Conflict of interest

X. Adhoute is a board member of Bayer; G. Penaranda has received grants from Bayer; J.L. Raoul is a board member of Bayer, BMS, Daichi; J.P. Bronowicki is a board member of Merck-Schering Plough, Janssen, Roche, BMS, Boehringer-Ingelheim, Gilead, Novartis, GSK, Bayer and a speaker for Merck-Schering Plough, Janssen, Roche, BMS, Boehringer-Ingelheim, Gilead, Novartis, GSK, and Bayer.

Authors’ contributions

XA and JPB collected the data; GP performed the statistical analyses; XA, JPB, JLR, and GP analysed the data; XA, JLR, and GP wrote the manuscript.

References


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Transient increase in urine protein excretion during treatment with terlipressin and albumin for type-1 hepatorenal syndrome

To the Editor:
We recently had a patient admitted to our unit with cirrhosis and type-1 hepatorenal syndrome (HRS) who developed marked proteinuria during treatment with terlipressin and albumin. This led us to investigate whether pharmacological treatment of type-1 HRS could be associated with an increase in urine protein excretion. The effects of terlipressin and albumin on kidney function in patients with type-1 HRS have been investigated extensively [1,2], but to our knowledge there is no information on the potential effects of treatment on urine protein. We evaluated a series of
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Fig. 1. Evolution of urine protein excretion in patients with type-1 hepatorenal syndrome. Evolution of urine protein excretion in patients with type-1 hepatorenal syndrome treated with terlipressin and albumin (left panel) and in patients treated with albumin alone (right panel).

29 patients with type-1 HRS, treated at our institution. Patients were selected from a database of 75 patients with type-1 HRS, treated in our unit in the last 15 years. Clinical and laboratory data from all patients were recorded prospectively in this database at the time of treatment. For this analysis we selected 29 patients who had urine protein measurements available before treatment and at two time points during treatment. There were no significant differences regarding baseline liver and kidney function tests and the percentage of response to treatment between these 29 patients and the remaining 46 patients included in the database. Urine analyses were performed before treatment, at days 3–4, and at the end of treatment. The individual values of urine protein excretion in all patients evaluated are shown in Fig. 1 (left panel). Treatment with terlipressin and albumin was associated with a statistically significant increase in urine protein excretion that returned towards baseline values at the end of treatment (239 ± 151, 675 ± 961, and 380 ± 459 mg/24 h at baseline, days 3–4, and at the end of treatment, respectively; mean ± standard deviation, p = 0.001). Interestingly, in 4 of the 29 patients (14%) urine protein excretion increased above 1 g/day during treatment. To assess whether the magnitude of the increase in urine protein excretion was related to the response to treatment, we categorized patients into two groups according to urine protein excretion during treatment with terlipressin and albumin (patients with urine protein ≥500 mg/24 h vs. patients with urine protein <500 mg/24 h). There were no significant differences between the two subsets of patients regarding baseline liver, kidney and circulatory function, dose of terlipressin used or length of therapy. In the overall series, the mean duration of therapy was 7 ± 4 days (7 ± 3 and 8 ± 45 days in patients with urine protein ≥500 mg/24 h vs. patients with urine protein <500 mg/24 h, respectively; p = 0.7). Overall, 18 out of the 29 patients (62%) had complete response to treatment (serum creatinine <1.5 mg/dl at the end of treatment). The development of proteinuria was not related to an impaired response to treatment. In fact, three out of the 7 patients (43%) with urine protein excretion ≥500 mg/24 h had a complete response to treatment compared to 15 out of the 22 patients (68%) with urine protein excretion <500 mg/24 h (p = 0.37). Moreover, of the 4 patients with excretion greater than 1 g/day had a complete response to therapy. Urine protein excretion in responders to treatment with terlipressin and albumin was 268 ± 157, 756 ± 1178, and 436 ± 571 mg/24 h (at baseline, days 3–4, and end of treatment, respectively) compared to 191 ± 133, 543 ± 439, and 287 ± 138 mg/24 h in non-responders (p = n.s.).

To assess to what extent the increase in urine protein excretion was related to treatment with terlipressin plus albumin or could be related to the administration of intravenous albumin alone we also investigated a historical control group of 12 patients with type-1 HRS, associated with bacterial infections that were treated with albumin alone, included in a previous study [3]. In this series of patients urialalysis was performed before treatment and at day 3. In patients with type-1 HRS, treated with albumin alone, there was no significant increase in urine protein excretion during treatment (108 ± 67 vs. 143 ± 118 at baseline and at day 3, respectively; p = n.s.). The individual values of urine protein excretion in patients treated with albumin alone are shown in Fig. 1 (right panel).

The pathogenic mechanisms responsible for the increase in urine protein during treatment with terlipressin and albumin were not assessed in this study. This effect could be related to the increased renal perfusion pressure caused by terlipressin administration. It is also possible that terlipressin treatment may uncover some preexisting parenchymal nephropathy [4]. In conclusion, regardless of the mechanism involved, our results indicate that treatment with terlipressin and albumin is associated with a transient increase in urine protein excretion that is significant in some patients. Based on our findings, the development of an increase in urine protein excretion during treatment of type-1 HRS should not modify the diagnosis and treatment of kidney failure. This information may be clinically useful for clinicians, caring for patients with acute complications of cirrhosis.

