

Hepatic fatty acid and glucose handling in metabolic disease: Potential impact on cardiovascular disease risk

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ABSTRACT

The prevalence of metabolic diseases, including type 2 diabetes mellitus (T2DM) and metabolic dysfunction-associated steatotic liver disease (MASLD) is increasing. Although invariably associated with obesity, the importance of fat deposition in non-adipose tissue organs has yet to be fully explored. Pathological ectopic fat deposition within the liver (known as MASLD) has been suggested to underlie the development of T2DM and is now emerging as an independent risk factor for cardiovascular disease (CVD). The process of hepatic *de novo* lipogenesis (DNL), that is the synthesis of fatty acids from non-lipid precursors (e.g. glucose), has received much attention as it sits at the intersect of hepatic glucose and fatty acid handling. An upregulation of the DNL pathway has been suggested to be central in the development of metabolic diseases (including MASLD, insulin resistance, and T2DM). Here we review the evidence to determine if hepatic DNL may play a role in the development of MASLD and T2DM and therefore underlie an increased risk of CVD.

Although it has long been known that type 2 diabetes mellitus (T2DM) predisposes individuals to cardiovascular disease (CVD) [1], the exact mechanisms for this association remain elusive; however, alterations in systemic fatty acid (FA) and glucose metabolism may be important. The liver acts as a metabolic homeostat for the body, and through uptake, storage, and production of FA and glucose, is a pivotal regulator of systemic fat and carbohydrate metabolism.

Insulin has pleiotropic regulatory roles within the liver including modulating the partitioning of glucose and FAs towards utilisation, storage, and secretion pathways [2]. Consequently, hepatic insulin resistance, as observed in T2DM, causes perturbations in circulating triglyceride (TG) and glucose concentrations [2], and may lead to intrahepatic TG (IHTG) accumulation; although it remains unclear which comes first, insulin resistance or IHTG accumulation. A pathological accumulation of IHTG (typically defined as steatosis affecting at least 5% of liver volume [3]) is known as metabolic dysfunction-associated steatotic liver disease (MASLD) (formerly known as non-alcoholic fatty liver disease (NAFLD) [4]). MASLD is present in ~50%–70% of people with T2DM (as compared to 25% in the wider population) [5] and individuals with T2DM have ~80% more liver fat than age-, weight-, and sex-matched individuals without T2DM [6]. Moreover, it has been suggested that approximately one in two individuals with MASLD have CVD, which is their primary cause of death [7].

The prerequisite for the development of MASLD is a net retention of IHTG. It has been suggested that an upregulation in the synthesis of FA within the liver from non-lipid precursors (i.e. glucose) via the *de novo* lipogenesis (DNL) pathway, underlies the development of obesity, MASLD, insulin resistance, diabetes and CVD, which collectively are referred to as cardiometabolic disease. MASLD is now emerging as an independent risk factor for CVD [8] and although the underlying mechanisms remain to be elucidated, a growing body of evidence supports the coexistence of IHTG accumulation, cardiac dysfunction and remodelling [7,9]. This review will focus on the intersect of hepatic glucose and FA metabolism – specifically the DNL pathway – and emphasise how hepatic DNL may play a role in the development of MASLD and T2DM and therefore underlie an increased risk of CVD.

1. Overview of hepatic fatty acid handling

The liver plays a key role in regulating systemic substrate metabolism in both the fed and fasted states, with hepatocytes being able to rapidly switch between metabolic tasks of energy supply and storage.

FAs from adipose tissue TG lipolysis, dietary FAs, and remnant particles (chylomicron or very-low-density lipoproteins (VLDL)) provide a constant supply to the hepatic FA pool [10,11]. FAs are also synthesised *de novo* from non-lipid precursors within hepatocytes; a process known as DNL. The hepatic FA pool is then broadly partitioned between two

