Pathogenesis of Insulin Resistance and Atherogenic Dyslipidemia in Nonalcoholic Fatty Liver Disease

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Abstract
Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the developed world, with a global prevalence of around 25%. NAFLD is considered to be the hepatic manifestation of metabolic syndrome and is strongly associated with obesity, insulin resistance and dyslipidemia. Insulin resistance plays a pivotal role in the development of NAFLD-related dyslipidemia, which ultimately increases the risk of premature cardiovascular diseases, a leading cause of morbidity and mortality in patients with NAFLD. Insulin affects hepatic glucose and lipid metabolism by hepatic or extrahepatic pathways. Aside from insulin resistance, several other factors also contribute to the pathogenesis of atherogenic dyslipidemia in patients with NAFLD. These include diet composition, gut microbiota and genetic factors, to name a few. The identification of potentially modifiable risk factors of NAFLD is of importance, so as to target those who may benefit from lifestyle changes and to help develop targeted therapies that decrease the risk of cardiovascular diseases in patients with NAFLD.

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Introduction
Nonalcoholic fatty liver disease (NAFLD) is a clinical spectrum of disease severity, ranging from isolated fatty infiltration of the liver (simple hepatic steatosis) to lobular inflammation, balloon degeneration, hepatic fibrosis, and cirrhosis. With epidemiological shifts due to lifestyle changes and modernization, NAFLD has become the most common cause of chronic liver disease in the developed world, with an estimated global prevalence of around 25%.¹⁻³ NAFLD may be associated with features of metabolic syndrome, including obesity, insulin resistance, and atherogenic dyslipidemia, predisposing to an increased risk of progressive liver damage that can lead to nonalcoholic steatohepatitis (commonly known as NASH), cirrhosis, diabetes and premature cardiovascular disease (CVD).⁴⁻⁹ Insulin resistance plays a major role in the development of atherogenic dyslipidemia in NAFLD and the subsequent development of premature CVD.¹⁰ In this article, we will review the role of insulin in hepatic glucose and lipid metabolism, the mechanisms that may lead to NAFLD-related dyslipidemia and ectopic lipid deposition, and how these factors contribute to cardiovascular morbidity and mortality.

Hepatic glucose and lipid metabolism
Liver plays a central role in the metabolism of carbohydrates, lipids and proteins under states of caloric excess and starvation. A key regulator of these homeostatic processes is insulin, which exerts its effects on hepatic glucose and lipid metabolism through a variety of different hepatic (direct) and extrahepatic (indirect) pathways. Fig. 1 illustrates these important pathways.

Hepatic glucose metabolism
Direct insulin-mediated regulation of hepatic glucose metabolism begins with the activation of insulin receptor tyrosine kinase (IRTK), phosphoinositide-dependent kinase-1 (referred to as PDK1) and the mammalian target of rapamycin (referred to as mTORC)-2, and ends with protein kinase B (known as AKT) phosphorylation.¹¹⁻¹³ Insulin, via this pathway, decreases hepatic gluconeogenesis by activating hepatocyte insulin receptors, which in turn trigger hepatic glycogen synthesis and downregulate the transcription of gluconeogenic enzymes through forkhead box protein O1 (referred to as FOXO1) phosphorylation.¹⁴,¹⁵ Indirectly, insulin further inhibits lipolysis in white adipose tissue, resulting in decreased fatty acid delivery to the liver by reducing hepatic acetyl-CoA content, an allosteric activator of pyruvate carboxylase. This occurs in conjunction with insulin-mediated suppression of glycerol conversion to glycerol and delivery to the liver.¹⁶⁻¹⁸ The direct and indirect actions of insulin may play a role in different metabolic states, with glycogen repletion...
states favoring direct insulin action and glycogen deplete states favoring the indirect effects of insulin.\textsuperscript{19–20}

