Ectopic fat accumulation is defined by the presence of lipid droplets within nonadipose tissues that do not normally contain much tissue lipid.

During the past 2 decades, clear evidence has emerged to show that lipid droplet accumulation in certain organs is able to decrease the efficiency of insulin signaling producing resistance to the actions of insulin to signal effectively within the cell to maintain tissue homeostasis. Ectopic lipid and ectopic liver fat to cause insulin resistance and to increase risk of both type 2 diabetes mellitus and cardiovascular disease. For this review, PubMed was searched for articles using the key words non-alcoholic fatty liver disease or fatty liver combined with diabetes risk, cardiovascular risk, and cardiovascular mortality between 1990 and 2014. Articles published in languages other than English were excluded. (Arterioscler Thromb Vasc Biol. 2014;34:00-00.)

Key Words: cardiovascular diseases ■ diabetes mellitus, type 2 ■ insulin resistance ■ non-alcoholic fatty liver disease

Ectopic fat accumulation is defined by the presence of lipid droplets within nonadipose tissues that do not normally contain much tissue lipid.

NAFLD as a Risk Factor for Type 2 Diabetes Mellitus and CVD

NAFLD has become one of the most common causes of chronic liver disease worldwide, causing considerable liver morbidity and mortality. As better specified below, it is now also becoming clear that NAFLD is an emerging risk factor for both type 2 diabetes mellitus and CVD, although the pathophysiological mechanisms that link NAFLD with these 2 diseases are not entirely clear.

How Is NAFLD Diagnosed?

Diagnosis of NAFLD is based on the following criteria: (1) hepatic steatosis on imaging or histology, (2) no significant alcohol consumption, and (3) no competing causes for hepatic steatosis. The liver is a key visceral organ that is affected by ectopic fat accumulation, and when excess body weight is present, the incidence of cirrhosis is markedly increased.

When liver fat accumulation >5% occurs that is not caused by excessive alcohol consumption or other known pathogenic factors, the presence of liver fat defines nonalcoholic fatty liver disease (NAFLD).

It is beyond the scope of this brief narrative review to discuss all aspects of ectopic fat accumulation. This review will focus on NAFLD and its relationships to insulin resistance/diabetes mellitus and CVD because NAFLD is emerging as an important condition that consistently modifies risks of these common diseases.
and although it is an inexpensive test, it has poor sensitivity for detecting liver fat at low levels and is really only effective for detecting liver fat infiltration >30% (particularly in non-obese subjects). Computed tomography has also been used to diagnose liver fat. The liver attenuation index can be derived and defined as the difference between mean hepatic and mean splenic attenuation, and some investigators have used a liver attenuation index <5 Hounsfield units to identify >5% liver fat and diagnose NAFLD. T1-weighted dual-echo MRI and proton magnetic resonance spectroscopy have the best diagnostic accuracy in defining hepatic steatosis. The advantage of proton magnetic resonance spectroscopy is that the fat peak areas and the signal fat fraction have a dynamic range for detecting 0% to 100% liver fat. Proton magnetic resonance spectroscopy also has excellent reproducibility and sensitivity with a coefficient of variation of only 8%. Hepatic steatosis is often associated with mild-to-moderate elevations of serum liver enzyme levels, but, at best, the liver enzymes only identify people who are at increased risk of NAFLD and who require further diagnostic tests. The sensitivity and specificity of some biomarkers for liver fibrosis have recently been described. The European Liver Fibrosis score uses an algorithm and measurements of tissue inhibitor of matrix metalloproteinase-1, hyaluronic acid, and the amino-terminal peptide of procollagen III and has excellent performance for the diagnosis of severe fibrosis, good performance for moderate fibrosis, and fair performance for identifying people without fibrosis. The NAFLD fibrosis score has good performance for identifying people without fibrosis, but poorer performance for diagnosing advanced fibrosis. Thus, a combination of both tests might improve diagnostic performance to diagnose different stages of liver fibrosis in NAFLD, without having to resort to liver biopsy.

