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Are there Racial Differences in β-cell Compensation among Pregnant Women with Gestational Diabetes?

Keywords: Pregnancy/β cell compensation /GDM / interracial differences/obese

Abstract

Introduction: To compare β cell compensation between foreign and Japanese women with gestational diabetes mellitus (GDM).

Methods: We retrospectively evaluated pregnant women diagnosed with GDM who underwent measurements of HOMA-IR and HOMA-β. Subjects were divided into subgroups based on the cutoff value of HOMA-IR (≥1.4) indicating GDM positivity and nationality. Based on this classification, we compared HOMA-β and HOMA-IR during pregnancy and the postpartum period, as well as changes in body weight from pre-pregnancy to postpartum. Data are expressed as a number or median.

Results: The study included the following groups: foreign women with HOMA-IR ≥1.4 (G-F, n=18), Japanese women with HOMA-IR ≥1.4 (G-JH, n=31), and Japanese women with HOMA-IR <1.4 (G-JL, n=27). During pregnancy, there was no significant difference in HOMA-β between G-F and G-JH (134% vs.127%, p=0.75), whereas G-JL showed the lowest value (72%). Postpartum HOMA-β was significantly higher in G-F compared to G-JH (98% vs. 63%, p<0.01), with G-JL showing the lowest value (40%). In G-F, there were no significant differences in HOMA-β or HOMA-IR between the pregnancy and postpartum periods. In contrast, both G-JH and G-JL showed significant decreases in postpartum HOMA-β and HOMA-IR. Postpartum body weight did not return to pre-pregnancy levels in G-F, while it was recovered in G-JH.

Conclusions: In comparison with the postpartum period, an augmentation of insulin secretion was observed in Japanese GDM women, whereas it was not prominent in foreign women with HOMA-IR ≥1.4. Elevated insulin resistance at the postpartum period, along with a lack of weight reduction, suggested that altered metabolic adaptation may be involved

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Introduction

Studies on type 1 diabetes have shown that insulin requirements during pregnancy increase by ca. 1.5 to 2 times compared to the non-pregnant state [1,2]. To meet this increased insulin demand, pancreatic β-cells undergo hypertrophy and neogenesis, thereby enhancing insulin production [3,4]. This adaptive process is referred to as **β-cell compensation during pregnancy**. Gestational diabetes mellitus (GDM) is thought to occur when this compensatory response is insufficient relative to the heightened insulin resistance associated with pregnancy [5,6].

It is well established that Japanese individuals are more susceptible to developing diabetes than Western populations, even in the absence of obesity. This predisposition is primarily attributed to an inherent defect in insulin secretion, which plays a central role in the pathogenesis of diabetes in the Japanese population [7]. This characteristic is also observed among Japanese women with GDM, ca. 40% of whom present a lean phenotype with both low insulin resistance and reduced insulin secretion capacity [8]. If this inherently low basal insulin secretory ability contributes to the development of GDM, it is reasonable to hypothesize that impaired β-cell compensation during pregnancy may also be involved. In an effort to investigate this possibility, cross-ethnic comparative studies including both GDM and non-GDM individuals are necessary. However, no such studies have been conducted in Japan to date.

Our hospital provides obstetric care to a diverse population, including foreign nationals such as women from Nepal. Although our current study is limited to individuals with GDM, this clinical setting allows for a comparison of insulin secretion capacity in relation to insulin resistance across different ethnic groups. In this study, we aimed to examine differences in insulin secretory function between Japanese and non-Japanese women with GDM.

Part of this study was presented as a poster presentation at the 77th Annual Scientific Meeting of the Japan Society of Obstetrics and Gynecology in Okayama, Japan, 2025.

Materials and Methods

This observational study was approved by the Ethics Committee of our institution (Kawakita General Hospital Approval Number: 2024-15). Opt-out consent was implemented through our hospital's website in accordance with the Helsinki Declaration. The publicly available study outline allowed potential participants to decline research participation.

