

# A Review on Some Biochemical Markers in Metabolic-Associated Fatty Liver Disease

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**Abstract-**Liver is a primary organ for lipid and glucose homeostasis and is the focus of cardio metabolic disease. The NAFLD definition combines the existence of steatosis in more than 5% of hepatocytes and metabolic risk factors, particularly obesity and T2DM, and exclusion of excessive alcohol consumption defined as  $\geq 30$  g per day for men and  $\geq 20$  g per day for women, or other chronic liver diseases. In the year of 2020, it was suggested that the nomenclature of nonalcoholic fatty liver disease (NAFLD) should be updated to metabolic-associated fatty liver disease (MAFLD). Moreover, it was found that diagnosis of MAFLD should be based on the presence of metabolic dysfunction not the absence of other conditions, MAFLD can coexist with other liver diseases and a reference to alcohol should not be included in the MAFLD acronym. Biochemical parameters play a significant role in the careful diagnosis and also for the risk assessment and adopting treatment that improves clinical outcome. This article, focused on the nomenclature and diagnosis of metabolic-associated fatty liver disease which before 2020 was called non-alcoholic fatty liver disease, and explain some of the biochemical parameters in this disease.

**Keywords:** metabolic-associated fatty liver disease, liver enzyme, lipid profile

## I. INTRODUCTION

Liver is a primary organ for the lipid and glucose homeostasis and is the focus of cardio metabolic disease. Nonalcoholic fatty liver disease is an expression suggested by (Schaner and Thaler) in 1986[1]. Nearly 10 years later, Leonardo et al. hypothesized that NAFLD could be correlated with cardiovascular disease (CVD) [2] and shortly after, the first NAFLD guidelines appeared [3-5]. The NAFLD definition is combines the existence of steatosis in more than 5% of hepatocytes and metabolic risk factors, particularly obesity and T2DM, and exclusion of excessive alcohol consumption defined as  $\geq 30$  g per day for men and  $\geq 20$  g per day for women, or other chronic liver diseases [6]. In 2020, it was suggest that the nomenclature of nonalcoholic fatty liver disease (NAFLD) should be updated to metabolic-associated fatty liver disease (MAFLD), Also it was found the diagnosis of MAFLD

should be based on the presence of metabolic dysfunction not the absence of other conditions, MAFLD can coexist with other liver diseases and A reference to alcohol should not be included in the MAFLD acronym [7].

### A. Suggested Criteria for a diagnosis of MAFLD [7].

In the past, the diagnosis of non-alcoholic fatty liver disease was determined only after excluding heavy alcohol intake or drug-induced liver disease. In 2020, Eslam M et al proposed a positive criteria for diagnosis of MAFLD are based on ((histological (biopsy), imaging or blood biomarker evidence of fat accumulation in the liver (hepatic steatosis)) in addition to one of the following three criteria:

- 1- Overweight/ obesity
- 2- Presence of type 2 diabetes mellitus (T2DM).
- 3- Evidence of metabolic dysregulation.

The metabolic dysregulation is defined by the presence of at least two metabolic risk abnormalities, which are shown in the following table:

TABLE I- Explains criteria defining metabolic risk factors.

<p><b>Increased cardiometabolic and MAFLD risk defined as the presence of at least two of the following at-risk criteria:</b></p> <p>Waist circumference <math>\geq 102/88</math> cm in Caucasian men and women or <math>\geq 90/80</math> cm in Asian men and women).</p> <p>Blood pressure <math>\geq 130/85</math> mmHg or specific drug treatment</p> <p>Plasma triglycerides <math>\geq 150</math> mg/dl (<math>\geq 1.70</math> mmol/L) or specific drug treatment.</p> <p>Plasma HDL-cholesterol <math>&lt; 40</math> mg/dl (<math>&lt; 1.0</math> mmol/L) for men and <math>&lt; 50</math> mg/dl (<math>&lt; 1.3</math> mmol/L) for women or specific drug treatment.</p> <p>Prediabetes (<i>i.e.</i>, fasting glucose levels 100 to 125 mg/dl [5.6 to 6.9 mmol/L], or 2-hour post-load glucose levels 140 to 199 mg/dl [7.8 to 11.0 mmol] or HbA1c 5.7% to 6.4% [39 to 47 mmol/mol])</p> <p>Homeostasis model assessment of insulin resistance score <math>\geq 2.5</math></p> <p>Plasma high-sensitivity C-reactive protein level <math>&gt; 2</math> mg/L.</p>
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The researchers indicated a method for detecting steatosis, which is done by ultrasound (Taking into consideration the



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amount of steatosis and body mass index) [7] Eslam *et al* (2020).