**Hepatic lipid metabolism**

Insulin directly regulates hepatic lipid metabolism by increasing mRNA expression of nuclear transcription factors, such as sterol regulatory element-binding protein-1c (referred to as SREBP-1c), which play a key role in the regulation of de novo lipogenesis (DNL) and triglyceride synthesis. This effect is amplified by an insulin-mediated increase in mTORC1 activity, which also activates SREBP1c mRNA expression and uncouples lipogenesis from gluconeogenesis. Indirectly, insulin acts peripherally by stimulating the uptake of fatty acids into muscle and adipose tissue that are produced by lipoprotein lipase-mediated triglyceride hydrolysis.\textsuperscript{21}

**Atherogenic dyslipidemia and ectopic lipid deposition**

Atherogenic dyslipidemia and ectopic lipid deposition in NAFLD are multifactorial and occur broadly as a result of diet, skeletal muscle, hepatic and adipose insulin resistance, and genetic factors. Table 1 summarizes these factors.

**Dietary content**

Diet may strongly influence the development of atherogenic dyslipidemia. Specifically, injurious effects of excess caloric intake are implicated in NAFLD, with one study demonstrating that patients with obesity and NAFLD may consume more calories than healthy lean individuals; in fact, a study examining patients with metabolic syndrome demonstrated a 3-fold higher rate of DNL.\textsuperscript{22,23} Furthermore, studies have shown that short-term caloric restriction can normalize hepatic insulin sensitivity and reverse NAFLD, thereby suggesting a causal role of ectopic lipids in insulin resistant states, such as NAFLD.\textsuperscript{24–26} It should be noted that excess fatty acid reservoirs (due to high-fat diets or increased caloric intake) promote hepatic lipid synthesis despite the presence of hepatic insulin resistance, as studies have shown that hepatic triglyceride synthesis is dependent on the rate of fatty acid delivery and independent of hepatocellular insulin signaling; on the contrary, DNL is insulin-dependent.\textsuperscript{27}

In addition to excess caloric consumption and high-fat diets, simple sugars, such as fructose, can also promote lipogenesis. Fructose is exclusively metabolized by the liver and thus, is converted into triglycerides via DNL. At the cellular level, fructose and glucose both increase SREBP1c expression and enlist lipogenesis-favoring transcription factors, such as carbohydrate response element binding protein (ChREBP), peroxisome proliferator-activated receptor (referred to as PPAR\textsubscript{g}) coactivator 1-\(\beta\), and liver X-receptor. Fructose-containing beverages have also been associated with the development of hyperlipidemia and insulin resistance.\textsuperscript{28,29} High-fructose diets also reduce PPAR\textsubscript{a} activity and stimulate the expression of inflammatory regulators, such as nuclear factor kappa-light-chain-enhancer of activated B cells (referred to as NF-\(\kappa\)B) and c-Jun N-terminal kinases (referred to as JNKs) which inhibit the phosphorylation of insulin receptor substrate-1 (referred to as IRS-1). This leads to insulin resistance and intrahepatic inflammation. Indeed, this is evident in rats that develop hepatic steatosis and hepatic fibrosis when fed high-fructose diets.\textsuperscript{30–32} To this end, multiple studies have demonstrated that diets with high saturated fat and simple carbohydrate content can significantly predispose individuals to a higher risk for ectopic lipid deposition and atherogenic dyslipidemia despite hepatic insulin resistance.\textsuperscript{33–35}

**Insulin resistance**

The human body encompasses complex metabolic pathways that are fundamental to the interplay between glucose and

| Factors involved in atherogenic dyslipidemia | Summary |
|--------------------------------------------|---------|
| Dietary content                           | Increases DNL and increases levels of hepatic inflammation |
| Skeletal insulin resistance               | Increases hepatic DNL |
| Liver insulin resistance                  | Increases hepatic DNL and ectopic lipid deposition |
| Adipose insulin resistance                | Increases inflammation, lipolysis, and incomplete fatty acid oxidation |
| Genetic factors                           | Unclear, but thought to be affected by genetic alterations that predispose to pro-inflammatory and profibrogenic mechanisms |
| Gut microbiota                            | Increases inflammation and increases production and absorption of gut-derived fatty acids, while also being associated with SIBO |

