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REVIEW

The role of lipid dysregulation in gestational diabetes mellitus: Early prediction and postpartum prognosis

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ABSTRACT

Gestational diabetes mellitus (GDM) is a pathological condition during pregnancy characterized by impaired glucose tolerance, and the failure of pancreatic beta-cells to respond appropriately to an increased insulin demand. However, while the majority of women with GDM will return to normoglycemia after delivery, they have up to a seven times higher risk of developing type 2 diabetes during midlife, compared with those with no history of GDM. Gestational diabetes mellitus also increases the risk of multiple metabolic disorders, including non-alcoholic fatty liver disease, obesity, and cardiovascular diseases. Lipid metabolism undergoes significant changes throughout the gestational period, and lipid dysregulation is strongly associated with GDM and the progression to future type 2 diabetes. In addition to common lipid variables, discovery-based omics techniques, such as metabolomics and lipidomics, have identified lipid biomarkers that correlate with GDM. These lipid species also show considerable potential in predicting the onset of GDM and subsequent type 2 diabetes post-delivery. This review aims to update the current knowledge of the role that lipids play in the onset of GDM, with a focus on potential lipid biomarkers or metabolic pathways. These biomarkers may be useful in establishing predictive models to accurately predict the future onset of GDM and type 2 diabetes, and early intervention may help to reduce the complications associated with GDM.

INTRODUCTION

Gestational diabetes mellitus (GDM) is diagnosed mostly during the second and third trimester of pregnancy, with a failure of pancreatic beta-cells to respond appropriately to the insulin requirements during gestation, leading to impaired glucose tolerance or hyperglycemia[1,2]. Depending on the diagnostic criteria used, it occurs in approximately 7–8% of pregnant women, and ranges up to 20%[3–5]. These diagnostic criteria encompass various standards, such as the National Diabetes Data Group (NDDG) criteria[6], the Carpenter and Coustan criteria[7], the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria[8], the World Health Organization (WHO) criteria[9], and the National Institute for Health and Care Excellence (NICE) criteria[10], among others.

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The complications of GDM include short-term (pre-eclampsia, cesarean section in mothers, and hypoglycemia and jaundice in infants) and long-term (type 2 diabetes, non-alcoholic fatty liver disease, cardiovascular, and renal diseases in mothers and obesity in new-born children)[11–20]. The majority of women with a history of GDM return to normoglycemia post-delivery, however, up to 35% of them develop glucose intolerance within the first 2 months postpartum[21]. It has been reported that women with a history of GDM have a higher risk of developing future type 2 diabetes compared with those who have a normoglycaemic pregnancy[22–24]. In fact, up to 50% women with gestational diabetes mellitus will progress to future type 2 diabetes within 10 years post-delivery[22,25]. Compared with the general population, the women who progress to type 2 diabetes at a younger age show a higher risk of developing renal and cardiovascular diseases, as well as non-alcoholic fatty liver disease (NAFLD), which may lead to early mortality[4,13,15,17,18,26].

There are several risk factors linked to the onset of GDM, such as a higher body mass index (BMI), increased maternal age, family history of GDM, and ethnicity[27,28]. Besides these risk factors, lipids also play vital roles in the development of GDM. Lipids exhibit various cellular functions such as energy support, cellular structure component, and cell signaling[29–32]. GDM-related traditional lipid profiles have been identified, such as triacylglycerols (TAGs), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), and high-density lipoprotein cholesterol (HDL-C)[33]. However, these lipids can not reflect the comprehensive lipid metabolism status, both in physiological and pathological conditions. To further explore the GDM-related lipid profiles, discovery-based omics techniques have been developed and applied to identify potential metabolic biomarkers or pathways that are correlated with diseases such as GDM[34–37].

This study provides a review of the relationships between lipid metabolism and GDM, aiming to enhance the awareness of the importance of lipid dysregulation in the onset of GDM. Besides, we aim to highlight several plasma biomarkers that can be used to predict GDM as early as the first trimester. Identifying biomarkers can provide a molecular rationale to further explore the regulation of lipid to avoid the onset of pregnancy disorders and further metabolic disorders at an early stage.

