completed the 12-month study (Table 2). Of the patients who completed 12 months of follow-up, the proportion achieving the $HbA_{1c}$

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Table 2. **Proportion of patients satisfying the therapeutic goals (except smoking and drinking) at baseline and 12 months later. Baseline (1) includes all patients enrolled at registration, and baseline (2) includes only patients who remained until the end of the 12 month study. (P < 0.05*, 0.01**, 0.001*** Compared to the group of baseline (2) by McNeuar test)**

| | | Total (%) | Newly treated (%) | Previously treated (%) |
|---|---|---|---|---|
| HbA1c < 6.5% | Baseline (1) | 20.4 | 23.4 | 17.9 |
| | Baseline (2) | 16.5 | 17.9 | 15.7 |
| | At 12th month | 36.5 *** | 46.9 *** | 29.9 *** |
| HbA1c < 7.0% | Baseline (1) | 29.3 | 32.3 | 26.8 |
| | Baseline (2) | 24.6 | 25.1 | 24.2 |
| | At 12th month | 54.1 *** | 63.1 *** | 48.4 *** |
| BMI < 24 kg/m$^2$ | Baseline (1) | 55.7 | 49.5 | 60.7 |
| | Baseline (2) | 54.4 | 47.9 | 58.6 |
| | At 12th month | 51.3 * | 49.1 | 52.7 |
| Systolic blood pressure < 130 mmHg and diastolic blood pressure < 85 mmHg | Baseline (1) | 32.2 | 33.9 | 30.9 |
| | Baseline (2) | 33.3 | 34.3 | 32.5 |
| | At 12th month | 43.5 *** | 44.8 * | 42.6 * |
| Total cholesterol < 200 mg/dl | Baseline (1) | 45.0 | 44.8 | 45.0 |
| | Baseline (2) | 38.5 | 37.1 | 39.5 |
| | At 12th month | 50.0 *** | 51.7 ** | 48.9 * |
| HDL cholesterol > 40 mg/dl | Baseline (1) | 86.6 | 86.5 | 86.6 |
| | Baseline (2) | 87.4 | 85.7 | 88.5 |
| | At 12th month | 88.3 | 89.3 | 87.6 |
| Triglycerides < 150 mg/dl | Baseline (1) | 67.8 | 67.7 | 67.9 |
| | Baseline (2) | 65.3 | 63.6 | 66.4 |
| | At 12th month | 69.4 | 74.1 * | 66.4 |
| All of the above (Regarding HbA1c , goal of < 6.5% was adapted) | Baseline (1) | 2.1 | 2.4 | 1.9 |
| | Baseline (2) | 1.2 | 1.0 | 1.3 |
| | At 12th month | 3.5 | 6.2 | 1.9 |
| All of the above (Regarding HbA1c , goal of < 7.0% was adapted) | Baseline (1) | 2.5 | 2.4 | 2.5 |
| | Baseline (2) | 1.2 | 1.0 | 1.3 |
| | At 12th month | 4.7* | 9.3** | 1.9 |

goal of 6.5% or less increased significantly from 16.5% at baseline to 36.5% at 12 months. The improvement was particularly evident in newly-treated patients (from 17.9% at baseline to 46.9% at 12 months). The proportion of patients achieving the $HbA_{1c}$ goal of 7.0% or less was 24.6% at baseline and 54.1% at 12 months. On the other hand, the proportion of patients who achieved the BMI goal ($\leq$24 kg/m$^2$) decreased significantly from 54.4% at baseline to 51.3% after 12 months. The proportions of patients achieving the blood pressure or total cholesterol goals increased significantly by approximately 10% during the 12-month period. Only newly-treated patients showed a significant improvement in achieving the triglyceride goal.

When adopting the $HbA_{1c}$ goal of 6.5% for analysis, the proportion of patients satisfying all of the therapeutic goals (except smoking and alcohol drinking) at baseline was 2.1%, when all patients who participated in the study were included, and 1.2% when only patients who completed the 12-month follow-up were included. The proportion increased to 3.5% after 12 months but this increase was not statistically significant. However, when the $HbA_{1c}$ goal of 7.0% was adopted for analysis, the proportion of patients satisfying all of the therapeutic goals increased significantly from 1.2% at baseline to 4.7% after 12 months.

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## Discussion

### Glycemic control and weight control

This prospective study highlights the current Japanese standards of diabetes management and care provided in specialist clinics and demonstrated, a reasonable improvement in the glycemic control of patients, especially in those with severe diabetes (Fig. 1). Most of the improvements in $HbA_{1c}$ levels seen in the first year occured within the first three months of commencing management (Fig. 1C). It should be emphasized that even patients who had previously been treated in primary care settings showed improvement in $HbA_{1c}$ levels. Of the patients receiving treatment for the first time, less than 40% started medication after their first visit, while at twelve months nearly 70% of those patients had been prescribed one or more medications (Fig. 2A). This probably accounts for the rapid improvement in $HbA_{1c}$ in these patients (Fig. 1).

