most (243 out of 284) of the patients had type 2 diabetes. This may explain the similarity of our findings with those of Tahara. In addition, we analyzed the correlation by restricting the analysis to the 243 patients with type 2 diabetes. The resulting equation was HbA1c = 0.211 × GA + 3.185 [$R^2 = 0.5307$, $P < 0.001$], which further supports the similarity of our results with those of Tahara. The differences in the intercepts between the two studies might have arisen because of the difference between the JDS value and the NGSP value. Moreover, by restricting the analysis to the 15 patients with type 1 diabetes, the resulting equation was HbA1c = 0.195 × GA + 3.173 [$R^2 = 0.9070$, $P < 0.001$]. Non-diabetic were 22 patients, the correlation between HbA1c and GA was not so strong. Therefore, we could not evaluate its equation model in non-diabetics in this study.

In clinical practice for diabetes treatment, patients suffering from other diseases that could affect the HbA1c data, even if they do not affect the glucose level, are frequently encountered. The HbA1c value can affect the lifespan of erythrocytes, while an aberrant GA value is possible if albumin turnover is changeable. Accordingly, in patients with conditions such as anemia, chronic renal failure, hypersplenism, chronic liver diseases, hyperthyroidism, or hypoalbuminemia, the relationship between HbA1c and GA may be affected. Thus, a careful selection of study participants is important to estimate a reliable correlation between HbA1c and GA.

In patients with hemolytic anemia, because the lifespan of the erythrocytes is shortened, the HbA1c values are lower relative to the plasma glucose level [6]. On the other hand, the HbA1c values are higher in patients with iron deficiency anemia, and false high HbA1c values are observed in iron-deficient states without anemia [7]. During pregnancy, the HbA1c values are higher during the third trimester because of iron deficiency, whereas the GA is not affected. Therefore, GA may be a more suitable marker for monitoring glycemic control during pregnancy [8-9]. In chronic liver diseases, such as chronic hepatitis and liver cirrhosis, hypersplenism lowers the HbA1c values because of the shortened lifespan of the erythrocytes, whereas it raises the GA values because of reduced albumin synthesis and the prolonged half-life of serum albumin [10]. In cases with chronic renal failure, renal anemia lowers the HbA1c values because the lifespan of the erythrocytes is shortened [11]. However, in patients with diabetic nephropathy presenting with marked proteinuria, the GA values are lower because of the increased turnover of albumin metabolism [12]. Hyperthyroidism and steroid treatment, in addition to nephropathy, are known to lower the GA values because of accelerated albumin synthesis. Thyroid hormone is also known to promote albumin metabolism. A study showed that the serum GA level was reduced in patients with thyrotoxicosis, but no apparent change in HbA1c was seen. In addition, GA had significant inverse correlations with the serum free T3 and free T4 levels, as well as a significant positive correlation with the serum TSH level [13]. Additionally, the BMI is known not to affect the HbA1c values, while a negative correlation exists between the BMI and GA. A previous study showed that in obese children, a significant positive correlation was seen between HbA1c and BMI, but a significant negative correlation was seen between GA and BMI [25]. Similarly, in adult diabetic patients, a significant negative correlation between the BMI and the GA level was seen. By contrast, no correlation between the BMI and the HbA1c level was seen [26]. While the reasons for these relations remain unknown, one possible explanation is that obesity increases albumin turnover. Furthermore, chronic inflammatory reactions might also increase albumin turnover. In our study, however, a stratified analysis according to the BMI showed no interaction between these parameters, although the reason for the lack of an interaction was not clear.

Our study had certain limitations. First, we retrospectively selected patients in whom simultaneous HbA1c and GA measurements had been obtained. Thus, a selection bias may exist. Second, as the data were collected from a single hospital and the GA values were not standardized, the present results might not be directly applicable to other hospitals. Although the bootstrap confidence intervals and the bias estimates supported the internal validity of our findings, external validation is needed before applying to other populations. Third, we enrolled patients with various types of diabetes as well as non-diabetic patients in our study. In the future, we are going to investigate the correlation between HbA1c and GA by sorting out the types of diabetes.

In conclusion, we propose an equation for calculating eHbA1c to evaluate the glycemic control of patients with altered hemoglobin metabolism.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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Prediction of response to GLP-1 receptor agonist therapy in Japanese patients with type 2 diabetes

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Abstract

Background: Glucagon-like peptide-1 (GLP-1) receptor agonists can maintain good glycemic control in some diabetic. Here we compared the clinical characteristics and parameters reflecting glucose metabolism at the time of the initiation of GLP-1 receptor agonist therapy between patients who responded well to therapy and those who did not.

Methods: The records of 43 patients with type 2 diabetes who started receiving GLP-1 receptor agonist therapy during hospitalization were retrospectively reviewed. Glucagon stimulation tests were performed, and patients were started on liraglutide or exenatide therapy. Preprandial blood glucose levels were measured on days 2 and 3 of GLP-1 receptor agonist therapy. We used the Cox proportional hazard model to compare clinical parameters between responders (HbA1c level <8% at more than 3 months after the initiation of treatment) and non-responders (HbA1c level ≥8% at more than 3 months after the initiation of treatment or a switch to insulin therapy at any time).

Results: Twenty-six of the 43 patients were classified as non-responders. At baseline, mean HbA1c levels were 9.9% among responders and 9.7% among non-responders. Compared with treatment with only diet or metformin, the hazard ratio [HR] for non-response was 5.3 (95% confidence interval [CI]: 1.16-24.6, $P = 0.03$) for insulin therapy and 5.0 (95% CI: 1.13-22.16, $P = 0.03$) for sulfonylurea therapy. Compared with the lowest tertile, the HRs for non-response in the highest tertile were 3.1 (95% CI: 1.04-8.97, $P = 0.04$) for the mean preprandial blood glucose level on days 2 and 3 and 3.4 (95% CI: 1.05-11.01, $P = 0.04$) for the body mass index. The response was not significantly associated with the duration of diabetes or the glucagon stimulation test results. A receiver operating curve analysis showed that the mean preprandial blood glucose level had the highest area under the curve value (=0.72) for the prediction of non-responders.

Conclusions: In patients with poorly controlled diabetes, the response to GLP-1 receptor agonist therapy was significantly associated with the treatment used before the initiation of therapy, the body mass index, and the mean preprandial blood glucose level during the 2 days after the initiation of therapy.

Keywords: Glycemic control, Glucagon-like peptide-1 agonist, Predictors of response, Preprandial blood glucose level, Liraglutide, Exenatide

Background

In patients with diabetes, the maintenance of good glycemic control is the most important method for preventing the progression of diabetes-related complications. According to the position statement of the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (AHA), glucagon-like peptide-1 (GLP-1) receptor agonists, such as liraglutide and exenatide, are recommended because of their ability to maintain good glycemic control in diabetic patients without resulting in weight gain or significant hypoglycemia [1,2]. They have also been shown to help maintain β-cell mass and function [3]. GLP-1 receptor agonist therapy has not yet been widely used in Japan [4]; however, it has recently begun to attract more attention [5,6].

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Some diabetic patients respond well to GLP-1 receptor agonist therapy and some do not. For medical and socio-economic reasons, it is important to determine methods of predicting the response to GLP-1 receptor agonists. In consideration of low risk of hypoglycemia and lesser effect on body weight gain, previous studies [7-9] have been switched from insulin therapy to GLP-1 receptor agonist therapy and certain number of the patients have been regarded effective.

Previous studies [7-11] have reported that a short history of diabetes, a high fasting serum C-peptide (CPR) level, a high stimulated CPR level at 6 min during glucagon stimulation (CPR6), and a high urinary C-peptide level at the start of treatment may predict the response to GLP-1 receptor agonist therapy in terms of reducing the blood glucose levels. Combined GLP-1 receptor agonist and insulin therapy has shown promising results in patients who are modestly obese and have a longer duration of diabetes [12]. These studies have demonstrated the importance of identifying predictors of response to treatment; however, whether other factors, such as previous antidiabetic treatment and glucose levels soon after the initiation of GLP-1 receptor agonist therapy, are capable of predicting the response to GLP-1 receptor agonist therapy remains uncertain.

Therefore, the present study investigated previous antidiabetic treatment and the preprandial blood glucose levels on days 2 and 3 of GLP-1 receptor agonist therapy as well as clinical characteristics and parameters reflecting glucose metabolism before the initiation of GLP-1 receptor agonist therapy, including the change in the serum CPR level during a glucagon stimulation test and the 24-h urinary CPR excretion (U-CPR) level. These data were used to investigate potential predictors of the response to treatment.

