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ORIGINAL RESEARCH

Associations Between Gestational Diabetes Mellitus and Neonatal Acyl Metabolic Profiles: An Empirical Study Based on a Birth Cohort

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Aim: This study aimed to identify gestational diabetes mellitus (GDM)-associated neonatal acylcarnitines (ACs), assess maternal glycemic control's impact on these ACs, and evaluate maternal lipids' mediating role, supporting early metabolic risk stratification in offspring.

Methods: Tandem mass spectrometry (TMS) measured AC levels in 4,974 newborns (836 GDMs,4,138 controls). Generalized linear models assessed GDM-neonatal AC associations. Non-parametric tests assessed differences among no-GDM (2769), well-controlled GDM (129), and suboptimally controlled GDM groups (425). Mediation analysis identified factors affecting neonatal ACs. Maternal clinical data were extracted from the electronic medical record (EMR) system.

Results: Of the 31 acylcarnitine species, 19 were significantly associated with GDM. Relative to the control group, 18 ACs exhibited significantly elevated levels, specifically malonylcarnitine+3-hydroxybutyrylcarnitine (C3DC+C4OH), isovalerylcarnitine+methylbutyrylcarnitine (C5), glutarylcarnitine+3-hydroxyhexanoylcarnitine (C5DC+C6OH), hexanoylcarnitine (C6), methylglutarylcarnitine (C6DC), decanoylcarnitine (C10), decenoylcarnitine (C10:1), dodecanoylcarnitine (C12), dodecenoylcarnitine (C12:1), tetradecanoylcarnitine (C14), tetradecenoylcarnitine (C14:1), palmitoylcarnitine (C16), palmitoleylcarnitine (C16:1), 3-hydroxypalmitoleylcarnitine (C16:1OH), 3-hydroxypalmitoylcarnitine (C16OH), stearoylcarnitine (C18), 3-hydroxyoleoylcarnitine (C18:1-OH),and 3-hydroxystearoylcarnitine (C18OH); only linoleoylcarnitine (C18:2) showed a significant decrease. In groups with progressively impaired glycemic control, triglyceride (TG) levels ($P < 0.001$) and propionylcarnitine (C3) levels ($P = 0.02$) exhibited a significant increasing trend, whereas high-density lipoprotein cholesterol (HDL-C) ($P = 0.01$) and C18:2 levels ($P = 0.02$) showed a consistent decreasing trend. Mediation analysis further demonstrated that maternal TG levels exerted a significant positive mediating effect on the elevation of neonatal C3 levels (10.7%, 95% CI: 0.0016, 0.0182, $P = 0.006$), whereas a significant masking effect was observed on C10:1 levels (−14.27%, 95% CI: −0.0006, −0.0001, $P < 0.001$). Additionally, maternal HDL-C levels exhibited significant masking effects on most acylcarnitine indicators, with the only exception being a significant positive mediating effect on C18:2 levels (2.94%,95% CI: −0.0018, −0.0001, $P = 0.0186$).

Conclusion: GDM correlates with offspring AC levels, with TG and HDL-C partially mediating this relationship. Newborn fat oxidation metabolism is influenced by maternal factors from birth.

Keywords: gestational diabetes mellitus, fatty acid metabolism, acylcarnitine, β-oxidation

Introduction

GDM constitutes one of the prevalent metabolic complications during gestation. As the global obesity rate keeps escalating, the incidence of GDM demonstrates a year-on-year ascending trend.[1] Additionally, GDM poses substantial immediate and long-term risks to the health of both mothers and infants. A considerable number of epidemiological studies have indicated that the risk of cardiovascular diseases and obesity among the offspring of GDM individuals is

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significantly higher than that in the general population.[2] However, systematic investigations into the association between GDM and offspring diseases, as well as their underlying mechanisms, remain relatively limited in the current literature. Consequently, an in-depth exploration of the mechanism by which GDM affects the metabolic levels of the offspring holds significant scientific significance and clinical value.

ACs play a crucial role in human fatty acid oxidation metabolism and energy balance regulation and can serve as important biomarkers for complex metabolic syndromes.[3,4] ACs levels have been linked to metabolic syndrome, obesity, and cardiovascular disease.[5] For example, accumulating evidence supports a potential causal association between C18:2 and deep vein thrombosis (DVT),[6] Plasma levels of short-chain acylcarnitines (SCAC) are positively associated with DPN risk.[7] However, current evidence remains limited to clinical observational findings. Based on the theoretical framework of the Developmental Origins of Health and Disease (DOHaD), this study conducted a retrospective case-control study of acylcarnitine profiles in neonates born to mothers with GDM. The core objectives were to address two interrelated scientific questions: (1) whether GDM correlates with aberrant neonatal acylcarnitine profiles; and (2) whether maternal dyslipidemia mediates the association between GDM and alterations in neonatal acylcarnitine levels. By addressing these questions, this study not only uncovers potential links between maternal GDM and offspring fatty acid metabolic dysfunction but also provides critical scientific evidence to elucidate the mechanisms underlying the intergenerational transmission of maternal metabolic disorders.

Methods

Objects and Selection of Study Population

The present study recruited pregnant women who attended prenatal examinations at our hospital between November 2022 and June 2023. All participants underwent an oral glucose tolerance test (OGTT) during the second trimester of pregnancy. Based on the diagnostic criteria of the American Diabetes Association (ADA), they were stratified into a normal control group (n=4138) and a GDM group (n=865) (The inclusion criteria are presented in the supplementary materials). Among the GDM cohort, 836 participants ultimately underwent late-pregnancy glycemic profile screening. In accordance with the ADA guidelines, these participants were categorized into a well-controlled glycemia group (n=194) and suboptimally controlled glycemia group (n=642). Among them, 3,323 pregnant women underwent lipid level tests in the third trimester of pregnancy, and acylcarnitine levels of the newborns delivered by 4,974 pregnant women were tested three days after birth. (Figure 1). The study design and protocol were reviewed and approved by the ethics committee of Changzhou Maternity and Child Health care Hospital.

