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Hepatic lipid quantity and quality in type 2 diabetes mellitus

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The incidence of type 2 diabetes mellitus (T2DM) has been increasing worldwide. In the pathophysiology of metabolic diseases, including T2DM, both the quantity and quality of lipids that accumulate in the body have attracted significant research attention. Excess lipids accumulate in non-adipose tissues, such as the liver and skeletal muscles, leading to insulin resistance and an increased risk of developing T2DM. The liver is the central organ for glucose and lipid metabolism, and impaired hepatic regulatory mechanisms lead to hyperglycemia, insulin resistance, and hepatic lipid accumulation. Hepatic triglyceride (TG) accumulation contributes to the development of hepatic insulin resistance; however, the quantity of TGs alone is insufficient to explain the development of glucose and lipid metabolic dysfunctions. Thus, we focus on lipid quality, particularly fatty acids. In addition to TGs, phospholipids store fatty acids, which vary in carbon chain length, number of double bonds, and position of double bonds (such as ω3 and ω6), resulting in lipid diversity. Changes in the fatty acid chains of phospholipids are also strongly associated with glucose and lipid metabolism. In this mini review, we discuss the involvement of hepatic lipid quantity and quality in T2DM, with the aim of contributing to the development of novel T2DM therapies.

KEYWORDS
lipid intermediate, lipid quality, lipid quantity, phospholipid diversity, type 2 diabetes mellitus

1 Introduction

The global incidence of diabetes mellitus, a chronic heterogeneous metabolic disease, has increased in recent years. According to the International Diabetes Federation Diabetes Atlas, 11th Edition, the global prevalence of diabetes in individuals aged 20–79 years was 588.7 million individuals in 2024, exceeding the combined population of the U.S., Canada, Mexico, and the Caribbean. Type 2 diabetes mellitus (T2DM), which accounts for over 90% of all diabetes cases, is characterized by insulin resistance and β-cell dysfunction (Muoio and Newgard, 2008; Banday et al., 2020). In the pathophysiology of metabolic diseases, including T2DM, both the quantity and quality of lipids (hereafter referred to as lipid quantity and quality) accumulated in the body have attracted attention. Excess lipids accumulate in non-adipose tissues such as the liver and skeletal muscle (Britton and Fox, 2011; Suganami et al., 2012). The liver is a principal metabolic organ that plays a crucial role in regulating glucose and lipid homeostasis. Hepatic lipid accumulation, a

hallmark of metabolic dysfunction-associated steatotic liver disease (MASLD), is strongly associated with the onset of insulin resistance (Samuel and Shulman, 2016) and an increased risk of T2DM (Mantovani et al., 2021).

Triglycerides (TGs) are the predominant lipid class stored in lipid droplets, and the quantity of lipids is a component of the MASLD grading system (Marra and Svegliati-Baroni, 2018). Hepatic TG accumulation contributes to the development of hepatic insulin resistance (Samuel and Shulman, 2016). However, the total amount of TGs stored in the liver is not the major determinant of lipotoxicity, as TGs are relatively inert storage forms. Rather, lipid intermediates are thought to play a key role. For example, diacylglycerols (DAGs) can activate protein kinase Cε and impair insulin receptor signaling. Lipotoxicity refers to the toxic effects of excessive lipid accumulation in non-adipose tissues, leading to cellular dysfunction and metabolic disturbances. Consistent with this, lipid intermediates, such as DAGs, lysophosphatidylcholine, and ceramides, exhibit toxicity and interfere with insulin signaling (Marra and Svegliati-Baroni, 2018). In addition, glycerophospholipids (phospholipids) in biological membranes have recently attracted attention as dynamic regulators of cellular metabolism and signaling (Hishikawa et al., 2014; Lamari et al., 2025). Phospholipids are biosynthesized from DAG and lysophospholipids through the Kennedy pathway and Lands cycle, respectively. Phospholipids consist of two fatty acids and one polar head group linked to a glycerol backbone. Changes in the fatty acid chains of phospholipids have been implicated in glucose and lipid metabolism (Valentine et al., 2022). In this mini review, we focus on the emerging concept that both lipid quantity and quality in the liver are associated with glucose and lipid metabolism in T2DM.

