

Microbiota and diabetes: an increasingly relevant association

Herbert Tilg, Christoph Grander

Department of Internal Medicine I, Gastroenterology, Hepatology, Metabolism & Endocrinology, Medical University Innsbruck, Innsbruck, Austria

The human intestinal tract contains an enormous number of bacteria, archaea, and viruses. Recent estimates announced that a ratio of 1.3 bacterial cells might exist for every 1 human cell.¹ Early studies believed that genes of this microbial world mainly encode functions affecting pathways favoring digestion of complex carbohydrates or the control of immunity, whereas recent evidence supports that the microbiota has major functions in the regulation of metabolic pathways in health and disease.² It has been shown in the past years that obese human subjects exhibit a gut microbiome signature.³ Two major studies from the following years showed that such a microbiome signature might also exist in humans with type 2 diabetes mellitus (T2DM).^{4,5} In the first metagenome-wide association study, researchers from China demonstrated an intestinal dysbiosis characterized by a decrease in butyrate-producing *Roseburia intestinalis* and *Faecalibacterium prausnitzii*.⁴ When analyzing potentially associated functions from this altered microbiota, an enrichment in the membrane transport of sugars, branched-chain amino acid transport and sulphate reduction, and decreased butyrate biosynthesis could be observed. Most importantly, enriched functions also included an increase in oxidative stress pathways, offering the hypothesis that there might be a direct link between an altered microbiota and the well-known proinflammatory state in T2DM patients. A second metagenome study in patients with T2DM from Europe exhibited an increase in the abundance of certain *Lactobacillus* species including *Lactobacillus gasseri*, *Streptococcus mutans*, and certain *Clostridium* bacteria, such as *Clostridium clostridioforme*, and decreases in other *Clostridium* species. *Roseburia intestinalis* and *Faecalibacterium prausnitzii*, both prototypic butyrate producers, were highly discriminant for T2DM.⁵ Although there were significant differences between these 2 studies, a new exciting research

field was opened for further investigations and the term “altered microbiota signature in T2D” was established.

In this issue of *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Salamon et al⁶ report on a small study where they investigated fecal microbiome in patients with T1DM, T2DM, and healthy controls. Using 16S ribosomal RNA next-generation sequencing, the authors observed that patients with T2DM differed with respect to their microbiome from both T1DM subjects and healthy controls. Patients with T2DM were characterized by a higher ratio of Firmicutes to Bacteroidetes and demonstrated reduced fecal concentrations of certain Ruminococcaceae, Lachnospiraceae, Clostridiales, Bacteroides, *Anaerostipes*, and *Roseburia*, whereas the concentrations of *Ruminococcus*, Enterobacteriaceae and Proteobacteria, all rather proinflammatory bacterial strains, were increased. Proteobacteria are considered proinflammatory and might be able to drive immune responses characterized by increased interferon- γ expression.⁷ Concentrations of *Akkermansia muciniphila*, a rather well-characterized commensal with mainly antidiabetic and anti-inflammatory properties,⁸ were increased in T2DM patients in the study by Salomon et al,⁶ and the authors proposed that accompanying metformin treatment might have caused this effect.⁹ The findings by Salamon et al⁶ with *A muciniphila* are in contrast to several other studies which have demonstrated that obesity and related metabolic dysfunction are characterized by decreased fecal concentrations of this bacterium.¹⁰ Interestingly, the microbiota composition in T1DM subjects did not differ significantly from that in healthy controls.⁶ Some attention regarding the presented results, however, is needed as authors could not provide data on dietary details and stool consistency, both factors substantially affecting gut microbiota composition. Furthermore, the number of analyzed patients was rather low (T1DM, n = 22; T2DM, n = 23; controls, n = 23). Despite these shortcomings,

Correspondence to:

Herbert Tilg, MD, Department of Internal Medicine I, Gastroenterology, Hepatology, Metabolism & Endocrinology, Medical University Innsbruck, Innsbruck, Austria, phone: +43 512 504 23539, email: herbert.tilg@i-med.ac.at

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this study also supports that a microbiome signature might exist in T2DM.

Several previous studies in addition to the above investigations^{4,5} have provided evidence that a gut microbiome signature exists in diabetes. Furthermore, in some studies certain bacterial strains could be identified that are potentially involved in the regulation of selected features of T2DM, such as insulin resistance. Pedersen et al¹¹ observed that the human gut microbiome influences the serum metabolome exhibiting increased levels of branched-chain amino acids and was clearly associated with insulin resistance in 277 nondiabetic Danish individuals. *Prevotella copri* and *Bacteroides vulgatus*, 2 bacterial strains identified in T2DM subjects, were able to cause insulin resistance in rodents and increased levels of branched-chain amino acids in these animals.¹¹ Bacterial DNA is present in mesenteric adipose tissue, reflecting an impaired intestinal barrier, and in another study in T2DM patients, *Ralstonia pickettii* was one of the most prevalent bacterial strains.¹² *Ralstonia*-treated diet-induced obese mice exhibited a deteriorated insulin resistance compared with control animals, suggesting that this bacterium reflects one candidate being potentially of relevance in T2DM. Overall, the intestinal epithelium might play a key role in health and metabolic balance, and an exciting recent study showed that glucose itself is able to impair intestinal mucosal integrity.¹³ Certain bacterial strains, such as *Eubacterium hallii*, can improve insulin resistance in rodent experiments.¹⁴ *E hallii* treatment improved energy expenditure, increased fecal concentrations of butyrate, and affected bile acid metabolism. Previously, these authors had demonstrated that a fecal transplant from lean donors increased intestinal levels of *E hallii*. In accordance with the study by Pedersen et al,¹¹ a recent report also showed that individuals with prediabetes exhibit an aberrant intestinal microbiota accompanied by decreased abundance of *A muciniphila*.¹⁵ While associations of an altered microbiota with T2DM are now substantial, only very few reports have so far shown such an association for T1DM. Huang et al¹⁶ studied a very small cohort with T1DM showing an increased ratio of Bacteroidetes to Firmicutes and a decrease in *F prausnitzii*.¹⁶ The sample size of this small study, however, does not allow to draw any conclusions. Interestingly, however, *A muciniphila* administration has been shown to reduce autoimmunity and diabetes incidence in nonobese diabetic mice.¹⁷

The intestinal microbiota, besides many other functions, exerts mainly metabolic and immune activities. The gut microbiota not only contributes to the integrity of the intestinal epithelial barrier but also might be able to affect many metabolic functions beyond the gastrointestinal tract. Several studies, especially in T2DM, have now demonstrated that a significantly aberrant intestinal microbiota is prevalent. The significance of these findings is currently unclear,

although several bacterial strains have already been characterized by either improving or deteriorating insulin resistance in rodent models. It remains unclear whether observed gut dysbiosis reflects an early rather causal or late bystander phenomenon of disease. What comes first? Hyperglycemia impairs epithelial integrity¹³ and could therefore reflect a major confounder affecting the composition of intestinal microbiota. In addition, an altered microbiota taking place early in T2DM progression might subsequently affect the diverse components of diabetes, such as insulin resistance. First data in prediabetes suggest that microbial alterations might rather reflect the early changes of the disease.^{11,15} More studies assessing well-characterized patients and considering numerous potential confounding factors, such as drugs, dietary factors, or stool consistency, are needed to further strengthen the association of an altered intestinal microbiota with diabetes. However, the real proof for the importance of such associations will only come from clinical trials where such newly identified bacteria will demonstrate beneficial metabolic effects when administered to patients.

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