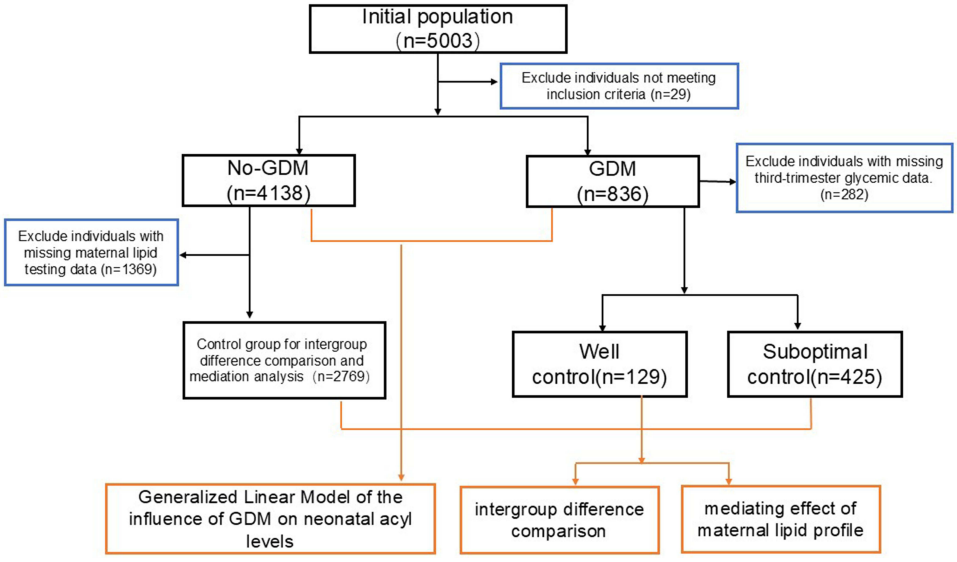

Figure 1 Study Design.

Detection of Acylcarnitine

Three days after the birth of the newborn and after sufficient breastfeeding, heel blood samples were collected from the newborn for the detection of 31 acylcarnitines, including free carnitine (C0), acetylcarnitine (C2), C3, C3DC+C4OH, butyrylcarnitine+isobutyrylcarnitine (C4), methylmalonylcarnitine+ 3-hydroxyisovalerylcarnitine (C4DC+C5OH), isovalerylcarnitine+MetC5, tiglylcarnitine (C5:1), C5DC+C6OH, C6, C6DC, octanoylcarnitine (C8), octenoylcarnitine (C8:1), C10, C10:1, decadienoylcarnitine (C10:2), C12, C12:1, C14, C14:1, tetradecadienoylcarnitine (C14:2), 3-hydroxytetradecanoylcarnitine (C14OH), C16, C16:1, C16:1OH, C16OH, C18, oleoylcarnitine (C18:1), C18:1OH, C18:2, C18OH were evaluated by TMS detection methods as described in our previous study.[8]

Determination of Serum Lipids

Serum lipid levels were examined using Wet Chemistry via an automated analyzer (AU5800, Beckman Coulter Inc, USA). The normal reference ranges of serum lipid indices for the local population are as follows: total cholesterol (TC) ≤ 5.17 mmol/L, TG ≤ 1.6 mmol/L, HDL-C: 1.03–1.55 mmol/L, low-density lipoprotein cholesterol (LDL-C) ≤ 3.36 mmol/L, apolipoprotein A (ApoA): 1.0–1.6 g/L, apolipoprotein B (ApoB):0.6–1.1 g/L, lipoprotein (a) (Lpa) ≤ 300 mg/L, and free fatty acids (FFAs): 0.1–0.77 mmol/L.

Statistical Analysis

Qualitative data were analyzed with the chi-square test, while quantitative data were assessed using the Student's *t*-test for normally distributed data and the Mann–Whitney *U*-test for non-normally distributed data. GDM was treated as the exposure factor for analysis, and a generalized linear model was employed to evaluate its association with neonatal acylcarnitine levels. Concurrently, maternal age at delivery, gestational age (GA), and pre-pregnancy body mass index (BMI) were incorporated as covariates in the model to adjust for potential confounding effects. We conducted mediation analyses using the Process SPSS macro (Process 4.1 for SPSS) to explore the relationships between variables. Specifically, we applied Macro Model 4,[9] a widely used analytical framework designed to test simple mediation effects of a single mediator (TG or HDL-C). Statistical significance was set at a two-tailed p-value of 0.05. The Benjamini-Hochberg (BH) procedure computes adjusted significance levels by sorting p-values in ascending order. The Jonckheere-Terpstra (J-T) test is employed to assess whether relevant indicators exhibit a consistent upward or downward trend across categories of blood glucose control status. The statistical analysis software employed was IBM SPSS Statistics Version 20.

Results

Characteristics of the Study Population

This study included a total of 5003 pregnant women, with 4,138 serving as normal controls and 865 in the GDM group. In the GDM group, 194 patients had their blood glucose levels effectively controlled, while 642 patients had poor control, according to the ADA (fasting blood glucose<5.3mmol/L and 2-hour postprandial blood glucose<6.7mmol/L). Third-trimester blood glucose data were missing for 29 GDM patients. Significant differences were observed between the two groups of pregnant women in aspects such as weight at admission, weight gain during pregnancy, pre-pregnancy weight, age, gestational weeks, and mode of delivery ($P < 0.05$). Although no significant difference in the neonatal weight was found between the two groups (P=0.391), it was conspicuously observed that the proportion of large-for-gestational-age infants in the GDM group (In reference to the standards of the Chinese population[10]) significantly rose (15.954% VS 11.382%) after re-grouping in combination with gestational age factors and according to specific gestational age curves ($P < 0.001$). In addition, significant differences were observed across fetal weight subgroups ($P = 0.031$); the incidence of macrosomia in the GDM group was higher than that in the normal control group, and this difference became more pronounced after adjusting for gestational age (Table 1).

