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Hyperglycemia During Pregnancy and Long-Term Offspring Outcomes

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Abstract

Purpose of Review—This review will focus on the long-term outcomes in offspring exposed to in utero hyperglycemia and gestational diabetes (GDM), including obesity, adiposity, glucose metabolism, hypertension, hyperlipidemia, nonalcoholic fatty liver disease, and puberty.

Recent Findings—There is evidence, mostly from observational studies, that offspring of GDM mothers have increased risk of obesity, increased adiposity, disorders of glucose metabolism (insulin resistance and type 2 diabetes), and hypertension. In contrast, evidence from the two intervention studies of treatment of mild GDM and childhood measures of BMI, adiposity, and glucose tolerance do not demonstrate that GDM treatment significantly reduces adverse childhood metabolic outcomes. Thus, more evidence is needed to understand the impact of maternal GDM on offspring's adiposity, glucose metabolism, lipid metabolism, risk of fatty liver disease, and pubertal onset.

Summary—Offspring of GDM mothers may have increased risk for metabolic and cardiovascular complications. Targeting this group for intervention studies to prevent obesity and disorders of glucose metabolism is one potential strategy to prevent adverse metabolic health outcomes.

Keywords

Exposure to gestational diabetes mellitus; Pregnancy; Childhood metabolic disease; Long-term offspring outcomes; Developmental programming of diabetes; Gestational diabetes treatment effect on offspring

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Conflict of Interest Monica E. Bianco and Jami Josefson declare that they have no conflict of interest.

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Introduction

The prevalence of diabetes has increased worldwide, especially in developing countries, over the last few decades [1]. More concerning is that the average age of onset of diabetes has decreased resulting in an increasing number of reproductive age women with diabetes [1]. From a public health standpoint, hyperglycemia during pregnancy has identifiable adverse offspring outcomes in the short and long term. Offspring outcomes following exposure to diabetes in pregnancy are directly related to glycemic levels during pregnancy [2–5]. Potential adverse offspring outcomes vary by age group, and avoidance of one outcome does not indicate reduction in risk of other adverse outcomes [4••, 6, 7]. This review will focus specifically on the long-term offspring outcomes following in utero exposure to gestational diabetes mellitus (GDM) and the milder form of hyperglycemia during pregnancy. Exposure to type 1 diabetes will not be addressed in this review and it is important to point out that it has been associated with a unique set of complications.

The effects of maternal hyperglycemia start in utero with a relative fetal hypoxia that may result in the risk of birth asphyxia and stillbirth [8]. Fetal hypoxia is also thought to induce increased erythropoietin production, the precursor to known complications in neonates born to mothers with GDM, i.e., polycythemia and hyperbilirubinemia [9]. Delivery complications in offspring born to women with GDM include high risk of cesarean section, shoulder dystocia, and birth injury and are often due to a large size fetus. Large size at birth is a consequence of fetal hyperinsulinemia and subsequent increased fetal production of insulin-like growth factor-1. Studies have demonstrated that offspring of mothers with GDM have higher amounts of fat mass as opposed to fat-free muscle mass and it is the increased fat mass that results in increased birthweight [10, 11]. Neonates are also predisposed to respiratory distress syndrome (RDS) secondary to fetal hyperinsulinemia that alters lung surfactant synthesis [12]. RDS is a life-threatening condition in the neonatal period that often times requires admission to the neonatal intensive care unit. Lastly, and the most common adverse outcome in neonates born to women with GDM, is hypoglycemia, secondary to fetal hyperinsulinemia [10]. Most often, the hypoglycemia is self-limited and resolves as the hyperinsulinemia resolves.

While recent improvements in maternal glycemic control have resulted in a reduction of perinatal complications, the frequency of adverse pregnancy outcomes remains higher in mothers with GDM than the general population [11, 13]. Although our focus for this review is to report on the long-term offspring outcomes, it is important to note that many of the studies that investigate associations between maternal hyperglycemia and long-term offspring outcomes were composed of mothers with different types of diabetes in pregnancy.