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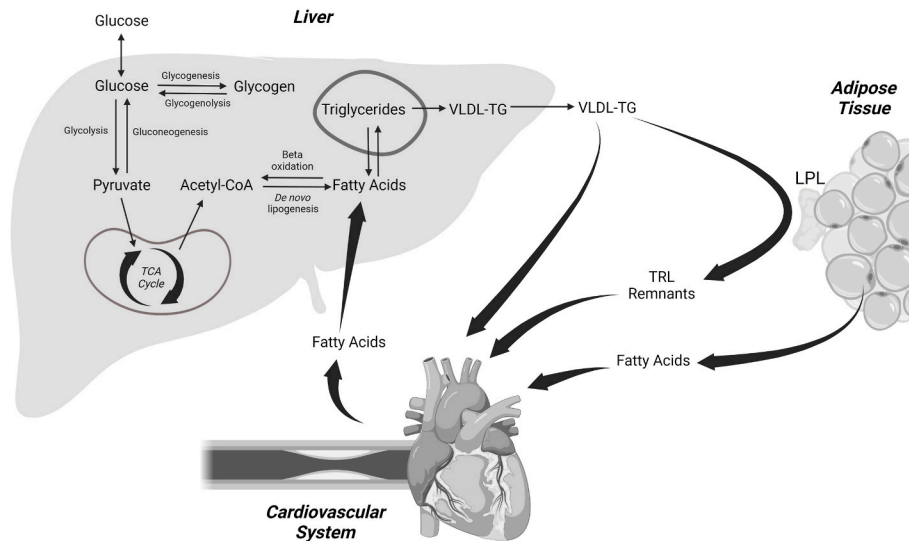


Fig. 1. Overview of fasting liver metabolism.

Glucose is taken up into the liver where it can be stored as glycogen or broken down into pyruvate. Pyruvate can enter the TCA cycle in the mitochondria to be metabolised into acetyl-CoA which can re-enter the cytosol and be utilised in the *de novo* lipogenic pathway to form fatty acids. Fatty acids are then stored as triglycerides which can be packaged into VLDL and secreted into the blood. VLDL particles are hydrolysed by LPL in the adipose tissue to form TRL remnants which remain in circulation. Fatty acids are also released into circulation from adipose tissue TG lipolysis. TCA, Tricarboxylic Acid; VLDL, Very-Low Density Lipoprotein; LPL, Lipoprotein Lipase; TRL, Triglyceride-Rich Lipoprotein.

pathways: i) esterification to form predominantly, but not exclusively, TG which may then enter storage or secretory pools, and ii) oxidation. The pathway FAs are partitioned toward is dependent on several factors, including nutritional and/or the physiological state of the individual, as previously reviewed [10,11]. The processes of hepatic FA uptake, synthesis, and then the intrahepatocellular partitioning into either storage, secretion or oxidation pathways are highly regulated, and dysregulation of one or more of these processes may result in the accumulation of IHTG (Fig. 1). It has been suggested, although not substantiated, that an upregulation of hepatic DNL underlies the pathological accumulation of IHTG [12] and therefore, may be pivotal in the aetiology of CVD and T2DM.

2. Overview of hepatic glucose handling

In the fasted state, hepatic glucose production (HGP) maintains plasma glucose levels whereas after consumption of a mixed meal, when plasma glucose levels are raised, suppression of HGP and glucose uptake by the liver play a role in maintaining normoglycaemia (Fig. 1).

Dysregulation of these processes results in a persistent elevation of plasma glucose levels in both the fasting and postprandial states, which is a hallmark of metabolic disease [13].

Endogenous glucose production occurs predominantly in the liver [14] and is one of the main drivers of hyperglycaemia in metabolic diseases such as T2DM [15]. HGP occurs through two processes: glycogenolysis, the breakdown of glycogen, and gluconeogenesis (GNG), the synthesis of glucose molecules from non-carbohydrate precursors. Euglycemic hyperinsulinemic clamp studies have clearly demonstrated that individuals with T2DM have a notably higher HGP than healthy controls and studies utilising stable isotope tracers or ^{13}C NMR spectroscopy have shown that this is likely due to an increase in GNG and glycogen cycling [16,17]. Glycogen cycling is the simultaneous breakdown and synthesis of glycogen from plasma or newly synthesised glucose [18], which limits the storage of glucose as glycogen. As such, those with T2DM have decreased hepatic glycogen levels and a reduction in glucose clearance which is physiologically significant as the liver is responsible for clearing a third of the enteral glucose load in healthy adults [19]. It is also plausible that glycogen cycling may cause excess