MATERNAL LIPID CHANGES DURING NORMAL PREGNANCY

Maternal lipid metabolism changes dramatically throughout the pregnancy and can be divided into two phases: anabolic and catabolic[38,39]. In the early stages of pregnancy (1st and 2nd trimester), the maternal pancreatic beta-cell mass increases to enhance insulin secretion, resulting in enhanced *de novo* lipogenesis (DNL) and leads to lipid storage[38,40–42]. During this period, the activity of adipose tissue lipoprotein lipase (LPL) can also be increased or unchanged[43,44], leading to enhanced hydrolysis of circulating triacylglycerols and the production of lipid products such as non-esterified fatty acids (NEFAs), 2-monoacylglycerol, and glycerol[45,46]. These products are then taken up and used for re-synthesis of TAGs. Whereas in late pregnancy (3rd trimester), it has been reported that insulin sensitivity may gradually decline to 40–50% of the normal range, both in women with normal glucose tolerance and in women with GDM[47–49]. Increased insulin resistance (IR) leads to enhanced lipolysis, decreased LPL activity, and biosynthesis of fatty acid, facilitating the process of fat breakdown in the late trimester of gestation[38,40–43,50–52].

CIRCULATING LIPID PROFILES AND GDM

Cholesterol metabolism was reported to be involved in the development of GDM[33,53–58]. Longitudinal studies have evaluated the lipid profile changes throughout the normal pregnancy, revealing that TC, LDL-C, and the TAG/HDL-C ratio increase progressively during pregnancy, while HDL-C increases from the 1st to the 2nd trimester along with a slight decrease in the 3rd trimester[54,55]. However, the ratio of LDL-C to HDL-C remains unchanged[56]. In contrast, women with GDM usually show increased insulin resistance and exhibit significantly higher levels of TC, LDL-C, and VLDL-C, as well as lower HDL-C levels than those with a normal pregnancy[33,54,56–58].

The adipose tissue secretes multiple adipokines which are mostly pro-inflammatory[59] and are associated with various metabolic diseases, such as GDM, type 2 diabetes, and obesity[60]. Adiponectins have been shown to be negatively associated with GDM[60], whereas leptin was linked with a higher risk of GDM[61]. An inverse association between the adiponectin/leptin ratio and the GDM risk was found in mild to moderate obese women (BMI < 35 kg/m^2)[62]. This finding was further supported by Ye *et al.*[61] who discovered that the leptin/adiponectin ratio was positively associated with GDM.

Despite these lipid species, discovery-based omics techniques have been used for efficient biological system investigations, including metabolic profiling[63]. Lipidomics comprise a major portion of metabolomics, which allows a large proportion of the lipidome to be analyzed. The workflow of lipidomics study usually includes the following steps: sample collection, sample preparation, identification and quantification of metabolites and lipids, data pre-processing, statistical analysis, biomarker discovery as well as clinical diagnosis, and early-stage prediction (Figure 1).

Lipid metabolism has been found to be involved in the progression of GDM, and consists of different types of lipid species, such as diacylglycerols (DAGs), TAGs, phospholipids, sphingolipids, fatty acids, and other metabolic substances that are converted to each other (Figure 2). Rahman *et al.*[64] discovered that women at a higher risk of developing GDM had elevated plasma DAGs and short, saturated/low unsaturated TAGs at 10–14 weeks gestation. Liu *et al.*[65] also reported fasting lipids including TAGs were positively associated with GDM. Similarly, GDM in obese women was also associated with elevated DAGs and TAGs[66,67]. Increased TAGs were correlated with impaired glucose metabolism in muscle tissue and inhibited insulin signaling pathway, leading to insulin resistance[68]. These findings indicate that increased *de novo* lipogenesis might be involved in the pathogenesis of GDM by affecting glucose homeostasis.

The metabolism of phospholipids and sphingolipids are also found to be associated with a risk of GDM. Zhan *et al.*[69] showed that glycerophospholipids were the most prevalent altered lipid species at the second and third trimesters, when compared women with GDM with healthy pregnant women. Similarly, Rahman *et al.*[64] discovered that plasma sphingomyelins (SMs) and phosphatidylcholines (PCs) were negatively correlated with GDM risk in the early trimester. In another study, the plasma lipid profile was measured in the early trimester, and a lipid score consisting of 10 lipid species (mainly glycerophospholipids and glycerolipids) was established, which was linked with increased GDM risk[70]. Dudzik *et al.*[71] found that