Ectopic Liver Fat, Insulin Resistance, and Inflammation

Several mechanisms of lipid-induced decreases in hepatic insulin sensitivity have been proposed from the results of in vitro and in vivo experiments. Most of the in vivo data have been obtained in mice, and to date, it is uncertain which mechanism of lipid-induced insulin resistance is most important in humans.

Two principal mechanisms of insulin resistance have been investigated:

1. Hepatic diacylglycerol-mediated activation of protein kinase Cε, with consequent inhibition of insulin-stimulated insulin receptor kinase phosphorylation of insulin receptor substrate proteins, producing impaired activation of downstream insulin signaling.

2. Increased saturated fatty acid concentration-mediated insulin resistance, induced by activation of inflammatory toll-like receptor 4 signaling, leading to increased de novo ceramide synthesis, and ceramide-mediated inhibition of insulin signaling through inhibition of Akt phosphorylation.

Studying which of these 2 mechanisms of lipid-induced insulin resistance is more important in vivo, these investigators found that saturated or unsaturated fat feeding in mice resulted in hepatic steatosis, increased intrahepatic diacylglycerol content, caused protein kinase Cε activation, and impaired insulin-stimulated insulin receptor substrate-2–associated phosphoinositide-3 kinase signaling. In contrast, neither of these diets led to an increase in hepatic ceramide content, thus dissociating ceramide content from hepatic insulin resistance in this rodent model. Furthermore, toll-like receptor 4 receptor signaling was not required for saturated fat–induced accumulation of ceramide, triglyceride, diacylglycerol, or impairment of hepatic insulin signaling.

Importantly, these results translate to humans in whom recent studies have found that increased hepatic diacylglycerol content and protein kinase Cε activation, and not ceramide content, are strongly associated with hepatic insulin resistance. Thus, the evidence to date suggests that regardless of how hepatic lipid accumulates, production of diacylglycerol is key and causes loss of insulin sensitivity. Therefore, strategies to decrease diacylglycerol production are likely, therefore, to improve Akt signaling and improve insulin signaling, leading to insulin-mediated suppression of hepatic glucose production. It has been suggested that the effects of diacylglycerol–protein kinase Cε to decrease effective hepatic insulin signaling explain the occurrence of hepatic insulin resistance that is observed in most cases of NAFLD associated with obesity and type 2 diabetes mellitus.

Hepatic lipids that are not esterified also induce endoplasmic reticulum stress, leading to the activation of c-Jun N-terminal kinases and nuclear factor κB, which are 2 major regulators of inflammatory pathways that can also inhibit phosphorylation of insulin receptor substrate-1, potentially aggravating hepatic insulin resistance and increasing intrahepatic cytokine production (Figure).

**Figure.** The central role of ectopic fat accumulation in the liver and specifically the role of lipid intermediates (eg, diacylglycerol [DAG]) in insulin resistance, resulting in (1) increased reactive oxygen species and increased production of proinflammatory cytokines, coagulation-fibrinolytic factors, and other hepatokines; and (2) decreased insulin signaling, increased hepatic glucose production, and increased very-low-density lipoprotein (VLDL) secretion. It is uncertain why increased VLDL secretion does not occur in all individuals with hepatic lipid accumulation. IRS indicates insulin receptor substrate; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor κB; PISK, phosphoinositide-3 kinase; PKC-ε, protein kinase Cε; and ROS, reactive oxygen species.
Epidemiological Evidence Linking NAFLD to CVD

Although it is plausible to argue that NAFLD can exert deleterious effects on the cardiovascular system via the coexistence of type 2 diabetes mellitus or other cardiometabolic risk factors, increasing evidence supports the notion that NAFLD is also an independent risk factor for CVD.\textsuperscript{3,4,34}