Methods

Subjects and procedures

We conducted a retrospective cohort study of patients with type 2 diabetes who were admitted to the National Center for Global Health and Medicine for the treatment of hyperglycemia between September 2009 and December 2012 and who started receiving GLP-1 receptor agonist therapy during their period of hospitalization. All the patients initially received inpatient diet therapy (the optimal caloric intake was calculated as the ideal body weight × 25), exercise therapy, and multiple insulin injection therapy to maintain their preprandial blood glucose levels at <200 mg/dL.

GLP-1 receptor agonist therapy was initiated after a glucagon stimulation test, starting with liraglutide (0.3 mg daily) or exenatide (5 μg twice daily). Insulin therapy was discontinued at the time of the initiation of GLP-1 receptor agonist therapy. A maximum of two oral hypoglycemic drugs were used at a time. The maximum glimepiride dose was 2 mg daily. Since we switched patients from insulin therapy to GLP-1 receptor agonist therapy during hospitalization, we carefully monitored the patients for glucose fluctuations.

After hospital discharge, the patients returned for follow-up visits at least every 2 months. Follow-up blood tests included liver and kidney function tests and measurements of the serum lipid level, the fasting plasma glucose level, and the HbA1c level. The medication doses were increased to the maximum dose at the discretion of the attending physician, and patients were cautioned about adverse effects such as marked anorexia, nausea, or diarrhea. The maximum dose of liraglutide was 0.9 mg/day in Japan, while that of exenatide was 10 μg twice daily. The present study was approved by the institutional review board of the National Center for Global Health and Medicine, and written informed consent was waived because of the retrospective design. This study was implemented in accordance with the provisions of the Declaration of Helsinki.

The primary objective of this study was to compare the clinical parameters at the time of the initiation of GLP-1 receptor agonist therapy between patients who had achieved an HbA1c level of <8% [1] at more than 3 months after the initiation of treatment (responders) and those who had not achieved an HbA1c level of <8% (non-responders). Non-responders also included patients who were switched to insulin therapy at any time because of insufficient glycemic control.

Laboratory evaluations

A glucagon stimulation test was conducted after an 8-h fast. The serum CPR level was measured before glucagon injection and 6 min after the injection of 1 mg of glucagon, and the difference between these two levels was calculated (ΔCPR) [13]. Urine was collected for 24 h and stored in a refrigerator. The serum and urinary CPR levels were measured using the electro-chemiluminescence method. Fasting plasma glucose concentrations were measured using the electrode method. HbA1c levels were measured using high-pressure liquid chromatography. The HbA1c values were recorded as Japan Diabetes Society (JDS) values and were then converted to the National Glycohemoglobin Standardization Program (NGSP) values as follows: HbA1c (NGSP) =1.02 × HbA1c (JDS) +0.25% [14]. All the blood samples were assayed at a central laboratory. The preprandial blood glucose levels were measured at least 3 times a day using a self-monitoring blood glucose device (One Touch® Ultra®; Johnson and Johnson, USA). The blood glucose levels were measured before breakfast, lunch, and dinner on days 2 and 3 of GLP-1 receptor agonist therapy to determine whether the long-term response could be predicted by these values.

Statistical analysis

The objective of this study was to identify factors that could predict the response to treatment at the time of the initiation of GLP-1 receptor agonist therapy. The non-response rate was analyzed using a time-to-event survival analysis. The person-time of the follow-up was calculated from the time of initiation of GLP-1 receptor agonist treatment until the definitive event (i.e., the achievement of an HbA1c level of ≥8% at more than 3 months after the initiation of treatment or a switch in treatment to insulin therapy) or the end of the follow-up period. The hazard ratios for the response to treatment were calculated using the Cox proportional hazards model. We selected the factors that were shown to be significantly associated with the response to treatment when evaluated using univariate Cox proportional hazards analyses ($P < 0.05$) in addition to the body mass index (BMI), the duration of diabetes, CPR6, and U-CPR, which have been reported to be related to patient outcome. The subjects were grouped into 3 groups (tertiles for continuous variables), and the long-term cumulative rate of treatment failure for each group was estimated using the Kaplan-Meier method. The assumption of proportional hazards was assessed using Schoenfeld residuals ($P > 0.05$ for all the tests).

Various cutoff points were calculated using a receiver operating characteristic (ROC) curve analysis of the area under the curve (AUC), true positives, false positives, true negatives, false negatives, sensitivity, and specificity of potential predictors of the response to GLP-1 receptor agonist therapy.

All the P values were two-tailed, and values less than 0.05 were considered significant. All the statistical analyses were performed using Stata statistical software (version 12.1; Stata Corp., TX, USA).

Results

This study included 43 patients with a mean follow-up period of 131 days (maximum follow-up, 585 days). Twenty-six patients were classified as non-responders, of which three discontinued GLP-1 receptor agonist therapy within 3 months because of high blood glucose levels. Table 1 shows a comparison of the baseline characteristics of responders and non-responders using univariate Cox proportional hazards analyses.

There were no significant differences in sex, age, type of GLP-1 receptor agonist, or HbA1c level at the time of initiation of treatment between responders and non-responders. When a P level <0.05 was regarded as indicating a significant difference between groups, previous treatment other than diet or metformin was found to be a potential predictor of a non-response to GLP-1 receptor agonist therapy (Table 1). Furthermore, the BMI, duration of diabetes, and CPR6 and U-CPR levels were divided into tertiles to evaluate the effects of long-term factors on response, and the rate of treatment failure in each tertile was estimated using the Kaplan-Meier method (Figure 1).

Compared with treatment with only diet or metformin, the hazard ratio for non-response was 5.3 (95% confidence interval [CI] 1.16-24.6, $P = 0.03$) for insulin therapy and 5.0 (95% CI 1.13-22.16, $P = 0.03$) for sulfonylurea therapy (Table 2). Compared with the lowest tertile for BMI, the hazard ratio for non-response was 3.9 (95% CI 1.23-12.38, $P = 0.02$) for the middle tertile and 3.4 (95% CI 1.05-11.01, $P = 0.04$) for the highest tertile. There was no significant difference in response among tertiles according to CPR6, U-CPR, or the duration of diabetes. Compared with a duration of diabetes of <5 years, the hazard ratio for non-response was 4.1 (95% CI 0.97-17.67, $P = 0.054$) in patients with a duration of diabetes of ≥5 years.

Blood glucose levels early after the initiation of GLP-1 receptor agonist therapy were analyzed using measurements taken before 3 meals on both day 2 and day 3 of therapy. There was no significant difference in the early-morning fasting blood glucose level between responders and non-responders. Significant differences in the mean preprandial blood glucose levels were observed between the responders and the non-responders, with a hazard ratio of 1.01 per 1-mg/dL increase (95% CI, 1.00-1.02; $P = 0.03$ for trend) for day 2, 1.01 per 1-mg/dL increase (95% CI, 1.00-1.02; $P = 0.04$ for trend) for day 3, and 1.01 per 1-mg/dL increase (95% CI, 1.00-1.02; $P = 0.03$ for trend) for days 2 and 3 combined. The hazard ratio of the mean preprandial blood glucose level for day 2 and 3 combined was 1.90 per 50-mg/dL increase (95% CI, 1.07-3.39; $P = 0.03$ for trend) and 3.61 per 100-mg/dL increase (95% CI, 1.14-11.49; $P = 0.03$ for trend).

Compared with the lowest tertile for the mean preprandial blood glucose level for days 2 and 3 combined, the hazard ratio for the non-response group was 3.5 per 1-mg/dL increase (95% CI, 1.19-10.12; $P = 0.02$ for trend) for the middle tertile and 3.1 per 1-mg/dL increase (95% CI, 1.04-8.97; $P = 0.04$ for trend) for the highest tertile.

The mean preprandial blood glucose level for days 2 and 3 combined was indicated by the ROC curve analysis that had the highest AUC value (AUC = 0.72; Table 1). The corresponding optimal cut-off point, at which the sum of the sensitivity and the specificity reached a maximum, was 138 mg/dL. Diagnostic parameters, including the sensitivity and specificity, depended strongly on the chosen cutoff point (Table 3).

