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LETTER TO THE EDITOR

Inflammatory biomarkers as cost-effective predictive tools in metabolic dysfunction-associated fatty liver disease

Davide Ramoni, Luca Liberale, Fabrizio Montecucco

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Abstract

Qu and Li emphasize a fundamental aspect of metabolic dysfunction-associated fatty liver disease in their manuscript, focusing on the critical need for non-invasive diagnostic tools to improve risk stratification and predict the progression to severe liver complications. Affecting approximately 25% of the global population, metabolic dysfunction-associated fatty liver disease is the most common chronic liver condition, with higher prevalence among those with obesity. This letter stresses the importance of early diagnosis and intervention, especially given the rising incidence of obesity and metabolic syndrome. Research advancements provide insight into the potential of biomarkers (particularly inflammation-related) as predictive tools for disease progression and treatment response. This overview addresses pleiotropic biomarkers linked to chronic inflammation and cardiometabolic disorders, which may aid in risk stratification and treatment efficacy monitoring. Despite progress, significant knowledge gaps remain in the clinical application of these biomarkers, necessitating further research to establish standardized protocols and validate their utility in clinical practice. Understanding the complex interactions among these factors opens new avenues to enhance risk assessment, leading to better patient outcomes and addressing the public health burden of this worldwide condition.

Key Words: Adipokines; Cardiometabolic risk assessment; Inflammatory biomarkers; Metabolic dysfunction-associated fatty liver disease; Metabolic syndrome; Osteopontin

Core Tip: Metabolic dysfunction-associated fatty liver disease is a rapidly growing condition that requires the identification of non-invasive diagnostic tools, particularly biomarkers that are readily detectable and cost-effective. In this article, we focused on inflammation-related biomarkers, which show promise due to their ability to impact both metabolic and cardiovascular diseases. Integrating these non-invasive tools into the clinical practice can reinforce risk stratification and facilitate early intervention. This approach not only enhances patient outcomes, but also addresses the rising prevalence of metabolic dysfunction-associated fatty liver disease. Continued research is essential to validate these biomarkers in clinical practice and to improve the management and personalization of care strategies.

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TO THE EDITOR

This article discusses the study by Qu and Li[1], published in a recent issue of *World Journal of Gastroenterology*, which explores the critical need for non-invasive diagnostic tools to assess risk of progression to advanced stages of metabolic dysfunction-associated fatty liver disease (MAFLD), especially given the limitations of liver biopsy, including invasiveness, cost, and variability in results. Their work emphasizes that several novel non-invasive biomarkers and diagnostic panels, such as serum biomarkers (*e.g.*, propeptide of collagen type 3 algorithm and cytokeratin-18), imaging biomarkers (*e.g.*, FibroScan, magnetic resonance, and elastography), and gut-microbiome-derived markers, are being developed and tested. These biomarkers show promise in identifying advanced fibrosis and distinguishing between the various stages of MAFLD. However, Qu and Li[1] noted that while the progress is promising, none of these non-invasive approaches have yet proven reliable enough to fully replace liver biopsy, particularly for the diagnosis of steatohepatitis and fibrosis. Their work underscores the importance of continued research and validation of these diagnostic methods.

MAFLD has emerged as the most common chronic liver condition globally, affecting approximately 25% of the global population and an even higher percentage "up to 50%" among overweight or obese individuals[2,3]. MAFLD is primarily characterized by hepatic steatosis, defined as the pathological accumulation of fat within liver cells in addition of metabolic dysregulation, which can lead to inflammation and fibrosis as the disease progresses[4]. MAFLD is closely linked with a range of serious health issues, including cardiometabolic and cardiovascular (CV) conditions. The disease also significantly increases the risk of liver-related complications and mortality, making it a critical public health concern [5,6]. Despite its widespread prevalence, MAFLD often remains undiagnosed until it reaches more advanced stages, emphasizing the need for greater awareness and early intervention. The management of MAFLD requires a multifaceted approach that includes lifestyle modifications, and, in some cases, pharmacological treatments. Given the rising incidence of obesity and metabolic syndrome (MetS) globally, MAFLD's impact is likely to grow, necessitating continued research and public health initiatives aimed at prevention and early management[7]. MetS is a group of conditions that significantly raise the risk of CV diseases, type 2 diabetes, and liver-related complications[8].

