Present status of insulin therapy for type 2 diabetes treated by general practitioners and diabetes specialists in Japan: Third report of a cross-sectional survey of 15,652 patients

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ABSTRACT

Aims/Introduction: Insulin therapy is often required to achieve good glycemic control in patients with type 2 diabetes mellitus. However, some providers, particularly general practitioners (GPs), are reluctant to prescribe insulin to their patients. The aim of the present study was to clarify any differences in, as well as any problems associated with, insulin therapy in patients with type 2 diabetes being treated by either a GP or a diabetes specialist in Japan.

Materials and Methods: Of 15,652 patients across 721 clinics and hospitals, 15,350 were diagnosed with type 2 diabetes (14,312 by GPs and 1038 by specialists). Data regarding glycated hemoglobin (HbA1c) levels, age, height, bodyweight and treatment modality were collected for each patient.

Results: Of the patients with type 2 diabetes, 9.1 and 22.9% had been prescribed insulin monotherapy, and 38.8 and 37.0% were also receiving insulin with an oral antidiabetic (OAD) by GPs or specialists, respectively. Diabetes specialists prescribed analog insulin more frequently than did GPs. GPs chose premixed insulin more frequently than did specialists, and this factor correlated with higher HbA1c levels. A younger age and daily insulin dose in groups being treated by both providers were correlated with high HbA1c levels on insulin monotherapy. Neither type of insulin nor OAD was correlated with HbA1c on insulin plus OAD therapy.

Conclusions: To achieve better glycemic control with insulin therapy, sufficient insulin dose and intensive treatment regimen, in addition to lifestyle interventions, might be necessary. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2012.00198.x, 2012)

KEY WORDS: General practitioner, Insulin therapy, Type 2 diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus is characterized by defects in both insulin secretion and insulin action. Consequently, insulin therapy is often required to achieve good glycemic control¹. With the recent development of insulin analogs, many types of rapid- and long-acting insulin analogs, as well as premixed insulin, are available and these advances have increased the variety of insulin therapy regimens². The aim of the bolus–basal regimen with rapid-acting insulin and neutral protamine Hagedorn (NPH) or long-acting insulin is physiological insulin replacement. Once or twice daily injections of premixed insulin, specifically a long-acting insulin combined with an oral antidiabetic (OAD), are convenient and easy, enabling general practitioners (GPs) to participate in the treatment of their diabetic patients. In fact, we have reported previously that convenient, twice-daily injections of a biphasic insulin analog are as effective in reducing glycated hemoglobin (HbA1c) levels over 6 months of therapy as more intensive insulin therapy³.

The number of diabetic patients in Japan is increasing. A recent national survey showed that there are likely to be 7.4 million patients with diabetes and 8.8 million patients with impaired glucose tolerance in Japan⁴. However, in 2006, there were just 3217 physicians who were certified as diabetes specialists by the Japan Diabetes Society (JDS). This is not a sufficient number of specialists to provide adequate medical care for all diabetic patients in Japan. Therefore, the care of diabetic patients needs to be managed by GPs in cooperation with specialists. In fact, in our previous cross-sectional study, the mean HbA1c level for all enrolled patients treated by GPs was even lower than those treated by specialists, although there were no significant differences between patients treated by GPs and those being treated by diabetes specialists in the mean HbA1c levels of the patients receiving insulin therapy or insulin plus OAD therapy⁵.

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The value for HbA1c was expressed by National Glycohemoglobin Standardization Program (NGSP) value.

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However, we wonder if any inappropriate treatment exists for patients receiving insulin therapy or insulin plus OAD therapy. Thus, the aim of the present study was to clarify any differences in, or any problems associated with, insulin therapy in patients with type 2 diabetes being treated by either a GP or a diabetes specialist, and the factors associated with high HbA1c levels that need to be considered for the most appropriate type of therapy, as well as the benefits of cooperation between GPs and diabetes specialists in the care of patients with type 2 diabetes.

