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Research Article

How Can Fatty Liver Lead to Liver Cancer and How Can We Simply Assess It?

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Abstract

Background: In 2016, more than 1.9 billion adult populations were overweight, 650 million of them were obese, which represents around 13% of the world's adult population. Liver steatosis has become the most common chronic liver disease in developed countries. In most cases, non-alcoholic fatty liver disease (NAFLD) is a benign and reversible liver disorder. Under certain circumstances, the disease may result through the image of non-alcoholic steatohepatitis (NASH) and hepatic fibrosis to liver cirrhosis with all known negative consequences, until formation of hepatocellular carcinoma (HCC).

Methods: We searched from the Pubmed, Google Scholar and Research gate database and looked for keywords NAFLD, steatohepatitis, steatohepatitic variant of HCC.

Results: The pathogenesis of NAFLD and metabolic syndrome seems to have common pathophysiological mechanisms. Although liver biopsy remains the gold standard for NAFLD diagnosis, it seems that new diagnostic procedures and scoring systems are emerging that could non-invasively distinguish simple steatosis from NASH.

Conclusion: A higher number of metabolic syndrome risk factors have been registered in patients with steatohepatitic HCC variant. HCC patients with clinical symptoms have a very poor prognosis (median 5-year overall survival is between 0-10%); on the other hand, patients with asymptomatic HCC detected by screening show a higher survival rate, with a total 5-year survival of more than 50 % due to radical treatment. Simple and unassuming diagnostic methods can be used in a wide range of patients, thus systematically preventing the development of diseases and related disorders. Early diagnosis and risk stratification are essential for effective treatment management.

Keywords: NAFLD; Steatohepatitis; Liver Cancer; Elastography; Obesity

Abbreviations

AAR: Aspartate Aminotransferase/Alanine Aminotransferase Ratio; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; AUROC: Area under the Receiver Operating Characteristic Curve; CT: Computed Tomography; FLI: Fatty Liver Index; FIB-4 Fibrosis 4 Scoring System; HBV: Chronic Hepatitis B; HCC: Hepatocellular Carcinoma; HCV: Chronic Hepatitis C; IL-6: Interleukin-6; MRI: Magnetic Resonance Imaging; MRE: Magnetic Resonance Elastography; NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; SWE: Shear Wave Elastography; TE: Transient Elastography; TNF-α: Tumour Necrosis Factor-α; USE: Ultrasound Elastography; USG: Ultrasonography.

Introduction

The global prevalence of obesity nearly tripled between 1975 and 2016. As the incidence of obesity in the population increases, the number of patients with liver steatosis also increases.

The aim of this article is to assess the diagnostic options in monitoring patients with fatty liver disease and to explain the pathological mechanisms that can lead to the development of liver cancer.

Search strategy and selection criteria

We searched from the Pubmed, Google Scholar and Research gate database and looked for keywords NAFLD, steatohepatitis, steatohepatitic variant of HCC.

Pathogenesis

The pathogenesis of non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome appears to have common pathophysiological mechanisms such as the role of insulin resistance, lipid peroxidation and oxidative stress, pro-inflammatory cytokines and adipokines. Abdominal obesity, atherogenic dyslipidemia, hypertension, elevated plasma glucose, a prothrombotic state, and a pro-inflammatory state are risk factors that appear to be crucial for the development and later progression of NAFLD [1]. Intestinal microbiota has also been recognized as one of the key factors in

the pathogenesis of NAFLD. It has an impact on the absorption and disposal of nutrients in the liver, but also stimulates hepatic inflammation by supplying toll-like receptor ligands, which can stimulate liver cells to produce pro-inflammatory cytokines [2].

