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Non-alcoholic fatty liver disease, a new and growing risk indicator for cardiovascular disease

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is a multisystem disease affecting extra-hepatic organs and regulatory pathways. It is characterised by the presence of ectopic fat in the liver which cannot be explained by alcoholic consumption.[1] Non-alcoholic steatohepatitis (NASH) is an advanced form of NAFLD, where steatosis coexists with hepatocellular injury and inflammation. Out of 100 patients with NAFLD about 20 patients will develop NASH. When progressing even further it leads to hepatic necrosis, fibrosis, cirrhosis and even hepatocellular carcinoma.[2,3] Is has been estimated that about one billion individuals worldwide have NAFLD with a prevalence of 20–30% in Western countries, making it the most frequent cause of liver disease in the Western world. These numbers are rapidly increasing in parallel with the global obesity pandemic.[4]

The progression of liver injury is a slow process, as is the case with atherosclerosis. Simple steatosis is considered to be a non-progressive condition. When present, NAFLD increases overall mortality by at least 35% and is associated with most risk factors of cardiovascular disease (CVD): obesity, type 2 diabetes mellitus, insulin resistance and the metabolic syndrome.[4] In particular, (central) obesity is highly predictive of hepatic steatosis and disease progression, while in morbid obesity almost all patients present with steatosis and more than one-third have NASH.[3]

Research has shown that NAFLD is associated with CVD, particularly in patients with NASH. Not only do cardiovascular (CV) events occur more frequently, but also CV mortality is increased twofold as compared to the general population, making CVD the number one cause of death for NAFLD followed by malignancies and, only then, liver disease.[5,6] Despite this association, NAFLD patients are currently not screened for CVD on a regular basis. More awareness is needed so that, ideally, each patient is referred upon (or even before) their diagnosis for CV risk factor screening and for treatment where needed.

Association of NAFLD and CVD

NAFLD is a risk factor for the development of CVD. When simple steatosis develops the CV risk already increases by 10–35%. When evolving into NASH and eventually cirrhosis, the CV risk increases even further by 12–40% for NASH and an extra 15% for cirrhosis.[7] Research is still inconsistent as to whether this is independent of the presence of other risk factors. A recent meta-analysis using Mendelian randomization suggests a non-causal relationship and that the association is a result of confounding due to a number of common risk factors such as age, body mass index, smoking and hypertension, and may also be influenced by reverse causation. In this Mendelian randomization the genetic variant patatin-like phospholipase domain containing 3 (PNPLA3) was used as a proxy for liver fat content and was not shown to be associated with the risk of ischaemic heart disease.[8,9]

The increased risk of CVD may be caused by multiple pathophysiological mechanisms including systemic inflammation, endothelial dysfunction, systemic insulin resistance, oxidative stress, plaque formation and altered lipid metabolism.[2,8] These mechanisms result in increased atherosclerosis, cardiomyopathy, arrhythmia and valvular heart disease, and ultimately increased CV mortality. Genetic factors also seem to be involved in the pathogenesis of CVD in patients with NAFLD.[2,3,10]

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Atherosclerosis

NAFLD has been shown to increase carotid intima media thickness and coronary artery calcification, with impaired flow-mediated vasodilation and increased carotid atherosclerotic plaques independent of metabolic syndrome characteristics. Patients are not only at risk of subclinical atherosclerosis but also require more frequent percutaneous coronary interventions with worse outcomes for patients with NAFLD who experience an acute coronary syndrome.[2]

Cardiomyopathy

NAFLD is associated with an abnormal left ventricular (LV) structure and impaired diastolic function. The duration and severity of these abnormalities contributes to the increased risk of heart failure.[6] More specifically, LV wall thickness and myocardial mass are greater in patients with NAFLD and echocardiography shows a lower early diastolic relaxation velocity, higher LV filling pressure and worse absolute global longitudinal strain.[2]

Valvular heart disease

The presence of aortic valve sclerosis and mitral annulus calcification is also linked with NAFLD, independently of established CVD risk factors.[1]

Cardiac arrhythmias

NAFLD seems to be linked with prolonged QTc interval, i.e. it is a powerful predictor of ventricular arrhythmias and sudden cardiac death,[1] and there is growing evidence of an increased risk for atrial fibrillation. NAFLD has also been shown to be associated with autonomic dysfunction, which is another risk factor for arrhythmias.[2]

While other diseases are automatically referred for CVD screening, patients with NAFLD are only seen when CVD is already present. Figure 1 illustrates the diseases with a known association with CVD, where preventive cardiology should always be included. This contributes to the concept of lifelong CVD prevention, where preventive cardiology is considered in every person at every stage of life, starting at conception and ending at death (or even post-mortem). Only in this way can we truly reduce the burden of CVD.

