The Circadian Rhythm–Related *MTNR1B* Genotype, Gestational Weight Gain, and Postpartum Glycemic Changes

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Context: Disturbed circadian rhythms and sleep quality during pregnancy have been related to gestational weight gain and gestational diabetes mellitus (GDM), which affect postpartum glucose metabolism and future risk of type 2 diabetes.

Objective: We assessed whether the circadian rhythm–related *melatonin receptor 1B* (*MTNR1B*) genotype was associated with 1 to 5 years of postpartum glycemic changes among women with a history of GDM and whether gestational weight gain modified such associations.

Design, Settings, and Participants: The established circadian rhythm-associated *MTNR1B* genetic variant (rs10830963) was genotyped in 1025 Chinese women with a history of GDM. Body weight and glycemic traits, during and after pregnancy, were longitudinally collected.

Main Outcome Measures: The main outcome measure was postpartum glycemic changes.

Results: We found that women carrying different *MTNR1B* genotypes showed distinct postpartum changes in 2-hour oral glucose tolerance test: 0.36, 0.20, and −0.19 mM per additional copy of the shorter sleep duration-related G allele in women with inadequate, adequate, and excessive gestational weight gain, respectively (for interaction, $P = 0.028$). The corresponding changes in fasting glucose were 0.14, 0.13, and 0.01 mM, although the modification effect of gestational weight gain on the genetic association was marginally significant (for interaction, $P = 0.067$).

Conclusions: Our findings suggest that gestational weight gain may modify the circadian rhythm–related *MTNR1B* genetic variant on long-term glycemic changes, highlighting the significance of gestational weight management in diabetes prevention among women with GDM. **(*J Clin Endocrinol Metab* 103: 2284–2290, 2018)**

Gestational diabetes mellitus (GDM), a state of impaired glucose tolerance during pregnancy, is one of the most frequent pregnancy complications associated with postpartum glucose metabolism and future risk of type 2 diabetes (1). Pregnancy may disturb circadian rhythms and therefore, affect sleep quality (2). Emerging data have shown that sleep alterations during pregnancy were associated with greater weight gain (3, 4) and an increased risk for GDM (5, 6).

Circadian rhythms and sleep quality are closely regulated by melatonin, a key hormone determining the

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Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; HbA1c, hemoglobin A1c; *MTNR1B*, melatonin receptor 1B; OGTT, oral glucose tolerance test.

sleep-wake cycle in humans (7). *Melatonin receptor 1B* (*MTNR1B*) is one of the seven transmembrane G-protein-coupled melatonin receptors expressed in the central nervous system and in the peripheral tissues, including pancreatic β-cells (8). The *MTNR1B* gene encodes one of the two high-affinity receptors of melatonin (9), which has been implicated in regulation of circadian rhythms. A variant in the *MTNR1B* gene, rs10830963, was recently identified to be associated with altered melatonin rhythm and melatonin signaling (10, 11). Of note, the *MTNR1B* genotype has also been associated with obesity, fasting glucose levels, type 2 diabetes, and GDM in genome-wide association studies (12, 13). Thus, we hypothesized that the *MTNR1B* genotype may affect postpartum glycemic changes in women with GDM.

In this study of a large cohort of women with a history of GDM, we examined the associations of the circadian rhythm–related *MTNR1B* genotype with postpartum changes in measures of glycemic traits. In addition, we particularly assessed the interactions between the *MTNR1B* genotype and gestational weight gain on the glycemic changes.

