Sustained Decrease of Early-Phase Insulin Secretion in Japanese Women with Gestational Diabetes Mellitus Who Developed Impaired Glucose Tolerance and Impaired Fasting Glucose Postpartum

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ABSTRACT

OBJECTIVE: The aim of this study was to compare glucose intolerance in the antenatal and the postpartum periods using a 75-g oral glucose tolerance test (OGTT) in the Japanese women with gestational diabetes mellitus (GDM) using a retrospective design.

PATIENTS AND METHODS: Data were obtained from 85 Japanese women with GDM who delivered from April 2011 through April 2015 and who underwent an OGTT 6–14 weeks postpartum. The women were divided into two groups based on the results of the postpartum OGTT: one group with normal glucose tolerance (NGT) and the other with impaired glucose tolerance (IGT) as well as impaired fasting glucose (IFG). We analyzed the associations between postpartum IGT–IFG and various factors.

RESULTS: Antenatally, a significant difference was observed between the groups only in the 1-hour plasma glucose level of the 75-g OGTT. Postpartum results of plasma glucose level were significantly higher at 0.5, 1, and 2 hours in the IGT–IFG group than those in the NGT group. Moreover, a significant decrease in the levels of 0.5-hour immunoreactive insulin and insulinogenic index was observed in the IGT–IFG group compared to those in the NGT group. Homeostasis model assessment-insulin resistance and homeostasis model assessment β-cell function of both groups were found to significantly decrease in the postpartum period; however, there was no significant change in the insulinogenic index of either group.

CONCLUSIONS: Our study clearly showed that the postpartum IGT and IFG levels of Japanese women with GDM are affected by impaired early-phase insulin secretion; however, insulin resistance promptly improves.

KEYWORDS: gestational diabetes mellitus, insulinogenic index, homeostasis model assessment-insulin resistance

Introduction

Diabetes mellitus (DM) is attracting increasing concern because of its high prevalence in the developed countries1 and the pathologic consequences of diseases of the small arteries and the peripheral nervous system, which leads to retinopathy, nephropathy, and peripheral neuropathy, as well as metabolic abnormalities that lead to hyperlipidemia and hypertension. Lifestyle changes add to the increased risk of developing not only DM but also gestational diabetes mellitus (GDM).2,3 Bellamy et al recently reported that habitual and behavioral effects prevent or delay the development of GDM to type 2 DM.4

In regard to the Japanese population, not only insulin resistance but also insulin secretion is thought to play an important role in the underlying mechanism of DM.5–7 GDM is also reported to be related to impaired insulin secretion.8 The aim of this study was to compare glucose intolerance in the antenatal and the postpartum periods using oral glucose tolerance test (OGTT) in the Japanese women with GDM using a retrospective design.

Patients and Methods

We conducted a retrospective study of 85 Japanese women with GDM who delivered a singleton pregnancy at Graduate School of Medicine, Osaka City University, from April 2011 through April 2015. The study protocol received the Institutional Review Board approval (no.2608) of Osaka City University Graduate School of Medicine. An informed consent was obtained from each subject for participation in the study. Our research complied with the principles of the Declaration of Helsinki.

If the Japanese women had any diabetes risk factors, such as casual hyperglycemia (>100 mg/dL [5.6 mmol/L]),...
polyhydramnios, or a heavy-for-date infant, a 75-g OGTT was performed. For the measurement of plasma glucose levels and immunoreactive insulin (IRI) concentration, an OGTT was performed after a 12-hour overnight fast. Venous blood samples were drawn in the fasting state at 0.5, 1, and 2 hours after ingestion of the glucose solution. GDM was diagnosed in accordance with the International Association of Diabetes and Pregnancy Study Groups criteria. To analyze the associations between postpartum glucose tolerance and risk factors, information regarding maternal characteristics and pregnancy outcomes was obtained.

The initial standard treatment for women with GDM is diet and self-monitoring of blood glucose. Based on the results of self-monitoring of blood glucose, insulin therapy was initiated if the patient exhibited fasting hyperglycemia (>95 mg/dL [5.3 mmol/L]) or 2-hour postprandial hyperglycemia (>120 mg/dL [6.7 mmol/L]).

Patients underwent a 75-g OGTT 6–14 weeks postpartum. We used the World Health Organization criteria to assess glucose tolerance and classified them into the following two groups: (1) normal glucose tolerance (NGT) group (fasting glucose level <110 mg/dL [6.1 mmol/L] and 2-hour glucose level <140 mg/dL [7.8 mmol/L]) and (2) impaired glucose tolerance–impaired fasting glucose (IGT–IFG) group (fasting glucose level ≥110 mg/dL [6.1 mmol/L] and <126 mg/dL [7.0 mmol/L] or 2-hour glucose level ≥140 mg/dL [7.8 mmol/L]). To eliminate the possibility of pregestational DM, we excluded women who had overt diabetes during pregnancy and women who were included in the DM group postpartum (fasting glucose level ≥126 mg/dL [7.0 mmol/L] or 2-hour glucose level ≥200 mg/dL [11.1 mmol/L]).

