

review article

Current Concepts

Risk of Cardiovascular Disease in Patients with Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease encompasses a spectrum of pathologic conditions, ranging from simple steatosis to nonalcoholic steatohepatitis and cirrhosis. The disease has reached epidemic proportions and is the most common cause of chronic liver disease in Western countries.¹⁻⁴ Approximately 20 to 30% of adults in the general population in Western countries have nonalcoholic fatty liver disease, and its prevalence increases to 70 to 90% among persons who are obese or have diabetes; such patients are also at increased risk for the development of advanced fibrosis and cirrhosis.¹⁻⁴

Recognition of the importance of nonalcoholic fatty liver disease and its strong association with the metabolic syndrome¹⁻⁴ has stimulated interest in its putative role in the development and progression of cardiovascular disease.⁵ Accumulating evidence suggests that cardiovascular disease dictates the outcome (or outcomes) in patients with nonalcoholic fatty liver disease more frequently and to a greater extent than does the progression of liver disease.^{2,4,5}

This review focuses on the rapidly expanding body of clinical evidence that supports a strong association between nonalcoholic fatty liver disease and the risk of cardiovascular disease. Because of the link between the two disorders, more careful surveillance of these patients will be needed.

Increased Prevalence of Cardiovascular Disease

Markers of Subclinical Cardiovascular Risk

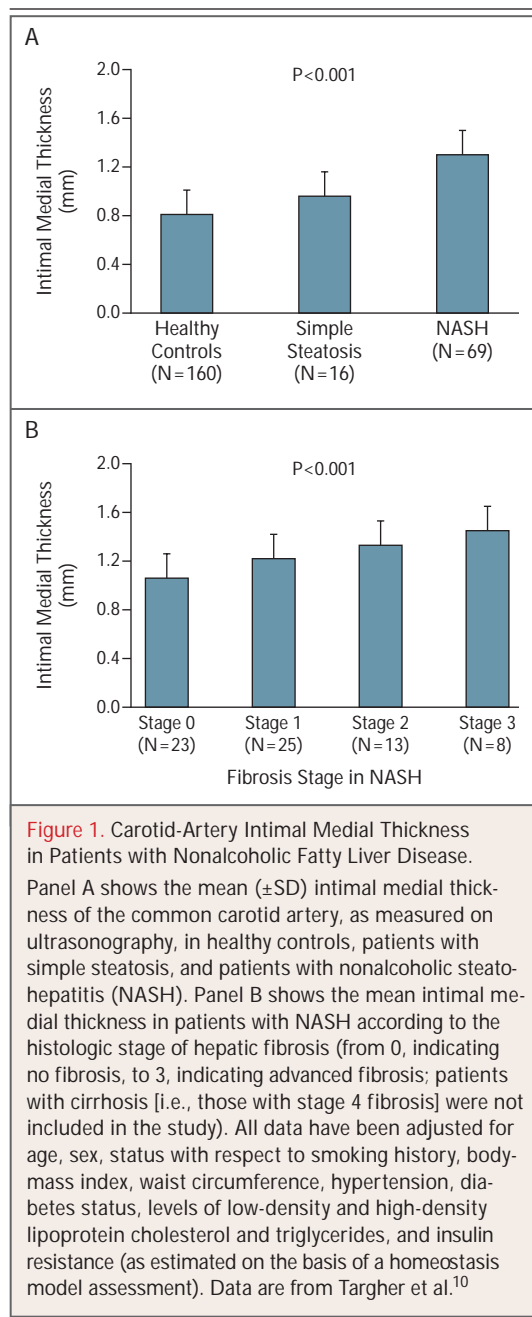
Patients with nonalcoholic fatty liver disease, both adults and children, typically meet the diagnostic criteria for the metabolic syndrome (i.e., abdominal obesity, hypertension, atherogenic dyslipidemia, and dysglycemia) and therefore have multiple risk factors for cardiovascular disease.¹⁻⁵ As compared with control subjects who do not have steatosis, patients with nonalcoholic fatty liver disease have impaired flow-mediated vasodilatation⁶ and increased carotid-artery intimal medial thickness⁷⁻¹² — two reliable markers of subclinical atherosclerosis — that are independent of obesity and other established risk factors. Although some recent studies have shown no significant association between nonalcoholic fatty liver disease and either carotid-artery intimal medial thickness or carotid-artery calcium (as quantified on computed tomography^{13,14}), a systematic review and meta-analysis of seven cross-sectional studies (involving a total of 3497 subjects) confirmed that nonalcoholic fatty liver disease diagnosed on ultrasonography is strongly associated with increased carotid-artery intimal medial thickness and an increased prevalence of carotid atherosclerotic plaques.¹⁵