The link between MetS and MAFLD is well establishment, as MetS is a major factor in both the development and progression of MAFLD. Indeed, most patients with MAFLD exhibit features of MetS, and the criteria used to diagnose MetS (at least three of the following five criteria), such as abdominal obesity, elevated fasting glucose levels, high blood pressure, elevated triglycerides, and low high density lipoprotein cholesterol levels, are closely linked to the patho-physiology of MAFLD[9]. These criteria are widely accepted in clinical practice and serve as a key framework to identify individuals at risk of metabolic complications.

Recent research in the field of MAFLD has made significant advancements over the past 5 years, particularly in the integration of novel diagnostic and prognostic tools into clinical practice, including the use of metagenomics, advanced imaging techniques, and visceral fat assessments to better understand and manage MAFLD. Among these, the role of biomarkers as predictive indicators of disease progression and long-term outcomes has garnered particular attention. Here, we aimed to focus on the significance of biomarkers as predictive indicators of risk of progression to end-stage and poor long-term outcomes.

INFLAMMATORY-RELATED BIOMARKERS IN MAFLD

Overview and outlook

Biomarkers present a promising approach to identify patients at high risk of progressing to severe liver disease and experiencing unfavorable long-term outcomes, while their ability to predict treatment response and assess disease development risk is crucial for tailoring personalized therapeutic strategies. As the clinical utility of these biomarkers continues to be validated, their incorporation into routine practice could transform the management of MAFLD, enabling earlier intervention and improving patient outcomes. Ongoing research is pivotal for the effective implementation of these biomarkers in clinical settings, aiming to reduce the burden of MAFLD through more precise and individualized

care strategies. In the last decade, we have moved from the obesity and body mass index paradox[10], to assessing body fat phenotypes, finding a close correlation between visceral fat (both abdominal and epicardial) and CV mortality, as well as the development of MAFLD and MetS[11]. The stratification of CV risk now includes not only classic risk factors, but is also evolving toward a global cardiometabolic risk assessment, considering visceral adipose tissue distribution, ectopic fat deposition, low-grade inflammatory status, and insulin resistance[12,13].

Biomarkers have recently been used as diagnostic tools in MAFLD[14,15], because their collection is often minimally invasive and inexpensive, being found in serum or urine. Several candidates have been proposed, although so far only a few have found general applicability. Among these, tools like the fibrosis-4 index and the aspartate aminotransferase (AST) to platelet ratio index (APRI) have gained significant clinical utility. These indices use routine clinical and laboratory data to predict fibrosis progression and stratify patients according to their risk, offering a practical and less invasive approach to liver disease assessment. The fibrosis-4 utilizes clinical parameters such as age, AST, alanine aminotransferase, and platelet count to predict the presence of advanced fibrosis. It is particularly useful to identify patients at higher risk of fibrosis progression, distinguishing them from those with severe fibrosis or cirrhosis, and thus, reducing the need for more invasive procedures like liver biopsy[16].

Similarly, the APRI is another non-invasive test used to evaluate severe liver fibrosis. APRI is calculated by taking the ratio of AST to platelet count, and like fibrosis-4, is commonly used due to its simplicity and the availability of required data from standard clinical tests[17]. These tools are particularly effective at identifying patients with advanced liver fibrosis, but are less useful in the early stages of the disease. For this reason, in the following sections, we focus on inflammation-related biomarkers, which have the potential to bridge cardiometabolic conditions and enhance this comprehensive approach.

Focus on osteopontin and adipokines: Pleiotropic molecules

Several inflammation-related biomarkers have been identified in MAFLD, which can help in assessing disease severity and progression. Osteopontin (OPN) has emerged as a promising candidate biomarker due to its multifunctional properties in mediating cell-to-cell interactions. OPN is a phosphorylated glycoprotein composed of approximately 300 amino acids, playing a significant role in immune regulation, inflammation, and tissue remodeling. A key characteristic of OPN is its arginine-glycine-aspartic acid (ARG) sequence, which facilitates binding to integrins and other receptors on cell surfaces. This interaction is crucial for cell adhesion, migration, and signaling. While OPN is primarily recognized for its function in bone metabolism - binding to hydroxyapatite in the bone matrix to regulate remodeling, its effects extend beyond the skeletal system. It is increasingly acknowledged as a mediator in immune responses and inflammatory processes, particularly in liver diseases due to its role in promoting fibrosis[18]. Additionally, OPN is significant in the pathophysiology of metabolic diseases such as MetS and MAFLD[19]. OPN levels are typically measured using enzyme-linked immunosorbent assay (ELISA), a sensitive and specific method commonly employed in both research and clinical studies.