Table 1 Clinical Baseline of the Recruitment Cohort

Characteristics	GDM	No-GDM	P value
Sample size (n)	865	4138	
Height (mean ± sd)	161.32 ± 5.0552	161.65 ± 5.6054	0.111
Weight (mean ± sd)	72.945 ± 11.538	71.861 ± 10.069	0.010
BMI (mean ± sd)	23.279 ± 4.1512	22.515 ± 33.248	0.508
Weight gain in pregnancy (mean ± sd)	12.336 ± 4.811	14.405 ± 4.4891	0.000
Weight before pregnancy (mean ± sd)	60.694 ± 11.635	57.505 ± 9.8566	0.000
Age (mean ± sd)	30.874 ± 4.5104	29.415 ± 4.3412	0.000
Gestational weeks (mean ± sd)	38.284 ± 1.7893	38.648 ± 1.7175	0.000
Newborn weight (mean ± sd)	3268.2 ± 543.38	3285.3 ± 493.93	0.391
Delivery mode (n)			0.000
Spontaneous vaginal delivery	445.000	2464.000	
Caesarean section	420.000	1674.000	
Weight grouping of newborns (n)			0.031
<2500g	63(7.283%)	217(5.244%)	
≥2500g and <4000g	749(86.59%)	3703(89.488%)	
≥4000g	53(6.127%)	218(5.268%)	
Grouping based on specific gestational age curves (n)			0.001
SGA	82(9.48%)	421(10.174%)	
AGA	645(74.566%)	3244(78.395%)	
LGA	138(15.954%)	471(11.382%)	

Notes: Data were presented as median (IQR), mean ± SD and N (%) for continuous variables with normal distribution, continuous variables with skewed distribution, and categorical variables, according to Mann–Whitney test for skewed-distributed continuous variables, Student's *t*-test for normally distributed continuous variables, and Chi-square test for categorical variables. Abbreviations: SGA/AGA/LGA small/appropriate/large for gestational age.

Association of GDM with Neonatal Acylcarnitine Profiles

The analysis results of the generalized linear model revealed that the differences of C3DC+C4OH (P=0.003), C5 (P=0.028), C5DC + C6OH(P=0.003), C6(P=0.014), C6DC(P=0.003), C10(P=0.009), C10:1(P=0.003), C12(P=0.003), C12:1(P=0.003), C14(P=0.003). C14:1(P=0.009), C16(P=0.003), C16:1(P=0.003), C16:1OH(P=0.003), C16:OH (P=0.003), C18(P=0.02),C18:1(P=0.017), C18:2(P=0.003) and C18:OH(P=0.044) were statistically significant. Compared with the normal control group, all the aforementioned differential indices were significantly elevated, except for C18:2 (Table 2).

The results demonstrated a highly significant statistical difference in neonatal C18:2 levels across the three groups (p. adj (BH) < 0.001). Further validation via Jonckheere-Terpstra test revealed a significant linear decrease in C18:2 levels with worsening glycemic control in GDM patients (p (J-T) = 0.02), with the lowest levels observed in the poor glycemic control group and the highest in the normal control group, indicating a clear intergroup trend effect. For C3 levels, intergroup differences did not reach statistical significance following B-H correction (p.adj (BH) = 0.06); however, Jonckheere-Terpstra test showed a significant increase in C3 levels with worsening glycemic control (p (J-T) = 0.02), suggesting a potential trend association that warrants further validation with an expanded sample size. Additionally, while indicators including C4DC+C5OH, C5DC+C6OH, C6, C6DC, C12, C12:1, C14, C14:1, C14OH, C16:1, C16:1OH, and C16OH exhibited intergroup differences and non-monotonic trends, they lacked a consistent directional pattern of increase or decrease. This inconsistency may be attributed to random within-group variability or the masking effect of confounding factors.

In addition, maternal TG, HDL-C, and FFAs levels differed significantly among the three groups (P < 0.05). TG was highest in the suboptimal glycemic control group, while HDL-C and FFAs were lowest in this group. No significant differences were found in maternal TC, LDL-C, APO-A, APO-B, or Lpa levels across groups (P > 0.05) (Table 3).

