projected the number of adults with diabetes to increase from 135 million in 1995 to 300 million in 2025, with the prevalence predicted to increase from 4.0% in 1995 to 5.4% in 2025 [1]. Such a dramatic rise in the prevalence of diabetes will have a great impact on the socioeconomic status of nations around the world.

The number of diabetic patients is also increasing in Japan. A recent national survey showed that between 1997 and 2002 the number of probable diabetic patients has increased from 6.9 million to 7.4 million and the number of probable impaired glucose tolerance (IGT) patients has increased from 6.8 million to 8.8 million [3]. Thus, 16.2 million people out of a total population of 120 million, or 13.5% of the population, are diabetic or have IGT. The prevalence of diabetes and IGT in adults of more than 40 years of age is around 23.8% [3]. These patients are at a significantly higher risk of diabetic complications if adequate medical care and patient education are not provided. The cost of treating diabetic complications, especially diabetic nephropathy that requires hemodialysis, continues to increase. Therefore, it is vital that diabetes mellitus is adequately managed to prevent such complications.

The effectiveness of medical care provided to diabetic patients can be estimated from an outcome study that analyzes the level of glucose control. Such outcome studies are necessary to determine the present status of diabetes medical care and the level of diabetic complications that may emerge in the future. A large-scale survey of the effectiveness of medical care in diabetes has not been performed in Japan. Therefore, we addressed this deficiency by surveying 38 clinics and hospitals. Laboratory data relating to diabetic medical treatment and complications, such as HbA1c and other clinical data, were collected and analyzed. The data show that Japan's medical performance in diabetes care is comparable or slightly superior to that of other countries.

2. Patients and methods

In 1998, we developed software (CoDiC) to store patient clinical data on personal computers [4], standardized the data format including the definition of type 1 and type 2 diabetes and complications, and recruited clinics and hospitals to join our Japan Diabetes Clinical Data Management Study Group (JDDM). The number of institutes recruited was 21 by the end of 2000, 25 by the end of 2001 and 38 by the end of 2002. At the end of January 2004, the total number of institutes stood at 61. The total number of registered diabetic patients increased from 15,500 at the end of 2000 to 59,000 at the end of January 2004. These patients are evenly distributed throughout Japan. The JDDM operates as a voluntary association under the supervision of a central analytical center and the ethical committee.

2.1. Collection of the data

The clinical data were collected from each institute on CD-R storage media and analyzed using SPSS and MS Access. The data received by the central analytical center were treated on an anonymous basis. Data were analyzed from 8170 patients (497 type 1 and 7673 type 2 diabetic patients) in 2000, from 11,831 patients (597 type 1 and 11,234 type 2 diabetic patients) in 2001, and from 16,934 patients (793 type 1 and 16,141 type 2 diabetic patients) in 2002. Twenty two to ninety five patients, i.e. 0.3–0.6% of total patients, in each year could not be identified as type 1 or type 2 diabetic patients and were excluded from the analysis. The inclusion criteria were: (i) patients older than 15 years of age who had their HbA1c checked at least once between May and July of each year during the 3 year period of the study; (ii) patients first seen by JDDM physicians by the end of December of the previous year. The most recent HbA1c data from May to July and other clinical data from January to July for each year were collected for analysis. Details of the drug therapy carried out between May and July each year were also collected for analysis.

2.2. Standardization of the data

Measurement of HbA1c and other data were standardized. The definitions of type 1 and type 2 diabetes were based on the criteria in the "Report of the Committee of Japan Diabetes Society (JDS) on the Classification and Diagnostic Criteria of Diabetes Mellitus" [5]. These criteria are almost identical to the WHO's criteria [6]. Diabetic complications were also standardized.

2.3. Analytical methods

An HPLC method was used to measure HbA1c. The normal range for HbA1c was defined as 4.3–5.8%. Other variables collected, including blood glucose, cholesterol, triglyceride, and HDL-cholesterol levels, were determined by standard methods.

2.4. Ethical consideration

Informed consent was obtained by each institute that met the requirements stated in the Guideline for Epidemiology Study in Japan. The JDDM ethical committee included the outside members, such as diabetic patients and experts in the ethical matters, discussed and approved the protocol.

