Indicators of the need for insulin treatment and the effect of treatment for gestational diabetes on pregnancy outcomes in Japan

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Abstract. This study assessed indicators of the need for insulin therapy and the effect of treatment on pregnancy outcomes in Japanese patients with gestational diabetes mellitus (GDM). All patients diagnosed with GDM were hospitalized for three days. Plasma glucose profiles in patients under strict dietary management and the characteristics of GDM patients with high daily glucose levels were investigated. Patients who failed to achieve glycemic targets were treated with insulin. Indicators of the need for insulin treatment were investigated. Pregnancy outcomes in patients prescribed dietary management and patients prescribed insulin treatment were compared. The study included 112 patients with GDM. GDM patients with high daily glucose levels in the hospital exhibited significantly higher 1-h and 2-h plasma glucose levels in oral glucose tolerance tests (OGTTs) at diagnosis. In our hospital, 102 GDM patients with singleton pregnancies were followed until delivery; 32 (31.3%) were treated with insulin. Univariate analysis identified significant associations of insulin requirement with family history of diabetes and with 1-h and 2-h OGTT values at diagnosis. Multivariate analysis showed that the 1-h OGTT plasma glucose level at diagnosis was an independent predictor of the need for insulin. In perinatal outcomes, insulin treatment was associated with low birth weight.

Key words: Gestational diabetes mellitus, Insulin therapy, Oral glucose tolerance test, Pregnancy outcome

Gestational Diabetes Mellitus (GDM) is defined as glucose intolerance identified during pregnancy. The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recently proposed new criteria for the diagnosis of GDM [1]. In Japan, the IADPSG criteria were adopted in 2010 [2]. Application of new GDM criteria indicated a GDM prevalence of 12% in Japanese pregnant women [3]. GDM is associated with numerous maternal and perinatal complications, such as gestational hypertension, stillbirth, cesarean delivery, macrosomia, shoulder dystocia, and increased neonatal intensive care unit admission [4, 5]. Studies have demonstrated that optimal glycemic control improves pregnancy outcomes [6, 7]. The management of women with gestational diabetes poses several problems. The decision of whether consultation with a diabetes mellitus specialist is required depends on the judgment of the gynecologist. Because it is difficult to control food intake in outpatients, glucose profiles cannot be accurately assessed. Furthermore, the timing of the start of insulin therapy varies among doctors.

This study was designed to address these particular problems. All patients diagnosed with GDM by a gynecologist were referred to a diabetologist. The daily glucose profile was examined under strict dietary management during hospitalization. Furthermore, the characteristics of GDM patients with high glucose profiles (an indicator of a need for insulin treatment) were investigated. In addition, factors associated with insu-
lin treatment were investigated. Perinatal outcomes were compared in patients who received dietary management alone as treatment and in those who received insulin treatment.

**Patients and Methods**

We conducted a retrospective study at Yokosuka Kyosai Hospital from June 2011 to August 2013. Yokosuka Kyosai Hospital is a local core hospital in Yokosuka city, Kanagawa prefecture, Japan, and there are almost 500~600 deliveries per year. This study was conducted with the approval of the institutional review boards of Yokosuka Kyosai Hospital. The following were exclusion criteria: overt diabetes, past history of diabetes mellitus, and fasting plasma glucose levels of ≥ 126 mg/dL. Women were screened universally to exclude overt diabetes at first prenatal visit.

In this study, a two-step screening strategy with GCT between 24-28 weeks of pregnancy was used in accordance with the clinical recommendations of Japan Society of Obstetrics and Gynecology (JSOG) [2]. The universal initial screening for GDM assessed whether the pregnant women had the following clinical risk factors: (1) pre-gravid overweight (body mass index (BMI) ≥ 30); (2) past history of GDM; (3) past history of macrosomia (birth weight ≥ 4,000 g); (4) family history of type 2 diabetes in first-degree relatives; and (5) random plasma glucose ≥ 95 mg/dL [8]. Women with one or more risk factors underwent a diagnostic 75-g oral glucose tolerance test (OGTT) to measure plasma glucose (mg/dL) in the fasting state and at 1-h and 2-h after the glucose load. Women with no risk factors or with a normal OGTT pattern underwent a 1-h 50-g oral glucose challenge test (GCT) between 24 and 28 weeks of gestation. If the GCT result exceeded 140 mg/dL, a diagnostic 75-g OGTT was then performed between 24 and 28 weeks of gestation. The IADPSG criteria were applied (fasting, 92 mg/dL; 1-h, 180 mg/dL; 2-h, 153 mg/dL [1]). GDM was diagnosed if at least one of the glucose values was abnormal. GDM patients underwent a 75-g OGTT again 12 weeks after delivery.