Several issues still remain concerning our care of glycemic control. The first is that the proportions of patients achieving the $HbA_{1c}$ goals were still very low even after 12 months of care (Table 2). The second issue is that the improvement in $HbA_{1c}$ was limited to patients with baseline $HbA_{1c}$ levels of 8% or higher (Fig. 1D). The third issue is that the $HbA_{1c}$ levels in patients with a baseline of 7.0% or more converged above the 7.0% level at the midpoint of the study and tended to increase (deteriorate) after that point (Fig. 1D). Finally, a slight but significant increase in BMI, which was possibly related to the effects of pharmacological therapy (20), was observed during the 12 months of care (Tables 1, 2). It is true that the mean BMI of Japanese patients with type 2 diabetes is much lower than that of the United Kingdom Prospective Diabetes Study (UKPDS) patients (21). However, the BMI cut-off for being overweight is now 23 $kg/m^2$ in Asian subjects (22), which is lower than the mean BMI of the present patients.

### Other therapeutic goals

At baseline, the proportion of patients satisfying all of the therapeutic goals (except smoking and alcohol drinking) was only 2.5%, even when a $HbA_{1c}$ goal of less than 7.0% was adopted (Table 2). Only 32.2% and 45.0% of the patients at baseline fulfilled the target goals for blood pressure and total cholesterol levels, respectively, which were lower than the proportions reported in the U.S. (35.8% for blood pressure and 51.8% for total cholesterol) (23), suggesting that under-treatment of cardiovascular risk factors in diabetic patients was common also in Japan.

After 12 months of specialist care, total cholesterol, HDL cholesterol, triglycerides and blood pressure, all critical factors associated with diabetic vascular complications (12, 24-26), were controlled at levels close to the treatment goals set by the JDS (Table 1). However, our results also demonstrated that, in spite of the dramatic increase in the proportion of patients taking medications for hypertension and/or hyperlipidemia (Table 1) only a small proportion of more patients achieved the treatment goals than at baseline, which was notably lower than the achievement rate for glycemic control noted above (Table 2). Although the prevalence of cardiovascular complications in Japanese patients with type 2 diabetes is known to be lower than in patients from other countries (27, 28), the incidences of cerebral infarction and coronary heart disease in Japanese patients with diabetes are both approximately three times higher than in non-diabetic subjects (29), suggesting that we also need to improve our management of hypertension and serum cholesterol in order to prevent macrovascular complications at the same time as we seek to control glycemia.

### Effects of DSME

A recent meta-analysis (30) and the results of the JDCS, the largest and longest trial focusing on the effects of lifestyle intervention (31, 32), have demonstrated a moderate, beneficial impact of DSME. However, a meta-analysis of educational intervention on the management of diabetes (33) failed to show a significant correlation between management effects and the number of visits or education type. We could not find a significant correlation between the frequency of DSME and glycemic control results (data not shown). However, this does not necessarily refute the significance of DSME since the quality of the DSME cannot be represented as a frequency measure. DSME is inevitably involved in a specialist's routine care and it is difficult to extract the genuine effects of DSME (34). It is conceivable that the potent effects of pharmacological therapy on glycemic control in the first few months of the study period masked the moderate effects of DSME. As a matter of fact, even previously treated patients (mostly direct referrals from primary care physicians) who underwent only limited changes in pharmacotherapy after starting specialist care (Fig. 2A) showed significant improvement in $HbA_{1c}$ levels (Table 1), suggesting that the DSME element of specialist care had some positive effects.

### Issues regarding lost to follow-up

A common barrier to improved patient care is that a considerable proportion of patients are lost to follow-up (35-38) and these defaulting patients have poorer outcomes than patients who continue to attend clinics (2, 35, 39, 40). Our study demonstrated a dropout rate of 35% which was close to that observed in many other studies (35). Unlike the situation in many other countries, visiting a clinic every month or two is a common characteristic of the Japanese healthcare system and reflects the facts that the government-based health insurance covers all citizens and extra patient expenditure for specialist care is unnecessary. However, the health insurance system does not seem to contribute to an improvement in the patient dropout rate. The significant differences in baseline $HbA_{1c}$ levels between the patients who dropped-out and those who completed the care program suggests that

patients with milder diabetes need to be encouraged not to abandon medical care.

### *Limitation of the study and future strategy*

There are several important limitations in our study. First, this is only a one-year prospective study and longer-term results, including chronic complications, need to be evaluated, especially as there was a slight deterioration in $HbA_{1c}$ during the last 6 months of the study period. A further study of the outcome of long-term care including actual changes in lifestyle parameters is necessary since only a few substantial studies lasting longer than two years (2, 41) are currently available. Second, the high dropout rate could affect the study result. Although those with lower $HbA_{1c}$ showed the highest dropout rate, a rapid deterioration in their glycemic control cannot be ruled out. Third, individual compliance to the DSME was not monitored but should be investigated in relation to the therapeutic outcome of each patient. At the same time, an analysis of adherence to practice guidelines in each clinic and their patient outcomes should be analyzed in more detail. Fourth, differences in ethnic (21, 42-47), socioeconomic or cultural background need to be considered as a possible source of bias when applying these results to other regions. Finally, a control group of patients treated by primary care physicians was not available and the eleven clinics that participated did so voluntarily. Consequently, we cannot tell from this particular study whether specialist care is superior to that of primary care physicians, although patient selection bias was minimized by registering all newly visited patients consecutively.

In conclusion, enhanced management and care of patients, especially those with relatively mild hyperglycemia, and ongoing therapy for those with $HbA_{1c}$ levels approaching 6.5%, together with continuing efforts to eliminate obesity and patient dropout, and to manage hypertension and dyslipidemia more carefully will probably result in an improved diabetes care outcome.