We undertook a retrospective study of pregnant women who were diagnosed with GDM who delivered at our hospital between January 2021 and March 2024. GDM was diagnosed based on the criteria of the Japan Diabetes Society [9]. Fasting insulin levels were also measured with the oral glucose tolerance test (OGTT). Cases without fasting insulin measurements were excluded. From the medical charts of the group under investigation, we extracted fasting plasma glucose and fasting insulin data from the patients' medical records. Using these data, we calculated the Homeostatic Model Assessment of beta-cell function (HOMA-β) and Homeostasis Model

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Assessment of Insulin Resistance (HOMA-IR) as indicators of insulin secretion and insulin resistance, respectively, during pregnancy and postpartum. HOMA-β was calculated using the formula: fasting insulin × 360/ (fasting glucose [mg/dL] – 63), and HOMA-IR with: fasting insulin × fasting glucose/405. The postpartum OGTT was performed at 6–8 weeks after delivery.

Background characteristics also extracted from medical records included ethnicity (Japanese or foreign national), parity (primiparous or multiparous), pre-pregnancy and postpartum body weight (measured at the time of postpartum OGTT), pre-pregnancy body mass index (BMI), and gestational age at GDM diagnosis.

We initially classified subjects based on HOMA-IR cutoff values (≥1.4 or <1.4), which indicate GDM positivity, and their nationality**.** Cutoff values were obtained from a previous study comparing pregnant women diagnosed with GDM and those with normal glucose tolerance following OGTT [8]. We then compared HOMA-β and HOMA-IR during pregnancy and postpartum between these groups, in addition to pre-pregnancy and postpartum body weight.

For the statistical analyses, categorical variables among groups were compared using the chi-square test, and continuous variables using the Kruskal–Wallis test followed by Steel–Dwass post hoc analyses. For comparisons between two groups, Welch's t-test and paired t-test (two-tailed) were employed. A p-value <0.05 was considered statistically significant. Data are presented as the number of cases and median (IQR).

Results

A total of 80 pregnant women with GDM were included in the study. Of these, 58 were Japanese and 22 were of foreign nationality, including 19 Nepalese women. Based on HOMA-IR cutoff value, participants were classified into four groups: 18 foreign nationals with HOMA-IR ≥1.4 (G-F), 31 Japanese with HOMA-IR ≥1.4 (G-JH), and 27 Japanese with HOMA-IR <1.4 (G-JL). Due to the small number of foreign participants with HOMA-IR <1.4 (n=4), this group was excluded from the intergroup comparison.

In the comparison of background characteristics among the three groups, G-F was the youngest (p<0.01), while there was no significant difference in age between G-JH and G-JL (p=0.96). The proportion of multiparous women was highest in G-JH (p<0.01). Pre-pregnancy BMI was lowest in G-JL (p<0.01), with no significant difference between G-F and G-JH (p=0.46). Gestational age at GDM diagnosis did not differ significantly among the three groups (p=0.75) (Table 1).

During pregnancy, there was no significant difference in HOMA-β between G-F and G-JH (134% vs.127%, p=0.75), while G-JL showed the lowest value (72%, p<0.01) (Figure 1). In the postpartum period, HOMA-β was significantly higher in G-F compared to G-JH (98% vs.63%, p<0.01), with G-JL again showing the lowest value (40%, p<0.01) (Figure 1).

Regarding HOMA-IR during pregnancy, no significant difference was observed between G-F and G-JH (2.6 vs.2.1, p=0.81), while G-JL had the lowest value (1.2, p<0.01) (Figure 2A). In the postpartum period, HOMA-IR remained significantly higher in G-F compared to G-JH (2.4 vs.1.0, p<0.01), with G-JL again having the lowest value (0.7, p<0.01) (Figure 2).

Table 1: Clinical Characteristics of the three GDM groups. Results are expressed as number or median. G-F: foreign nationals with HOMA-IR ≥1.4, G-JH: Japanese with HOMA-IR ≥1.4, G-JL: Japanese with HOMA-IR <1.4. Three groups were compared using the chi-square test and the Kruskal–Wallis test followed by Steel–Dwass post hoc analyses. A p-value <0.05 was considered statistically significant. GDM: gestational diabetes mellitus.