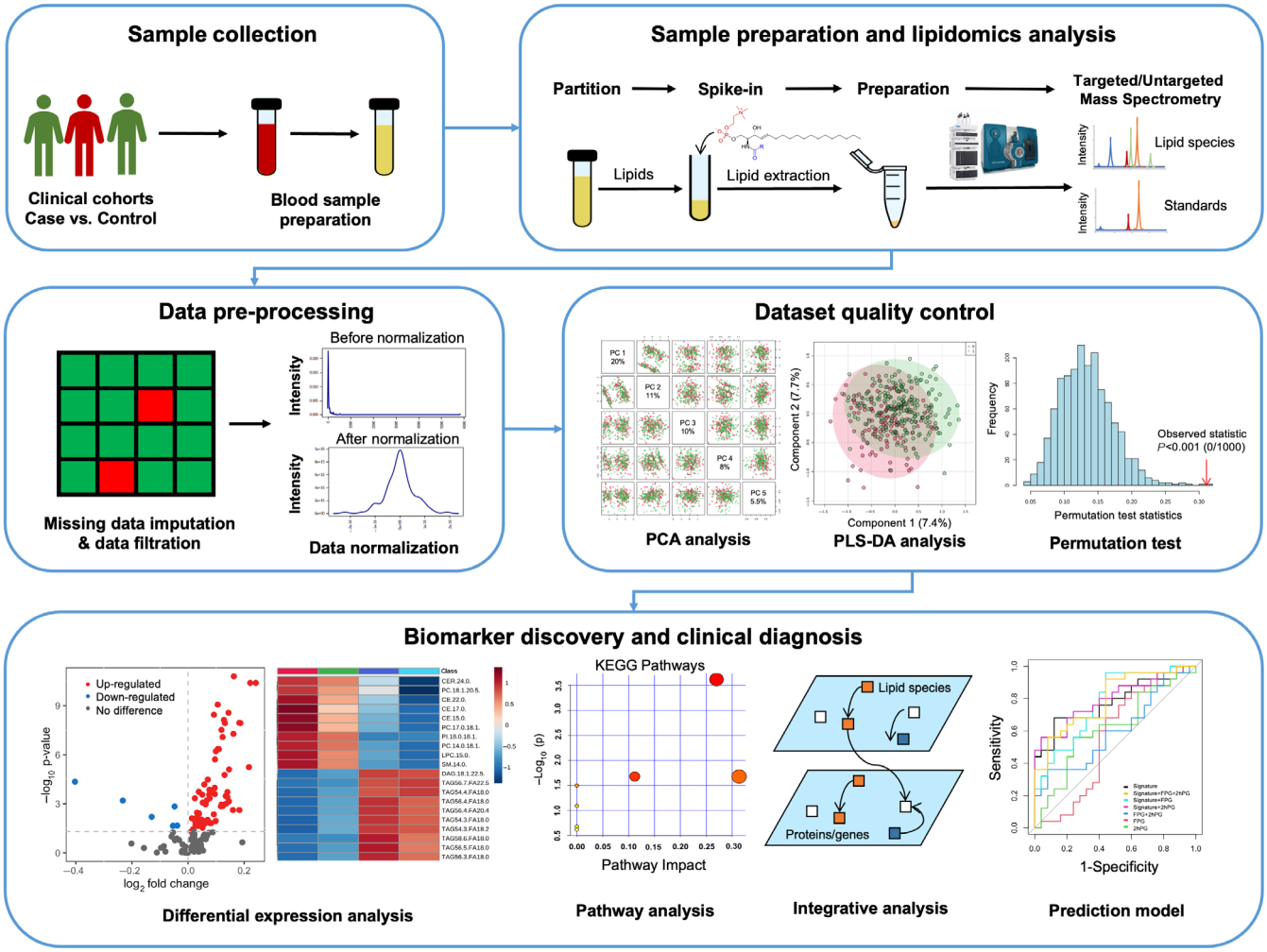

Figure 1 | Schematic representation of the lipidomics study workflow. This figure illustrates the comprehensive workflow of lipidomics studies, encompassing key stages such as sample collection, sample preparation, acquisition of lipidomics data, data pre-processing, data quality assessment, and the identification of top candidates to serve as potential biomarkers and signaling pathways.

lysoglycerophospholipids (LPCs) had a close association with the glycemic state of women. Wang *et al.* discovered ten lipids that were significantly associated with GDM independent of confounding factors, five of them (phosphatidylinositol 40:6, alkylphosphatidylcholine 36:1, phosphatidylethanolamine plasmalogen 38:6, DAG 18:0/18:1, and alkylphosphatidylethanolamine 40:5) were positively correlated and five of them (sphingomyelin 34:1, dihexosyl-ceramide 24:0, mono hexosyl ceramide 18:0, dihexosyl ceramide 24:1, and PC 40:7) were negatively correlated with GDM[72]. These findings were further supported by Liu *et al.*[73] who showed that disturbances of glycerophospholipid and sphingolipid metabolism were associated with GDM, and may contribute to the onset of GDM through the dysregulation of glucose homeostasis and beta-cell function.