In a study from 2006, we found that carotid-artery intimal medial thickness was greatest in patients with nonalcoholic steatohepatitis, intermediate in those with simple steatosis, and lowest in healthy controls matched for age, sex, and

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body-mass index (Fig. 1A).¹⁰ In addition, the histologic severity of nonalcoholic steatohepatitis was associated with the degree of carotid-artery intimal medial thickness, independently of classic cardiovascular risk factors, insulin resistance, and metabolic syndrome components (Fig. 1B). Larger studies will be needed to confirm the reproducibility of these results. Young patients with nonalcoholic fatty liver disease who are not obese and who do not have diabetes or hypertension have echocardiographic features

of early left ventricular dysfunction¹⁶ and impaired left ventricular energy metabolism, as measured on cardiac phosphorus-31 magnetic resonance spectroscopy.¹⁷

Clinically Manifested Cardiovascular Disease
Given the strong association between nonalcoholic fatty liver disease and markers of subclinical cardiovascular disease, it is certainly not surprising that patients with ultrasonographically diagnosed nonalcoholic fatty liver disease have a higher prevalence of clinically manifested cardiovascular disease than do control subjects without steatosis.¹⁸⁻²⁰ In a large study involving approximately 3000 unselected patients with type 2 diabetes, the prevalence of coronary, cerebrovascular, and peripheral vascular disease was remarkably higher among patients with nonalcoholic fatty liver disease than among those without this disease, independently of traditional risk factors, duration of diabetes, extent of glycemic control, use of lipid-lowering, hypoglycemic, antihypertensive, or antiplatelet medications, and components of the metabolic syndrome.¹⁸ The findings were similar in a study of adults with type 1 diabetes.¹⁹ In a community-based cohort of 2088 male workers, the presence of ultrasonographically diagnosed nonalcoholic fatty liver disease was independently associated with an increased prevalence of ischemic heart disease.²⁰ In patients consecutively referred for elective coronary angiography, nonalcoholic fatty liver disease was associated with more severe coronary artery disease independently of established risk factors.²¹ Moreover, nonalcoholic fatty liver disease, as assessed by magnetic resonance spectroscopy, was associated with reduced myocardial perfusion in patients with type 2 diabetes who were known to have coronary artery disease, independently of traditional risk factors, visceral fat mass, and insulin sensitivity (as assessed with the use of the euglycemic hyperinsulinemic clamp).²² Finally, an autopsy study involving 742 children showed that the prevalence of coronary heart disease was increased by a factor of 2 among those with nonalcoholic fatty liver disease.²³

Increased Incidence of Cardiovascular Disease

The main prospective and retrospective studies assessing the relationship between nonalcoholic fatty liver disease (as detected by means of biop-

Table 1. Principal Prospective Studies of the Association between Nonalcoholic Fatty Liver Disease and the Incidence of Major Cardiovascular Events.*

Investigators	Study Population	Age	Length of Follow-up years	Outcomes	Main Results
Hamaguchi et al. ⁴⁰	Community-based cohort of 1637 healthy subjects in Japan	22–83	5	Nonfatal coronary heart disease, ischemic stroke, and cerebral hemorrhage events	Increased risk of nonfatal CVD events associated with NAFLD independently of age, sex, BMI, smoking status, alcohol consumption, blood pressure, LDL cholesterol, triglycerides, and HDL cholesterol
Targher et al. ⁴¹	Nested case-control study in an outpatient cohort of patients with type 2 diabetes in Italy: 248 patients and 496 control subjects matched for age and sex, who did not have CVD or viral hepatitis at baseline	40–79	5	Death from CVD and nonfatal myocardial infarction, ischemic stroke, and revascularization procedures	Increased risk of fatal and nonfatal CVD events associated with NAFLD independently of age, sex, BMI, waist circumference, smoking status, medication use (lipid-lowering, hypoglycemic, antihypertensive, and antiplatelet drugs), alcohol consumption, duration of diabetes, and levels of blood pressure, glycated hemoglobin, LDL cholesterol, triglycerides, HDL cholesterol, and GGT activity
Targher et al. ⁴²	Valpolicella Heart Diabetes Study: outpatient cohort of 2103 patients with type 2 diabetes in Italy who did not have CVD or viral hepatitis at baseline	40–79	6.5	Death from CVD and nonfatal myocardial infarction, ischemic stroke, and revascularization procedures	Increased risk of fatal and nonfatal CVD events associated with NAFLD independently of age, sex, BMI, waist circumference, smoking status, medication use, alcohol consumption, blood pressure, diabetes duration, glycated hemoglobin, LDL cholesterol, triglycerides, HDL cholesterol, and GGT
Haring et al. ⁴³	Study of Health in Pomerania: population-based study of 4160 men and women in Germany who did not have viral hepatitis or cirrhosis at baseline	20–79	7.3	Death from any cause and death from CVD	Increased risk of death from any cause and death from CVD among men with NAFLD, independent of age, sex, waist circumference, alcohol consumption, physical activity, educational level, civil status (living alone vs. living with a spouse or partner), blood pressure, status with respect to diabetes, and Groll functional comorbidity index ⁴⁴