Conflict of interest

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

References

Deficiency of periostin protects mice against methionine-choline-deficient diet-induced non-alcoholic steatohepatitis

To the Editor:
Non-alcoholic fatty liver disease (NAFLD), the most common cause of chronic liver disease worldwide, encompasses a spectrum of diseases ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) [1,2]. Periostin (encoded by POSTN), a matricellular protein, plays an important role in various inflammatory disorders, such as airway inflammation, skin inflammation, atherosclerosis and fibrosis [3,4], and actively contributes to tumour metastasis [5–7]. However, until the recent publication by Lu et al. [8], there was no known link between periostin and NAFLD. Lu et al. [8] found that hepatic periostin expression is dramatically increased in high-fat diet (HFD)-fed mice, ob/ob mice and db/db mice, as well as in NAFLD patients. Lu et al. [8] further demonstrated that periostin is a crucial contributing factor in aberrant hepatic triglyceride (TG) accumulation and in the pathogenesis of obesity-induced hepatosteatosis. However, the role of periostin in the pathogenesis of NASH remains unknown [9]. As an aggressive form of fatty liver disease, NASH is characterized by histopathological features, such as steatosis, inflammation and fibrosis, and is often accompanied by the metabolic syndrome, such as diabetes, insulin resistance and obesity. Moreover, some individuals with NASH eventually advance to liver cirrhosis and/or hepatocellular carcinoma, whereas hepatic steatosis usually has no serious clinical consequences [2,9]. Because genetically induced rodent obesity or HFD-induced hepatic steatosis does not progress to steatohepatitis, we now present data to determine the role of periostin in the development of methionine-choline-deficient (MCD) diet-induced NASH in mice.

To reveal the role of periostin in the development of NASH, we fed two groups of C57BL/6J mice with either regular chow or the MCD diet for 4 weeks. MCD diet-fed mice developed hepatic steatosis whereas chow-fed mice did not develop steatosis. The MCD diet also resulted in inflammation and fibrosis in mouse liver tissue (data not shown). We found that periostin was markedly upregulated and mainly distributed around steatoitic hepatocytes in the MCD diet-fed mice by immunohistochemical staining (Fig. 1A). Western blotting and qRT-PCR analyses further demonstrated that the protein and mRNA levels of liver periostin were dramatically increased in MCD diet-fed mice compared with control mice (Fig. 1B and C). Moreover, we found that mice fed the MCD diet for 8 weeks, also developed NASH and showed phenotypes of steatosis, inflammation and fibrosis. The protein and mRNA levels of liver periostin in mice fed the MCD diet for 8 weeks were also significantly upregulated (data not shown). These data suggest that periostin may be involved in the development of MCD diet-induced NASH.

To determine whether periostin deficiency abrogates the progression of NASH, we used a periostin-deficient mouse model. Heterozygous B6;129-Postn<sup>tm1jmol</sup> (Postn<sup>+/−</sup>) mice were purchased from the Jackson Laboratory (Bar Harbor, Maine, USA). Periostin-deficient and periostin wild type mice were generated from crossing Postn<sup>+/−</sup> with Postn<sup>+/+</sup> mice. After feeding the MCD diet for 4 weeks, periostin-deficient mice exhibited significantly less TGs in their livers compared to the wild type group (Fig. 1D). The serum level of alanine aminotransferase was markedly less in Postn<sup>−/−</sup> mice compared to wild type mice (Fig. 1E), indicating that the MCD diet produced a more severe liver injury in wild type mice than in Postn<sup>−/−</sup> mice. Moreover, MCD diet feeding resulted in an increased collagen deposition in wild type mice, as shown by Sirius red staining; however, collagen deposition was significantly lower in Postn<sup>−/−</sup> mice than in wild type mice after being on the MCD diet (Fig. 1F and G), suggesting that Postn<sup>−/−</sup> mice exhibited significantly less histological fibrosis compared to the wild type group. We also found that mRNA levels of the inflammatory and fibrotic factors IL-6, TGF-β1, and α-SMA were markedly increased in livers of MCD diet-fed wild type mice compared to the chow diet-fed wild type controls; however, the mRNA levels of IL-6, TGF-β1, and α-SMA were significantly lower in the liver tissue of Postn<sup>−/−</sup> mice than in wild type mice after being on the MCD diet for 4 weeks (Fig. 1H). Therefore, these data suggest that a deficiency in periostin abrogates the development of MCD diet-induced NASH in mice.

In conclusion, our work demonstrates that periostin is highly expressed in MCD diet-induced NASH and that periostin knock-out mice show a markedly lower degree of steatosis, inflammation and fibrosis compared with wild type mice after being fed the MCD diet. As previously mentioned, hepatic periostin levels are significantly upregulated in monogenic-induced obese mice and HFD-fed mice, as well as in patients with fatty liver disease [8]. Therefore, these data demonstrate that periostin is a potential diagnostic marker and therapeutic target for hepatosteatosis, NASH and even other liver diseases.