Table 2 Generalized Linear Model of the Influence of GDM on Neonatal Acyl Levels

Outcome Variable	B value	Bootstrap Bias	Bootstrap Standard Error	Two-Sided Significance Level	95% Confidence Interval		p. adj_BH
					Lower Limit	Upper Limit	
C0	0.1190	0.0180	0.299	0.700	−0.4610	0.695	0.775
C2	−0.603	0.018	0.267	0.032	−1.091	−0.032	0.050
C3	−0.055	0.005	0.029	0.044	−0.109	−0.001	0.065
C3DC+C4OH	−0.014	1.737×10^{-5}	0.002	0.001	−0.019	−0.009	0.003
C4	−0.005	0	0.003	0.086	−0.01	0.001	0.110
C4DC+C5OH	−0.021	0.001	0.010	0.287	−0.042	−0.007	0.342
C5	0.005	0	0.002	0.016	0.001	0.008	0.028
C5:1	1.237×10^{-5}	1.249×10^{-5}	0.000	0.920	0	0	0.951
C5DC+C6OH	−0.008	3.348×10^{-5}	0.001	0.001	−0.011	−0.006	0.003
C6	−0.002	-5.209×10^{-5}	0.001	0.007	−0.003	−0.001	0.014
C6DC	−0.012	0	0.002	0.001	−0.016	−0.009	0.003
C8	0	-4.879×10^{-5}	0.001	0.780	−0.002	0.002	0.834
C8:1	−0.003	0	0.002	0.089	−0.005	0.001	0.110
C10	−0.004	-9.601×10^{-5}	0.001	0.004	−0.007	−0.001	0.009
C10:1	−0.003	-4.026×10^{-5}	0.001	0.001	−0.005	−0.002	0.003
C10:2	0	-3.980×10^{-6}	0.000	0.066	−0.001	6.226×10^{-6}	0.089
C12	−0.008	0	0.002	0.001	−0.012	−0.005	0.003
C12:1	−0.005	0	0.001	0.001	−0.008	−0.002	0.003
C14	−0.013	-1.059×10^{-5}	0.003	0.001	−0.018	−0.007	0.003
C14:1	−0.006	0	0.002	0.004	−0.01	−0.003	0.009
C14:2	0	-2.743×10^{-5}	0.000	0.371	−0.001	0	0.426
C14OH	0	5.034×10^{-6}	0.000	0.048	−0.001	1.903×10^{-5}	0.068
C16	−0.189	0.005	0.048	0.001	−0.281	−0.093	0.003
C16:1	−0.013	0	0.003	0.001	−0.02	−0.007	0.003
C16:1OH	−0.003	-4.787×10^{-5}	0.001	0.001	−0.004	−0.002	0.003
C16OH	0.001	1.479×10^{-6}	0.000	0.001	−0.002	−0.001	0.003
C18	−0.029	0.001	0.011	0.011	−0.051	−0.006	0.020
C18:1	−0.001	0.002	0.017	0.956	−0.034	0.035	0.956
C18:1OH	−0.001	3.204×10^{-6}	0.000	0.009	−0.001	0	0.017
C18:2	0.031	9.745×10^{-5}	0.004	0.001	0.023	0.04	0.003
C18OH	0	1.204×10^{-6}	0.000	0.027	−0.001	-3.537×10^{-5}	0.044

Notes: The model was constructed using "intercept + grouping + gestational age + age + BMI", with [grouping = GDM] as the reference group, and the parameter redundancy was set to 0. Gestational age, age, and pre-pregnancy BMI were all standardized (mean = 0, standard deviation = 1) to eliminate dimensional differences. The Bootstrap results were calculated based on 1000 resamplings, and significance was determined using a two-sided test. The Benjamini-Hochberg (BH) procedure calculates adjusted significance levels by ordering p-values in ascending order, ensuring that the overall false discovery rate (FDR) does not exceed a predefined threshold.

Abbreviations: C0, Carnitine free; C2, Acetylcarnitine; C3, Propionylcarnitine; C3DC+C4OH, Malonylcarnitine+3-Hydroxybutyrylcarnitine;C4, Butyrylcarnitine +Isobutyrylcarnitine; C4DC+C5OH, Methylmalonylcarnitine+3-Hydroxyisovalerylcarnitine; C5, Isovalerylcarnitine+Methylbutyrylcarnitine; C5:1, Tiglylcarnitine; C5DC +C6OH, Glutarylcarnitine+3-Hydroxyhexanoylcarnitine; C6, Hexanoylcarnitine; C6DC, Methylglutarylcarnitine; C8, Octanoylcarnitine; C8:1, Octenoylcarnitine; C10, Decanoylcarnitine; C10:1, Decenoylcarnitine; C10:2, Decadienoylcarnitine; C12, Dodecanoylcarnitine; C12:1, Dodecenoylcarnitine; C14, Tetradecanoylcarnitine; C14:1, Tetradecenoylcarnitine; C14:2, Tetradecadienoylcarnitine; C14OH, 3-Hydroxytetradecanoylcarnitine; C16, Palmitoylcarnitine; C16:1, Palmitoleylcarnitine; C16:1OH, 3-Hydroxypalmitoleylcarnitine; C16OH, 3-Hydroxypalmitoylcarnitine; C18, Stearoylcarnitine; C18:1, Oleoylcarnitine; C18:1OH, 3-Hydroxyoleoylcarnitine; C18:2, Linoleoylcarnitine;C18OH, 3-Hydroxystearoylcarnitine.

Mediation Analyses

A model with TG as the mediating variable

Specifically, the total effect of C3 exhibited a significant positive association (effect size = 0.0840, 95% CI: 0.0112, 0.1568, P = 0.024), with both its direct effect (0.0750, 95% CI: 0.0066, 0.1434, P = 0.0317) and TG-mediated indirect effect (0.0090, 95% CI: 0.0016, 0.0182, P = 0.006) reaching statistical significance. The mediating proportion of TG in this association was 10.7%, indicating that TG served as a partial mediator in the relationship between GDM and C3. For

