Website address:
https://www.gesundheitsindustrie-bw.de/en/article/press-release/clusters-metabolic-dysfunction-associated-steatotic-liver-disease-precision-medicine

Clusters of Metabolic Dysfunction-Associated Steatotic Liver Disease for Precision Medicine

Globally more than 30% of the adult population has metabolic dysfunction-associated steatotic liver disease (MASLD). People with MASLD and more so with metabolic dysfunction-associated steatohepatitis (MASH) and MASLD-associated hepatic fibrosis can progress to cirrhosis and hepatocellular carcinoma and are at increased risk of developing type 2 diabetes, cardiovascular disease, chronic kidney disease, and extrahepatic cancers. However, MASLD is a heterogeneous disease regarding its pathophysiology and clinical outcomes. In a News & Views article in Nature Reviews Gastroenterology & Hepatology Norbert Stefan and Giovanni Targher discuss novel findings about this heterogeneity of MASLD and how future research applying data dimensionality reduction approaches might be beneficial for implementing precision medicine in MASLD.

It is well established that unhealthy diets, a lack of physical activity and genetic risk promote MASLD. However, there is a large variability in the pathophysiology of MASLD and its clinical outcomes. Professor Norbert Stefan from the University of Tübingen, Helmholtz Munich, and German Center for Diabetes Research (DZD) Germany, highlights: 'This variability in the pathophysiology of MASLD appears to be particularly important regarding the incidence of CVD and type 2 diabetes. In the field of cardiometabolic disease research data dimensionality reduction approaches based on clustering strategies using anthropometrics, metabolic parameters and genetics proved promising for future implementation of precision medicine in clinical practice for obesity, CVD and T2D. Novel findings from two studies most recently published in *Nature Medicine* now suggest that such clustering approaches may also be important for MASLD'.

Among the six clusters identified by Raverdy *et al.*, people in clusters 2 and 5 had a high prevalence of MASH and advanced fibrosis ($F \geq 3$) diagnosed by liver biopsy samples versus the other clusters combined. The cardiometabolic cluster (cluster 2) and the liver-specific cluster (cluster 5), had a similarly elevated risk of chronic liver disease compared with the control cluster, comprising the clusters 1, 3, 4 and 6. Importantly, the liver-specific cluster was enriched with the MASLD at-risk genetic variants that are associated with increased liver disease progression to MASH, cirrhosis and hepatocellular carcinoma. Interestingly, people assigned to the liver-specific cluster, although having had a rapid progression of chronic liver disease, had a relatively low risk of CVDs. People assigned to the cardiometabolic cluster had a similarly elevated incidence of chronic liver disease but an increased risk of CVDs and T2D.

In agreement, Jamialahmadi *et al.* who specifically focused on genetic information in MASLD, found that people assigned to the liver-specific or so-called discordant (that is, high liver fat content but relatively low circulating triglycerides) MASLD phenotype had aggressive liver disease but a decreased risk of CVDs. The other, a systemic or so-called concordant MASLD phenotype, was also associated with a similarly increased risk of aggressive liver disease but an increased risk of CVDs and T2D. In this respect Professor Giovani Targher from the Metabolic Diseases Research Unit, IRCCS Sacro Cuore - Don Calabria Hospital, Negrar di Valpolicella, and the Department of Medicine, University of Verona, Verona, Italy, emphasizes: 'Because the major causes of death in people with MASLD are CVDs the findings of these two studies are very important as they may help to better stratify the risk of CVDs in people with MASLD.'.

The authors of the News & Views article believe that in the future, the knowledge about these MASLD risk clusters will enable a personalized risk prognosis and individualized treatment of MASLD. In addition, researchers may be able to specifically develop lifestyle modification programs and drugs for the respective subtypes based on the various aspects of this disease.

Publications:
Raverdy V. *et al.* Data-driven cluster analysis identifies distinct types of metabolic dysfunction-associated steatotic liver disease. *Nat. Med.* 30, 3624–3633 (2024)

Jamialahmadi O *et al.* Partitioned polygenic risk scores identify distinct types of metabolic dysfunction-associated steatotic liver disease. *Nat. Med.* 30, 3614–3623 (2024).

Stefan N, Targher G. Clusters of metabolic dysfunction-associated steatotic liver disease for precision medicine. *Nat Rev Gastroenterol Hepatol.* doi.org/10.1038/s41575-025-01048-w (2025)

Press release

04-Mar-2025
Source: Deutsches Zentrum für Diabetesforschung e.V.

Further information

Prof. Norbert Stefan
University of Tübingen, Helmholtz Munich and
German Center for Diabetes Research (DZD)
Tel.: +49 (0) 7071 2980390
E-Mail: norbert.stefan(at)med.uni-tuebingen.de

Prof. Giovanni Targher
Department of Medicine, University of Verona,
Verona, Italy
Tel.: +39 (0) 045 6014530
E-Mail: giovanni.targher(at)univr.it

- German Center for Diabetes Research (DZD)