Abbreviations: DNL, de novo lipogenesis; NAFLD, nonalcoholic fatty liver disease; SIBO, small intestinal bacterial overgrowth.
insulin at the molecular level. Dysfunction of this interplay in states of nutritional imbalance is evident in metabolic syndrome. The inability of insulin to promote glucose uptake in muscle and the suppression of gluconeogenesis in the liver leads to a progressive reduction in beta cell function and ultimately insulin resistance. Insulin resistance plays a major role in the development of NAFLD and atherogenic dyslipidemia, and can manifest in multiple tissues, including skeletal muscle, liver, and adipose.36 Fig. 2 illustrates the mechanism of insulin resistance in skeletal muscle, liver and adipose tissue.

**Skeletal muscle insulin resistance**

Skeletal muscle insulin resistance is caused by the accumulation of intramyocellular lipid (IMCL) content, which impairs insulin-stimulated glucose transport and glycogen synthesis. Studies examining skeletal muscle in the context of obesity have demonstrated that IMCL content predicts insulin resistance more accurately than fat mass in varying sedentary populations.37–39 Additional studies have further demonstrated that glucose transport is the rate-limiting step responsible for impaired insulin-stimulated glycolysis and that IMCL accumulates when there is a mismatch between lipid oxidation and lipid delivery in muscle cells.16,40–44 These findings suggest an IMCL metabolite, such as diacylglycerol (DAG), acts as a potential mediator of insulin resistance, with high-fat fed and lipid-infused rats demonstrating DAG accumulation.45 Specifically, DAG accumulation has been shown to promote increased protein kinase C (PKC) translocation in skeletal muscle, resulting in the phosphorylation of IRS-1 at serine 1101, and this blocks the AKT pathway to cause impaired insulin signaling.46–48 This has been validated in genetic mouse models with IRTK and glucose transporter type 4 (referred to as GLUT4) mutations, which demonstrate a predisposition for hepatic steatosis and increased adiposity.49,50 Furthermore, progression to atherogenic dyslipidemia through increased liver triglyceride synthesis and plasma triglyceride concentrations with reduced high-density lipoprotein concentrations were observed in young, lean healthy humans with skeletal muscle insulin resistance. This illustrates that ingested glucose is diverted to the liver and not utilized by skeletal muscle in insulin-resistant states.49 These results suggest that in insulin responsive states, glucose is stored as muscle and liver glycogen; however, in insulin resistant states, defects in glycogen storage in muscle result in glucose being diverted to the liver. This resultant hyperglycemia and hyperinsulinemia further stimulate the enzymes involved in hepatic DNL, thereby promoting the conversion of glucose into fat. Ultimately, this increased plasma triglyceride level is the precursor to atherogenic dyslipidemia that leads to premature CVD and NAFLD.10,19,50

**Liver insulin resistance**

Many different models hypothesize on the mechanisms of hepatic insulin resistance. Initial studies involving patients with generalized lipodystrophy and lipodystrophic mouse models showed significant hepatic insulin resistance and recovery of insulin action post-leptin therapy and fat transplantation respectively.51,52 These findings were augmented

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**Fig. 2.** Mechanism of insulin resistance in skeletal muscle, liver and adipose tissue.
by Kim et al.,53 who demonstrated that the overexpression of lipoprotein lipase and short-term high-fat diets in mouse models resulted in hepatic steatosis and hepatic insulin resistance without muscle lipid accumulation or peripheral insulin resistance. This highlights the specific association between ectopic lipid deposition in the liver and hepatic insulin resistance.

At the cellular level, current evidence indicates hepatic insulin resistance may share similarities with skeletal muscle insulin resistance, with evidence supporting a role for DAG accumulation and PKC activation.10,54 Specifically, studies examining fat-fed rats have shown that the intrahepatic accumulation of DAG promotes PKCε translocation in the liver and results in the increased phosphorylation of IRS-1 at threonine (Thr) 1160 (Thr1150 in mice). This subsequently results in impaired IRTK activation.55–59 Furthermore, these findings have been validated in studies in human patients undergoing bariatric surgery. Lipidomic analysis in these patients demonstrate increases in specific lipid metabolites, such as DAGs, while other studies show that hepatic DAG content and PKCε activity are the strongest predictors of insulin sensitivity.