Insulin resistance and insulin secretion were evaluated using measurements from the results of the OGTT as follows. Homeostasis model assessment–insulin resistance (HOMA-IR) is an indicator of insulin resistance, and this was calculated using the following equation: HOMA-IR = (fasting plasma glucose level × fasting insulin)/405. Homeostasis model assessment β-cell function (HOMA-B) is an indicator of insulin secretion, and this was calculated using the following equation: HOMA-B = (fasting insulin) × (fasting plasma glucose level – 63). The insulinogenic index is a surrogate for early-phase insulin secretion from the pancreas, and it was calculated using the following equation: insulinogenic index = (0.5-hour insulin – fasting insulin)/(0.5-hour plasma glucose level – fasting plasma glucose level).

Statistical analysis was performed with SPSS (version 20.0; IBM). Continuous variables were presented as the median.

| Maternal characteristics and pregnancy outcomes. | NGT (n = 69) | IGT-IFG (n = 16) | P     |
|--------------------------------------------------|--------------|-----------------|-------|
| Maternal age (years)                             | 34 (19–45)   | 37 (25–45)      | 0.237 |
| Primipara (%)                                    | 61           | 44              | 0.266 |
| Pregestational BMI                                | 23.2 (16.4–51.7) | 22 (16.2–32.5) | 0.525 |
| Maternal weight change during pregnancy (kg)     | 6.9 (–24–26) | 7.3 (1.3–18)    | 0.657 |
| Postpartum BMI                                   | 23.1 (16.9–39.1) | 22.4 (17.8–30.0) | 0.537 |
| Gestational age at OGTT (week)                   | 28 (9–38)    | 26.5 (7–36)     | 0.636 |
| Gestational weeks at delivery                    | 39 (32–41)   | 39 (37–41)      | 0.237 |
| Birth weight (g)                                 | 3070 (1900–4205) | 3245 (2415–3980) | 0.080 |
| Proportion of C/S (%)                            | 29           | 19              | 0.311 |
| Proportion of insulin dosage                     | 0 (0–32)     | 8 (0–70)        | 0.185 |
| Proportion of insulin usage (%)                  | 45           | 62              | 0.161 |
| Weight of placenta (g)                           | 570 (325–980) | 570 (490–895)   | 0.645 |
| Proportion of breast feeding (%)                 | 93           | 75              | 0.050 |
| Ap.(1)                                           | 8 (4–9)      | 8 (6–10)        | 0.093 |
| Ap.(5)                                           | 9 (7–10)     | 9 (8–10)        | 0.431 |
| 2-h PG of neonate (mg/dL)                        | 71 (33–132)  | 68 (56–106)     | 0.697 |
| Proportion of HFD (%)                            | 13           | 18              | 0.401 |
| Proportion of TTN (%)                            | 16           | 12              | 0.539 |
| Proportion of low PG                             | 11%          | 0%              | 0.230 |

Abbreviations: NGT, normal glucose tolerance; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; BMI, body mass index (calculated as weight in kilograms divided by the square of the height in meters); OGTT, oral glucose tolerance test; C/S, cesarean section; Ap., Apgar score; h, hour; PG, plasma glucose level; HFD, heavy-for-date; TTN, transient tachypnea of the newborn.
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Table 2. 75-g OGTT results of the NGT and IGT–IFG groups classified by OGTT in the postpartum period.