Discussion

The results of this study suggest that the treatment used before the initiation of GLP-1 receptor agonist therapy and the mean preprandial blood glucose level during the 2 days after the initiation of therapy predicted the long-

Table 1 Baseline characteristics of patients*

	Responder (N =17)	Non-responder (N =26)	Hazard ratio (95% CI)	*P* value	AUC
Male (%)	64.7	61.5	0.85 (0.39-1.89)	0.70	NA
Age (years)	57.1 ± 12.2	61.9 ± 16.1	1.01 (0.98-1.04)	0.63	0.62
Body mass index (kg/m^2) †	29.1 ± 9.8	29.5 ± 5.5	1.04 (0.98-1.10)	0.21	0.66
Exenatide (%)	58.8	65.4	1.56 (0.67-3.63)	0.31	NA
Duration of diabetes (years)	10.6 ± 8.6	14.8 ± 10.6	1.04 (0.99-1.08)	0.051	0.62
Fasting C-peptide (ng/mL)	2.4 ± 1.5	2.2 ± 1.1	0.91 (0.60-1.38)	0.66	0.52
CPR6 (ng/mL)‡	4.0 ± 2.5	4.4 ± 2.4	1.05 (0.87-1.27)	0.60	0.57
ΔCPR (ng/mL)§	1.5 ± 1.1	2.1 ± 1.5	1.15 (0.90-1.47)	0.27	0.62
C-peptide index¶	1.8 ± 1.2	1.4 ± 0.7	0.79 (0.46-1.34)	0.37	0.55
U-CPR (μg/day)	87.2 ± 47.7	91.0 ± 71.1	1.00 (0.99-1.01)	0.82	0.45
Preprandial glucose of the previous day GLP-1 initiated (mg/dL)	162.6 ± 50.4	174.2 ± 36.9	1.00 (0.99-1.01)	0.40	0.60
Average preprandial glucose level over 2 days after the initiation of GLP-1 receptor agonist treatment (mg/dL)	140.0 ± 26.1	165.1 ± 31.8	1.01 (1.00-1.02)	0.03	0.72
HbA1c (%)	9.9 ± 1.8	9.7 ± 1.6	0.93 (0.74-1.16)	0.51	0.49
Previous antidiabetic treatment (%)					
Diet and/or metformin	47.1	11.5	1.0 (Reference)		NA
Sulfonylurea	23.5	38.5	5.0 (1.13-22.16)	0.03	NA
Insulin	29.4	50.0	5.3 (1.16-24.56)	0.03	NA
Dose of insulin (unit)	21.2 ± 5.9	26 ± 8.4	NA	NA	NA

*Values for responders and non-responders to treatment are shown as the percentage (number) or mean ± standard deviation. Hazard ratios for response to treatment were analyzed using the Cox proportional hazards model. Areas under the receiver operating characteristic curve (AUC) were compared using a logistic regression analysis.
†The body mass index is the weight in kilograms divided by the square of the height in meters.
‡Serum C-peptide level at 6 min during a glucagon stimulation test.
§Change in serum C-peptide level between baseline and 6 min during a glucagon stimulation test.
¶Fasting serum C-peptide level divided by fasting plasma glucose level.

term response to treatment, while the ability to secrete insulin and the duration of the diabetes history were not useful predictors. Some patients with a higher BMI and a higher CPR6 did not respond to GLP-1 receptor agonist therapy.

Pancreatic β-cell function is reduced by 20% in patients with glucose intolerance and 50% in patients with diabetes [15]. GLP-1 receptor agonist therapy has been reported to be more effective in patients with relatively high levels of insulin secretion, as determined by the 24-h urinary CPR excretion, the fasting serum CPR level, the CPR index [9], and the CPR6 [10]. In this study, however, these markers of insulin secretion were not predictors of the response to GLP-1 receptor agonist therapy.

There are two possible explanations for these results. First, our study included patients who could maintain their insulin secretion levels to some extent, while previous studies included patients with a U-CPR of less than 20 μg/day, indicating severely impaired insulin secretion [9]. The inclusion of patients treated with sulfonylureas also likely contributed to the difference in results when compared with those of a previous study [10]. Second, glycemic control is affected by both the level of insulin secretion and the degree of insulin resistance [16]. Patients with a higher BMI, which is correlated with an increased CRP6 level (r = 0.68), tended not to respond to GLP-1 receptor agonist therapy. This finding suggested that the stimulation of insulin secretion by a GLP-1 receptor agonist might be insufficient to lower the blood glucose level when insulin resistance is present. In this context, good glycemic control might have been relatively achieved among the second tertile of patients whose insulin secretion might have been modestly preserved and who might not have had insulin resistance.

Previous studies reported that liraglutide therapy is more effective in patients with a shorter duration of diabetes [8-10]. However, other studies have reported that patients with long-term diabetes may achieve better glycemic control with exenatide therapy [11]. Most of the patients in our study had a long duration of diabetes. Therefore, the duration of diabetes was not associated with efficacy when the patients were divided into tertile groups. Although the number of patients was relatively small, patients with a ≥5-year history of diabetes were less likely to achieve good glycemic control with GLP-1

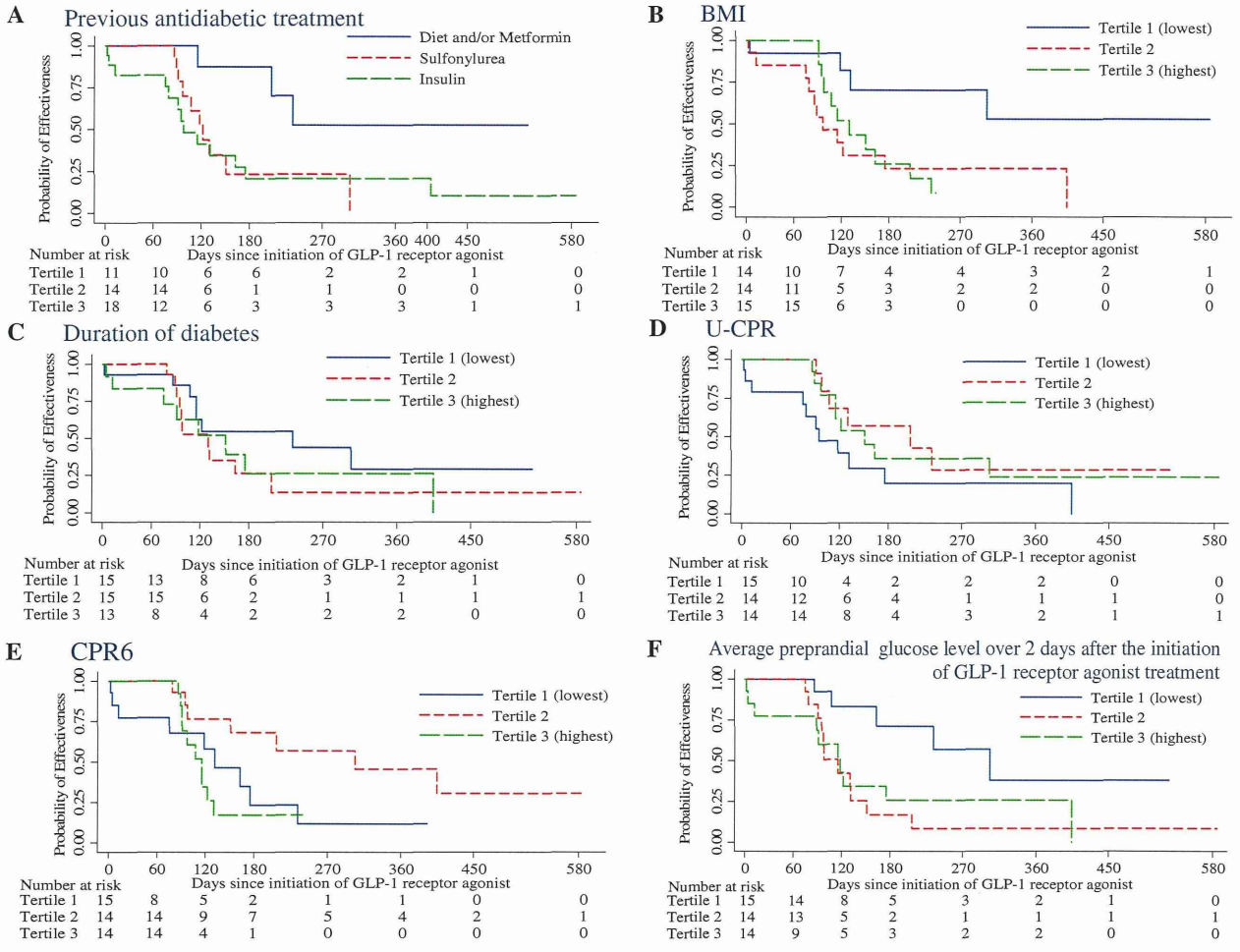

Figure 1 Kaplan-Meier estimates of the cumulative incidence of non-response to treatment, up to 600 days. (A) Previous antidiabetic treatment, **(B)** BMI: body mass index, **(C)** Duration of diabetes, **(D)** U-CPR: 24-h urinary C-peptide excretion, **(E)** CPR6: stimulated C-peptide level at 6 min during glucagon stimulation, **(F)** Average preprandial glucose level over 2 days after the initiation of GLP-1 receptor agonist treatment, GLP-1: Glucagon-like peptide-1.

receptor agonist therapy than patients with a <5-year history.

