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REVIEW ARTICLE OPEN ACCESS

A REVIEW ON REDUCTION IN LIVER STIFFNESS PARAMETERS BY MODULATING INFLAMMATORY MEDIATORS IN NASH

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ABSTRACT

NASH is an advanced form of NAFLD. NASH is a more severe form of NAFLD characterized by hepatic steatosis, inflammation, hepatocellular injury and fibrosis. NASH has emerged as the most common cause of end stage liver disease worldwide. NASH is a chronic inflammation that transforms hepatic stellate cells to myofibroblast. These cells produce extracellular matrix that can lead to liver fibrosis. Extracellular vesicle act as a signaling mediator that result in lipid accumulation, macrophage and hepatic stem cell activation that causes inflammation and liver fibrosis during development of NASH. Life style interventions are most effective and essential for preventing or controlling NASH. Pharmacological management of NASH remains elusive. Incorporation of drugs with personalized mechanism can lead to improved efficacy to better benefit patients with NASH.

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INTRODUCTION

Nonalcoholic fatty liver disease is the presence of liver steatosis in the absence of factors that induce lipid accumulation in hepatocytes, such as alcohol consumption or use of steatogenic drug[1]. NAFLD has emerged as most prevalent chronic liver diseases with a prevalence rate of 23% and 38% based on geographical region. NAFLD is represented by excessive accumulation of lipids exceeding 5% of its weigh in individuals without alcohol consumption[2]. NASH is characterized by hepatocytic steatosis, hepatocellular damage, inflammation and varying degrees of fibrosis which then progress to cirrhosis and end stage liver disease[3]. Clinical progression of NASH occurs at different rate among individuals. Hepatic inflammation is driven by innate and adaptive immune cells and it is a critical component for initiation and progression from steatosis to NASH[4]. It involve complex pathogenesis explains by two impacts which is lipid accumulation in hepatocytes and oxidative stress damage. In oxidative stress damage produce lipotoxicity that triggers inflammatory responses which activate the innate immunity that lead to hepatic inflammation[5]. The rate of disease progression is slow about 20% of patients with NAFLD will develop NASH from three to seven years.

Pathophysiology: The development of Non-Alcoholic Steatohepatitis (NASH) is characterized by multiple cellular stressors in hepatocytes, including endoplasmic reticulum (ER) stress, mitochondrial dysfunction, oxidative stress, and lipotoxicity[5]. These stress responses are often triggered by factors such as the accumulation of saturated fatty acids, increased de novo lipogenesis due to excessive fructose intake, and cholesterol buildup in the ER[6]. Fructose increases intestinal permeability, which may contribute to liver inflammation by facilitating gut-derived inflammatory signals that activate hepatic immune cells[7]. As a result, a cascade of inflammatory responses is produced, ultimately leading to hepatocyte damage and death[6]. Hepatocyte stress not only initiates liver inflammation but also leads to the release of pro-inflammatory mediators, which further intensify immune activation and promote fibrosis[8]. Endoplasmic reticulum stress activates the unfolded protein response in endoplasmic reticulum. One of the unfolded protein response mediates cell apoptosis through TNF receptor-associated factor 2 and c-jun N-terminal kinase activation[9]. Endoplasmic reticulum stress activates transcription factor[ATF6α], inositol requiring enzyme 1 [IRE1α], protein kinase RNA like ER kinase [PERK][10]. The signaling IRE1α leads to activation of X-box-binding protein 1 [XBP]1, IRE1α dependent decay and TRAF2 mediated signaling. This signaling controls hepatic steatosis, liver

injury and inflammation[11]. The activation of unfolded protein response causes cell death and apoptosis in NASH. NASH can lead to increased intestinal permeability that can lead to migration of pathogen associated molecular patterns [PAMPs] and lipopolysaccharides to liver which in turn activates Toll-like receptors [TLRs][12,18]. The activation of TLRs leads to the release of pro-inflammatory cytokines such as TGF-β, interleukin-1 (IL-1β) and TNF-α[13,21]. Activation of TLR2, TLR4 and TLR9 causes lipid accumulation and stellate cells activation. The hepatocytes is highly expressed with NOD1 and NOD2 that is associated with inflammation[14]. The lipotoxicity also leads to inflammatory response in endoplasmic reticulum stress that leads to the release of pro-inflammatory extracellular vesicles (EVs)[15]. EVs include exosomes, microvesicles, and apoptotic vesicles that are non-nucleated membrane particles secreted by cells to extracellular spaces[16]. Lipotoxicity can lead to hepatocellular stress that causes the release of EVs from hepatocytes and adipose tissue that can trigger inflammation by activating monocyte and macrophages and leads to fibrosis[20].

Diagnosis

Liver Biopsy: Histological features of liver biopsy can be determined by liver biopsy. Liver biopsy is not suitable for routine screening due to its invasive nature[21]. It is primarily indicated for patients at high risk of advanced liver disease and distinguishing nonalcoholic Steatohepatitis (NASH) from simple fatty liver (NAFL) and determining fibrosis severity[22]. Liver biopsy continues to play a crucial role in later-stage clinical trials for NASH, where it is used to determine the effectiveness of emerging treatments[23]. Several histological scoring systems are used to evaluate liver biopsies, with the most prominent being the NASH Clinical Research Network (NASH CRN) system, which includes the NAFLD Activity Score (NAS), and the Steatosis-Activity-Fibrosis (SAF) score[24]. The NASH primarily intended for research purposes, scores liver histology on a scale from 0 to 8 by summing the grades for steatosis, lobular inflammation, and hepatocellular ballooning[25]. However, this system has certain limitations: it does not separate steatosis from inflammatory activity, assigns greater weight to lobular inflammation over ballooning, and lacks a standardized definition for ballooning, which can lead to inconsistencies in interpretation[26]. The SAF score measures steatosis (S), activity (A), and fibrosis (F). The activity score in this model is calculated by adding the grades for lobular inflammation and ballooning, each rated from 0 to 2[27]. The SAF system provides clearer definitions, including a specific criterion for severe ballooning, defined as a hepatocyte reaching twice its normal diameter[28]. Although both NAS and SAF use a similar approach to fibrosis staging, SAF is often preferred for both clinical and research settings due to its more structured and reproducible framework[29].