## II. BIOCHEMICAL TESTS

Biochemical parameters play a significant role in careful diagnosis and also for risk assessment and adopting treatment that improves clinical outcome. Liver biochemistry, most common It is indicated to as "liver function tests (LFTs)", Includes aspartate aminotransferase, alanine transaminase, bilirubin, gamma-glutamyl transferase and alkaline phosphatase. However, the expression of "liver function tests" is a misnomer as not all tests represent liver 'function' and is therefore misleading. Aspartate aminotransferase and alanine transaminase are found in high concentrations within hepatocytes and are therefore markers of hepatocellular injury. Alkaline phosphatase and gamma-glutamyl transferase rises are associated with biliary or obstructive liver pathology, or in response to hepatic enzyme induction secondary to alcohol or drugs such as phenytoin or rifampicin. Bilirubin is a metabolite of haem generated from senescent red cells and other haem containing proteins such myoglobin. The liver is involved in the conjugation and elimination of bilirubin and hence abnormalities in bilirubin levels can represent pre-hepatic, hepatic and post-hepatic pathologies. The liver is involved in the production of albumin and clotting factors and gluconeogenesis to generate glucose from non-carbohydrate substrates. Therefore, bilirubin together with albumin, prothrombin time (or often international normalised ratio (INR)) and glucose (a marker of gluconeogenesis) are markers of (synthetic) function of the liver [8]. In this article we will explain some of these parameters in metabolic-associated fatty liver disease (MAFLD).

### A. Aspartate aminotransferase (AST)

Serum aspartate aminotransferase (AST) is a transaminase enzyme that catalyses the conversion of aspartate and  $\alpha$ -ketoglutarate to oxaloacetate and glutamate[9]. AST is present in cells across all organs except the bone, with the highest levels found in the liver, heart, and skeletal muscles [10]. High AST levels may be caused by considerable tissue damage and have low specificity for any single disease. However, marked increases in AST levels are useful for prognostic and clinical prediction. Johnson *et al.*, who first reported the prognosis of patients with extreme AST level elevations ( $\geq 3000$  U/L), concluded that serum AST concentrations of 3000 U/L or higher occurred in approximately 2 per 1000 admissions, and that extreme AST elevations were most often attributable to hypoxic hepatitis[11,12]. In the context of an abnormal hepatic triglyceride accumulation, circulating aminotransferases rise as a consequence of the need for increased reactions of transamination to cope with the liver metabolic derangement that is associated with greater gluconeogenesis and insulin resistance. Hence, to maintain homeostasis, the liver upregulates these enzymes, leading to changes in the amounts of amino acids released into the circulation[13]. In the study of Mansour-Ghanaei *et al* 2019, the mean levels of hepatic enzymes were higher in the NAFLD group, in other cases, a significant relationship was observed with NAFLD [14]. In the study of

Novakovic *et al.*[15] a significant relationship was observed between hepatic enzymes (ALT, GGT, AST/ALT ratio) apart from AST and NAFLD. Most previous studies have shown that there is a significant relationship between NAFLD and AST,[16,5].

In the study of Kyung-Soo *et al*, it was found the levels of AST in patients with MAFLD were higher in comparison with other groups [17]. The study of Ana *et al* 2023 shows a significant association between AST and AAR levels and advanced fibrosis[18].