Subjects and Methods

Study population

The current study was a retrospective analysis based on the baseline survey of the Tianjin Gestational Diabetes Mellitus Prevention Program, an ongoing, randomized clinical trial among Han Chinese women with a history of GDM. The study protocol was approved by the Human Subjects Committee of the Tianjin Women's and Children's Health Center, and written consent was obtained from all participants at the baseline survey. Details of methodological issues have been described previously (14–16). In brief, all pregnant women in six main areas of Tianjin, China, who had a diagnosis of GDM at 26 to 30 gestational weeks between 2005 and 2009 were invited to participate in a postpartum survey from August 2009 to July 2011 (n = 4644). The World Health Organization criteria for GDM (17) were adopted in the current study. Of the 4644 women who participated in the postpartum survey at 1 to 5 years after delivery, women who could not be contacted, refused, or did not meet the eligibility criteria were excluded (n = 3381). Chronic diseases that could seriously reduce life expectancy were excluded in the baseline survey of the Tianjin GDM Prevention Program because these diseases might affect weight change, and the patients might take medicines that affected the metabolic outcomes of interest. Other criteria for exclusion were the following: age <20 or ≥ 50 years, taking medicines known to alter 2-hour oral glucose tolerance test (OGTT), pregnant during the follow-up period, or unable to give informed consent. Thus, a total of 1263 women with a history of GDM completed the postpartum survey (participation rate 27%). There were no differences in 2-hour OGTT concentration, fasting glucose concentration, and the prevalence of impaired glucose tolerance and diabetes at 26 to 30 gestational weeks among women who participated in the postpartum survey and those who did not (15). In addition, we further excluded 238 women without genotype information, and these women were not different in clinical characteristics and biochemical markers from those included in the final analysis. After these exclusions, a total of 1025 women were included in the current study.

Measurements of weight change and other variables

Data on medical eligibility and lifestyle measures were collected by self-administered questionnaires. The questionnaire inquired about socio-demographic information, history of GDM, medical history (pregnancy hypertension, diabetes, hypertension, and hypercholesterolemia), family history of diseases (diabetes, hypertension, stroke, and cancer), smoking, alcohol intake, physical activity, sleeping, stress, and use of supplements. Dietary intake data were collected by means of a 3-day, 24-hour food record. The questionnaires and the 3-day, 24-hour food record have been validated in the China National Nutrition and Health Survey (18, 19). Body weight and height had been collected longitudinally based on medical records before the baseline survey of the Tianjin Gestational Diabetes Mellitus Prevention Program. Postpartum weight was measured on the day of delivery, and prepregnancy and current body mass index (BMI; in kilograms per square meter) were calculated (Supplemental Fig. 1). The 2009 Institute of Medicine guideline was used to classify gestational weight gain into inadequate, adequate, and excessive (20). Adequate gestational weight gain was defined by prepregnancy BMI as follows: 12.5 to 18 kg if prepregnancy BMI < 18.5 kg/m^2, 11.5 to 16 kg if prepregnancy BMI = 18.5 to 24.9 kg/m^2, 7 to 11.5 kg if prepregnancy BMI = 25.0 to 29.9 kg/m^2, and 5 to 9 kg if prepregnancy BMI $\geq$ 30 kg/m^2. Gestational weight gain below or above the recommendation was defined as inadequate or excessive, respectively.

Measurements of glycemic traits

Changes in glycemic traits were calculated as difference in glucose and hemoglobin A1c (HbA1c) levels between postpartum 1 to 5 years (at the postpartum survey) and pregnancy. The glycemic traits were measured in plasma both during the pregnancy (26 to 30 gestational weeks, the time point when the women were diagnosed with GDM) and at the postpartum survey (Supplemental Fig. 1). Blood samples were collected from all participants after an overnight fast of at least 12 hours. Fasting glucose and 2 hour OGTT were measured using an automatic analyzer (TBA-120FR; Toshiba, Tokyo, Japan). Glycated HbA1c was measured by using automatic glycohemoglobin analyzer (ADAMS A1c HA-8160; Arkray, Kyoto, Japan).

Genotyping

DNA was extracted from the buffy coat fraction of centrifuged blood using a QIAamp Blood Maxi Kit (Qiagen, Chatsworth, CA). The *MTNR1B* single nucleotide polymorphism rs10830963 was genotyped by a quantitative real-time TaqMan PCR (Applied Biosystems, Foster City, CA). The success rate of genotyping was >98%. Replicated quality control samples (10%) were conducted with >99% concordance.

