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Non-Invasive Tests of Non-Alcoholic Fatty Liver Disease: Perspective Review

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ABSTRACT

Cirrhosis and hepatocellular carcinoma often develop from Non-Alcoholic Fatty Liver Disease (NAFLD), a progressive condition characterized by hepatic steatosis, inflammation and varying degrees of fibrosis. The increasing incidence of non-alcoholic steatohepatitis (NASH) highlights the need for effective diagnostic and treatment methods. Non-invasive tests (NITs) have emerged as promising tools for evaluating and monitoring NAFLD, offering safer and more cost-effective alternatives to invasive liver biopsies. This review focuses on the current state of NITs in NAFLD management, emphasizing their diagnostic accuracy, prognostic significance, and role in guiding treatment. NITs discussed include transient elastography, magnetic resonance imaging (MRI), magnetic resonance elastography (MRE) and serum biomarker panels such as the NAFLD fibrosis score, Fibro Test, and Enhanced Liver Fibrosis (ELF) test. Recent advancements in MRI and MRE have greatly improved the non-invasive assessment of liver fibrosis and steatosis, enhancing sensitivity and specificity for early detection and risk stratification. Additionally, combined serum biomarker panels have shown promise in predicting disease severity and progression, aiding in the identification of high-risk patients who could benefit from early intervention. By enabling prompt diagnosis, comprehensive risk assessment and monitoring of disease progression, the integration of NITs into standard clinical practice offers significant potential for improving NAFLD management. Ongoing research efforts are focused on developing new NITs and optimizing existing methods to enhance diagnostic precision and prognostic evaluation in NAFLD patients. This evolving landscape of non-invasive assessment tools could revolutionize the approach to managing this increasingly prevalent liver disease.

Keywords: Fatty liver, Liver biopsy, Transient Elastography, Serum biomarkers, Hepatic Cell Carcinoma.

INTRODUCTION

NAFLD is most common kind of chronic liver disease in adults and children's and possess a significant risk to public health [1]. Recently thirty percent of adult Asians suffer from non-alcoholic fatty liver disease [NAFLD], which is currently the most prevalent chronic liver disease affecting globally [2]. Globally, non-alcoholic fatty liver disease (NAFLD) is becoming more common and is predicted to overtake liver transplantation as the primary cause by 2030, resulting in rising healthcare system costs [3]. NAFLD includes a wide range of disease conditions, including cirrhosis, liver fibrosis,

non-alcoholic steatohepatitis (NASH), hepatocellular carcinoma (HCC), cardiovascular diseases and simple hepatic steatosis. In the United States, it has become a leading reason for liver transplants and a significant cause of hepatocellular carcinoma. However, only a small percentage of NAFLD patients will develop cirrhosis and Hepatic Cell Carcinoma [4]. Clinically, non-alcoholic fatty liver disease (NAFLD) is defined by hepatic fatty infiltration without appreciable alcohol intake or Wilson's disease, hepatitis C virus infections, steatogenic drug usage, parenteral nutrition and malnutrition are additional chronic liver diseases [5]. An estimated 25% of people in the general population have NAFLD, and the prevalence is significantly higher in people who have metabolic disorders [6]. Higher rates of prevalence and progression to FIB4 and NASH have been linked to the Hispanic community [7]. Gene polymorphisms, including those in PNPLA3, can influence how a disease develops. [8] NAFLD is identified in patients who do not consume excessive amounts of alcohol (less than 20 g per day for women and less than 30 g per day for men). The severity of NAFLD varies from simple steatosis, which is defined as fat accumulation without significant hepatic inflammation or hepatocellular injury, to steatohepatitis, which is defined as fat accumulation with hepatocellular injury and hepatic inflammation, to advanced fibrosis and cirrhosis.[9] NAFLD frequently coexists with other liver diseases such as hepatitis C, haemochromatosis and alcoholic liver disease and has been shown to cause more rapid disease progression.[10] Fatty infiltration of the liver can also be secondary to treatment with steatogenic drugs such as tamoxifen, amiodarone and steroids. Numerous non-invasive assays have been used in clinical care routes and pharmacological trials. With an emphasis on recent advancements, we examine the field's progress in this article. [11]