* Nonalcoholic fatty liver disease (NAFLD) was diagnosed on the basis of ultrasonographic findings in all the studies, with one exception: in the Study of Health in Pomerania, NAFLD was diagnosed on the basis of ultrasonographic findings, an elevated γ -glutamyltransferase (GGT) level, or both. BMI denotes body-mass index, CVD cardiovascular disease, HDL high-density lipoprotein, and LDL low-density lipoprotein.

sy, ultrasonography, or serum liver enzyme measurements) and the incidence of cardiovascular disease²⁴⁻⁴³ are described in the table in the Supplementary Appendix, available with the full text of this article at NEJM.org. Table 1 shows the relevant data from the principal trials that have used liver ultrasonography for the diagnosis of nonalcoholic fatty liver disease.⁴⁰⁻⁴³

Liver Biopsy

Overall, the published studies showed that mortality among patients with nonalcoholic fatty liver disease was higher than that in the general population, mainly owing to concomitant cardiovascular disease and liver dysfunction. The magnitude of the risk of death depended on the study setting and the methods of ascertainment.

In a retrospective, community-based cohort of 420 patients with nonalcoholic fatty liver disease who were followed for a mean period of 7.6 years, the rate of death from any cause (with the most common causes being cardiovascular disease or cancer) was higher among patients with nonalcoholic steatohepatitis or cirrhosis than in the general population,²⁶ and cardiovascular disease was the most frequent cause of death in 173 patients with biopsy-proven nonalcoholic fatty liver disease who were followed for 13 years.²⁷ Ekstedt et al. found that the 14-year risk of death from cardiovascular disease was higher by a factor of 2 among 129 patients with nonalcoholic steatohepatitis than in the general population.²⁸ Furthermore, Söderberg et al. recently confirmed that nonalcoholic steatohepatitis (but not simple steatosis) was associated with increased mortality from all causes and from cardiovascular disease and liver-related causes among patients with nonalcoholic fatty liver disease who were followed for a mean period of 21 years.²⁹

All these data provide clear evidence that cardiovascular disease is a serious threat to patients with nonalcoholic steatohepatitis. However, these studies, which examined the natural history of histologically proven nonalcoholic fatty liver disease, were retrospective cohort studies with relatively small numbers of patients who were seen at tertiary care referral centers²⁴⁻²⁹ — features that limit the generalizability of the findings to a broader patient population.

Serum Liver Enzymes

Many large population-based studies³⁰⁻³⁹ that used elevated serum liver enzyme levels as surrogate

markers of nonalcoholic fatty liver disease (and should therefore be interpreted cautiously)¹⁻⁵ have shown that this disease is associated with an increased risk of cardiovascular disease independently of alcohol consumption and several established cardiovascular risk factors. In a systematic review and meta-analysis of 11 prospective studies, Fraser et al. confirmed that an elevated serum γ -glutamyltransferase level was an independent, long-term predictor of incident cardiovascular events in both men and women.³⁵ The meta-analysis of the only 2 prospective studies that used an elevated serum alanine aminotransferase level as a surrogate marker of nonalcoholic fatty liver disease failed to show any independent association with cardiovascular disease outcomes.³⁵ Some of the studies,^{37,38} but not all of them,^{32,36,39} confirmed that an increased serum alanine aminotransferase level is less predictive of incident cardiovascular disease than is an increased serum γ -glutamyltransferase level, which is thought to be a marker not only of nonalcoholic fatty liver disease but also of oxidative stress.³⁻⁵