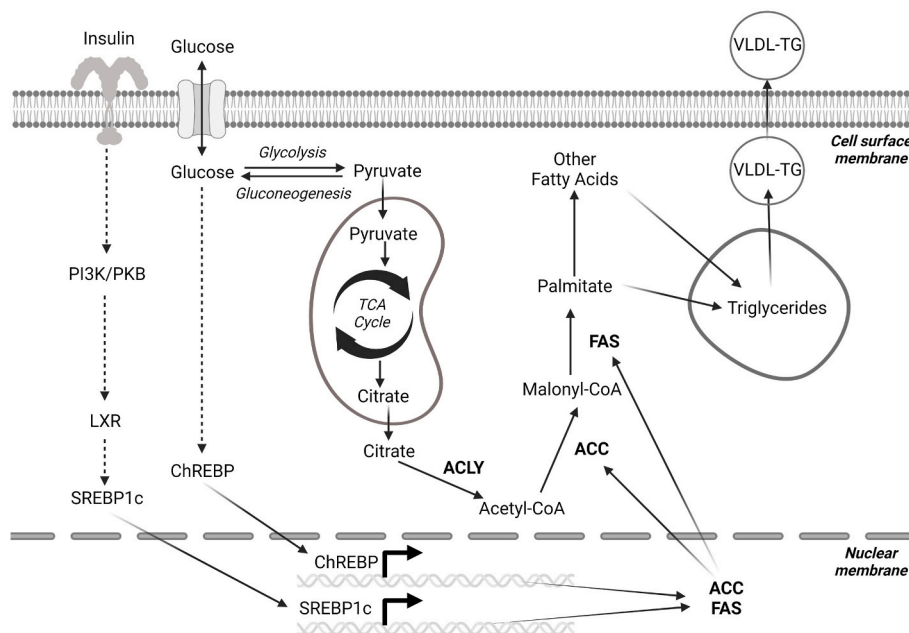


Fig. 2. Overview of *de novo* lipogenesis and the main transcriptional regulators.

Glucose enters the cell and can be broken down into pyruvate which enters the mitochondria and is further metabolised into citrate via the TCA cycle. Citrate leaves the mitochondria and is converted to acetyl-CoA which is carboxylate to malonyl-CoA. Elongation of malonyl-CoA to palmitate is catalysed by the enzyme FAS and further complex fatty acids can be made from palmitate. Fatty acids can be esterified and stored as triglyceride and packaged into VLDL for secretion. Both glucose and insulin increase the rate of *de novo* lipogenesis by activating transcription factors SREBP1c and ChREBP, respectively which upregulate expression of key lipogenic genes such as ACC and FAS. PI3K/PKB, Phosphoinositide-3-Kinase/Protein Kinase B; LXR, Liver X Receptor; SREBP1c, Sterol Regulatory Element-Binding Protein 1c; ChREBP, Carbohydrate Response Element Binding Protein; TCA, Tricarboxylic Acid; ACLY, ATP Citrate Lyase; ACC, Acetyl-CoA Carboxylase; FAS, Fatty Acid Synthase; VLDL, Very-Low Density Lipoprotein.

intrahepatocellular glucose to be shunted towards other pathways such as DNL.

Due to the nature of euglycemic-hyperinsulinemic clamps, the aberrant increase in GNG in those with T2DM was traditionally attributed to hepatic insulin resistance [20], which is also now seen in individuals with MASLD [21,22]. However, studies have since shown that the direct effect of insulin on the liver and transcription of key GNG genes has limited impact on GNG flux [23,24]. Attention has since turned to indirect actions of insulin involving other tissues (e.g. adipose and skeletal muscle) where insulin resistance may increase GNG in the liver through increased GNG substrate and allosteric modification of GNG enzymes [25]. Similarly, the potential role of glucagon in HGP appears to have been somewhat overlooked but work is now emerging to suggest that hyperglucagonemia, characteristic of T2DM, may also drive hyperglycaemia [26,27].

It has been proposed that hepatic DNL is regulated by substrate availability (e.g. glucose which is a transcriptional inducer of DNL genes [28]) and in situations where there is a high flux of glucose to the liver, such as in the postprandial phase or in individuals with insulin resistance or T2DM, this may induce an increase in the rate of DNL. Intrahepatic glucose can undergo glycolysis, where citrate is metabolised to acetyl-CoA by the enzyme ATP citrate lyase (ACLY) and enter the DNL pathway. Taken together, the DNL pathway may have a potentially important role in disposing of excess non-lipid precursors [12]; however, in so doing, may confer an increase in IHTG and circulating TG.