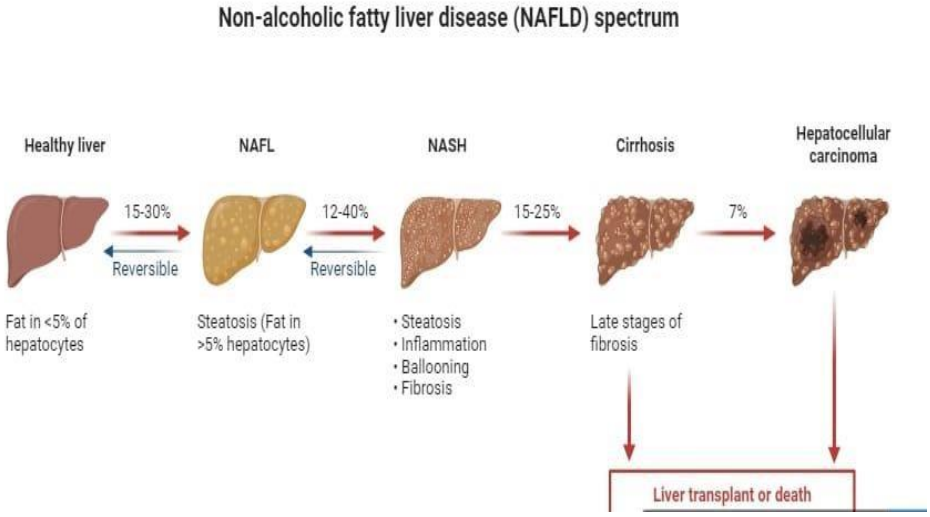

Fig1: Non-Alcoholic Fatty Liver Disease [NAFLD] Spectrum

Risk Factors for NAFLD

Finding patients at risk for NAFLD requires identifying those who have the metabolic syndrome. Any three or more of the following characteristics such as central obesity, impaired fasting glucose, hypertriglyceridemia, low HDL cholesterol, hypertension, make up the metabolic syndrome [12]. More than 90% of people with NAFLD have at least one characteristic, and about one-third have the entire metabolic syndrome. NASH and fibrosis are more common in patients with greater metabolic risk factors and the severity of NAFLD is correlated with the severity of the metabolic syndrome [13].

Age 2- As age increases, the chances of occurrence increases
The metabolic illness: 70–90% of patients suffer from NAFLD and Fibrosis is independently predicted by metabolic syndrome.
Gender: Men are more likely to have NAFLD, Advanced fibrosis is more common in women [14].
ethnic groups- Hispanics are at high risk; Black people are less dangerous.
Dietary considerations: Saturated fats and elevated cholesterol levels [15], High consumption of fructose, Minimal carbohydrate, Caffeine might have protective properties [16].
Sleep apnoea: With obstruction there will be an elevated risk of liver fibrosis [17].
Biological influences: patatin-like phospholipase domain-containing 3 (PNPLA3) gene [18].

Pathophysiology of NAFLD

Since NAFLD includes a clinical spectrum ranging from simple steatosis to cirrhosis as the final stage of liver disease, it is evident that the pathogenesis of this disease is complex and diverse. There are numerous variables that contribute to the hepatic metabolic alterations. The gastrointestinal tract may become dysbiotic due to excessive nutrient intake, additionally the liver may experience pro-inflammatory responses because of the translocation of microbial-associated molecular patterns via the portal vein and into the systemic circulation through an increased intestinal barrier permeability. Some food ingredients can also directly trigger pertinent liver tissue disease mechanisms [19-21].

Diagnosis of NAFLD

Hepatic steatosis must be evident on imaging or histology and other causes of liver disease or steatosis must have been ruled out for NAFLD to be diagnosed [22]. Because NAFLD is typically asymptomatic, abnormal liver enzymes or steatosis on imaging are typically the first signs of the disease. Two distinct approaches, including invasive and non-invasive tests, are needed to diagnose NAFLD. Liver biopsies are among the invasive diagnostics.

Liver biopsy - A liver biopsy, which evaluates hepatic steatosis, hepatocellular damage, inflammation and fibrosis is the conclusive test for NAFLD, even though it is typically not necessary for diagnosis. Hepatocyte ballooning degeneration in conjunction with steatosis is the primary histological characteristic that sets NASH apart from ordinary steatosis shows that the most used histological grading and staging system for NAFLD is the "NAFLD activity score" (NAS) [23]. More recently, the SAF score was established, which includes an assessment of fibrosis (F), activity (A), and steatosis (S). It may be more reliable in detecting NASH [24]. Non-invasive methods can, however, be used to diagnose and appropriately stage the majority of NAFLD patients [25]. Due to the growing benefits of NITs, liver biopsies are no longer always required to diagnose NAFLD. To define the stages of liver fibrosis, rule out other complicating hepatic diseases or for research purposes, a liver biopsy is recommended if NITs are not consistent [26,27].