Liver Ultrasonography

Hamaguchi et al. reported that nonalcoholic fatty liver disease diagnosed on ultrasonography in a community-based cohort of healthy adults was associated with an increased risk of nonfatal cardiovascular events independently of cardiometabolic risk factors (Table 1),⁴⁰ and nonalcoholic fatty liver disease has also been found to be an independent predictor of incident cardiovascular events in patients with type 2 diabetes.^{41,42} More recently, in a population-based study of 4160 middle-aged subjects, Haring et al. found that ultrasonography of the liver was useful in patients with increased levels of γ -glutamyltransferase not only for the diagnosis of nonalcoholic fatty liver disease but also for better cardiovascular-risk stratification.⁴³

To date, the evidence from published prospective studies suggests that patients with nonalcoholic fatty liver disease have multiple risk factors for cardiovascular disease; that cardiovascular disease is much more common than liver disease as a cause of death in such patients, especially those with nonalcoholic steatohepatitis; and that nonalcoholic fatty liver disease is linked to an increased risk of cardiovascular events both in patients without diabetes and in those with type 2 diabetes. However, further

Figure 2 (facing page). Possible Mechanisms Leading to Cardiovascular Disease in Patients with Nonalcoholic Fatty Liver Disease.

The putative underlying mechanisms that link nonalcoholic fatty liver disease and cardiovascular disease might originate from the expanded and inflamed visceral adipose tissue, with the liver functioning as both the target of the resulting systemic abnormalities and the source of several proatherogenic factors. Nonalcoholic fatty liver disease — especially its necroinflammatory form, nonalcoholic steatohepatitis — might play a part in the pathogenesis of cardiovascular disease through the systemic release of several inflammatory, hemostatic, and oxidative-stress mediators or through the contribution of nonalcoholic fatty liver disease to insulin resistance and atherogenic dyslipidemia. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, NAFLD nonalcoholic fatty liver disease, and NASH nonalcoholic steatohepatitis.