Among its immunoregulatory functions, OPN is particularly important in macrophage senescence. Macrophages, which are key immune cells within adipose tissue, can enter a state of senescence in response to chronic metabolic stress. This senescence is characterized by the secretion of pro-inflammatory cytokines and other factors that exacerbate tissue inflammation and fibrosis. Elevated serum OPN not only contributes to the expansion of adipocytes and the recruitment of macrophages in adipose tissue, but also regulates their transition into a senescent state, thereby perpetuating a cycle of chronic inflammation[20]. The role of OPN as a regulator of both adipose tissue and macrophage senescence underscores its importance in the development and progression of metabolic diseases. In liver, OPN expression has been shown to identify a distinct subset of recruited macrophages that differ from the resident Kupffer cells in the context of fatty liver disease. In conditions such as MAFLD, there is an influx of monocyte-derived macrophages that contribute to the inflammatory response and tissue remodeling[21]. OPN is highly expressed in these recruited macrophages, highlighting their functional roles in the pathological processes of fatty liver. Serum OPN-expressing macrophages are associated with increased inflammation and the development of fibrosis[22,23]. The presence of OPN in recruited macrophages correlates with the severity of liver inflammation and injury, suggesting that OPN makes a valuable indicator of disease progression in patients with MAFLD.

Moreover, elevated levels of serum OPN promote the recruitment of T cells, particularly pro-inflammatory subsets, which exacerbate the inflammatory environment characteristic of obesity and metabolic disorders[24]. The OPN-driven mechanisms underlying T cell dynamics in both adipose tissue and the liver underscore the importance of this biomarker in linking inflammation to metabolic dysfunction. In adipose tissue, OPN facilitates the infiltration of T cells, leading to chronic inflammation that disrupts insulin signaling pathways, thereby contributing to the development of insulin resistance[25]. In the liver, OPN-activated T cells further aggravate hepatic inflammation and steatosis, driving the progression of MAFLD. The pro-inflammatory cytokines released by these T cells can worsen liver injury and promote fibrotic changes, further advancing the disease and increasing the risk of advanced liver pathology[24]. Therefore, serum OPN could correlate with histological findings in liver biopsies, supporting its use in clinical settings for risk stratification and monitoring treatment responses. Finally, OPN appears to be correlated with MetS not only in serum, but also in urine samples, where urinary OPN has been shown to outperform traditional anthropometric measures in predicting improvements in MetS parameters[26]. The ability of urinary OPN to complement anthropometric assessments provides a non-invasive and accessible method to evaluate patient progress and guide therapeutic interventions. Furthermore, the reciprocal interactions between insulin and adipokines, such as leptin and adiponectin, are of great interest in MAFLD, as they significantly influence hepatic fat accumulation and inflammation[27]. Leptin, a 16-kDa peptide hormone secreted by adipose tissue, plays a key role in energy homeostasis, and is closely linked to obesity, insulin resistance, and inflammation[28]. Leptin levels can be determined using ELISA or radioimmunoassay, both of which are reliable methods to accurately quantify hormone concentrations in serum samples.

Adiponectin, another hormone produced by adipose tissue, stands out for its beneficial metabolic effects, especially in relation to glucose regulation and fatty acid metabolism. Structurally, adiponectin is a 30-kDa protein consisting of 244 amino acids that exists in the circulation in various molecular weight forms, which are produced by multimerization. These different forms allow adiponectin to act in multiple tissues. It has direct actions in the liver, skeletal muscle, and the vasculature, where it enhances insulin sensitivity, regulates glucose uptake, promotes fatty acid oxidation, and exhibits anti-inflammatory effects[29]. Given its protective role in metabolic health, adiponectin is an important biomarker for assessing metabolic and liver function.