Childhood Complications

Obesity

Some observational studies have shown that offspring of mothers with glycemic disorders in pregnancy have increased obesity in childhood compared to offspring not exposed to maternal hyperglycemia. Specifically, the Pima Indian and Northwestern University studies, which included women with pre-gestational, type 1, type 2, and GDM, were long-term

follow-up studies with repeat measures of weight and glucose metabolism throughout childhood. [5, 14] While the Pima Indian population had a high prevalence of obesity and type 2 diabetes mellitus (T2DM), the Northwestern cohort was primarily composed of White women, and obesity and T2DM rates were similar to the general population. These two studies reported higher weight among children exposed to diabetes in pregnancy compared to children who were not exposed. Interestingly, not all offspring exposed to maternal hyperglycemia were large at birth [15]. The timing of obesity development was different in these two cohorts. The offspring of Pima mothers with diabetes in pregnancy weighed more compared to offspring of non-diabetic mothers at every age throughout childhood [15]. However, the Northwestern cohort reported that offspring of mothers with diabetes were noted to have emerging obesity in the peri-pubertal years [16]. The sibling pair studies in the Pima Indian population of offspring born prior to maternal diabetes compared to offspring born after maternal diagnosis of diabetes support the hypothesis that hyperglycemia in utero results in an elevated risk of obesity in the offspring, separate or perhaps additive to the genetic risk and home environment [17]. This finding was replicated in a study of Swedish male siblings born to mothers with diabetes in pregnancy, and similar to the Pima Indians and Northwestern cohorts, the Swedish cohort included mothers with type 1, type 2, and gestational diabetes [18].

The Australian Carbohydrate Intolerance Study (ACHOIS), a multicenter randomized control trial, studied treatment of mild GDM and perinatal and offspring outcomes. This trial demonstrated that infants born to mothers with treated GDM were less likely to be LGA/macrosomic at birth [11]. A follow-up study of the 4–5-year-old children found that there was no difference in the BMI of the children in the intervention group compared to the routine care control group [19]. Similarly, in a separate randomized study of treatment for mild GDM conducted in the USA, children born to mothers with untreated mild GDM did not have higher BMI Z-scores compared to children born to mothers without GDM [20]. A possible explanation for these negative studies, compared to other positive observational studies, is that the childhood metabolic impact of maternal GDM exposure may not appear until later in childhood.

In summary, many studies, in separate cohorts, have demonstrated associations between maternal GDM and higher childhood BMI [4••, 21–24]; yet, treatment of mild GDM in the few randomized studies did not lead to differences in childhood BMI.

Adiposity

More recent studies have explored body composition measures beyond weight or BMI in offspring of mothers with GDM. In the Hyperglycemia and Adverse Pregnancy Outcomes Follow Up Study (HAPO FUS) offspring exposed to mild, untreated maternal hyperglycemia at a mean age of 11.4 years had increased adiposity, as measured by air displacement plethysmography, skinfold thickness with calipers, and waist circumference [4••]. Figure 1 demonstrates the odds ratio of adiposity outcomes in the 11.4-year-old children exposed to GDM. HAPO FUS corroborates the findings of other studies which have used different methodologies of anthropometry [25], BIA [26], DEXA [27], and MRI [28] to

demonstrate increased adiposity among offspring of mothers with GDM. In all these studies, maternal BMI attenuated the results.

There are studies that have reported no association between GDM and adiposity. For example, in Project Viva, increased adiposity was initially demonstrated among children at 3 years of age born to mothers with hyperglycemia, but by adolescence, that association was no longer demonstrated [29, 30]. It is possible that cohort size, timing of puberty in relation to the study, and differences in glycemic control of mothers enrolled in the study played a role in the contrasting association between maternal glycemia and childhood adiposity. Interestingly, in one of the randomized studies of treatment for mild GDM described above [20], maternal glycemia was associated with increased childhood sum of skinfolds, a measure of adiposity, but not BMI Z-score in the offspring of women with untreated mild GDM compared to offspring of mothers without GDM. Higher adiposity, as opposed to higher weight, has important implications for cardiometabolic diseases and early death [31]. Separating the independent effects of maternal hyperglycemia and maternal obesity will help guide targeting of preventative strategies to decrease risk of obesity in the offspring.