Several large cross-sectional population and hospital-based studies, involving both subjects without diabetes mellitus and patients with diabetes mellitus, have consistently shown that the prevalence of clinical CVD is remarkably increased in people with NAFLD (for more detailed reviews, see Bhatia et al,\textsuperscript{3} Targher et al,\textsuperscript{4} and Anstee et al\textsuperscript{34}). For example, NAFLD on ultrasound was associated with an increased prevalence of CVD independently of several CVD risk factors, including features of the metabolic syndrome, in a large cohort of US adults.\textsuperscript{35} Similarly, in the cohort of =3000 patients with type 2 diabetes mellitus of the Valpolicella Diabetes Heart Study, those with NAFLD had a higher prevalence of coronary, cerebrovascular, and peripheral vascular disease than their counterparts without NAFLD, independently of traditional CVD risk factors, medication use, and diabetes mellitus–related variables.\textsuperscript{36} Finally, in patients referred for clinically indicated coronary angiography, NAFLD was associated with a greater severity of coronary artery disease, independent of cardiometabolic risk factors.\textsuperscript{3,4,34}

Although the relationship between NAFLD and increased CVD prevalence seems to be robust and consistently replicated across populations of different ethnicities, the specific contribution of NAFLD per se to the increased incidence of CVD remains more controversial.\textsuperscript{3,4,34} Nevertheless, accumulating evidence suggests that CVD is a serious threat to patients with NAFLD. As summarized in Table 1, several retrospective and prospective studies have assessed the relationship between NAFLD and the risk of incident CVD events. The main characteristics of the study populations, the length of follow-up, and the relative risks of developing CVD events have been specified in Table 1. In most of these studies, NAFLD was associated with an increased risk of fatal and nonfatal CVD events, independently of coexisting cardiometabolic risk factors, both in patients with and without diabetes mellitus. Again, some retrospective studies with a reasonably long duration of follow-up that examined the natural history of patients with biopsy-confirmed NAFLD have shown that the presence and severity of hepatic fibrosis is the main determinant of all-cause and liver-related mortality and that CVD is a common cause of mortality among such patients. Ekstedt et al\textsuperscript{37} and Söderberg et al\textsuperscript{38} also reported that patients with NASH, but not those with simple steatosis, have an increased risk of CVD mortality compared with the matched control population. However, it should be noted that a complete adjustment for potentially confounding cardiometabolic factors was not performed in these studies.\textsuperscript{45,46} In addition, a recent meta-analysis concluded that patients with NAFLD have a greater risk of developing CVD events than the matched control population, but that the severity of NAFLD histology does not increase CVD mortality.\textsuperscript{47} However, further larger and longer prospective studies in patients with biopsy-confirmed NAFLD are needed to improve understanding of this issue.

Putative Mechanisms Linking NAFLD to CVD

The precise mechanisms by which NAFLD may increase risk of CVD are poorly understood. However, NAFLD is increasingly recognized as a pathogenic component of the metabolic syndrome, and it is, therefore, not uncommon for patients with NAFLD to have all features of the metabolic syndrome.\textsuperscript{35}

Growing evidence suggests that NAFLD, especially in its necroinflammatory form (NASH) may cause atherogenic dyslipidemia (an increase in triglyceride-rich lipoproteins, such as very-low-density lipoproteins, increased small dense low-density lipoproteins as well as decreased concentrations of high-density lipoproteins). The pathogenesis of dyslipidemia in NAFLD is not well understood, but it is likely related to hepatic overproduction of large very-low-density lipoprotein particles and dysregulated clearance of lipoproteins from the circulation.\textsuperscript{34} Increasing evidence suggests that perturbation of cholesterol occurs in NAFLD as gain- and loss-of-function studies have demonstrated that the bile acid receptors, that is, farnesoid X receptor and TGR5 (a G protein–coupled receptor) play important roles in regulating lipid and carbohydrate metabolism and inflammatory responses. Importantly, activation of farnesoid X receptor/TGR5 lowers intrahepatic triglyceride content and inhibits inflammation.\textsuperscript{55} In addition, farnesoid X receptor/TGR5 activation coordinates the immune phenotype of monocytes and macrophages both in vitro and in vivo,\textsuperscript{64} and taken together, this evidence suggests that farnesoid X receptor and TGR5 may be both ideal targets for NAFLD treatment.

