International Journal of Sustainable Biome and Life Care
Volume No. 3; Issue No.1, October 2026, Pages 11-16
https://doi.org/10.31632/ijsblc.2026.v03i01.002

International Journal of Sustainable Biome and Life Care
Online ISSN: 2581-4877
Journal homepage https://ijsblc.org



Review Article

Role of C Reactive Protein in NAFLD: An Umbrella of Diseases

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a clinicopathologic entity increasingly recognized as a major health burden in children and adolescent in developed countries. It includes a spectrum of liver damage ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), advanced fibrosis, and rarely, progression to cirrhosis. Recent studies emphasize the role of insulin resistance, oxidative stress and subsequent lipid peroxidation, proinflammatory cytokines, adipokines, obesity, metabolic syndrome mitochondrial dysfunction and hyperuricemia in the development and progression of NAFLD. Physiology of fat accumulation, ensuing hepatocyte damage, fibrosis, role of the gut microbiota, the role of the immune system, genetic and epigenetic predispositions are unwinding episodes relevant with substantial inter-individual variation in this disease severity, phenotypic expressions and progression. Apart from lifestyle changes, dietary modulations or bariatric surgery, other medical interventions are not always effective. Several strategic targeting of pathophysiological mechanisms of cell injury and inflammation are currently under exploration. NAFLD are associated with visceral adiposity, other cardiometabolic risk factors, and elevated inflammatory biomarkers like C-reactive protein (CRP). This review summarizes the current knowledge on the epidemiology, pathophysiology and diagnosis of NAFLD and the intertwining relation of CRP and NAFLD.

Keywords: *C Reactive Protein; Fatty Liver Diseases; Non-Alcoholic; Obesity*

Introduction

Nonalcoholic fatty liver disease (NAFLD), a major hepatic consequence of obesity, covers a wide histological spectrum ranging from asymptomatic elevated liver enzyme levels, simple fatty liver (SFL), asymptomatic steatosis, simple steatosis, fibrosis, to nonalcoholic steatohepatitis (NASH). It may escalate to cirrhosis with complications of hepatocellular carcinoma and liver failure. NAFLD is presented by the accumulation of fat in the liver parenchyma of individuals without significant alcohol consumption (Teli *et al*.,1995) (Figure 1-2). The foremost risk factors are obesity, hyperlipidemia and non-insulin-dependent diabetes mellitus (Angulo, 2002). Cardiovascular complications rather than liver disease mainly cause morbidity and mortality in NAFLD patients (Han *et al*., 2022; Adams *et al*.,2005).

Hepatic steatosis, the most clinically benign form is estimated by the accumulation of hepatocytic fat droplets (lower threshold level, mostly triglycerides>5% of the hepatocytes) because of breakdown of the homeostasis between synthesis versus utilization of fat in the liver (Perry *et al*., 2014). Characteristics of steatohepatitis embrace inflammation, hepatocellular injury (ballooning, Mallory's hyaline, apoptosis/necrosis, giant mitochondria), and fibrosis (pericellular perisinusoidal) (Hübscher, 2006; Kleiner *et al*., 2005).

Received on :27th July 2026; Revised version received on :26th August 2026; Accepted: 28th August 2026

Though there are different school of suggestions on the level of alcohol intake that can clearly distinguish between NAFLD and alcoholic fatty liver. Much research accepts that for definition the maximum allowable level of alcohol consumption of NAFLD is 2 standard drinks per day (140 g ethanol/week) for normal men, and one standard drink per day (70 g ethanol/week) for women (Adams *et al*.,2005). Women with polycystic ovary syndrome may have an increased prevalence risk of NAFLD (Setji *et al*., 2006). Individuals with chronic hepatic steatosis may not develop the risk of cirrhosis, but in case of complicated steatosis, it may end up to nonalcoholic steatohepatitis. NASH may improve back to steatosis or even better to normal liver histology, but in cases of complicated stable form it may end up to fibrous scar that eventuates in cirrhosis (Abdelmalek *et al*.,2018).