It was previously reported that patients who had been previously treated with diet and exercise achieved a greater reduction in their HbA1c levels with GLP-1 receptor agonist therapy than patients who had previously received other treatments [17]. Patients who had been previously treated with monotherapy, particularly metformin, were also reported to achieve better glycemic control with GLP-1 receptor agonist therapy than patients who had been previously treated with multiple oral hypoglycemic agents [18]. These findings are consistent with guidelines recommending the use of GLP-1 receptor agonists as second-line therapeutic agents [1] and are also consistent with our results.

Most of the patients included in the present study exhibited sustained postbreakfast hyperglycemia before the introduction of GLP-1 therapy [19]. A glycemic control of HbA1c <8.0% could be achieved only when the blood glucose levels before lunch and before dinner as well as those before breakfast were lowered [20,21]. Accordingly, we evaluated the predictive ability of the mean preprandial blood glucose level during the 2 days after the initiation of GLP-1 receptor agonist therapy. Of note, the effectiveness of the reduction in the glucose level in response to GLP-1 receptor agonist therapy after the initiation of therapy was preserved and possessed the ability to predict a long-term improvement in glycemic control. Evaluations using blood glucose measurements performed soon after the introduction of GLP-1 receptor agonist therapy might also possess the ability to predict the achievement of more strict glycemic control, such as HbA1c <7.0%. For this purpose, more precise measurements of blood glucose, including postprandial glucose levels [22] and continuous glucose monitoring [23], might be beneficial.

Table 2 Hazard ratios for non-response to treatment

	N	Median (Range)	Hazard ratio (95% CI)	*P* value
BMI (kg/m^2)	43	26.31 (19.8-52.6)		
Tertile 1 (lowest)	14	23.6 (19.8-25.0)	1.0 (Reference)	
Tertile 2	14	26.3 (25.1-30.3)	3.9 (1.24-12.37)	0.02
Tertile 3 (highest)	15	33.2 (30.4-52.6)	3.4 (1.04-11.01)	0.04
Duration of diabetes (years)	43	11 (0.1-38)		
Tertile 1 (lowest)	15	4 (0.1-6)	1.0 (Reference)	
Tertile 2	15	12 (8-17)	1.7 (0.67-4.4)	0.25
Tertile 3 (highest)	13	23 (18-38)	1.7 (0.63-4.5)	0.30
CPR6 (ng/mL)	43	3.9 (0.5-11.0)		
Tertile 1 (lowest)	15	2.0 (0.5-2.7)	1.0 (Reference)	
Tertile 2	14	4.0 (2.8-4.9)	0.4 (0.13-1.01)	0.054
Tertile 3 (highest)	14	6.7 (5.3-11.0)	1.3 (0.51-3.28)	0.59
U-CPR (μg/day)	43	71.6 (16.0-249.8)		
Tertile 1 (lowest)	15	33.7 (16.0-49.7)	1.0 (Reference)	
Tertile 2	14	73.7 (50.8-112.8)	0.4 (0.16-1.18)	0.10
Tertile 3 (highest)	14	160.0 (121.7-249.8)	0.6 (0.23-1.34)	0.19
Average preprandial glucose level over 2 days after the initiation of GLP-1 receptor agonist treatment (mg/dL)	43	149.3 (99.8-246.2)		
Tertile 1 (lowest)	15	130.3 (99.8-137.7)	1.0 (Reference)	
Tertile 2	14	149.7 (140.2-161.0)	3.5 (1.19-10.12)	0.02
Tertile 3 (highest)	14	188.7 (161.5-246.2)	3.1 (1.04-8.97)	0.04
Previous antidiabetic treatment	43			
Diet and/or metformin	11		1.0 (Reference)	
Sulfonylurea	14		5.0 (1.13-22.16)	0.03
Insulin	18		5.3 (1.16-24.56)	0.03

Abbreviations: *CI* confidence interval, *BMI* body mass index, *GLP-1* Glucagon-like peptide-1, *CPR* C-peptide, *CPR6* stimulated C-peptide level at 6 min during glucagon stimulation, *U-CPR* 24-h urinary C-peptide excretion.

Table 3 Diagnostic measures at various cutoff points for the prediction of non-response to treatment

Predictors, Cutoff point	TP/FP	TN/FN	Sensitivity	Specificity
Average preprandial glucose level over 2 days after the initiation of GLP-1 receptor agonist treatment (mg/dL)				
<120	26/12	5/0	100	29.4
<130	25/11	6/1	96.2	35.3
<140	21/7	10/5	80.8	58.8
<150	15/6	11/11	57.7	64.7
<160	10/5	12/16	38.5	70.6
<170	9/3	14/17	34.6	82.4
<180	8/1	16/18	30.8	94.1
<190	6/0	17/20	23.1	100.0
<200	4/0	17/22	15.4	100.0

Abbreviations: *TP* number of true positives, *FP* number of false positives, *TN* number of true negatives, *FN* number of false negatives, *GLP-1* Glucagon-like peptide-1.

Limitations

First, this was an observational study with a small sample size, leading to wide confidence intervals for our estimates. Second, the tertile analysis may have reduced the statistical power, since it discards within-category information, especially in studies with small sample sizes. However, this analysis avoids making the assumption of a linear relation. Third, the study population consisted of patients who began receiving GLP-1 receptor agonist therapy during hospitalization for the treatment of hyperglycemia. Both of the mean HbA1c for responders (9.9%) and non-responders (9.7%) were high. Therefore, the subjects are not representative of the general type 2 diabetic population. Fourth, for patients who were already introduced insulin therapy, switching to GLP-1 receptor agonist therapy is less common. Fifth, the discontinuation of GLP-1 receptor agonist therapy was performed at the discretion of the attending physician, and there were no clearly defined criteria for discontinuation. Finally, in this study, we could not perform separate analyses according to the use of liraglutide or exenatide because of the small number of samples. Therefore, a prospective clinical study with a stricter protocol and a larger number of patients utilizing each formulation is necessary to further evaluate the effectiveness of GLP-1 receptor agonist therapy.

Conclusions

In patients with poorly controlled diabetes, our findings suggest that patients who have received previous treatments for diabetes other than diet and exercise or metformin, who have a high BMI, and who have a high mean preprandial blood glucose level do not tend to respond well to GLP-1 receptor agonist therapy.

Abbreviations

GLP-1: Glucagon-like peptide-1; HR: Hazard ratio; CI: Confidence interval; EASD: European Association for the Study of Diabetes; ADA: American Diabetes Association; CPR: C-peptide; CPR6: Stimulated C-peptide level at 6 min during glucagon stimulation; U-CPR: 24-h urinary C-peptide excretion; ΔCPR: Change in serum CPR between 0 min and 6 min during a glucagon stimulation test; JDS: Japan Diabetes Society; NGSP: National Glycohemoglobin Standardization Program; BMI: Body mass index; ROC: Receiver operating characteristic; AUC: Analysis of the area under the curve; TP: The number of true positives; FP: The number of false positives; TN: The number of true negatives; FN: the number of false negatives.

Competing interests

MN and AG have received a research grant from Novo Nordisk. MN has received speaker honoraria from Eli Lilly and Novo Nordisk.

Authors' contributions

KI conceptualized the idea for the study, collected the data, performed a literature review, and wrote the manuscript. TT, MK, and RYH participated in the design of the study, participated in the discussion, and was involved in drafting the manuscript. MG and AG were involved in performing the statistical analysis, participated in the discussion, and were involved in drafting the manuscript. HN and HK participated in the discussion. MN presented the initial concept and reviewed the manuscript. All the authors have read and approved the final manuscript.

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Original Article

Descriptive Epidemiology of Diabetes Prevalence and HbA1c Distributions Based on a Self-Reported Questionnaire and a Health Checkup in the JPHC Diabetes Study

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ABSTRACT

Background: The present study examined the prevalence of diabetes in Japan during the late 1990s and early 2000s using the Japan Public Health Center-based Prospective Diabetes cohort. We also investigated the distributions of HbA1c values in noncompliant diabetic participants in the cohort.