These studies did not demonstrate any association between insulin sensitivity and other factors implicated in hepatic insulin resistance, such as ceramide content, endoplasmic reticulum stress markers, or inflammatory cytokine concentrations.60–63 Studies with mice lacking glycogen synthase demonstrate increased lipogenesis and NAFLD in the presence of hepatic insulin resistance.19,64 These findings may suggest a mechanism by which hepatic insulin resistance impairs glycogen synthesis and directs glucose into lipogenic pathways that lead to atherogenic dyslipidemia and the promotion of NAFLD.

**Adipose insulin resistance**

Insulin primarily functions to suppress lipolysis and promote lipid and glucose uptake in adipocytes. Adipose insulin resistance may be explained by reduced IRTK activity in combination with decreased plasma membrane insulin receptor content. Interestingly, weight loss corrected both adipose insulin resistance and defective adipocyte insulin receptor kinase activity. However, further research is warranted to better understand these mechanisms.54 An important regulator of adipose metabolism is ChREBP. ChREBP is directly related to insulin sensitivity in humans and has been implicated in the synthesis of fatty acid esters that are associated with improved glucose tolerance.65,66 Furthermore, patients with NASH and severe insulin resistance have lower levels of ChREBP on liver biopsy.67 Additionally, adipocytes can secrete adipocytokines, such as leptin and resistin (inflammatory), and adiponectin (anti-inflammatory), which exert their effects through cytokine signaling pathways. These adipocytokines are associated with increased insulin resistance and sensitivity respectively.32–71

Other factors that impact ectopic lipid deposition and affect the role of insulin in adipose lipolysis suppression include inflammatory agents involved in chemokine signaling, such as tumor necrosis factor (referred to as TNF)-alpha, interleukin (referred to as IL)-1β and interferon gamma (referred to as IFNγ), central nervous system-mediated pathways involving the hypothalamus, and reactive oxygen species produced as a result of increased mitochondrial fat oxidation.72–80 Conversely, abnormal hepatic mitochondrial function demonstrated in steatohepatitis can also result in reactive oxygen species due to the incomplete oxidation of fatty acids, which impairs insulin signaling.81 This resultant subclinical inflammation plays a role in the pathogenesis of NAFLD and may contribute to the development of atherogenic dyslipidemia with high-sensitivity C-reactive protein, a strong cardiovascular risk predictor, also shown to be elevated in patients with NAFLD.82 In combination, these factors all play a role in disrupting the effect of insulin on adipose tissue and may predispose to atherogenic-favoring metabolic states that precede NAFLD.

**Genetic factors**

Genetic variations in different populations have been shown to influence the risk of NAFLD. Genome-wide association studies have identified multiple genes with numerous polymorphisms that may be responsible for predisposing individuals to NAFLD and atherogenic dyslipidemia. The mechanism by which these genes influence the pathogenesis of NAFLD is unclear and may include inflammatory, profibrogenic, or energy regulating pathways. A recent systematic review highlighted six genes that were replicated in more than one histologically characterized cohort: patatin-like phospholipase domain-containing protein 3 (referred to as PNPLA3), apolipoprotein E (referred to as APOE), superoxide dismutase 2, mitochondrial (referred to as SOD2), TNF, transmembrane 6 superfamily member 2 (referred to as TM6SF2), and glucokinase regulator (referred to as GCKR). Only PNPLA3 (rs738409 variant) was consistently associated with NAFLD susceptibility, from among these genes.83 Polymorphisms in APOC3 have also been associated with NAFLD, which may predispose to dyslipidemia and insulin resistance through the inhibition of lipoprotein lipase activity.84–86 The membrane-bound O-acyltransferase domain-containing 7 gene and transmembrane channel-like 4 gene (referred to as MBOAT7-TMC4) and SCL16A11 are other examples of polymorphisms that may be associated with NAFLD.87–91 Further research is warranted to elucidate the role of genomic variations in NAFLD.