**MATERIALS AND METHODS**

**Ethical Considerations**

The present study was approved by the Ethics Committee of the Japanese Ministry of Health, Labour and Welfare. All patients were asked to participate in the study, in accordance with the Guidelines for Epidemiological Study of the Japanese Ministry of Health, Labour and Welfare.

**PATIENTS AND METHODS**

As described previously, 8,112 clinics and hospitals, randomly selected across Japan and comprising approximately 40% of all members of the JMDPIMC, were asked to participate in the study. In all, 721 clinics and hospitals agreed to participate and 15,652 patients with type 1 diabetes or type 2 diabetes, ranging in age from 15 to 97 years, were enrolled in the study. JMDPIMC was organized by medical and dental practitioners, and this organization covered almost 65% of the whole Japanese practitioners. In the present study, a ‘diabetes specialist’ was defined as a JDS board-certified diabetes care physician, whereas any other physician was regarded as a GP. A total of 60 specialists and 661 GPs participated in the present study, and this ratio was almost comparable to the ratio of JDS board-certified diabetes care physicians to other physicians reported in each prefecture in Japan.

The type of diabetes was determined on the basis of the criteria of the JDS for the diagnosis of diabetes, which are almost identical to those of the World Health Organization. Briefly, patients who were permanently insulinopenic and ketosis prone (idiopathic type 1 diabetes mellitus) or those who were positive for autoimmune destruction markers, such as glutamic acid decarboxylase (immunemediated type 1 diabetes mellitus), were diagnosed as having type 1 diabetes. Of the 15,652 patients enrolled in the study, 15,350 were diagnosed as having type 2 diabetes and, of these, 14,312 were being treated by a GP and 1038 were being treated by a specialist. The clinical characteristics of patients treated by GPs and specialists differed significantly, including age (67.7 ± 11.0 vs 63.3 ± 12.0 years, respectively), the ratio of women to men in the group (47.9/52.1 vs 47.6/52.4%, respectively) and body mass index (BMI; 24.4 ± 3.9 vs 24.1 ± 3.7 kg/m², respectively), as described previously. Also, the proportion of treatment modalities of all enrolled subjects being treated by GPs was different from those being treated by diabetes specialists. The proportion of type 1 diabetes mellitus, type 2 diabetes mellitus with diet, type 2 diabetes mellitus with OAD, type 2 diabetes mellitus with insulin and type 2 diabetes mellitus with insulin plus OAD were 1.7, 17.8, 71.7, 3.3 and 5.5%, respectively by GPs, and 5.0, 12.6, 61.3, 7.6 and 13.5%, respectively, by diabetes specialists. In the present study, 759 and 148 patients treated with insulin monotherapy by GPs and specialists, respectively, and 490 and 85 patients treated with insulin plus OAD by either care provider were subjected to analysis (Table 1).

Data were collected over the period 1–31 July 2006. To be included in the study, patients had to have visited clinics or hospitals regularly and had to have had HbA1c levels determined at least once every 3 months. Each clinic or hospital was encouraged to enrol up to 30 patients in order of arrival. The most recent data for HbA1c level, bodyweight and drug therapy (including insulin), as well as the age and sex of the patients, were collected for analysis. Weight and height were measured using standard techniques and equipment. The BMI was calculated as the patient’s weight (in kg) divided by height squared (m²). These data were filled out in questionnaires by physicians at each clinic or hospital, and were sent by fax to the central analytical facility, where the information was treated anonymously and subsequently analyzed.

**Methods of HbA1c Analysis**

Almost all GPs used the latex agglutination (LA) method to determine HbA1c, whereas almost all specialists used the high-performance liquid chromatography (HPLC) method. Although the number of GPs in the present study was greater than that of diabetes specialists, a good correlation has been confirmed for HbA1c values measured by the LA and HPLC methods, so we used HbA1c levels determined by the LA method for comparisons in the present study. The HbA1c measurement was carried out at each clinic or hospital, it was not centralized. The value for HbA1c was expressed by National Glycohemoglobin Standardization Program (NGSP) value.