Glucose Metabolism

Potential long-term complications among offspring exposed to GDM include insulin resistance, impaired glucose tolerance, and type 2 diabetes mellitus (T2DM), collectively termed disorders of glucose metabolism. For example, HAPO FUS demonstrated that there is an increased risk of impaired glucose tolerance in the offspring of mothers with mild, untreated hyperglycemia [32, 33] as displayed in Fig. 2 [34•]. It is important to clarify that this association is observed independent of maternal BMI. In the study of women with mild GDM randomized to treatment or usual care discussed earlier, female offspring of treated mothers had lower fasting blood glucose [35]. As reviewed by Kawasaki et al. [36], measurement of glucose tolerance following a glucose load, rather than a fasting glucose level, is better at detecting abnormalities in glucose metabolism in children exposed to GDM. In addition, disposition index, a measure of pancreatic beta cell function and a predictor of progression to T2DM among youth with disorders of glucose metabolism, was significantly lower among offspring of GDM mothers [33, 37].

Many epidemiological studies have found higher rates of T2DM in youth who were exposed to maternal GDM as assessed by maternal recall or a national database [37–39]. HAPO FUS provides further evidence that in utero exposure to hyperglycemia, below the diagnostic criteria for GDM, increases future risk of disorders of glucose metabolism potentially as a result of adverse intrauterine fetal programming of the pancreas [34•]. However, it is important to note that smaller studies have not found that exposure to GDM is associated with insulin resistance or other glycemic outcomes in offspring [30, 40]. It is unclear if this difference is an issue of power, a difference in study population (well-controlled GDM vs poorly controlled GDM), or a difference in the timing of offspring follow-up study (pre-pubertal vs pubertal).

Hypertension

Studies have also evaluated hypertension as a potential adverse outcome in offspring of GDM mothers. Hypertension is associated with changes in the adolescent cardiac structure [41–43]. In adults, a 2 mmHg rise in SBP is associated with increased mortality [44]. Intrauterine hyperglycemia, throughout pregnancy or only in the latter two-thirds of the pregnancy, in animal studies has demonstrated decreased nephron numbers, increased angiotensin converting enzyme activity in cardiovascular system, and disrupted fetal vascular development all resulting in increasing the risk for hypertension in the offspring [45–48]. Hypertension is an important contributor to cardiovascular mortality and morbidity and discerning if a relationship between maternal GDM increases the risk of offspring hypertension is a public health concern.

As with disorders of glucose metabolism, sorting out which contributors are responsible for the differences in blood pressure is difficult. There are a number of studies examining the association of GDM on offspring blood pressure with conflicting findings. The initial Pima Indian studies reported elevated systolic blood pressure in the offspring exposed to maternal diabetes (T2DM or GDM), independent of adiposity, compared to offspring born to mothers with a normal glucose tolerance during pregnancy who subsequently developed T2DM after pregnancy but before 40 years of age [49]. A small prospective Chinese cohort studied at a median age of 8 years showed that children born to mothers with GDM had significantly higher systolic and diastolic blood pressures. However, when these children were later restudied at a mean age of 15 years old, there was no significant difference in blood pressure between the control group and those born to mothers with GDM [40, 50]. Interestingly, a larger Chinese cohort from the Hong Kong HAPO FUS site was studied at a median age of 7 years and offspring of GDM mothers were noted to have higher blood pressures at that follow-up compared to those born to mothers without GDM [32]. However, the KiGGS cross-sectional study in Germany of children 3–17 years old reported that there was no difference in blood pressure in offspring of GDM mothers compared to those of non-GDM mothers [51]. A meta-analysis including 15 different studies published before 2012 concluded that children born to mothers with GDM had higher systolic blood pressures but similar diastolic blood pressures compared to non-GDM offspring [52]. A more recent prospective population-based cohort in Portugal, which followed children at ages 4, 7, and 10, reported increased blood pressure in offspring of mothers with mixed types of diabetes at 10 years, with boys being at higher risk than girls [53••].