**Gut microbiota**

The gut microbiota is a growing area of research with regards to the development of metabolic diseases and associations with insulin resistance. Alterations in normal gut flora can lead to the increased production and absorption of gut short-chain fatty acids, altered dietary choline metabolism, altered bile acid pools, and changes in gut permeability.92 These changes are evident in disease states such as small intestinal bacterial overgrowth (commonly known as SIBO), where there is a higher prevalence of NAFLD. Specifically, SIBO induces hepatic expression of toll-like receptor 4 (referred to as TLR4), and release of IL-8 and TNF-alpha.93–95 Pederson et al.96 demonstrated an increased prevalence of Prevotella copri (P. copri) and Bacteroides vulgatus in insulin-resistant subjects that was supported by mouse models in which P. copri had induced insulin resistance. These findings implicate gut microbiota with insulin resistance and suggest that gut microbiomes can influence disease severity in NAFLD. Further research is underway to better elucidate the role of gut microbiota on the pathogenesis of NAFLD.97,98
| Study                      | Study description                                                                 | Number of studies in meta-analysis | Results                                                                                                                                 |
|---------------------------|------------------------------------------------------------------------------------|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Ampuero et al. (2015)     | Meta-analysis showing an association between NAFLD and subclinical atherosclerosis and CAD | 14 studies included, of which 10 were aimed at the presence of subclinical atherosclerosis and 4 studies at the presence of CAD | NAFLD showed a higher prevalence of pathological carotid intima-media thickness and carotid plaques; with regards to CAD, subjects with NAFLD were more likely to have CAD |
| Zhou et al. (2018)        | Meta-analysis showing that NAFLD contributes to subclinical atherosclerosis       | 26 studies were included in this meta-analysis, with a total participant size of 85,395 (including 29,493 with NAFLD) | The presence of NAFLD demonstrated a higher risk of increased carotid intima-media thickness/plaques, arterial stiffness, coronary artery calcification, and endothelial dysfunction |
| Jaruvongvanich et al. (2016) | Meta-analysis showing an association between NAFLD and coronary artery calcification | 12 studies involving 42,410 subjects were included in this meta-analysis | Mean coronary artery calcium scoring was significantly higher in subjects with NAFLD and higher aspartate aminotransferase levels were also associated with increased subclinical atherosclerosis |
| Fan et al. (2016)         | Meta-analysis showing an association between NAFLD and impaired endothelial function | 11 observational studies were included, in which endothelial function was compared between NAFLD patients and healthy controls | NAFLD was associated with a reduction in brachial artery flow-mediated dilation |
| Cai et al. (2015)         | Meta-analysis showing an association between NAFLD and carotid atherosclerosis    | 9 studies were included involving 2446 subjects (925 with NAFLD) | The carotid intima-media thickness was increased 0.16 mm with a 95% confidence interval (0.11, 0.21) with a 3.73-times greater risk for carotid plaque |
| Valbusa et al. (2016)     | Prospective study showing NAFLD is an independent risk factor for acute heart failure readmissions | Cohort study with a total sample of 314 elderly patients with confirmed consecutive admissions for acute heart failure | Patients with NAFLD had remarkably higher 1-year all-cause and cardiac rehospitalizations compared with their counterparts without NAFLD |
| Hung et al. (2015)        | Cross-sectional analysis showing an association between NAFLD and QT prolongation in the general population | Observational study of 31,116 patients were included | Mild, moderate, and severe NAFLD was associated with increases in QTc interval (2.55, 6.59 and 12.14 ms) compared with no NAFLD (p < 0.001); NAFLD was also associated with an increased risk of QTc prolongation |
| Mantovani et al. (2017)   | Retrospective cohort study showing an independent association between NAFLD and increased risk of heart block in hospitalized patients with type 2 diabetes mellitus | Retrospective study evaluating a cohort of 751 patients with type 2 diabetes mellitus during the years 2007-2014 | Overall, patients with NAFLD had a higher prevalence of persistent heart block than those without NAFLD (31.3% vs. 16.7%, p < 0.001). NAFLD was associated with a three-fold increased risk of prevalent heart block |
| Targher et al. (2013)     | Retrospective cohort study showing an association between NAFLD and increased risk of atrial fibrillation in hospitalized patients with type 2 diabetes mellitus | 702 patients with type 2 diabetes mellitus were evaluated for the prevalence of atrial fibrillation during 2007-2011 | NAFLD was associated with an increased risk of prevalent atrial fibrillation |
Cardiovascular risk