### B. Alanine aminotransferase (ALT)

Alanine aminotransferase (ALT) is an enzyme which exists profusely in the cytosol of hepatocytes. commonly, less ALT levels can be discovered in the serum of health population, once the apoptosis and injury of hepatocytes were occurred, the ALT levels in the serum increased significantly [19]. As a criterion index of liver function, serum ALT value is usual used to reflect hepatic inflammation and liver injury in patients with different chronic liver diseases. Most of the time, only subjects who with increased ALT values were enrolled in the clinical investigation or trials. In most of the previous studies, the higher ALT values were tightly correlating with the higher risk of NAFLD particularly with the NASH [20,21], but some other studies showed that NAFLD or NASH with the normal levels of ALT, measured by histology, MRI and ultrasonography possessed [22-24]. Moreover, some studies showed that patients with normal ALT levels had the histological features of disease progression [25,26]. NAFLD patients with normal ALT values were often neglected because most physicians evaluate the hepatic risk of NAFLD based on the change of ALT value [27]. In the study of Ma *et al* in conclusions it was found 25% NAFLD patients and 19% NASH patients possess the normal ALT levels in the clinical manifestation. The levels of ALT in the clinical diagnosis of NAFLD and NASH remains need be further testified. In many studies on patients suffering from NAFLD, increased levels of aminotransferases along with diabetes have been considered as independent predictors of moderate to severe fibrosis [28] in patients with fatty liver who are at risk of progression to advanced fibrosis and only these two variables have been shown to have a significant association with steatohepatitis[29]. High waist circumference, high body mass index (BMI), male sex, alcohol consumption and young age are considered as strong predictors for rising ALT level[30]. Moreover, ALT level has been shown to have a positive association with the number of signs and symptoms of metabolic syndrome present [31]. Some studies show demonstrated that some patients suffering from NAFLD have normal serum level of ALT. In a study on a United States' population (the Dallas Heart Study), 79% of the adults with fatty liver had normal aminotransferase level(32), which was the same as the 55% of the Italian adults suffering from this disease in another study (the Dionysos Study)[33]. In a study of 2287 individuals from different tribes, almost one-third of the population had hepatic steatosis, among whom 79% showed normal ALT level [34,35]. In previous studies, ALT has been shown to be correlating with NAFLD. Even ALT levels within the

normal reference range have been correlating with a risk of NAFLD [36-38]. In the study of Mansour-Ghanaei et al 2019, the mean levels of hepatic enzymes were higher in the NAFLD group, in other cases, a significant relationship was observed with NAFLD [14]. When measuring a level of AST and ALT, We advise any researcher to take into consideration the ratio of AST/ ALT. Because ALT/AST ratio >1 could be independently correlating with MetS [39,72] and fatty liver disease [38,40].

### C. Alkaline Phosphatase (ALP)

Biomarkers of cholestasis, namely serum alkaline phosphatase (ALP), have been closely used as prognostication vibes in cholestatic liver diseases [41]. However, the importance of serum ALP in NAFLD, particularly in obese patients undergoing metabolic surgery, has been scarcely addressed. Other abnormalities correlating with obesity, including the presence of hypertension, insulin resistance, type 2 diabetes, sleep apnea, and liver enzymes abnormalities have been used to predict NASH in patients undergoing metabolic surgery [42]. Prashanth et al it was found ALP to be significantly higher in NASH patients, even when within normal range [43] Rafiq et al in their studies it was reported the increased level of ALP as an independent predictor for hepatic diseases-related death [44]. In 2021, Ahmad et al it was found Serum ALP, in addition to ALT, HbA1c, and BMI, was found to be an independent predictor of significant fibrosis in obese subjects with NAFLD. it was introduced a new treebased model using the four noninvasive significant variables for prediction of significant liver fibrosis, which, if validated, may be used for patient counseling and for identifying high-risk patients who might benefit from intraoperative liver biopsy for staging in patients undergoing metabolic surgery [45]. In a small cohort of patients with liver disease, 10% of patients with NAFLD/NASH presented with isolated serum ALP elevation with normal transaminases levels, of whom nearly one-third were found to have advanced liver fibrosis at the time of presentation [46]. Thus, serum ALP may be of prognostic relevance in patients with NAFLD and its role as a predictor of liver fibrosis, particularly in obese patients undergoing metabolic surgery, requires further investigation. Given the rapidly growing burden of NAFLD and obesity, assessment of fibrosis risk in obese patients undergoing metabolic surgery is instrumental in the management of these patients [45]. During study of Sheng et al it was found only 53 people had ALP toward the upper limit of the normal reference range. In other words, the ALP levels of 99.49% of the population in this study were within the normal reference range, so malnutrition, inflammation and immune response do not seem like likely explanations for this association [46].

