Hepatic Insulin Resistance Is an Early Determinant of Declining β-Cell Function in the First Year Postpartum After Glucose Intolerance in Pregnancy

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OBJECTIVE—The increased risk of type 2 diabetes in women with glucose intolerance in pregnancy is mediated by deterioration of their β-cell function, which occurs as early as the first year postpartum. We thus sought to identify early determinants of their declining β-cell function.

RESEARCH DESIGN AND METHODS—Women with recent gestational glucose intolerance (166) underwent oral glucose tolerance test at 3 and 12 months postpartum. They were stratified into those in whom β-cell function (Insulin Secretion-Sensitivity Index-2 [ISSI-2]) declined over this time (decliners; n = 92) and those in whom it did not (nondecliners; n = 74).

RESULTS—Between 3 and 12 months, hepatic insulin sensitivity (1/homeostasis model assessment of insulin resistance [HOMA-IR]) decreased in decliners but not in nondecliners. Over this time, the change in 1/HOMA-IR emerged as an independent predictor of the change in ISSI-2 (1 = 5.5; P < 0.0001). Increased hepatic insulin sensitivity independently predicted a lower likelihood of declining β-cell function (odds ratio = 0.13 [95% CI 0.06–0.29]; P < 0.0001).

CONCLUSIONS—Hepatic insulin resistance is an early determinant of declining β-cell function after gestational dysglycemia.

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**RESULTS**—Table 1 shows the comparison of characteristics at 3 and 12 months postpartum between women in whom β-cell function (ISSI-2) declined over this time (decliners; \( n = 92 \)) and those in whom it did not (nondecliners; \( n = 74 \)). Lipids, adipokines, and C-reactive protein are shown in Supplementary Table 1. Although glucose measures did not differ between the groups at 3 months, each postload glucose value on the OGTT was higher in the decliners than in the nondecliners by 12 months postpartum. Matsuda index, 1/HOMA-IR, fasting C-peptide:insulin, and ISSI-2 were all lower in the decliners at 12 months, as was the prevalence of breastfeeding. Although decliners lost less weight, the two groups did not differ in their baseline-adjusted changes in waist, BMI, and whole-body insulin sensitivity (Matsuda) between 3 and 12 months. In contrast, however, both measures of hepatic insulin sensitivity (1/HOMA-IR and fasting C-peptide:insulin) decreased in decliners but increased in nondecliners.

On Spearman correlation analysis (Supplementary Table 2), the factor most strongly associated with the baseline-adjusted change in ISSI-2 between 3 and 12 months was the change in 1/HOMA-IR \( (r = 0.45; \ P < 0.0001) \). Similarly, the change in fasting C-peptide:insulin was also a significant correlate of the change in ISSI-2 \( (r = 0.22; \ P = 0.008) \), whereas the change in whole-body insulin sensitivity (Matsuda) did not reach significance \( (r = 0.15; \ P = 0.08) \).

On multiple linear regression analyses (Supplementary Table 3) adjusted for age, ethnicity, family history of diabetes, breastfeeding, BMI, and ISSI-2 at 3 months, the only independent determinant of the change in ISSI-2 was the change in hepatic insulin sensitivity, measured by either 1/HOMA-IR \( (t = 5.5; \ P < 0.0001) \) or fasting C-peptide:insulin \( (t = 3.24; \ P = 0.0015) \). The changes in weight or Matsuda index were not significant predictors.

On logistic regression analysis (Supplementary Table 4), an increase in 1/HOMA-IR independently predicted a lower likelihood of declining β-cell function \( (OR = 0.13 \ [95\% \ CI 0.06–0.29]; \ P < 0.0001) \), after adjustment for age, ethnicity, family history of diabetes, breastfeeding, and BMI at 3 months. Similarly, an increase in fasting C-peptide:insulin also predicted a lower risk of declining β-cell function \( (OR = 0.95 \ [0.91–0.98]; \ P = 0.0018) \), whereas the changes in weight