Lipids

There are few studies on the effects of maternal glycemia on lipid metabolism in the offspring. A rat study found no significant changes in lipid metabolism on offspring of GDM rats from birth to 12 months [54]. In humans, the KiGGS study also reported that there was no differences in cholesterol levels in offspring of GDM mothers at mean age of 10.3 years compared to those of non-GDM mothers [51]. A small Chinese cohort reported lower high-density lipoprotein cholesterol at a median age of 8 years, but at a mean age of 15 years old, there were no significant differences in the lipid profiles of those born to mothers with GDM

compared to controls [40, 50]. With the limited data available, it appears that in childhood, we cannot conclude on associations between maternal GDM and offspring lipid metabolism.

Nonalcoholic Fatty Liver Disease

Considering the effect of GDM on disorders of glucose metabolism and hypertension, one could hypothesize that in utero hyperglycemia would also have a negative impact on liver metabolism. In rat models induced to have severe hyperglycemia throughout pregnancy, researchers found that the offspring of the normal weight diabetic rats had more hepatic steatosis than control rats on the same diet [55]. However, with the prevalence of obesity at reproductive age increasing, there is a concern that this model is not typical of what is seen in humans. In a different study, obese GDM rats were studied and the offspring again had higher hepatic steatosis and an altered lipid metabolism within the liver [56]. Nevertheless, this makes separating the effects of obesity from those of GDM on hepatic steatosis difficult. A small human study of 25 neonates found that pre-pregnancy BMI was more strongly associated with neonatal hepatic fat storage than maternal GDM. This suggests that maternal obesity may be a stronger predictor of NAFLD [57]. A more recent study from the EPOCH cohort supports this finding as well as demonstrating that maternal obesity is associated with higher hepatic fat fraction in children and adolescents independent of maternal GDM [58]. Further studies are needed to better understand the relationship between maternal GDM exposure and risk of NAFLD.

Puberty

Associations between GDM exposure and earlier pubertal onset in offspring are currently being explored. An earlier study that did not distinguish between boys and girls reported that there were no differences in age of pubertal onset between offspring of GDM mothers and those of non-GDM mothers [59]. Two recent studies have found that girls born to mothers with GDM have an earlier onset of puberty but not boys [60, 61]. However, it is important to mention that increased BMI and fat mass in childhood have also been associated with earlier onset of puberty [62, 63]. It is unclear if the female offspring of GDM mothers are at increased risk for earlier puberty because of the in utero environment or if earlier puberty is occurring in this group because of the increased fat mass/BMI. In a more recent study, which also demonstrated earlier onset of puberty in girls born to GDM mothers, this association remained even after adjusting for the girls' BMI [64]. This association is important to note because a more rapid decline in insulin response and disposition index across pubertal Tanner Stages is seen in offspring of GDM mothers [59].

GDM Treatment and Effects on Offspring Outcomes

Considering associations between GDM exposures and short-and long-term offspring outcomes, some studies have attempted to understand whether GDM is a modifiable risk factor. An observational study on the associations of maternal glycemia on offspring obesity found that worsening hyperglycemia in pregnancy was associated with an increased risk of obesity at ages 5–7 [22]. In this study, there was a small group of mothers with GDM that were treated and the association with childhood obesity disappeared, suggesting that GDM treatment may decrease the risk for childhood obesity. Studies have also looked at the long-term offspring outcomes of different pharmacotherapy modalities of GDM. The MiG TOFU

randomized control trial reported that offspring of GDM mothers randomized to treatment with metformin or insulin had similar adiposity and metabolic measures at age 7–9 years old [65]. Other randomized control studies comparing metformin to insulin treatment have reported no significant growth or development differences between the two treatment modalities in offspring at age 2 [66, 67]. At this time, it is early to make a definitive conclusion; however, the available data suggests that there is no significant difference between offspring born to metformin- or insulin-treated GDM mothers.

Conclusion

Rates of GDM have been increasing and with the rising prevalence of obesity among women of reproductive age, it is likely that they will continue to increase. More troubling is the evidence from observational long-term follow-up studies that substantiates the presence of a cycle of diabetes between mother and child. Children exposed to GDM and hyperglycemia in pregnancy represent a population at risk for development of metabolic diseases. To date, the few intervention studies comparing children of euglycemic to untreated GDM mothers have failed to demonstrate metabolic differences in young children under the age of 10 years. Yet, the large, epidemiological observational HAPO FUS provides evidence that untreated maternal hyperglycemia is associated with increased adiposity and disorders of glucose metabolism in pubertal offspring. Longer follow-up evaluation of offspring from mothers involved in prior GDM intervention studies is necessary to definitively address the impact of maternal GDM on offspring metabolic health. In conclusion, optimizing diagnoses and treatment of GDM may be an important strategy to prevent adverse metabolic health outcomes in offspring.