Patients with NAFLD are at an increased risk of mortality from cardiovascular events, including atherosclerosis, systolic or diastolic cardiac dysfunction, conduction abnormalities, and arrhythmias. Subclinical atherosclerosis begins as a result of endothelial dysfunction and can eventually manifest as carotid disease. Carotid disease can manifest as increased carotid intima-media thickness and the presence of carotid plaque on ultrasound, coronary artery calcification evident on computerized tomography, left ventricular hypertrophy seen on electrocardiogram and echocardiogram, and peripheral arterial disease seen on ankle-brachial pressure index. A plethora of studies report an association between NAFLD and carotid disease. Carotid disease can manifest as increased epicardial adipose tissue. This increased epicardial adipose tissue is associated with sympathovagal imbalances that can predispose to cardiac arrhythmias, such as first degree heart block prolongation and atrial fibrillation. A recent systematic review and meta-analysis by Zhou et al. demonstrated that NAFLD is associated with an increased risk of mortality with increasing fibrosis severity in NAFLD. A recent Swedish cohort study in liver biopsy-diagnosed NAFLD with the longest documented follow-up time (of over 18 years) supported these findings by showing that patients with NAFLD are at increased risk for CVD compared to matched controls but histological parameters do not seem to independently predict this risk.

Cardiovascular outcomes and mortality in NAFLD

CVD has been incriminated as the leading cause of mortality among patients with NAFLD, even surpassing the mortality associated with chronic liver disease. Recently, a meta-analysis by Targher et al. demonstrated that NAFLD is associated with an increased risk of both fatal and nonfatal CVD events. Another meta-analysis by Wu et al. showed that NAFLD was associated with an increased prevalence of adverse cardiovascular events but did not show an association with overall or CVD mortality; similarly, NASH was not associated with overall or CVD mortality but was associated with an increased incidence of CVD. This increase in incidence may correlate with another systematic review by Dulai et al. that demonstrated an increased risk of mortality with increasing fibrosis severity in NAFLD. A recent Swedish cohort study in liver biopsy-diagnosed NAFLD with the longest documented follow-up time (of over 18 years) supported these findings by showing that patients with NAFLD are at an increased risk for CVD.

Although more studies are needed to confirm a causal relationship between NAFLD and CVD, these findings highlight
the importance of risk factor modification and interventions aimed at preventing CVD progression in NAFLD. Table 2 summarizes below the current literature evaluating the association between NAFLD and CVD.

Conclusions

The pathophysiologial pathways that link NAFLD to premature CVD events result from the development of atherogenic dyslipidemia and ectopic lipid deposition. It involves an altered hepatic metabolism of lipids and glucose due to insulin resistance and a constellation pathogenetic factors associated with the gut microbiome, genetics, and individual lifestyle. The significant association between NAFLD and CVD warrants screening of NAFLD and its associated risk factors in high-risk patients in order to effectively intervene, with a focus on novel approaches that target insulin resistance and dyslipidemia. These novel approaches encompass both non-pharmacological approaches, such as weight loss, lifestyle modifications and bariatric surgery, as well as pharmacologic targets aimed at improving insulin sensitivity. A better understanding of the pathogenesis of insulin resistance will allow the development of newer treatment options that can address the growing health concerns posed by NAFLD and insulin resistance.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (AA and BBD), literature search and drafting of the manuscript (DHA, UI, and LMV), critical revision of manuscript for important intellectual content, senior authorship guidance and supervision (AA and BBD).

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