How to Disentangle Liver and Cardiovascular Outcomes in NAFLD

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Q. What are the complications of nonalcoholic fatty liver disease (NAFLD) and how frequent are they?

Nonalcoholic fatty liver disease (NAFLD), now the leading cause of liver injury worldwide, is defined by excessive fat accumulation in the liver not accounted for by at-risk alcohol intake, and is a potentially progressive condition to advanced liver fibrosis and hepatocellular carcinoma (HCC). However, there is a huge interindividual variability in the susceptibility to develop nonalcoholic steatohepatitis (NASH), the inflammatory and progressive form of this condition, and liver-related complications.

NAFLD is epidemiologically associated with obesity, insulin resistance, dyslipidemia and type 2 diabetes, the main risk factors for cardiovascular events, and independently contributes to these outcomes. Therefore, cardiovascular disease is the main determinant of morbidity and mortality even in patients with progressive NASH, until they develop cirrhosis[1,2]. This picture is further complicated by the frequent occurrence of HCC in older patients with NAFLD and type 2 diabetes, at very high cardiovascular risk, even in the absence of NASH and severe fibrosis[3].

Since it is estimated that NAFLD affects 20-40% of the general population[4], and most determinants of liver and cardiovascular outcomes are shared, currently it is difficult to identify individuals at higher risk of hepatic events amenable of treatment, for whom for example HCC surveillance may be cost-effective. Therefore, screening is currently limited to patients with advanced fibrosis at relatively low risk, with high costs and at the risk of missing many early diagnoses in patients with less severe liver damage.

Q. What is the role of genetic factors in the pathogenesis of NAFLD?

Inherited factors also play an important role in determining NAFLD predisposition. In recent years, common variants in *PNPLA3*, *TM6SF2*, *MBOAT7* and *GCKR* have been demonstrated to predispose to the full spectrum of NAFLD pathology by facilitating hepatic fat accumulation in the presence of environmental triggers. Other variants regulating inflammation and fibrogenesis then modulate liver disease progression in those at higher risk. Evidence is also accumulating that rare variants, for example mutations in *APOB* impairing very low-density lipoproteins (VLDL) secretion are involved in disease predisposition[5].

Remarkably, the genetically determined component of the susceptibility to store fat within intracellular lipid droplets in hepatocytes has now been causally linked with increased risk of NAFLD, NASH, fibrosis, and in particular

HCC[6]. What's more, the impact is maintained also in patients with other triggers of liver steatosis, such as alcohol abuse and chronic hepatitis C virus infection. The magnitude of the association is clinically relevant, as for example carriage of the *PNPLA3* I148M variant, the main genetic risk factor, has a moderate specificity to rule out NAFLD-HCC risk at the general population level, while homozygosity for this variant is enriched almost nine-fold from healthy individuals to those with HCC (from 5% to 45% in European populations). Evaluation of a larger set of genetic factors may further improve risk prediction. For example, we have reported that a simple instrument such as the sum of risk variants carried by each individual in *PNPLA3*, *TM6SF2*, *MBOAT7*, which is associated with hepatic fat in the general population, can predict HCC risk in patients with NAFLD independently of classic risk factors, including the severity of liver fibrosis[7,8]. We have recently shown that the development of a more comprehensive genetic score (GRS) based on the assessment of the weighted impact of a wider panel of genetic mutations may further refine the risk.

Q. What is the potential use of genetics in discriminating the risk of hepatic vs. the cardiovascular complications in patients with NAFLD?

An important concept is that most of these genetic factors determine a specific increase in the risk of liver disease, providing an instrument to forecast the organ-specific damage related to dysmetabolism and insulin resistance. Actually, as the mechanism underlying the association of many genetic risk variants with NAFLD encompasses the compartmentalization of fat within the hepatocytes, curtailing the secretion within VLDL into the circulation, these reduce at the same time the risk of cardiovascular disease by protecting against dyslipidemia. This phenomenon is more marked for the variants in *TM6SF2* and mutations in *APOB*, for example, which increase the risk of liver disease but protect from cardiovascular events, but it is also true for the *PNPLA3* variant in obese individuals[9]. It is thus more likely that individuals with an unfavorable genetic risk profile may develop HCC before succumbing or having significant disability due to cardiovascular events.

In the future, evaluation of the genetic risk profile (GRS) may therefore be exploited to stratify the risk of liver-related over cardiovascular complications of the disease, and to guide hepatocellular carcinoma surveillance. Prospective studies are currently in progress (e.g. the Serena study sponsored by the Italian Association for the Study of the liver – AISF) to test the feasibility and efficacy of this approach.

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