Genetic factors

Genetic factors play a key role in the susceptibility and progression of NAFLD. The most consistent genetic associations are seen with the PNPLA3 I148M gene and the transmembrane 6 superfamily member 2 (TM6SF2) E167K gene. Both of these genes are involved in lipid droplet remodelling and very low-density lipoprotein secretion. These findings suggest that hepatocellular accumulation of neutral lipids is harmful for the liver.[11] This increase of hepatic fat is likely causally related to liver fibrosis, independent of inflammation, and also seems to modestly increase insulin resistance and the risk of type 2 diabetes mellitus.[12] Other data also suggest an association with proprotein convertase subtilisin kexin type 9 (PCSK9), which is one of the key regulators of the low-density lipoprotein receptor. It could play a key role in the metabolism of triglyceride-rich lipoproteins. Circulating PCSK9 is correlated with the severity of steatosis, independently of metabolic confounders and liver damage.[10,13]

More research is needed in this area to specify the exact role of these (and other) genetic variants.

Diagnosis

The gold standard for the diagnosis of NAFLD is a liver biopsy, mainly for diagnosing NASH and staging fibrosis. However, diagnosis is often incidental on physical examination, through imaging or routine blood testing, accounting for approximately 7–11% of abnormal liver function tests.[6] Clinical features that can be associated with NAFLD are obesity, metabolic syndrome, hypertension, insulin resistance, family history of NAFLD and hepatomegaly. Elevated levels of circulating biomarkers that should be considered are aspartate aminotransferase and alanine aminotransferase, cytokeratin 18 (CK-18) fragments, apolipoproten A1, total bilirubin, hyaluronic acid, C-reactive protein, fibroblast growth factor-21, interleukin 1 receptor antagonist, adiponectin and tumor necrosis factor alpha (TNF-α). However, at present, there is no readily available biomarker that reliably differentiates between simple steatosis and NASH. Regarding imaging techniques, the abdominal ultrasound is most commonly used, followed by magnetic resonance imaging and computed tomography.[3,6]

The role of CVD prevention in the treatment of NAFLD

The prevention and treatment of NAFLD is inseparably linked with CVD prevention since common risk factors are shared. In primary prevention of NAFLD the main focus is on lifestyle modifications which include weight loss, adjusting nutrition, limiting alcohol consumption and increasing physical activity. In patients with confirmed NAFLD lifestyle, modifications are pivotal to achieve regression of fibrosis and

