ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2024 September 27; 16(9): 1199-1311

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

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Monthly Volume 16 Number 9 September 27, 2024

LETTER TO THE EDITOR

World Journal of Hepatology

Monthly Volume 16 Number 9 September 27, 2024

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The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (ESCI), Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 Edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJH* as 2.5; JIF Quartile: Q2. The *WJH*'s CiteScore for 2023 is 4.1 and Scopus CiteScore rank 2023: Hepatology is 41/82.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

PUBLICATION DATE
September 27, 2024

PUBLISHING PARTNER
Department of Infectious Diseases, the Second Affiliated Hospital of Xi'an Jiaotong University

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

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ONLINE SUBMISSION
https://www.f6publishing.com

PUBLISHING PARTNER's OFFICIAL WEBSITE
http://2yuan.xjtu.edu.cn/Html/Departments/Main/Index_21148.html

E-mail: office@baishideng.com https://www.wjgnet.com

World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2024 September 27; 16(9): 1206-1210

DOI: 10.4254/wjh.v16.i9.1206

ISSN 1948-5182 (online)

EDITORIAL

Kick-start for metabolomics in liver disease

Armando Guerra-Ruiz

Specialty type: Medical laboratory technology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A
Novelty: Grade A
Creativity or Innovation: Grade A
Scientific Significance: Grade A

P-Reviewer: Huang ZT

Received: May 18, 2024
Revised: July 12, 2024
Accepted: July 17, 2024
Published online: September 27, 2024
Processing time: 128 Days and 9.3 Hours

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Abstract

It is not complicated for the clinician to diagnose a patient with advanced fibrosis or liver cirrhosis when he has already presented some decompensation of his liver disease. However, it is in the earliest stages when the patient's prognosis can be modified the most. Since liver disease is generally asymptomatic, not invasive markers are of great relevance. In the era of omics, it is time for metabolomics to accompany genomics and proteomics, which are more established in the diagnostics and prognostics clinical toolbox. Metabolomics, understood as the comprehensive evaluation of the metabolites present in the organism in a specific physiological situation, has undoubted advantages in the study and identification of serum markers relevant to a specific pathology. Last year, I read with interest two articles published in this journal: "Baseline metabolites could predict responders with hepatitis B virus-related liver fibrosis for entecavir or combined with FuzhengHuayu tablet" by Dai *et al* and "Metabolomics in chronic hepatitis C: Decoding fibrosis grading and underlying pathways" by Ferrasi *et al*. Both papers illuminate the power of metabolomics to provide us with new tools in the management of liver disease. In this editorial, I comment on these studies and others, and note how they can contribute to our understanding of liver disease in more than one way.

Key Words: Metabolomics; Liver disease; Biomarkers; Hepatology; Mass spectrometry; Hepatitis; Clinical biochemistry

Core Tip: This editorial explores the transformative potential of metabolomics in liver disease research and management. Highlighting four key studies, we explore how metabolomics aids in biomarker discovery, reveals altered biochemical pathways, supports personalized medicine, and elucidates disease mechanisms. By integrating metabolomics in clinical practice, we can enhance early diagnosis, optimize treatment strategies, and develop targeted therapies, ultimately improving patient outcomes. This comprehensive approach underscores the versatility and importance of metabolomics in advancing precision medicine for liver diseases.

Citation: Guerra-Ruiz A. Kick-start for metabolomics in liver disease. *World J Hepatol* 2024; 16(9): 1206-1210
URL: https://www.wjgnet.com/1948-5182/full/v16/i9/1206.htm
DOI: https://dx.doi.org/10.4254/wjh.v16.i9.1206

INTRODUCTION

Diagnosing advanced fibrosis or cirrhosis in patients with obvious liver decompensation is relatively straightforward for clinicians. However, it is in the early stages that intervention can significantly alter a patient's prognosis. Given that liver disease is often asymptomatic, non-invasive markers are of paramount importance. In the era of omics, it is time for metabolomics to join the ranks of genomics and proteomics, both more established in diagnostics and prognostics, in the clinical toolbox.

All three - genomics, proteomics, and metabolomics - are branches of 'omics' sciences, which aim to collectively characterize and quantify pools of biological molecules that translate into the structure, function, and dynamics of an organism. They all contribute to our understanding of biological systems and have significant applications in various areas, including medicine and biological sciences.

As to the differences between them, genomics is the study of the complete set of genetic instructions (*i.e.* potential) encoded in DNA. Proteomics focuses on the identification, characterization, and quantification of proteins present in a given sample. It aims to unravel the complex network of protein interactions and their functions within a biological system. Metabolomics, on the other hand, primarily deals with the comprehensive analysis of small molecules, known as metabolites, present in a biological sample. It aims to understand the metabolic pathways and processes occurring within an organism. In summary, while genomics provides the blueprint of life, proteomics gives us an understanding of the machinery that carries out the instructions in the blueprint, and metabolomics provides a snapshot of the final products of these processes.