|                   | NGT          | n  | IGT–IFG     | n  | P       |
|-------------------|--------------|----|-------------|----|---------|
| **OGTT results in** |              |    |             |    |         |
| **the antenatal**  |              |    |             |    |         |
| period (n = 85 or 49) |              |    |             |    |         |
| Fasting PG (mg/dL) | 86.5 (51–117)| 69 | 83.5 (75–106)| 16| 0.828   |
| 0.5-h PG           | 146 (112–193)| 40 | 172 (127–196)| 9 | 0.052   |
| 1-h PG             | 178 (119–258)| 69 | 191 (102–226)| 16| 0.037   |
| 2-h PG             | 158 (88–216)| 69 | 162 (101–200)| 16| 0.365   |
| Fasting iRi (μU/mL)| 9.95 (1.9–34)| 40 | 9.5 (6.8–17.4)| 9| 0.090   |
| 0.5-h iRi          | 47.7 (20.5–196)| 40 | 42.8 (20.8–131)| 9| 0.549   |
| 1-h iRi            | 72.3 (28.3–158)| 40 | 72.9 (20.2–169)| 9| 0.602   |
| 2-h iRi            | 77.7 (21.7–275.8)| 40 | 75.4 (39.1–189.3)| 9| 0.815   |
| HOMa-IR            | 2.25 (0.36–8.81)| 40 | 1.93 (1.41–4.55)| 9| 0.929   |
| HOMa-B             | 149.1 (48.8–698.4)| 40 | 145.7 (100.8–257.1)| 9| 1.000   |
| Insulinogenic index| 0.723 (0.177–2.643)| 40 | 0.449 (0.180–1.349)| 9| 0.086   |
| HbA1c at diagnosis (%)| 5.4 (4.9–6.3) | 69 | 5.9 (5.0–6.2) | 16| 0.600   |
| **OGTT results in** |              |    |             |    |         |
| **the postpartum**  |              |    |             |    |         |
| period (n = 85)     |              |    |             |    |         |
| Fasting PG (mg/dL) | 90 (73–109) | 69 | 91 (75–117)| 16| 0.589   |
| 0.5-h PG            | 144 (89–171)| 69 | 156 (115–193)| 16| 0.013   |
| 1-h PG              | 140 (70–191)| 69 | 176 (82–233)| 16| <0.001  |
| 2-h PG              | 116 (72–139)| 69 | 152 (83–184)| 16| <0.001  |
| Fasting iRi (μU/mL)| 5.7 (1.1–25.5)| 69 | 5.2 (2.1–10) | 16| 0.378   |
| 0.5-h iRi           | 40.6 (9.1–149)| 69 | 29.8 (13.8–94.2)| 16| 0.048   |
| 1-h iRi             | 42.2 (9.3–175.2)| 69 | 31.8 (15.8–100.6)| 16| 0.245   |
| 2-h iRi             | 33.1 (13.1–167.7)| 69 | 34.8 (14.2–122.4)| 16| 0.723   |
| HOMa-IR             | 1.28 (0.20–5.73)| 69 | 1.12 (0.42–2.42) | 16| 0.527   |
| HOMa-B              | 78.8 (34.3–327.8)| 69 | 56 (26.1–163.4)| 16| 0.091   |
| Insulinogenic index | 0.68 (0.18–2.9) | 69 | 0.38 (0.13–1.15) | 16| 0.006   |
| HbA1c (%)           | 5.6 (4.9–6.3) | 69 | 5.7 (5.3–6.0) | 16| 0.332   |

Abbreviations: OGTT, oral glucose tolerance test; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; h, hour; PG, plasma glucose level; iRi, immunoreactive insulin; HOMa-IR, homeostasis model assessment-insulin resistance; HOMa-B, homeostasis model assessment β-cell function.
the postpartum period, while the insulinogenic index did not change in regard to the measured periods in either group.

Elevated 1-hour plasma glucose level after a 75-g OGTT, even with a normal glucose level at fasting and/or at 2 hours, was recently reported to be a high risk for subsequent DM, and this phenomenon is thought to be caused by impaired early-phase insulin secretion. As shown in our study, antenatal 1-hour plasma glucose level was significantly higher in the IGT–IFG group and the insulinogenic index was decreased in the postpartum period. A significant increase in the 0.5- and 1-hour glucose levels may suggest impaired early-phase insulin secretion of the IGT–IFG group.

O’Reilly et al reported that breast-feeding might reduce the prevalence of abnormal postpartum glucose tolerance in women with prior GDM, and the authors concluded that breast-feeding may confer beneficial metabolic effects after GDM and should be encouraged. Interestingly, also in our study, the percentage of breast-feeding was higher in the NGT group, although it did not reach statistical significance. The mechanisms are not fully understood, but lactation is thought to enhance pancreatic β-cell proliferation and function and reduce insulin resistance.

In our study, both the HOMA-IR and HOMA-B levels in the postpartum period showed a significant decrease in comparison to those levels during pregnancy, suggesting a rapid improvement of insulin resistance postpartum. Sustained elevation of HOMA-IR through pregnancy and postpartum is a high risk factor for the development of type 2 DM. Conversely, Kugishima et al reported that among Japanese women with GDM, a lower insulinogenic index and use of insulin therapy during pregnancy are associated with early postpartum IGT–IFG. In our study, use of insulin was not associated with postpartum IGT–IFG; this might be due to the small sample size. In some GDM patients, impaired early-phase insulin secretion would be involved in the future pathogenesis of DM. This explanation is supported by our observation that an antenatal decrease in the insulinogenic index was sustained even in the postpartum period.

A limitation of the present study is that it involves a relatively small number of cases. The antenatal data of plasma glucose level at 0.5 hours and IRI were limited because the 75-g OGTT was performed without these measurements in some
cases (previous care at another facility). However, we considered that conducting an additional 75-g OGTT to obtain the plasma glucose level at 0.5 hours and an IRI during pregnancy is not always necessary.

In conclusion, our study suggested that the postpartum IGT and IFG levels of Japanese women with GDM affected by impaired early-phase insulin secretion; however, insulin resistance promptly improves. Our findings might add essential information for the management of GDM.

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Author Contributions
Conceived and designed the experiments: HK. Analyzed the data: HK, DT. Wrote the first draft of the manuscript: HK, DT. Contributed to the writing of the manuscript: HK, DT. Agree with manuscript results and conclusions: AH, TM, KM, TM, SF, MI. Jointly developed the structure and arguments for the paper: ME. Made clinical revisions and approved final version: HK, MK. All authors reviewed and approved of the final manuscript.

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