NON-INVASIVE TESTS FOR NAFLD

The foundation for diagnosing NAFLD is hepatic steatosis. Hepatic steatosis is also linked to more severe liver injury and an increased risk of Hepatocellular carcinoma in patients with concomitant liver disorders, such as chronic hepatitis B [28]. Histologic improvements in NASH and fibrosis following pharmacological treatment may be correlated with improvements in hepatic steatosis. Hepatic steatosis may be a desirable early readout in clinical trials since it can alter more quickly than inflammation and fibrosis.

Serum biomarkers and scores

Non-invasive testing falls into three categories, under European guidelines: blood-based tests, techniques evaluating the physical characteristics of liver tissue and

imaging techniques evaluating the liver organs' structure Nowadays, serum biomarkers are utilized either alone or in conjunction with anthropometric measures to create models for the diagnosis or grading of steatosis. A collection of factors known as serum biomarkers are assessed and monitored as markers of biological activity. Several biomarker panels were created in previous decades to evaluate hepatic steatosis. Serum biomarkers and scoring systems are increasingly used to assess non-alcoholic fatty liver disease (NAFLD) and its progression. Common biomarkers include liver enzymes (ALT, AST), as well as markers of inflammation (C-reactive protein) and fibrosis (e.g., hyaluronic acid, type IV collagen). Scoring systems like the NAFLD fibrosis score (NFS), FIB-4, and the FibroTest combine these biomarkers to estimate the degree of liver fibrosis and the risk of liver-related complications. These non-invasive tests help in screening, diagnosing, and monitoring NAFLD, reducing the need for liver biopsy while providing useful prognostic information. While serum biomarkers and scoring systems are useful for screening and monitoring NAFLD, they cannot replace liver biopsy in certain cases, particularly when precise staging of fibrosis is needed. Nonetheless, these non-invasive tests provide a practical, cost-effective alternative for risk stratification, guiding clinical decision-making, and reducing the need for more invasive procedures

NASH biomarkers

Numerous serum biomarkers have been explored for the diagnosis of NASH, with cytokeratin 18 (CK-18) emerging as a validated physiological degradation marker. CK-18 fragments originate from hepatocyte apoptosis induced by the enzyme caspase 3 and can be quantified in serum through immunoassay techniques. In patients with NAFLD, serum CK-18 levels have demonstrated an AUROC of 0.83 for predicting NASH, along with a sensitivity of 0.75 and a specificity of 0.81 at a CK-18 threshold of approximately 250 U/L, based on the initial validation study [29].

FIB biomarkers

Scoring systems have often shown more value in advanced FIB identification than in early stages when evaluating liver FIB. To prevent or treat the disease's consequences, patients with FIB need to be managed. The FIB-4 test, NFS, BARD score, BAAT score and two proprietary algorithms, Fibro Test and Fibro Meter, are among the liver FIB scores that have been suggested for detection and staging [30].

Fibro Test® By combining five biochemical markers—haptoglobin, a2-macroglobulin, apolipoprotein A1, total bilirubin and GGT—and correcting for age and gender, Fibro Test®, a patented panel for the detection of FIB in NAFLD, showed a mean standardized AUROC of 0.84 for advanced FIB in patients with NAFLD [31].

Fibro Meter® is another commercial algorithm which was first created to stage FIB in patients with viral hepatitis. It incorporates seven variables: age, weight, fasting glucose, AST, ALT, ferritin, and platelet count29. The AUROC for stages F2-F4 was 0.883, compared to 0.808 for the Fibro Test [32].

Imaging:

Imaging is a crucial diagnostic tool for non-alcoholic fatty liver disease (NAFLD) and is typically ordered when there is clinical uncertainty due to the patient's obesity, type 2 diabetes, or hyperlipidaemia, as well as when the patient has abnormal liver function tests or when imaging studies conducted for other reasons show irregular findings.