**Statistical Analysis**

Student’s t-test was used to compare differences in mean HbA1c levels, BMI, age, and number of OAD in combination with insulin and total insulin dose per day between patients treated by GPs and those treated by diabetes specialists. The chi-squared test was used to compare differences in the proportion of male and female patients in the two groups, as well as differences in the types of OAD and insulin being used, the use of analog insulin and the insulin treatment regimen between the two groups. Furthermore, to assess the strength of association between HbA1c as an objective variable and other parameters as explanatory variables, multiple regression analysis was carried out and standard regression coefficients (β) and 95% confidence intervals (CI) with P-values were calculated and summarized in Table 2. All statistical analyses were carried out using JMP Version 6.0 software (SAS Institute, Cary, NC, USA) and P < 0.05 was considered significant. All results are expressed as the mean ± SD.
Table 1 | Characteristics of patients with type 2 diabetes mellitus treated with insulin therapy by general practitioners and diabetes specialists

|                      | Insulin monotherapy |                      | Insulin + OAD |                      |
|----------------------|---------------------|---------------------|---------------|---------------------|
|                      | GPs | Specialists | P     | GPs | Specialists | P     |
| No. patients         | 759 | 148        |       | 490 | 85         |       |
| Mean HbA1c (%)       | 7.3 ± 1.3           | 7.3 ± 1.2           | 0.897 | 7.5 ± 1.4 | 7.7 ± 1.2 | 0.229 |
| Age (years)          | 68.7 ± 11.2         | 64.4 ± 11.0         | <0.0001 | 66.9 ± 10.8 | 63.2 ± 10.0 | 0.003 |
| No. men/women (%)    | 49.5/50.5           | 57.4/42.6           | 0.076 | 51.0/49.0 | 48.2/51.8 | 0.635 |
| BMI (kg/m²)          | 23.4 ± 3.8          | 23.2 ± 3.7          | 0.473 | 24.2 ± 3.8 | 25.2 ± 3.5 | 0.023 |
| **Insulin therapy**  |                  |                     |       |                   |                   |
| Total dose (U)       | 261 ± 183           | 245 ± 116           | 0.283 | 258 ± 229.9 | 295 ± 15.3 | 0.159 |
| Analog/human insulin (%)| 33.6/66.7          | 48.7/51.3           | 0.0005 | 31.7/68.3 | 41.6/58.4 | 0.091 |
| Type of insulin      |                  |                     |       |                   |                   |
| (basal/premixed/bolus/basal–bolus/premixed-bolus/other, %) | 15.0/56.4/11.1/11.2/3.6 | 16.2/44.6/9.5/18.9/3.6 | 0.023 | 26.0/48.4/10.9/14.1/6.1 | 22.4/48.2/7.1/14.1/3.5 | 0.027 |
| Combined OAD treatment |              |                     |       |                   |                   |
| Mean no. OAD         | 1.3 ± 0.5           | 1.3 ± 0.5           | 0.362 | 1.4/1.8/9.6/39.6/5.3 | 4.7/14.1/21.2/23.5/5.9 | 0.004 |
| Type of OAD          |                  |                     |       |                   |                   |
| (Glinide/SU/BG/αGI/TZD/2O A D, %) | 0.004 | 0.004 | 0.004 | 0.004 | 0.004 | 0.004 |

α-GI, α-glucosidase inhibitor; BG, biguanide; BMI, body mass index; GPs, general practitioners; HbA1c, glycated hemoglobin; OAD, oral antidiabetic; SU, sulfonylurea; TZD, thiazolidinedione.

