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The effects of different high-fat diets on the intestinal microenvironment and systemic inflammation and metabolic dysfunction in diet-induced obese C57Bl/6 male mice.

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Objectives: High fat diets (HFDs) are commonly used to induce obesity in rodent models, however, the nutritional composition (e.g. fat level) often varies dramatically which may result in variable effects on the obese phenotype. Therefore, the objective was to compare the effects of two commonly used HFDs on the intestinal microenvironment, inflammation and metabolic dysfunction in mice.

Methods: 3 week old male C57Bl/6 mice were fed diets comprised of 17% fat (%kcal; low fat diet; LFD), 45% fat (%kcal; 45HFD), or 60% fat (%kcal; 60HFD) for 12wks and aspects of the obese phenotype (weight gain, body mass index (BMI), oral glucose tolerance, homeostatic model assessment of insulin resistance (HOMA-IR), adipose dysfunction) and colonic microenvironment (microbiota community structure (16S rRNA gene sequencing), mucosal inflammation and barrier integrity) were assessed.

Results: Mice consuming 60HFD gained more weight compared to 45HFD and LFD, resulting in significant differences in final BMI and white adipose tissue (WAT) weights. WAT dysfunction was more severe in the 60HFD group (e.g. increased crown-like structures (macrophage infiltration) and serum adipokines (leptin and resistin)) compared to the 45HFD and LFD. Blood glucose clearance following an oral glucose load and HOMA-IR were significantly higher in the 60HFD group compared to 45HFD and LFD. Cecal microbial dysbiosis was also more severe in the 60HFD group compared to the 45HFD and LFD, including reduced phylogenic diversity, as well as reduced *Akkermansia muciniphila* and *Bifidobacterium pseudolongum* abundances. Colon mRNA expression of TLR2 and IL-6 were significantly increased by 60HFD, while tight junction protein expression (JAM-A) was decreased, compared to LFD and 45HFD, whereas both HFDs increased TNF-α and MCP-1 expression. Serum lipopolysaccharide binding protein, a biomarker of endotoxemia, was increased by the 60HFD compared to 45HFD and LFD.

Conclusion: Despite interchangeable use of HFD compositions (45% vs 60% as kcal) in diet-induced obesity models, clear differences in the obese phenotype and intestinal microenvironment composition and function result, highlighting the importance of properly defining the HFD composition to accurately recapitulate the human clinical phenotype in obesity research.