2 Hepatic lipid quantity and metabolic dysfunction

Hepatic TG accumulation is strongly associated with the induction of insulin resistance and impaired glucose metabolism. Both experimental and clinical studies have demonstrated a close correlation between intrahepatic lipid content and metabolic abnormalities, including elevated fasting glucose levels, increased hepatic glucose production, and reduced insulin sensitivity (Samuel et al., 2004; Kotronen et al., 2007; Fabbrini et al., 2009; Fabbrini et al., 2010; Lim et al., 2011). Elevated hepatic lipid content is posited to impair glucose metabolism by disrupting insulin signaling pathways and enhancing hepatic glucose production. The prevalence of MASLD, formerly known as nonalcoholic fatty liver disease, in patients with T2DM is estimated to be approximately 60%–70% (Younossi et al., 2024). These observations have established that hepatic lipid accumulation is closely linked to T2DM.

Experimental evidence further supports a causal relationship between hepatic TG content and glucose metabolism. Pharmacological interventions have shown that reducing hepatic TG content frequently leads to improvements in glucose metabolism. For example, bezafibrate treatment reduced hepatic steatosis and improved hepatic insulin sensitivity in diabetic TallyHo mice (Franko et al., 2017). Empagliflozin, a specific sodium–glucose cotransporter 2 inhibitor, protects mice against diet-induced obesity, hepatic steatosis, and insulin resistance (Radlinger et al., 2023). In patients with MASH, pioglitazone administration significantly decreased hepatic lipid content and increased hepatic insulin sensitivity (Belfort et al., 2006). In genetic interventions, liver-specific overexpression of lipoprotein lipase, which plays a major role in lipid metabolism through the hydrolysis of TG in chylomicrons and very low-density lipoproteins, improved glucose metabolism in high-fat diet-fed mice (Shimizu et al., 2022). In this model, hepatic overexpression of lipoprotein lipase decreased lipid droplet formation in the liver and improved fasting blood glucose levels. These findings indicate that hepatic lipid quantity influences glucose metabolism and contributes to T2DM. Although TGs constitute the predominant lipid class within droplets and the abundance of lipids is integral to the grading system of MASLD, lipids, as signaling intermediates, encompass a diverse array of molecules with distinct functions. Lipid intermediates and lipid composition, such as fatty acids, may impair glucose metabolism. These observations highlight the importance of lipid quantity and quality in regulating glucose metabolism.

3 Hepatic lipid quality and metabolic regulation

3.1 Lipid intermediates

Although hepatic TG accumulation is strongly associated with insulin resistance, increasing evidence indicates that TG itself is not the primary lipid responsible for metabolic dysfunction. Rather, lipid storage in the form of TG is considered protective against lipotoxicity (Marra and Svegliati-Baroni, 2018; Geng et al., 2021). TG synthesis facilitates the sequestration of excess fatty acids into lipid droplets, thereby limiting the accumulation of potentially toxic lipid intermediates such as DAGs and ceramides. Consistent with this concept, inhibition of TG synthesis has been shown to exacerbate oxidative stress, inflammation, and fibrosis (Yamaguchi et al., 2007).

DAG, a lipid intermediate comprising glycerol and two fatty acids, has been identified as a key mediator of hepatic insulin resistance. Although intrahepatic DAG levels are increased in MASLD (Geng et al., 2021), their metabolic impact depends primarily on subcellular localization rather than total cellular abundance. In particular, DAG accumulation within membrane compartments represents the bioactive pool that promotes the recruitment, activation, and translocation of protein kinase Cε (PKCε), the predominant PKC isoform in the liver, to the plasma membrane, thereby impairing insulin signaling (Perry et al., 2014; Samuel and Shulman, 2016; Samuel and Shulman, 2018). PKCε activation reduces insulin-stimulated phosphorylation of insulin receptor substrate-2 (IRS2), IRS2-associated phosphatidylinositol 3-kinase activity, and phosphorylation of Akt2, leading to impaired suppression of gluconeogenesis (Perry et al., 2014). Moreover, insulin resistance further exacerbates DAG accumulation, creating a vicious metabolic cycle. Impaired insulin signaling enhances adipose tissue lipolysis, increasing the influx of fatty acids to the liver, and promotes *de novo* lipogenesis, both of which contribute to increased hepatic DAG levels and further activation of PKCε (Perry et al., 2014; Samuel and Shulman, 2016; Samuel and Shulman, 2018). Collectively, these

findings indicate that hepatic DAG accumulation is a critical mediator in the pathogenesis of hepatic insulin resistance, a key component of metabolic dysfunction.

