



Editorial

NAFLD/MAFLD: New Evidence

Alessandro Mantovani ^{1,*}  and Andrea Dalbeni ²

¹ Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, 37126 Verona, Italy

² Section of General Medicine C and Liver Unit, University and Azienda Ospedaliera Universitaria Integrata of Verona, 37126 Verona, Italy

* Correspondence: alessandro.mantovani@univr.it; Tel.: +39-045-812-7672

The aim of the second edition of our Special Issue, entitled “Nonalcoholic Fatty Liver Disease/Metabolic Associated Fatty Liver Disease: New Insights 2.0”, is to report the recent experimental and observational studies about NAFLD/MAFLD, which is the most common chronic liver disease worldwide to date [1]. Overall, nine original articles and eight narrative reviews have been published. Among original articles, Mantovani et al. showed that the presence of Fibroscan[®]-assessed significant fibrosis was independently associated with an increased risk of developing worse glycaemic control in female patients with type 2 diabetes (T2DM) and NAFLD/MAFLD [2]. These findings further support the assertion that the relationship between NAFLD/MAFLD and T2DM is complex and bidirectional [3]. In addition, the study by Mantovani et al. also highlights the need for a multidisciplinary and holistic approach to patients with T2DM and NAFLD [4]. Viganò et al. reported that the FIB-4 score might be suboptimal to identify patients with advanced forms of NAFLD/MAFLD referring to liver centers, given that the Authors found that approximately one-fifth of patients included in the study were false negative at FIB-4 score, despite a liver stiffness measurement ≥ 8 kPa [5]. Therefore, maybe, the use of more techniques to identify (non-invasively) patients with NAFLD/MAFLD and liver fibrosis might be more appropriate in clinical practice. In another observational study, Bourgonje et al. documented that higher plasma calprotectin levels were independently associated with suspected NAFLD/MAFLD, as well as with an increased risk of all-cause mortality [6]. Although further studies are needed, these results might suggest that circulating levels of calprotectin might be a potential and novel biomarker of NAFLD/MAFLD. The other original articles published in our Special Issue discussed other important issues about NAFLD/MAFLD, such as the adipokines and cytokines in the saliva of obese people with NAFLD/MAFLD [7], the relationship between FXR (farnesoid X receptor) transcriptional activity and the mTORC1 (mammalian target of rapamycin1)/S6K1 (ribosomal protein S6 kinase beta-1)/PGC1 α (peroxisome proliferator receptor gamma coactivator1 α) pathway [8], the association between liver alterations and insulin resistance in pediatric patients with NAFLD/MAFLD [9], the role of ERMCS (endoplasmic reticulum–mitochondria contacts) in the progression of advanced forms of NAFLD/MAFLD [10], the role of mitochondrial electron transport chain (ETC) [11] and histone lysine demethylase KDM7A (also called JHDM1D) [12] in the development of NAFLD/MAFLD.

Among narrative reviews, Teng et al. discussed the recent information about the pathological progression of NAFLD/MAFLD and its advanced forms, as well as the potential therapeutic targets [13], including GLP-1 receptor agonists and other glucose-lowering agents. In this regard, Subramanian et al. discussed the cellular crosstalk between hepatic stellate cells and other cells within the liver, able to promote liver fibrosis in NAFLD/MAFLD [14]; biological mechanisms that should be used for the development of additional drugs in order to treat NAFLD/MAFLD. The other narrative reviews published in our Special Issue discussed other relevant issues about NAFLD/MAFLD, including the role of fibroblast growth factors [15], hydrogen sulfide [16], nuclear receptors [17],



Citation: Mantovani, A.; Dalbeni, A. NAFLD/MAFLD: New Evidence. *Int. J. Mol. Sci.* **2023**, *24*, 7241. <https://doi.org/10.3390/ijms24087241>

Received: 8 April 2023

Accepted: 11 April 2023

Published: 14 April 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

calcium signaling [18] in the development and progression of NAFLD/MAFLD, the role of various natural products in the treatment of NAFLD/MAFLD [19] as well as the association between MAFLD and chronic kidney disease (CKD) [20].

We hope that the second edition of the Special Issue will help produce new evidence about NAFLD/MAFLD, in order to improve the lives of these people.