Methods: A total of 28 183 registered inhabitants aged 46–75 years from 10 public health center areas were included in the initial survey. The 5-year follow-up survey included 20 129 participants. The prevalence of diabetes was estimated using both a self-reported questionnaire and laboratory measurements. Among the participants who reported the presence of diabetes on the questionnaire (self-reported diabetes), the distributions of HbA1c values were described according to their treatment status.

Results: The age-standardized prevalence of diabetes in 55- to 74-year-old adults was 8.2% at the initial survey and 10.6% at the 5-year follow-up. At the initial survey, among participants with self-reported diabetes, the mean HbA1c values in the participants who had never and who had previously received diabetes treatment were 7.01% (standard deviation [SD] 1.56%) and 6.56% (SD 1.46%), respectively. Approximately 15% of the participants who had self-reported diabetes but had never received diabetes treatment had an HbA1c $\geq$ 8.4%.

Conclusions: The prevalence of diabetes increased in the JPHC cohort between the late 1990s and early 2000s. A certain proportion of participants who were aware of their diabetes but were not currently receiving treatment had poor diabetic control. Efforts to promote continuous medical attendance for diabetes care may be necessary.

Key words: diabetes mellitus; prevalence; self-report; HbA1c

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease that imposes a considerable burden on both individual patients and healthcare systems. A dramatic increase in the number of diabetic patients has been observed in Japan during the past several decades because of the aging population and changes in dietary patterns and lifestyles.[1,2] At present, Japan has the eighth highest number of diabetic patients in the world.[3] According to national surveys performed by the Japanese Ministry of Health, Labour, and Welfare (MHLW) in 2002[4] and 2007,[5] which sampled 4000–5000 people from the

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general population and estimated the prevalence of diabetes, the prevalence of probable diabetes was 12.8% for males and 6.5% for females in 2002 and 15.3% for males and 7.3% for females in 2007. Thus, the estimated number of diabetic people in Japan increased from 7.4 million to 8.9 million during the 5-year period.

Regarding the prevalence of diabetes according to area, many studies have reported the prevalence in a single area, while one review reported area variations in the prevalence of diabetes.[6] However, few studies have described the prevalence of diabetes according to area across Japan using a standardized methodology. Estimating the prevalence according to area could be important for both providing diabetes care and for assessing the quality of diabetes healthcare.

The Japan Public Health Center-based (JPHC) Prospective Diabetes study examined registered inhabitants in public health center (PHC) areas across Japan in the initial survey (1998–2000) and in the 5-year follow-up survey (2003–2005) using a standardized questionnaire and laboratory measurements. The large population-based sample and strict standardization of hemoglobin A1c (HbA1c) provided an opportunity to accurately estimate prevalence of diabetes according to area and to describe the 5-year change in the prevalence between the late 1990s and the early 2000s.

In addition, the JPHC cohort enabled us to examine the glycemic control of patients with diabetes according to treatment status. The Japanese MHLW National Nutrition Survey in 2007[5] reported that only 50.8% of diabetic patients were currently receiving diabetes treatment, although the proportion was higher than in the previous survey in 2002.[5] This finding suggests that poor medical attendance for diabetes treatment may still be prevalent across Japan, despite increasing awareness of the clinical importance of diabetes. To clarify the situation of glycemic control in noncompliant patients with diabetes, we additionally described the distributions of HbA1c values in noncompliant diabetic participants in the cohort.

METHODS

Data from the JPHC Study, which was a large longitudinal cohort study investigating cancer, cardiovascular disease, and other lifestyle-related diseases in Japan, were used in the present study. The details of the study design have been described elsewhere.[7] Briefly, the JPHC Study was initiated in 1990 for Cohort I, and subjects were added in 1993 for Cohort II. The study population consisted of all registered Japanese inhabitants in 11 PHC areas ranging in age from 40 to 59 years old in Cohort I (the Ninohe PHC area in Iwate Prefecture, Yokote PHC area in Akita Prefecture, Saku PHC area in Nagano Prefecture, Ishikawa PHC area in Okinawa Prefecture, and Katsushika PHC area in Tokyo Metropolis) and from 40 to 69 years old in Cohort II (the Kasama PHC area in Ibaraki Prefecture, Kashiwazaki PHC area in Niigata Prefecture, Tosayamada PHC area in Kochi Prefecture, Arikawa PHC area in Nagasaki Prefecture, Miyako PHC area in Okinawa Prefecture, and Suita PHC area in Osaka Prefecture). The names of the PHC areas shown here are those used at that time.

The diabetes study (the JPHC Diabetes Study) was performed in all PHC areas other than the Suita PHC area. The initial survey was performed in 1998–1999 for Cohort II and in 2000 for Cohort I. Among the registered inhabitants participating in the JPHC Study, those who received annual health checkups in each PHC-administered area were recruited; a self-reported questionnaire specific to diabetes research and measurement of HbA1c was added to their routine health checkup examinations. A 5-year follow-up survey was performed in the same way in 2003–2004 for Cohort II and in 2005 for Cohort I.

A flow chart of the study participants is shown in Figure. In the present study, 28 363 participants who responded to the questionnaire were eligible for the initial survey. We excluded 180 participants because of missing anthropometric or laboratory data. Accordingly, a total of 28 183 participants (10 268 men and 17 915 women) were therefore included in the analysis of the initial survey. Regarding the 5-year follow-up survey, 20 264 participants responded to the questionnaire. Among them, 12 215 participated in both the initial and the 5-year follow-up survey, while 8049 participated in the 5-year follow-up survey only. Of these 20 264 participants, 135 were excluded because of missing data, and a total of 20 129 participants (7639 men and 12 490 women) were included. The incidence of diabetes during the 5 years among those who participated in both the initial and the 5-year follow-up survey was reported by Noda et al.[8] A fasting blood sample, which was defined as a sample collected ≥8 hours after the last caloric intake, was collected from 11 832 participants at the initial survey and from 7296 participants at the 5-year follow-up. If a blood sample was collected <8 hours after the last caloric intake, it was classified as a casual blood sample. This study was approved by the ethics committee of the International Medical Center of Japan, which was the former name of the National Center for Global Health and Medicine.

Questionnaire used for the diabetes survey

A self-reported questionnaire regarding family history of diabetes, results of previous examinations for diabetes, physicians' diagnosis of diabetes, current medication for diabetes, signs of diabetic complications, brief history of body weight changes, physical activity, and history of childbirth was distributed at health checkups.

Definition of diabetes mellitus

In the present study, diabetes was defined in several ways, which are summarized in Table 1. "Self-reported diabetes" was defined as a reply to the questionnaire that met either or

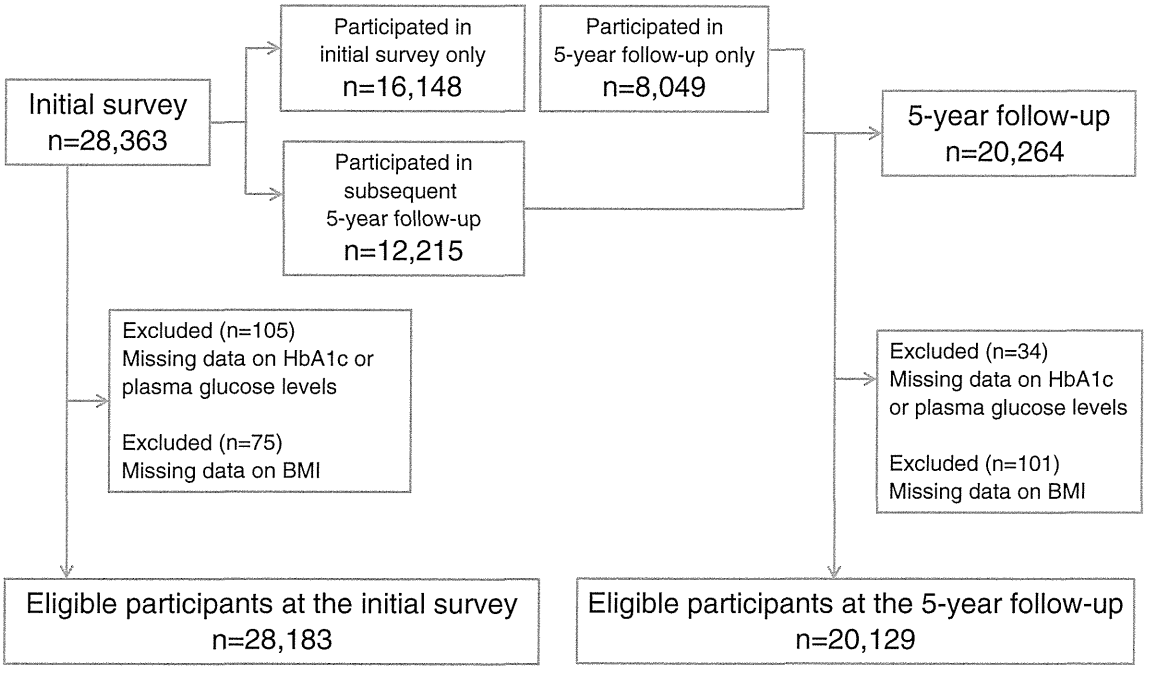

Figure. Flow chart of the study participants.