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**Appendix:** The following members of the JDDM group participated in this study (in alphabetical order); Dr. Hiroshi Hayashi (Matsuzaka), Dr. Koichi Hirao (Yokohama), Dr. Koichi Kawai (Tsukuba), Dr. Mikihiko Kudo (Aomori), Dr. Yoshio Kurihara (Sapporo), Dr. Mariko Oishi (Kyoto), Dr. Fuminobu Okuguchi (Sendai), Dr. Takeshi Osonoi (Naka), Dr. Hideo Sasaki (Niigata), Dr. Hiromichi Sugiyama (Shizuoka), Dr. Katsuya Yamazaki (Toyama). The JDDM consists of many investigators at participating institutes all over Japan.

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# Actual usage and clinical effectiveness of insulin preparations in patients with Type 1 diabetes mellitus in Japan: CoDiC®-based analysis of clinical data obtained at multiple institutions (JDDM 3)☆

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**Abstract**

To clarify the actual usage of insulin preparations and their effectiveness on glycaemic control in patients with Type 1 diabetes mellitus in Japan, we analyzed clinical data collected via CoDiC®, an electronic system for diabetes data collection and management, at 28 institutes. Of 18,470 diabetic patients registered with CoDiC® in June, 2003, 12,279 patients were being treated with insulin preparations and/or oral hypoglycemic agents, with 861 of these patients having Type 1 diabetes mellitus and 11,418 patients having Type 2 diabetes. Three analytical surveys were carried out with the Type 1 diabetes patients. *Study I*: Cross-sectional survey on the treatment in 2002. Six hundred and thirteen patients received intensive conventional insulin treatment (ICT). The number of patients receiving rapid-acting insulin analogue (RA) was greater than that of patients receiving regular insulin (R). Serum CPR was lower in the patients with ICT than in the patients with conventional insulin treatment (CT). *Study II*: Survey on the changes in the actual usage and clinical effectiveness of insulin preparations, based on the data input in 2001 and 2002. The number of patients with ICT using RA insulin markedly increased. *Study III*: Analysis of the participants' clinical course over the 18-month period of the study from the time of first consultation. The dose of insulin increased during the term. The average HbA1c level fell drastically and reached to 7.5% over the first 9 months of the study and then remained between a range of 7.5% and 8% for the rest of the study period. In conclusion, ICT is actively performed and the RA insulin analogues are widely used in Type 1 diabetic patients

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in Japan. Basal-bolus therapy should be used to treat Type 1 diabetic patients with postprandial serum CPR of less than 0.5 ng/ml. It is difficult to obtain the ideal glycaemic control in Type 1 diabetic patients with the currently available insulin preparations.


*Keywords:* Outcome research; Type 1 diabetes mellitus; Insulin treatment; Insulin preparation; Glycaemic control

## 1. Introduction

Diabetes mellitus is a heterogeneous disorder and classified into four categories: Type1, Type 2, other specific types and gestational diabetes mellitus, according to the etiology [1–3]. Type 1 diabetes mellitus is caused by destruction of the pancreatic β-cells induced by auto-immune and non-auto-immune responses [1–3]. It is treated with life style arrangement and insulin preparation. Many insulin preparations have been developed and used in patients with Type 1 diabetes. Recently, novel insulin preparations, human insulin analogues and new types of premixed insulin have been developed [4–6]. We can treat patients with many types of insulin preparations according to the patient's life style and pathophysiology. It is important to clarify the actual usage and the clinical effectiveness of insulin preparations in relation to pathophysiology in order to develop a manual of treatment for Type 1 diabetic patients and a nationwide strategy for the treatment of Type 1 diabetes.

In 2001, Japan Diabetes Clinical Data Management Study Group (JDDM)[1] was established to promote the clinical research for diabetes in Japan. Patients' clinical data from healthcare institutes across Japan were collated in the CoDiC® database, a diabetes data collection and diabetes management information system developed by the JDDM [7,8]. To clarify the actual usage of insulin preparations and their effectiveness in improving glycaemic control of patients with Type 1 diabetes mellitus, we analyzed clinical data from CoDiC®. The data was collected from institutes specialized in diabetes, according to the criteria developed by the board of the JDDM.

## 2. Materials and methods

Diabetes mellitus was diagnosed and classified based on the criteria in the "Report of the Committee of Japan Diabetes Society (JDS) on the Classification and Diagnostic Criteria of Diabetes Mellitus" [3]. Eighteen thousand four hundred and seventy diabetic patients were registered in CoDiC® by the members of the JDDM [8] at 28 institutes specialized in diabetes in Japan until June, 2003. The clinical data were collected in the central analytical center established by JDDM on CD-R storage disk. At the time of collection at the clinic/hospital, the private data, such as name, address, telephone number, etc., were removed to protect the privacy of the patients [8]. The protocol of the studies was developed by the board of the JDDM and approved by the JDDM ethics committee [8]. The JDDM ethics committee confirmed that informed consent, based on the requirements stated in the Guideline for Epidemiology Study in Japan [9], was obtained from patients at each institute participating in the studies.