3. Results

3.1. Demographics

The clinical characteristics of the patients are summarized in Table 1. The majority of patients (95%) were diagnosed as having type 2 diabetes. The

Table 1
Baseline characteristics and therapeutic contents of participating patients with type 1 and type 2 diabetes in 2002

	All subjects	Type 1	Type 2
Baseline characteristics			
Number of patients (*n*)	16934	793	16141
Men/Women (*n*)	10241/6693	347/446	9894/6247
Age (years)	61.9 ± 11.9	47.0 ± 15.8	62.7 ± 11.2
BMI (kg/m^2)	24.0 ± 3.7	22.4 ± 3.1	24.1 ± 3.7
HbA1c (%)	7.1 ± 1.3	7.8 ± 1.5	7.0 ± 1.3
Blood pressure systolic (mmHg)	130.9 ± 16.7	124.5 ± 17.3	131.2 ± 16.6
Blood pressure diastolic (mmHg)	75.6 ± 10.4	73.3 ± 10.2	75.7 ± 10.4
Total serum cholesterol (mg/dl)	199.7 ± 34.0	199.6 ± 36.5	199.7 ± 33.9
HDL cholesterol (mg/dl)	54.5 ± 15.6	69.6 ± 19.2	53.9 ± 15.1
Triglycerides (mg/dl)	141.7 ± 114.0	101.3 ± 100.6	143.5 ± 114.2
HbA1c, therapeutic contents (mean (%))			
Diet only	6.3 ± 1.1 (24.2)		6.3 ± 1.1 (25.4)
OHA w/o insulin	7.2 ± 1.2 (49.1)	7.5 ± 1.3 (3.2)	7.2 ± 1.2 (51.4)
OHA w insulin	7.7 ± 1.3 (8.1)	7.9 ± 1.4 (13.4)	7.7 ± 1.3 (7.8)
Insulin	7.6 ± 1.5 (18.6)	7.8 ± 1.6 (83.5)	7.5 ± 1.4 (15.4)
Total on all regimens	7.1 ± 1.3 (100.0)	7.8 ± 1.5 (100.0)	7.0 ± 1.3 (100.0)
HbA1c, therapeutic modality of insulin (mean (%))			
Insulin only	7.6 ± 1.5 (69.6)	7.8 ± 1.6 (86.2)	7.5 ± 1.4 (66.2)
Insulin + aGI	7.5 ± 1.3 (10.4)	7.8 ± 1.4 (8.5)	7.5 ± 1.2 (10.8)
Insulin + SU	8.0 ± 1.3 (5.4)		8.0 ± 1.3 (6.4)
Insulin + BG	8.0 ± 1.4 (4.5)		7.9 ± 1.4 (4.8)
Insulin + OHAs	7.7 ± 1.3 (10.0)	8.1 ± 1.4 (5.3)	7.8 ± 1.3 (11.8)
Amount of insulin dosage (IU/day)	28.4 ± 17.1	38.3 ± 18.7	26.3 ± 16.1
Frequency of insulin injection (times/day)	2.7 ± 1.1	3.6 ± 1.0	2.5 ± 1.0

Data are mean ± S.D. (%).

mean age of all the patients in 2002 was 61.9 ± 11.9 years, with the majority (59.2%) aged between 50 years and 70 years. The percentages of male and female patients were 60.5% and 39.5%, respectively. The mean body mass index (BMI, kg/m^2) in 2002 was 24.0 kg/m^2 with 46.9% exceeding the Japanese criteria for obesity (BMI ≥ 25 kg/m^2) [7].

3.2. *HbA1c values, patient type and treatment modality*

As shown in Table 1, the mean HbA1c level for all patients was 7.1%. Fig. 1 shows that the mean HbA1c for type 1 patients in 2000–2002 was 7.8–7.9%. In contrast, the HbA1c for type 2 patients was 0.8% lower at 7.0–7.1%. The mean HbA1c values in each of the three years of the study were comparable suggesting that the yearly assessment is reliable and reproducible. The JDS guidelines define "poor glycemic control" as a HbA1c level greater than 8.0%. In 2002, 20.3% of the patients fell into this category while 34% fell into the "good control" category with a HbA1c level less than 6.5%. The mean HbA1c value was around 6.3% for the diet treatment group, 7.2% for the oral hypoglycemic agents group, 7.6% for the insulin treatment group and 7.7% for the oral hypoglycemic agents (OHA) plus insulin treatment group (see Table 1).