Overt diabetes in pregnancy was diagnosed if any of the following four criteria were fulfilled: (1) fasting plasma glucose ≥ 126 mg/dL; (2) HbA1c ≥ 6.5%; (3) definite diabetic retinopathy; and (4) random plasma glucose ≥ 200 mg/dL or 2-h plasma glucose levels in the OGTT of >200 mg/dL with either (1), (2), or (3) [2]. Insulin treatment was considered when patients have a fasting glucose level of ≥ 100 mg/dL or a 2-h postprandial glucose level of ≥ 120 mg/dL, according to the recommendations of Japan Diabetes Society [9]. First, we investigated the characteristics of GDM in patients with a high daily glucose level, which is an indicator of a need for insulin treatment. To evaluate glucose profile or educate GDM patients about dietary management, all pregnant women who met the GDM criteria were routinely hospitalized for three days, and daily plasma glucose levels were investigated under strict hospital dietary management. The plasma glucose level was determined in the laboratory using the glucose oxidase method at six time points: fasting, 2-h post-breakfast, before lunch, 2-h post-lunch, before dinner, and 2-h post-dinner. The daily calorie count was calculated from the ideal body weight. GDM patients received 30 kcal/kg + 150 kcal in the early gestational stage and 30 kcal/kg + 350 kcal in the late gestational stage, according to the recommendations of Japan Diabetes Society and previous report [8]. Patients with GDM consumed calories three times a day in the hospital. After discharge, all patients with GDM were prescribed strict dietary management, which included three meals and three snacks. The women with GDM were divided into two groups (Non-targeted group and Targeted group) according to the glucose level during hospitalization. Women in Non-targeted group had normal glucose levels (fasting level of < 100 mg/dL and 2-h postprandial glucose level of < 120 mg/dL), whereas those in Targeted group had high glucose levels (fasting level of ≥ 100 mg/dL or 2-h postprandial glucose level of ≥ 120 mg/dL). The clinical characteristics of each group, such as age, gestational age at the time of diagnosis of GDM, BMI at diagnosis, family history, prior fetal macrosomia, OGTT at diagnosis, glycoalbumin, and OGTT after delivery, were compared.

Insulin treatment was started based on self-monitored blood glucose (SMBG) at home or the plasma glucose level which was measured at a follow-up visit every two weeks. SMBG were obtained four times a day: fasting blood glucose and 2-h postprandial blood glucose. The target glucose levels were < 100 mg/dL at fasting and < 120 mg/dL at the 2-h postprandial time point. Women who failed to maintain the target glucose levels were treated with insulin. Human regular insulin, or rapid-acting insulin (insulin aspart, or lispro), and NPH insulin were used to achieve the glycemic target. None of GDM patients were treated with oral agents.

The need for insulin therapy and the pregnancy out-
comes were investigated in GDM with singleton pregnancies who were followed until delivery. The patients with GDM were divided into two groups: those treated with dietary management only (diet group) and those who received insulin treatment (insulin group). Clinical characteristics such as age, gestational age at the time of GDM diagnosis, BMI at the time of diagnosis, family history, prior fetal macrosomia, OGTT at diagnosis, glycoalbumin, and OGTT after delivery, were compared. Outcomes such as cesarean section, gestational age at delivery, birth weight, large for gestational age (LGA), small for gestational age (SGA), Apgar score (1min, 5min) and macrosomia were also compared in the two groups. Birth weight (percentile) was calculated using the Japanese standard sex- and parity-specific birth weight percentile curves. Birth weight in the 90th percentile or above was defined as LGA, and birth weight below the 10th percentile was defined as SGA. Macrosomia was defined as a birth weight of ≥ 4,000 g.

Statistical analysis was performed using JMP (SAS Institute, Cary, NC, USA). Variable distributions were checked for each continuous variable. Student’s t test was applied for normally distributed data and Kruskal Wallis test was used for not normally distributed data. Categorical variables were compared by Pearson’s χ² test. Multivariate logistic regression analysis was used to assess the effects of various factors on the requirement for insulin. Logistic regression was used to determine the odds ratios (OR) and 95% confidence intervals (CI) of perinatal outcomes. Maternal age and BMI were considered as potential confounders, as well as type of conception in general analysis. The ORs was adjusted for maternal age and BMI at diagnosis. The cold-deck method was used to impute missing values. A value of p < 0.05 was considered statistically significant.