Twelve thousand two hundred and seventy nine patients were treated with insulin preparations and/or oral hypoglycemic agents (66.4% of total patients registered). Eight hundred and sixty one patients had Type 1 diabetes mellitus and 11,418 patients had Type 2 diabetes. Three analytical surveys, *Study I*, *Study II* and *Study III*, were carried out in the patients with Type 1 diabetes. HbA1c was measured by using the HPLC method and the normal range was defined 4.3–5.8% [8]. Other variables collected, including body mass index (BMI), blood pressure (BP), plasma glucose (PG), total cholesterol (TC), triglyceride (TG) were determined by standard methods. Plasma C-peptide reactivity (CPR) was determined by a radioimmunoassay method and anti-glutamic acid decaroxylase antibody (anti-GAD

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antibody) was assayed by a radioimmunoassy using human recombinant GAD 65.

### 2.1. Study I

Cross sectional survey of the treatment in Type 1 diabetic patients in 2002. The type of insulin therapy and the type of insulin preparation were examined from the data collected between January and June, 2002. Rapid-acting (RA) insulin analogues, insulin aspart and insulin lispro, were introduced to Japan in 2000. The number of patients receiving the analogues was compared with that of patients receiving regular (R) human insulin. The clinical and biochemical characteristics were compared between patients receiving conventional insulin treatment (CT) and intensive conventional insulin treatment (ICT). CT was defined to be one or two subcutaneous injections of insulin preparation per day and ICT to be more three injections per day.

### 2.2. Study II

Survey on the changes in the actual usage and clinical effectiveness of insulin preparations, based on the data collected in 2001 and 2002. The type of insulin preparation used were compared between 2001 and 2002. The number of patients, insulin dosage, frequency of insulin injection, BMI and HbA1c level were compared between patients receiving ICT using RA insulin analogues and R insulin.

### 2.3. Study III

Analysis of the clinical course over the 18 months from the time of first consultation. We analyzed the clinical course of 56 patients in the whole Type 1 diabetic patients, whose clinical data were input into CoDiC® database at an interval of at least every 3 months over the 18-month period after registration in CoDiC®. The changes in insulin dosage, physical status, glycaemic control and lipids levels during the term were examined.

### 2.4. Statistical analyses

The clinical data were extracted and collated using F-basic software® and MS excel software®. Statistical analyses were performed using SPSS®, a statistical software package. Clinical and biochemical characteristics were analyzed using the Student's *t*-test. The status of insulin preparations usage was analyzed with the chi-squared test. The data were presented in the format, mean (S.D.).

## 3. Results

In *Study I*, 95% of patients with Type 1 diabetes mellitus were treated with insulin preparation (Fig. 1A). Only 5.2% of the patients were treated with oral hypoglycemic agent. These patients had positive levels of anti-GAD antibody, but were not yet insulin dependent. More than 70% of the patients received ICT using R insulin or an RA insulin analogue, insulin aspart and insulin lispro, at each meal plus NPH insulin, usually at bed-time. While RA insulin was introduced in Japan in 2000, the number of patients receiving RA insulin preparation was greater than that of patients receiving R insulin in 2002 (Fig. 1B).

Tables 1A and 1B show that the patients treated with ICT were significantly younger than those with CT. The duration of disease was shorter in the patients with ICT than that in the patients with CT. BMI was greater in the patients with ICT than in the patients with CT. Systolic BP was higher in CT patients than in ICT patients, although diastolic BP did not differ between both patient groups. Glycaemic control level was fair in both CT patients and ICT patients: postprandial plasma

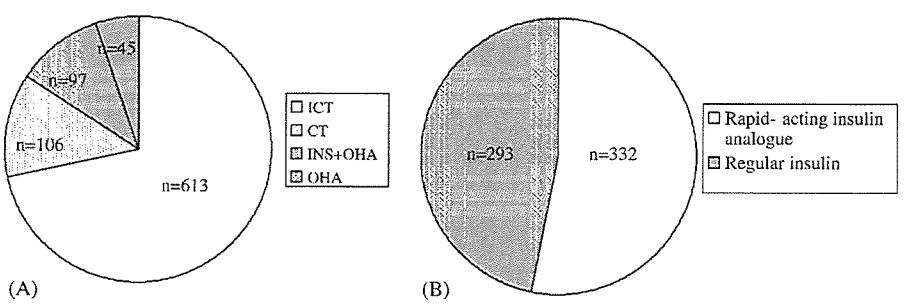


Fig. 1. Cross-sectional survey of the treatment in Type 1 diabetic patients in 2002. (A) The number of patients receiving intensive conventional insulin treatment (ICT), conventional insulin treatment (CT), combination treatment with insulin preparation and oral hypoglycemic agent (OHA) (INS + OHA) and OHA. (B) The number of patients receiving medication with rapid-acting insulin (RA) and regular insulin (R).

Table 1A
Clinical characteristics of patients with Type 1 diabetes mellitus receiving conventional insulin treatment and intensive conventional insulin treatment

| | CT | ICT | $p$-Value |
|---|---|---|---|
| Age (years) | 53.5 (14.5) | 43.8 (16.0) | 0.000 |
| Duration of disease (years) | 14.4 (9.2) | 12.1 (8.7) | 0.014 |
| BMI (kg/m$^2$) | 21.7 (2.9) | 22.2 (3.0) | 0.012 |
| sBP (mmHg) | 128.3 (21.1) | 123.6 (17.4) | 0.000 |
| dBP (mmHg) | 73.4 (12.5) | 73.1 (11.8) | 0.685 |

CT: conventional insulin treatment; ICT: intensive conventional insulin treatment; BMI: body mass index; sBP: systolic blood pressure; dBP: diastolic blood pressure. The data are presented by mean (S.D.) and analyzed by Student's $t$-test.

