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Masashi Kobayashi, Katsuya Yamazaki, Koichi Hirao, Mariko Oishi  
Azuma Kanatsuka, Mikio Yamauchi, Hirofumi Takagi, Koichi Kawai

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## The status of diabetes control and antidiabetic drug therapy in Japan—A cross-sectional survey of 17,000 patients with diabetes mellitus (JDDM 1)

Masashi Kobayashi <sup>a,\*</sup>, Katsuya Yamazaki <sup>a</sup>, Koichi Hirao <sup>b</sup>, Mariko Oishi <sup>c</sup>,  
Azuma Kanatsuka <sup>d</sup>, Mikio Yamauchi <sup>b</sup>, Hirofumi Takagi <sup>e</sup>, Koichi Kawai <sup>f</sup>

Japan Diabetes Clinical Data Management Study Group

<sup>a</sup> *Department of Internal Medicine, Toyama Medical and Pharmaceutical University, Toyama, Japan*

<sup>b</sup> *H.E.C. Science Clinic, Yokohama, Japan*

<sup>c</sup> *Oishi Clinic, Kyoto, Japan*

<sup>d</sup> *Chiba Central Medical Center, Chiba, Japan*

<sup>e</sup> *Niigata University, Niigata, Japan*

<sup>f</sup> *Kawai Clinic, Tsukuba, Japan*

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### Abstract

The number of diabetic patients has been increasing in Japan and consequently diabetic complications are the most important target to be prevented through improving glycemic control. In order to describe the glycemic control status and treatment of diabetic patients by specialists in Japan over three years, from 2000 to 2002, we examined HbA1c, other laboratory data and the modality of drug therapy in the study population, 8170 in 2000, 11,831 in 2001, and 16,934 in 2002. Patients were registered at clinics and hospitals that were members of the Japan Diabetes Clinical Data Management Study Group (JDDM). HbA1c levels, other laboratory data, and details of drug therapy were collected and analyzed using SPSS and MS Access. The mean HbA1c levels were essentially unchanged during the study periods, ranging from 7.9% to 7.8%, and from 7.1% to 7.0%, in type 1 and type 2 diabetic patients, respectively. In type 2 diabetes, the frequency of oral hypoglycemic agents (OHA) use increased from 44.9% to 51.4%, while the use of diet-only therapy decreased from 29.9% to 25.4% over the study period. Although the systolic blood pressure was slightly above target, the mean blood pressure and the mean lipid profile were mostly within the treatment goals set by the Japan Diabetes Society. This first report from a large scale study of the daily management of diabetes in Japan revealed that the average HbA1c level was superior to most of the results reported from other countries. Nonetheless, 66% of the patients still had HbA1c levels and half of the patients had other laboratory parameters including blood pressure and lipid profile that were greater than those recommended by the Japan Diabetes Society. The nature of diabetes drug therapy in Japan has gradually changed as new drugs have appeared in the market.

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**Keywords:** Drug therapy; Control status; Cross-sectional survey; Japan

### 1. Introduction

The incidence and prevalence of type 2 diabetes mellitus are rapidly increasing worldwide in both developing and developed nations [1,2]. The WHO

\* Corresponding author. Tel.: +81 764 34 7700.

E-mail address: [mkobayas@ms.toyama-mpu.ac.jp](mailto:mkobayas@ms.toyama-mpu.ac.jp)  
(M. Kobayashi).

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
<b>Baseline characteristics</b>			
Number of patients ( <i>n</i> )	16934	793	16141
Men/Women ( <i>n</i> )	10241/6693	347/446	9894/6247
Age (years)	61.9 ± 11.9	47.0 ± 15.8	62.7 ± 11.2
BMI (kg/m <sup>2</sup> )	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
<b>HbA1c, therapeutic contents (mean (%))</b>			
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)
<b>HbA1c, therapeutic modality of insulin (mean (%))</b>			
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<sup>2</sup>) in 2002 was 24.0 kg/m<sup>2</sup> with 46.9% exceeding the Japanese criteria for obesity (BMI ≥ 25 kg/m<sup>2</sup>) [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