Table 3 Comparative Analysis of the Intergroup Differences

Characteristics	Normal	Well Control	Suboptimal Control	p.adj_BH	p (J-T)
n	2769	129	425		
TC	6.18 (5.42, 7.01)	6.03 (5.3275, 6.8025)	6.14 (5.39, 6.94)	0.63	0.47
TG	3.28 (2.57, 4.22)	3.325 (2.6075, 4.3675)	3.74 (2.85, 5.03)	0.00	0.00
HDL-C	2.05 (1.8, 2.34)	2.03 (1.8175, 2.3125)	1.97 (1.71, 2.26)	0.00	0.01
LDL-C	3.59 (3.08, 4.13)	3.515 (3.06, 3.9725)	3.53 (3.07, 4.04)	0.52	0.08
APO-a	2.23 (1.9375, 2.6)	2.26 (1.87, 2.625)	2.2 (1.93, 2.56)	0.69	0.94
APO-b	1.18 (0.99, 1.39)	1.13 (0.96, 1.3225)	1.19 (1, 1.39)	0.56	0.76
Lpa	130.7 (70.6, 248.2)	113.7 (66.275, 265.43)	126.6 (66.7, 259)	0.72	0.18
FFAs	0.515 (0.33, 0.73)	0.62 (0.4, 0.8425)	0.5 (0.33, 0.7)	0.01	0.58
C0	21.93 (17.32, 26.89)	20.82 (16.763, 25.855)	21.62 (17.58, 26.98)	0.57	0.64
C2	19.11 (14.79, 23.69)	19.16 (15.507, 24.205)	19.86 (15.78, 25.33)	0.05	0.00
C3	1.71 (1.32, 2.21)	1.755 (1.4075, 2.32)	1.8 (1.4, 2.38)	0.06	0.02
C3DC+C4OH	0.1 (0.07, 0.15)	0.12 (0.09, 0.1625)	0.12 (0.08, 0.18)	0.00	0.00
C4	0.23 (0.19, 0.27)	0.24 (0.2, 0.29)	0.24 (0.2, 0.28)	0.05	0.17
C4DC+C5OH	0.18 (0.16, 0.22)	0.2 (0.16, 0.25)	0.2 (0.16, 0.23)	0.00	0.00
C5	0.09 (0.07, 0.12)	0.1 (0.08, 0.12)	0.09 (0.08, 0.11)	0.72	0.44
C5:1	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.54	0.62
C5DC+C6OH	0.11 (0.09, 0.13)	0.12 (0.1, 0.14)	0.12 (0.1, 0.14)	0.00	0.00
C6	0.04 (0.03, 0.05)	0.04 (0.03, 0.05)	0.04 (0.03, 0.05)	0.00	0.00
C6DC	0.1 (0.08, 0.13)	0.11 (0.09, 0.15)	0.11 (0.09, 0.14)	0.00	0.00
C8	0.08 (0.06, 0.1)	0.08 (0.06, 0.0925)	0.08 (0.06, 0.1)	0.57	0.95
C8:1	0.09 (0.07, 0.12)	0.09 (0.07, 0.12)	0.09 (0.07, 0.12)	0.71	0.21
C10	0.08 (0.06, 0.1)	0.09 (0.06, 0.11)	0.08 (0.07, 0.11)	0.02	0.07
C10:1	0.05 (0.04, 0.07)	0.06 (0.0475, 0.07)	0.06 (0.04, 0.07)	0.05	0.04
C10:2	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.57	0.33
C12	0.07 (0.05, 0.11)	0.08 (0.0675, 0.12)	0.08 (0.06, 0.12)	0.00	0.00
C12:1	0.04 (0.03, 0.06)	0.05 (0.03, 0.07)	0.04 (0.03, 0.07)	0.00	0.00
C14	0.18 (0.14, 0.23)	0.19 (0.1575, 0.24)	0.2 (0.15, 0.24)	0.00	0.01
C14:1	0.08 (0.06, 0.11)	0.08 (0.06, 0.12)	0.08 (0.06, 0.12)	0.00	0.01
C14:2	0.02 (0.01, 0.02)	0.02 (0.02, 0.02)	0.02 (0.01, 0.02)	0.40	0.36
C14OH	0.01 (0.01, 0.01)	0.01 (0.01, 0.0125)	0.01 (0.01, 0.02)	0.00	0.00
C16	3.09 (2.3, 3.94)	3.19 (2.4975, 4.095)	3.25 (2.53, 4.03)	0.05	0.02
C16:1	0.17 (0.12, 0.23)	0.18 (0.14, 0.24)	0.18 (0.13, 0.24)	0.01	0.01
C16:1OH	0.04 (0.03, 0.05)	0.04 (0.03, 0.05)	0.04 (0.03, 0.05)	0.01	0.01
C16OH	0.02 (0.01, 0.02)	0.02 (0.01, 0.02)	0.02 (0.01, 0.02)	0.00	0.01
C18	0.87 (0.7, 1.08)	0.875 (0.715, 1.12)	0.88 (0.74, 1.14)	0.19	0.12
C18:1	1.48 (1.22, 1.79)	1.525 (1.27, 1.79)	1.48 (1.22, 1.79)	0.84	0.89
C18:1OH	0.02 (0.02, 0.03)	0.02 (0.02, 0.03)	0.02 (0.02, 0.03)	0.18	0.37
C18:2	0.23 (0.16, 0.32)	0.215 (0.15, 0.2725)	0.21 (0.15, 0.28)	0.00	0.02
C18OH	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.01 (0.01, 0.02)	0.07	0.25

Notes: The BH procedure calculates adjusted significance levels by ordering p-values in ascending order, ensuring that the overall FDR does not exceed a predefined threshold. The J-T test is used to examine whether the relevant indicators show a consistent upward or downward trend as the blood sugar control status deteriorates step by step in the ordered grouping ("non-gestational diabetes → well-controlled gestational diabetes → poorly controlled gestational diabetes"). Acylcarnitine unit: ummol/L, CHO, TG, HDL-C, LDL-C, NEFA unit: mmol/L, Apo-a, Apo-b unit: g/L, Lpa unit: mg/L.

Abbreviations: TC, Total cholesterol; TG, Triglyceride; HDL-C, High-Density Lipoprotein Cholesterol; LDL-C, Low-Density Lipoprotein Cholesterol; APO-a, Apolipoprotein A; APO-b, Apolipoprotein B; Lpa, Lipoproteins; FFAs, Free fatty acids.

C10:1, the total effect was also significant (0.0021, 95% CI: 0.0001, 0.0041, P = 0.036), and the direct effect showed a significant positive association (0.0024, 95% CI: 0.0005, 0.0043, P = 0.012). However, the TG-mediated indirect effect was significantly negative (−0.0003, SE = 0.0001, 95% CI: −0.0006, −0.0001, P < 0.001), with a mediating proportion of −14.27%, suggesting the presence of a suppression effect of TG in the GDM-C10:1 association. Regarding C14:2, neither the total effect nor the direct effect was statistically significant, whereas the TG-mediated indirect effect was

significantly negative (−0.0001, 95% CI:-0.0002, 0.0000, P = 0.007), with a mediating proportion of −33.0%. These findings imply that the influence of GDM on C14:2 may be primarily exerted via the TG pathway, though further validation is warranted.