For type 1 diabetes, 96.6–97.1% of the patients were treated with insulin or insulin plus oral OHAs as shown in Fig. 2A. Thus, insulin treatment appears not

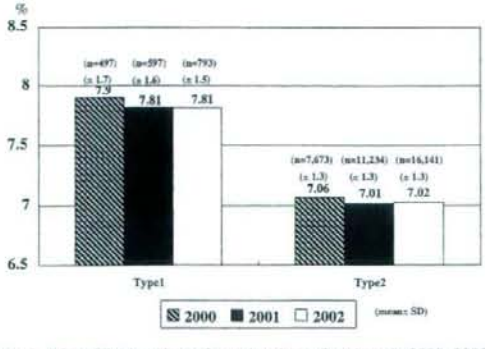

Fig. 1. Mean HbA1c values of type 1 and type 2 patients in 2000–2002.

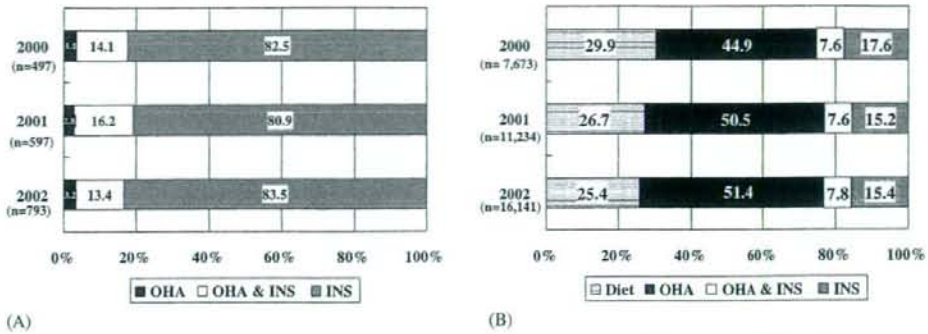

Fig. 2. Percentage of each therapeutic modality in type 1 (A) and type 2 (B) patients in 2000–2002.

to be required in 3–4% of type 1 diabetic patients in Japan because patients with slowly progressive type 1 diabetes may have been included in this group of patients. OHAs used in the treatment of type 2 diabetes patients over the 3 years of the study are shown in Fig. 2B. The percentage of diabetic patients on diet and exercise treatment alone fell from 29.9% in 2000 to 25.4% in 2002. The percentage of patients on OHAs alone increased from 44.9% in 2000 to 51.4% in 2002. The percentage of patients on insulin treatment alone ranged from 15.2% to 17.6%, and the percentage of patients on a combination of oral therapy and insulin treatment ranged from 7.6% to 7.8% over the 3 years of the study. Thus, about half of the type 2 patients were treated with OHAs and about 23–25% of type 2 patients were treated with insulin or insulin plus oral therapy.

Various OHAs were used in type 2 diabetic patients and the frequency of their use is shown in Fig. 3A. Drugs from the sulphonylurea class are most frequently used in Japan, i.e. 72–78% of the patients on OHAs. However, a clear downward trend in the usage of sulphonylureas alone was evident, the percentage of patients being prescribed this class drugs falling from 42.9% in 2000 to 37.1% in 2002. In contrast, the use of other oral drugs, including nateglinide and pioglitazone, and combination oral therapy gradually increased during the course of the study. The glycemic control achieved by OHAs, both mono and combination therapies, is shown in Fig. 3B. Alpha-glucosidase inhibitors, nateglinide, and the biguanides are apparently used in patients suffering from less severe diabetes, with the associated HbA1c values being relatively lower than those of other patients taking sulphonylurea agents.