I have to admit that, as an enthusiast of clinical biochemistry and hepatology, my interest in metabolomics has been growing in recent years. The comprehensive evaluation of metabolites present in an organism under specific physiological conditions offers undeniable advantages in identifying serum markers pertinent to particular pathologies.

In the past year, I have been particularly captivated by two articles published in this journal: "Baseline metabolites could predict respon-ders with hepatitis B virus-related liver fibrosis for entecavir or combined with FuzhengHuayu tablet" by Dai *et al*[1]; and "Metabolomics in chronic hepatitis C: Decoding fibrosis grading and underlying pathways" by Ferrasi *et al*[2]. Both studies illuminate the power of metabolomics in providing novel insights and tools for managing liver disease. This editorial explores these studies and highlights their contributions to our understanding of liver disease in more than one way. To further underscore this point, I will also incorporate insights from two additional studies: "Obesity-dependent metabolic signatures associated with nonalcoholic fatty liver disease progression" by Barr *et al*[3]; and "ACOX2 deficiency: An inborn error of bile acid synthesis identified in an adolescent with persistent hypertransaminasemia" by Monte *et al*[4]. These studies will help me highlight the utility of metabolomics in liver disease research.

BIOMARKER DISCOVERY

In the article by Dai *et al*[1], titled "Baseline metabolites could predict responders with hepatitis B virus-related liver fibrosis for entecavir or combined with FuzhengHuayu tablet," researchers explored baseline serum metabolite profiles to predict therapeutic responses in hepatitis B virus (HBV)-related liver fibrosis. Patients were categorized as responders or non-responders based on their histological response to entecavir and combined therapy with FuzhengHuayu tablet (FZHY). The study identified key metabolic pathways and differential metabolites, including linoleic acid metabolism, aminoacyl-tRNA biosynthesis, cyanoamino acid metabolism, and alanine, aspartate, and glutamate metabolism. Metabolites like hydroxypropionic acid, tyrosine, and citric acid emerged as potential therapeutic efficacy predictors.

These findings emphasized the significance of baseline metabolic profiling in managing HBV-related liver fibrosis. Identifying likely responders allows clinicians to optimize treatment strategies and improve outcomes. Additionally, insights into metabolic pathways offer valuable targets for new treatments.

This study also identified specific serum metabolites that can predict the therapeutic response in patients with HBV-related liver fibrosis. By distinguishing between responders and non-responders to treatments, the research was able to highlight the potential of these metabolites as biomarkers. This finding will aid in early diagnosis and monitoring the effectiveness of treatments, emphasizing the role of metabolomics in personalized patient care.

Biomarker Discovery. Metabolomics identifies specific metabolites associated with liver diseases. These biomarkers can aid in early diagnosis, disease monitoring, and treatment response assessment.

PATHWAY INSIGHTS

The study by Ferrasi *et al*[2], titled "Metabolomics in chronic hepatitis C: Decoding fibrosis grading and underlying pathways," employed metabolomic profiling to uncover metabolic alterations linked to various stages of fibrosis in patients with chronic hepatitis C. Using high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS), the researchers identified a set of metabolites distinguishing different fibrosis grades. Significant disruptions in metabolic pathways, including amino acid metabolism, bile acid synthesis, and energy production, were noted. For example, variations in citric acid levels, a key tricarboxylic acid cycle component, correlated with fibrosis severity, suggesting energy metabolism disruptions play a crucial role in fibrosis progression.

Importantly, the study identified potential non-invasive biomarkers for fibrosis grading, which could replace invasive methods like liver biopsy. This could lead to simpler, more accurate diagnostic tools for monitoring disease progression and tailoring therapeutic interventions.

Ferrasi *et al*'s research[2] delved into the metabolic pathways altered in chronic hepatitis C patients with varying fibrosis stages. The study uncovered significant disruptions in various metabolic pathways. These insights into the biochemical processes altered by liver disease will help identify potential therapeutic targets, ultimately showcasing how metabolomics can reveal critical pathway changes.

Pathway Insights. By analyzing metabolic pathways, metabolomics reveals altered biochemical processes in liver diseases. Understanding these pathways helps identify potential therapeutic targets.

PERSONALIZED MEDICINE

There are previous studies that can further illuminate the utility of metabolomics in the field of hepatology. The study by Barr *et al*[3] titled "Obesity-dependent metabolic signatures associated with nonalcoholic fatty liver disease progression" focused on how metabolic profiles change with disease progression in nonalcoholic fatty liver disease (NAFLD). This comprehensive study analyzed 540 serum metabolites in patients with normal liver histology, simple steatosis, and nonalcoholic steatohepatitis (NASH). The findings revealed significant metabolic alterations associated with obesity levels and inflammation, including changes in lipid and amino acid metabolism.