There is inadequate research on the association of inflammatory biomarkers with NAFLD as its pathophysiology includes chronic low-grade inflammation. The clinical use of serum biomarkers to distinguish patients with simple steatosis from those with NASH has not been reported. CRP was used as acute-phase inflammatory biomarker has turned to be an evident predictor of coronary episode by high-sensitivity assay method employing high-sensitivity CRP (hs-CRP) concentration (Zimmermann *et al*., 2011; Kumar *et al*., 2020). As liver plays a pivotal role in NAFLD and is the main source of the acute phase reactant, CRP; so, the role of CRP needs to be enriched.

Epidemiology

The global prevalence of NAFLD is nearly 25.24 % with wide geographical variations worldwide. Nearly 30% people from South American and Middle East countries and a low prevalence of NAFLD (~ 13%) was found in African countries. All these studies were mostly based on ultrasound-based reports as studies based on serum markers revealed a low prevalence rate. USA and North America have a higher prevalence of nearly 21–24.7%. Most of the epidemiological studies on NAFLD was based on North America and USA. About 20% prevalence rate has also been reported from Europe based on meta-analysis study (Younossi *et al*., 2016). In the upcoming days, the expanding population, the rapidly urbanizing society, genetic predisposition, lifestyle swift, the upward economic drift may shift the burden of NAFLD in Asia than European or American countries. Therefore, 9–32% in India, 12–51% in Taiwan, 12.5–38% in China, 23–26% in Japan, 27% in Korea, about 28% in Hongkong, and to nearly 5–30% in Malayasia, Srilanka and Indonesia like Southeast Asian countries (Mitra *et al*., 2020; Wong *et al*., 2019; Li *et al*., 2019; Fan, 2013; Kojima *et al*., 2003; Park *et al*., 2006; Jeong, *et al*., 2013; Shen *et al*., 2003; Zhai, *et al*., 2016). NAFLD in lean individuals will take its own course through expanded adipose tissue but with similar pattern of clinical effects (Das & Chowdhury, 2013).

Relation between NAFLD and CRP

There were limited numbers of research showing the role of CRP in NAFLD. CRP synthesis increases in response to a pathological process. CRP is mostly used as nonspecific biochemical marker of chronic inflammation. Study confirmed that the elevated circulating CRP levels could be a marker of NAFLD. In conjunction with other laboratory information, CRP values can be interpreted. Serial measurements of CRP can be useful in clinical management and progression of NAFLD patients (Figure 1). Visceral fat considerably contributes to CRP production and related to adiposity. Elevation of IL-6 cytokine stimulates CRP synthesis (Kao *et al*., 2006; Oruc *et al*., 2009).