Table 1B
Biochemical characteristics of patients with Type 1 diabetes mellitus receiving conventional insulin treatment and intensive conventional insulin treatment

| | CT | ICT | $p$-Value |
|---|---|---|---|
| PPPG (mg/dl) | 182.0 (84.7) | 183.2 (96.1) | 0.810 |
| HbA1c (%) | 7.8 (1.8) | 7.8 (1.5) | 0.379 |
| TC (mg/dl) | 201.7 (34.4) | 199.9 (34.5) | 0.559 |
| TG (mg/dl) | 119 (119.7) | 98.9 (69.2) | 0.006 |
| CPR (ng/ml) | 1.0 (0.9) | 0.5 (0.92) | 0.015 |

PPPG: post-prandial plasma glucose; TC: total cholesterol; TG: triglyceride; CPR: C-peptide reactivity. The data are presented by mean (S.D.) and analyzed by Student's $t$-test.

glucose and HbA1c levels did not differ between both patient groups. TG concentration was higher in CT patients, although the TC concentration did not differ between two patient groups. Interestingly, postprandial serum CPR concentration was significantly lower in ICT patients than in CT patients.

In *Study II*, changes in the actual usage of insulin preparations and their clinical effectiveness were investigated in 214 patients whose clinical data were input into the CoDiC® database over the period from 2001 to 2002. Insulin preparations used differed significantly in 2002 compared to 2001 ($p = 0.01663$) (Fig. 2). The number of ICT patients using RA insulin markedly increased (versus number of ICT patients with R insulin: $p = 0.001$, versus number of CT patients with premixed type of insulin: $p = 0.001$), while ICT patients using R insulin and CT patients using premixed type of insulin preparations were both on decreasing trend. Table 2 compares clinical data for ICT patients using RA insulin and ICT patients using R insulin. The dose of insulin used per day was greater in ICT patients using RA insulin than that in ICT patients using R insulin ($p < 0.05$). The frequency of injection per day was also more in the former than that in the later ($p < 0.05$).

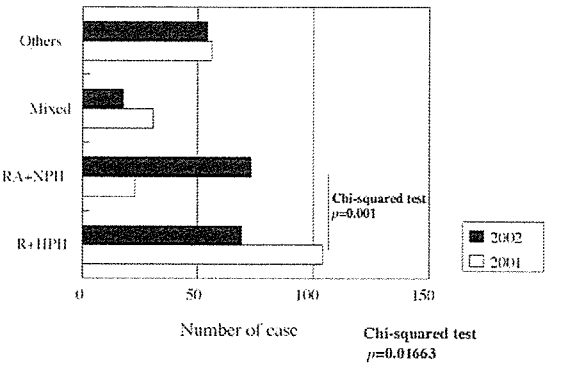


Fig. 2. Changes in the actual usage of insulin preparations over the period from 2001 to 2002. (□) The number of patients in 2001; (■) the number of patients in 2002. Data was analyzed with the chi-squared test.

In *Study III*, we analyzed the clinical course of 56 patients in the whole Type 1 diabetic patients, whose clinical data were input into the CoDiC® database at an interval of at least 3 months over the 18-month period

Table 2
Number of patients receiving intensive conventional insulin treatment with regular insulin or rapid-acting insulin analogue, dose of insulin, frequency of insulin injection, BMI and HbA1c in 2001 and 2002

| | Number of patients | | Dose of insulin (U/day) | | Frequency of injection (day$^{-1}$) | | BMI (kg/m$^2$) | | HbA1c (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 2001 | 2002 | 2001 | 2002 | 2001 | 2002 | 2001 | 2002 | 2001 | 2002 |
| R + NPH | 104 | 69 | 38.2 (16.6) | 39.8 (17.5) | 4 (0.2) | 4.2 (0.4)[a] | 21.3 (2.8) | 21.8 (3.2)[a] | 8.5 (2.0) | 7.7 (1.3)[a] |
| RA + NPH | 23 | 73 | 41.8 (20.6) | 47.4 (19.3)[b] | 4.4 (0.5)[c] | 4.4 (0.5)[b] | 21.0 (4.0) | 22.1 (2.4) | 8.8 (1.5) | 8.2 (1.7) |

R: regular insulin; NPH: NPH insulin; RA: rapid-acting insulin analogue. The data are presented by mean (S.D.) and analyzed with the Student's $t$-test.

[a] $p < 0.05$ (vs. 2001).
[b] $p < 0.05$ (vs. R + NPH).
[c] $p < 0.01$ (vs. R + NPH).