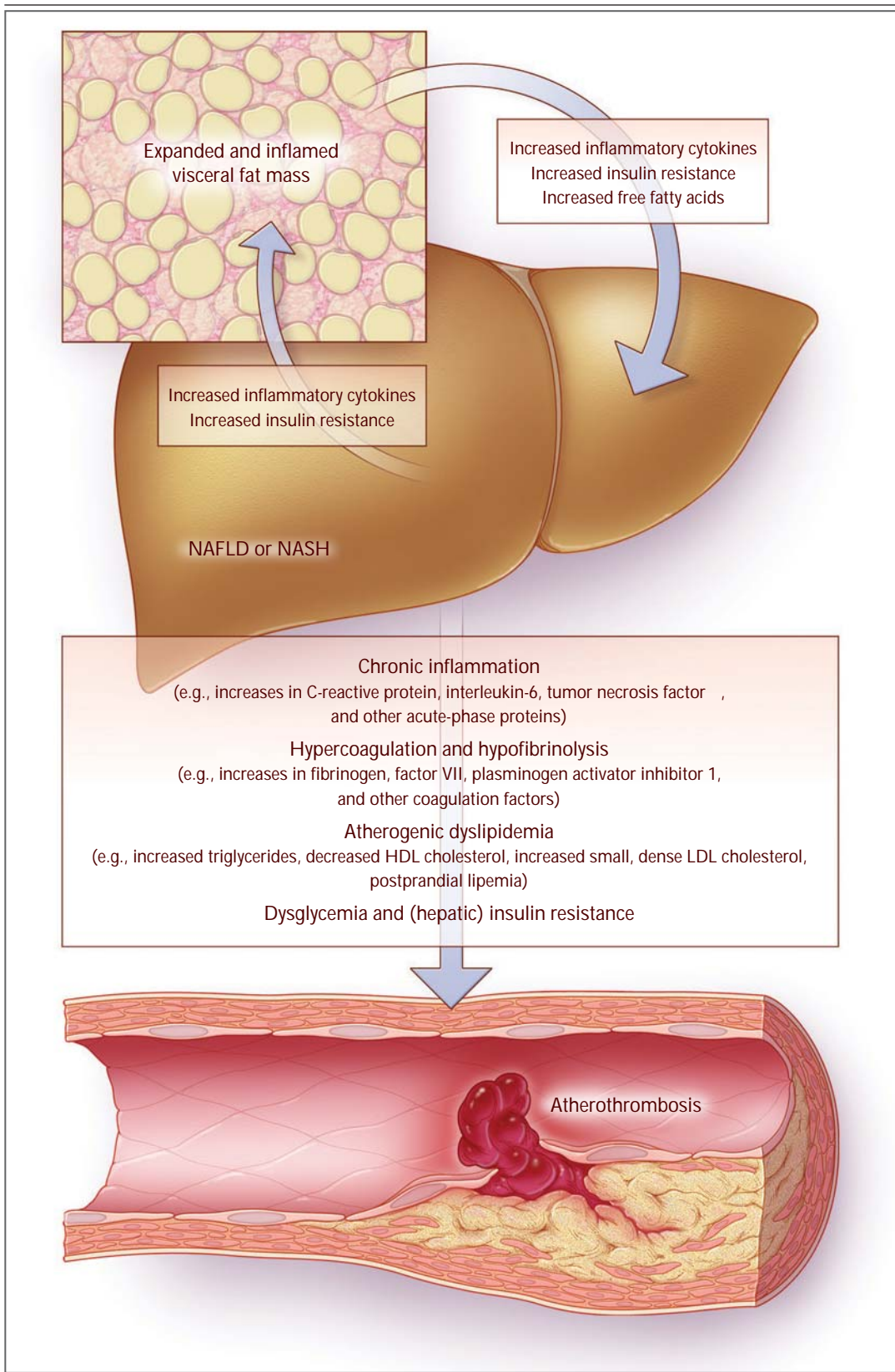
study is needed to determine whether nonalcoholic fatty liver disease poses an independent risk above and beyond known cardiovascular risk factors. Although the evidence for this is suggestive, too few studies have been carried out and they have not been methodologically rigorous. Additional large-scale prospective studies of a more extensive panel of known risk factors are needed to draw firm conclusions about any independent hepatic contribution to the increased cardiovascular risk observed among patients with nonalcoholic fatty liver disease.

Putative Mechanisms Linking Nonalcoholic Fatty Liver Disease to Cardiovascular Disease

From a pathophysiological perspective, there are two key questions that should be addressed. First, is nonalcoholic fatty liver disease associated with cardiovascular disease as a consequence of the shared risk factors, or does nonalcoholic fatty liver disease contribute to cardiovascular disease independently of these factors? Second, is the risk of cardiovascular risk also increased in patients with simple steatosis, or is the necroinflammatory milieu of nonalcoholic steatohepatitis a necessary proatherogenic stimulus?

The close correlations among nonalcoholic fatty liver disease, abdominal obesity, and insulin resistance make it extremely difficult to distinguish the precise causal relationships underlying the increased risk of cardiovascular disease among patients with nonalcoholic fatty liver disease.

As shown in Figure 2, the biologic mecha-



nisms potentially responsible for accelerated atherogenesis in nonalcoholic fatty liver disease probably have their origin in the expanded visceral adipose tissue, with the liver being both the target of the resulting systemic abnormalities and a source of proatherogenic molecules that amplify the arterial damage.

Visceral Obesity, Inflammation, and Insulin Resistance

Expanded and inflamed visceral adipose tissue releases a wide array of molecules potentially involved in the development of insulin resistance and atherosclerosis, including free fatty acids, interleukin-6, tumor necrosis factor (TNF- α), monocyte chemoattractant protein 1 (also known as CC chemokine ligand 2), and other proinflammatory cytokines.⁴⁵⁻⁴⁹ These cytokines may derive from adipocytes themselves, infiltrating macrophages, or both.⁴⁵⁻⁴⁹ As reviewed in detail elsewhere,^{47,49} the resulting adipose-tissue inflammation is one of the earliest steps in the chain of events leading to insulin resistance, especially in obese and overweight persons. Activation of proinflammatory pathways is mediated by cytokine receptors and pattern-recognition receptors, including toll-like receptors and receptors for advanced glycation end products, which are gatekeepers of the innate immune system.^{47,49,50} These pathways converge on two main intracellular transcription factor–signaling pathways — namely, the nuclear factor κ B (NF- κ B) pathway, which is activated by the inhibitor of NF- κ B kinase beta, and the c-Jun N-terminal kinase (JNK) pathway.⁴⁶⁻⁴⁹ Experimental findings in mice indicate that the activation of JNK 1 in adipose tissue can translate into insulin resistance within the liver.⁵¹