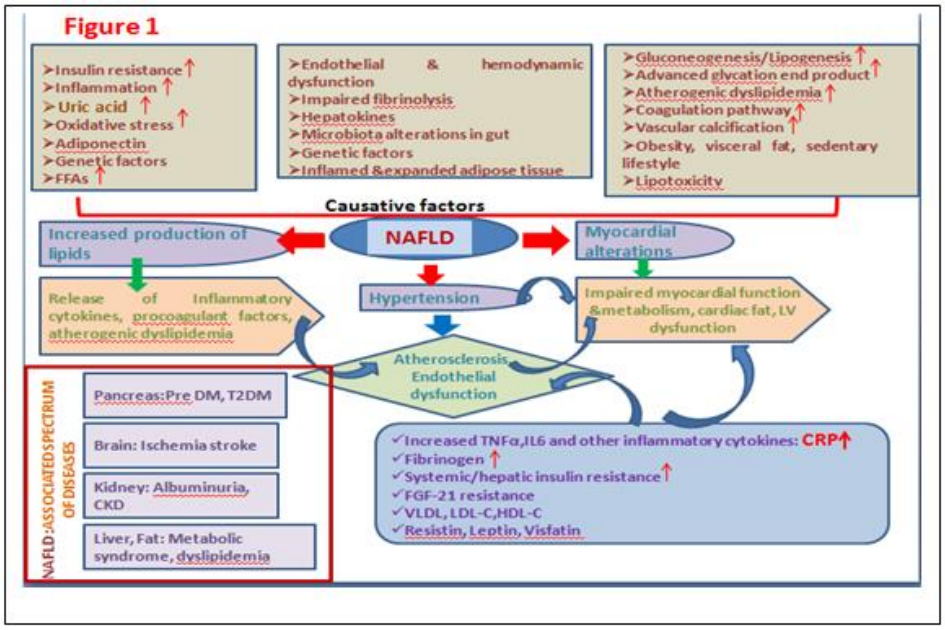

Figure 1: *The Multifactorial Pathogenesis of NAFLD Leading to Spectrum of Diseases*

The causative factor of NAFLD includes insulin resistance, oxidative stress, obesity etc. NAFLD causes hypertension, increased lipid deposition and myocardial changes. NAFLD leads to unfavorable cardiac outcomes and a spectrum of diseases of pancreas, kidney etc. CRP: C-reactive protein; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; FGF-21: Fibroblast growth factor-21; NAFLD: Nonalcoholic fatty liver disease; preDM: prediabetes mellitus; T2DM: type 2 diabetes mellitus; CKD: chronic kidney disease; CVD: cardiovascular disease FFA: Free fatty acid; LV: left ventricular (Han & Lee, 2017; Di Sessa *et al*., 2017).

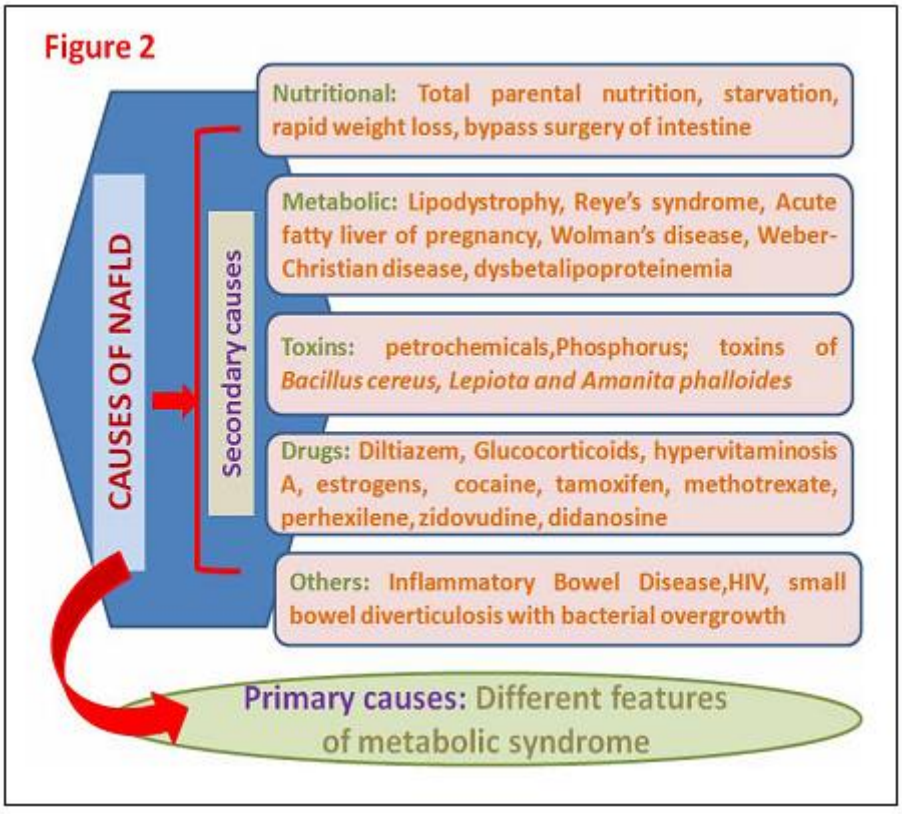

Figure 2: *Different Causative Factors of Non-Alcoholic Fatty Liver Diseases*

The factors causing NAFLD may be primary and secondary (Adams *et al*., 2005). The role of hs-CRP in screening NASH as a hepatic expression of MetS was revealed in patients by elevated concentration of hs-CRP in grade 2-3 NASH patients (more active form) than those with simple steatosis or grade1 NASH (quiescent form) (Uchihara & Izumi, 2006). Patients with NAFLD had higher hs-CRP concentration than control group (patients with no clinical manifestation of NAFLD) though no significant difference was observed between NASH and SFL patients (with normal liver function test) (Yeniova *et al*., 2014).