Statistical analysis

The Hardy-Weinberg equilibrium of the genotype and comparison of categorical variables were assessed by a χ^2 test. Differences in continuous variables by gestational weight gain were

tested by using general linear models. Changes in glycemic traits associated with each additional copy of the *MTNR1B* rs10830963 G allele by gestational weight gain categories were estimated using general linear models. Statistical adjustments were made for age, follow-up time, prepregnancy BMI, dietary fat (percent energy), sitting time, postpartum weight change, the level of corresponding glucose trait (continuous variable), family history of diabetes (yes or no), current smoking (yes or no), current alcohol drinking (yes or no), leisure-time physical activity (0, <30, or ≥30 minutes per day), and GDM therapy (yes or no). The interaction between *MTNR1B* rs10830963 genotype and gestational weight gain was tested by the introduction of a product term for these variables in the model. We also calculated the multivariable-adjusted mean values of changes in glycemic traits according to gestational weight gain and the *MTNR1B* rs10830963 genotype by use of general linear models. Two-sided $P < 0.05$ was considered as statistically significant. Statistical analyses were calculated using SAS version 9.4 (SAS Institute, Cary, NC).

Results

The frequency of the circadian rhythm–related *MTNR1B* rs10830963 G allele was 45%, and genotype distribution was in accordance with the Hardy-Weinberg equilibrium ($P = 0.41$). Table 1 shows the characteristics of women with a history of GDM, according to the *MTNR1B* rs10830963 genotype. The *MTNR1B* genotype was not associated with any glycemic traits (fasting glucose, 2-hour OGTT, and HbA1c) during pregnancy but had a positive association with postpartum fasting glucose levels ($P < 0.03$). The frequency of the three categories of gestational weight gain was not different by the *MTNR1B* genotype.

When all women were analyzed together, no association was found between the *MTNR1B* genotype and postpartum glycemic changes (all $P \geq 0.08$). We then performed a stratified analysis to examine the associations of the *MTNR1B* genotype with 1 to 5 years of postpartum glycemic changes, according to gestational weight gain categories (Table 2). Gestational weight gain significantly modified the association of the *MTNR1B* genotype with postpartum changes in 2-hour OGTT. After multivariable adjustment, changes in 2-hour OGTT, associated with each additional copy of the risk G allele, were 0.36, 0.20, and −0.19 mM in women with inadequate, adequate, and excessive gestational

Table 1. Characteristics of Participants With a History of GDM by *MTNR1B* rs10830963 Genotype

	***MTNR1B* rs10830963 Genotype**[a]			
	CC (n = 313)	**CG (n = 495)**	**GG (n = 217)**	***P* Value**[b]
Age, y	32.3 ± 3.7	32.4 ± 3.5	32.0 ± 3.3	0.37
Follow-up time, y	2.0 ± 0.6	2.1 ± 0.7	2.0 ± 0.6	0.95
Prepregnancy BMI, kg/m^2	23.2 ± 3.4	23.1 ± 3.2	23.2 ± 3.5	0.91
Weight, kg				
Prepregnancy	60.1 ± 9.3	59.3 ± 9.1	59.5 ± 9.6	0.44
Postpartum	62.9 ± 11.0	62.2 ± 10.9	62.3 ± 10.7	0.54
Gestational weight gain, %				
Inadequate	11.8	15.2	13.8	0.31
Adequate	32.6	33.9	28.1	
Excessive	55.6	50.9	58.1	
Fasting glucose, mM				
At GDM diagnosis	5.3 ± 0.8	5.3 ± 0.8	5.4 ± 0.8	0.06
Postpartum	5.3 ± 1.0	5.4 ± 0.9	5.5 ± 1.0	0.03
2-hour OGTT, mM				
At GDM diagnosis	9.2 ± 1.3	9.1 ± 1.2	9.1 ± 1.1	0.09
Postpartum	7.1 ± 2.4	7.0 ± 2.3	7.1 ± 2.8	0.94
HbA1c, %				
At GDM diagnosis	5.8 ± 0.6	5.8 ± 0.6	5.8 ± 0.6	0.54
Postpartum	5.6 ± 0.9	5.6 ± 0.7	5.7 ± 0.7	0.80
Family history of diabetes, %	31.6	33.7	24.5	0.46
Current smoking, %	1.0	2.2	2.3	0.37
Current alcohol drinking, %	20.4	20.2	21.2	0.95
Leisure-time physical activity, %				
0 min/d	79.9	80.2	80.6	0.16
<30 min/d	19.2	18.8	16.1	
≥30 min/d	1.0	1.0	3.2	
Sitting time, h/d	3.2 ± 2.2	3.3 ± 2.1	3.2 ± 2.2	0.69
Fat, % energy	33.6 ± 6.7	33.4 ± 6.4	33.4 ± 5.6	0.26
GDM therapy, %	15.3	13.3	14.8	0.73