NAFLD, even without fibrosis, provides a nourishing environment for the development of hepatocellular carcinoma (HCC) with insulin resistance and steatosis, providing the inflammation, adipokines, oxidative stress and lipotoxicity required for hepatocellular carcinogenesis [3]. In a study of 1500 patients, non-alcoholic steatohepatitis (NASH) was found to be the third most common risk factor for HCC development [4]. The development of HCC in NASH cirrhosis ranges from 2.4% and 12.8% in the period of 3.2 and 7.2-year period [5]. The pathway from cirrhosis to liver cancer involves multiple genetic and epigenetic events that result in the transformation of hepatocytes to first dysplastic and then directly neoplastic clones [6]. 80% of this time occurs in the setting of cirrhotic liver, where mitotic signaling pathways are activated, as well as increased oxidative stress, activation of nuclear factor-kB, and also the influence of immunological alterations leading to dysplastic nodule formation. Forthright malignancy arises after exposure to additional genomic insults, including point mutations, chromosomal arm gains or losses, or aberrant promoter methylation of key genes. In particular, this is accomplished by activation of telomerase reverse-transcriptase, vascular endothelial growth factor and platelet-derived growth factor, leading to unabated growth and absent apoptosis [7]. Obese patients are in a chronic inflammatory state that correlates with IR as elevation of both tumour necrosis factor-α (TNF-α) and monocyte chemotactic protein-1 which causes impairment of adipocyte insulin sensitivity [8,9]. Inflammation and activation of several immune pathways in obese patients affect hepatic lipid metabolism, leading to hepatic injury [10]. Hepatic steatosis is associated with increased production of interleukin-6 and other pro-inflammatory cytokines by hepatocytes and non-parenchymal cells, including Kupfer cells [11,12]. This overexpression of cytokines is likely to play a key role in the progression of NAFLD and cardiovascular disease as well. Several case control studies have shown that inflammatory markers also reflecting inflammation in atherosclerosis patients, such as CRP, interleukin-6 (IL-6), and fibrinogen were highest in NAFLD patients, moderate in simple steatosis patients and lowest in control subjects without steatosis [13]. NASH with continuous insulin resistance leads to high levels of TNF-α, IL-6, as well as a low levels of adiponectin [14]. IL-6 is mainly produced by hepatic stellate cells that are responsible for hepatic fibrosis [15]. As well the high levels of IL-6 have been shown in obesity and weight loss is likely to reduce IL-6 and TNF-α levels. Elevated levels of TNF-α and IL-6 in patients with IR induce inflammation as well as fibrosis and may stimulate NASH severity as well as hepatic carcinogenesis [16,17].

The correlation of HCC and NAFLD

70-90% of all detected HCC occurs in patients with chronic liver disease or cirrhosis [18]. Non-alcoholic steatohepatitis (NASH) is a well-known cause of cirrhosis and is increasingly associated with the development of HCC. Recent data suggest that the annual incidence is 2.6-2.7%, compared with 4 to 4.7% in cirrhosis with hepatitis C [19, 20]. The development of HCC in the course of chronic liver disease without cirrhosis is not typical and can be usually observed in patients with chronic hepatitis B and hepatitis C, particularly in the fibrosis stage [21]. A Japanese study of 1,168 patients who underwent hepatic resection for HCC revealed 8 cases of HCC in NASH liver, 6 of which were non-cirrhotic patients. All patients had at least one metabolic disease, including obesity, type II diabetes, hypertension or hyperlipidemia [22]. Some of the NASH shaping criteria are becoming increasingly common and thus correlate with HCC. Characteristics of metabolic syndrome, such as obesity and diabetes mellitus, are strongly associated with NASH and increase in prevalence. Obesity may have an effect on disease progression, as confirmed by a large prospective study demonstrating the link between weight gain and overall cancer mortality [23]. Obesity and diabetes mellitus closely correlated with an increased risk of several malignancies, specifically HCC [24-27]. In people with chronic hepatitis B (HBV) or C (HCV), the coexistence of obesity has shown an increased risk of HCC more than 100 times [28]. It looks like it is truly possible that the associations between obesity/diabetes and HCC are related to the progression of non-alcoholic fatty to cirrhosis. NAFLD and NASH may progress to cirrhosis and can cause liver failure in 3-15% [29]. In recent decades, there are many reports of HCC in the NAFLD setting [30-33]. A new variant of steatohepatitic HCC has also been described. Histopathologically, there are some common features like steatohepatitis (inflammation, hepatocyte ballooning, Mallory-Denk bodies, and pericellular fibrosis), and first appeared in the HCV-related HCC patient population [34]. The steatohepatitic HCC variant patients showed higher number of metabolic syndrome risk factors [35]. HCC associated with NASH has become the major contributor to an increased HCC incidence in the United States [36]. The multifactorial features of NASH and its progression determine the pathogenic complexity of HCC development in a steatotic microenvironment. The association between NASH and HCC represents a growing area of study and concern as metabolic syndrome and obesity rates continue to rise. Also, the importance of intestinal microbiota in NASH progression, registered by the study of Yoshimoto., *et al.* has shown that senescent hepatic stellate cells may be critical for the transformation of steatotic hepatocytes into malignant cells [37]. Of all common cancers in the US, HCC is the only tumour with increasing mortality [38]. Patients with NASH have a 20%–50% risk of developing progressive inflammation or liver fibrosis and have a 2%–20% 5-year cumulative incidence of hepatocellular carcinoma [39-41].