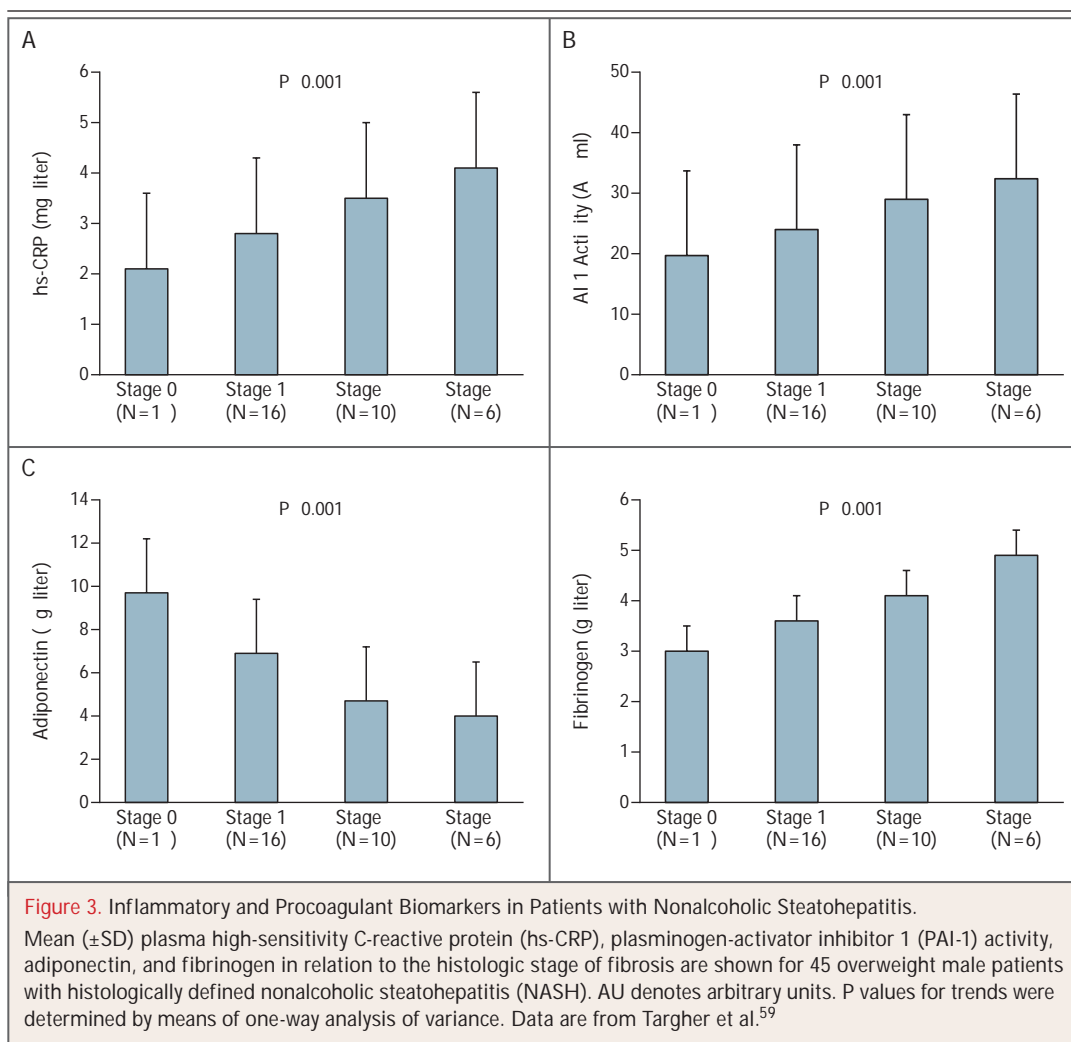
Some evidence suggests that in lean persons, insulin resistance may be dissociated from adipose-tissue inflammation in the earliest phases, and this dissociation seems to be due mainly to cellular lipid accumulation in skeletal muscle and inhibition of the insulin-signaling cascade.⁵² Insulin resistance in skeletal muscle is in turn associated with hyperinsulinemia in peripheral and portal veins, which promotes hepatic insulin resistance and hepatic steatosis, at least in part by inducing hepatic lipogenesis mediated by sterol regulatory element-binding protein 1c, and by inhibiting fatty acid oxidation.^{52,53}