[a]Data are presented as means ± standard deviation and percentage for continuous and categorical variables, respectively.

[b]Based on general linear models or χ^2 test for continuous and categorical variables, respectively.

Table 2. Changes in Glycemic Traits Associated With Each Additional Copy of the *MTNR1B* rs10830963 G Allele by Gestational Weight Gain

	Inadequate		Adequate		Excessive		
	β (SE)	*P* Value	β (SE)	*P* Value	β (SE)	*P* Value	*P* Interaction
Fasting glucose, mM							
Age-adjusted	0.03 (0.16)	0.87	0.14 (0.08)	0.08	−0.04 (0.06)	0.49	0.559
Multivariable adjusted[a]	0.14 (0.17)	0.41	0.13 (0.06)	0.02	0.01 (0.05)	0.83	0.069
2-hour OGTT, mM							
Age-adjusted	0.32 (0.34)	0.36	0.33 (0.20)	0.10	−0.11 (0.13)	0.40	0.046
Multivariable adjusted[a]	0.36 (0.33)	0.28	0.20 (0.17)	0.25	−0.19 (0.11)	0.09	0.028
HbA1c, %							
Age-adjusted	−0.11 (0.12)	0.34	0.19 (0.07)	0.005	−0.04 (0.05)	0.49	0.602
Multivariable adjusted[a]	−0.02 (0.12)	0.82	0.12 (0.05)	0.02	−0.05 (0.04)	0.22	0.143

β represents the change in each glycemic trait per additional copy of the rs10830963 G allele.

Abbreviation: SE, standard error.

[a] Adjustment for age, follow-up time, prepregnancy BMI, dietary fat (percent energy), sitting time, postpartum weight change, the level of corresponding glucose trait (continuous variable), family history of diabetes, current smoking, current alcohol drinking, leisure-time physical activity, and GDM therapy (categorical variables).

weight gain, respectively (for interaction, $P = 0.028$). Gestational weight gain had a marginally significant effect modification on the genetic associations of postpartum changes in fasting glucose levels after multivariable adjustment but had no significant effect modification on the genetic associations of postpartum changes in HbA1c. Each additional copy of the risk G allele was associated with changes in fasting glucose of 0.14, 0.13, and 0.01 mM across categories of inadequate, adequate, and excessive gestational weight gain, respectively (for interaction, $P = 0.069$), and the corresponding changes in HbA1c were −0.02%, 0.12%, and −0.05% (for interaction, $P = 0.143$).

The mean value (standard deviation) of postpartum changes of 2-hour OGTT in all participants was −2.11 (2.44) mM. Figure 1 presents multivariable-adjusted postpartum changes of 2-hour OGTT stratified by gestational weight gain and the *MTNR1B* genotype. An increasing number of the G alleles were associated with a decrease in 2-hour OGTT levels in women with excessive gestational weight gain, whereas an opposite directional association was found among women with inadequate or adequate gestational weight gain.

We also analyzed the association between 2-hour OGTT and gestational weight gain, according to the *MTNR1B* genotype. Figure 2 shows the predicted changes in 2-hour OGTT with gestational weight gain (per 1 kg) by the *MTNR1B* genotype. Gestational weight gain was associated with a greater postpartum reduction of 2-hour OGTT in women carrying the *MTNR1B* rs10830963 GG genotype ($\beta = -0.10$ mM, $P = 0.001$) than that in women carrying the CC or CG genotype ($\beta = -0.02$ mM, −0.03 mM, respectively; $P = 0.34$, 0.11, respectively).