**Results**

This study included 112 cases that met the GDM criteria from June 2011 to August 2013. Basal characteristics and glucose levels are shown in Table 1. At diagnosis, the 1-h and 2-h OGTT plasma glucose values in Targeted group were significantly higher than those in Non-targeted group (Table 1). There were no significant differences in age, gestational age at diagnosis, BMI, family history, prior fetal macrosomia, OGTT fasting plasma glucose, daily calorie consumption in hospital, or glycoalbumin. Seventy (62.5%) GDM women were tested for glucose tolerance test at 12 weeks postpartum. Of the 70 women with test results,

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**Table 1** Basal characteristics of GDM in Non-targeted and Targeted group of plasma glucose

|                          | Non-targeted group* (n=35) | Targeted group** (n=77) | p      |
|--------------------------|-----------------------------|-------------------------|--------|
| Age of patient (year)    | 34.4 ± 5.6                  | 33.9 ± 5.4              | 0.610  |
| Gestational age at diagnosis (wk) | 19.5 ± 7.0                  | 20.6 ± 8.0              | 0.498  |
| BMI at diagnosis (kg/m²) | 23.9 ± 3.5                  | 23.6 ± 4.0              | 0.631  |
| Family history of diabetes (n) | 7 (20.0 %)                  | 25 (32.4 %)             | 0.179  |
| Prior fetal macrosomia (n) | 0 (0 %)                     | 1 (1.3 %)               | 0.502  |
| 75-g OGTT at diagnosis   |                             |                         |        |
| Fasting plasma glucose (mg/dL) | 90.5 ± 9.1                  | 90.4 ± 8.1              | 0.961  |
| 1-h plasma glucose (mg/dL) | 145.0 ± 32.9                | 168.0 ± 34.7            | 0.001  |
| 2-h plasma glucose (mg/dL) | 127.7 ± 31.1                | 143.9 ± 27.6            | 0.007  |
| Glycoalbumin (%)         | 12.9 ± 1.1                  | 13.2 ± 1.0              | 0.236  |
| Daily calorie at diagnosis (Kcal) | 1769 ± 130                  | 1769 ± 132              | 0.992  |
| Plasma glucose profile (mg/dL) |                    |                         |        |
| Before breakfast          | 82.2 ± 4.6                  | 85.4 ± 7.2              | 0.010  |
| 2-h after breakfast       | 101.1 ± 12.0                | 112.1 ± 17.6            | 0.002  |
| Before lunch              | 83.2 ± 7.0                  | 87.4 ± 13.4             | 0.134  |
| 2-h after lunch           | 102.4 ± 8.5                 | 122.4 ± 21.1            | <0.001 |
| Before dinner             | 85.4 ± 6.6                  | 85.3 ± 14.7             | 0.790  |
| 2-h after dinner          | 103.0 ± 10.1                | 122.1 ± 18.9            | <0.001 |
| 75-g OGTT after delivery (n=70) | (n=17)                    | (n=53)                  |        |
| Fasting plasma glucose (mg/dL) | 90.2 ± 8.4                  | 91.8 ± 8.6              | 0.513  |
| 1-h plasma glucose (mg/dL) | 133.4 ± 34.9                | 156.6 ± 44.9            | 0.056  |
| 2-h plasma glucose (mg/dL) | 108.7 ± 17.6                | 126.0 ± 35.9            | 0.076  |

Data are means ± standard deviation or percentage as indicated. GDM, gestational diabetes mellitus; BMI, body mass index; OGTT, oral glucose tolerance test. * Non-targeted group included GDM with normal glucose levels during hospitalization (fasting level of < 100 mg/dL and 2-h postprandial glucose level of < 120 mg/dL). ** Targeted group included GDM with high glucose levels during hospitalization (fasting level of ≥ 100 mg/dL or 2-h postprandial glucose level of ≥ 120 mg/dL).
Ito et al. cited a statistically significant difference with respect to the presence of a positive family history of diabetes. Patients who required insulin had higher glucose levels in the OGTT at 1-h, OGTT at 2-h, after breakfast, after lunch, and after dinner when compared with those who did not. After delivery, the 75-g OGTT was examined in 66 cases (diet group, n = 39; insulin group, n = 27). The 1-h OGTT glucose values in the insulin group tended to be higher than those in the diet group (p = 0.064). Multivariate analysis showed that the 1-h OGTT plasma glucose level at diagnosis was an independent predictor of the need for insulin treatment in GDM (Table 3).