Ultrasonography

Abdominal ultrasound is the most used imaging method for steatosis detection since it is widely available, well-tolerated, and cheap, but its diagnostic sensitivity is lower when there are mild degrees of liver fat infiltration. Typical ultrasonography features of fatty infiltration are based on visual assessment of the echogenicity intensity-

Grade 0 presents a normal echogenicity
Grade 1 a slight and diffuse increase in echogenicity in the hepatic parenchyma, with diaphragm and intra hepatic vessel borders standard visualization
Grade 2 a moderate and diffuse increase in fine echoes, with intrahepatic vessels impaired visualization and Grade 3 a marked increase in echogenicity, with poor or no visualization of the intrahepatic vessel borders and diaphragm [33].
Although there is no evidence to support the use of ultrasound as a screening tool, it must meet clinical criteria to be used as a first-line diagnostic test, particularly in patients with elevated liver enzymes and risk factors. However, as advised by the European recommendations for the management of NAFLD in individuals at risk, ultrasound is likely the imaging method of choice for fatty liver detection in clinical facilities because of its affordability, safety, and accessibility [34].

Transient elastography

By using low-amplitude, low-frequency vibrations that are conveyed by a transducer and create an elastic cutting wave that travels through the hepatic tissue, transient elastography was created to measure the rigidity of the liver. The velocity of the wave, which is directly correlated with tissue stiffness, can be measured and the wave's propagation tracked using pulse-echo ultrasound collection. The degree of liver FIB can be ascertained by measuring the shear wave's speed in relation to the tissue's rigidity. The results are expressed in kilopascals (kPa) and vary from 2.5 to 75 kPa, with average values of about 5 kPa, which are higher in patients with metabolic syndrome or excessive BMI [35]. Transient elastography uses an algorithm that computes the ultrasonic signal attenuation and is expressed in dB/m, with ranges of 100-400 dB/m, to evaluate the degree of steatosis as indicated by the controlled attenuation parameter (CAP). Transient elastography is therefore best suited for use in people without morbid obesity who have risk factors to identify early stages of fatty infiltration or in the follow-up of patients with chronic liver disease to rule out severe cirrhosis or FIB.

Acoustic radiation force impulse (ARFI)

This imaging technique uses an ARFI to compress the tissue instead of a human, which causes the tissue to deform. The displacement is then detected following the application of a pressure pulse. In order to detect a quantitative shear-wave velocity (m/s), it relies on the creation of pulsed beams using long-lasting trains to produce radiation stresses that cause displacements within the tissue. Without the use of an outside force, ultrasonography records these displacements to create a map of the tissue's flexibility [36]. This procedure is repeated for each scan line, resulting in two pre- and post-compression images. These images are then processed using a cross-correlation algorithm, which allows the tissue position differences between the states of compression and relaxation at each point along the axial axes to be calculated. The amount of displaced tissue indicates the tissue's elasticity and is inversely correlated with the tissue's stiffness and directly proportional to the force applied [37].

Computed tomography (CT)

By measuring the decrease in liver attenuation, which manifests as hypodense liver parenchyma and is quantified in Hounsfield unit, computed tomography assesses steatosis. With a specificity of 100% when the fat content is greater than 30%, the attenuation value in a healthy liver is approximately 50–57 HU without contrast. This value is decreased because of the liver's lipid overload, which makes it easier to determine the degree of steatosis [38]. Nevertheless, there is insufficient histological association to rule out the coexistence of early cirrhosis or NASH. Its exorbitant cost and the radiation it emits prevent it from being used frequently [39].

Magnetic resonance imaging (MRI)

The most precise technique for detecting and measuring the amount of fat in the liver is magnetic resonance imaging (MRI). Hepatic steatosis is detected in MRI by looking at images of chemical changes, where protons in fat and water can be in-phase or out-of-phase. When comparing the out-of-phase modality to the "in phase" pictures, fat liver content resulted in a drop in the hepatic signal intensity; this intensity difference allowed for the measurement of the extent of fat infiltration. Because MRI is expensive and there is little comparability among MRI techniques, it is not a good screening method [40].

Controlled attenuation parameters

A steatotic liver dissipates ultrasound energy more quickly. To determine the extent of hepatic steatosis, CAP using vibration-controlled transient elastography (VCTE) measures the decrease in the amplitude of ultrasonic waves in the liver parenchyma [41]. The Smart Exam and CAP measurement using the continuous technique are supported by the most recent VCTE model. In the original model, the degree of steatosis is represented by the median value of 10 CAP measurements that an operator obtains [42].