In NASH, there is also a variety of proinflammatory markers (eg, C-reactive protein, interleukin–6), procoagulant factors (eg, fibrinogen, plasminogen activator inhibitor–1), pro-oxidant molecules (eg, thiobarbituric acid–reacting substances, nitrotyrosine), and profibrogenic mediators (eg, tumor growth factor–β, endothelin-1) that may adversely affect the vasculature.\textsuperscript{64,65} The experimental finding that NASH is associated with abnormal intrahepatic mRNA expression of these potential mediators of vascular injury provides further evidence that it is the steatotic, inflamed liver per se that is primarily responsible for the increased plasma concentrations of these molecules.\textsuperscript{3,4,34,57}

Not only does abdominal obesity frequently occur with NAFLD, but also there is often evidence of ectopic fat accumulation in other sites (eg, myocardial, pericardial, and perivascular). Developing extrahaepatic fat tissue contains a variety of cell types that include adipocytes, preadipocytes, stromal cells, and inflammatory cells, including Th1 and Th2 macrophages. Development of new fat tissue and blood vessel formation are closely coupled processes that begin in prenatal life and continue throughout adult life. Adipocytes produce multiple angiogenic factors, including leptin, angiopoietins, hepatocyte growth factor, granulocyte macrophage colony-stimulating factor, vascular endothelial growth factor, fibroblast growth factor-2, and transforming growth factor–β, which either alone or collectively are capable of influencing other cell types and stimulating new blood vessel growth.\textsuperscript{58}

There is evidence of increased adipose tissue triglyceride lipolysis in NAFLD,\textsuperscript{59} and therefore, the increased flux of adipose tissue–derived free fatty acids to the liver has the potential...
# Table 1. Principal Observational Studies of the Association Between NAFLD and the Incidence of CVD Morbidity and Mortality