3.3. Insulin treatment in type 1 and type 2 diabetes

The average total daily doses of insulin for type 1 and type 2 diabetic patients were 38.3 and 26.3 units, respectively, in 2002 (Table 1). Table 1 also shows the average number of insulin injections per day. For type 1 patients, four daily injections were most frequently used, whereas two daily injections were common in

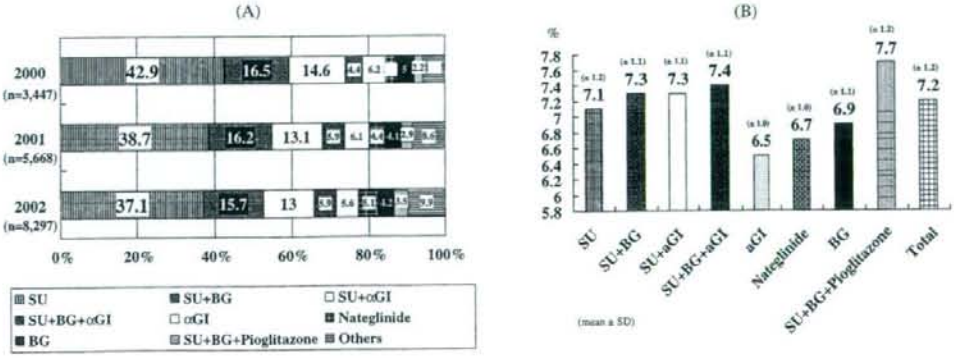

Fig. 3. Frequency (A) and HbA1c levels (B) of OHA therapeutic modality in type 2 patients in 2000–2002.

type 2 diabetics. In 2002, the combination of insulin and oral therapy was used in 33.8% of type 2 patients and in 13.8% of type 1 patients.

3.4. Control of blood pressure and lipid levels

In addition to glycemic controls, the prevention of diabetic complications requires control of other parameters. Table 1 shows data relating to these complications, including blood pressure and lipid levels. Half of the type 2 patients met the JDS blood pressure guidelines of 130 mmHg/80 mmHg [8]. Over half of type 1 and type 2 patients met the JDS guidelines for total cholesterol i.e. <5.17 mmol/L (200 mg/dL). HDL-cholesterol,i.e. >1.03 mmol/L (40 mg/dL), and triglycerides, i.e., <1.68 mmol/L (150 mg/dL) [8].

4. Discussion

Diabetic outcome studies were important for understanding the current management of diabetes and thereby improving the diabetic treatment. For example, in Asia, the glycemic control of a significant number of diabetic patients is poor [9,10]. Consequently, these patients will develop more severe diabetic complications if further intervention is not taken [9,10]. Collecting clinical data is not simple because of potential biases in selecting patients. The Japan Diabetes Clinical Data Management Study Group has been established as a voluntary association to collect and analyze clinical data from diabetic patients in Japan. Fortunately, about 59,000 patients and 61 medical institutes now participate in this study. The physicians of these institutes are mostly diabetic specialists and the standard of medical care may be higher than that provided by general practitioners.

The average BMI value for type 2 diabetic patients was 24.1 kg/m^2, which is significantly lower than the average BMI of type 2 patients in Western countries [11,12] but equal to that of type 2 patients in Asian countries [9,10]. The average HbA1c of all the patients was 7.1%, which is an excellent result by comparison to that achieved by daily practice in other countries [9–16]. In US, Koro et al. reported that the average HbA1c was 7.9% during 1999–2000 NHANES study[12,13], and Wens et al. reported that the mean average HbA1c was 8.1% in type 2 diabetes treated by general practices in Belgium [14]. In UKPDS, the average HbA1c was 8.0% in conventional treatment group [15] and in Asian countries, the average HbA1c was 8.5% in type 2 diabetes [9,10]. Our results are unlikely to be due to selection bias since the medical institutes in this study are evenly distributed throughout Japan on both a geographic and socioeconomic basis. The accuracy of most of the institutes and laboratories conducting HbA1c measurements was confirmed with standardized samples supplied by the JDS. Therefore, the results are unlikely to be due to selection biases or measurement errors.

As stated above, the patients were cared by specialists in this study. However, general practitioners have had comparable results, and a survey showed that the average HbA1c achieved by general practitioners was 7.0% by our survey.[1] This was almost equal to the level achieved by specialists who were treating more clinically complicated patients. One possible explanation for the better HbA1c control in Japan may be the monthly outpatient clinic visits and HbA1c measurements that are carried out under the Japanese medical insurance system. In contrast, in most western and Asian countries, outpatient clinic visits are typically every three months and HbA1c measurement is much less frequent. Nevertheless, 66% of the patients in Japan still fail to meet the HbA1c target of less than 6.5% and methods to further improve patient care should be sought.