The pregnancy outcomes are shown in Table 4. Although birth weight (g) and gestational age at delivery were significantly lower in the insulin group than in the diet group. There were no significant differences in cesarean section, LGA, SGA, Apgar score, or macrosomia.

### Table 2 Characteristics of GDM with and without insulin treatment

| Parameter                          | Diet (n=70) | Insulin (n=32) | p   |
|------------------------------------|-------------|----------------|-----|
| Age of patient (year)              | 34.4 ± 5.6  | 33.3 ± 5.6     | 0.383|
| Gestational age at diagnosis (wk)  | 20.8 ± 7.5  | 18.6 ± 8.4     | 0.190|
| Gestational age to start insulin (wk) | -           | 23.1 ± 8.3     | -   |
| BMI at diagnosis (kg/m²)           | 23.3 ± 3.6  | 24.6 ± 4.3     | 0.104|
| Family history of diabetes (n)     | 16 (22.9 %) | 15 (46.9 %)    | 0.016|
| Prior fetal Macrosomia (n)         | 0 (0 %)     | 1 (3.1 %)      | 0.126|
| 75-g OGTT at diagnosis             |             |                |     |
| Fasting plasma glucose (mg/dL)     | 89.6 ± 8.7  | 91.5 ± 7.9     | 0.313|
| 1-h plasma glucose (mg/dL)         | 155.3 ± 33.6| 179.9 ± 34.9   | 0.001|
| 2-h plasma glucose (mg/dL)         | 135.3 ± 29.7| 150.5 ± 28.5   | 0.017|
| Glycoalbumin (%)                   | 13.1 ± 1.1  | 13.2 ± 1.2     | 0.892|
| Daily calorie at diagnosis (Kcal)  | 1780 ± 123  | 1746 ± 143     | 0.235|
| Plasma glucose profile (mg/dL)     |             |                |     |
| Before breakfast                   | 83.3 ± 5.7  | 86.5 ± 8.6     | 0.164|
| 2-h after breakfast                | 104.6 ± 13.5| 117.9 ± 19.0   | <0.001|
| Before lunch                       | 84.1 ± 8.9  | 87.5 ± 11.9    | 0.293|
| 2-h after lunch                    | 112.4 ± 19.4| 125.9 ± 21.0   | 0.002|
| Before dinner                      | 84.9 ± 9.7  | 87.7 ± 10.6    | 0.184|
| 2-h after dinner                   | 110.4 ± 16.4| 129.8 ± 19.4   | <0.001|
| 75-g OGTT after delivery (n=66)    |             |                |     |
| Fasting plasma glucose (mg/dL)     | 90.8 ± 7.7  | 93.2 ± 9.4     | 0.251|
| 1-h plasma glucose (mg/dL)         | 142.9 ± 40.7| 162.2 ± 41.2   | 0.064|
| 2-h plasma glucose (mg/dL)         | 118.0 ± 29.0| 124.2 ± 31.4   | 0.410|

Data are means ± standard deviation or percentage as indicated. GDM, gestational diabetes mellitus; BMI, body mass index; OGTT, oral glucose tolerance test.

### Table 3 Regression analysis of predictors for the need of insulin therapy

| Parameters                          | Odd ratio | 95% CI         | p   |
|-------------------------------------|-----------|----------------|-----|
| Age of patient                      | 0.965     | 0.883-1.055    | 0.432|
| Gestational age at diagnosis        | 0.958     | 0.891-1.025    | 0.216|
| BMI at diagnosis                    | 1.115     | 0.971-1.288    | 0.122|
| Family history of diabetes          | 1.823     | 0.609-5.387    | 0.279|
| 75-g OGTT at diagnosis              |           |                |     |
| Fasting plasma glucose              | 2.542     | 0.672-11.327   | 0.175|
| 1-h plasma glucose                  | 1.477     | 1.059-2.142    | 0.021|
| 2-h plasma glucose                  | 1.265     | 0.838-1.920    | 0.261|
| Glycoalbumin                        | 1.402     | 0.865-2.343    | 0.172|

95% CI, 95% confidence interval; BMI, body mass index

12.9 % (n = 9) had impaired glucose tolerance (IGT) and 4.2% (n = 3) had provisional diabetes.