<table>
<thead>
<tr>
<th>Investigators (Reference)</th>
<th>Study Population</th>
<th>Length of Follow-Up (Diagnosis of NAFLD)</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matteoni et al(^3^9)</td>
<td>Retrospective cohort of 132 patients with NAFLD and raised serum liver enzymes</td>
<td>18 y (biopsy)*</td>
<td>Patients with NASH had higher rates of all-cause and liver-related mortality than those without. CVD death rate did not differ between the groups.</td>
</tr>
<tr>
<td>Dam-Larsen et al(^4^0)</td>
<td>Retrospective cohort of 109 patients with nonalcoholic simple steatosis (without NASH at baseline)</td>
<td>16.7 y (biopsy)*</td>
<td>No significant difference in death rates between patients with simple steatosis and the general population.</td>
</tr>
<tr>
<td>Rafiq et al(^4^1)</td>
<td>Retrospective cohort of 173 patients with NAFLD and raised serum levels of liver enzymes</td>
<td>13 y (biopsy)*</td>
<td>CVD, malignancy, and liver-related complications were the most common causes of mortality.</td>
</tr>
<tr>
<td>Adams et al(^4^2)</td>
<td>Retrospective community-based cohort of 420 patients with NAFLD</td>
<td>7.6 y (biopsy/imaging)*</td>
<td>Patients with NAFLD (especially those with cirrhosis or NASH) had higher rates of all-cause, CVD, and liver-related mortality than the matched general population.</td>
</tr>
<tr>
<td>Ekstedt et al(^4^3)</td>
<td>Retrospective cohort of 129 patients with NAFLD and raised serum levels of liver enzymes</td>
<td>13.7 y (biopsy)*</td>
<td>Patients with NASH, but not those with simple steatosis, had higher rates of all-cause (≈2-fold), CVD (≈2-fold), and liver-related (≈10-fold) mortality than the reference population.</td>
</tr>
<tr>
<td>Söderberg et al(^4^4)</td>
<td>Retrospective cohort of 118 patients with NAFLD and raised serum levels of liver enzymes</td>
<td>24 y (biopsy)*</td>
<td>Patients with NASH, but not those with simple steatosis, had higher rates of all-cause (≈2-fold), CVD (≈2-fold), and liver-related mortality than the matched general population.</td>
</tr>
<tr>
<td>Jepsen et al(^4^5)</td>
<td>Retrospective cohort of 1800 patients discharged with a hospital diagnosis of NAFLD</td>
<td>6.2 y (ultrasound/liver enzymes)*</td>
<td>Patients with NAFLD had higher rates of all-cause (2.6-fold), CVD (2.1-fold), and liver-related (19.7-fold) mortality than the general population.</td>
</tr>
<tr>
<td>Hamaguchi et al(^4^6)</td>
<td>Community-based cohort of 1637 apparently healthy individuals</td>
<td>8 y (ultrasound)†</td>
<td>NAFLD was independently associated with increased risk of nonfatal CVD events (HR, 4.10; 95% CI, 1.6–10.7).</td>
</tr>
<tr>
<td>Targher et al(^4^7)</td>
<td>Prospective cohort of 2103 patients with T2DM without baseline viral hepatitis and CVD</td>
<td>6.5 y (ultrasound)‡</td>
<td>NAFLD was independently associated with increased risk of fatal and nonfatal CVD events (HR, 1.87; 95% CI, 1.2–2.6).</td>
</tr>
<tr>
<td>Haring et al(^4^8)</td>
<td>Population-based cohort study of 4160 adult men and women without baseline viral hepatitis or cirrhosis</td>
<td>7.3 y (ultrasound)*</td>
<td>NAFLD was independently associated with increased risk of all-cause and CVD mortality in men (HR, 6.2; 95% CI, 1.2–31.6).</td>
</tr>
<tr>
<td>Zhou et al(^4^9)</td>
<td>Community-based cohort study of 3543 adult men and women</td>
<td>4 y (ultrasound)*</td>
<td>Patients with NAFLD had =3-fold higher rates of all-cause and CVD mortality than those without NAFLD.</td>
</tr>
<tr>
<td>Stepanova et al(^5^0)</td>
<td>National-based cohort study of 11 371 adult participants from the Third National Health and Nutrition Examination Survey 1988–1994</td>
<td>14.5 y (ultrasound)*</td>
<td>No significant association between NAFLD and all-cause and cause-specific mortality.</td>
</tr>
<tr>
<td>Wong et al(^5^1)</td>
<td>465 consecutive patients with ischemic heart disease as diagnosed by coronary angiography</td>
<td>1.8 y (ultrasound)§</td>
<td>No significant association between NAFLD and CVD events.</td>
</tr>
<tr>
<td>Treeprasertsuk et al(^5^2)</td>
<td>309 patients with NAFLD</td>
<td>11.5 y (ultrasound/CT)‖</td>
<td>NAFLD patients have a higher 10-year CHD risk than the general population of the same age and sex.</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; CI, confidence interval; CT, computed tomography; CVD, cardiovascular disease; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; and T2DM, type 2 diabetes mellitus.

*Study outcome: all-cause and cause-specific mortality.
†Study outcome: nonfatal coronary heart disease and stroke.
‡Study outcome: a combined end point of CVD mortality and nonfatal myocardial infarction, ischemic stroke, and revascularization procedures.
§Study outcome: combined end point of CVD mortality and nonfatal myocardial infarction and revascularization procedures.
‖Study outcome: new-onset CVD.

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to increase hepatic triglyceride accumulation. Interesting new evidence suggests that variation in temperature could also indirectly affect the development of hepatic steatosis via an uncoupling protein-1–mediated effect in adipose tissue to increase adipose tissue lipolysis and thereby increase flux of free fatty acids to the liver. Thus, an improved understanding of the fundamental mechanisms by which angiogenesis and external stimuli, such as cold and tissue hypoxia, modulate adipose tissue functions may provide new therapeutic options for treatment of ectopic fat accumulation that includes hepatic fat accumulation in NAFLD.