With regard to drug therapy in this study, half of the type 2 patients were treated with oral agents and one quarter were treated with insulin (Fig. 2B). In contrast, type 1 patients were mostly treated with insulin (Fig. 2A). For oral therapy, the sulphonylureas remain the most popular first line drug class (Fig. 3A). However, oral drug therapy has recently become more diverse with a trend away from sulphonylurea monotherapy towards multi-agent therapy, including the biguanides, nateglinide, α-glucosidase inhibitors and thiazolidinedione derivatives (Fig. 3A). The recent launch of new drugs, such as nateglinide and thiazolidinedione derivatives, and the results of clinical trials, such as the UKPDS [15,16] and the STOP-NIDDM [17], could be responsible for this trend. The combination of insulin and oral agents is not common in Japan, and constitutes only 10% of insulin treated patients compared to the significantly higher percentage seen in Western countries. This difference can be explained by the lack of evidence from a Japanese study population for the superiority of combined insulin and oral therapy over insulin monotherapy [18–20]. A small proportion of type 1 patients (3–4%) received treatment with oral agents alone. This finding probably arose because we included slowly progressive patients within

[1] M. Kobayashi, et al., in preparation.

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.

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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.	6.1±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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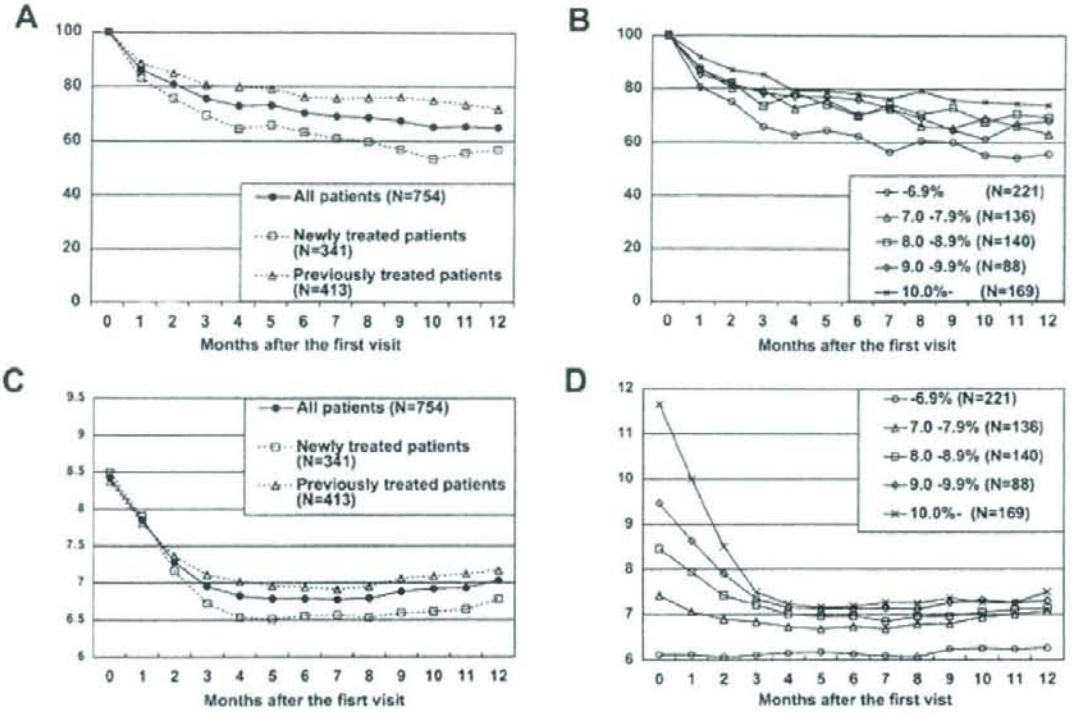

