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Matthew T. Kitson
William Kemp
Stuart K. Roberts*
Department of Gastroentrology, Alfred Hospital, Melbourne, Australia
*Corresponding author.
E-mail address: s.roberts@alfred.org.au

Lisa Murnane
Nutrition and Dietetics Department, Alfred Hospital, Melbourne, Australia

Reply to: "Industrial, not fruit fructose intake is associated with the severity of liver fibrosis in genotype 1 chronic hepatitis C patients"

Fructose intake and liver damage in chronic hepatitis C

To the Editor:

Prof. Kitson's comments give us the opportunity to clarify some issues that were not completely dealt with in our manuscript. In the study we reported a link between fructose intake and the severity of liver fibrosis in a cohort of Italian patients with genotype 1 chronic hepatitis C (CHC) [1], with an association found for industrial, but not for fruit fructose intake. Our results were in keeping with data already reported in patients with non-alcoholic fatty liver disease [2,3].

Prof. Kitson and his colleagues question firstly the appropriateness of using a web-based calculator of U.S. origin (www.healthdiet.us/fructose) to assess fructose intake in the Italian population, due to a presumed much lower fructose consumption in the latter. Actually, we considered industrial fructose as any amount of fructose derived from food sources containing high fructose corn syrup (beverages like soft drink and fruit juices, processed foods like fast-food, especially when enriched with industrial sauces). The U.S. database for the calculation of fructose intake is most likely valid also for use in Italian patients, since the majority of foods and beverages with added fructose are produced by multinational companies, and the concentration of fructose does not change among countries. In addition, our data on fructose consumption are in keeping with another Italian report [4]. Prof. Kitson and colleagues also question the validity of a three-day food diary. It has been reported that a three-day diary record correlates closely with a longer 9-day diary [5], providing a solid dietary assessment. In a cross-sectional analysis no inference can be made regarding a possible causal relationship, but this possibility may be postulated. We have simply described the positive association between industrial fructose and advanced fibrosis, but the two conditions might also share common pathogenic mechanisms.

As a second point, our study was performed in an Italian population, not in an Australian or U.S. population, where much higher rates of fructose consumption are recorded. The accuracy of our computation of fructose intake is in keeping with the industrial fructose intake reported in the Italian population [4], but lower than in the U.S. population. In the participants of the LOOK Ahead study consuming $\geqslant$15 g/day of fructose (high-fructose consumers), a fructose challenge identified metabolic abnormalities potentially responsible for NAFLD progression [6]. This threshold was observed in most of our cases with fibrosis, and the higher industrial fructose intake was the major source of difference between cases with advanced *vs.* mild hepatic fibrosis. When industrial fructose intake as continuous variable was replaced in the model by industrial fructose as categorical variable, 14/25 patients consuming $\geqslant$8 g/day industrial fructose had F3-F4 fibrosis *vs.* 18/89 in the group with lower intake ($p = 0.01$).

Thirdly, Kitson *et al.* remark the lack of association between severe liver fibrosis and both insulin resistance (IR) and steatosis in this specific population. In the present series, steatosis was linked to fibrosis at both univariate and multivariate analysis. Both IR and steatosis, the phenotypic hepatic expression of IR, are risk factors for fibrosis; they both might play an important role in fibrosis progression and are likely to be variably combined in different settings [7,8]. As to the possible reason(s) why industrial, not fruit fructose intake, is associated with the severity of liver fibrosis in CHC, several tentative hypotheses may be suggested. In fresh fruit the deleterious effects of fructose might be counterbalanced by the positive effects of other nutrients (e.g., fibers) and antioxidants, not present in industrial fructose. In processed food, the glucose of high-fructose corn syrup might accelerate fructose absorption, making industrial sugars unhealthy. Finally, even if the link between industrial fructose and the clinico-pathological features (i.e., liver fibrosis and obesity) was independent of energy intake on a statistical basis, we cannot rule out a pivotal role of calories and/or of a less healthy diet and lifestyle in the reported association, considering that higher amounts of industrial fructose were associated with high-calorie diets.