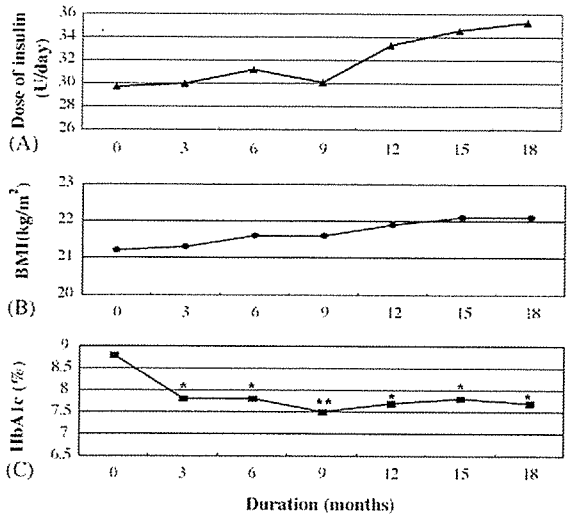


Fig. 3. Analysis of the clinical course over the 18 months from the time of first consultation: (A) change in dose of insulin injected per day; (B) change in body mass index (BMI); (C) change in HbA1c levels. Data was presented by mean and statistically analyzed with the Student's *t*-test. $^{**}p < 0.01$, $^{*}p < 0.05$, compared with the data at the time of first consultation.

after registration in CoDiC®. As shown in Fig. 3, the dose of insulin injected gradually increased from 29.7 to 35.3 U/day (mean) during the term, although the dose at each time was statistically not significant compared with that at the first time. BMI gradually and slightly, but not significantly, increased over the 18 months. HbA1c levels drastically decreased and reached to 7.5% at 9 months. But after that time the levels did not improve and tracked between 7.5% and 8%. Clinical data including systolic and diastolic BP, postprandial PG, TC and TG did not differ from the time of first consultation to the consultation at the conclusion of the study 18 months later (Table 3).

Table 3
Changes in clinical data of 56 patients from the first time of consultation to 18 months after the first time consultation

| | The first | 18 mo. | *p*-Value |
|---|---|---|---|
| sBP (mmHg) | 116.4 (17.3) | 121.8 (16.3) | 0.138 |
| dBP (mmHg) | 70.8 (9.4) | 70.4 (9.4) | 0.851 |
| PPPG (mg/dl) | 204.9 (102.2) | 182.7 (72.9) | 0.249 |
| TC (mg/dl) | 182.1 (34.3) | 175.6 (26.5) | 0.633 |
| TG (mg/dl) | 77.8 (44.8) | 103.9 (111.39 | 0.377 |

The first: the first time consultation; 18 mo.: 18 months after the first time consultation; sBP: systolic blood pressure; dBP: diastolic blood pressure; PPPG: postprandial plasma glucose; TC: total cholesterol; TG: triglyceride. The data are presented by mean (S.D.) and analyzed by Student's *t*-test.

## 4. Discussion

We analyzed the CoDiC® database, a large scale clinical database based on data collected from multiple institutes across Japan specialized in the treatment of diabetes. The CoDiC® data were input by the members of the JDDM [8], medical doctors specialized in diabetes, according to the criteria developed by the board of JDDM, to help ensure the reliability of the data for analysis. Thus, the results show the actual usage of insulin preparations and their effectiveness for glycaemic control in Japanese patients with Type 1 diabetes mellitus.

We diagnosed Type 1 diabetes mellitus according to clinical status, namely abrupt onset of diabetes mellitus and insulin dependency and secondly, the positive levels of anti-GAD antibody [1–3,10]. Thus, 5% of the patients were not yet insulin-dependent at the time analyzed and not treated with insulin, although they had possibly insulitis gradually destroying the pancreatic β-cells. Therefore, it is possible that they gradually progress to be insulin-dependent and some of them would be expected to require insulin treatment in future [11]. Their clinical course is interesting and has to be followed up for long term.

Intensive insulin therapy become routine treatment of patients with Type 1 diabetes in some countries [12,13]. Our results: with 70% of the patients with Type 1 diabetes on ICT treatment show that this treatment approach has become routine in Japan. Furthermore, RA insulin is progressively increasing in a proportion of insulin therapy (Fig. 2). The number of ICT patients using RA insulin was greater than that of ICT patients using R insulin (Fig. 1B). While RA insulin was mainly used in newly diagnosed Type 1 diabetes patients, RA insulin has also been substituted for R insulin used in ICT and for mixed type insulin preparations used in CT. Considering the pharmacokinetic and pharmacodynamic advantages of RA insulin [14,15], postprandial glucose excursions are expected to improve [16]. However, we failed to find that RA insulin in ICT is more effective on the improvement of HbA1c compared to R insulin (Table 2), similar to the previous reports [17,18]. Furthermore, the dose of insulin used per day was greater in ICT patients using RA insulin than that in the ICT patients using R insulin. The frequency of injection per day was also more in the former than that in the latter. These findings may be related to the inadequate substitution of basal insulin by NPH insulin, in part inducing higher preprandial glucose concentration [19,20]. Recently, ICT using RA insulin: insulin aspart and long-acting insulin analogue: detemir has

been reported to be more effective in improving glycaemic control than ICT using R insulin and NPH insulin [21]. We should examine the effectiveness of novel insulin preparations and traditional insulin preparations in ICT in large scale Type 1 diabetes therapy, like this study. We did not examine hypoglycemic episodes, comparing the groups receiving R insulin and RA insulin analogues. Several researchers reported that RA insulin analogues reduced frequency of severe hypoglycemic episodes [17,18]. We should also examine the influence on hypoglycemic episodes of novel insulin preparations and traditional insulin preparations in large scale samples, like this study.