Prospective Pathways and Innovative Methods for Biomarker Identification

NAFLD has grown to be a serious and difficult epidemic. The gold standard for diagnosing NASH and determining the degree of fibrosis is still liver biopsy. To ascertain treatment plans, responsiveness to medicines, and prognosis, more precise non-invasive techniques that are dependable and easily accessible are desperately needed.

New rational non-invasive blood biomarkers that represent the pathobiology of the disease, such as indicators of OS, inflammation, apoptosis, and fibrosis, are being explored as significant strides are made in the understanding of the etiology of NAFLD [43]. The clinical usefulness of these tests has not yet been established and all of these markers are still in the early stages of research. There is still a need for prospective, independent validation studies in different labs and populations. Promising new methods that combine genomes, proteomics, and metabolomics may aid in the discovery of novel biomarkers that could inform clinical judgment, either enhancing or displacing existing methods. These technologies have only been applied to NAFLD in a restricted number of single-centre pilot trials thus far. Collecting a large number of well-characterized cases and controls is crucial for these kinds of investigations, which will probably necessitate multicentre cooperation.

A recent study on genetic markers in over 900 patients with chronic hepatitis C provides a clear example, revealing two single-nucleotide polymorphisms that are significantly linked to progressive fibrosis. Lastly, molecular imaging technologies are another interesting new technology that may noninvasively show the level of a particular molecular target as well as the target's functional state in vivo. These methods might make it possible to directly assess the degree of fibrosis, inflammation, and apoptosis in NAFLD patients' livers.

MANAGEMENT OF NAFLD

Effective medication therapy is still lacking, even though the prevalence of NAFLD and NASH is significantly rising and already a global burden. The two main causes of death for persons with NAFLD are cardiovascular disease and cancer. Effective medication therapy is still lacking. Thus, lowering the risk of CVD, cancer, hepatic steatosis, and inflammation is the primary therapy objective [22]. Here, we provide an overview of various potential.

NAFLD/NASH treatment approaches; however, we will not go into detail about the significance of other CVD risk-reducing medications, such statins, etc. There are more and more therapy alternatives available today to treat NAFLD.

1. Probiotics
2. Lifestyle changes
3. SGLT2 Inhibitors

4. Glucagon like peptide 1 receptor agonists
5. Bas, BA metabolites and FXR agonists
6. PPAR agonists
7. Bariatric surgery
8. Therapeutic options in the future

CONCLUSION

Fatty liver disease can now be evaluated and diagnosed using a number of non-invasive techniques that are highly beneficial to the attending physician and can be applied based on the capabilities of the various care facilities. In the first case, the initial recommendation is to check for related comorbidities, such as obesity, metabolic syndrome, diabetes, or abnormal liver function tests, in patients with suspected fatty liver. Since a liver ultrasound is a reasonably priced imaging method for primary care, it is advised to undertake one in the event of variations. If the results show changes, it is also advisable to prepare a few biochemical tests to rule out liver FIB. The next step would be to proceed with an imaging technique if this evaluation yields changes. This could be either MRI, which is the most accurate imaging method to quantify fatty liver disease because it can distinguish between non-progressive NAFLD and NASH, or transition elastography, which has the advantage of evaluating both steatosis and FIB degree at the same time. Although CK 18 is now the best blood marker for detecting NASH, there are a number of helpful assays and algorithms that can be used to identify liver FIB. Lastly, the doctor could ask for a liver biopsy if he is still unsure. Because an early diagnosis of liver steatosis could decrease the progression and, consequently, the prevalence of the illness, as well as minimize expenses, the recommended methodology for the use of non-invasive testing in patients with suspected NAFLD is primarily for first-contact physicians. Additionally, the algorithm provides a variety of cost-effective biochemical and imaging tool options for all kinds of patients or healthcare facilities. However, studies on the expression of epigenetic factors and their functional impact on the development of NAFLD are still lacking. As a result, it would be of great interest to identify and characterize the differential expression profile of epigenetic factors in order to search for a molecular signature or a biomarker that can predict the development and severity of the disease and aid in the early diagnosis. On the other hand, the genomics and transcriptomics of liver diseases have undergone significant change in the last ten years, thanks to the development of technologies like microarrays and massive sequencing. Furthermore, it is desirable to understand the physiological microenvironment that may contribute to the patient's health issues.

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