Ceramides, precursors of sphingomyelin, represent another class of bioactive lipids implicated in insulin resistance, inflammation, oxidative stress, and cell death (Marra and Svegliati-Baroni, 2018). Ceramide levels are increased in MASLD and T2DM due to enhanced *de novo* ceramide synthesis driven by excess fatty acid availability, particularly saturated fatty acids, as well as alterations in sphingolipid metabolism (Chavez and Summers, 2012). Accumulation of ceramides activates various signaling pathways, leading to disruption of normal cellular functions, including insulin activity. Ceramides directly inhibit Akt phosphorylation, induce endoplasmic reticulum stress, and cause mitochondrial dysfunction (Chavez and Summers, 2012; Chaurasia and Summers, 2015). In particular, a specific ceramide species, C16:0-ceramide, has been implicated as a key mediator of insulin resistance pathophysiology (Raichur et al., 2014; Turpin et al., 2014). Pharmacological and genetic interventions have shown that the inhibition of *de novo* ceramide synthesis, for example, using serine palmitoyltransferase inhibitors such as myriocin, significantly improves several metabolic parameters, including insulin resistance, atherosclerosis, and cardiomyopathy (Holland and Summers, 2008). These findings highlight the importance of ceramide metabolism in the regulation of hepatic insulin sensitivity.

In addition to DAGs and ceramides, other lipid species, such as lysophosphatidylcholine and specific fatty acid species, have been implicated in the regulation of metabolic processes. Alterations in the composition and distribution of these lipid species may disrupt cellular homeostasis and contribute to metabolic abnormalities. Moreover, the quality of fatty acids plays an important role in determining metabolic outcomes. Saturated fatty acids, such as palmitate, promote ceramide synthesis and are more likely to induce lipotoxicity and insulin resistance, whereas monounsaturated fatty acids, such as oleate, favor TG storage and may reduce the accumulation of lipotoxic intermediates, including DAGs and ceramides (Listenberger et al., 2003; Chavez and Summers, 2012). Collectively, these observations indicate that the metabolic consequences of hepatic lipid accumulation depend not only on the total quantity of stored lipids but also on their molecular composition, intracellular distribution, and partitioning into distinct lipid species.

3.2 Phospholipid diversity

Phospholipids, along with cholesterol, are major lipid components of cellular membranes. Their basic structure consists of a glycerol backbone, a polar headgroup, and two hydrophobic fatty acyl chains, which support lipid bilayer formation and cellular functions. Phospholipid diversity is primarily attributed to combinatorial variations in polar headgroups and fatty acids. Phosphatidic acid contains a phosphate group as its polar headgroup. Other phospholipid classes are formed through esterification of the phosphate group with molecules such as choline, ethanolamine, serine, inositol, or glycerol, giving rise to the major phospholipid classes phosphatidylcholine (PC), phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, and phosphatidylglycerol, respectively, as well as cardiolipin, which has a unique diphosphatidylglycerol-based structure (Valentine et al., 2023). The fatty acid chains of phospholipids are typically 12–24 carbons in length and contain 0–6 double bonds. These fatty acids differ in carbon chain length, double-bond numbers, and double-bond positions, such as ω3 and ω6. As a result, phospholipids comprise >1,000 molecular species arising from variations in polar headgroups and fatty acyl chains. Phospholipid composition contributes to membrane properties (van Meer et al., 2008; Harayama and Riezman, 2018).

Phospholipids undergo fatty acyl chain remodeling through the Lands cycle (Lands, 1958). In this cycle, phospholipases A_1 and A_2 cleave fatty acids from phospholipids, generating lysophospholipids. These lysophospholipids are subsequently reacylated to form phospholipids by lysophospholipid acyltransferases (LPLATs) (Figure 1) (Shindou and Shimizu, 2009; Kita et al., 2019; Valentine et al., 2022). To date, 14 mammalian LPLATs have been identified. LPLATs contribute to phospholipid diversity and are involved in glucose and lipid metabolism.