3. Overview of hepatic *de novo* lipogenesis (DNL)

DNL is the synthesis of FAs from predominately carbohydrate precursors [29] and is a potentially important contributor to the hepatic lipid pool that is utilised for secretion and storage. Newly synthesised FAs may be directed toward the endoplasmic reticulum (ER) for esterification to produce predominantly TG [30], which can then be secreted into systemic circulation in VLDL or stored as lipid droplets within the cytosol (Fig. 2).

3.1. Hepatic DNL - the effect of phenotype and nutritional state

In humans, hepatic DNL can be measured using stable isotope tracers, such as heavy water ($^2\text{H}_2\text{O}$) to determine the relative contribution of newly synthesised DNL-derived FAs into circulating VLDL-TG [31,32]. Others, particularly large observational studies, have utilised the FA composition and/or FA ratios in various circulating blood lipid fractions to infer hepatic DNL [33–36]. We have previously reported that the use of blood FAs or FA ratios may not discriminate between healthy individuals with high and low hepatic DNL when consuming their habitual diet [37]. In men and women free from known disease, the contribution of DNL-derived FAs to VLDL-TG is reported to be between 1 and 7% following an overnight fast [37–44]. The variation in findings may, in part, be explained by the macronutrient composition of the background diet, with a consistent observation being that a carbohydrate-enriched diet upregulates hepatic DNL [29]. For example, in healthy participants, a 10-fold increase in fasting fractional DNL was observed after short-term (5 days) consumption of a high- compared to low-carbohydrate diet [42]. Thus, the macronutrient composition of the preceding days diet should be considered when assessing hepatic DNL. In the transition to the postprandial state, hepatic DNL is often upregulated and has been reported to be between 3 and 18% ([38,39, 41–46]).

An individual's phenotype may also influence hepatic DNL. For example, the fractional contribution of fasting DNL-derived FAs to VLDL-TG for individuals defined as insulin resistant, hyperinsulinemic or T2DM has been reported to range from 9 to 43% [41,44,47,48]. This wide range of values may, in part, be due to the presence of metabolic comorbidities, including obesity, pathological IHTG accumulation, or hyperlipidaemia, which appear to have an additive effect on DNL: in

individuals with obesity, DNL was reported to be 19%, whereas in individuals with obesity, MASLD, and insulin resistance this increased to 39% [49]. Relative to healthy individuals, the contribution of DNL-derived FAs to VLDL-TG does not appear to increase markedly from the fasted to postprandial state (an ~ 1 - and ~ 1.5 -fold having been observed [44,47]). Umpleby et al. [50] observed that men with MASLD (IHTG, $17.2 \pm 2.7\%$ (mean \pm SEM)) had a significantly higher contribution of DNL-derived FAs to VLDL-TG compared to men without MASLD (IHTG $2.5 \pm 0.3\%$) after consumption of a low-sugar diet for 12 weeks. This difference disappeared between the groups after consumption of a high-sugar diet for 12-weeks, as the participants with MASLD failed to upregulate DNL in response to the high-sugar diet [50].

Taken together, fasting hepatic DNL is low in individuals without metabolic disease and the pathway is highly responsive, with a notable upregulation, as dietary carbohydrate intakes are increased. In contrast, in the presence of metabolic disease (e.g. T2DM, MASLD), DNL appears to be constitutively activated and notably less responsive to increased intakes of dietary carbohydrate. Whilst the presence of metabolic comorbidity makes establishing causality challenging, DNL is clearly dysregulated in insulin resistant states (e.g., those with obesity, MASLD, T2DM), but it remains unclear what comes first: the metabolic comorbidity or an upregulation of hepatic DNL.

3.2. Effect of DNL on intrahepatic FA partitioning: do they stay or do they go?

Intrahepatic FAs can be broadly partitioned into esterification or oxidation pathways. Within the hepatocyte, an important branch point between esterification and oxidation resides with the transport of fatty acyl-CoA into the mitochondrion for oxidation. An upregulation in hepatic DNL is suggested to shift cellular metabolism away from oxidation toward the esterification of FAs to produce predominantly TG, which then enters pools with distinct rates of turnover, to be either stored in lipid droplets or be secreted in VLDL. Within the liver, mitochondrial oxidation (complete and ketogenesis) is a route for FA disposal, thus a downregulation in FA oxidation may contribute to IHTG accumulation. Findings for FA oxidation are mixed across individuals with MASLD, with some observing markers of FA oxidation to be lower [51], not different [41,52,53], or higher [54] compared to individuals without MASLD. The inconsistency in findings may, in part, be due to the methodology used to assess FA oxidation or the duration an individual has had MASLD, as this is often not known. Thus, it is challenging to disentangle the discrete contribution DNL and FA oxidation may have in IHTG accumulation in humans. In obesity and T2DM, the lipogenic capacity of the liver does not become resistant to insulin and hepatic TG production may be further enhanced [20], suggesting that the metabolic flexibility, of switching between esterification and oxidation pathways is impaired.