In this study, 102 GDM patients with singleton pregnancies were followed until delivery in our hospital (4 of 112 cases were followed at hospitals in the patients’ hometowns; 6 cases were multifetal pregnancies). Seventy (68.6%) patients received diet therapy alone, and 32 (31.3%) patients were treated with insulin. The clinical characteristics in the diet group and insulin group are shown in Table 2. There were no significant differences in age, gestational age at diagnosis, BMI, prior fetal macrosomia, glycoalbumin, and plasma glucose (fasting level in the diagnostic OGTT and before breakfast, lunch and dinner levels in the daily profile). The insulin group exhibited a statistically significant difference with respect to the presence of a positive family history of diabetes. Patients who required insulin had higher glucose levels in the OGTT at 1-h, OGTT at 2-h, after breakfast, after lunch, and after dinner when compared with those who did not. After delivery, the 75-g OGTT was examined in 66 cases (diet group, n = 39; insulin group, n = 27). The 1-h OGTT glucose values in the insulin group tended to be higher than those in the diet group (p = 0.064). Multivariate analysis showed that the 1-h OGTT plasma glucose level at diagnosis was an independent predictor of the need for insulin treatment in GDM (Table 3).

The pregnancy outcomes are shown in Table 4. Although birth weight (g) and gestational age at delivery were significantly lower in the insulin group than in the diet group. There were no significant differences in cesarean section, LGA, SGA, Apgar score, or macrosomia.

### Discussion

The clinical management of women with gestational diabetes poses many problems. First, the decision of whether consultation with a diabetologist is required depends on the judgment of a gynecologist. Second, because it is difficult to control food intake in outpatients, glucose profiles cannot be assessed precisely.
Bakiner [10] and Pertot [11] have described the limitations in maintaining dietary compliance. Third, the timing of the start of insulin therapy varies among doctors. We observed a clear relationship between the 75-g OGTT and the daily glucose level in GDM patients. Several studies have described risk factors that indicate a need for insulin therapy for glycemic control in patients with GDM [10-17]. Fasting hyperglycemia measured with a diagnostic OGTT has been identified as an independent predictor of the need for insulin therapy [10-12, 14-16]. In contrast, our results indicated that the fasting glucose value in the diagnostic OGTT was not a suitable predictor of a high daily glucose level and need for insulin therapy. Fasting glucose levels of insulin treatment group in other reports were higher than those in our report (Bakiner group [10]: 97.3 ± 12.1 mg/dL, Gonzalez-Quintero group [12]: 104.1 ± 27.2 mg/dL, Akinci group [15]: 99.53 ± 21.4 mg/dL, Our group: 91.5 ± 7.9 mg/dL, Pertot group [11], Juutinen group [14], McFarland MB group [16]: data not available), and 1-h and 2-h OGTT values in other reports were also higher than those in our report. Glucose tolerance in our GDM patients was milder than that in other reports. Hanna F.W. and Peters J.R. have reported that the worsening insulin resistance with pregnancy is initially compensated for by augmentation of insulin production, resulting in normal fasting state. Therefore, as in Type 2 diabetes, the initial abnormality is only postprandial [18]. Because our study included mild glucose tolerance patients, it was possible that fasting glucose in insulin treatment group was similar to that in diet group. Moreover, it has been reported that fasting glucose has diverse results in different populations [19, 20]. In our Japanese study, fasting glucose is not thought to be useful in predicting the need for insulin treatment.

In this study, the 1-h OGTT value, not the fasting value, was predictive of the need for insulin. The association was confirmed with regression analysis. Moreover, a high 1-h OGTT value was associated with a high daily glucose level (fasting, ≥ 100 mg/dL or 2-h postprandial glucose, ≥ 120 mg/dL) during hospitalization. The 1-h OGTT after delivery also tended to be higher in the insulin treatment group than in the diet management group. These results indicated that the diagnostic 1-h 75-g OGTT value was important in predicting the need for insulin treatment. Other studies have also demonstrated that the 1-h OGTT value is associated with the need for insulin treatment [11, 15-17].

Pregnant women with hyperglycemia in the 1-h OGTT have greater impairment in measures of ß-cell function [21-23]. Hyperglycemia in the 1-h OGTT is associated with severe impairment of insulin secretion and sensitivity. Consequently, insulin might be required for the strict control of postprandial hyperglycemia to improve pregnancy outcomes. Control of early postprandial hyperglycemia in GDM is associated with better neonatal outcomes [24].