A model with HDL-C as the mediating variable

In the model with HDL-C as the mediator, the mediating effects of distinct acylcarnitine species fell into two categories. The first category comprised species with significant total effects. For instance, C2 exhibited a significant positive total effect (0.8254, 95% CI: 0.1872, 1.4636, P = 0.0113), with its direct effect also being significantly positive (0.8800, 95% CI: 0.2354, 1.5245, P = 0.0075). However, the HDL-C-mediated indirect effect was significantly negative (−0.0613, 95% CI:-0.1153, −0.0114, P = 0.0037), yielding a mediation proportion of −6.62%, indicative of a suppression effect of HDL-C in this association. Species including C6, C6DC, C12:1, C14, C14:1, C16, and C16:1OH shared a consistent pattern: both total and direct effects were significant, with the indirect effect being significantly negative and mediation proportions ranging from −4.17% to −9.09%, all consistent with the characteristics of a suppression effect. C18:2 exerts a predominant direct negative effect (−0.0272,0.0060,95% CI:-0.0389, −0.0155, P <0.001) on the outcome, while also inducing a statistically significant but relatively minor indirect negative effect (−0.0008,-0,0004,95% CI:-0.0018, −0.0001, P =0.0186) mediated by HDL-C. The second category included species with non-significant total effects (C8:1, C18, and C14:2), where neither total nor direct effects reached statistical significance, but the HDL-C-mediated indirect effect was significantly negative. These findings suggest that the influence of GDM on these Acs is primarily exerted via the negative HDL-C pathway, yet the absence of a significant total effect indicates that HDL-C may act as an independent mediator rather than a component of the overall association (Table 4).

Table 4 Mediated Effects by TG and HDL-C on the Associations of Acylcarnitine Levels with GDM

Variable	Path/Effect	Effect size (SE)	95% CI	P value
C3	**Proportion mediated by TG (10.7%)**			
	Total effect	0.0840 (0.0372)	0.0112, 0.1568	0.024
	Direct effect	0.0750 (0.0349)	0.0066, 0.1434	0.0317
	Indirect effects	0.0090 (0.0042)	0.0016, 0.0182	0.006
C10:1	**Proportion mediated by TG (−14.27%)**			
	Total effect	0.0021 (0.0010)	0.0001, 0.0041	0.036
	Direct effect	0.0024 (0.0010)	0.0005, 0.0043	0.012
	Indirect effects	−0.0003(0.0001)	−0.0006, −0.0001	<0.001
C14:2	**Proportion mediated by TG (−33%)**			
	Total effect	0.0003 (0.0004)	−0.0004, 0.0010	**0.453**
	Direct effect	0.0004 (0.0004)	−0.0003, 0.0011	0.3
	Indirect effects	−0.0001 (0.0000)	−0.0002, 0.0000	0.007
C2	**Proportion mediated by HDL-C (−6.62%)**			
	Total effect	0.8254 (0.3259)	0.1872, 1.4636	0.0113
	Direct effect	0.8800 (0.3287)	0.2354, 1.5245	0.0075
	Indirect effects	−0.0613 (0.0185)	−0.1153, −0.0114	0.0037
C6	**Proportion mediated by HDL-C (−9.09%)**			
	Total effect	0.0022 (0.0007)	0.0008, 0.0036	0.0017
	Direct effect	0.0024 (0.0007)	0.0010, 0.0038	0.0011
	Indirect effects	−0.0002 (0.0001)	−0.0003, 0.0000	<0.001

(*Continued*)

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Table 4 (Continued).

Variable	Path/Effect	Effect size (SE)	95% CI	P value
C6DC	**Proportion mediated by HDL-C (−4.64%)**			
	Total effect	0.0112 (0.0021)	0.0071, 0.0153	<0.001
	Direct effect	0.0117 (0.0021)	0.0074, 0.0159	<0.001
	Indirect effects	−0.0005 (0.0002)	−0.0009, −0.0002	<0.001
C8:1	**Proportion mediated by HDL-C (14.29%)**			
	Total effect	0.0014 (0.0018)	−0.0021, 0.0049	**0.4369**
	Direct effect	0.0012(0.0018)	−0.0023, 0.0047	0.5077
	Indirect effects	0.0002(0.0001)	0.0000, 0.0005	0.0438
C10:1	**Proportion mediated by HDL-C (- 9.52%)**			
	Total effect	0.0021 (0.0010)	0.0001, 0.0041	0.0357
	Direct effect	0.0023 (0.0010)	0.0004, 0.0042	0.019
	Indirect effects	−0.0002 (0.0001)	−0.0004, 0.0000	0.0016
C12:1	**Proportion mediated by HDL-C (- 4.17%)**			
	Total effect	0.0048 (0.0018)	0.0013, 0.0083	0.0077
	Direct effect	0.0050 (0.0018)	0.0017, 0.0085	0.0054
	Indirect effects	−0.0002 (0.0001)	−0.0005, 0.0000	0.0305
C14	**Proportion mediated by HDL-C (- 4.5%)**			
	Total effect	0.0111 (0.0003)	0.0043, 0.0179	0.0015
	Direct effect	0.0116 (0.0035)	0.0047, 0.0185	0.001
	Indirect effects	−0.0005 (0.0003)	−0.0011, −0.0001	0.009
C14:1	**Proportion mediated by HDL-C (- 4.92%)**			
	Total effect	0.0061 (0.0024)	0.0014, 0.0108	0.011
	Direct effect	0.0064 (0.0024)	0.0020, 0.0109	0.009
	Indirect effects	−0.0003 (0.0002)	−0.0007, 0.0000	0.031
C14:2	**Proportion mediated by HDL-C (- 33%)**			
	Total effect	0.0003 (0.0004)	−0.0004, 0.0010	**0.453**
	Direct effect	0.0004 (0.0004)	−0.0003, 0.0010	0.2876
	Indirect effects	−0.0001 (0.0000)	−0.0002, 0.0000	<0.001
C16	**Proportion mediated by HDL-C (- 9.09%)**			
	Total effect	0.1482 (0.0570)	0.0368, 0.2596	0.0094
	Direct effect	0.1550 (0.0574)	0.0455, 0.2655	0.007
	Indirect effects	−0.0068 (0.0042)	−0.0164, −0.0004	0.0373
C16:1OH	**Proportion mediated by HDL-C (- 10%)**			
	Total effect	0.0020 (0.0007)	0.0006, 0.0034	0.0043
	Direct effect	0.0022 (0.0007)	0.0009, 0.0035	<0.001
	Indirect effects	−0.0002 (0.0001)	−0.0004, −0.0001	<0.001
C18	**Proportion mediated by HDL-C (8.85%)**			
	Total effect	0.0226 (0.0139)	−0.0047, 0.0499	**0.104**
	Direct effect	0.0246 (0.0140)	−0.0026, 0.0525	**0.0798**
	Indirect effects	−0.0020 (0.0011)	−0.0045, −0.0004	0.0119

