Signs of Gut-Related Disease may Reveal by Blood that Stool Samples Miss

Researchers compared the diagnostic performance of serum and fecal short-chain fatty acid (SCFA) profiles for distinguishing colorectal cancer, celiac disease, obesity, and healthy controls.

The gut microbiota has a key role in maintaining host health. The production of microbial metabolites is one of the central mechanisms through which the gut microbiota influences host physiology. SCFAs, e.g., acetate, butyrate, and propionate, alongside branched-chain fatty acids isovalerate, 2-methylbutyrate, and isobutyrate, are the most studied microbial metabolites.

Fecal SCFAs have been extensively studied as non-invasive biomarkers; altered fecal SCFA profiles have been reported in metabolic and gastrointestinal diseases, including colorectal cancer (CRC), celiac disease (CD), inflammatory bowel disease, and obesity (OB). The systemic dimension of SCFAs remains relatively understudied. This matters because a substantial fraction of SCFAs enters systemic circulation after absorption in the colon.



Study

In the present study, researchers compared the diagnostic performance of serum and fecal SCFA profiles. The analysis used previously collected clinical data and samples from CRC, OB, and CD patients and healthy controls (HCs) in Florence, Italy. Subjects were excluded if they were pregnant or recently postpartum, on nutritional interventions or medications that affect food intake, body weight, or energy expenditure, or used antibiotics, synbiotics, probiotics, or prebiotics in the two months preceding enrolment.

A questionnaire was administered to capture dietary habits. Whole-blood and fecal samples were collected at diagnosis, before treatment, and serum and fecal SCFAs were quantified using gas chromatography–mass spectrometry. The Kruskal-Wallis test was performed to evaluate group differences in serum and fecal SCFAs, and Dunn's test was used for pairwise comparisons. A principal component analysis (PCA) was conducted to explore the multivariate structure of SCFA datasets.

Researchers used a multiclass machine learning model to evaluate the ability of the serum SCFA dataset, fecal SCFA dataset, or the combined dataset to discriminate among OB, CRC, CD, and HC groups. Models were trained on 80% of the data and assessed using the remaining 20%,

alongside internal validation procedures. Researchers used SHAP and LIME analyses to identify which fatty acids had the greatest influence on the model's predictions. Finally, regression models were used to assess relationships between serum and fecal SCFAs.

Results

The study included 35 CD, 30 CRC, and 33 OB patients, and 95 HCs. All CRC patients had non-metastatic colon cancer, all OB patients had a body mass index ≥ 30 kg/m^2, and all CD patients had villous atrophy. Seven SCFAs were quantified in serum and fecal samples: Acetic, butyric, isovaleric, isobutyric, propionic, valeric, and 2-methylbutyric acids. PCA revealed group separation for serum and fecal SCFAs, more pronounced in serum; multivariate testing confirmed significant differences in both datasets.

The fecal SCFA model had an overall classification accuracy of 59% in the held-out test set; it correctly identified about 63% of HCs, 57% of patients with OB or CD, and 50% of patients with CRC. The serum SCFA model achieved very high accuracy (95%), with some CD test samples misclassified as CRC. The combined serum-fecal SCFA model marginally improved accuracy to 97%. Researchers then examined which circulating fatty acids contributed most strongly to the model's predictions for each diagnostic group. SHAP analysis of the serum SCFA dataset identified valeric, propionic, 2-methylbutyric, and isovaleric acids as the most influential SCFAs for CD prediction.

For CRC prediction, 2-methylbutyric, isovaleric, isobutyric, and valeric acids were the most influential features. The main contributors to OB classification were 2-methylbutyric, propionic, valeric, and acetic acids. For HCs, the strongest contributors were valeric and propionic acids. LIME analysis of the serum dataset provided complementary insights into directional contributions of individual SCFAs.

Isobutyric acid had a positive contribution to CRC prediction, whereas valeric, isovaleric, and 2-methylbutyric acids had negative contributions. In CD classification, contributions from isobutyric, valeric, propionic, and butyric acids were all negative. For OB, propionic acid had a negative contribution, while isobutyric, isovaleric, and 2-methylbutyric acids contributed positively.

In HC classification, valeric acid had a negative contribution, whereas propionic, 2-methylbutyric, and isobutyric acids had positive contributions. These contributions describe how the model classified samples; they do not establish causal effects of these acids. SHAP and LIME analyses were also performed on fecal and combined datasets, which yielded lower feature-importance values. These differences in feature attribution did not change the combined model's slightly higher classification accuracy.

Finally, weak predictive relationships were observed between serum and fecal SCFAs, and fecal profiles could not predict serum concentrations at the study's predefined performance threshold, suggesting that the two biological compartments provide complementary, non-redundant information.

Conclusion

Serum SCFA profiles outperformed fecal SCFAs in discriminating HCs and CD, OB, and CRC patients. Adding fecal SCFAs to serum-based models yielded a marginal gain in accuracy, indicating that serum SCFAs capture most of the classification information in this cohort. Valeric,

propionic, isovaleric, and 2-methylbutyric acids were the most informative contributors to serum SCFA-based classification. These results suggest that serum SCFAs may better reflect disease-related changes than fecal SCFAs. Fecal measurements remain useful for investigating intestinal microbial activity, and the two sample types provide distinct biological information.

The study was small, with serum model accuracy estimated from a held-out test sample of approximately 39 participants. Substantial differences in age, body mass index, and other characteristics between groups may have influenced the results. Larger, independently recruited cohorts are needed before serum SCFA profiling can be considered a clinical diagnostic test.

Source:

https://www.news-medical.net/news/20261103/Blood-may-reveal-signs-of-gut-related-disease-that-stool-samples-miss.aspx