As GDM progresses, the circulating metabolic profile including amino acids (AAs) also undergoes corresponding changes. By comparing the metabolome of pre-GDM and GDM, Walejko *et al.*[74] discovered that pre-GDM women had increased branched-chain amino acids (BCAAs) and sugars, whereas women with GDM showed increased lipids and decreased AAs. A longitudinal study revealed that polyunsaturated phospholipids rather than saturated phospholipids were significantly lower in women with GDM throughout the pregnancy, even before the onset of GDM[75]. Another longitudinal study showed the fold change (2nd trimester/1st trimester ratio) of lysophosphatidylcholine (LysoPC(20:4)), uric acid, and six AAs strongly differed between the GDM and control groups[76].

Furthermore, the association between fatty acids and GDM onset has been explored, but the results have not shown consistent agreement across various studies. Short-chain fatty acids (SCFAs), such as alpha-hydroxybutyric acid (alpha-HB), myristic acid (beta-HB), palmitic acid, and butyric acid were strongly

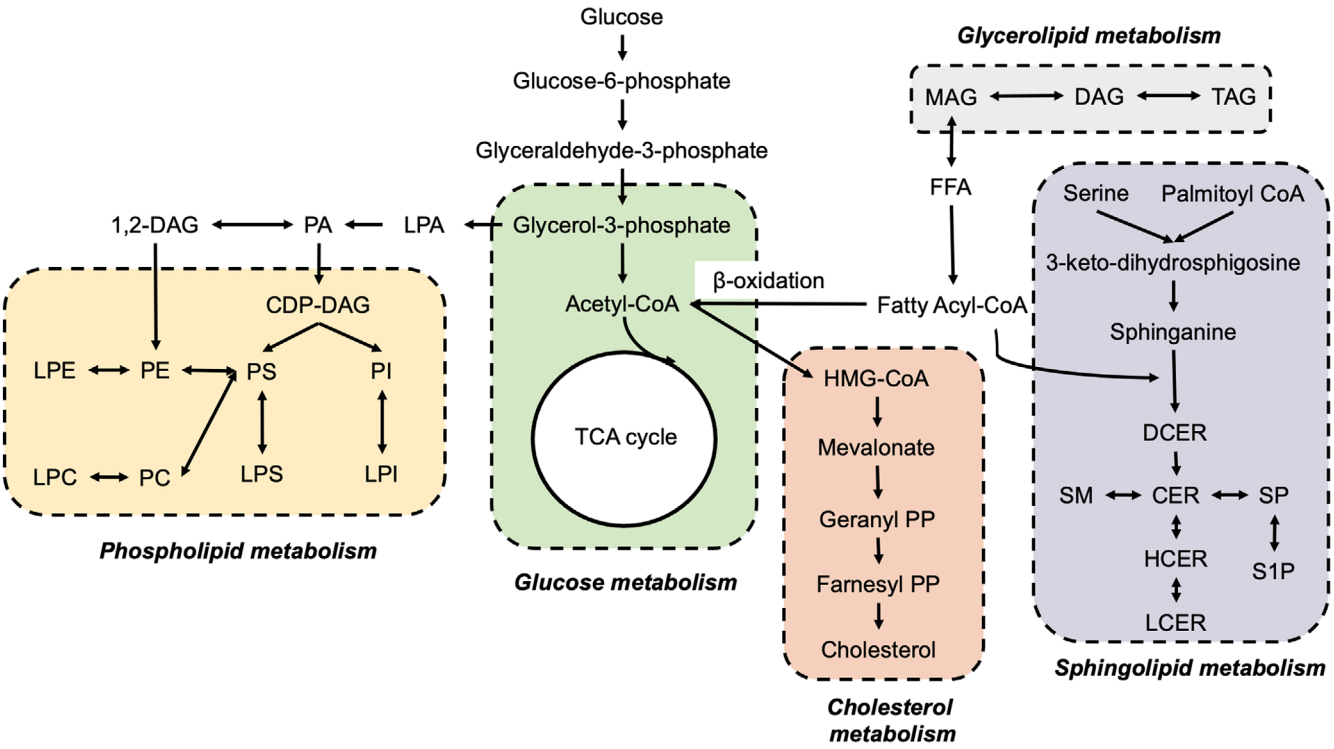

Figure 2 | Lipid metabolism pathways involved in the onset of gestational diabetes mellitus (GDM). The interconnected metabolic pathways of lipid biosynthesis, encompassing fatty acids, neutral lipids, phospholipids, sphingolipids, and cholesterol metabolism, all of which play pivotal roles in the development of GDM.

