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Genetic Risk of Progression to Type 2 Diabetes and Response to Intensive Lifestyle or Metformin in Prediabetic Women With and Without a History of Gestational Diabetes Mellitus

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OBJECTIVE

The Diabetes Prevention Program (DPP) trial investigated rates of progression to diabetes among adults with prediabetes randomized to treatment with placebo, metformin, or intensive lifestyle intervention. Among women in the DPP, diabetes risk reduction with metformin was greater in women with prior gestational diabetes mellitus (GDM) compared with women without GDM but with one or more previous live births.

RESEARCH DESIGN AND METHODS

We asked if genetic variability could account for these differences by comparing β-cell function and genetic risk scores (GRS), calculated from 34 diabetes-associated loci, between women with and without histories of GDM.

RESULTS

β-Cell function was reduced in women with GDM. The GRS was positively associated with a history of GDM; however, the GRS did not predict progression to diabetes or modulate response to intervention.

CONCLUSIONS

These data suggest that a diabetes-associated GRS is associated with development of GDM and may characterize women at risk for development of diabetes due to β-cell dysfunction.
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In the Diabetes Prevention Program (DPP), women with prediabetes and prior gestational diabetes mellitus (GDM) were 71% more likely to develop diabetes compared with women without prior GDM and one or more previous live births. Interestingly, intensive lifestyle intervention (ILS) was equally effective at preventing progression to diabetes in both groups of women compared with placebo (53 vs. 49% risk reduction), whereas metformin was more effective in women with a history of GDM (50 vs. 14% risk reduction) (1). Individual genetic risk scores (GRS), developed from a composite of single nucleotide polymorphisms (SNPs) at loci associated with type 2 diabetes, predicted progression to diabetes among DPP participants (2). Here, we compared β-cell function between GDM and non-GDM women in the DPP and examined the utility of this GRS and its individual

risk alleles in predicting progression to diabetes and response to intervention in women with or without prior GDM.

RESEARCH DESIGN AND METHODS

The DPP trial design and baseline characteristics have been described in detail previously (3,4). In brief, across 27 U.S. clinical centers, 3,234 participants aged ≥25 years with impaired glucose tolerance, elevated fasting glucose (95–125 mg/dL), and BMI ≥24 kg/m^2 were randomized to placebo, metformin, or ILS. Primary study end point was development of diabetes. At the time of enrollment, all women completed a questionnaire regarding gravidity, parity, and GDM history.

Among 1,416 women with one or more live births and without GDM and 350 with a history of GDM, a subset ($n = 1,102$ without GDM; $n = 281$ with GDM) underwent genotyping. DNA samples were extracted from peripheral leukocytes, and 34 type 2 diabetes–associated SNPs were genotyped, as described previously (2). A GRS for each participant was calculated using the 34 loci by weighting each risk allele by its effect size (β-estimate) on diabetes risk and summing these values, with a theoretical range of 0–68 (2).

Statistical Analyses

Similar numbers of GDM and non-GDM women who underwent genotyping were assigned to placebo, metformin, or ILS (Table 1). Insulinogenic index calculated from the 75-g, 2-h oral glucose tolerance test [log(Δinsulin/Δglucose)$_{(0–30\ min)}$] (5) was used as a measure of β-cell function in general linear models at baseline and at 1 year to determine differences between GDM and non-GDM women. Independent variables included GDM status, race/

ethnicity, age at randomization, parity, and intervention (at 1 year only).

Logistic regression was used to evaluate the association between GRS and baseline history of GDM adjusted for ethnicity, age, and parity. We examined the GRS, treatment interventions, and history of GDM in Cox regression models as independent variables predicting diabetes incidence. Models were adjusted for ethnicity and parity. Next, ANCOVA was used to assess the effect of DPP treatments, GRS, and history of GDM on β-cell function adjusted for concomitant insulin sensitivity, as measured by the oral disposition index (DIo) (2,6) at 1 year. In contrast to the insulinogenic index, DIo captures β-cell function adjusted for insulin sensitivity and therefore takes into account physiological compensation (2,6). Models were adjusted for baseline DIo, ethnicity, age, and parity. Individual effects of SNPs were tested in similar ANCOVA models using SNP as an additive term. Genotype, treatment, and GDM three-way and two-way interaction tests were performed for all models testing postrandomization outcomes. Treatment groups were analyzed together if there were no significant interactions. Analyses were also performed after adjustment for waist circumference, which was a significant predictor of development of diabetes in the DPP cohort (2). Nominal two-sided P values are reported.

