



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

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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<sup>®</sup>, an electronic system for diabetes data collection and management, at 28 institutes. Of 18,470 diabetic patients registered with CoDiC<sup>®</sup> 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.

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## 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  $\beta$ -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)<sup>1</sup> was established to promote the clinical research for diabetes in Japan. Patients' clinical data from healthcare institutes across Japan were collated in the CoDiC<sup>®</sup> 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<sup>®</sup>. 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<sup>®</sup> 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 decarboxylase antibody (anti-GAD

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antibody) was assayed by a radioimmunoassay 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<sup>®</sup> database at an interval of at least every 3

months over the 18-month period after registration in CoDiC<sup>®</sup>. 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<sup>®</sup> and MS excel software<sup>®</sup>. Statistical analyses were performed using SPSS<sup>®</sup>, 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

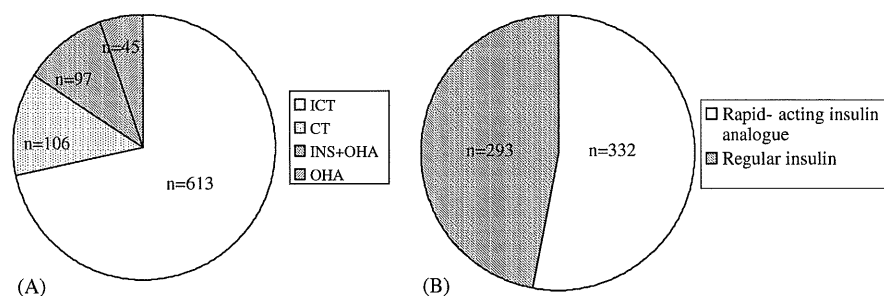


Fig. 1. Cross-sectional survey of the treatment in Type 1 diabetic patients in 2002. (A) The number of patients receiving intensive conventional insulin treatment (ICT), conventional insulin treatment (CT), combination treatment with insulin preparation and oral hypoglycemic agent (OHA) (INS + OHA) and 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	<i>p</i> -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 <sup>2</sup> )	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	<i>p</i> -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

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 <sup>-1</sup> )		BMI (kg/m <sup>2</sup> )		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) <sup>a</sup>	21.3 (2.8)	21.8 (3.2) <sup>a</sup>	8.5 (2.0)	7.7 (1.3) <sup>a</sup>
RA + NPH	23	73	41.8 (20.6)	47.4 (19.3) <sup>b</sup>	4.4 (0.5) <sup>c</sup>	4.4 (0.5) <sup>b</sup>	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.

<sup>a</sup> *p* < 0.05 (vs. 2001).

<sup>b</sup> *p* < 0.05 (vs. R + NPH).

<sup>c</sup> *p* < 0.01 (vs. R + NPH).

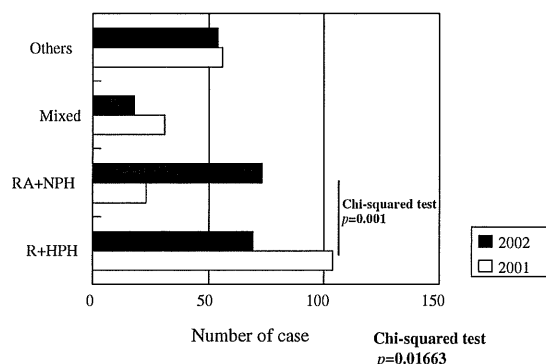


Fig. 2. Changes in the actual usage of insulin preparations over the period from 2001 to 2002. (□) The number of patients in 2001; (■) the number of patients in 2002. Data was analyzed with the chi-squared test.

investigated in 214 patients whose clinical data were input into the CoDiC<sup>®</sup> 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).

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<sup>®</sup> database at an interval of at least 3 months over the 18-month period

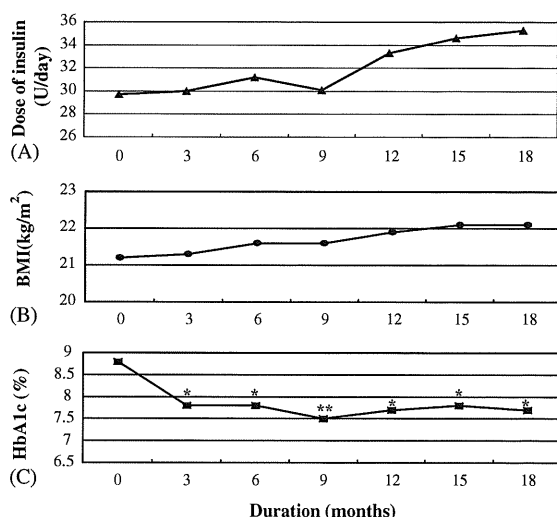


Fig. 3. Analysis of the clinical course over the 18 months from the time of first consultation: (A) change in dose of insulin injected per day; (B) change in body mass index (BMI); (C) change in HbA1c levels. Data was presented by mean and statistically analyzed with the Student's *t*-test. \*\**p* 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

after registration in CoDiC<sup>®</sup>. 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.	<i>p</i> -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<sup>®</sup> database, a large scale clinical database based on data collected from multiple institutes across Japan specialized in the treatment of diabetes. The CoDiC<sup>®</sup> 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 insulinitis gradually destroying the pancreatic  $\beta$ -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  $\beta$ -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,  $\beta$ -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  $\beta$ -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<sup>®</sup> database at an interval of at least 3 months over the 18-month period after registration in CoDiC<sup>®</sup>, 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  $\beta$ -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<sup>®</sup> is useful tool for large-scale surveys of diabetic patients at multiple institutions.

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