LPLAT12, also known as lysophosphatidylcholine acyltransferase 3 (LPCAT3) or membrane-bound *O*-acyltransferase domain-containing 5 (MBOAT5), is a major hepatic LPLAT that preferentially incorporates arachidonic acid into PC to generate polyunsaturated PCs (Hishikawa et al., 2008; Hashidate-Yoshida et al., 2015; Rong et al., 2015). LPLAT12 deficiency reduces arachidonic acid-containing PC, resulting in impaired very low-density lipoprotein secretion (Hashidate-Yoshida et al., 2015; Tian et al., 2023b). Liver-specific knockout of LPLAT12 improves insulin sensitivity (Tian et al., 2023a; Tian et al., 2023b). In addition, the administration of antisense oligonucleotides against LPLAT12 improves obesity and insulin sensitivity in both high-fat diet–fed and ob/ob mice (Tian et al., 2023b). These findings indicate that LPLAT12-mediated membrane phospholipid composition is a novel regulator of insulin sensitivity. Although alterations in LPLAT12 expression or activity in T2DM are not fully established, these observations suggest that reduced incorporation of arachidonic acid into membrane phospholipids may alter membrane properties and lipid signaling, thereby influencing insulin sensitivity.

LPLAT11, also known as lysophosphatidylinositol acyltransferase 1 or MBOAT7 (Lee et al., 2008; Lee et al., 2012), is a significant genetic modifier in fatty liver diseases. The rs641738C > T genetic variant, located near LPLAT11, is associated with reduced hepatic LPLAT11 expression. In the context of fatty liver disease, this variant is linked to an increased risk of MASLD, including hepatic lipid accumulation and fibrosis (Mancina et al., 2016; Teo et al., 2021). Hepatocyte-specific LPLAT11-knockout mice exhibited spontaneous development of steatosis and hepatic fibrosis when fed a high-fat diet (Tanaka et al., 2021). Depletion of LPLAT11 in hepatocytes increases phosphatidylinositol turnover, leading to sustained generation of DAG, a key intermediate for TG synthesis (Tanaka et al., 2021). While increased DAG generation in LPLAT11-deficient hepatocytes may contribute to TG synthesis and hepatic lipid accumulation, its direct impact on insulin sensitivity remains to be fully elucidated. These findings provide insights into the pathogenesis of MASLD and may inform the development of therapeutic strategies.

Recent experimental evidence has revealed that modulation of hepatic LPLAT improves glucose metabolism. Overexpression of

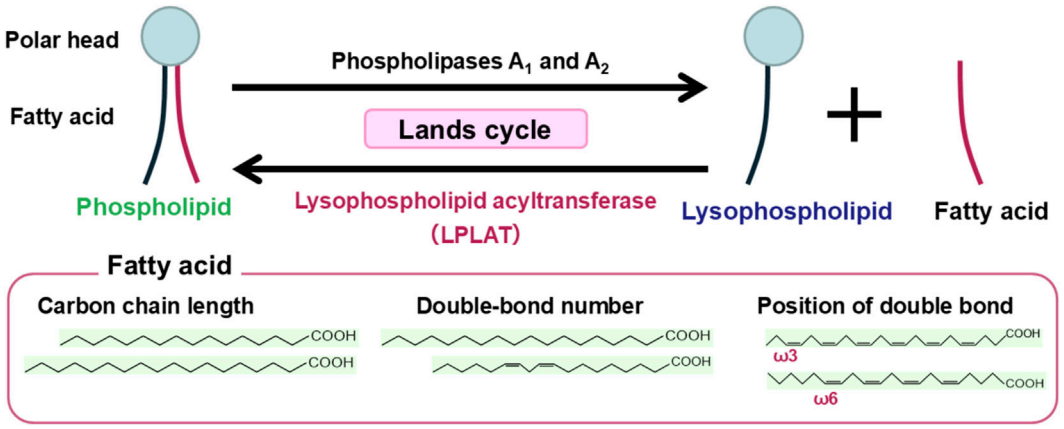


FIGURE 1
Lands cycle and phospholipid diversity. Phospholipids are cleaved by phospholipases A_1 and A_2 to form lysophospholipids, which are subsequently remodeled back to phospholipids by lysophospholipid acyltransferases. The fatty acids in phospholipids differ in carbon number, number of double bonds, and types of double bonds, thus creating phospholipid diversity.

