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**Toxicological impact of high fructose intake on gut microbiota and liver/intestine integrity: any differences between solid and liquid formulations?**

Mastrocola R<sup>1</sup>, Cento AS<sup>1</sup>, Chiazza F<sup>2</sup>, Ferrocino I<sup>3</sup>, Kalliopi R<sup>3</sup>, Bitonto V<sup>4</sup>, Cutrin J<sup>4</sup>, Aragno M<sup>1</sup>, Liberto E<sup>2</sup>, Masini E<sup>5</sup>, Cordero C<sup>2</sup>, Cocolin L<sup>3</sup>, Collino M<sup>2</sup>.

<sup>1</sup>Dept. of Clinical and Biological Sciences, University of Turin, Italy; <sup>2</sup>Dept. of Drug Science and Technology, University of Turin, Italy; <sup>3</sup>Department of Agricultural, Forest and Food Sciences, University of Turin, Italy; <sup>4</sup>Dept. of Molecular Biotechnology and Health Sciences, University of Turin, Italy; <sup>5</sup>Dept. Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Italy.

**Background and aims:** We previously demonstrated the deleterious effects of fructose feeding on liver through production of advanced glycation end products (AGEs) and the induction of hepatic steatosis and inflammation. Moreover, it has been reported that high fructose intake alters microbiota composition, resulting in reduced bacterial diversity and altered expression of genes involved in specific metabolic pathways. A recent paper demonstrated that liquid high-sugar diets compared to solid high-sugar diets differentially modulate intestinal sugar transporters and hormone expression. To date, however, the peculiar effects of intake of different forms of fructose, liquid or solid, on intestine integrity and microbiota, and hepatic outcomes, have never been investigated.

**Materials and methods:** For this aim, C57 mice were fed a standard diet (SD) plus water to drink, a standard diet plus 60% fructose syrup (L-Fr), or a 60% fructose solid diet plus water (S-Fr), for 12 weeks. At the end of protocol, analysis on liver lipogenesis, fibrosis, and inflammation were performed by western blotting and histological analysis. Intestinal absorption, accumulation of AGEs, and integrity have been assessed by immunofluorescence and histologic score. Gut microbiota population has been characterized by metagenomic sequencing.

**Results:** L-Fr intake induced higher levels of hepatosteatosis (liver TG: +80% vs. SD, +33% vs. S-Fr,  $p < 0.05$ ), with greater activation of the lipogenic SCAP/SREBP signaling, and of markers of fibrosis, than the S-Fr. In contrast, S-Fr evoked a stronger local AGEs accumulation, RAGE expression, and barrier injury in the ileum intestinal mucosa, leading to higher concentration of LPS in the portal plasma (+300% vs. SD, +210% vs. L-Fr,  $p < 0.05$ ). This effect was associated to a stronger activation of the LPS-dependent pro-inflammatory pathway NLRP3 inflammasome in the liver of S-Fr mice than of L-Fr mice. Interestingly, the local accumulation of fructose in the intestine led to alterations of the gut microbiota depending on the fructose formulation, with increase in the saccharides metabolizing *Lactobacillus* genus in the L-Fr, and increased colonization by populations related to intestinal inflammation and barrier disruption, such as *Clostridium*, in the S-Fr group.

**Conclusion:** These results suggest that consumption of fructose under different forms, liquid or solid, has a different impact on intestinal mucosa, thus differently affecting liver homeostasis. We hypothesize that the liquid fructose is more rapidly absorbed by intestine and metabolized by the liver to produce considerable amounts of lipids. In contrast, the solid form might be slowly absorbed by enterocytes producing glycated proteins and affecting barrier integrity, with developing of systemic inflammation. Such alterations of intestinal integrity and microbial population might predispose to the development of chronic metabolic and inflammatory diseases.