Treatments of Benefit to NAFLD and CVD

In Table 2, we have schematically summarized the potential treatments of benefit to NAFLD and CVD (for more detailed reviews, see Targher and Byrne, Ratziu, Nascimbeni et al, and Chalasani et al). Currently, there is no licensed pharmacological treatment for liver disease per se in NAFLD. However, NAFLD and CVD share numerous cardiometabolic risk factors, and treatment strategies for NAFLD and CVD should be similar and aimed primarily at reducing insulin resistance and modifying the associated cardiometabolic risk factors. Current recommendations for NAFLD therapy are limited to weight reduction, through diet and physical exercise, and to the treatment of individual features of the metabolic syndrome with the use of therapies that may have potential beneficial liver effects, including bariatric surgery for morbid obesity, insulin-sensitizing agents for type 2 diabetes mellitus, and drugs directed at the renin–angiotensin–aldosterone system to control hypertension. Thiazolidinediones have the best evidence-based data for efficacy in NASH, but long-term adverse CVD and noncardiovascular side effects attributed to these drugs are a serious issue and are likely to prevent licensing of thiazolidinediones as a treatment for NAFLD. Preliminary evidence suggests some benefit of vitamin E, high-dose ω-3 fatty acids, and other hepatoprotectants; but, to date, there are insufficient data to advocate the use of any of these agents in NAFLD/NASH.

Conclusions

The adverse impact of NAFLD on the risk of CVD and type 2 diabetes mellitus deserves particular attention among cardiologists, in view of the growing number of patients with NAFLD, exacerbated by the increasing burden of obesity, contributing to ectopic liver fat accumulation. Clinicians who manage patients at risk of NAFLD (ie, people with metabolic syndrome risk factors) should focus on identifying and diagnosing NAFLD and then should consider whether affected patients may be at higher absolute risk of CVD than anticipated. Early aggressive risk factor modification of coexisting CVD risk factors in people with NAFLD may be particularly advantageous, because accumulating evidence suggests that patients with NAFLD are at higher absolute risk of CVD than has previously been appreciated.

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Table 2. Summary of Potential Treatments of Benefit to NAFLD and CVD

<table>
<thead>
<tr>
<th>Therapeutic Benefits</th>
<th>Type of Intervention/Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven benefits to NAFLD and CVD</td>
<td>Weight loss (lifestyle interventions, bariatric surgery)</td>
</tr>
<tr>
<td></td>
<td>Increased physical activity</td>
</tr>
<tr>
<td>Proven benefits to CVD and possible benefits to NAFLD</td>
<td>Statins</td>
</tr>
<tr>
<td></td>
<td>Angiotensin receptor blockers</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>Possible benefits to NAFLD and CVD</td>
<td>Metformin</td>
</tr>
<tr>
<td></td>
<td>Glucagon-like peptide-1 agonists</td>
</tr>
<tr>
<td></td>
<td>Fibrates</td>
</tr>
<tr>
<td></td>
<td>Ezetimibe</td>
</tr>
<tr>
<td></td>
<td>High-dose ω-3 fatty acids</td>
</tr>
<tr>
<td>Possible benefits to NAFLD but not to CVD</td>
<td>Dietary manipulation (decrease carbohydrate)</td>
</tr>
<tr>
<td></td>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td></td>
<td>Vitamin E</td>
</tr>
<tr>
<td></td>
<td>Bile acid receptors</td>
</tr>
</tbody>
</table>

Data schematically summarized in the table are based on recent reviews and guidelines. ACE indicates angiotensin-converting enzyme; CVD, cardiovascular disease; NAFLD, nonalcoholic fatty liver disease; and NASH, nonalcoholic steatohepatitis.
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References


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Christopher D. Byrne and Giovanni Targher

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