associated with the risk of GDM[53,77–79]. Lower levels of long-chain fatty acids, including three saturated fatty acids (SFAs) and one unsaturated fatty acid (UFA) were found in women with GDM, compared with healthy pregnant women[80]. In contrast, Pan *et al.*[81] showed that SFAs were positively correlated with GDM risk. Zhu *et al.*[82] discovered that increased levels of serum even-chain SFAs and decreased levels of serum odd-chain SFA enhanced the risk of GDM in pregnant women. Pan *et al.*[81] indicated omega-6 polyunsaturated fatty acids (PUFAs) were found to be negatively associated with GDM onset. However, on the contrary, another study showed no difference in omega-6 PUFA and arachidonic acid between the GDM and non-GDM groups[83]. The fatty acid composition of cholesteryl esters and SFAs were found to be related to GDM as well[84,85]. These inconsistent results may result from a different sample size and type of lipid profiling, and further studies with more participants are strongly warranted.

BIOMARKERS USED FOR THE EARLY PREDICTION OF GDM

A standard test for GDM diagnosis is the 75 g 2 h oral glucose tolerance test (OGTT) performed at 24–28 weeks of gestation, as recommended by the International Association of Diabetes and Pregnancy Study Groups[8]. While the National Institutes of Health (NIH) recommends a 'two-step approach' which includes a 50 g 1 h OGTT followed by a 100 g 3 h OGTT[86]. The American Diabetes Association (ADA) recommends both options to diagnose GDM[87]. However, both tests are usually performed in late second trimester, which is too late to incorporate effective interventions and to prevent potential GDM-related complications both in mothers and infants. Hence, there is a pressing need to develop non-invasive and precise predictive models capable of identifying high-risk GDM populations at early gestation, to facilitate early intervention.

Lipidomics acts as an effective tool to screen potential biomarkers and to establish a predictive model to identify women with high risk of developing GDM at early gestation, superior to common clinical variables. Recent studies focused on establishing predictive models to predict GDM onset are summarized in Table 1. Briefly, these studies employed metabolomics or lipidomics to analyze the pre-onset metabolome in GDM, and successfully identified lipid species with a strong predictive capability for the onset of GDM, compared with traditional risk factors of GDM. Nonetheless, the effectiveness of these predictive models should be confirmed through validation in additional clinical cohorts, ensuring their applicability in real-world scenarios.

Table 1 | Summary of predictive lipid biomarkers of GDM.