RESULTS

As summarized in our previous report, the proportion of patients receiving insulin therapy with or without OAD was significantly greater in the group being treated by the diabetes specialists (21.1% of whole enrolled participants) than that by GPs (8.8%, P < 0.0001, \( \chi^2 = 194.5 \), \( \chi^2 \)-test). Of the patients with type 2 diabetes on insulin, 39.3% were treated with insulin plus an OAD. Also, mean HbA1c levels were higher in patients treated with insulin plus an OAD than in those receiving insulin monotherapy, regardless of the care provider.5 From the results of multiple regression analysis, a positive correlation was found between HbA1c and total daily insulin dose (P = 0.001 and P = 0.001, GPs and specialists, respectively), whereas age was negatively correlated with HbA1c in both groups being treated by GPs (P = 0.002) and specialists (P = 0.04, Table 2). In contrast, the prescription of premixed-type insulin was positively correlated with HbA1c only in a group being treated by GPs (P = 0.006, Table 2).

Insulin Plus OAD Therapy

The mean age of patients on insulin plus OAD therapy was significantly higher and BMI was lower in the GP-treated group (66.9 ± 10.8 years and 24.2 ± 3.8 kg/m², respectively) than in the specialist-treated group (63.2 ± 10.0 years; P = 0.003 and 25.2 ± 3.5 kg/m²; P = 0.023, respectively). There were no significant differences between the two groups in terms of the mean HbA1c levels (7.5 ± 1.4 vs 7.7 ± 1.2%; P = 0.229), men to women ratio (51.0/49.0 vs 48.2/51.8%; P = 0.091), frequency of analog insulin use (31.7 vs 41.6%, respectively; P = 0.0005), type of insulin (P = 0.473), or the mean number of OAD used in combination with insulin (1.3 ± 0.5 vs 1.3 ± 0.5, respectively; P = 0.362, Table 1). The type of insulin prescribed (P = 0.283), total daily insulin dose (P = 0.004, \( \chi^2 = 27.254 \)) were different between the GP- and specialist-treated groups. GPs prescribed basal insulin more frequently than did specialists (26.0 vs 22.3%, respectively), whereas specialists prescribed basal–bolus or premixed-bolus insulin more frequently than did GPs (14.1 and 47.6 vs 61.1 and 14.1%, respectively). GPs prescribed an α-glucosidase inhibitor (GI) more frequently than did diabetes specialists (39.6 vs 23.5%, respectively), whereas specialists prescribed biguanide...
more frequently than did GPs (21.2 vs 9.6%, respectively; Table 1).

From the results of multiple regression analysis, a positive correlation was found between HbA1c and human (not analog) insulin prescription (P = 0.02), whereas age was negatively correlated with HbA1c in the group being treated by GPs (P = 0.000, Table 2). In contrast, no factor was correlated with HbA1c in the group being treated by specialists (Table 2).

**DISCUSSION**

Another cross-sectional survey of Japanese specialists from 2002 to 2004 showed that approximately 20 and 10% of patients with type 2 diabetes were treated with insulin monotherapy and insulin plus OAD, respectively. In comparison, in the USA, over the period 1999–2000, 16 and 11% of patients with type 2 diabetes received insulin monotherapy and insulin plus OAD, respectively. Results of the Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM) study in seven European countries (Spain, France, UK, Norway, Finland, Germany and Poland) showed that 3.4 and 26.1% of patients with type 2 diabetes were treated with insulin monotherapy and insulin plus OAD respectively. In China, the proportion of insulin monotherapy and insulin plus OAD therapy in patients with type 2 diabetes in 2006 was reported to be 21.8 and 27.0%, respectively. The Diabcare-Asia 1998 study, including Bangladesh, China, India, Indonesia, Malaysia, Philippines, Singapore, South Korea, Sri Lanka, Taiwan, Thailand and Vietnam, reported that the prevalence of insulin therapy in patients with type 2 diabetes is likely to be influenced by health-care policies, economic considerations or the medical insurance system in individual countries. The figures reported in these previous studies in conjunction with the present study suggest that the prevalence of insulin therapy in type 2 diabetes is higher in Asian than Western countries, although the prevalence of insulin therapy in Japan is closer to that in Western countries.