Figure 1. **Sequential changes in the proportion of patients under follow-up (A, B), and HbA_{1C} levels (C, D) during the twelve months following the first visit to a specialist clinic. The results were stratified according to the patients' previous follow-up status (A, C) or HbA_{1C} levels at baseline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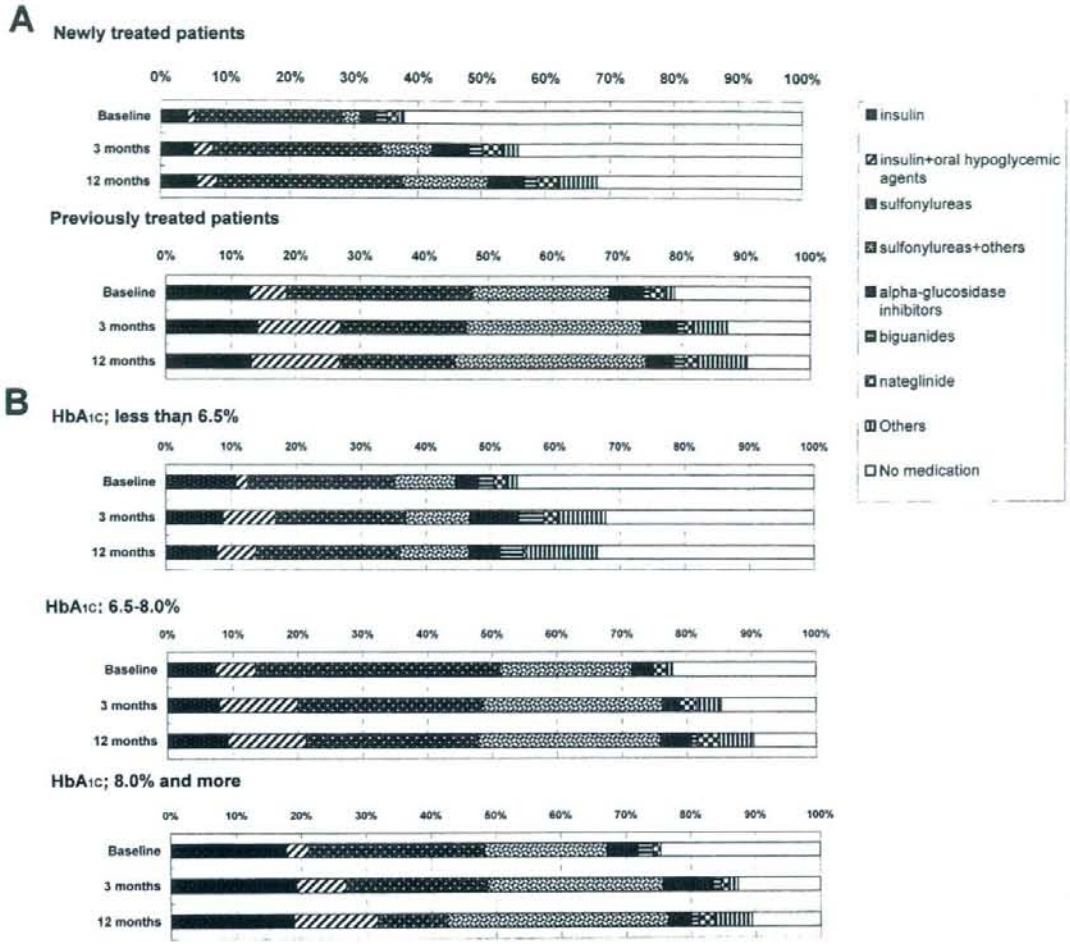

Figure 2. **Pharmacotherapeutic status of the patients at baseline, three months and twelve months after start of the study, stratified according to previous follow-up status (A) or HbA_{1c} levels at baseline (B).**

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 (%)
HbA_{1c} < 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 ***
HbA_{1c} < 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	Baseline (1)	32.2	33.9	30.9
diastolic blood pressure < 85 mmHg	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 HbA_{1c}, 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 HbA_{1c}, 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