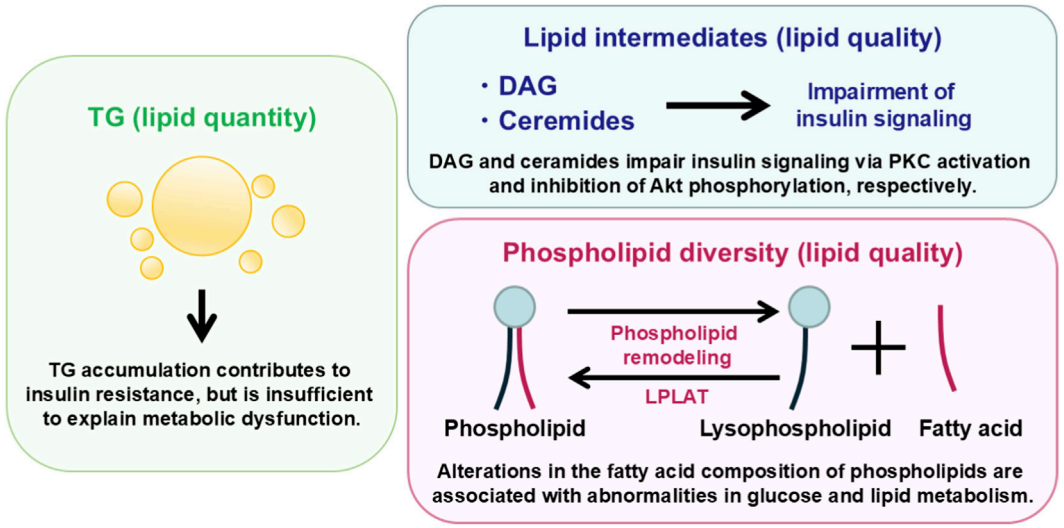


FIGURE 2
Lipid quantity and quality in metabolic regulation. TG accumulation represents lipid quantity, whereas lipid quality is defined by lipid intermediates and phospholipid composition, which are regulated by phospholipid remodeling pathways.

LPLAT10, also known as LPCAT4 and lysophosphatidylethanolamine acyltransferase 2 (Cao et al., 2008; Eto et al., 2020), in the liver has been shown to attenuate postprandial hyperglycemia by enhancing glucose-stimulated insulin secretion in mice (Shimizu et al., 2024). In this model, liver-specific LPLAT10 overexpression altered hepatic and serum phospholipid composition and improved glucose metabolism without affecting body weight or food intake. The underlying mechanism is thought to involve changes in hepatic phospholipid composition that alter circulating phospholipid species, which may act on pancreatic β-cells to enhance glucose-stimulated insulin secretion. These observations indicate that changes in phospholipid composition in the liver can influence systemic metabolic homeostasis, potentially through the modulation of membrane composition, intracellular signaling, and inter-organ metabolic communication. However, pharmacological agents that specifically target LPLATs remain limited. Although several experimental and genetic approaches have been used to modulate LPLAT activity in preclinical studies, their effects on insulin sensitivity are still under investigation, highlighting the need for the development of selective LPLAT modulators as potential therapeutic strategies for metabolic diseases.

Collectively, these lipid-mediated mechanisms contribute to insulin resistance and insulin secretion in T2DM, although their

relative impact may differ. Accumulation of DAG and subsequent activation of PKCε represent a central mechanism that directly impairs hepatic insulin signaling. Ceramides also play an important role by modulating cellular stress responses and inhibiting insulin signaling pathways. In parallel, alterations in phospholipid remodeling and fatty acid composition may exert more modulatory effects by influencing membrane properties, lipid signaling, and inter-organ communication. These pathways are interconnected and collectively contribute to the development and progression of metabolic dysfunction (Figure 2).

4 Conclusion

In this mini review, we focused on hepatic lipids as a key factor in understanding the pathology of T2DM and as a novel therapeutic target. Hepatic lipids are mainly composed of TGs; however, the quantity of TGs alone is insufficient to explain the development of glucose and lipid metabolic dysfunction. Lipid intermediates, such as DAGs and ceramides, also play important roles in abnormalities of glucose and lipid metabolism. Phospholipid diversity results from differences in their head groups and fatty acid chains. Alterations in the fatty acid composition of phospholipids are associated with abnormalities in glucose and lipid metabolism. In contrast, controlled modification of phospholipid fatty acid composition may improve metabolic regulation, thereby providing a potential therapeutic strategy for T2DM. Thus, both lipid quality and quantity should be considered in the development of novel treatments for T2DM.

Author contributions

KS: Funding acquisition, Writing – original draft, Conceptualization, Writing – review and editing. HS: Funding acquisition, Writing – review and editing. KT: Writing – review and editing. HM: Writing – review and editing.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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