Study group	G-F	G-JH	G-JL	p
(n)	18	31	27	
Age (years)	30 (27-32)	35(32-38)	35(31-38)	<0.01
Parity (primiparous)	7	19	5	<0.01
Pre-pregnancy BMI	24 (23-28)	24 (21-27)	20 (19-22)	<0.01
Gestational age at GDM diagnosis (weeks)	28 (19-29)	26 (16-30)	25 (20-29)	0.75

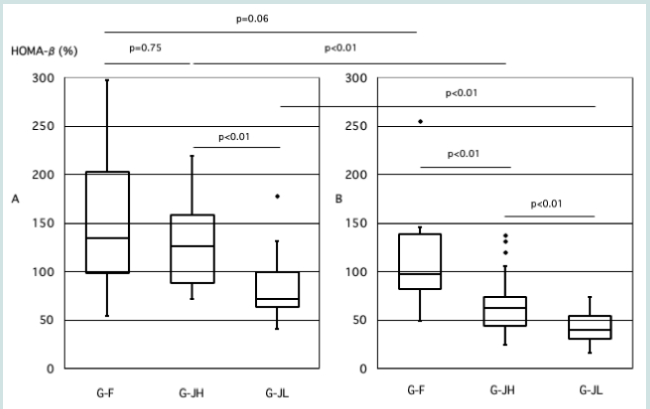

Figure 1: Comparison of HOMA-β during pregnancy and postpartum among the three groups. A: During Pregnancy, B: Postpartum, G-F: foreign nationals with HOMA-IR ≥1.4, G-JH: Japanese with HOMA-IR ≥1.4, G-JL: Japanese with HOMA-IR <1.4. Three groups were compared using the Kruskal–Wallis test followed by Steel–Dwass post hoc analyses. Welch's t-test was used for comparisons between two groups. A p-value <0.05 was considered statistically significant. GDM: gestational diabetes mellitus.

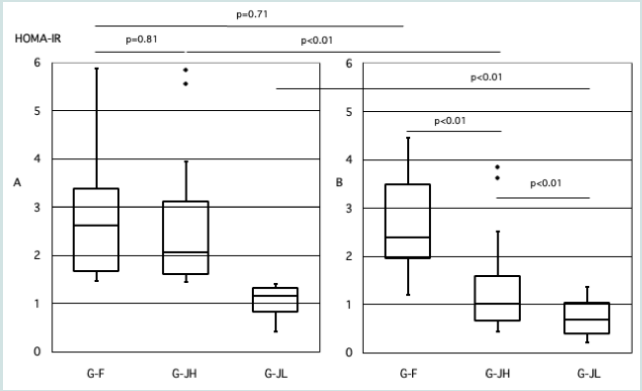

Figure 2: Comparison of HOMA-IR during pregnancy and postpartum among the three groups. A: During Pregnancy, B: Postpartum, G-F: foreign nationals with HOMA-IR ≥1.4, G-JH: Japanese with HOMA-IR ≥1.4, G-JL: Japanese with HOMA-IR <1.4. Three groups were compared using the Kruskal–Wallis test followed by Steel–Dwass post hoc analyses. Welch's t-test was used for comparisons between two groups. A p-value <0.05 was considered statistically significant. GDM: gestational diabetes mellitus.

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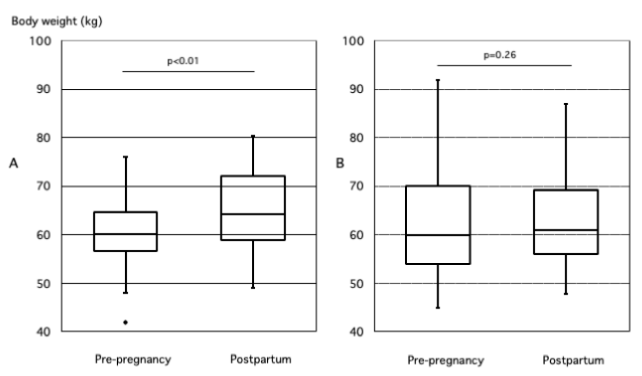

Figure 3: Comparison of pre-pregnancy and postpartum body weight in GDM cases with HOMA-IR ≥ 1.4 during Pregnancy. A: Foreign nationals with HOMA-IR ≥1.4, B: Japanese with HOMA-IR ≥1.4. A paired t-test was used for comparisons. A p-value <0.05 was considered statistically significant. GDM: gestational diabetes mellitus.