(*Continued*)

Table 4 (Continued).

Variable	Path/Effect	Effect size (SE)	95% CI	P value
C18:1	**Proportion mediated by HDL-C (32.89%)**			
	Total effect	0.0401(0.0207)	−0.0480, 0.0328	**0.713**
	Direct effect	−0.0051(0.0207)	−0.0454, 0.0372	**0.8062**
	Indirect effects	−0.0020(0.0014)	−0.0058, −0.0002	0.0383
C18:2	**Proportion mediated by HDLC (2.94%)**			
	Total effect	−0.0272(0.0060)	−0.0389, −0.0155	<0.001
	Direct effect	−0.0264(0.0060)	−0.0371, −0.0161	<0.001
	Indirect effects	−0.0008(−0,0004)	−0.0018, −0.0001	0.0186

Notes: Total effect = direct effect + indirect effect. The proportion of each effect is calculated as (value of the respective effect/total effect value) × 100%.Bolded text denotes mediator subgroups (eg, TG) and their corresponding mediation proportions. Indicators with a P-value > 0.05 are presented in bold, indicating that the respective effect did not achieve statistical significance.

Discussion

GDM refers to the diabetes that is diagnosed for the first time during pregnancy. Its pathogenesis is rather complex, involving genetic factors, environmental influences, and lifestyle, among other aspects. In recent years, GDM has risen due to obesity, advanced age, and excessive pregnancy weight gain and this trend is expected to continue.[11,12] GDM can lead to various adverse outcomes. For example, maternal complications include preeclampsia, gestational hypertension, postpartum hemorrhage, and lactation issues. From a long-term perspective, the probability of GDM patients evolving into type 2 diabetes in the later period is approximately ten times higher than that of the normal population.[13] Additionally, the blood glucose level of the mother during pregnancy may have an impact on the long-term glucose tolerance and pancreatic islet cell sensitivity of the offspring, thereby increasing the risk of obesity and impaired metabolic function in the offspring.[14] However, the relevant mechanisms by how GDM influences the metabolism of the offspring remain largely undefined. Many related mechanisms are still hypothetical and require further verification through scientific evidence. Clinically, robust systematic evidence in metabolomics is urgently needed to define the long-term effects of GDM on offspring and to uncover its underlying mechanistic pathways.

Acylcarnitine (AC), as an important metabolic intermediate product, plays a crucial role in energy metabolism and fatty acid oxidation. It is a conjugate of fatty acids and carnitine, promoting the entry of fatty acids into mitochondria to complete the β-oxidation process[15] (Figure 2). As the research on metabolic regulatory mechanisms proceeds in depth, the biological functions of ACs have gradually come into focus, particularly their potential roles in metabolic disorders such as diabetes, obesity and cardiovascular diseases[13,16] Currently, mass spectrometry serves as the gold standard for the detection of ACs. In this study, this technique was employed to quantify AC levels in neonates born to mothers with GDM. A total of 19 ACs are associated with GDM, among which 18 exhibit a positive correlation and one demonstrates a negative correlation. The 19 ACs with significant differences between the two groups cover three categories: short-chain, medium-chain, and long-chain. Medium- and long-chain acylcarnitines have been reported to be associated with insulin resistance and mitochondrial dysfunction.[17,18] SCACs are metabolites formed by the conjugation of acyl groups containing 2–6 carbon atoms with carnitine, which play crucial roles in energy metabolism, metabolic regulation, and disease screening. For instance, Luo et al[19] reported that elevated levels of maternal SCACs are associated with an increased risk of GDM.

In this study, the level of C18:2 (a conjugate of linoleic acid and carnitine) in neonates was significantly reduced in the GDM group and was correlated to some extent with the blood glucose control status. Previous research indicates that an elevation in C18:2 levels contributes to improving energy metabolism.[20] Based on the findings of our study, it is hypothesized that GDM affects the energy metabolism of neonates, and this impact may be adverse. Yong-Hwa Lee et al[5] have evidenced that the C3 levels in middle-aged and elderly individuals exhibit a positive correlation with the components related to metabolic syndrome, insulin resistance, and cardiovascular risk factors. After BH correction in this study, the statistical difference in C3 levels was marginally significant; however, the J-*T* test revealed that neonatal