Author Contributions: A.M.; writing—original draft preparation, A.M. and A.D.; writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

- Mantovani, A.; Scorletti, E.; Mosca, A.; Alisi, A.; Byrne, C.D.; Targher, G. Complications, morbidity and mortality of nonalcoholic fatty liver disease. *Metabolism* **2020**, *111S*, 154170. [\[CrossRef\]](#) [\[PubMed\]](#)
- Mantovani, A.; Taverna, A.; Cappelli, D.; Beatrice, G.; Csermely, A.; Sani, E.; Byrne, C.D.; Targher, G. Long-Term Adverse Effect of Liver Stiffness on Glycaemic Control in Type 2 Diabetic Patients with Nonalcoholic Fatty Liver Disease: A Pilot Study. *Int. J. Mol. Sci.* **2022**, *23*, 12481. [\[CrossRef\]](#) [\[PubMed\]](#)
- Targher, G.; Corey, K.E.; Byrne, C.D.; Roden, M. The complex link between NAFLD and type 2 diabetes mellitus-mechanisms and treatments. *Nat. Rev. Gastroenterol. Hepatol.* **2021**, *18*, 599–612. [\[CrossRef\]](#) [\[PubMed\]](#)
- Mendez-Sanchez, N.; Bugianesi, E.; Gish, R.G.; Lammert, F.; Tilg, H.; Nguyen, M.H.; Sarin, S.K.; Fabrellas, N.; Zelber-Sagi, S.; Fan, J.G.; et al. Global multi-stakeholder endorsement of the MAFLD definition. *Lancet Gastroenterol. Hepatol.* **2022**, *7*, 388–390. [\[CrossRef\]](#) [\[PubMed\]](#)
- Vigano, M.; Pugliese, N.; Cerini, F.; Turati, F.; Cimino, V.; Ridolfo, S.; Rocchetto, S.; Foglio, F.; Terrin, M.; La Vecchia, C.; et al. Accuracy of FIB-4 to Detect Elevated Liver Stiffness Measurements in Patients with Non-Alcoholic Fatty Liver Disease: A Cross-Sectional Study in Referral Centers. *Int. J. Mol. Sci.* **2022**, *23*, 12489. [\[CrossRef\]](#) [\[PubMed\]](#)
- Bourgonje, A.R.; van den Berg, E.H.; Kieneker, L.M.; Nilsen, T.; Hidden, C.; Bakker, S.J.L.; Blokzijl, H.; Dullaart, R.P.F.; van Goor, H.; Abdulle, A.E. Plasma Calprotectin Levels Associate with Suspected Metabolic-Associated Fatty Liver Disease and All-Cause Mortality in the General Population. *Int. J. Mol. Sci.* **2022**, *23*, 15708. [\[CrossRef\]](#) [\[PubMed\]](#)
- Zysk, B.; Ostrowska, L.; Smarkusz-Zarzecka, J.; Witczak-Sawczuk, K.; Gornowicz, A.; Bielawska, A. Pro-Inflammatory Adipokine and Cytokine Profiles in the Saliva of Obese Patients with Non-Alcoholic Fatty Liver Disease (NAFLD)—A Pilot Study. *Int. J. Mol. Sci.* **2023**, *24*, 2891. [\[CrossRef\]](#) [\[PubMed\]](#)
- Roglans, N.; Fauste, E.; Bentanachs, R.; Velazquez, A.M.; Perez-Armas, M.; Donis, C.; Panadero, M.I.; Alegret, M.; Otero, P.; Bocos, C.; et al. Bempedoic Acid Restores Liver H(2)S Production in a Female Sprague-Dawley Rat Dietary Model of Non-Alcoholic Fatty Liver. *Int. J. Mol. Sci.* **2022**, *24*, 10473. [\[CrossRef\]](#) [\[PubMed\]](#)
- Berndt, N.; Hudert, C.A.; Eckstein, J.; Loddenkemper, C.; Henning, S.; Bufler, P.; Meierhofer, D.; Sack, I.; Wiegand, S.; Wallach, I.; et al. Alterations of Central Liver Metabolism of Pediatric Patients with Non-Alcoholic Fatty Liver Disease. *Int. J. Mol. Sci.* **2022**, *23*, 11072. [\[CrossRef\]](#) [\[PubMed\]](#)