Year	Author	Technique	Sample	GW	Lipid biomarkers	Predictive power
2015[88]	Enquobahrie *et al.*	GC–MS	Serum	16 weeks	Linoleic acid, oleic acid, myristic acid, D-galactose, D-sorbitol, o-phosphocolamine, L-alanine, L-valine, 5-hydroxy-L-tryptophan, L-serine, sarcosine, L-pyroglutamic acid, L-mimosine, L-lactic acid, glycolic acid, fumaric acid, and urea	AUC 0.871
2015[89]	Pinto *et al.*	NMR	Plasma	2–21 weeks	26 resonances	Q^2 0.6
2016[90]	Lu *et al.*	MS	Serum	15.2 ± 0.07 weeks	TAG(51.1), TAG(48:1), PC(32:1) and PCae(40:3)	AUC 0.71
2016[91]	Nevalainen *et al.*	MS	Serum	1st trimester	Arginine, glycine, and 3-hydroxy-isovalerylcarnitine	AUC 0.72
2018[92]	Hou *et al.*	LC–MS, GC, NMR	Serum	12 weeks	BMI, retinol binding protein 4 (RBP4), n-acetylaspartic acid, and C16:1 (cis-7)	AUC 0.751
2020[93]	McBride *et al.*	NMR	Serum	BiB cohort: 24–28 weeks, UPBEAT cohort: 27–28 + 6 weeks	Monounsaturated fatty acids (MUFA), ratios of MUFA to omega 3 fatty acids and total fatty acids, ratio of apolipoprotein B to apolipoprotein A-1 (APOA:APOB1)	AUC 0.69
2021[73]	Liu *et al.*	LC–MS	Serum	10 weeks	PC (40:6), LPCs (16:0, 17:0, 18:0, 18:1), LPEs (16:0, 18:0), Cer (36:2), FA (20:0), GCA, GDCA, GCDCA, GUDCA, TDCA, TCDCA, TMA and L-carnitine	AUC 0.91
2021[94]	Lu *et al.*	GC–MS	Serum	2nd and 3rd trimesters	Group 1: methyl-2-oxovaleric acid, D-gluconolactone, D-glucose, hydroxybutyric acid, alpha-hydroxyisobutyric acid, isobutyric acid, isovaleric acid, octanoic acid, glycocholic acid, nonanoic acid, myristic acid, DHA, and palmitic acid. Group 2: glycylproline, alpha-ketoisovaleric acid, ketoleucine, acetic acid, hydroxybutyric acid, isobutyric acid, isovaleric acid, caproic acid, heptanoic acid, pyruvic acid, arachidonic acid, adrenic acid, and citramalic acid	AUC 0.807 (at 2nd trimester) AUC 0.81 (at 3rd trimester)
2021[78]	Raczkowska *et al.*	GC–MS	Serum	8–14 weeks	Myristic acid, alpha-hydroxybutyric acid and beta-hydroxybutyric acid	AUC 0.791
2021[95]	McMichael *et al.*	UPLC–MS	Plasma	10–16 weeks	SM 14:0, hypoxanthine, alpha-hydroxybutyrate, and xanthine	AUC 0.833
2021[72]	Wang *et al.*	HPLC–MS	Plasma	6–15 weeks	Phosphatidylinositol 40:6, alkylphosphatidylcholine 36:1, phosphatidylethanolamine plasmalogen 38:6, diacylglyceride 18:0/18:1, alkylphosphatidylethanolamine 40:5, sphingomyelin 34:1, dihexosyl-ceramide 24:0, mono hexosyl ceramide 18:0, dihexosyl ceramide 24:1, and phosphatidylcholine 40:7	AUC 0.801
2021[69]	Zhan *et al.*	UPLC/Q-TOF-MS	Serum	2nd and 3rd trimesters	Phosphatidylcholine (22:6(4Z,7Z,10Z,13Z,16Z,19Z)/P-18:1(11Z)), phosphatidylethanolamine (22:2(13Z,16Z)/P-18:1(11Z)), monoacylglycerol (15:0/0:0/0:0), lysophosphatidylethanolamine (0:0/18:0), and cyclic phosphatidic acid (16:0/0:0).	AUC 0.701–0.873 (2nd trimester); AUC 0.702–0.889 (3rd trimester)
2021[96]	Zhang *et al.*	LC–MS	Plasma	12–16 weeks and 24–28 weeks	17(S)-HDoHE and sebacic acid	AUC 0.71 (at 12–16 weeks); AUC 0.78 (at 24–28 weeks)
2022[80]	He *et al.*	GC–MS	Plasma and urine	11–14 weeks	Cysteine, malonic acid, alanine, 11,14-eicosadienoic acid, stearic acid, arachidic acid, and 2-methyloctadecanoic acid	AUC 0.928
2022[97]	Peng *et al.*	UPLC-MS	Serum	3rd trimester	27 metabolic peaks; 5-metabolite panel: L-valine, hypoxanthine, eicosapentaenoic acid, 2-amino-1,3,4-octadecanotriol, and choline.	AUC 0.90–0.93 (27 metabolic peaks); AUC 0.769 (5-metabolite panel)

Table 1. (*Continued*)

Year	Author	Technique	Sample	GW	Lipid biomarkers	Predictive power
2022[98]	Zhu *et al.*	GC–MS	Serum	10–13 weeks, and 17–19 weeks	(GW10-13) 17-metabolite panel: 3 amino acids, 4 lipids, 5 purine and pyrimidine metabolites, and 8 carbohydrate metabolites. (GW17-19) 13-metabolite panel: 3 amino acids, 3 lipids, 2 purine and pyrimidine metabolites, and 5 carbohydrate metabolites	AUC 0.832 (at 10–13 weeks); AUC 0.797 (at 17–19 weeks)

AUC, area under the curve; BMI, body mass index; GC–MS, gas chromatography/ mass spectrometry; GW, gestational week; HPLC, high-performance liquid chromatography; LC–MS, liquid chromatography-mass spectrometry; MS, mass spectrometry; NMR, nuclear magnetic resonance; Q-TOF, quadrupole time-of-flight; Sens, sensitivity; Spec, specificity; UPLC, ultra-performance liquid chromatography.