The study's key contribution was the identification of a body mass index (BMI)-dependent serum metabolic profile that can distinguish NASH from simple steatosis with high accuracy. This finding highlights the potential of metabolomics to identify biomarkers for early disease detection and progression, paving the way for personalized therapeutic strategies.

Barr *et al*[3] also demonstrated how metabolic profiles change with disease progression in NAFLD. These findings will enable tailored therapeutic strategies based on an individual's metabolomic profile, optimizing drug selection and dosage for personalized treatment.

Personalized Medicine. Metabolomics enables personalized treatment by tailoring interventions based on an individual's metabolic profile. This approach optimizes drug selection and dosage.

MECHANISTIC STUDIES

Another noteworthy study is "ACOX2 deficiency: An inborn error of bile acid synthesis identified in an adolescent with persistent hypertransaminasemia" by Monte *et al*[4]. This research shed light on a rare genetic disorder affecting bile acid synthesis, presenting as persistent hypertransaminasemia. The study highlighted the case of an adolescent with a homozygous mutation in the *ACOX2* gene, leading to an accumulation of toxic C27 bile acid intermediates. Through advanced techniques like LC-MS/MS and genetic sequencing, the study was able to provide crucial insights into the metabolic consequences of *ACOX2* deficiency and its potential as a target for therapeutic intervention.

The study had utilized LC-MS/MS to analyze serum and urine samples. This technique allowed for the precise detection and quantification of bile acid species, crucial for diagnosing the patient's condition. The metabolomics analysis revealed a significant deficiency of C24 bile acids in the patient's serum and urine, alongside elevated levels of C27 intermediates, particularly tauroconjugated trihydroxycholestanoic acid. This biochemical profile was indicative of ACOX2 deficiency, a novel cause of persistent hypertransaminasemia.

Furthermore, this paper describes the investigation of a rare genetic disorder affecting bile acid synthesis, providing insights into the disease mechanisms. The study highlighted how *ACOX2* deficiency leads to the accumulation of toxic C27 bile acid intermediates, causing persistent hypertransaminasemia. By LC-MS/MS and genetic sequencing, the research was able to elucidate the role of oxidative stress and that of disrupted bile acid metabolism in liver disease, providing guidance for the development of targeted therapies.

Mechanistic Studies. Metabolomics sheds light on disease mechanisms, such as oxidative stress, inflammation, and lipid metabolism dysregulation, providing insights for drug development.

COMPREHENSIVE APPROACH

Needless to say, while each of the highlighted studies contributes uniquely to our understanding of liver disease through distinct roles, these roles are not isolated. The interconnected nature of metabolomics allows for a comprehensive approach where multiple studies concurrently address various aspects of liver disease research.

The study by Ferrasi *et al*[2], "Metabolomics in chronic hepatitis C: Decoding fibrosis grading and underlying pathways," primarily illustrates pathway insights by uncovering disrupted metabolic pathways. However, the identification of specific metabolites that correlate with fibrosis stages also serves as crucial biomarker discovery. These biomarkers can be used for early diagnosis and monitoring disease progression, bridging the gap between understanding biochemical pathways and practical clinical applications.

Similarly, the study by Dai *et al*[1] on "Baseline metabolites could predict responders with hepatitis B virus-related liver fibrosis" highlights biomarker discovery by identifying metabolites predictive of treatment response. Yet, the analysis of metabolic pathways involved in these predictions provides significant pathway insights, enhancing our understanding of the biochemical underpinnings of treatment efficacy.

Each study exemplifies how metabolomics transcends a single role, providing a holistic approach to liver disease research. Biomarker discovery often necessitates understanding underlying pathways, while insights into these pathways can reveal mechanisms of disease and inform personalized treatments. As these studies show, the interconnected nature of metabolomics facilitates a multi-faceted exploration of liver disease, driving advancements in diagnostics, therapeutics, and personalized medicine.

CONCLUSION

The integration of metabolomics in liver disease research and treatment marks a significant advancement towards precision medicine. Decoding complex metabolic changes linked to disease progression and treatment response opens new avenues for personalized healthcare. The studies discussed exemplify metabolomics' transformative potential, offering hope for more effective diagnostics, targeted therapies, and improved patient outcomes. As the field evolves, further research and clinical validation will be essential to fully harness metabolomics' power in liver disease management.

By leveraging insights from these metabolomic studies, the medical community can develop more accurate, non-invasive diagnostic tools and tailored treatments, enhancing care quality for liver disease patients. The journey has just begun, and the future of metabolomics in liver disease looks promising.

ACKNOWLEDGEMENTS

To all my colleagues, whose continual research efforts and collaborative spirit advance our field.

FOOTNOTES

Author contributions: As the sole author, Guerra-Ruiz A was responsible for all aspects of the work, including conception, design, research, writing, and finalization of the manuscript. No external contributions or assistance were involved in the preparation of this editorial.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Liu H
L-Editor: A
P-Editor: Cai YX

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