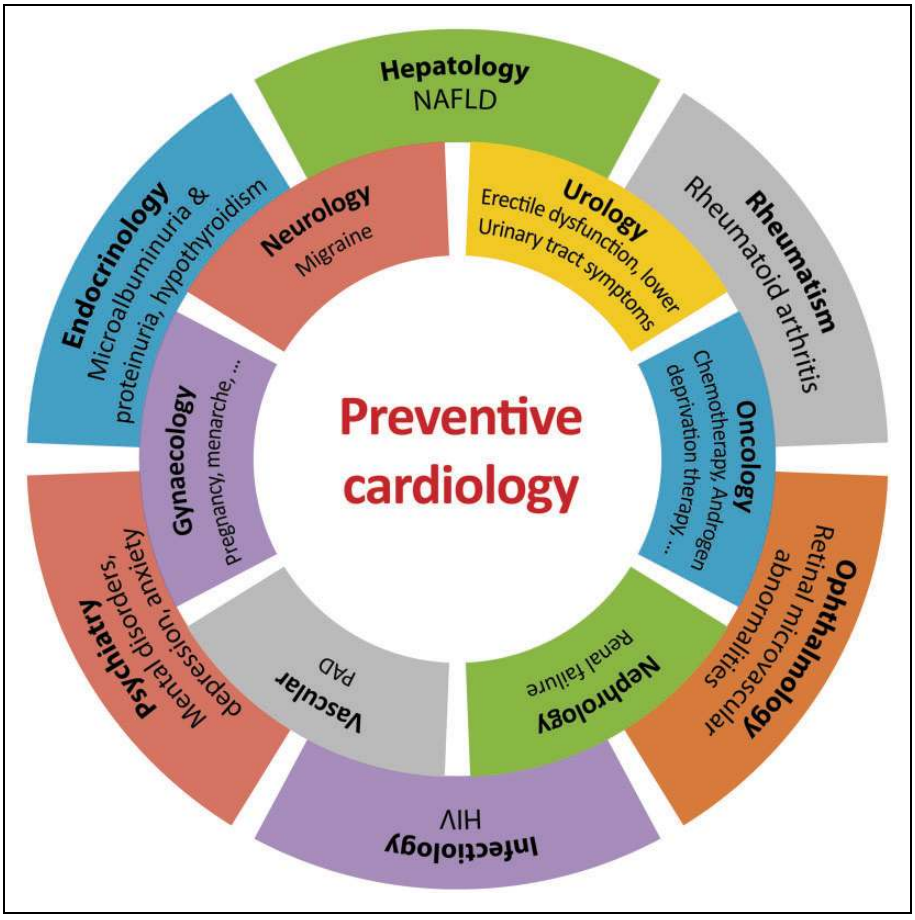

Figure 1. Overview of diseases that have a known association with cardiovascular disease (CVD). Preventive cardiology is intertwined in these disciplines and should be included in the care paths of these diseases. This contributes to the concept of lifelong CVD prevention, where preventive cardiology is considered in every person in every stage of life, starting at conception and ending at death (or even post mortem). Even though the increased risk for CVD in non-alcoholic fatty liver disease (NAFLD) is clearly demonstrated, these patients are still not spotted on the preventive cardiology radar (Please refer to references[17-31]).

resolution of steatohepatitis.[2] A recent study has shown that a Mediterranean/low-carbohydrate diet decreases hepatic fat content even further in comparison with a low-fat diet, with a beneficial effect on cardiometabolic risk parameters.[14]

CV risk assessment can also play a role in primary prevention. It has been shown that Framingham Risk Score correlates with the degree of fibrosis in NAFLD patients. Risk scores should be routinely included in patients with NAFLD to stratify their risk.[2]

CV risk factors should be targeted individually. Statins should be considered in dyslipidaemia as previous studies suggest that statin therapy not only reduces CV morbidity but also improves liver enzyme test results.[5] Statins also affect NAFLD itself, as research has shown an independent association between statin use and protection against steatosis, steatohepatitis (NASH) and fibrosis. This effect seems to be stronger when the PNPLA3 variant is not present.[15] Currently, statins are under-prescribed because of an unjustified fear of hepatotoxicity. The CV as well as hepatic benefits seen with statin use appear to heavily outweigh the risk of hepatic toxicity.[2] Similarly to statins, aspirin is thought to be effective against NAFLD by inhibiting the production of TNF-a and stimulating the expression of endothelial nitric oxide synthase and vascular endothelial growth factor, resulting in antioxidant activity. In hypertensive patients, angiotensin II receptor blockers (ARBs) have demonstrated a significant decrease in serum liver enzyme levels in several smaller trials. Well-designed randomised controlled trials are needed to confirm the effects of ARBs on NAFLD.[2]

Other treatments

There is currently no accepted targeted treatment of NAFLD and NASH. Treatment is focused on targeting present risk factors and co-morbidities, as mentioned

above.[3] CV risk factors can be treated through use of statins, aspirin and anti-hypertensive drugs. Insulin resistance should be treated with insulin-sensitising agents, like glucagon-like peptide-1 analogues or metformin, improving insulin sensitivity and reducing hepatic gluconeogenesis.[2] There is no approved specific treatment for the liver disease itself, although vitamin E could be used, with caution, in non-diabetic patients with NASH and fibrosis, but without cirrhosis and with no expected increased risk for prostate cancer.[3] Note, however, that long-term use of this supplement has had no significant benefit in preventing major CV events.[2]

Bariatric surgery is another effective treatment for NAFLD, leading to a significant improvement in liver histology and even disappearance of NASH, and a reduction in fibrosis. Besides the effect on NASH, bariatric surgery also reduces CV risk factors. At present, bariatric surgery is only recommended for severely obese adolescents with significant steatohepatitis in whom therapeutic lifestyle intervention has been unsuccessful.[2,3,6]

Recently various pathogenic mechanisms are being tested for the treatment of NAFLD and NASH. This includes obeticholic acid (agonism of farnesoid X receptor), which decreases insulin sensitivity and hepatic gluconeogenesis but increases total serum cholesterol and low-density lipoprotein. Another potential mechanism is cenicriviroc, a chemokine receptor 2 and 5 antagonist, which promotes anti-inflammatory and antifibrotic effects in the liver. A recent study showed significant improvement in fibrosis without worsening NASH. Elafibranor, a dual peroxisome proliferator-activated receptor α/δ agonist, has also shown promising results in phase 2 trials by reducing fibrosis and improving liver transaminases and cardiometabolic parameters. There are many other mechanisms being investigated such as the inhibition of galectin-3 protein or the antagonism of toll-like receptors. Emerging data are promising and further updates from ongoing clinical trials are eagerly awaited.[2,16]

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