Intra-group comparisons revealed no significant difference between pregnancy and postpartum HOMA-β or HOMA-IR in G-F (0.06 and 0.71, respectively). However, in both G-JH and G-JL, HOMA-βand HOMA-IR during pregnancy was significantly higher, being ca. twice that observed postpartum ($p<0.01$ and $p<0.01$, respectively).

Among four foreign participants with HOMA-IR <1.4 who were excluded from the intergroup comparison, the median HOMA-β during pregnancy was 121% (89-189), the median HOMA-β in the postpartum period was 62% (54-74), and the median HOMA-IR in the postpartum period was 0.8 (0.64-0.95).

When comparing body weight before pregnancy and postpartum, G-F had not returned to pre-pregnancy weight by the time of postpartum testing ($p=0.26$), unlike the case with G-JH ($p<0.01$) (Figure 3). Among four foreign participants with HOMA-IR <1.4 who were excluded from the intergroup comparison, three out of the four cases had returned to their pre-pregnancy weight.

Discussion

During normal pregnancy, insulin requirements typically increase by 50–100% [1,2]. To meet this demand, insulin secretion must increase by ca. 1.5- to 2-fold. In the present study, although Japanese women with GDM exhibited lower insulin secretory capacity in the postpartum period compared to foreign GDM women, their insulin secretion during pregnancy was significantly higher, being ca. twice that observed postpartum. This relative increase suggested that β-cell compensation during pregnancy is active in Japanese women with GDM. In contrast, foreign GDM women (primarily of Nepalese origin), who exhibited higher insulin resistance during pregnancy, showed no significant difference in insulin secretion or insulin resistance between the pregnancy and postpartum periods. This finding indicated a limited amplification of β-cell compensation during pregnancy in this group (Figure 1) (Figure 2). On the otherhood, in foreign participants with HOMA-IR <1.4 who were excluded from the intergroup comparison, insulin secretory capacity was reduced by half in the postpartum period, accompanied by a decrease in insulin resistance.

In the present study, foreign GDM women, who exhibited higher insulin resistance during pregnancy, did not return to their pre-pregnancy weight by the postpartum period. Notably, their pre-pregnancy BMI did not differ from that of Japanese GDM women who had high insulin resistance during pregnancy. Furthermore, with increasing age or multiparity, insulin resistance due to obesity tends to increase [10,11]. Japanese GDM women with high insulin resistance were generally older and more likely to be multiparous than their foreign national counterparts, suggesting that foreign GDM women may be at higher risk of developing insulin resistance due to obesity. Nevertheless, these Japanese GDM women returned to their pre-pregnancy weight by the postpartum period, and their insulin resistance significantly decreased. These sequential changes observed in Japanese GDM women with high insulin resistance appear to parallel the pattern of fat mass gain during pregnancy and its subsequent reduction in the postpartum period [12]. In contrast, among foreign GDM women, insulin resistance remained elevated even at 6 to 8 weeks postpartum, a period when the physiological effects of pregnancy typically subside. This persistent insulin resistance may be explained by minimal postpartum changes in fat mass. Most of the foreign GDM women in this study were of Nepalese origin, whose dietary habits differ substantially from those of Japanese women. Traditionally, the Nepalese diet has been high in carbohydrates and low in protein and fat. However, the recent introduction of Westernized dietary patterns has led to excessive intake of both carbohydrates and fats, raising concerns about increased risk of non-communicable diseases [13]. It is therefore plausible that foreign GDM women with high insulin resistance had already experienced qualitative and/or quantitative alterations in fat metabolism prior to pregnancy, in contrast to their Japanese counterparts.