Discussion

In this study of Chinese women with a history of GDM, we found bidirectional interactions between the circadian rhythm–related *MTNR1B* genetic variant and gestational weight gain on 1- to 5-year postpartum changes in 2-hour OGTT. The *MTNR1B* genotype was related to distinct postpartum changes in 2-hour OGTT in women with inadequate, adequate, and excessive gestational weight gain. In addition, women carrying the *MTNR1B* GG genotype showed a more pronounced relationship between gestational weight gain and improvement in 2-hour OGTT than women carrying the other genotypes.

Numerous studies suggest that gestational weight gain plays an important role in women's long-term weight

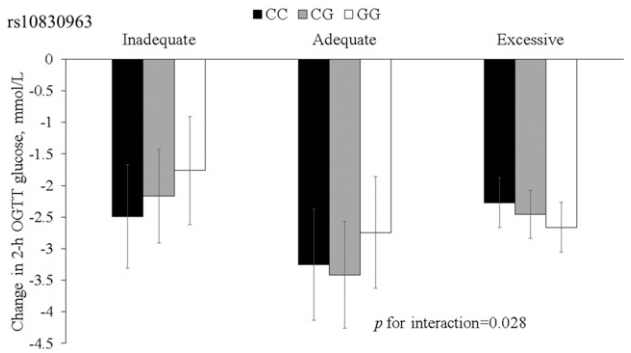

Figure 1. Changes in 2-hour OGTT, according to gestational weight gain and the *MTNR1B* rs10830963 genotype. Black bars, CC genotype; gray bars, CG genotype; white bars, GG genotype. Data are means ± standard error values, adjusted for age, follow-up time, prepregnancy BMI, dietary fat (percent energy), postpartum weight change, sitting time, level of the corresponding glucose trait during the pregnancy (continuous variables), family history of diabetes, current smoking, current alcohol drinking, leisure-time physical activity, and GDM therapy (categorical variables).

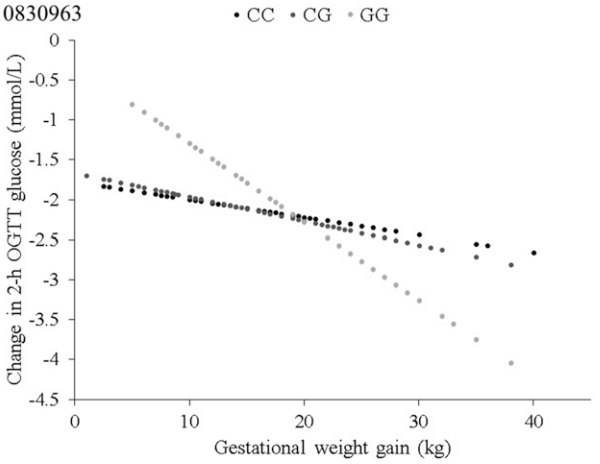

Figure 2. Predicted changes in 2-hour OGTT, according to gestational weight gain by rs10830963. The slope represents the β coefficient.

trajectory and affects postpartum hyperglycemia and type 2 diabetes in later life, especially among those with a history of GDM (21, 22). This study assesses the effect of gestational weight gain on the association between the circadian rhythm–related *MTNR1B* genotype and postpartum glycemic changes among women with a history of GDM. A unique finding in the current study is that the relation between gestational weight gain and postpartum changes in 2-hour OGTT significantly differed by the *MTNR1B* rs10830963 genotype. Insulin plays a central role in regulation of glucose metabolism. Both *in vivo* and *in vitro*, insulin secretion by the pancreatic islets is in a circadian manner, as a result of the melatonin action on the melatonin receptors inducing a phase shift in the cells (23). The genetic variant in the *MTNR1B* gene may directly affect the circadian manner of insulin secretion by the pancreatic islets and subsequently affect glucose metabolism (8, 24). The modification of gestational weight gain on the association between the *MTNR1B* and the postpartum changes in 2-hour OGTT did not exclude the existence of the potential direct genetic effect; instead, our data suggest that the genetic effect might differ among women with distinct gestational weight gain. Our findings are biologically plausible, as gestational weight gain may also disturb the circadian manner of insulin secretion (3, 4)—the pathway where interaction between gestational weight gain and the genotype may occur.