In this study, the birth weight (g) in the insulin group was lower than that in the diet group. This is explained by the earlier gestational age at birth. However, this difference did not depend on the glucose level. The latest glycoalbumin level determined before delivery was similar between the diet group (12.8 ± 1.0 %) and insulin group (12.9 ± 1.1 %). Crowther et al. reported similar results [6] and associated them with the increased use of induced labor in the intervention group. Although the use of induced labor might also have affected our

| Indicators for insulin requirement | Diet (n=70) | Insulin (n=32) | Unadjusted odd ratio (95% CI) | Unadjusted p value | Adjusted odd ratio (95% CI) | Adjusted p value |
|-----------------------------------|------------|---------------|-----------------------------|-------------------|-----------------------------|------------------|
| Cesarean section (n)              | 19 (27.1%) | 11 (34.4%)    | 1.41 (0.56-3.44)            | 0.460             | 1.24 (0.47-3.16)            | 0.656            |
| Gestational age at delivery (wk)  | 39.0 ± 1.3 | 38.1 ± 1.8    | 0.65 (0.45-0.88)            | 0.004             | 0.63 (0.43-0.86)            | 0.003            |
| Birth weight (g)                  | 3009 ± 433 | 2736 ± 531    | 0.9986 (0.9974-0.9996)      | 0.006             | 0.9986 (0.9975-0.9997)      | 0.012            |
| Birth weight (percentile)         | 51.2 ± 30.4| 43.6 ± 30.3   | 0.992 (0.978-1.006)         | 0.241             | 0.992 (0.978-1.007)         | 0.338            |
| LGA (n)                           | 9 (12.8%)  | 1 (3.1%)      | 0.22 (0.01-1.24)            | 0.093             | 0.22 (0.01-1.26)            | 0.096            |
| SGA (n)                           | 7 (10.0%)  | 6 (18.8%)     | 2.08 (0.62-6.84)            | 0.232             | 2.04 (0.59-6.86)            | 0.250            |
| Apgar score 1 min                 | 8.1 ± 0.9  | 7.6 ± 1.6     | 0.80 (0.54-1.12)            | 0.183             | 0.76 (0.52-1.08)            | 0.127            |
| Apgar score 5 min                 | 8.8 ± 0.6  | 8.6 ± 0.9     | 0.67 (0.36-1.18)            | 0.165             | 0.58 (0.30-1.05)            | 0.074            |
| Macrosomia (n)                    | 1 (1.4%)   | 0 (0%)        | 1.384 (0.31-4.43)           | 0.384             | -                           | 0.435            |

Data are means ± standard deviation or percentage as indicated. GDM, gestational diabetes mellitus; LGA, large for gestational age; SGA, small for gestational age; CI, confidence interval. * Diet group was the reference group. Values were adjusted for maternal age and BMI at diagnosis.
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In conclusion, this study demonstrates that the 1-h OGTT value predicts the need for insulin treatment in Japanese, rather than fasting glucose those reported in Caucasian. Difference in the birth weight was significant between patients who received dietary management alone and those who received insulin treatment, and insulin treatment was associated with low birth weight.

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Conflicts of Interest

Terauchi Y has received honoraria for lectures from MSD K.K.; Ono Pharmaceutical Co., Ltd.; Nippon Boehringer Ingelheim Co., Ltd.; Novartis Pharma K.K.; Takeda Pharmaceutical Co., Ltd.; Mitsubishi Tanabe Pharma Corp.; Daiichi Sankyo Co., Ltd.; Sanwa Kagaku Kenkyusho Co., Ltd.; Kowa Pharmaceutical Co., Ltd.; Novo Nordisk Pharma Ltd.; Eli Lilly Japan K.K.; Sanofi K.K.; Shionogi & Co., Ltd.; Bayer Yakuhin, Ltd.; and AstraZeneca K.K. and has obtained research support from MSD K.K.; Ono Pharmaceutical Co., Ltd.; Nippon Boehringer Ingelheim Co., Ltd.; Novartis Pharma K.K.; Takeda Pharmaceutical Co., Ltd.; Mitsubishi Tanabe Pharma Corp.; Daiichi Sankyo Co., Ltd.; Novo Nordisk Pharma Ltd.; Eli Lilly Japan K.K.; Sanofi K.K.; Dainippon Sumitomo Pharma Co., Ltd.; Shionogi & Co., Ltd.; Bayer Yakuhin, Ltd.; Astellas Pharma, Inc.; Pfizer Japan, Inc.; and AstraZeneca K.K.

Ito Y, Shibuya M, Hosokawa S, Motoki Y, Nagata R, Konishi H, Miyazaki T, Matsunaga T, Nomura Y, Mihara T, Ito S, Sugiyura K declare that there is no conflict of interest regarding to this work.

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