Like leptin, adiponectin is commonly measured using ELISA, allowing for precise detection and monitoring in clinical settings. One of the key advantages of ELISA is its ability to use smaller amounts of reagents compared to other techniques, such as radioimmunoassay or more advanced molecular tests, which significantly reduces costs, particularly when processing large numbers of samples. Its flexibility allows for efficient high-throughput testing, making it suitable for routine clinical applications. Additionally, ELISA's straightforward methodology, which involves minimal specialized training, further enhances its cost-effectiveness by reducing labor costs and the time required for assay development, further contributing to its widespread adoption in laboratories globally. Its simplicity and use of standard blood tests make it a practical tool in routine clinical practice.

Beyond their metabolic functions, adipokines have been implicated in various immune processes, highlighting a critical intersection between metabolism and immunity. In the innate immune system, leptin enhances the activation and proliferation of macrophages and neutrophils, promoting the release of pro-inflammatory cytokines like tumor necrosis factor alpha and interleukin-6. In adaptive immunity, leptin modulates T cell responses, favoring T helper type 1 over T helper type 2 polarization, thereby enhancing cell-mediated immunity[30]. Adiponectin negatively regulates the innate immune response by inhibiting macrophage activation and reducing the secretion of pro-inflammatory cytokines[31].

Balance between leptin and adiponectin is often disrupted in metabolic diseases, leading to immune dysfunctions that contribute to the pathophysiology of obesity-related complications. Furthermore, insulin resistance promotes hepatic lipogenesis, while simultaneously inhibiting fatty acid oxidation, leading to an increased triglyceride accumulation in hepatocytes (a primary characteristic of MAFLD). While leptin regulates appetite and energy expenditure, elevated leptin levels due to obesity can lead to a state of leptin resistance. This pathophysiological event diminishes leptin's ability to signal appropriately, contributing to insulin resistance and promoting hepatic steatosis and inflammation[32]. Elevated leptin levels have been correlated with the severity of liver damage in MAFLD patients[33].

Conversely, adiponectin is known for its anti-inflammatory and insulin-sensitizing properties. Low levels of adiponectin are commonly observed in individuals with obesity and MAFLD. The decline in adiponectin is associated with increased hepatic lipogenesis and reduced fatty acid oxidation, facilitating the progression to advanced stages of MAFLD, which is characterized by inflammation and fibrosis[34,35]. Together, the dysregulation of insulin, leptin, and adiponectin creates a complex hormonal environment that promotes the development and progression of MAFLD. Understanding the specific roles of these hormones can aid in the development of targeted therapies that address both the metabolic and hepatic aspects of MAFLD.

GAPS IN KNOWLEDGE AND FUTURE RESEARCH DIRECTIONS

The article highlighted significant gaps in knowledge surrounding the management of MAFLD, particularly regarding the clinical implementation of non-invasive diagnostic tools and biomarkers. Although recent advancements were highlighted, such as the identification of biomarkers and its role in linking inflammation with metabolic dysfunction, further research is needed to establish standardized protocols for their use in clinical settings and algorithms. Future research should focus on validating the efficacy of various biomarkers in predicting disease progression and tailoring personalized treatment strategies. Additionally, persistent elevated levels of OPN are linked to a higher likelihood of experiencing major adverse CV events, and serum concentration is a significant predictor of CV disease, regardless of conventional risk factors.

Understanding the interplay between CV risk, adipose fat distribution, and inflammation in MAFLD progression could inform the development of targeted therapies that address both cardiometabolic and hepatic factors. There is a pressing need for longitudinal studies to assess how changes in biomarker levels correlate with disease outcomes and treatment responses. Moreover, exploring the accessibility and cost-effectiveness of these diagnostic tools is essential to ensure they can be widely adopted in diverse healthcare settings. Addressing these gaps will be crucial in moving toward a more individualized approach to MAFLD management, aiming to improve patient outcomes and reduce the burden of this increasingly prevalent condition.

CONCLUSION

This overview underscores the vital role of inflammation-related biomarkers in the assessment and management of MAFLD. Biomarkers, such as OPN, not only reflect the inflammatory status, but also provide insights into the risk of disease progression. By integrating these biomarkers into practice, clinicians can enhance risk stratification, enable timely personalized interventions, and potentially improve patient outcomes. Continued research into these inflammatory and cardiometabolic related biomarkers will be essential for addressing the growing public health burden of MAFLD.

FOOTNOTES

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