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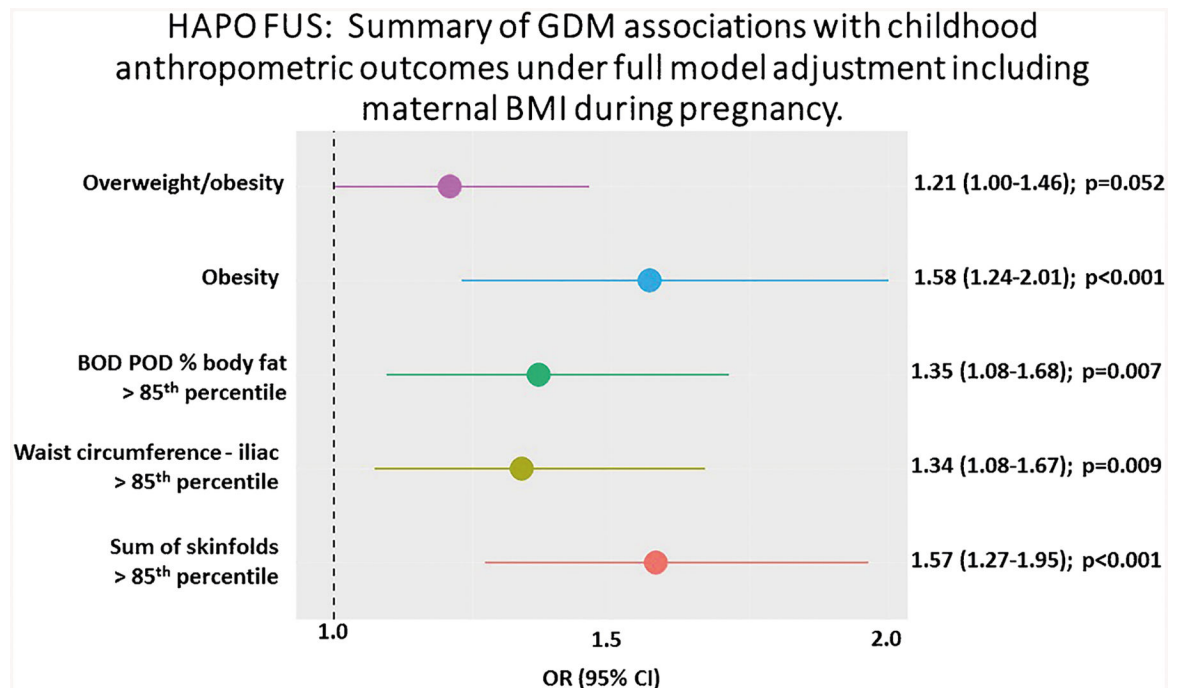


Fig. 1.

This Forest plot shows that the five dichotomous measures of child adiposity at mean age of 11.4 years are significantly associated with GDM and the associations are strongest for obesity alone and sum of skinfolds