| Table 1—Demographic, clinical, and metabolic characteristics of study population stratified into two groups: women in whom β-cell function did not decline between 3 and 12 months postpartum (nondecliners) and women in whom β-cell function declined between 3 and 12 months postpartum (decliners) |
|---|---|---|---|
| **n** | **Nondecliners** | **Decliners** | **P** |
| **At 3 months postpartum** | | | |
| Age (years) | 35.3 [31.8–38.5] | 35.2 [33.8–38.3] | 0.4204 |
| Ethnicity (%) | | | 0.4097 |
| White | 77.0 | 72.8 | | |
| Asian | 13.5 | 10.9 | | |
| Other | 9.5 | 16.3 | | |
| Family history of diabetes (%) | 62.2 | 53.3 | 0.2492 |
| Current smoking (%) | 4.1 | 6.5 | 0.7325 |
| Current breastfeeding (%) | 97.3 | 91.3 | 0.1876 |
| Blood pressure (mmHg) | | | |
| Systolic | 108 [104–117] | 111 [103–116] | 0.6593 |
| Diastolic | 65 [59–70] | 64 [59–71] | 0.9634 |
| Physical activity | | | |
| Sport index | 2.0 [1.8–2.5] | 1.8 [1.5–2.5] | 0.6019 |
| Leisure-time index | 2.8 [2.5–3.3] | 2.8 [2.5–3.3] | 0.8009 |
| Waist circumference (cm) | 87 [82–99] | 90 [84–96] | 0.5303 |
| Weight (kg) | 70.2 [59.0–81.0] | 69.9 [62.1–80.7] | 0.7014 |
| (BMI kg/m²) | 26.5 [23.2–31.2] | 26.6 [24.0–30.2] | 0.6745 |
| Fasting insulin (pmol/L) | 36.5 [28.0–59.0] | 26.0 [20.0–49.5] | 0.0130 |
| Whole-body insulin sensitivity | | | |
| Matsuda index | 8.3 [5.7–14.0] | 9.8 [6.0–12.9] | 0.5413 |
| 1/HOMA-IR | | | |
| 1/HOMA-IR | 0.94 [0.56–1.32] | 1.3 [0.65–1.71] | 0.0112 |
| Fasting C-peptide:insulin | 15.6 [12.9–21.5] | 18.5 [14.5–27.0] | 0.0115 |
| β-Cell function | | | |
| ISSI-2 | 785 [624–952] | 914 [748–1,207] | 0.0004 |
| OGTT | | | |
| Fasting glucose (mmol/L) | 4.8 [4.3–5.0] | 4.7 [4.3–5.0] | 0.1234 |
| 30-min glucose (mmol/L) | 8.4 [7.4–9.5] | 8.7 [7.5–9.8] | 0.5027 |
| 1-h glucose (mmol/L) | 8.6 [7.1–10.1] | 8.7 [7.2–10.0] | 0.9948 |
| 2-h glucose (mmol/L) | 6.4 [5.3–7.3] | 6.7 [5.5–7.9] | 0.4479 |
| AUC<sub>gluc</sub> | 14.1 [12.3–15.8] | 14.2 [12.4–15.9] | 0.9288 |
| Glucose tolerance status (%) | | | 0.1356 |
| NGT | 78.4 | 72.8 | | |
| Isolated IFG | 2.7 | 0 | | |
| Isolated IGT | 17.6 | 27.2 | | |
| Combined IFG and IGT | 1.4 | 0 | | |
| At 12 months postpartum | | | |
| Current breastfeeding (%) | 96.0 | 83.7 | 0.0123 |
| Physical activity | | | |
| Sport index | 2.1 [1.8–3.0] | 2.0 [1.8–2.5] | 0.3252 |
| Leisure-time index | 3.0 [2.8–3.5] | 3.0 [2.8–3.3] | 0.7867 |
| Work index | 2.9 [2.5–3.4] | 2.9 [2.4–3.4] | 0.7499 |
| Waist circumference (cm) | 85 [79–96] | 89 [82–95] | 0.2181 |
| Weight (kg) | 68.1 [56.5–78.0] | 68.3 [59.3–78.7] | 0.3084 |
| BMI (kg/m²) | 25.4 [21.5–29.4] | 25.9 [23.4–29.3] | 0.2976 |
| Fasting insulin (pmol/L) | 31.0 [20.0–48.0] | 45.5 [27.5–73.0] | 0.0015 |
| Whole-body insulin sensitivity | | | |
| Matsuda index | 9.1 [5.8–13.9] | 7.2 [4.4–10.9] | 0.0436 |
| Hepatic insulin sensitivity | | | |
| 1/HOMA-IR | 1.11 [0.73–1.68] | 0.73 [0.45–1.18] | 0.0015 |
| Fasting C-peptide:insulin | 17.7 [14.0–23.9] | 15.1 [10.9–20.9] | 0.0116 |
and Matsuda index were not significant predictors.

**CONCLUSIONS**—Although studies beginning at 15–30 months postpartum have shown that insulin resistance contributes to declining β-cell function after GDM (3,4), the current data specifically implicate hepatic insulin resistance as relevant to the earlier deterioration of β-cell function in the first year postpartum. Interestingly, Buchanan and colleagues (14) have demonstrated that increased endogenous glucose production in pregnancy (indicative of hepatic insulin resistance) independently predicts the subsequent development of diabetes by 11–26 months postpartum. The current findings thus may reflect the early postpartum continuation of this chronic hepatic insulin resistance in those women in whom β-cell function deteriorates, leading to type 2 diabetes. Indeed, this model may be further supported by the demonstration of altered hepatic lipid storage as an early abnormality in women with GDM, even when maintaining normal glucose tolerance (15). It should also be noted that, when compared with nondecliners, the decliners had slightly higher hepatic insulin sensitivity at 3 months postpartum, which then deteriorated over the next 9 months, accompanied by worsening glycemia. This observation suggests that consideration of the pattern of change in hepatic insulin sensitivity over time may be more informative than a single one-time measurement.

Limitations of this study include the observational design that precludes definitive commentary on causality and the use of surrogate indexes. Nevertheless, these data raise the possibility that worsening hepatic insulin resistance may provide an early marker for identifying those women with GDM/GIGT who are most likely to progress to prediabetes/diabetes. Further study is thus needed to determine whether the liver or aspects of its physiology could provide a target for risk stratification and possibly modification in this high-risk patient population.

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R.R. designed the analysis plan, researched data, wrote the manuscript, and was involved in the design and implementation of the overall study. Y.Q. and C.Y. performed the statistical analyses. A.J.G.H., P.W.C., M.S., and B.Z. were involved in the design and implementation of the overall study.

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