Table 1. Definitions of diabetes used in the present study

1. Self-reported diabetes
   - Participants who replied to the self-reported questionnaire that met either or both of the following criteria: 1) having been told 'you have diabetes' by a physician, or 2) taking medication for diabetes.
2. Diabetes solely confirmed by laboratory data[a]
   - Absence of self-reported diabetes

   AND
   - Any of the following laboratory results: 1) a fasting plasma glucose (FPG) value of 126 mg/dL or more, 2) a casual plasma glucose value of 200 mg/dL or more, 3) an HbA1c value of 6.5% or more.
3. Diabetes solely confirmed by laboratory data (1985 WHO)
   - Absence of self-reported diabetes

   AND
   - Either or both of the following laboratory results: 1) an FPG value of 140 mg/dL or more, 2) a casual plasma glucose value of 200 mg/dL or more.
4. Diabetes definition used for estimating diabetes prevalence
   - Presence of self-reported diabetes

   OR
   - Presence of diabetes solely confirmed by laboratory data
5. Diabetes confirmed by laboratory data and/or current treatment status
   - Any of the following criteria: 1) an FPG value of 126 mg/dL or more, 2) a casual plasma glucose value of 200 mg/dL or more, 3) an HbA1c value of 6.5% or more.

   AND/OR
   - Participants who replied to the self-reported questionnaire with "currently receiving diabetes treatment".

Abbreviations: FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; WHO, World Health Organization.
[a]"Diabetes solely confirmed by laboratory data" was referred as "newly diagnosed diabetes" in a previously published paper of the JPHC Diabetes study.[9]

both of the following criteria: 1) having been told 'you have diabetes' by a physician, or 2) taking medication for diabetes. "Diabetes solely confirmed by laboratory data" was defined as the absence of self-reported diabetes and the presence of any of the following laboratory results: 1) a fasting plasma glucose (FPG) value of 126 mg/dL or more, 2) a casual plasma glucose value of 200 mg/dL or more, or 3) an HbA1c value of 6.5% or more in the National Glycohemoglobin Standardization Program equivalent value. "Diabetes solely confirmed by laboratory data" was referred to as "newly diagnosed diabetes" in a previously published paper regarding the prevalence of diabetes in the JPHC Study.[9] In addition, "diabetes solely confirmed by laboratory data" was also examined using the criteria used in the clinical settings of the initial survey performed in 1998–2000. The definition was based on the World Health Organization (WHO) criteria in

1985 but was modified because results for the oral glucose tolerance test were not always available. The definition involved meeting either of the following criteria: 1) an FPG value of 140 mg/dL or more, or 2) a casual plasma glucose value of 200 mg/dL or more. To avoid confusion, "diabetes solely confirmed by laboratory data" based on the WHO criteria in 1985 was stated as "diabetes solely confirmed by laboratory data (1985 WHO)" in the present study.

Regarding the estimates of the prevalence of diabetes, diabetes was defined as the presence of "self-reported diabetes" or "diabetes solely confirmed by laboratory data." Namely, the definition referred to any of the following criteria: 1) an FPG value of 126 mg/dL or more, 2) a casual plasma glucose value of 200 mg/dL or more, 3) an HbA1c value of 6.5% or more, or 4) self-reported diabetes. We also computed the frequency of participants (diabetes confirmed by laboratory data and/or current treatment status) who met any of the following criteria: 1) an FPG value of 126 mg/dL or more, 2) a casual plasma glucose value of 200 mg/dL or more, 3) an HbA1c value of 6.5% or more, or 4) currently receiving diabetes treatment.

Standardization of HbA1c levels

The HbA1c measurement method differed by PHC-administered areas. Therefore, standardization of HbA1c was strictly performed to minimize variations among laboratories. Either a high-performance liquid chromatography (HPLC) assay system or an immunochemical assay system was used in each PHC, except for one PHC where the immunochemical system was changed to an HPLC system during the 5-year follow-up period. Details regarding the procedure used for standardization have been described previously.[8] Briefly, standard samples were provided to each PHC at the time of the initial survey and the 5-year follow-up survey. The calibration procedure was conducted using the standard samples. The original standard samples were examined and approved by the Japan Diabetes Society (JDS). The procedure for HbA1c calibration used by the JDS has been described elsewhere.[9] The averages for these standard samples were used to compute a linear regression equation using the least squares method, and the actual values were calibrated according to the regression equation. The HbA1c data were converted to equivalent values of the National Glycohemoglobin Standardization Program according to a statement made by the JDS.[10]

Statistical analysis

The mean and standard deviation (SD) of age, body mass index (BMI), plasma glucose values, and HbA1c values were calculated according to the definitions of diabetes in the overall population at the initial survey and the 5-year follow-up. The distributions of HbA1c values were described according to the definitions of diabetes. In addition, participants with self-reported diabetes were further categorized into three groups according to their treatment status (never, previously, and currently receiving treatment), and the distributions of HbA1c values were described.

With regard to the estimation of the prevalence of diabetes, as mentioned above, diabetes was defined as the presence of "self-reported diabetes" or "diabetes solely confirmed by laboratory data." The prevalence of diabetes was calculated at the initial survey and the 5-year follow-up in the overall population and each PHC-administered area. In order to grasp the socioeconomic characteristics of each PHC-administered area, the industrial composition was obtained from the previous JPHC report,[11] which was based on the 1990 population census of Japan. The prevalence was standardized to the 1985 Japanese model population.[12] The age-standardized prevalence was restricted to participants aged 55–74 years, since this was the only age range common to all PHC areas. Regarding sex-specific analysis, the prevalence standardized to a study population of each sex at the initial survey was calculated because no information on the sex-specific age distribution was included in the 1985 Japanese model population.[12] The male and female populations at the initial survey, which were used for the standardization, were graphically confirmed to have similar age distributions. To examine time trends in the prevalence of diabetes, we used a logistic regression model fit by the generalized estimating equation method with covariate adjustment for age and sex, which took into account the participants who were included in the two surveys.[13,14]

All analyses were performed using Stata version 11 for Windows (Stata Corp., College Station, TX, USA). A value of $P < 0.05$ was considered statistically significant in the statistical tests.

RESULTS

Prevalence of diabetes in the JPHC diabetes cohort

The prevalences of self-reported diabetes and diabetes solely confirmed by laboratory data at the initial survey and the 5-year follow-up survey in the cohort are shown in Table 2. Of the 28 183 participants at the initial survey, 1195 participants with diabetes (4.2%) were identified by self-report and 1087 participants with diabetes (3.9%) were confirmed solely by the laboratory measurements performed at the initial survey. Thus, a total of 2282 participants had diabetes, resulting in an overall crude prevalence of 8.1%. Participants with self-reported diabetes were further categorized into three groups according to the diabetes treatment status. Of the 1195 participants with self-reported diabetes, 74.7% (893 participants) were currently receiving diabetes treatment, while the remaining participants were not currently receiving treatment (namely, they had never or had previously received treatment). If diabetes solely confirmed by laboratory data was based on the WHO criteria in 1985, the number of participants with diabetes decreased dramatically.

