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Author's reply: Fructose, uric acid and zonal differences in NASH

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Refers to: Mann J.P., Armstrong M.J. "Fructrose, uric acid, and zonal differences in NASH"

Dear Editor,

We read with interest the letter by Mann & Armstrong, referring to our article entitled "Serum uric acid concentrations and fructose consumption are independently associated with NASH in children and adolescents" [1,2]. The liver has a unique dual blood supply receiving both arterial blood and blood from the portal vein. This phenomenon and the liver cellular architecture results in hepatocytes being exposed to differential oxygen tensions and varying concentrations of dietary nutrients, according to their position across the liver lobule. Venous blood from the portal vein mixes with arterial blood from the hepatic artery in the periportal zone of the liver (where biliary ductules are also located), so that hepatocytes in this region are exposed to a higher oxygen tension, and receive blood that is rich in dietary nutrients [3]. In contrast, perivenous hepatocytes are exposed to a lower oxygen tension and lower concentrations of dietary nutrients, because blood flows along the sinuses from the periportal region towards the central veins which are located in the perivenous zones. As a consequence of this unique blood supply, metabolic functions in lobular

hepatocytes vary, dependent on the position of any given hepatocyte in the liver lobule [4]. For example, in the periportal zone, where oxygen tension is highest, levels of β-oxidation in hepatocytes is also highest, because this metabolic activity requires high oxygen tension.

In their letter, Mann & Armstrong suggest that high fructose exposure should cause hepatic zonal injury and features of non alcoholic steatohepatitis (NASH), specifically in the perivenous zone [1]. The authors assert that fructose (and alcohol) should induce a perivenous pattern of steatosis and inflammation by increasing *de novo* lipogenesis and oxidative stress in this region. However, we reason that if there is fructose-induced differential damage to hepatocytes across the liver lobule; in our opinion, the detrimental influence of fructose should be greatest in hepatocytes in the periportal region. This is because, hepatocytes in the periportal zone would receive the highest concentrations fructose via the portal vein. Consequently, we would expect a periportal pattern of development of inflammation and fibrosis occurring in this zone, induced by generation of free radicals (as oxygen tension is also highest in this zone). As stated above, the concentration of oxygen decreases along a gradient from the periportal to the perivenous zone of the liver lobule. Based on a reduced oxygen tension in the perivenous region, high levels of cytosolic triglyceride synthesis occurs in hepatocytes in this zone, since lower oxygen tension does not affect this metabolic function. Thus, we reason that we might also expect increased levels of de novo lipogenesis, (induced by fructose stimulation of lipogenesis in hepatocytes) in the perivenous zone, but without inflammation or fibrosis, because the oxygen tension is low in this zone.

That said, regardless of who is correct, the hypothesis of differential zonal injury induced by high levels of dietary fructose consumption, proposed by Mann & Armstrong, is very interesting. To date, we have not defined the pattern of zonal injury associated with high levels of dietary fructose consumption and hyperuricaemia in this cohort. However, in our population of 271 biopsy-proven NAFLD patients, a positive correlation was observed between fructose consumption and portal

inflammation ($r = 0.19$, $p = 0.05$), fibrosis ($r = 0.27$, $p < 0.001$) and between fructose consumption and steatosis ($r = 0.32$, $p < 0.001$). No significant correlations were noted between fructose consumption and ballooning of hepatocytes or lobular inflammation were observed.

We suggest that further study is needed to elucidate the relationships between specific pathogenetic stimuli and patterns of zonal injury in NAFLD. Such study may give better insight into why NAFLD progresses in some patients to serious end stage liver disease or hepatocellular carcinoma, and in other patients the liver condition remains relatively quiescent.

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