Inflammation, Coagulation, and Disordered Lipid Metabolism

Hepatic steatosis results from increased hepatic uptake of free fatty acids derived mainly from the hydrolysis of adipose-tissue triglycerides (increased because of insulin resistance) but also from dietary chylomicrons and hepatic lipogenesis.^{1-4,46-49} Insulin resistance is a pathogenic factor in the development and progression of nonalcoholic fatty liver disease^{1-4,46-49} and also plays a major role in the development of the metabolic syndrome and cardiovascular disease.⁵⁴

In the presence of increased free fatty acid flux and chronic, low-grade inflammation, the liver is again both the target of and a contributor to systemic inflammatory changes. Activation of the NF- κ B pathway in the liver of patients with nonalcoholic steatohepatitis leads to increased transcription of several proinflammatory genes that amplify the systemic, low-grade inflammation.^{48,49} Hepatic steatosis is associated with increased production of interleukin-6 and other proinflammatory cytokines by hepatocytes and nonparenchymal cells, including Kupffer cells and hepatic stellate cells.⁴⁶⁻⁴⁹ Increased intrahepatic cytokine expression results from local activation of the NF- κ B pathway, as mediated by hepatocellular damage and fat-derived factors, and is likely to play a key role in the progression of nonalcoholic fatty liver disease⁴⁶⁻⁴⁹ and cardiovascular disease.^{4,5}

As recently reviewed in detail,⁵⁵ some studies have shown that a number of the genes involved in fatty acid metabolism, lipolysis, monocyte and macrophage recruitment, coagulation, and inflammation are overexpressed in patients with nonalcoholic fatty liver disease. Moreover, in a number of case–control studies, circulating levels of several inflammatory markers (e.g., C-reactive protein, interleukin-6, monocyte chemoattractant protein 1, and TNF- α), procoagulant factors (e.g., plasminogen activator inhibitor 1 [PAI-1], fibrinogen, and factor VII), and oxidative stress markers (e.g., oxidized low-density lipoprotein cholesterol, thiobarbituric acid–reacting substances, and nitrotyrosine) are highest in patients with nonalcoholic steatohepatitis, intermediate in those with simple steatosis, and lowest in control subjects without steatosis, and the differences are independent of obesity and other potentially confounding factors.⁵⁵ Notably, some studies also



showed a strong, graded relationship between intrahepatic messenger RNA expression of C-reactive protein, interleukin-6, or PAI-1 and the severity of histologic changes in patients with nonalcoholic fatty liver disease.⁵⁶⁻⁵⁸ Recently, we also reported that men with nonalcoholic steatohepatitis had higher plasma high-sensitivity C-reactive protein, fibrinogen, and PAI-1 activity levels and lower adiponectin levels than did overweight men without steatosis but with similar levels of visceral adiposity, suggesting that nonalcoholic steatohepatitis can contribute to a more atherogenic risk profile over and above the contribution of visceral adiposity.⁵⁹ This hypothesis was supported by the strong, graded relationships of these plasma inflammatory and procoagulant markers with the histologic severity of

nonalcoholic steatohepatitis, independently of age, visceral adiposity, and other metabolic abnormalities (Fig. 3).⁵⁹

The atherogenic role of hepatic necroinflammation, which is a feature of nonalcoholic steatohepatitis, is supported by the observation that cardiovascular risk is greater among patients with nonalcoholic steatohepatitis than among those with simple steatosis^{24,26-29} and by the observation that the risk of incident cardiovascular events is strongly associated with elevated serum liver enzyme levels — a marker of hepatic necroinflammation. We have also found that patients with nonalcoholic steatohepatitis and those with chronic viral hepatitis both have markedly greater carotid-artery intimal medial thickness than do healthy control subjects, which is consistent

with the hypothesis that liver inflammation plays a role in the pathogenesis of cardiovascular disease.⁶⁰

Ample evidence indicates that nonalcoholic fatty liver disease, especially in its necroinflammatory form (nonalcoholic steatohepatitis), can exacerbate both hepatic and systemic insulin resistance and promote the development of atherogenic dyslipidemia,^{3-5,10,47,48} thus favoring progression of cardiovascular disease. Finally, nonalcoholic fatty liver disease may also contribute to cardiovascular risk through abnormal lipoprotein metabolism, especially during the postprandial phase.^{61,62}

Further research is required to define the major sources of some proinflammatory and procoagulant mediators (i.e., to determine the relative contributions of visceral adipose tissue and the liver itself), as well as to uncover other specific mechanisms by which nonalcoholic fatty liver disease and nonalcoholic steatohepatitis may contribute to the development and progression of cardiovascular disease.