Evidence for the partitioning of newly synthesised FA into storage and secretion is sparse as it is challenging to measure the contribution to both these pathways simultaneously in humans. Previously Donnelly et al. [47] quantified, using stable-isotope methodologies, the contribution of different FA sources to IHTG and VLDL-TG in patients with MASLD (5 males, 4 females), who were undergoing a liver biopsy. It was found that the contribution of DNL-derived FAs in IHTG and VLDL-TG was $\sim 26\%$ and $\sim 23\%$, respectively, suggesting the fate of newly synthesised FAs is approximately equally distributed between storage and export pathways. However, it remains unclear if a similar distribution between pathways would be observed in individuals without MASLD.

Plasma TG concentrations are proposed to increase proportionally with hepatic DNL [55], and several studies have reported positive, albeit weak to moderate correlations between DNL and plasma TG concentrations [37,39,46]. We have observed a positive correlation between postprandial DNL and VLDL-TG concentrations in individuals defined as normoinsulinemic, but no association was observed in hyperinsulinemic individuals [41]. These observations are consistent with the hypothesis

that hyperinsulinemia/insulin resistance drives DNL to be constitutively active in the fasting state, thus decreasing the pathways flexibility to upregulate flux in response to dietary carbohydrates. Taken together, it appears, from the limited data available that there may be a dissociation between the processes of hepatic DNL and FA oxidation, in some individuals, which may represent further pathways for redirection of FA into export from the liver or oxidation to prevent IHTG accumulation. Whilst in others, despite hepatic DNL typically being positively associated with VLDL-TG concentrations, it is plausible that when DNL is constitutively active, VLDL-TG production is unable to be further upregulated, leading to an increased risk of IHTG accumulation.

3.3. Secretion of hepatic TG

Rodent work has suggested that DNL-derived FAs may be preferentially partitioned to endoplasmic reticulum (ER)-associated pools for immediate secretion in VLDL [56] and although evidence for this in humans is sparse [44,55], hepatic DNL has been positively associated with VLDL-TG production rates [39,55,57]. The liver secretes the apolipoprotein (apo)B100-containing TG-rich VLDL, a precursor for low-density lipoprotein (LDL), in a wide variety of sizes and compositions [58]. When sub-divided by density, VLDL is classified as VLDL₁ (large buoyant) and VLDL₂ (small, dense) [58] with the size and composition of the VLDL particle influencing metabolic fate. VLDL₂ can either be secreted directly from the liver, or formed by the peripheral hydrolysis of VLDL₁. Insulin regulates the production of VLDL₁ but not VLDL₂ [59].

Individuals with MASLD and T2DM with MASLD have an overproduction of VLDL₁-TG [60,61] compared to healthy control subjects; however, VLDL₁-apoB secretion was only greater in individuals with T2DM and MASLD [60]. This suggests that in the presence of MASLD only, the particles secreted are more TG-rich leading to an increase in particle size rather than number, whilst T2DM with MASLD may lead to an increase in both particle size and number. Fabbrini and colleagues [62] observed that total VLDL-TG secretion rates were over 2-fold greater in insulin resistant individuals with MASLD compared with insulin sensitive individuals with low IHTG, whereas VLDL-apoB secretion rate was not different between groups. For VLDL₂, Adiels et al. [60] found a higher direct production rate of VLDL₂-TG with no difference in VLDL₂-apoB between individuals with T2DM and those without. Umpleby et al. [50] observed no difference in either parameter in men with or without MASLD. Taken together, this suggests that VLDL-TG particles are more TG-laden in individuals with high IHTG and insulin resistance and this may, in part, be mediated by insulin resistance, as insulin has been shown to suppress VLDL₁ production in insulin sensitive but not insulin-resistant individuals [59,63]. The secretion of VLDL appears to increase with an increase in IHTG content [60]; however, it is suggested there is a limit to VLDL-TG production. Fabbrini and colleagues [62] found a strong and positive correlation between IHTG content and total VLDL-TG secretion rate in insulin sensitive individuals with normal IHTG, but no association in insulin resistant individuals with MASLD, suggesting that TG export pathways plateau relatively early in the process of MASLD (plausibly when DNL contribution to VLDL-TG reaches 5%–10%) [62]. The ability to upregulate VLDL-TG secretion may represent a compensatory mechanism to prevent IHTG accumulation, and the associated implications on metabolic health and when the secretion capacity is met, the liver then stores TG to accommodate FA which have accumulated in excess of requirement for disposal pathways [64].

