Type 2 diabetes treatment found to impact fungal community in human gut

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From left are graduate student Sophia Kenney and postdoctoral scholar Emily Van Syoc with Erika Ganda, assistant professor of food animal microbiomes. Credit: Pennsylvania State University
Metabolic diseases, such as type 2 diabetes, are associated with compositional shifts in the human gut microbiome, including the fungal fraction called the mycobiome. But research on the mycobiome and how type 2 diabetes or its common treatment, metformin, may interact remains relatively limited despite suggestions that these fungi can influence the overall health of the microbiome, according to a research team at Penn State.

The team, led by Emily Van Syoc, postdoctoral researcher at the One Health Microbiome Center, and Erika Ganda, assistant professor of food animal microbiomes, curated the largest international cohort characterizing the human gut mycobiome and investigated how type 2 diabetes (T2D) and metformin impact it.

Their findings, which the researchers said have implications for understanding how pharmaceutical interventions may influence investigations into the gut microbial ecosystem, were published on May 20 in mBio.

"We found that metformin—the most common first-line treatment for T2D—and T2D account for subtle but significant and distinct variation in the gut mycobiome across human populations," Van Syoc said. "This work highlights for the first time that metformin can confound associations of gut fungi with T2D and warrants the need to consider pharmaceutical interventions in investigations of linkages between metabolic diseases and gut microbial inhabitants."

The researchers assessed the mycobiome composition of subjects without T2D, untreated patients with T2D and metformin-treated patients with T2D. Their dataset comprised more than 1,000 samples based on existing human gut microbiome data and metadata from nine previous studies spanning multiple countries. They then filtered the data for the most abundant fungi, producing a baseline mycobiome profile
independent of geography and diet.

"Gut microbiomes are very different between individuals, which means that we need to analyze a large sample size to detect signal above the noise," Van Syoc said. "Many previous studies of the gut mycobiome and type 2 diabetes were conducted with small numbers of individuals, because these trials are expensive and time-consuming to run.

"By combining data across multiple studies, we can not only expand our sample size and increase statistical power, but we can also report differences that persist across geographies, diets and cultures."

Across all samples, the researchers identified 34 fungal genera, the taxonomic category comprising species, consisting primarily of Saccharomyces. They then investigated potential links between certain fungal groups and clinical metabolic markers.

Increased Saccharomyces was linked to increased fasting blood glucose, high levels of which are a proxy for diabetes, and a decrease in Zygosaccharomyces was linked to an increase in fasting plasma insulin, another indicator of diabetes. According to the researchers, these results suggest a link between perturbed mycobiomes and hyperglycemia and obesity.

"The most exciting aspect of this project is that it is the first to show that gut fungi may be affected by oral pharmaceutical treatment," Van Syoc said. "We are just starting to learn about how the gut microbiome may interact with medications and change how they work in the body. However, this field has focused entirely on interactions with drugs and gut bacteria, and fungi have been left out of the equation—until now."

The researchers then tested their findings in a rodent model and found that metformin contributed to 30% of the variability observed in the
mycobiome. Additionally, metformin treatment resulted in shifts to the genera Fusarium, Thermothielavioides, Cryptococcus that were comparable to the metformin treated T2D human samples.

According to Van Syoc, the detection of similar perturbations on gut fungi in mice as in humans suggests that metformin may interact with some microorganisms regardless of the host, as her previous work has shown with metformin supplementation and effects on gut bacteria in broiler breeder chickens.

"We hope that this study will inspire researchers and the field at large to consider gut fungi as an integral part of the gut microbiome and to expand the way we think about multi-dimensional microbial communities that interact with human physiology," Ganda said.

"This study is a testament to the use of publicly available data to generate new knowledge and open up new lines of investigation."


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