Recently, rapid-acting insulin analogs have become available and these are now widely used for the treatment of type 2 diabetes in Japan. Modern rapid-acting insulin analogs have been shown to elicit a better reduction in HbA1c than regular insulin, because of their more rapid glucose-lowering effects. Although it is recommended that regular insulin is injected 30 min before meals, many patients inject this formulation of insulin just before eating. Thus, because rapid-acting insulin analogs have been formulated to allow injection immediately before meals, they might be more effective in a practical sense than regular insulin in preventing postprandial hyperglycaemia, as well as more convenient for the different lifestyles today’s diabetic patients might have. In the present study, diabetes specialists prescribed analog insulin more frequently than did GPs. In fact, the use of human

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Table 2 | Factors affecting glycated hemoglobin as determined by the multiple linear regression analysis

|                | GPs (95% CI) | P     | Specialists (95% CI) | P     |
|----------------|-------------|-------|----------------------|-------|
| Age            | –0.11 (–0.22 to –0.005) | 0.002 | –0.17 (–0.04 to –0.001) | 0.04  |
| Male sex       | –0.04 (–0.14 to 0.06)  | 0.30  | 0.007 (–0.19 to 0.21)  | 0.93  |
| BMI            | 0.03 (0.015 to 0.05)   | 0.43  | –0.1 (–0.09 to 0.02)   | 0.25  |
| Total insulin dose | 0.13 (0.004 to 0.14)   | 0.001 | 0.02 (0.01 to 0.05)    | 0.30  |
| Use of human (not analog) insulin | 0.01 (–0.09 to 0.13)   | 0.73  | –0.09 (–0.34 to 0.11)  | 0.31  |
| Type of OAD    |             |       |                      |       |
| Glime          |             |       |                      |       |
| SU             |             |       |                      |       |
| BG             |             |       |                      |       |
| α-Gl           |             |       |                      |       |
| T2D            |             |       |                      |       |

α-Gl, α-glucosidase inhibitor; β, standard regression coefficient; BG, biguanide; BMI, body mass index; CI, confidence interval; GP, general practitioner; OAD, oral antidiabetic; SU, sulfonylurea; T2D, thiazolidinedione.
insulin had a significant impact on higher HbA1c levels in the group being treated by GPs with insulin plus OAD in the present study. In contrast, in insulin monotherapy, the use of human insulin did not have an impact on higher HbA1c levels. This finding might be compatible with reports that analog insulins are as effective as human insulin in controlling HbA1c levels.

The Diabetes Control and Complication Trial (DCCT) reported that intensified insulin therapy, consisting of a regimen of thrice daily injections of regular insulin with or without NPH insulin, provides better glycemic control than convenience-oriented insulin therapy using twice daily human insulin in patients with type 1 diabetes. Similar results were reported by Ohkubo et al. in patients with type 2 diabetes. These studies suggest that postprandial plasma glucose levels, as well as fasting plasma glucose levels, might be better controlled, hence resulting in better HbA1c levels, in patients with type 2 diabetes if a regimen in combination with basal–bolus insulin or premixed-bolus insulin is prescribed. In the present study, specialists prescribed a regimen of basal–bolus insulin or premixed-bolus insulin more frequently than GPs either in insulin monotherapy or insulin plus OAD therapy. Also, the prescription of premixed insulin alone had a significant impact on higher HbA1c levels in the group being treated by GPs in monotherapy. Premixed insulin might not be appropriate for controlling postprandial plasma glucose in some patients because of a fixed ratio of rapid or long-acting insulin or a regimen of once or twice daily injection. Unfortunately, we could not discuss this point, because we did not survey the frequency of daily injections.