Overall, it would appear that a constitutive upregulation in hepatic DNL contributes to hypertriglyceridemia. Although it is evident that IHTG accumulation and/or an upregulation in hepatic DNL may increase VLDL-TG production, and ultimately plasma TG concentrations, data examining the relationship between hepatic DNL and lipoprotein profiles is sparse. Based on the available, albeit limited evidence between hepatic DNL and VLDL production, it could be speculated that a

constitutive upregulation in hepatic DNL would induce an atherogenic lipoprotein profile, as often observed in individuals with MASLD, insulin resistance or T2DM and this may confer increased CVD risk.

3.4. Are DNL-derived FA associated with risk of cardiometabolic disease?

In obese, compared to lean individuals there is a downregulation of adipose tissue FA trafficking [65] and fractional clearance of TG-rich lipoproteins (TRL) [66,67]. This may lead to a greater production of TRL remnants, which have known atherogenic properties [68] as they can, due to their size, then be transported across the endothelium of blood vessels [69]. From there, TRL remnants can be directly taken up into macrophages and converted to foam cells [70]. TRL remnants contain substantially more cholesterol than other lipoprotein particles, including low-density lipoproteins (LDL), and it is cholesterol, not TG, which accumulates in foam cells and atherosclerotic plaques [71]. Indeed, isolation of lipoproteins from human femoral and carotid endarterectomy samples found that a large proportion of lipoproteins in plaques were from liver-derived TRL remnant particles [72]. Thus, suggesting that an overproduction of VLDL, due to an upregulation of DNL or IHTG accumulation, may be causally associated with atherosclerosis.

As the assessment hepatic DNL using tracer methodology is expensive, requires specialist equipment and is challenging to undertake in large numbers of individuals, studies have utilised the FA composition and/or FA ratios in various circulating blood lipid fractions to infer hepatic DNL [33–36]. For example, Lai et al. [73] reported that in a large cohort of predominately white, older US adults (46,974 person years of follow-up) cumulative levels of plasma phospholipid palmitate were positively associated with all-cause, total CVD, non-CVD mortality and incidence of CVD. Comparison of a smaller cohort (n = 265) aged 25–74 y that had experienced a sudden cardiac arrest with 415 participants matched for age and sex, associations were observed between increased erythrocyte membrane levels of palmitate and sudden cardiac arrest [35]. Large observational studies have assessed the relationship between individual FAs and FA ratios with outcomes such as MASLD, T2DM or the metabolic syndrome [33,34,36] and it was found FAs in the DNL pathway in erythrocytes and plasma phospholipids were positively associated with a fatty liver index [33], T2DM [34] and the metabolic syndrome [36]. Whether the FA composition of erythrocyte and plasma phospholipids directly reflects the DNL pathway and are a good marker of hepatic DNL remains to be determined [37]. Taken together, the findings from large, observational studies suggest circulating levels of FAs that have been associated with DNL, appear to be associated with metabolic diseases. While there is evidence from animal and *in vitro* models for saturated FA causing endoplasmic reticulum stress, cellular apoptosis, insulin resistance and inflammatory activation [74–77], there is, as of yet, no clinical evidence supporting a causal link between systemic saturated FAs and CVD. It is perhaps more likely, that the observed associations reflect these FAs being biomarkers for DNL, which may confer an increased risk through effects on IHTG content and lipoprotein atherogenicity.

