Metabolic signature might be an option to identify patients with early CP

Bálint Erőss , Andrea Szentesi, Peter Hegyi

Metabolites are biomarkers measured in blood, urine, stool and tissue samples, determined by several factors, most importantly by the gut microbiota and changes in the metabolism from underlying diseases. Theoretically, specific diseases lead to changes in both factors that result in specific metabolomic profiles characterising these disorders. In recent years, metabolomic profiling for the diagnosis and the prognostic assessment of GI diseases has been an emerging and new tool; there are examples of metabolomics in diagnosing and assessing chronic GI disorders such as cancers, IBD and cirrhosis.

The recent studies on metabolomics have assessed its potential roles in gastroenterology patients’ care, but it is not yet part of the daily routine.

In Gut, Adam et al report a very important study, which aimed to assess metabolomics’ diagnostic potential in chronic pancreatitis (CP). Patients with unequivocally diagnosed CP had been identified by a set of criteria, including radiological changes and severely abnormal pancreatic function tests. Their metabolomic profiles were compared against three control groups, the first in the identification and then two control groups in the external validation studies. In the three steps of the study, there were three independent CP groups. The authors identified eight metabolites with which the tool can identify CP with an area under the curve (AUC) 0.85 (95% CI: 0.801 to 0.91) from an EDTA blood sample and an AUC 0.87 (95% CI: 0.81 to 0.95) from serum. These results prove that their metabolomic profiling tool has good diagnostic accuracy. We shall ask the question: In which area of daily clinical practice could this tool be used most effectively? Is it the established CP or early CP?

We all know that CP is characterised by the irreversible loss of exocrine and endocrine function of the pancreas from chronic inflammation. It is often accompanied by morphological changes of the pancreas detectable by various radiological methods.

Notably, the diagnosis of established CP is rarely challenging. Therefore, assessing the cost/benefit ratio and the limited access to the methodology, it is very unlikely that this specific metabolomic profile will be routinely used to diagnose CP. However, the most exciting clinical question is how to identify patients who will develop CP when there are no detectable radiologic features, significant clinical symptoms or overt exocrine insufficiency. Patients with early CP could benefit from interventions, and the full-blown CP could be prevented or significantly delayed. Therefore, we propose that the metabolic profiles of patients with early CP and a high risk for developing advanced CP are analysed. The question arises, which patient population would benefit the most from the metabolomic test?

Our study group just published an analysis of a small cohort in which patients with three or more acute pancreatitis episodes have a high probability of developing CP. Therefore, based on Adam et al’s study, we decided to retest our observation in a large international cohort of patients with acute pancreatitis (AP). Between 2012 and 2019, from 13 countries and 30 medical centres, 2461 patients were enroled into the Acute Pancreatitis Registry initiated by the Hungarian Pancreatic Study Group. The AP diagnosis was defined according to the International Association of Pancreatology (IAP)/American Pancreatic Association (APA) guidelines. The analysed cohort was representative of the complete AP cohort. The proportion of mild, moderately severe and severe cases was 71.0%, 23.7% and 5.3%. Our data analysis showed that the proportion of patients developing CP is exponentially and directly associated with the number of AP episodes (1.6%, 5.8% and 21% with 1, 2 and 3 AP episodes, respectively, table 1).

Therefore, we believe that patients with three or more AP episodes with no morphological changes would be the best candidates in a longitudinal clinical trial to test the hypothesis of whether this newly developed metabolomic profile would be a good diagnostic tool to identify patients with early CP.

Table 1: The proportion of patients in percentages developing CP

| Number of acute pancreatitis episodes | CP (n) | no-CP (n) | Number of patients (n) | Percentage (%) of the patients developing CP |
|--------------------------------------|--------|-----------|------------------------|---------------------------------------------|
| 1                                    | 28     | 1706      | 1734                   | 1.6                                         |
| 2                                    | 18     | 295       | 313                    | 5.8                                         |
| 3                                    | 22     | 83        | 105                    | 21                                           |
| 4                                    | 21     | 47        | 68                     | 30.9                                        |
| 5                                    | 15     | 22        | 37                     | 40.5                                        |
| 6                                    | 14     | 12        | 26                     | 53.8                                        |
| 7                                    | 10     | 9         | 19                     | 52.6                                        |
| B+                                   | 15     | 11        | 26                     | 57.7                                        |
| Total cases                          | 143    | 2185      | 2328                   | 6.1                                         |

Notches developed metabolomic profile would be an option to identify patients with early CP.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study was approved by the National Public Health Centre (Nemzeti Népegészségügyi Központ), under the ID: 17787-8/2020/EÜIG. All participants in this study provided written informed consent.

Provenance and peer review Not commissioned; internally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

To cite Erőss B, Szentesi A, Hegyi P. Gut 2021;70:2023–2024.

Received 21 January 2021
Revised 6 February 2021
Accepted 7 February 2021
Published Online First 25 February 2021

http://dx.doi.org/10.1136/gutjnl-2020-320723
REFERENCES

1. Katagiri R, Goto A, Nakagawa T, et al. Increased levels of branched-chain amino acid associated with increased risk of pancreatic cancer in a prospective case-control study of a large cohort. *Gastroenterology* 2018;155:1474–82.

2. Uchiyama K, Yagi N, Mizushima K, et al. Serum metabolomics analysis for early detection of colorectal cancer. *J Gastroenterol* 2017;52:677–94.

3. De Preter V. Metabolomics in the clinical diagnosis of inflammatory bowel disease. *Dig Dis* 2015;33 Suppl 1:2–10.

4. Daniluk U, Daniluk J, Kuchanski R, et al. Untargeted metabolomics and inflammatory markers profiling in children with Crohn’s disease and ulcerative colitis-A preliminary study. *Inflamm Bowel Dis* 2019;25:1120–8.

5. Bajaj JS, Fan S, Thacker LR, et al. Serum and urinary metabolomics and outcomes in cirrhosis. *PLoS One* 2019;14:e0223061.

6. Minidokulu AL, Opekun AR, Putluri N, et al. Unique metabolomic signature associated with hepatorenal dysfunction and mortality in cirrhosis. *Transl Res* 2018;195:25–47.

7. Adam MG, Beyer G, Christiansen N, et al. Identification and validation of a multivariable prediction model based on blood plasma and serum metabolomics for the distinction of chronic pancreatitis subjects from non-pancreas disease control subjects. *Gut* 2021;70:2150–8.

8. Ito T, Ishiguro H, Ohara H, et al. Evidence-Based clinical practice guidelines for chronic pancreatitis 2015. *J Gastroenterol* 2016;51:85–92.

9. Mayerle J, Hoffmeister A, Werner J, et al. Chronic pancreatitis—definition, etiology, investigation and treatment. *Dtsch Arztebl Int* 2013;110:387–93.

10. Whitcomb DC, Shimosegawa T, Chari SS, et al. International consensus statements on early chronic pancreatitis: recommendations from the Working group for the International consensus guidelines for chronic pancreatitis in collaboration with the International association of Pancreatology, American pancreatic association, Japan pancreas Society, PancreasFest Working group and European pancreatic Club. *Pancreatology* 2018;18:516–27.

11. Löhr JM, Dominguez-Munoz E, Rosendahl J, et al. United European gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). *United European Gastroenterol J* 2017;5:153–99.

12. Hegyi PJ, Sös A, Tóth E, et al. Evidence for diagnosis of early chronic pancreatitis after three episodes of acute pancreatitis: a cross-sectional multicentre international study with experimental animal model. *Sci Rep* 2021;11:1367.

13. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013;13:e1–15.