We found that the risk G allele of the *MTNR1B* variant was associated with increased 2-hour OGTT levels among women with inadequate or adequate gestational weight gain but was related to the decreased 2-hour OGTT levels among women with excessive gestational weight gain. Such an opposite genetic effect could be fairly explained by the differential-susceptibility hypothesis, a theory suggesting that genes may be conceptualized as plastic because genetic risk can be modified by environmental factors, such as change in body weight (25, 26). Previous studies suggested that the risk G allele was associated with the outcome of an intervention that targeted weight loss (27), whereas only those not carrying the risk G allele benefited from the lifestyle intervention among women at high risk of GDM (28). We assume that the magnitude of gestational weight gain may differently affect expression or activity of the *MTNR1B* genetic variant and subsequently affect glucose metabolism during the postpartum period.

Intriguingly, we found that the relation between gestational weight gain and postpartum glycemic changes differed according to the *MTNR1B* genotype—women carrying the GG genotype showed a stronger association of reduction in 2-hour OGTT changes with gestational weight gain than women carrying other genotypes. In a recall by genotype of the *MTNR1B* study, Tuomi *et al.* (11) demonstrated that the effect of melatonin on insulin secretion was inhibitory and in a genotype-specific fashion. For example, measures of insulin secretion were lower in the GG carriers of the *MTNR1B* genotype after 3 months of melatonin treatment, whereas the metabolic consequences of melatonin treatment in CC carriers were modest and restricted to fasting plasma glucose levels (11). On the other hand, Grotenfelt *et al.* (28) found that women carrying the CC genotype of the *MTNR1B* had a lower risk of GDM in response to a lifestyle intervention than women carrying other genotypes. Further studies are warranted to explore the potential mechanisms underlying the different effects of the *MTNR1B* genotypes on glucose metabolism.

A major strength of our study is the repeated measures of weight and glycemic traits during and after pregnancy. Other strengths include the large sample size of women with a prior GDM and longitudinal analysis. However, a number of limitations should be noted. First, the measurement of clock parameters was not done in this study. We used a genetic marker related to circadian rhythm that could be a better marker than biomarkers in causal inference, according to the Mendelian randomization theory (29). Second, even though the current study focused on women with a history of GDM, we acknowledged that it was also of interest to assess the relation between the *MTNR1B* genotypes and glucose metabolism in women without GDM, which were unfortunately not available in our study samples, and future studies are warranted to verify our findings in women without GDM. Third, we did not collect sufficient reproductive data, such as postpartum depression, which may influence weight change and glucose metabolism. In addition, we acknowledged that exclusions might affect the presence of the association; however, there were no

differences between the women with GDM at 26 to 30 gestational weeks who participated and those who did not, with regard to age, fasting glucose, 2-hour OGTT concentrations, and the prevalence of impaired glucose tolerance and diabetes. Although the results of our study might not be generalized to other populations, future studies in different populations are warranted.

In summary, the results of the current study showed that gestational weight gain might modify the effect of the circadian rhythm–related *MTNR1B* rs10830963 variant on postpartum changes in 2-hour OGTT, and *vice versa*, among Chinese women with a history of GDM. These findings suggest that women carrying the GG genotype might particularly benefit by controlling gestational weight gain to avoid postpartum hyperglycemia.

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Author Contributions: H.N. conceived of the study and design, performed the statistical analysis, interpreted the data, and drafted and critically revised the manuscript. K.H.T.Q., J.L., T.Z., H.L., W.L., L.W., N.L., and G.H. were involved in the critical revision of the manuscript. G.H. and L.Q. were involved in collection and assembly of data and obtained funding for the study. L.Q. conceived of the study and design, provided statistical advice, interpreted the data, critically revised the manuscript, is the guarantor of the present work, and takes responsibility for the integrity of the contents of the article.

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