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Dietary resistant starch alters gut microbiota, microbially produced metabolites and albuminuria in diabetic mice

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Dietary resistant starch (RS) may be nephroprotective in diabetes, however whether this occurs via affecting glycaemic control or via modulation of the gut microbiota and the production of microbial metabolites has not been explored.[(1)] Six-week-old non-diabetic mice (db/m), diabetic mice (db/db) and db/db mice on a regular chow diet supplemented with 15% RS (db/db+RS) were maintained for ten weeks. 24-hour urine was collected for albumin measurement by ELISA. At 15 weeks of age, mice were fasted and an oral glucose tolerance test (OGTT; 2 g/kg lean body mass) was performed. Glycated haemoglobin was assessed using a Roche cobas b101 analyser. Portal vein blood was collected for targeted metabolomics by mass spectrometry. Cecal digesta were collected for microbiota analysis by 16S rRNA gene sequencing. Univariate data was assessed for normality by Shapiro–Wilk test and normally distributed data were analysed by one-way ANOVA with Tukey's multiple comparison tests. Linear discriminant analysis (LDA) with effect size measurements (LEfSe)[(2)] was used to identify differentially abundant bacterial taxa. Diabetes was associated with an increase in albuminuria (23.4 ± 14.4 v. 381.2 ± 274.0 μg/24h, $p < 0.001$, db/m v. db/db), which was reduced in diabetic mice receiving RS supplementation (381.2 ± 274.0 μg v. 136.7 ± 130.0 μg/24h, $p < 0.01$, db/db v. db/db+RS). Principal component analysis demonstrated that the metabolite profile of db/db+RS mice clustered with that of db/m mice along PC1 (55.7% of variance explained), distinct from db/db mice receiving the regular chow diet. There was no separation between groups along PC2 (4.8% of variance explained). The short chain fatty acids acetate, propionate and butyrate were all reduced in the db/db mice compared with db/m mice (all P<0.05, db/m v. db/db), and this was restored for propionate and butyrate in the db/db mice receiving RS supplementation (both $p < 0.05$, db/db v. db/db + RS). Conversely, the uremic retention solutes *p*-cresol sulphate and *p*-cresol glucuronide, and their precursor *p*-cresol, were increased in diabetes (all $p < 0.001$, db/m v. db/db), which was reduced with RS supplementation (all $p < 0.001$, db/db v. db/db + RS). Between db/db mice, RS favourably altered the microbiome, specifically an expansion of Verrucomicrobia, driven largely by the genus *Akkermansia* ($\log_{10}$ LDA score = 4.8), and a contraction in Proteobacteria, driven by the sulphate reducing bacterial family *Desulfovibrionaceae* ($\log_{10}$ LDA score = −4.0). Between db/db mice, RS supplementation did not significantly alter fasting blood glucose, fasting insulin, glucose response to OGTT or HbA1c levels. These studies support the notion that dietary RS may be protective against diabetic nephropathy independently of alterations in glucose tolerance and that this protection may occur via alteration of the gut microbiota and the subsequently produced microbial metabolites.

References

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2. Segata N, Izard J, Waldron L, *et al.* (2011) *Genome Biol* **12**, R60.