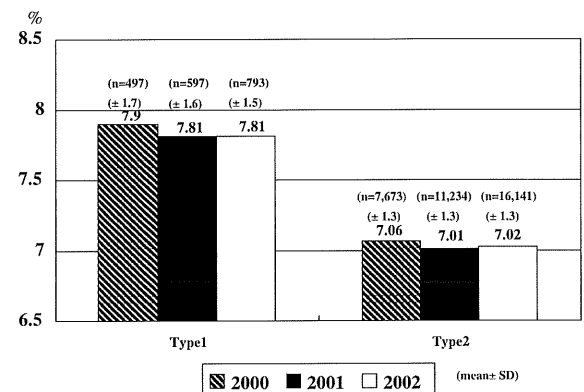


Fig. 1. Mean HbA1c values of type 1 and type 2 patients in 2000–2002.

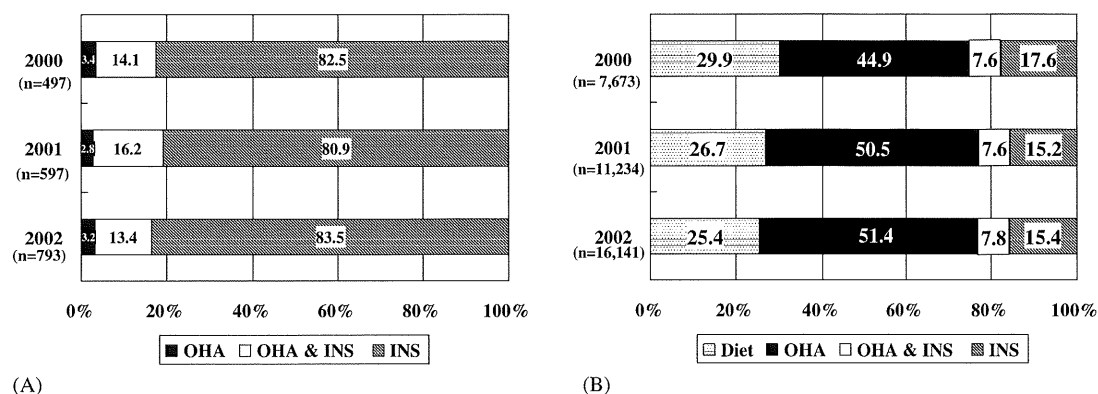


Fig. 2. Percentage of each therapeutic modality in type 1 (A) and type 2 (B) patients in 2000–2002.

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

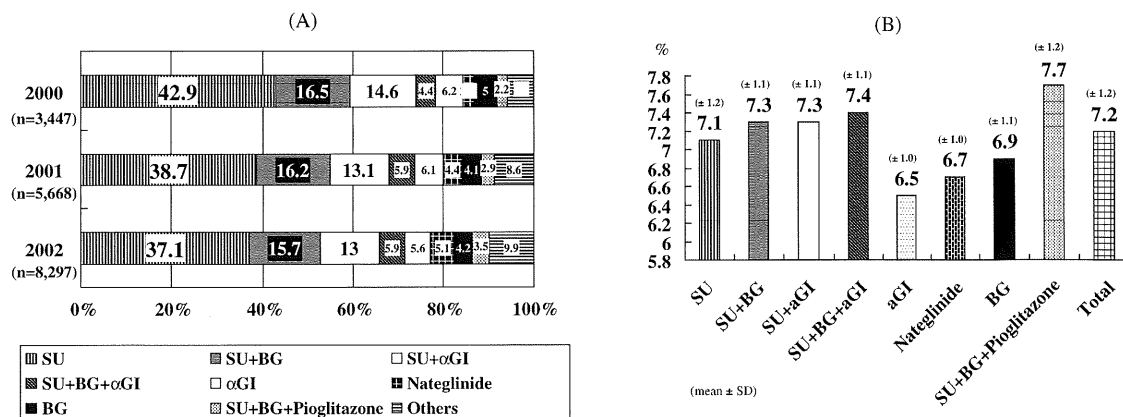


Fig. 3. Frequency (A) and HbA1c levels (B) of OHA therapeutic modality in type 2 patients in 2000–2002.

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  $24.1 \text{ kg/m}^2$ , 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.<sup>1</sup> 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,  $\alpha$ -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

<sup>1</sup> 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. Mikihiro 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 Kobar 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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