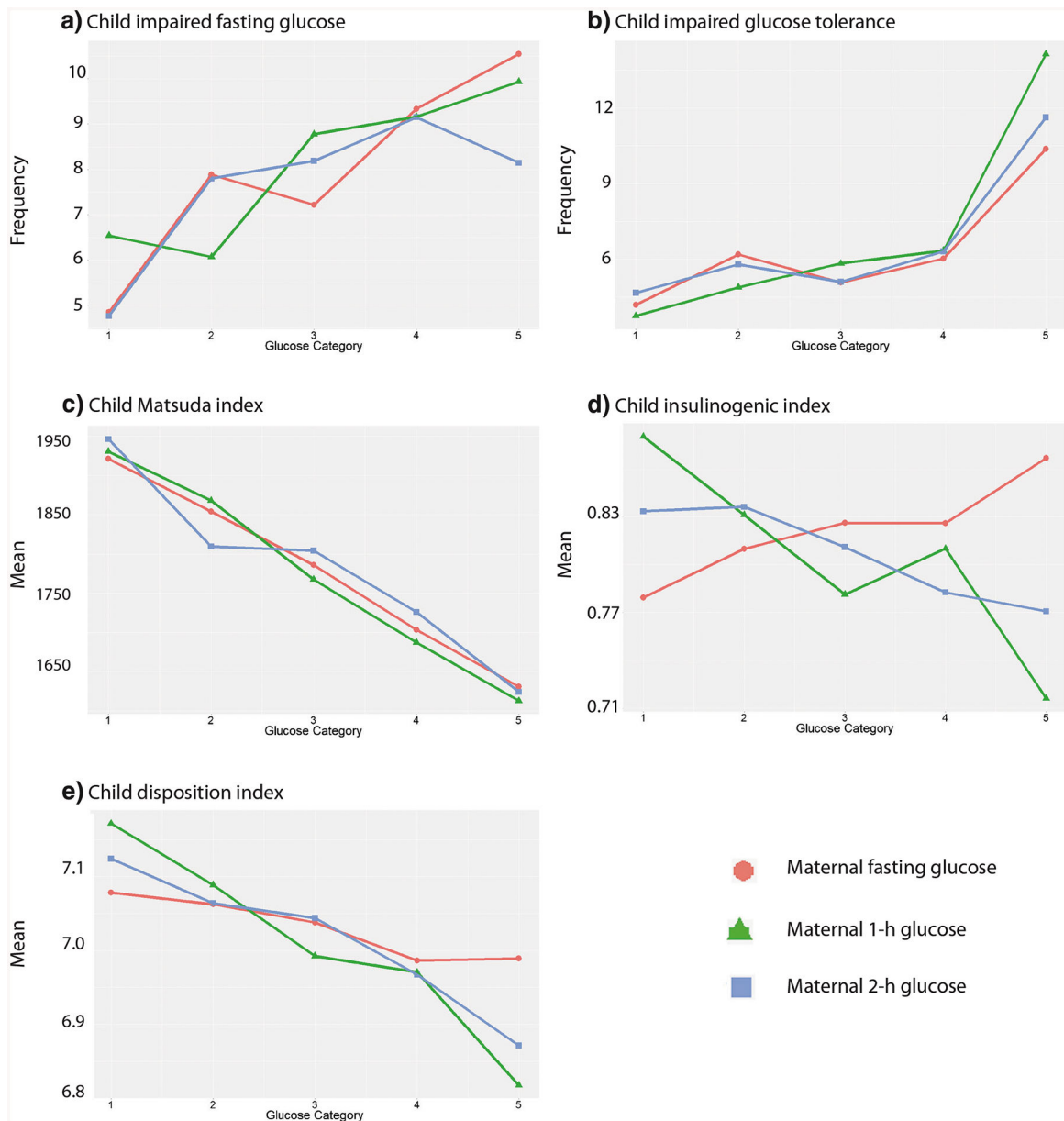


Fig. 2. Child glucose outcomes across categories of maternal glucose levels. The frequency of childhood IFG (a) and IGT (b) and means of the Matsuda index (c), insulinogenic index (d), and disposition index (e) across categories of fasting, 1-h, and 2-h PG is shown. Glucose categories are defined as follows: fasting PG level—category 1, < 4.2 mmol/L; category 2, 4.2–4.4 mmol/L; category 3, 4.5–4.7 mmol/L; category 4, 4.8–5.0 mmol/L; and category 5, 5.1 mmol/L or more; 1-h PG level—category 1, 5.8 mmol/L or less; category 2, 5.9–7.3 mmol/L; category 3, 7.4–8.6 mmol/L; category 4, 8.7–9.9 mmol/L; and category 5, 10.0 mmol/L or more; 2-h PG level—category 1, 5.0 mmol/L or less; category 2, 5.1–6.0 mmol/L; category 3, 6.1–6.9 mmol/L; category 4, 7.0–8.4 mmol/L; and category 5, 8.5 mmol/L or more (from: Scholtens et al. *Diabetes Care*. 2019;42 [3]:381–92. American Diabetes Association [*Diabetes Care*, American Diabetes Association, 2019]. Copyright and all rights reserved.

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