It is very interesting that the patients receiving ICT were markedly younger than the patients receiving CT and the duration of disease of the former patients was shorter than that of the latter patients. Together with the finding that serum CPR concentration was markedly lower in the patients treated with ICT than in the patients with CT, this study reconfirms that Type 1 diabetes is heterogeneous in clinical characteristics [22–24]. For some Type 1 diabetic patients, pancreatic β-cells are rapidly destroyed and ICT is necessary for glycaemic control within a short time of the disease onset; the extreme example is Fulminant Type 1 diabetes proposed by Imagawa et al. [25] and examined by a nationwide survey in Japan [26]. On the other hand, for some Type 1 diabetic patients, β-cells are gradually destroyed and pancreatic endocrine function are comparatively preserved [11]. Thus, CT can provide fair glycaemic control in these patients.

The number of ICT patients was six-times larger than that of CT patients (Fig. 1). In the present study, HbA1c level of the CT patients did not differ from that of the ICT patients, while in the diabetes control and complications trial (DCCT), glycaemic control with ICT was better than that with CT [27]. DCCT was prospective study on comparison of glycaemic control and the prevention of complications between ICT and CT in which the patients were recruited according to the diagnosis of Type 1 diabetes mellitus, but not considering the reserved pancreatic endocrine function in grouping. On the other hand, the present study was retrospective one in which medical doctors specialized in diabetes would be apt to treat patients with severe insulin deficiency by ICT. Glycaemic control would be largely depend on the reserve of the endogenous insulin secretion even in insulin treatment. Indeed, CPR levels of the ICT patients was markedly lower than that of the CT patients (Table 1B), suggesting that the pancreatic endocrine function in patients with ICT was more severely impaired than that in patients with CT. The results suggest that fair glycaemic control can be obtained by CT even in Type 1 diabetic patient when the serum CPR level at postprandial condition is more than 1 ng/ml. We have to consider both the patient's life style and the degree of β-cell dysfunction in the selection of insulin treatment. However, Type 1 diabetic patients with postprandial serum CPR concentration of less than around 0.5 ng/ml should be given ICT to ensure strict glycaemic control.

In 56 patients of the whole Type 1 diabetic patients, whose clinical data were input into the CoDiC® database at an interval of at least 3 months over the 18-month period after registration in CoDiC®, glycaemic control rapidly improved with the insulin treatment and the arrangement of life style during the first 3 months of treatment after the first consultation. In patients who had not received any treatment before the registration, insulin treatment might start and in patients who had have CT treatment, insulin treatment might be changed from CT to ICT. After this initial 3-month treatment period, fair glycaemic control was maintained by gradual increase of insulin dose (Fig. 3). However, glycaemic control that met the criteria proposed by the committee of Japan Diabetes Society [3] was not achieved. Glycaemic control achieved is insufficient for prevention of chronic complications [27,28]. Insulin dose was not further increased even though adequate glycaemic control was not achieved, suggesting the risk of hypoglycemia with the traditional insulin preparations, although the risk become to be less with RA insulin analogues [18]. We will need to adopt therapy using newly developed insulin preparations in basal-bolus therapy in Type 1 diabetic patients to achieve desirable glycaemic control with less hypoglycemia.

In summary, intensive insulin therapy is actively performed and the rapid-acting insulin analogues are widely used in Type 1 diabetic patients in Japan. Although we have to consider both the patient's life style and the degree of β-cell dysfunction in the selection of insulin treatment, Type 1 diabetic patients with postprandial serum CPR concentration of less than around 0.5 ng/ml should receive basal-bolus therapy to ensure strict glycaemic control. In a clinical setting, it is difficult to obtain ideal glycaemic control with currently available insulin preparations in Type 1 diabetic patients. Thus, it is hoped novel insulin preparations continue to be developed. Furthermore, the effectiveness of these novel insulin preparations in basal-bolus therapy should be examined in the large scale clinical studies of patients with Type 1 diabetes similar to this study. Finally, CoDiC® is useful tool for large-scale surveys of diabetic patients at multiple institutions.

## Acknowledgment

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研究報告

# 強化インスリン療法における2型糖尿病に対する超速効型インスリン(インスリン アスパルト)の有効性に関する研究(JDDM 5)

## ーヒトインスリンとの比較検討ー

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糖尿病データマネジメント研究会

要　約

日本人2型糖尿病患者において，ヒトインスリン製剤による強化インスリン療法から超速効型インスリンによる強化インスリン療法に治療方法を切り替えた場合，血糖コントロールが改善するかという検討を行った．解析には，糖尿病データマネジメント研究会(JDDM)によって糖尿病患者情報集積ソフト"CoDiC®"を用いて収集された情報を用いた．ヒトインスリン製剤による強化インスリン療法を行っている2型糖尿病患者を対象とし，ヒトインスリン製剤から超速効型インスリンに治療法を切り替えた群(インスリン アスパルト群)と切り替えなかった群(ヒトインスリン群)における$HbA_{1c}$とPPG(食後血糖)の経時的変化率の比較を行った．切り替え後半年は$HbA_{1c}$，PPGともにヒトインスリン群に比べインスリン アスパルト群が有意な改善を認め，改善後も平均的に低い値を保持する結果となった．