[1] 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. Takahiro Konno (Yakumo General Hospital); Dr. Hiroki Yokoyama (Jiyugaoka Yokoyama Internal Medicine Clinic); Dr. Mikihiko Kudo (Kudo Internal Medicine Clinic); Dr. Fuminobu Okuguchi (Okuguchi Internal Medicine Clinic); Dr. Hiroshi Fujiya (Fujiya Internal Medicine Clinic); Dr. Osamu Tomonaga (Shinjyuku Koushin Clinic); Dr. Hiroshi Takamura (Takamura Internal Medicine Clinic); Dr. Hajime Maeda, Dr. Ritsuko Yamamoto (H.E.C. Science Clinic); Dr. Masahiko Takai (Takai Internal Medicine Clinic); Dr. Hiromichi Sugiyama (Sugiyama Clinic); Dr. Hideo Sasaki (Niigata Kobari Hospital); Dr. Michiyo Takada (Shimizumachi Internal Medicine Clinic); Dr. Hiroshi Hayashi (Saiseikai Matsusaka General Hospital); Dr. Kunihiro Doi (Doi Internal Medicine); Dr. Koichi Iwasaki (Iwasaki Internal Medicine); Dr. Yosiyuki Hattori (Hattori Clinic); Dr. Nobuyuki Abe (Internal Medicine Abe Clinic); Dr. Hidekatsu Sugimoto (Sugimoto Clinic); Dr. Yoshifumi Yokomizo (Yokomizo Internal Medicine Clinic); Dr. Yoshihide Fukumoto (Fukumoto Clinic); Dr. Noriharu Yagi (Yagi Internal Medicine Clinic).

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

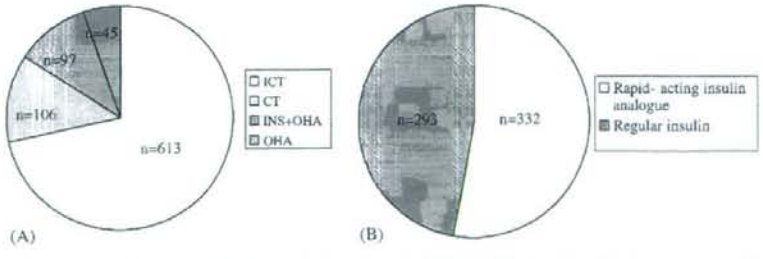

Fig. 1. Cross-sectional survey of the treatment in Type 1 diabetic patients in 2002. (A) The number of patients receiving intensive conventional insulin treatment (ICT), conventional insulin treatment (CT), combination treatment with insulin preparation and oral hypoglycemic agent (OHA) (INS + OHA) and 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 ($p < 0.05$).

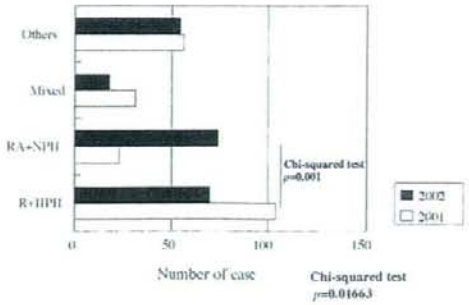

Fig. 2. Changes in the actual usage of insulin preparations over the period from 2001 to 2002. (□) The number of patients in 2001; (■) the number of patients in 2002. Data was analyzed with the chi-squared test.

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).

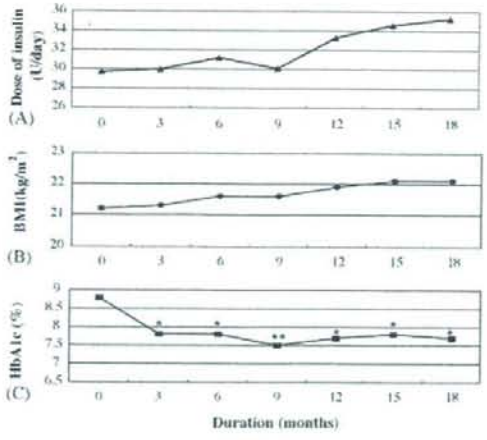

Fig. 3. Analysis of the clinical course over the 18 months from the time of first consultation: (A) change in dose of insulin injected per day; (B) change in body mass index (BMI); (C) change in HbA1c levels. Data was presented by mean and statistically analyzed with the Student's *t*-test. $^{**}p 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