- Jin, C.; Felli, E.; Lange, N.F.; Berzigotti, A.; Gracia-Sancho, J.; Dufour, J.F. Endoplasmic Reticulum and Mitochondria Contacts Correlate with the Presence and Severity of NASH in Humans. *Int. J. Mol. Sci.* **2022**, *23*, 8348. [\[CrossRef\]](#) [\[PubMed\]](#)
- Fahlbusch, P.; Nikolic, A.; Hartwig, S.; Jacob, S.; Kettel, U.; Kollmer, C.; Al-Hasani, H.; Lehr, S.; Muller-Wieland, D.; Knebel, B.; et al. Adaptation of Oxidative Phosphorylation Machinery Compensates for Hepatic Lipotoxicity in Early Stages of MAFLD. *Int. J. Mol. Sci.* **2022**, *23*, 6873. [\[CrossRef\]](#) [\[PubMed\]](#)
- Kim, J.H.; Nagappan, A.; Jung, D.Y.; Suh, N.; Jung, M.H. Histone Demethylase KDM7A Contributes to the Development of Hepatic Steatosis by Targeting Diacylglycerol Acyltransferase 2. *Int. J. Mol. Sci.* **2021**, *22*, 11085. [\[CrossRef\]](#) [\[PubMed\]](#)
- Teng, T.; Qiu, S.; Zhao, Y.; Zhao, S.; Sun, D.; Hou, L.; Li, Y.; Zhou, K.; Yu, X.; Yang, C.; et al. Pathogenesis and Therapeutic Strategies Related to Non-Alcoholic Fatty Liver Disease. *Int. J. Mol. Sci.* **2022**, *23*, 7841. [\[CrossRef\]](#) [\[PubMed\]](#)
- Subramanian, P.; Hampe, J.; Tacke, F.; Chavakis, T. Fibrogenic Pathways in Metabolic Dysfunction Associated Fatty Liver Disease (MAFLD). *Int. J. Mol. Sci.* **2022**, *23*, 6996. [\[CrossRef\]](#) [\[PubMed\]](#)
- Tian, H.; Zhang, S.; Liu, Y.; Wu, Y.; Zhang, D. Fibroblast Growth Factors for Nonalcoholic Fatty Liver Disease: Opportunities and Challenges. *Int. J. Mol. Sci.* **2023**, *24*, 4583. [\[CrossRef\]](#) [\[PubMed\]](#)
- Li, X.; Jiang, K.; Ruan, Y.; Zhao, S.; Zhao, Y.; He, Y.; Wang, Z.; Wei, J.; Li, Q.; Yang, C.; et al. Hydrogen Sulfide and Its Donors: Keys to Unlock the Chains of Nonalcoholic Fatty Liver Disease. *Int. J. Mol. Sci.* **2022**, *23*, 12202. [\[CrossRef\]](#) [\[PubMed\]](#)
- Puengel, T.; Liu, H.; Guillot, A.; Heymann, F.; Tacke, F.; Peiseler, M. Nuclear Receptors Linking Metabolism, Inflammation, and Fibrosis in Nonalcoholic Fatty Liver Disease. *Int. J. Mol. Sci.* **2022**, *23*, 2668. [\[CrossRef\]](#)
- Chen, C.C.; Hsu, L.W.; Chen, K.D.; Chiu, K.W.; Chen, C.L.; Huang, K.T. Emerging Roles of Calcium Signaling in the Development of Non-Alcoholic Fatty Liver Disease. *Int. J. Mol. Sci.* **2021**, *23*, 256. [\[CrossRef\]](#) [\[PubMed\]](#)

19. Guo, X.; Yin, X.; Liu, Z.; Wang, J. Non-Alcoholic Fatty Liver Disease (NAFLD) Pathogenesis and Natural Products for Prevention and Treatment. *Int. J. Mol. Sci.* **2022**, *23*, 15489. [[CrossRef](#)] [[PubMed](#)]
20. Mantovani, A.; Lombardi, R.; Cattazzo, F.; Zusi, C.; Cappelli, D.; Dalbeni, A. MAFLD and CKD: An Updated Narrative Review. *Int. J. Mol. Sci.* **2022**, *23*, 7007. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.