On the other hand, Zimmermann *et al*., 2011 observed that increased hs-CRP levels among 627obese patients was due to fat accumulation in liver and adipose tissue causing liver steatosis. NAFLD-stage did not influence hs-CRP and body mass index (BMI). This study showed that hs-CRP doesnot predict severity of NAFLD, it is a marker of steatosis (Zimmermann *et al*., 2011).

The episode of NAFLD was an independent predictive factor for future CVD risk ≧10% with odds ratio: 1.89 (after adjusting other conventional CVD risk factors), p=0.004; mostly among aged individuals having higher baseline hsCRP level than those without NAFLD. The severity score of NAFLD was significantly correlated with higher CRP and Framingham risk score (Chiang *et al*., 2010).

The relation of hs-CRP as a surrogate marker with disease severity of NAFLD in north Indian cohort population was carried with univariate analysis where hs-CRP, waist-hip circumference ratio, HbA1c showed the noteworthy association with NAFLD. This association pertains even after adjusting HbA1c and waist-hip circumference ratio. The mean hs-CRP level was significantly elevated in NAFLD patients (ranked as grade 1, grade 2 and grade 3) 1in comparison with the control group. The baseline variables were adjusted with age, weight, BMI, blood pressure and waist-hip circumference ratio.

High-sensitivity C-reactive protein (hs-CRP) level should be taken as an independent risk factor for metabolic dysfunction associated fatty liver disease (MAFLD) in both males and female Chinese patients as analyzed by logistic regression. Not only as risk factor, but hs-CRP has also strong association with MAFLD. Control subjects include non-MAFLD where thyroid peroxidase autoantibody, Serum thyroid hormone, hsCRP, serum lipid profile, glucose and liver enzymes, blood pressure were measured to pinpoint relation wise determinants by One-Way ANOVA test, Multiple Logistic Regression models and Wilcoxon Signed Rank Test (Zhang *et al*., 2020).

Discussion

NAFLD is a state of chronic inflammation because of complex interaction between genetic and environmental factors, inflammatory molecules seem to mediate the process. Assessment of the circulating inflammatory molecules/biomarkers that accompany this liver disease might provide therapeutic modalities to transform the inflammatory responses and thereby alter disease progression. Metabolic syndrome, Obesity, Insulin resistance, hypertension, high triglycerides are the key factors of NAFLD.

Previous investigators extensively explored risk factors for NAFLD. The risk factors for cardiovascular diseases like VLDL, overproduction of glucose, coagulation factors also significantly contribute to insulin resistance during MetS and NAFLD (Seppälä-Lindroos *et al*., 2002). It is mostly known that NAFLD is closely linked with MetS as well as cardiovascular disease (Verrijken *et al*., 2008; Baba *et al*., 2007). As NAFLD may progress to clinically relevant NASH therefore, it is wise to predict development of NAFLD in the asymptomatic subjects.

High-sensitivity C-reactive protein has been found to be associated with MetS. Though, hs-CRP may serve as early marker for CVD and MetS, there is less evidence about relationship between hs-CRP level and the severity of MetS.

Conclusion

NAFLD is one of the primary causes of chronic liver disease with increasing prevalence worldwide. It is leaping with dyslipidemia, diabetes epidemics and global obesity. It covers a spectrum ranging from

chronic NASH to simpler hepatic steatosis. One of the main causes of hepatocellular carcinoma and liver transplantation is NASH. The non-invasive biomarker of NAFLD is hs-CRP. For pro-inflammation prediction, helps in early identification, healthcare management and policies.

Conflict of Interest

The authors do not have anything to declare.

Acknowledgment

The author acknowledges its host institute.

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