

The gut microbiome in long-standing type 1 diabetes.

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**Background:** The presence of Type 1 diabetes (T1D) leads to various complications that are associated with altered immune responses including an increased risk for infections and vascular disease. Although changes in the microbiome during the development of T1D have been linked to alterations in the immune response, not much is known about the role of the gut microbiome in long-standing type 1 diabetes. We therefore set out to determine differences in the gut microbiome of T1D patients compared to healthy controls and to associate the microbiome with diabetes-related complications.

**Methods:** 239 T1D patients were included with an average disease duration of 28,4 years. Clinical characteristics and faecal samples were collected. Metagenomic shotgun sequencing was performed and the results were associated to T1D-related characteristics and complications including HbA1c, and macrovascular and microvascular complications. Microbiome data were compared to a healthy cohort, consisting of 2937 age and sex matched individuals.

**Results:** No significant difference in diversity of the gut microbiome was found between T1D patients and healthy controls. However, the proportions of several bacterial taxa were altered in T1D. 20 bacterial taxa were significantly depleted in T1D, for examples *S. Alistipes Putredinis* (FDR=1.6x10<sup>-12</sup>). Furthermore, 76 bacterial taxa were significantly enriched in T1D, such as *G. Clostridium* (FDR=4.0x10<sup>-15</sup>). Glycaemic control, measured by HbA1c (ranging from 34 to 136 mmol/mol), explained a significant part of variation in gut microbiome (R<sup>2</sup>>0.010, FDR<0.05). Furthermore, variation in gut microbiome was also explained significantly by the absence or presences of vascular complications (R<sup>2</sup>>0.0075, FDR < 0.05).

**Conclusion:** Although the diversity is not affected, the composition of the gut microbiome T1D patients is significantly different compared to healthy controls. T1D related characteristics and vascular complications are associated with changes in the gut microbiome. These data suggest that the gut microbiome is not only important in the context of disease development, yet may also contribute to the development of diabetes-associated complications.