It has long been thought that DNL is a quantitatively important contributor to IHTG content and thus, a major driver of MASLD [48,49]. Lambert and colleagues [48] showed that the contribution of DNL-derived FAs to VLDL-TG was significantly greater in individuals with high compared to low liver fat. They also reported a significant moderately positive linear correlation between liver fat and DNL but while these variables were correlated across the entire cohort of participants, there appeared to be no association when low and high liver fat groups were investigated separately [48]. This paradox makes interpreting associations and establishing causality between IHTG content and DNL-derived FAs challenging [78]. Similarly, Smith and colleagues [49] showed a relationship between IHTG content and DNL-derived FAs, whereby there appeared to be a linear strong positive correlation between these variables in lean individuals and in

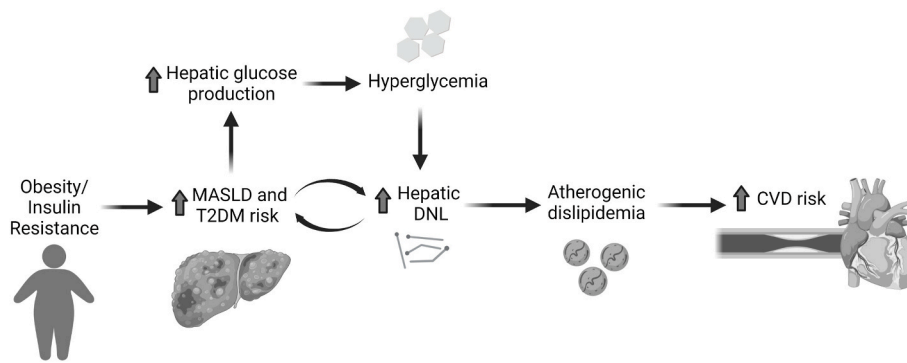


Fig. 3. Obesity and insulin resistance are associated with an increased risk of metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes mellitus (T2DM).

Compared to those free from metabolic disease, individuals with MASLD and/or T2DM have higher rates of hepatic *de novo* lipogenesis (DNL) and glucose production, which may drive the atherogenic dyslipidaemia and hyperglycaemia (respectively) observed in these individuals. Elevated plasma glucose levels may provide more substrate for hepatic DNL which, in turn, may also contribute to the development of MASLD and T2DM. Atherogenic dyslipidaemia in those with MASLD and/or T2DM contributes to their overall higher risk of cardiovascular disease (CVD).

individuals with obesity, but no association in individuals with obesity, MASLD and insulin resistance. A plausible explanation is that DNL is a quantitatively important contributor to IHTG content in the early stages in the development of IHTG accumulation but relatively quickly plateaus. Evidence to support this hypothesis comes from studies showing that the contribution of palmitate to fasting VLDL-TG was constant even after a 10 day high-sugar diet that markedly elevated the fractional contribution of hepatic DNL-derived FAs to VLDL-TG [55,79], suggesting flux through this pathway had reached its peak.

Increased IHTG is emerging to be an independent risk factor for CVD [8]. A small number of studies have found that this association is independent of other risk factors related to lipemia, glycemia, diabetes status, as well as phenotypic, environmental, and socioeconomic factors [80,81]. Mendelian randomisation studies provide a useful tool to interrogate the causality of the relationship between IHTG content and CVD [82]. Using a genetic instrument for MASLD, Peng and colleagues [68] recently demonstrated that MASLD is significantly associated with arterial stiffness and heart failure. For insight into the underlying mechanism, a study using data from the UK Biobank showed that IHTG accumulation was independently associated with higher cardiac remodelling (higher eccentricity ratio and lower remodelling index) and lower left and right ventricular volumes [8]. This early cardiac remodelling was thought to be due to an accumulation of fat in myocardial tissue and adipose tissue surrounding the heart leading to increased synthesis of proinflammatory cytokines and activation of inflammatory and profibrotic pathways which drive the structural change. However, it remains to be elucidated if IHTG accumulation is simply a marker for ectopic fat accumulation in myocardial tissue or an independent driver of CVD.

4. Conclusion

The liver sits at the cross-roads for glucose and FA metabolism and is plays a key role in the regulation of systemic fat and carbohydrate levels (Fig. 3). Hepatic DNL is a pathway that sits at the intersect of both glucose and FA metabolism and an upregulation in DNL has been suggested to be associated with an increased risk of metabolic diseases including MASLD and T2DM. Indeed, hepatic DNL is observed to be greater in individuals with obesity, MASLD, insulin resistance and T2DM compared to those without. As MASLD is now emerging as an independent risk factor for CVD, and DNL may underpin the development of hypertriglyceridemia and/or MASLD, it remains unclear, due to the paucity of studies directly investigating DNL and risk of CVD, whether DNL may have an independent role in risk of CVD.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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