Diagnostic methods

The diagnosis of NAFLD is established as a four-step approach:

Hepatic steatosis (by imaging or histology); alcohol consumption is ruled out (not regularly consume excessive alcohol >30 g/day for males or 20 g/day for females); there are no competitive

aetiologies; and no other causes for chronic liver disease have been identified [42].

Liver biopsy belongs to invasive diagnostic methods and has a number of disadvantages for the patient, such as fear of procedure and anaesthesia or pain after taking the sample. Ultimately, the high prevalence of NAFLD implies that liver biopsy is not a viable tool for widespread NAFLD risk stratification. In order to avoid liver biopsy, a highly invasive procedure, new simple and non-invasive diagnostic methods are sought to diagnose advanced liver fibrosis. The ability of various diagnostic tests was evaluated by analyzing the area under the receiver operating characteristic curve (AUROC). AUROC of 1.0 indicates perfect discrimination, while AUROC of 0.5 indicates a lack of discrimination. A value of 0.90–1.0 has been classified as excellent, a value of 0.80–0.90 as good, a value of 0.70–0.80 as fair, and a value < 0.70 as poor [43].

Fatty liver index (FLI)

The FLI has limited applicability to quantify liver steatosis, but has been confirmed by abdominal ultrasonography in several populations with an AUROC curve between 0.930 and 0.840 in western countries for the identification of fatty liver disease [44,45].

Cheng., *et al*. and Rogulj., et al. suggested that the FLI may also be the optimal diagnostic method for metabolic syndrome in terms of sensitivity and specificity with the AUROC curve of 0.871 and 0.875 [46,47].

FLI was calculated using the following formula (48): FLI = (e 0.953 ∗ loge (TG) + 0.139 ∗ BMI + 0.718 ∗ loge (GGT) + 0.053 ∗ WC − 15.745)/(1 + e 0.953 ∗loge (TG) + 0.139 ∗ BMI + 0.718 ∗ loge (GGT) + 0.053 ∗ WC − 15.745) ∗ 100.

AAR

The aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio (AAR), also known as De-Ritis ratio, is an easy-to-use blood test. With elevated liver fibrosis, ALT typically decreases, while AST remains stable or increases, and as a result the AAR increases [49,50]. A cut-off >1 for the AAR is identified as a diagnostic test for cirrhosis [51]. However, in NAFLD patients, AAR <0.8 had high predictive ability to exclude advanced fibrosis with AUROC of 0.83 [50].

NAFLD fibrosis score

According to Angulo., *et al.* a score below –1.455 (low cut-off) excludes advanced fibrosis, while a score above 0.676 (high cut-off) predicts advanced fibrosis. Scores between these values are defined as indeterminacy [52]. Shah., *et al.* found that the AUROC curve for NAFLD fibrosis score was 0.768 [53]. Cichoż-Lach., *et al.* found that the AUROC score was 0.865. NAFLD fibrosis score has relatively high sensitivity and specificity of 96.00 % and 83.87 respectively [54]. NAFLD fibrosis score is capable of excluding advanced liver fibrosis and significantly reducing the incidence of liver biopsies in NAFLD patients. It has also been used to predict mortality (all causes, liver, and cardiovascular) in NAFLD patients [55].

The scoring system produces a score - <1.45 has a negative predictive value of over 90% for advanced liver fibrosis of multiple aetiologies. A score >3.25 has a positive predictive value of 65% for advanced fibrosis with a specificity of 97% [49,56].

Fibrosis 4 scoring system (FIB-4)

FIB-4 is one of the simplest non-invasive scores and has been validated in many cohort studies [57,58].