Table 2. Characteristics of study participants according to the presence of diabetes and diabetes treatment at the initial survey and 5-year follow-up

	Total	Self-reported diabetes				Diabetes confirmed solely by laboratory data[a]	Neither self-reported diabetes nor diabetes solely confirmed by laboratory data	Diabetes confirmed solely by laboratory data (1985 WHO)[b]	Neither self-reported diabetes nor diabetes solely confirmed by laboratory data (1985 WHO)[b]	Diabetes confirmed by 1) abnormal laboratory data and/or 2) currently receiving diabetes treatment[c]	
		Total	Treatment status								
			Never	Previously	Currently					Yes	No
Initial survey											
Number of subjects	28 183	1195	161	141	893	1087	25 901	368	26 620	2141	26 042
Age, years	62.0 (7.0)	63.9 (6.4)	63.4 (7.0)	63.1 (6.9)	64.2 (6.2)	62.8 (6.7)	61.9 (7.0)	62.2 (7.1)	62.0 (7.0)	63.4 (6.5)	61.9 (7.0)
Sex, male (%)	10 268 (36.4)	605 (50.6)	88 (55.0)	80 (56.7)	437 (48.9)	572 (52.6)	9091 (35.1)	221 (60.1)	9442 (35.5)	1105 (51.6)	9163 (35.2)
BMI	23.7 (3.2)	24.3 (3.4)	24.3 (3.4)	23.6 (2.9)	24.4 (3.4)	24.6 (3.5)	23.6 (3.1)	24.2 (3.7)	23.7 (3.2)	24.5 (3.4)	23.6 (3.1)
PG, mg/dL	106.4 (29.3)	163.4 (64.4)	156.9 (64.5)	146.4 (68.3)	167.2 (63.3)	157.2 (58.3)	101.6 (17.9)	213.4 (65.0)	102.4 (18.6)	163.4 (62.2)	101.7 (18.0)
PG (fasting)[d], mg/dL	99.6 (19.4)	148.4 (43.3)	150.8 (50.2)	120.7 (23.4)	151.5 (42.7)	135.5 (28.2)	95.4 (9.5)	165.7 (32.3)	96.4 (10.9)	143.3 (36.8)	95.5 (9.6)
HbA1c, %	5.58 (0.70)	7.27 (1.47)	7.01 (1.56)	6.56 (1.46)	7.43 (1.41)	6.92 (1.20)	5.45 (0.39)	7.28 (1.75)	5.49 (0.46)	7.19 (1.35)	5.45 (0.40)
5-year follow-up											
Number of subjects	20 129	1232	117	97	1018	1029	17 868	n.a.	n.a.	2151	17 978
Age, years	66.5 (6.8)	67.7 (6.5)	67.3 (6.8)	67.9 (7.5)	67.7 (6.4)	67.2 (6.6)	66.3 (6.8)			67.4 (6.5)	66.4 (6.8)
Sex, male (%)	7639 (38.0)	613 (49.8)	56 (47.9)	66 (68.0)	491 (48.2)	506 (49.2)	6520 (36.5)			1055 (49.1)	6584 (36.6)
BMI	23.9 (3.3)	24.7 (3.5)	24.1 (3.1)	24.0 (3.2)	24.8 (3.5)	25.1 (3.9)	23.8 (3.2)			24.9 (3.7)	23.8 (3.2)
PG, mg/dL	111.0 (30.9)	162.1 (57.7)	147.5 (56.3)	147.8 (65.9)	165.1 (56.7)	154.5 (55.2)	104.9 (18.6)			160.6 (57.2)	105.0 (18.7)
PG(fasting)[e], mg/dL	102.9 (22.1)	148.3 (44.3)	131.7 (41.7)	137.2 (49.4)	150.8 (43.7)	138.0 (28.0)	97.2 (9.3)			145.1 (37.9)	97.3 (9.4)
HbA1c, %	5.76 (0.71)	7.22 (1.23)	6.80 (1.09)	6.75 (1.69)	7.31 (1.18)	6.90 (1.04)	5.59 (0.39)			7.13 (1.16)	5.59 (0.39)

BMI, body mass index; HbA1c, hemoglobin A1c; n.a., not applicable; PG, plasma glucose; WHO, World Health Organization.
Values are the mean (SD) or *n* (%).
[a]"Diabetes solely confirmed by laboratory data" was diagnosed if a subject met any of the following criteria: 1) a fasting PG value of 126 mg/dL or more, 2) a casual PG value of 200 mg/dL or more, 3) an HbA1c value of 6.5% or more.
[b]"Diabetes solely confirmed by laboratory data (1985 WHO)" was diagnosed if a subject met either of the following criteria: 1) a fasting PG value of 140 mg/dL or more, or 2) a casual PG value of 200 mg/dL or more.
[c]Subjects who met any of the following criteria: 1) a fasting PG value of 126 mg/dL or more, 2) a casual plasma glucose value of 200 mg/dL or more, 3) an HbA1c value of 6.5% or more, 4) currently receiving diabetes treatment.
[d]A total of 11 832 participants were evaluated under fasting conditions.
[e]A total of 7296 participants were evaluated under fasting conditions.

Only 368 participants (1.3%) had diabetes solely confirmed by laboratory data according to the 1985 criteria. When diabetes was defined by laboratory data and/or current treatment status, the number of diabetic participants was 2141 (7.6%).

At the 5-year follow-up survey, the crude prevalence of diabetes increased. Of the 20 129 participants, 1232 participants with diabetes (6.1%) were identified by self-reporting and 1029 (5.1%) solely by laboratory measurements. The overall crude prevalence of diabetes at the 5-year follow-up was 11.2%. Of the 1232 participants with self-reported diabetes, 82.6% (1018 participants) were currently receiving treatment. The number of participants with diabetes defined by laboratory data and/or current treatment status was 2151 (10.7%).

Distributions of HbA1c values in different diabetic populations

Table 3 shows the distributions of the HbA1c values in different subsets of the diabetic population at the initial survey and the 5-year follow-up survey. At the initial survey, the mean (standard deviation [SD]) HbA1c values in the participants with self-reported diabetes and those with diabetes confirmed solely by laboratory data were 7.27% (SD 1.47%) and 6.92% (SD 1.20%), respectively. Among the participants with self-reported diabetes, the mean HbA1c values in the never treated, previously treated, and currently treated participants were 7.01% (SD 1.56%), 6.56% (SD 1.46%), and 7.43% (SD 1.41%), respectively. Of the participants who had self-reported diabetes but had never received diabetes treatment, 14.9% had an HbA1c $\geq$ 8.4% (HbA1c $\geq$ 8.0% for the JDS value). The corresponding proportion was 7.1% among the participants who had self-reported diabetes and had previously received diabetes treatment.

At the 5-year follow-up, the mean HbA1c values in the participants with self-reported diabetes and diabetes confirmed solely by laboratory data were 7.22% (SD 1.23%) and 6.90% (SD 1.04%), respectively. Among the participants with self-reported diabetes, the mean HbA1c values in the never treated, previously treated, and currently treated groups were 6.80% (SD 1.09%), 6.75% (SD 1.69%), and 7.31% (SD 1.18%), respectively. Regarding the patients with poorly controlled diabetes, 12.8% of the participants with self-reported diabetes who had never received diabetes treatment and 10.3% of those who had previously received treatment had an HbA1c $\geq$ 8.4% (HbA1c $\geq$ 8.0% for the JDS value).

Table 3. Distributions of HbA1c values according to the presence of diabetes and diabetes treatment at the initial survey and 5-year follow-up

	Total	Self-reported diabetes				Diabetes confirmed solely by laboratory data[a]	Neither self-reported diabetes nor diabetes solely confirmed by laboratory data	Diabetes confirmed solely by laboratory data (1985 WHO)[b]	Neither self-reported diabetes nor diabetes solely confirmed by laboratory data (1985 WHO)[b]	Diabetes confirmed by 1) abnormal laboratory data and/or 2) currently receiving diabetes treatment[c]	
		Total	Treatment status								
			Never	Previously	Currently					Yes	No
Initial survey											
Number of subjects	28 183	1195	161	141	893	1087	25 901	368	26 620	2141	26 042
HbA1c, % mean (SD)	5.58 (0.70)	7.27 (1.47)	7.01 (1.56)	6.56 (1.46)	7.43 (1.41)	6.92 (1.20)	5.45 (0.39)	7.28 (1.75)	5.49 (0.46)	7.19 (1.35)	5.45 (0.40)
HbA1c, %	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
≥5.6	10 972 38.9	1095 91.6	141 87.6	108 76.6	846 94.7	989 91.0	8888 34.3	313 85.1	9564 35.9	1995 93.2	8977 34.5
≥6.0	3917 13.9	970 81.2	119 73.9	82 58.2	769 86.1	898 82.6	2049 7.9	271 73.6	2676 10.1	1824 85.2	2093 8.0
≥6.5	1564 5.5	791 66.2	90 55.9	54 38.3	647 72.5	773 71.1	0 0.0	224 60.9	549 2.1	1564 73.0	0 0.0
≥8.4	322 1.1	225 18.8	24 14.9	10 7.1	191 21.4	97 8.9	0 0.0	77 20.9	20 0.1	322 15.0	0 0.0
≥10.5	71 0.3	46 3.8	8 5.0	5 3.5	33 3.7	25 2.3	0 0.0	24 6.5	1 0.0	71 3.3	0 0.0
5-year follow-up											
Number of subjects	20 129	1232	117	97	1018	1029	17 868	n.a.	n.a.	2151	17 978
HbA1c, % mean (SD)	5.76 (0.71)	7.22 (1.23)	6.80 (1.09)	6.75 (1.69)	7.31 (1.18)	6.90 (1.04)	5.59 (0.39)			7.13 (1.16)	5.59 (0.39)
HbA1c, %	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)			*n* (%)	*n* (%)
≥5.6	10 975 54.5	1182 95.9	105 89.7	85 87.6	992 97.4	979 95.1	8814 49.3			2073 96.4	8902 49.5
≥6.0	4432 22.0	1085 88.1	92 78.6	65 67.0	928 91.2	896 87.1	2451 13.7			1926 89.5	2506 13.9
≥6.5	1652 8.2	856 69.5	62 53.0	36 37.1	758 74.5	796 77.4	0 0.0			1652 76.8	0 0.0
≥8.4	250 1.2	182 14.8	15 12.8	10 10.3	157 15.4	68 6.6	0 0.0			250 11.6	0 0.0
≥10.5	48 0.2	30 2.4	1 0.9	4 4.1	25 2.5	18 1.7	0 0.0			48 2.2	0 0.0

