

# Cardiovascular disease in patients with non-alcoholic fatty liver disease

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**Title:** Coronary artery disease and cardiovascular outcomes in patients with non-alcoholic fatty liver disease

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## Summary

As it affects almost every third individual in the general population in the Western world, non-alcoholic fatty liver disease (NAFLD) represents the most common cause of chronic liver disease and the most common cause of liver transplantation. Recently, NAFLD has gained much attention in the metabolic field. A continuously increasing amount of evidence suggests that NAFLD is strongly associated with the obesity epidemic and its complications (e.g. insulin resistance, hypertension and dyslipidemia) and precedes the manifestation of type 2 diabetes and cardiovascular disease. However, it remains a matter of debate whether the close relationship to cardiovascular disease is explained because NAFLD simply represents a manifestation of the obesity-related metabolic disorders (collectively called the metabolic syndrome) or whether NAFLD is an independent determinant of metabolic dysfunction leading to cardiovascular disease. Another intriguing issue is the fact that, while the association between NAFLD and cardiovascular disease (CVD) is undisputed, some studies fail to show a similar relationship of NAFLD to incident cardiovascular events.

A study by Wong et al [1] addressed these 2 issues by prospectively following 612 consecutive patients who were first screened for fatty liver by ultrasonography and then underwent a coronary angiogram. Significant (defined as  $\geq 50\%$  stenosis

in at least one coronary artery) coronary artery disease was present in 84.6% of those with fatty liver and 64.1% of those without, which confirmed a strong association between fatty liver and coronary artery disease. After adjustment for many demographic and metabolic factors in a multiple regression analysis, fatty liver and serum alanine aminotransferase levels remained independently associated with coronary artery disease. The patients with coronary artery disease were then followed for the occurrence of a cardiovascular event, defined as cardiovascular death, non-fatal myocardial infarction and the need for further coronary intervention. After a mean follow-up of about 22 months, there was no difference in the rate of events between patients with and without fatty liver. The authors concluded that fatty liver is an independent determinant of coronary artery disease; however, it cannot be used as a marker to predict clinical events in patients with established coronary artery disease.

## Opinion

Two are the most interesting findings of this study. First, fatty liver was associated with CVD independently of several demographic and metabolic factors including gender, age, fasting glucose levels, blood pressure, serum lipids, serum creatinine, and, most importantly, waist circumference, which is a surrogate of visceral adiposity and the primary criterion of the metabolic syndrome according to the WHO classification. This finding is in line with some other studies, which showed that associations of ectopic fat accumulation in the liver with insulin resistance, type 2 diabetes and cardiovascular risk factors are stronger than the respective of visceral fat [2,3]. The data support the notion that fatty liver is probably not simply another manifestation of the metabolic syndrome, but it may itself induce or worsen insulin resistance, type 2 diabetes and CVD. In search for a possible mechanism, recent studies indicate that fatty liver may produce factors that possess signaling properties in insulin-sensitive tissues. The glycoprotein fetuin-A, for instance, is a natural inhibitor

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of the tyrosine kinase in the liver and skeletal muscle and is secreted almost exclusively from a fatty liver. Polymorphisms in the gene coding for fetuin-A, as well as its plasma levels were found to be related to type 2 diabetes and cardiovascular events in humans [4-7]. There are also other liver (but not exclusively fatty liver) - derived factors demonstrating similar effects, such as retinol-bound protein 4 [8] and sex hormone-binding globulin [9], the relevance of which remains to be established.

The second important finding of this study is the lack of an association of fatty liver with future cardiovascular events. There are several explanations for this intriguing finding. First, despite the clear strengths of this study, that is the rather large population and the prospective design, a type 2 error may have occurred. The follow-up period was relatively short (about 22 months) and only few cardiovascular events were noted in both groups. The authors claimed that there was no trend of increased mortality in the fatty liver group for up to 120 weeks, but even this period is not really long, not to mention that other events were not considered. Furthermore, the two groups may be heterogeneous, in terms e.g. of the medication and the intervention they undertook. The authors tested the effect of treatment statistically, but in the whole cohort and not separately in the two groups. To clarify that, stratification of the subjects in each group was needed. Most importantly, the 2 groups may have been not accurately separated. Ultrasonography is sensitive enough to detect fatty liver only when liver fat exceeds 30%, which is about 6 times the upper normal limit (5.56%). Thus, the group 'without fatty liver' may have included individuals with a high amount of liver fat. In this case, the difference between the two groups in terms of liver fat would be small and the difference in the incidence of events not significant.

If the finding is a true negative one, then the apparent conflict between the results of the present and many other studies (reviewed in [10]) should be explained. There are 2 possible explanations. First, fatty liver may be closely associated with CVD risk factors (such as inflammatory cytokines, dyslipidemia, hyperglycemia, hypercoagulation and hypofibrinolysis) and markers of subclinical cardiovascular disease (such as impaired flow-mediated vasodilatation, increased carotid-artery intima-media thickness, carotid atherosclerotic plaques), but not with incident CVD (events). Support for this notion would provide a very recent analysis from the US NHANES III, which showed in 11,371 adults followed for up to 18 years no association of NAFLD with death from CVD [11]. Nevertheless, in this study the prevalence of fatty liver was very low (up to 16.4%), thus raising questions about a possible selection bias. On the other hand, there is vast evidence for an association of fatty liver with cardiovascular risk, but only few prospective studies on the relationship of fatty liver with cardiovascular

events [10]. One could speculate that simple steatosis may be not related to cardiovascular events, but steatohepatitis or 'malignant' fatty liver may be [12]. However, evidence for such an assumption is lacking in the literature. Second, fatty liver may be related also to incident CVD, but not in patients having already advanced CVD, such as the patients in the study under consideration. If either of the above explanations applies, it has to be postulated that the occurrence of (future) events depends on factors that are largely different from the traditional cardiovascular risk factors, which are undoubtedly associated with NAFLD. This is an attractive hypothesis, which however has to be investigated in future studies. But as long as no such mechanism or factor is known, the close relationship of fatty liver with cardiovascular disease in general should not be questioned.

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