According to a study by Yen., *et al*. published in 2018, FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. The results of the AUROC analysis distinguishing cirrhosis (F4) from non-cirrhosis (F0–F3) were 0.85. The optimal FIB-4 cut-off values for the diagnosis of cirrhosis were 1.4 in patients with normal AST and 2.2 in higher AST levels [59]. The scoring system produces a score - <1.45 has a negative predictive value of over 90% for advanced liver fibrosis of multiple aetiologies. A score >3.25 has a positive predictive value of 65% for advanced fibrosis with a specificity of 97% [49,56].

Imaging examination of liver parenchyma

Ultrasonography (USG)

Steatosis is reported to be detectable by sonography if more than 20% of hepatocytes contain histologically visible fat droplets, with a reported sensitivity of 79.7% and specificity of 86.2% [60]. Steatosis is manifested as increased echogenicity and ray suppression, islands of normal liver tissue within the sea of hepatic steatosis. Liver USG is often the first imaging modality used for the clinical evaluation of fatty liver, especially for screening of suspected NAFLD, due to its lack of invasiveness, widespread availability and relatively low cost. Conventional sonography cannot surely distinguish steatosis and steatohepatitis or stage fibrosis, but may lead to other imaging and diagnostic methods [61].

Ultrasound elastography (USE)

USE quantitatively evaluates liver stiffness to make non-invasive evaluation of liver fibrosis and NASH clinically possible. It can provide information on the presence and degree of fibrosis. USE can be broadly categorized into two methods; Transient elastography (TE) as a non-imaging ultrasound-based technique; and imaging-based elastographic techniques such as strain elastography and shear wave elastography (SWE).

TE measures hepatic elasticity by quantifying shear wave speed with pulse-echo ultrasound from low frequency vibrations transmitted to the liver [62]. It is able to detect liver cirrhosis with high accuracy and liver stiffness measurements correlate with liver fibrosis stages. The AUROCs for the detection of F ≥ 2 and F ≥ 3 were 0.84 and 0.93, respectively, and the sensitivity and specificity for F

≥ 3 were 91% and 75% at a cut-off of 7.9 kPa. Lower TE seems to reliably exclude advanced fibrosis [63].

SWE is an ultrasound-based technique that provides real-time visualization of the viscoelastic properties of soft tissue. A recent study showed that the SWE was essentially independent of hepatic liver fat content and was not comparable to a subjective evaluation of liver echogenicity in terms of hepatic steatosis evaluation [64].

Computed tomography (CT)

CT has a better specificity for the diagnosis of NAFLD than the US. To estimate the NAFLD, CT must demonstrate reduced attenuation in the liver parenchyma, which correlates with the degree of intrahepatic fat accumulation [65]. The recent Dual-energy CT study by Lamb., *et al*. showed its potential for valuing steatosis [66].

Magnetic resonance imaging (MRI) and magnetic resonance elastography (MRE)

The sensitivity and specificity of MRI for detecting histologically confirmed steatosis are almost 90.0% and 91% [67]. MRI is considered to be one of the most accurate imaging methods for quantifying and evaluating liver steatosis. MRE is MRI modification. It estimates the degree of fibrosis in the liver, which is manifested as an increase in liver stiffness. At a high specificity of 87.1 % and sensitivity of 89.7 %, it can differentiate fibrosis between F ≥ 2 and F1. Similarly, severe F3 fibrosis can be segregated from liver cirrhosis with sensitivity of 100% and specificity of 92.2% [68]. MRI and MRE both demonstrated a very accurate liver parenchyma status, but their high cost and low regional availability do not allow sufficient clinical use.

Discussion

In 2016, over 1.9 billion adult populations were overweight, of which 650 million were obese, which represents about 13% of the world's adult population -11% of men and 15% of women. The global prevalence of obesity nearly tripled between 1975 and 2016. As the incidence of obesity in the population increases, the number of patients with liver steatosis increases. A goal of better understanding of the factors that predict those who are most at risk for HCC is essential. Patients with NAFLD are at risk of steatohepatitis and progressive liver fibrosis culminating in cirrhosis, typically for several decades. Early diagnosis and risk stratification are essential for effective management. Current imaging methods such as ultrasound, computed tomography and magnetic resonance elastography have shown that their values serve as non-invasive imaging biomarkers to asses NAFLD progression.

Conflict of Interest

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