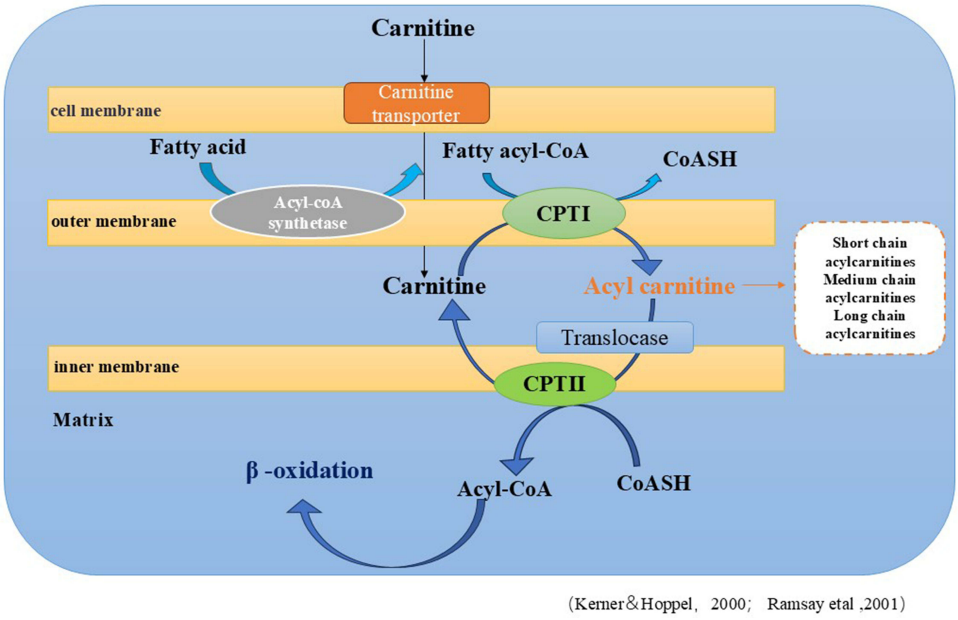

Figure 2 Working Mechanism of Acylcarnitine.

C3 levels exhibited a significant upward trend with increasing severity of maternal glycemic abnormality. As the sample size increases, the statistical significance of this difference may be further strengthened. We also found that offspring of mothers with GDM had significantly higher C3 levels than those in the normal population during the early postnatal period, with the difference increasing under suboptimal maternal glycemic control. This finding is in accordance with the phenomenon that the offspring of GDM patients are more susceptible to metabolic syndrome, cardiovascular diseases, and an increased risk of obesity.[21–23] C6DC has been reported as a potential biomarker for the prediction of cardiovascular diseases among the diabetic population,[24] while C16:1OH has been reported as a predictor for diabetic cardiomyopathy.[25] All the aforementioned indicators demonstrated significant differences in the present study. The findings of this study indicate that these predictive indicators have already exhibited differential characteristics during the neonatal period.

A multitude of studies have indicated that lipid metabolism assumes a crucial role in the genesis and progression of GDM.[26–28] There exist significant disparities in lipid metabolism levels in the serum of GDM patients compared with the normal population. Particularly, TG level and HDL-C level might serve as a predictive target for GDM.[27,29,30] Through mediation analysis, we discovered that 10.7% of the influence of GDM on the C3 level of neonates was mediated by the TG level. HDL-C mediates the effect of GDM on the levels of multiple ACs (including C2, C6, and C14 and so on) in neonates, with a predominant masking effect. These suggest that the true direct association between GDM and ACs may be stronger than that indicated by the total effect. The findings from the mediation analysis confirm that lipid metabolism plays a critical role in the onset and progression of GDM, suggesting that lipid profile testing may be integrated into the clinical management of GDM. Nevertheless, its widespread implementation requires validation and support from additional high-quality prospective studies.

Limitations

This study has several limitations. First, as a single-center study, its findings may lack generalizability. Second, while the results suggest that GDM affects neonatal acylcarnitine levels early on, the absence of long-term growth data limits conclusions about the persistence of this effect. Finally, some neonatal data were sourced from the neonatal disease screening database, which has limited capacity to reflect overall neonatal metabolic status. Furthermore, the missing maternal lipid data compromised the completeness and comprehensiveness of the baseline lipid profile characterization for the entire cohort. It also hindered the full elucidation of maternal lipid profile distribution differences across distinct

glycemic control states, which may further interfere with the assessment of intergroup baseline characteristic balance and the accurate interpretation of lipid-related mediating effects. Future studies should accumulate additional data to further validate these findings.

Conclusion

This study measured acylcarnitine levels, identifying distinct early metabolic profiles in offspring of mothers with GDM compared to those from the general population. Moreover, our findings indicate that the impact of GDM on offspring begins in the neonatal period, potentially providing a new direction for early screening of metabolic syndrome, cardiovascular diseases, and diabetes.

Furthermore, our mediation analysis uncovered a critical mechanistic insight: maternal lipid parameters play dual roles in the association between GDM and neonatal AC levels. These findings highlight that neonatal fat oxidation metabolism is intricately programmed by maternal GDM and lipid status from birth, revealing the intergenerational transmission pathway of metabolic risk.

Data Sharing Statement

The datasets used and analysed in this study are available upon contact with the corresponding author.

Ethics Approval and Consent to Participate

This study followed the principles of the Declaration of Helsinki. The study design and protocol were approved by the ethics committee of Changzhou Maternity and Child Health Care Hospital (Approval No.: 2022015). Neonatal acylcarnitine data were obtained from the neonatal disease screening database. Ethical approval for the study was also obtained from the same committee (Approval No.: 201608). All participants with gestational diabetes mellitus provided informed consent. Guardians of the neonates were informed prior to screening that the data would be used for future research and signed the relevant consent forms.

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Author Contributions

Yuqi Yang: Conceptualization, Writing–Original Draft, Funding Acquisition.
Yue Peng: Data Curation, Investigation, Formal Analysis, Writing–Review & Editing.
Fang Guo: Investigation, Formal Analysis, Writing–Review & Editing.
Chenbo Jia: Investigation, Formal Analysis, Writing–Review & Editing.
Bin Yu: Conceptualization, Writing–Review & Editing, Supervision.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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