Conclusions

Nonalcoholic fatty liver disease has emerged as a growing public health problem worldwide. Increases in morbidity and mortality from cardiovascular disease are probably among the most important clinical features associated with nonalcoholic fatty liver disease. To date, there is a growing body of evidence suggesting that cardiovascular disease is the leading cause of death in patients with advanced nonalcoholic fatty liver disease and that nonalcoholic fatty liver disease is associated with an increased risk of incident cardiovascular disease that is independent of the risk conferred by traditional risk factors and components of the metabolic syndrome. Although additional research is required to draw a definitive conclusion, these observations raise the possibility that nonalcoholic fatty liver disease — especially its necroinflammatory variant, nonalcoholic steatohepatitis — not only is a marker of cardiovascular disease but also may be involved in its pathogenesis. This process may occur through the systemic release of proatherogenic mediators from the steatotic and inflamed liver or through the contribution of nonalcoholic fatty liver disease itself to insulin resistance and atherogenic dyslipidemia, which are important risk factors for cardiovascular disease.

The treatment strategies for nonalcoholic fatty liver disease and cardiovascular disease are similar, aimed primarily at reducing insulin resistance and modifying the associated cardiometabolic risk factors.^{1-5,63} Pharmacotherapy for nonalcoholic fatty liver disease should probably be reserved for patients with nonalcoholic steatohepatitis who are at highest risk for disease progression. The lack of data from large, randomized, controlled trials with both histologic follow-up and cardiovascular end points makes it difficult to offer definitive recommendations regarding the treatment of nonalcoholic steatohepatitis. Current recommendations are limited to weight reduction by means of diet and exercise and to the treatment of individual components of the metabolic syndrome with the use of therapies that may have beneficial hepatic effects, including bariatric surgery for obesity, insulin sensitizers (metformin and thiazolidinediones) for type 2 diabetes, and drugs directed at the renin–angiotensin–aldosterone system to control hypertension.^{4,63-66} Pioglitazone is probably the thiazolidinedione of choice, since most of the evidence supporting a beneficial effect of this class of drugs on nonalcoholic steatohepatitis comes from studies of pioglitazone. Unlike rosiglitazone, pioglitazone has not been associated with an increased risk of cardiovascular events.^{67,68} There is no convincing evidence that lipid-lowering agents, including statins, are beneficial for patients with nonalcoholic steatohepatitis; however, they can be safely prescribed for conventional indications, such as diabetes and high cardiovascular risk, since there is no evidence that patients with preexisting nonalcoholic fatty liver disease are at increased risk for statin-induced idiosyncratic hepatotoxicity or that statins are associated with an increased frequency of hepatic steatosis or serum alanine aminotransferase abnormalities in these patients.⁶⁹ Preliminary evidence also supports a role for antioxidants, anti-cytokine agents, and hepatoprotectants, including bile acids^{4,70}; however, there are insufficient data to either support or refute the use of these agents as standard therapy for patients with nonalcoholic fatty liver disease.

It is not known whether ameliorating nonalcoholic fatty liver disease will ultimately prevent or slow the development and progression of cardiovascular disease. Moreover, the prognostic value of nonalcoholic fatty liver disease in cardiovascular risk stratification remains debatable.

Nevertheless, the strong association between nonalcoholic fatty liver disease and cardiovascular risk deserves particular attention in view of its potential implications for screening and surveillance strategies in clinical practice. The current body of evidence argues for careful monitoring and evaluation of the risk of cardiovascular disease in all patients with nonalcoholic fatty liver disease. Such patients, especially those with nonalcoholic steatohepatitis, are candidates not only for early treatment of their liver disease but also

for early and aggressive treatment aimed at their associated cardiovascular risk factors, because many patients with more severe forms of nonalcoholic fatty liver disease will have major cardiovascular events and will ultimately die from cardiovascular disease before advanced liver disease develops.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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