In the present study, more than one-third of patients with insulin therapy in both the GP- and specialist-treated groups had some OAD. Mixed-type insulin was prescribed most frequently in combination with OAD by both GPs and diabetes specialists. GPs most frequently prescribed α-GI in combination with insulin, whereas α-GI and metformin were prescribed at almost the same frequency by diabetes specialists. Metformin used in combination with insulin has been reported to improve glycemic control and to decrease the insulin dose needed, whereas combined treatment with α-GI and insulin in patients with type 2 diabetes has been reported to decrease postprandial glucose and HbA1c levels. The findings of these studies suggest that the combined use of insulin with any OAD might improve glycemic control over that achieved with insulin monotherapy. However, in the present study, mean HbA1c levels in patients treated with insulin plus any OAD were higher than in patients on insulin monotherapy, regardless of the care provider, as reported previously. Furthermore, the type of OAD or insulin was not associated with HbA1c levels in the present study (Table 2). These results suggest that any OAD might be added to the treatment regimen of patients whose glycemic control is insufficient on insulin therapy alone. It has not been elucidated whether the addition of OAD to insulin monotherapy is effective in lowering HbA1c levels, because we did not evaluate this scenario in the present study. However, unfortunately treatment with insulin plus OAD was still insufficient for good glycemic control.

On the basis of the results summarized in Table 2, higher total daily insulin dose correlated with higher HbA1c in groups being treated by both GPs and specialists in the case of insulin monotherapy. This suggests that increasing the dose might not be involved in satisfactory glycemic control or some patients had strong insulin resistance, although BMI was not correlated with HbA1c in the present study. Sufficient dose of insulin with consideration for insulin resistance might be necessary to lower HbA1c levels. In addition, younger age correlated with higher HbA1c. Younger people might be busy with their social and family life, so it might be difficult for them to concentrate on diet or exercise as therapy. This might be one of the explanations for the result. Therefore, lifestyle interventions might be another therapeutic strategy to achieve better glycemic control.

Some providers, specifically GPs, are reluctant to prescribe insulin to their patients. In the USA, insulin use in diabetes centers is twofold higher than in general practice. In the present study, insulin use was approximately 2.5-fold higher in the specialist-treated group compared with the GP-treated group. To avoid potential delays in initiating insulin therapy for patients with poor glycemic control, cooperation between GPs and diabetes specialists might be necessary. The creation of a networking system to enable easy communication and/or consultation between GPs and diabetes specialists might overcome some of these issues.

There were some limitations to the present study. First, the present study was a cross-sectional and observational study. Second, the clinics and hospitals that participated in the study compromised approximately 10% of all practitioners in Japan. It is likely that only practitioners who have an interest in diabetes care might have agreed to take part in the study, because participation was voluntary. This might suggest that the actual condition might be worse than the present results. In addition, the number of subjects included was not sufficient to enable us to analyze the effects of the type of OAD or insulin. Third, because the present survey was carried out before the use of basal supported oral therapy (BOT) with long-acting insulin plus sulfonyleneurea became common in Japan, the impact of this regimen was not evaluated. Fourth, for the ease of replying, our questionnaire did not include some information, such as the frequency of daily injections, incidence of hypoglycemia, diabetes duration and who decided on the therapeutic regimen. Therefore, we could not evaluate whether concerns about hypoglycemia might have affected the choice of regimen or whether GPs might affect the therapeutic strategy by specialists. Fifth, we compared HbA1c levels measured by LA methods. Potential bias might still exist, because some studies showed a difference of values between LA and HPLC. A number of hemoglobin variants are known to interfere with HbA1c determined by HPLC, and the coefficient of the immunoassay methods were higher than that of HPLC.

In summary, overall 8.8 and 21.1% of patients treated by GPs and diabetes specialists in Japan, respectively, received insulin therapy and more than one-third of these patients were prescribed any OAD in combination with insulin. To achieve better
glycemic control in patients on insulin therapy, a sufficient insulin dose and an intensive regimen might be necessary. To this end, cooperation between GPs and diabetes specialists might prove important.