Liver Stiffness Measurement (LSM): Using vibration-controlled transient elastography (VCTE) that is commonly performed with the Fibro Scan device is a widely used non-invasive method to assess liver fibrosis[30]. This method measures liver stiffness by measuring the velocity of a 50 Hz shear wave induced by a mechanical pulse. The probe tracks wave propagation using pulse-echo ultrasound, with velocity correlating to fibrosis severity[31]. The advantage of VCTE over liver biopsy is by sampling a liver volume approximately 100 times larger. It is useful for screening, baseline assessment, monitoring disease progression, and evaluating treatment response[40]. Lower thresholds, such as 7.9 kPa, have high negative predictive value (NPV), making them effective for ruling out advanced fibrosis, while higher thresholds improve positive predictive value (PPV), helping to confirm severe fibrosis[41].

Vibration Controlled Transient Elastography (VCTE): VCTE calculates liver stiffness by using speed of mechanically induced shear waves in liver. VCTE is performed by fibro scan 502 touch software after an hour of overnight fasting[42]. VCTE is a widely used and cost-effective tool for evaluating liver fibrosis, but its accuracy can be limited by factors such as obesity, elevated central venous pressure, and the presence of ascites, which can prevent reliable measurements[43]. Additionally, acute liver inflammation may temporarily elevate liver stiffness readings by 1.3 to 3 times. Various ultrasound-based techniques are available to assess liver stiffness, utilizing either strain imaging or shear wave imaging. Strain imaging includes modalities like strain elastography (SE) and acoustic radiation force impulse (ARFI), while shear wave imaging is employed in tools such as Fibro Scan[44]. Point shear wave elastography (pSWE), which is based on ARFI technology, determines liver stiffness by measuring the displacement of tissue in response to an acoustic pulse[45]. A notable advantage of pSWE is that it can be performed using conventional ultrasound systems, allowing real-time visualization of liver structures and enabling the operator to avoid large blood vessels or bile ducts. Unlike VCTE, pSWE is not influenced by ascites and has a lower failure rate (1–2%), although it requires interpretation by trained radiologists[46].

Magnetic Resonance Elastography (MRE): (MRE) is an MRI-based technique that quantifies tissue stiffness and can capture measurements quickly during breath-hold imaging. It is effective in detecting NAFLD even in its early stages and has greater diagnostic accuracy for liver fibrosis and steatosis than VCTE™ and CAP™[46]. NAFLD patients reported SROC values of 0.89 for ≥F1, 0.93 for ≥F2, 0.93 for ≥F3, and 0.95 for F4. However, due to its high cost, MRE is not routinely used for NAFLD screening.

Management: Antioxidant effect of vitamin E due to which it is is used in management of NASH. Patients who had treated with vitamin E had an improvement in steatosis and inflammation but fibrosis does not improve. Vitamin E reduces intrahepatic triglycerides by reducing denovolipogenasis[47]. A bidirectional pathway of oxidative stress in which vit E exacerbate denovolipogenasis and intrahepatic triglyceride formation forming harmful cycles of steatosis and injury[48]. vitamin E drugs where used for the management of NASH. Thiazolidiones such as pioglitazone improves NASH histology by reducing liver fat and redistributing adipose tissue, with antifibrotic effect via hepatic stellate cells. GLP-1 receptor agonist produces better glycemic control, reduce body weight and improve liver enzyme[49]. Liraglutide and semaglutide significantly effects on NASH but not fibrosis regression in clinical trials. SGLT-2 inhibitors promote glucose excretion and reduce hepatic steatosis in type2DM patients and no histological effects on fibrosis been observed[50].

DISCUSSION

NASH is the most prevalent chronic liver disease all over world. Management of progression can be done by preventing the progression of fibrosis and promoting the regression of existing fibrosis[51]. Innate immunity is a key factor for multiplying hepatic inflammation. Liver biopsy can be used for estimation of disease severity as well as to discriminate between NAFLD and NASH[52]. Other methods involve blood test of liver function, ultrasound and proton magnetic resonance spectroscopy[53]. The treatment of fibrosis is based on modification of lifestyle factors, such as reduction in body weight combined with healthy nutrition[54]. The study was comparable to the study conducted by Tereza C.M. Fontes-Call which shows NASH patients have an imbalance between pro-inflammatory and anti-inflammatory markers. New approaches aimed at modulating gut microbiota and immune response is the emerging promising therapeutic strategies[55].

CONCLUSION

Chronic inflammation plays a major role in the development of liver stiffness, primarily through the activation of fibrogenic pathways. Targeting inflammatory mediators offers a promising approach to not only halt disease progression but also to reverse existing fibrosis. Recent studies have demonstrated that modulating key cytokines, chemokines, and immune pathways can significantly reduce liver stiffness, highlighting the therapeutic potential of anti-inflammatory

strategies. A deeper understanding of these pathways could ultimately lead to improved clinical outcomes for patients with NASH.

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