### D. Albumin (Alb)

Albumin (Alb) is the most abundant protein of blood plasma. It is a single-chain, polypeptide with a molecular weight of 66,500 Da containing 585 amino acids. Serum albumin represents 60% of total plasma proteins and it has half-life is ~ 20 days in normal conditions [48 -50]. Younossi et al and Rafiq et al explain the role of Alb as an independent predictor of hepatic-related mortality [51,44]

.In 2021 study of Kawaguchi et al, It was show a findings from the retrospective multicenter study show that decline in serum albumin over a clinical course of several years following a diagnosis of NAFLD is an important factor associated with the incidence of severe events. The results in that study highlight the importance of careful monitoring of changes in serum albumin concentration for predicting the occurrence and prognosis of severe events in advanced NAFLD/NASH [52]. Hypoalbuminemia may develop in a diversity of condition like inflammation, insufficient, infections, nutrition, oxidative stress, cancer a, protein-loss diseases and liver function disorder [53-56]. Several studies found that albumin levels decrease in liver disease, one of them is a study [57].

### E. Lipid profile

Lipoproteins are complex aggregates of lipids and proteins that render the lipids compatible with the aqueous environment of body fluids (HDL, LDL, VLDL, chylomicrons) [71]. The hallmark of non-alcoholic fatty liver disease (58-61) is the expansion of lipid droplets in hepatocytes (LDs) containing triglycerides, cholesterol esters, and other types of lipids. To better reflect the metabolism-related etiology, Especially after reaching a recent consensus to change the name of this disease to metabolic fatty liver disease (MAFLD) [7]. At the level of tissue, the accumulation of fat can be benign, occurring without inflammation (hereafter referred to as metabolic-associated fatty liver; MAFL). Also it can progress to a state of chronic inflammation accompanied by tissue damage (steatohepatitis). In particular, this is frequently associated with fibrosis of varying degree, a condition characterized by collagen production through transformation of hepatic stellate cells to fibroblastlike cells. Although steatohepatitis is not directly life-threatening, the patients have an increased risk of developing advanced liver disease (fibrosis, cirrhosis, and hepatocellular carcinoma) and cardiovascular disease, the latter being the major cause of death in patients with MAFLD [61-63]. The following plasma lipid traits are hallmarks of MAFLD-associated dyslipidemia: hypertriglyceridemia due to large VLDL particles (VLDL1), elevated concentrations of small dense LDL, and low HDL cholesterol [64,65]. this change in LDL and HDL is regarded as a major reason for increased cardiovascular risk of individuals with MAFLD [66]. Mechanistically, small dense LDL are particularly harmful, as they can easily enter the vascular intima, which accelerates cholesterol deposition in atherosclerotic plaques. In case of HDL, the lower particle number observed in MAFLD subjects may impair cholesterol homeostasis. The following plasma lipid traits are hallmarks of MAFLD-associated dyslipidemia: hypertriglyceridemia due to large VLDL particles (VLDL1), elevated concentrations of small dense LDL, and low HDL cholesterol [67]. This change in LDL and HDL is regarded as a major reason for increased cardiovascular risk of individuals with MAFLD [66]. Mechanistically, small dense LDL are particularly harmful, as they can easily enter the vascular intima, which accelerates cholesterol deposition in atherosclerotic plaques. In case of HDL, the lower particle number observed in MAFLD subjects may impair cholesterol homeostasis. Liver steatosis develops when hepatocyte triglyceride

synthesis exceeds VLDL triglyceride secretion. Consequently, the development of MAFLD is tightly linked to VLDL production. Disturbances in VLDL secretion can not only cause the accumulation of triglycerides, but equally that of lipotoxic lipids carried by VLDL [68], and there by the development and progression of the disease. Conversely, excessive lipid storage in MAFLD promotes the secretion of VLDL and hence dyslipidemia. The study presented by Mansour-Ghanaei, et al, the individuals in NAFLD group had a higher TC, TC/HDL ratio and LDL/HDL ratio and lower HDL as compared to those in the non-NAFLD group. Furthermore, it was found a significant correlating between NAFLD group and TG, while no significant correlating was seen between LDL and NAFLD [14]. In a study presented by Santhos-hakumari et al., it was found marked increase in the levels of (TC, LDL, and TG) in patients group incompared with control group. Also it was found marked decrease in the levels of HDL in patients group incompared with control group [69]. In another study, presented by Novakovic et al, Also it was found the levels of LDL, and TC was higher than the normal range among NAFLD patients. [70].

### III. CONCLUSIONS

Metabolic fatty liver disease is closely associated with obesity and metabolic syndrome. Inflammation and fibrosis are the main factors determining the progression of liver disease. Liver fat accumulation is independent risk factor for CVD. According to previous studies NAFLD is linked with CVD risk. Fibrosis in MAFLD patients has not only correlated with liver-disease mortality and morbidity, but also with cardiovascular risk.

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