LIPID CHANGES IN THE TRANSITION FROM GDM TO FUTURE TYPE 2 DIABETES POST-DELIVERY

Several studies have investigated the role of lipid dysregulation in the transition from GDM to the future incidence of type 2 diabetes after delivery. The Study of Women, Infant Feeding, and Type 2 Diabetes after GDM Pregnancy (SWIFT) is a well-established, ethnically diverse prospective cohort that enrolled 1,035 women with GDM pregnancy who delivered a singleton, live-born infant from 2008 to 2011. Participants have been followed up for the onset of type 2 diabetes for up to 10 years[99]. By using this clinical cohort, Allalou *et al.*[34] conducted targeted metabolomics on a subset of the SWIFT cohort ($N = 244$), and identified 22 metabolites significantly differentiating women who developed type 2 diabetes after a GDM pregnancy from those who did not. These metabolites include 8 amino acids, 6 sphingolipids, 3 phospholipids, 3 biogenic amines, and 1 fatty acid[34]. Lai *et al.*[35] also applied targeted metabolomics in a larger subset ($n = 658$) of the SWIFT study, and showed an overall increase in diacyl-PCs, as well as a decrease in sphingolipids and acyl-alkyl-PCs among women with a history of GDM who progressed to future type 2 diabetes. To further investigate the lipid profiles associated with the transition from GDM to type 2 diabetes, Lai *et al.*[36] used targeted lipidomics to detect up to 1,008 lipid species, and found that upregulation of glycerolipid metabolism (including DAGs and TAGs) as well as impaired sphingolipid metabolism (including sphingomyelins, hexosylceramide, and lactosylceramide) were associated with future type 2 diabetes risk, and these changes were present years prior to the onset of diabetes and were revealed during the early postpartum period. Lappas *et al.*[100] reinforced these findings by highlighting that the cholesteryl ester species, alkenyl phosphatidylethanolamine species, and phosphatidylserine species exhibited the strongest associations with the risk of type 2 diabetes following GDM pregnancy. Khan *et al.*[101] provided additional evidence supporting the previous findings that diminished sphingolipid metabolism was linked to the progression from GDM to type 2 diabetes. Additionally, their study demonstrated that blocking sphingolipid metabolism impaired pancreatic beta-cell function in a mouse model[101].

Besides phospholipid and sphingolipid dysmetabolism, there are other metabolites involved in the development of type 2 diabetes after GDM pregnancy. In a pilot study, significant alterations were observed in the levels of 2-hydroxybutyrate, 3-hydroxybutyrate, and stearic acid when comparing women with GDM who subsequently developed type 2 diabetes after delivery with those who did not[102]. Liu *et al.*[65] discovered a group of metabolites (such as TAGs, glycerol, long-chain acylcarnitines, 3-hydroxybutyrate, NEFA) that mediated the relationship between GDM and postpartum abnormal glucose metabolism (AGM) postpartum. Batchuluun *et al.*[103] also found that short-chain acylcarnitines were associated with the onset of type 2 diabetes following a GDM pregnancy. Additionally, in a Singapore cohort, Wang *et al.*[104] identified 23

metabolites that were associated with postpartum abnormal glucose metabolism.

Despite lipid dysregulation, amino acid metabolism was also found to be involved in the transition from GDM to type 2 diabetes. This was highlighted by studies conducted by Lai *et al.*[35] and Allalou *et al.*,[34] where they found that activation of amino acid metabolism was strongly associated with the development of type 2 diabetes in women with a recent history of GDM. Similarly, Andersson-Hall *et al.*[105] discovered that in women with GDM with future incident type 2 diabetes, levels of BCAAs and 3-hydroxyisobutyrate were elevated, which were linked with insulin resistance and lipid metabolism (Table 2).

To predict the future transition from GDM to type 2 diabetes, Lai *et al.*[35,36] established two predictive models using metabolites and lipid species, respectively, which both achieved superior performance compared with common clinical variables such as fasting plasma glucose and 2 h plasma glucose. Similarly, one study also established a predictive model including three lipid species (CE 20:4, the alkenylphosphatidylethanolamine species PE(P-36:2) and the phosphatidylserine species PS 38:4) which could accurately predict the onset of type 2 diabetes in women with previous GDM[100]. Liu *et al.*[65] found that the addition of leucine/isoleucine, valine, 3-hydroxybutyrate, and acetylcarnitine (AC C2) to clinical factors improved the prediction of later glucose dysregulation following GDM pregnancy, with the area under the curves (AUCs) ranging from 0.707–0.725. Wang *et al.*[104] identified five metabolites [p-cresol sulfate, linoleic acid, glycocholic acid, lysoPC(16:1), and lysoPC(20:3)] that predicted postpartum abnormal glucose metabolism with an AUC value of 0.92–0.94, along with traditional risk factors.