## はじめに

2型糖尿病における強化インスリン療法は，Kumamoto Studyにてその有用性が十分に示されている[1)]．一方，2001年に超速効型インスリンが発売され，その薬理学的特性から利便性と食後血糖の低下作用が示されており[2,3)]，強化インスリン療法に広く用いられるようになっている．しかし，治験データや一部臨床研究を除き，わが国では2型糖尿病患者の強化インスリン療法において，速効型ヒトインスリンを超速効型インスリンに変更して，血糖コントロールがどう変化したのかを示すデータはない．そこで，糖尿病患者情報集積ソフト"CoDiC®"によりJDDM(糖尿病データマネジメント研究会)に集積された全国59施設[4)]，63,550例の2型糖尿病患者のうち，データ提供および解析が可能であった32施設，40,150例において，ヒトインスリン製剤による強化インスリン療法からインスリン アスパルト(製剤名：ノボラピッド®)に変更した患者群とヒトインスリン製剤による強化インスリン療法を継続した患者群について血糖コントロールを指標として比較検討を行った．

## 対象と方法

### 1．対　象

研究目的等を説明の上，同意が得られ，CoDiC®によりJDDMに登録された2型糖尿病患者のうち，経口糖尿病薬の使用のない状態でヒトインスリン製剤を使用し，1日10単位以上で半年間以上にわたって強化インスリン療法を継続した上で，2001年12月から2002年8月までの間に，ヒトインスリン製剤をインスリン アスパルトに変更して1年以上経過観察を行った83例(以

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表1　0時点と0時点より6カ月前での患者背景

| 群 | | ヒトインスリン | インスリン アスパルト |
|---|---|---|---|
| n | | 564 | 83 |
| 年齢(歳) | | 60.5±12.0 (564) | 54.4±14.0 (83)** |
| 性別(男性/女性)(人) | | 308/256 | 50/33 |
| 罹病期間(年) | | 14.2± 9.5 (555) | 13.7± 9.9 (83) |
| BMI(kg/m$^2$) | 0時点 | 24.1± 3.7 (474) | 24.5± 4.0 (73) |
| | 0時点より半年前の平均 | 24.0± 3.6 (2,281) | 24.2± 4.1 (317) |
| $HbA_{1c}$(%) | 0時点 | 7.5± 1.5 (552) | 8.0± 1.7 (82)* |
| | 0時点より半年前の平均 | 7.5± 1.4 (2,566) | 7.7± 1.5 (362)* |
| PPG(mg/dL) | 0時点 | 187 ±87 (483) | 210 ±91 (78)* |
| | 0時点より半年前の平均 | 184 ±77 (2,209) | 195 ±83 (325) |
| FPG(mg/dL) | 0時点 | 170 ±69 (88) | 263 ±86 (9)** |
| | 0時点より半年前の平均 | 180 ±74 (88) | 183 ±84 (50) |
| インスリン投与量(単位/日) | 0時点 | 31.5±16.2 (564) | 40.9±19.7 (83)** |
| | 0時点より半年前の平均 | 30.9±15.8 (2,519) | 37.8±18.5 (358)** |
| 切り替え前の投与パターン(%) | | | |
| R-R-R-N | | 48.0 | 63.9 |
| R-R-R | | 19.0 | 16.9 |
| R-R-30R | | 11.7 | 3.6 |
| その他 | | 21.3 | 15.6 |

平均±SD(測定者数)(0時点より半年前の平均では，(測定者数×時点))
*：$p<0.05$，**：$p<0.01$

下，インスリン アスパルト群)と同様の条件でヒトインスリン製剤による強化インスリン療法を継続した564例(以下，ヒトインスリン群)を研究対象とした．以上の研究対象には観察期間において，二相性インスリンアナログ製剤や持効型溶解インスリンアナログ製剤を使用する症例は含まれていない．

**2．評価項目**

**1）観察期間**

観察期間は18カ月，評価時点は19時点とした．まず，個々の患者ごとにベースライン(0時点)を設定した．インスリン アスパルトに切り替えた患者に関しては切り替え時点を0時点に設定し，ヒトインスリン製剤を継続した患者に関しては観察開始から6カ月目を0時点に設定した．

**2）評価時点**

評価は1カ月に1回，外来での診察時に行った．評価項目は，インスリン投与回数，インスリン投与量，BMI，PPG(食後血糖)，$HbA_{1c}$の5項目であった．切り替えが行われた患者に関しては，低血糖イベントの有無に関しても医師により観察と評価が行われた．

**3．治 療 法**

0時点前までの6カ月間は全対象者がヒトインスリン製剤の強化インスリン療法を受けた．0時点において，ヒトインスリン製剤をインスリン アスパルト(ノボラピッド®)に切り替えた患者群と，ヒトインスリン製剤を切り替えずに継続投与した患者群の2群に分かれ，0時点から12時点までは2種類の治療法が継続して行われた．

**4．統計解析**

はじめに患者の背景因子を集計し，群間比較を行った．患者背景因子の群間比較にはWilcoxon検定を行った．次に，0時点より前の6カ月間のデータを用いて，線形混合モデルにより，前値として調整すべき要因(治療効果に関する交絡要因)の検討を行った．また，0時点以降得られたデータに個人の効果を変量効果とした線形混合効果モデルを当てはめ，12時点ごとに調整すべき要因で調整した最小二乗平均値の推定を行い，各群における経時的変化を比較した．モデルの当てはめを行うに当たり，$HbA_{1c}$，PPGの値はともに対数変換を行い解析に用いた．

有意水準は5％とし，解析ソフトウエアにはSAS ver.8.2を用いた．