Hence we are confident that our study provides reliable evidence, albeit of an associative nature. Further research is clearly needed to provide external validation and to eventually elucidate the pathophysiological basis, aiming to a healthy diet as an additional tool to manage patients with HCV-induced chronic liver disease.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Salvatore Petta*
Sezione di Gastroenterologia, Di.Bi.M.I.S, Università di Palermo, Italy
*Corresponding author.
E-mail address: petsa@inwind.it

Giulio Marchesini
Dipartimento di Medicina e Gastroenterologia, "Alma Mater Studiorum", Università di Bologna, Italy

Antonio Craxì
Sezione di Gastroenterologia, Di.Bi.M.I.S, Università di Palermo, Italy

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To close the stable door before the horse has bolted

To the Editor:

We read with interest the studies by Fagundes and colleagues [1], Piano and colleagues [2] and the accompanying editorial [3].

Both studies evaluated large numbers of patients with cirrhosis (375 and 233, respectively) and assessed the impact of acute kidney injury (AKI), assessed both by AKIN criteria and the more conventional finding of a creatinine level of $\geqslant$1.5 mg/dl. Piano and colleagues only included patients with hospital acquired AKI, thus excluding patients who already had renal impairment on admission. In this study, all patients had ascites, while in the study by Fagundes and colleagues this was present in two thirds. In both studies, patients with stage 1 AKI with a peak creatinine <1.5 mg/dl did not have an increased mortality as compared to patients without AKI. The accompanying editorial therefore suggests the conclusion that stage 1 AKI with a peak creatinine of <1.5 mg/dl is a benign condition.

The importance of renal failure in cirrhosis is well established. It increases the risk of dying 7-fold and carries a 1 month mortality of up to 50% [4], an impact on the natural history of a magnitude similar to that of bacterial infections [5]. Creatinine as an indicator of renal function is an essential component of prognostic scores such as MELD and UKELD. Both the stage of AKI and the peak creatinine level are associated with increased mortality [6]. Tsien and colleagues [7] recently published a prospective study on 90 outpatients with cirrhosis and ascites. Episodes of AKI (as per AKIN criteria) were common, and the mean peak creatinine value was within normal laboratory values. Importantly, patients with an episode of AKI had decreased survival on follow up.

While widely used, creatinine remains an imperfect marker of renal function in cirrhosis. Not only can high levels of bilirubin interfere with creatinine measurements, but levels also correlate with total muscle mass, which is often markedly reduced in patients with cirrhosis and ascites [8]. As a consequence, baseline creatinine levels in patients with cirrhosis are frequently substantially lower than the upper limit of normal used by laboratories, and substantial increases in creatinine level may not exceed the "normal values" and may thus not be spotted by the non-hepatologist.

We would therefore like to disagree with the conclusion that stage 1 AKI with a peak creatinine of <1.5 mg/dl is a "benign" condition. Both Fagundes' and Piano's study had standard interventions for patients whose creatinine increased (even if below 1.5 mg/dl), and these measures were implemented rapidly since all patients were in hospital. These included such crucial measures as withdrawal of diuretics and nephrotoxic drugs, diagnosis and treatment of bacterial infections and fluid challenges with crystalloids or albumin. In Tien's study, blood tests were taken every 4–6 weeks but clinical evaluation for assessment of AKI only occurred every 4 months – this raises the question whether interventions in patients with increasing renal markers were not carried out in a similarly timely fashion. This is in line with a recently published trial reporting improved survival in patients with cirrhosis and ascites who were allocated to closely monitored outpatient management under the care of a specialised clinical team at a dedicated Hepatology centre [9].

In our opinion, the correct conclusion from the current evidence should be that stage 1 AKI with a peak creatinine of <1.5 mg/dl in patients with cirrhosis is a potentially benign condition if promptly treated and correctly managed. If ignored and untreated, it is likely to progress to higher stages of AKI and carry an increased mortality. Our vigilance should therefore be aimed at the timely detection of renal impairment in patients with