Overall, these findings suggest that lipid and AAs dysregulation both contribute to the progression from GDM to type 2 diabetes, and the shift from glycerolipid to phospholipid and sphingolipid metabolism appears to be a possible mechanism involved in this transition, as illustrated in Figure 2. However, additional research conducted in well-established clinical cohorts is warranted to identify the type 2 diabetes-related metabolome at the early stage.

DISCUSSION AND CONCLUSION

Human maternal lipid metabolism during normal pregnancy is well understood, but there are still questions regarding the pathogenesis of GDM and the transition to future type 2 diabetes. Several studies have attempted to use different methodologies to measure lipid profiles and have identified lipid biomarkers or metabolic pathways associated with GDM and type 2 diabetes. These lipid biomarkers include certain types of fatty acids, glycerolipids, phospholipids, sphingolipids, cholesterol, and lipoproteins. However, the findings are inconsistent across studies and quite inconclusive, which could be due to the heterogeneities in cohort and study design, as well as study populations (race/ethnicity), sample sizes, diagnostic criteria, potential confounding factors, and statistical methods used during the analysis. Additionally, the regulation and interactions among the lipid metabolism pathways are quite complex and not entirely known. Functional studies that interfere with specific target proteins/genes to regulate lipid metabolism and to prevent the onset of GDM and type 2 diabetes are strongly recommended. However, while predictive models consisting of different lipids have been established and are superior to the common clinical variables, further verification in other cohorts is necessary for clinical translation. With the rapid development of artificial intelligence, more methods can be used to build predictive models and to facilitate early

Table 2 | Summary of lipid changes in the transition from GDM to future type 2 diabetes.

Year	Author	Technique	Sample	Lipid biomarkers
2015[100]	Lappas *et al.*	HPLC–MS	Plasma	CE 20:4, PE(P-36:2) and PS 38:4
2016[34]	Allalou *et al.*	LC–MS/MS	Plasma	2-AAA, Gly, Ile, Leu, Thr, Trp, Tyr, Val. xLeu+, Hexoses, SM(OH)C16:1, SM(OH)C22:2, SM C18:0, SM C18:1, SM C20:2, SM C24:1, PC ae C40:5, PC ae C42:5, PC ae C44:5, AC10, AC3, Palmitoleic acid (C16:1 n9)
2018[105]	Andersson-Hall *et al.*	NMR	Plasma	BCAAs and 3-hydroxyisobyturate
2019[101]	Khan *et al.*	LC–MS/MS	Plasma	Increased TAG and decreased CE, Cer, NEFA, LCer, LPC, LPE, PE, and SM in women with future type 2 diabetes
2020[35]	Lai *et al.*	LC–MS/MS	Plasma	Increased AAs as well as diacyl-glycerophospholipids and decreased sphingolipids and acyl-alkyl-glycerophospholipids among women with future type 2 diabetes
2020[36]	Lai *et al.*	LC–MS/MS	Plasma	Increased TAG, DAG, and decreased SM, HCer, and LCer among women with future type 2 diabetes
2021[104]	Wang *et al.*	LC–MS	Serum	P-cresol sulfate, linoleic acid, glycocholic acid, lysoPC(16:1) and lysoPC(20:3)

2-AAA, 2-aminoadipic acid; AA, amino acid; AC, acylcarnitine; AGM, abnormal glucose metabolism; BCAA, branched-chain amino acid; CE, cholesteryl ester; Cer, ceramide; DAG, diacylglycerol; GDM, gestational diabetes mellitus; Gly, glycine; HCer, hexosylceramide; HPLC, high-performance liquid chromatography; Ile, isoleucine; LCer, lactosylceramide; LC-MS, liquid chromatography-mass spectrometry; Leu, leucine; LPC, lysophosphatidylcholine; LPE, lysophosphatidylethanolamine; MS, mass spectrometry; NEFA, non-esterified fatty acid; NMR, nuclear magnetic resonance; PE, phosphatidylethanolamine; PS, phosphatidylserine; SM, sphingomyelin; TAG, triacylglycerol; Thr, threonine; Trp, tryptophan; Tyr, tyrosine; Val, valine.

recognition of high-risk populations for early intervention to prevent severe diabetic complications.

Overall, this review has summarized recent findings over the past few decades, and has identified the role that lipids play in the pathogenesis of GDM and progression to type 2 diabetes. Additional research on the liver/pancreatic cell/muscle cell/adipocyte function and related molecular biology would provide a better understanding of lipid metabolism under diabetic conditions.

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DISCLOSURE

The authors declare no conflict of interest.
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Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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