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REFERENCES
1. De Witt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: a scientific review. JAMA 2003; 289: 2254–2264.
2. Brange J, Volund A. Insulin analogs with improved pharmacokinetic profiles. Adv Drug Deliv Rev 1999; 35: 307–335.
3. Hirao K, Arai K, Yamauchi M, et al. Six-month multicentric, open-label, randomized trial of twice-daily injections of biphasic insulin aspart 30 versus multiple daily injections of insulin aspart in Japanese type 2 diabetic patients (JDDM 11). Diabetes Res Clin Pract 2008; 79: 171–176.
4. Ministry of Welfare, Japan. Report of national survey of Diabetes, 2002.
5. Arai K, Hirao K, Matsuba I, et al. The status of glycemic control by general practitioners and specialists for diabetes in Japan: A cross-sectional survey of 15,652 patients with diabetes mellitus. Diabetes Res Clin Pract 2009; 83: 397–401.
6. Kuzuya T, Nakagawa S, Satoh J, et al. The Committee of the Japan Diabetes Society on the diagnostic criteria of diabetes mellitus. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. Diabetes Res Clin Pract 2002; 55: 65–85.
7. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998; 15: 539–553.
8. Kanatsuka A, Kawai K, Hirao K, et al. Research on antihyperglycemic therapies in patients in with type 2 diabetes mellitus in Japan (1): drug therapies and actual drug use. Jpn Diabetes Soc 2006; 49: 409–415.
9. Koro CE, Bowlin SJ, Bourgeois N, et al. Glycemic control from 1988 to 2000 among U.S. adults diagnosed with type 2 diabetes. Diabetes Care 2004; 27: 17–20.
10. Guisasola FA, Marvos P, Nocea G, et al. Glycemic control among patients with type 2 diabetes mellitus in seven European countries: findings from the Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM) study. Diabetes Obes Metab 2008; 10(Suppl 1): 8–15.
11. Pan C, Yang W, Jia W, et al. Management of Chinese patients with type 2 diabetes, 1998–2006: the Diabcare-China surveys. Curr Med Res Opin 2009; 25: 39–45.
12. Chuang LM, Tsai T, Hunang BY, et al. The status of diabetes control in Asia-a cross-sectional survey of 24317 patients with diabetes mellitus in 1998. Diabet Med 2002; 19: 978–985.
13. Home PD, Lindholm A, Rilist A, et al. Insulin aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes mellitus: a randomized controlled trial. Diabet Med 2000; 17: 762–770.
14. Raskin P, Guthrie RA, Leiter L, et al. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. Diabetes Care 2000; 23: 583–588.
15. Jorgensen LN, Nielsen FS. Timing of pre-meal insulin in diabetic patients on a multiple daily injection regimen. A questionnaire study. Diabetologia 1990; 33: A116.
16. Boehm BO, Honme PD, Behrend C, et al. Premixes insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in Type 1 and type 2 diabetic patients. Diabet Med 2002; 19: 393–399.
17. Hsia SH. Insulin glargine compared to NPH among insulin-naive, U.S. inner city, ethnic minority type 2 diabetic patients. Diabetes Res Clin Pract 2011; 91: 293–299.
18. The Diabetes Control Complication Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977–986.
19. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995; 28: 103–117.
20. Giogulino D, Quatto A, Consoli G, et al. Metformin for obese, insulin-treated diabetic patients: improvement in glycemic control and reduction of metabolic risk factors. Eur J Clin Pharmacol 1993; 44: 107–112.
21. Nemoto M, Tajima N, Kawamori R. Efficiency of combined use of miglitol in type 2 diabetes patients receiving insulin therapy-placebo-controlled double-blind comparative study. Acta Diabetol 2011; 48: 15–20.
22. Riddle MC. The underuse of insulin in North America. Diabetes Metab Res Rev 2002; 18(Suppl. 3): S42–S49.
23. Huang ES, Gleason S, Gaudeette R, et al. Health care resource utilization associated with a diabetes center and a general medicine clinic. J Gen Intern Med 2004; 19: 28–35.
24. Scuderi RC, Griffin TL, Mehta SP, et al. Interferes with hemoglobin A1c determination by the hemoglobin variant Sherby. Am J Clin Pathol 2007; 128: 440–444.
25. Tran DV, Hofer TL, Lee T, et al. Unique approach to derivation of random error in laboratory assays: application to glucoselobulin testing demonstrates poor clinical performance for immunochemistry assay. Diabetes Technol Ther 2003; 5: 975–978.