HbA1c, hemoglobin A1c; n.a., not applicable; WHO, World Health Organization.

[a]"Diabetes solely confirmed by laboratory data" was diagnosed if a subject met any of the following criteria: 1) a fasting PG value of 126 mg/dL or more, 2) a casual PG value of 200 mg/dL or more, 3) an HbA1c value of 6.5% or more.

[b]"Diabetes solely confirmed by laboratory data (1985 WHO)" was diagnosed if a subject met either of the following criteria: 1) a fasting PG value of 140 mg/dL or more, or 2) a casual PG value of 200 mg/dL or more.

[c]Subjects who met any of the following criteria: 1) a fasting PG value of 126 mg/dL or more, 2) a casual plasma glucose value of 200 mg/dL or more, 3) an HbA1c value of 6.5% or more, 4) currently receiving diabetes treatment.

Prevalence of diabetes according to area

The prevalence of diabetes in each PHC-administered area across Japan is given in Table 4. In the overall population, the age-standardized prevalence, which was restricted to participants aged 55–74 years, was 8.2% at the initial survey and 10.6% at the 5-year follow-up. The difference in the prevalence of diabetes between the two surveys was statistically significant after adjustment for age and sex ($P < 0.001$). In the sex-specific analysis, the age-standardized prevalence of diabetes in men was 11.3% at the initial survey and 14.1% at the 5-year follow-up, and the age-standardized prevalence of diabetes in women was 6.5% at the initial survey and 8.6% at the 5-year follow-up. The differences in the prevalence between the two surveys were also significant in both sexes after adjustment for age ($P < 0.001$ for men; $P < 0.001$ for women).

As for the area-specific prevalence of diabetes, the prevalence varied widely across PHC-administered areas, ranging from 5.6% to 9.2% at the initial survey and from 5.0% to 13.5% at the 5-year follow-up. Generally, higher values were observed in the prevalence of diabetes at the 5-year follow-up survey than at the initial survey in most areas.

DISCUSSION

The present study estimated the prevalence of diabetes in the JPHC cohort in the late 1990s and early 2000s. The large population-based sample and strict standardization of HbA1c enabled us to estimate the prevalence of diabetes with accuracy. The main finding is that the age-standardized prevalence of diabetes in 55- to 74-year-old adults was 8.2% at the initial survey and 10.6% at the 5-year follow-up, suggesting that the prevalence increased during that period. As for area variations, the present study reported a two-fold difference in the prevalence of diabetes among some regions. A similar degree of area variations has been reported in a previous study, which showed that a relatively urban area had an approximately two-fold higher prevalence of diabetes than a rural area.[15] When looking at the industrial composition of each PHC-administered area (Table 4), wide variations were observed, which could reflect differences in local lifestyles. While it appears that two-fold area variations were observed across areas with different lifestyles in Japan, there is too little information to assess the link between urbanization and the prevalence of diabetes in the present study. Of course, there is a possibility that sampling errors could have affected the results.

Regarding the sex-specific analysis (Table 4), our data suggests that the prevalence was higher and area variations wider in men than in women. Further understanding of the differences between sexes is important for the development of targeted health promotion programs to prevent diabetes.

When the prevalence of diabetes was compared with the estimates from one review[1] that investigated the prevalence

Table 4. Prevalence of diabetes[a] in PHC-administered areas across Japan

PHC-administered areas	A		B		C		D		E		F		G		H		I		J		Overall	
Industrial composition of the area Primary: Secondary:Tertiary (%)	25.9:32.3:41.8		19.4:29.8:50.8		26.9:37.1:36.0		11.5:30.2:58.3		0.3:40.3:59.4		10.5:41.6:47.9		25.9:44.9:29.2		26.5:25.8:47.6		37.0:19.9:43.1		28.4:24.3:47.3			
	Initial	5-year	Initial	5-year	Initial	5-year	Initial	5-year	Initial	5-year	Initial	5-year	Initial	5-year	Initial	5-year	Initial	5-year	Initial	5-year	Initial	5-year
Total																						
Number of subjects	3160	2345	4579	2511	4464	2571	1488	1887	734	—	5343	4677	1226	889	2018	1359	1734	385	3437	3505	28 183	20 129
Crude prevalence	8.2	11.1	7.8	9.4	8.8	9.2	9.1	12.8	6.7		8.3	13.8	5.5	10.8	8.0	9.8	6.3	5.7	9.0	11.0	8.1	11.2
Age-standardized prevalence[b] (%)	8.2	10.3	8.1	8.5	8.7	8.2	9.2	11.8	n.a.	n.a.	8.8	13.5	5.6	11.2	8.7	8.6	6.7	5.0	8.5	11.2	8.2	10.6
Males																						
Number of subjects	1055	896	1586	919	1872	909	542	735	280	—	1876	1767	493	355	705	477	463	124	1396	1457	10 268	7639
Crude prevalence	13.0	14.6	10.5	11.5	12.5	11.2	10.3	16.6	12.5		11.7	18.3	7.1	13.2	12.2	14.0	9.5	11.3	11.7	14.2	11.5	14.6
Age-standardized prevalence[b] (%)	13.3	13.4	10.9	11.4	12.2	9.8	9.7	15.7	n.a.	n.a.	12.4	18.7	7.9	14.4	13.1	12.2	8.7	7.0	10.6	14.8	11.3	14.1
Age-standardized prevalence[c] (%)	13.8	14.6	11.5	11.2	13.0	10.1	10.3	16.5	n.a.	n.a.	12.4	18.7	6.7	15.1	13.7	12.6	9.0	8.4	11.7	14.4	11.7	14.4
Females																						
Number of subjects	2105	1449	2993	1592	2592	1662	946	1152	454	—	3467	2910	733	534	1313	882	1271	261	2041	2048	17 915	12 490
Crude prevalence	5.8	9.0	6.3	8.2	6.1	8.1	8.5	10.4	3.1		6.4	11.1	4.4	9.2	5.8	7.5	5.1	3.1	7.2	8.7	6.2	9.1
Age-standardized prevalence[b] (%)	5.6	8.5	6.5	7.2	6.3	7.3	8.7	9.5	n.a.	n.a.	7.0	10.8	4.4	9.2	6.4	6.7	5.7	4.1	7.0	9.0	6.5	8.6
Age-standardized prevalence[d] (%)	6.0	8.6	6.9	7.4	6.6	7.0	8.7	9.9	n.a.	n.a.	7.2	11.0	4.5	9.0	6.4	7.2	5.6	3.3	7.7	9.1	6.8	8.8

FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; n.a., not applicable; PHC, public health center.
Age-standardized prevalence was restricted to participants aged 55–74 years because this is the only age range that is common to all areas.
[a]Diabetes was defined by any of the following criteria: 1) an FPG value of 126 mg/dL or more, 2) a casual plasma glucose value of 200 mg/dL or more, 3) an HbA1c value of 6.5% or more, 4) self-reported diabetes.
[b]Standardized to the 1985 Japanese model population.
[c]Standardized to the overall male population at the initial survey.
[d]Standardized to the overall female population at the initial survey.