During pregnancy, insulin production increases to meet rising insulin demands, primarily through pancreatic β-cell hypertrophy and neogenesis [3,4]. This β-cell expansion is stimulated by pregnancy-related hormones such as human placental lactogen (hPL) and prolactin (PRL) [4]. Independently, obesity also induces β-cell compensation. As insulin resistance increases with obesity, the demand for insulin rises, leading to β-cell proliferation and an overall increase in β-cell mass [14,15]. If both pregnancy-related hormonal stimulation and obesity-induced insulin resistance act independently, it would be expected that insulin secretion capacity during pregnancy would increase even further due to their cumulative effects. However, in the present study, foreign GDM women with high insulin resistance exhibited no significant changes in insulin secretion capacity or insulin resistance between the pregnancy and postpartum periods. This suggested that synergistic enhancement of β-cell compensation did not occur. One possible explanation is that β-cell compensation due to obesity was already active prior to pregnancy, and the capacity for further β-cell hypertrophy or neogenesis had reached its physiological limit. As a result, in foreign GDM women with high insulin resistance, additional β-cell compensation during pregnancy may have been limited or mitigated. In contrast, among the four foreign GDM women with low insulin resistance, who were not included in the intergroup comparison, both insulin secretion capacity and insulin resistance declined in the postpartum period as observed in Japanese women with GDM. This suggests that, rather than reflecting ethnic differences, variations in fat metabolism may

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account for the presence of two types of women with GDM: those who exhibit elevated insulin resistance during pregnancy followed by a decline in the postpartum period, and those in whom insulin resistance remains unchanged.

Maternal nutritional status, including obesity, is thought to influence β-cell compensation during pregnancy, although no consensus has been reached regarding this issue [16]. For instance, although insulin resistance is typically increased in obese women, reports on insulin secretory responses during pregnancy are conflicting, with some studies indicating an increase, while others suggest a decrease compared to non-obese women [17,18]. In contrast, animal studies have provided important insights into the mechanisms underlying changes in β-cell compensation. In one study, mice fed a high-calorie diet more than three months before conception exhibited β-cell hypertrophy accompanied by increased apoptosis and expression of inflammatory markers in pancreatic islets [19]. Another study demonstrated that pregnant rats fed a high-fat diet exhibited enhanced glucose-stimulated insulin secretion *in vivo*, while isolated islet perfusion experiments showed a reduced insulin secretory response to glucose stimulation [20]. The former study suggested that morphological adaptations of β-cells, such as hypertrophy, may be accompanied by apoptosis, indicating functional decline. The latter study suggested that while β-cell function may be impaired, a compensatory response to increased insulin resistance during pregnancy still occurred. These experimental findings help to explain our clinical observation: in foreign GDM women with high insulin resistance, the amplification of β-cell compensation during pregnancy appeared limited, and elevated insulin resistance persisted even into the postpartum period.

Whether the observed differences in β-cell compensation during pregnancy among women with GDM truly originate from differences in pre-pregnancy fat metabolism requires precise assessment not only of insulin secretion capacity and insulin resistance prior to pregnancy, but also of qualitative and quantitative changes in fat metabolism. In our experience, abdominal ultrasonography performed in GDM cases often revealed fatty liver predominantly in foreign women with GDM, suggesting a metabolic state prone to hepatic fat accumulation. Therefore, future prospective studies incorporating evaluations of body fat volume and fat tissue distribution, including imaging diagnostics, are warranted. Additionally, this study focused exclusively on women with GDM and did not include comparisons with non-GDM pregnant women. It is also necessary to investigate whether the ethnic differences in β-cell compensation identified here are similarly observed in non-GDM pregnant women. Generally, sustained β-cell compensation leads to oxidative and endoplasmic reticulum stress in β-cells, resulting in progressive functional decline [21, 22, 23]. A study conducted in Japan similarly reported more pronounced β-cell dysfunction in obese individuals [24]. Based on these observations, women with a history of GDM who maintain prolonged β-cell compensation may experience rapid β-cell deterioration and an earlier transition to overt diabetes.

In conclusion, irrespective of basal insulin secretory capacity, Japanese women with GDM exhibited an approximately twofold increase in insulin secretory capacity during pregnancy compared with the postpartum period, whereas it was not prominent in foreign GDM women with high insulin resistance. These differences are considered to arise not from ethnic disparities but rather from variations in metabolic states that induce insulin resistance prior to pregnancy. Metabolic alterations resulting in excessive insulin resistance may induce functional changes in β-cells. Therefore, longitudinal investigations are needed to evaluate the risk of progression to impaired glucose tolerance or type 2 diabetes in this population.

Conflicts of interest: There is no conflict of interest.

Approval code issued by the institutional review board (IRB) and the name of the institution(s) that granted the approval; Ethics Committee of Kawakita General Hospital (Approval Number: 2024-15).

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