RESULTS

At baseline, β-cell function (insulinogenic index) was decreased in GDM (mean 4.19 [95% CI 4.10–4.29]) versus non-GDM (mean 4.35 [4.30–4.40]) women ($P < 0.01$). At 1 year, there was a significant interaction between treatment group and GDM

status ($P = 0.02$); therefore, analysis was stratified by GDM status and treatment group. After adjustments, 1-year insulinogenic index was also lower in GDM compared with non-GDM women ($P < 0.01$) (Table 1).

Adjusted for ethnicity and age, the GRS was positively associated with GDM history (odds ratio 1.05 [95% CI 1.00–1.08], $P = 0.04$), such that for every one unit increase in the GRS, the odds of GDM increased by 5%. This association was unaffected by additional adjustment for parity (1.04 [1.00–1.08], $P = 0.04$); however, it was no longer significant after adjustment for waist circumference (1.04 [1.00–1.08], $P = 0.07$). There was no difference in the hazard ratios (HRs) for the GRS predicting progression to diabetes in women with GDM compared with women without GDM after adjustment for ethnicity, age, and treatment arm ($P = 0.09$).

Because β-cell function as measured by insulinogenic index was lower in GDM than in non-GDM women, we next examined the relationship of individual SNPs within the GRS with β-cell function after adjustment for concomitant insulin sensitivity, as measured by DIo. Four of the 34 SNPs comprising the GRS are primarily associated with insulin resistance (KLF14, rs972283; PPARG, rs1801282; IRS1, rs7578326; GCKR, rs780094) (7) and thus were excluded from this analysis in order to isolate any genetic component of β-cell function in GDM women. After adjusting for ethnicity, age, and parity, none of the remaining 30 SNPs comprising the GRS independently associated with DIo in women with GDM compared with women without GDM.

CONCLUSIONS

We found that among parous women in the DPP, β-cell function defined by insulinogenic index was reduced in women with a history of GDM compared with women without prior GDM. This is consistent with the reduced insulin-to-glucose ratio previously reported in GDM women in this cohort (1). Further, a GRS calculated using SNPs strongly associated with type 2 diabetes was higher in women with GDM compared with women without GDM;

Table 1—β-Cell function [insulinogenic index: log(Δinsulin/Δglucose)$_{(0–30\ min)}$] at 1 year, after adjustment for baseline β-cell function, race/ethnicity, age at randomization, and parity

	Non-GDM*		GDM*		
	n	Year 1 adjusted mean (95% CI)	n	Year 1 adjusted mean (95% CI)	P value
Placebo	394	5.16 (5.04–5.27)	93	4.73 (4.52–4.96)	0.164
Metformin	345	5.06 (4.99–5.14)	93	5.09 (4.93–5.26)	0.775
ILS	363	5.19 (5.77–8.36)	95	5.05 (4.89–5.22)	0.002

*Data are back transformed.

thus, GRS is positively associated with prior GDM in DPP women. This association remained significant after adjustment for age, ethnicity, and parity, consistent with epidemiological data demonstrating that increasing parity or gravidity do not alter future diabetes risk in women with (8) or without (9) previous GDM who have been pregnant.

On the other hand, these data suggest the GRS is not associated with progression to diabetes in high-risk women either with or without a GDM history, in any of the study arms. This is of interest because a prior analysis from the DPP showed that risk reduction for progression to diabetes in response to metformin was greater among women with GDM compared with women without GDM (1), leading us to hypothesize that genetic variability may play a role. Our data showed that GRS predicted the presence of GDM but not progression to diabetes among affected women. That said, the HR for the GRS predicting progression to diabetes in this small cohort of female DPP participants with prior GDM (HR 1.04 [95% CI 1.00–1.08]) is similar to the significant HR for the GRS predicting progression to diabetes among the entire DPP cohort with genetic information (1.02 [1.02–1.03]) (2), indicating that analysis of a larger population of prediabetic women with prior GDM may strengthen the relationship between this GRS and diabetes progression.

Limitations of our study include small sample size and a relatively long diabetes-free interval (mean 12 years) since the index pregnancy among women with GDM at enrollment. This suggests the DPP excluded GDM women with the highest risk for diabetes progression, possibly diminishing differences in GRS between women with and without GDM.

β-Cell function is reduced in women with GDM compared with women without GDM. Accordingly, GRS comprising 34 diabetes-associated loci is higher in women with prediabetes and histories of GDM compared with women with prediabetes without GDM and one or more prior live births. This

GRS does not, however, differentiate diabetes risk or response to treatment with metformin or ILS between high-risk women with and without GDM.

planned the analysis, supervised the genotyping, and reviewed and edited the manuscript. D.D., P.W.F., C.K., and C.A.C. reviewed and edited the manuscript. S.D.-J. and W.C.K. reviewed and edited the manuscript and planned and performed the clinical trial. R.R. planned the analysis, reviewed and edited the manuscript, and planned and performed the clinical trial. The full DPP Research Group planned and performed the clinical trial. S.D.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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