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Pro-coagulant imbalance in patients with chronic liver disease

To the Editor:

We saw with interest the paper by Lisman et al. [1], published in a recent issue of the Journal of Hepatology reporting normal or even increased thrombin generation in patients undergoing liver transplantation (LT) as compared to healthy subjects. This has been interpreted as an *in vitro* "resistance" to the anti-coagulant action of thrombomodulin [the physiological activator of protein C (PC)]. This resistance is apparently due to the pro-coagulant imbalance consequent to decreased levels of the anti-coagulant drivers PC and antithrombin combined with increased levels of the pro-coagulant driver factor (F)VIII. This is an interesting issue and deserves comments.

We have already shown that patients with stable cirrhosis possess a pro-coagulant imbalance detectable by thrombin generation assays performed with/without thrombomodulin [2]. The pro-coagulant imbalance observed in our cohort was mainly due to decreased levels of PC and antithrombin combined with increased levels of FVIII [2], which are typical features in cirrhosis. Furthermore, we also showed that the pro-coagulant imbalance increases with the severity of the disease, as patients classified as Child C had a more pronounced pro-coagulant imbalance than patients classified as Child A–B [2]. Finally, we showed that the extent of the imbalance observed in the Child C class was slightly greater than that observed in plasma from patients who were carriers of congenital-PC deficiency [2], a condition associated with an increased risk of venous thromboembolism. It can, therefore, be concluded that the pro-coagulant imbalance is a general and typical feature of patients with cirrhosis, and not only of patients undergoing LT.

Concerning the cohort of patients investigated by Lisman et al. [1], it is intriguing that they were still "pro-coagulant" even 5–10 days after LT when PC was normalized. The authors surmise that the pro-coagulant imbalance persists because of the persisting increased levels of FVIII observed after LT. This requires further comments. While PC levels are reduced pre-transplant because of the impaired synthetic liver capacity, the increased levels of FVIII are not explained by increased synthesis, but probably by decreased clearance from circulation (reviewed in Ref. [3]). This is apparently mediated by two mechanisms involving the von Willebrand factor (VWF) and the low density lipoprotein receptor-related protein (LRP) [3]. VWF binds FVIII *in vivo* and protects it from cleavage by plasma proteases and premature clearance. Increased levels of VWF are typical features of patients with cirrhosis and, therefore, they may be causally involved in maintaining elevated circulating levels of FVIII in this condition [3]. LRP, on the other hand, is a multi-functional ligand that mediates the cellular up-take and degradation of plasma FVIII. LRP is poorly expressed in cirrhosis and in conjunction with high VWF might sustain the increased circulating levels of FVIII [3]. If the above mechanisms hold true one would expect that, after transplantation, patients have normal levels of PC as well as FVIII. The reason why FVIII is persistently high after LT is of interest. One reason could be that as FVIII is an acute phase reactant, it persists to be high solely because of the pro-inflammatory effect mediated by surgery [4,5].

We agree with Lisman et al. [1] that the pro-coagulant imbalance observed in cirrhotics [2] supports the restrictive use of plasma infusion in patients undergoing LT, but the restriction should be extended also to stable patients when they undergo invasive procedures, where plasma infusion is still common practice. We also agree that a more extensive use of anti-coagulant drugs should be explored to reduce the incidence of post-transplant thromboses, but again this should also be extended to pre-transplant patients who develop portal- or peripheral-vein thromboses. In this respect, we surmise that if the mechanism of the pro-coagulant imbalance (i.e., decreased levels of PC combined with increased levels of FVIII) holds true, thromboprophylaxis with vitamin-K antagonists (VKA), as it is currently done for other categories of patients, could prove (at least in principle) less suitable for patients with cirrhosis. VKA work, in fact, by decreasing the activity of vitamin-K-dependent coagulation factors including PC [6], which is already considerably reduced because of impaired liver synthesis capacity. Therefore, one might speculate that VKA in cirrhosis might (paradoxically) exacerbate the pro-coagulant imbalance leading to a much higher, increased FVIII-to-PC ratio than that observed in patients with cirrhosis not on VKA [2], especially if high initial doses of VKA are used. Perhaps, the new oral antithrombotic drugs, which act directly by inhibiting FXa or thrombin [7] might be more effective than VKA in preventing recurrences in patients with cirrhosis after a first episode of venous thromboembolism. Furthermore, at variance with VKA, the new drugs do not require laboratory monitoring to adjust their dosage [8], thus also circumventing the problem of standardization of the INR, whose validity, as a laboratory tool to monitor anticoagulation in patients with cirrhosis, has been questioned and not yet resolved [9]. However, the efficacy and safety of the new antithrombotic drugs in the setting of cirrhosis require investigation by appropriate clinical trials.

Conflicts 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.

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Non-alcoholic fatty liver disease, alcohol intake and psoriasis

To the Editor:

We read the interesting report by Gisondi et al. published in a recent issue of the Journal of Hepatology [1]. In this study, the authors found that patients affected by severe psoriasis exhibited an undiagnosed non-alcoholic fatty liver disease (NALFD) in almost 50% of cases and suggested that psoriasis might be a major risk factor for NALFD development.

The study shed light on this important issue, but there are some concerns regarding selection of patients and the method used to measure alcohol consumption.

Gisondi et al. state that the following amounts of alcoholic beverages were considered one drink: "330 ml beer (containing ~5% of alcohol), 150 ml wine (containing ~12% of alcohol), and 40 ml strong alcohol (containing ~50% of alcohol)". Calculating the amount of ethanol (EtOH) of each drink, it appears that the beer contains about 13.2 g of EtOH, the wine 14.4 g and the strong alcohol about 16 g. These data indicate that the group of 33 patients consuming $\leqslant$2 drinks had an alcohol intake of 26.4–32.0 g, depending on the type of beverages, whereas the group of 20 patients consuming 3–4 drinks had an alcohol intake of 39.6–64.0 g. Literature data have demonstrated that male patients consuming more than 30 g and female patients consuming more than 20 g of EtOH daily should be excluded from the cohort when dealing with NAFLD because it is plausible that they may already have an alcohol-related liver disease [2]. Consequently, the authors should have excluded from their study the group of patients consuming 3–4 beverages/day and apply different cut-offs for males and females to include only patients fitting the above-mentioned criteria for NAFLD.

Moreover, Gisondi et al. have calculated the prevalence of NAFLD in non-drinking patients (37%), which is lower compared to the psoriasis-affected population considered in their study, which include drinker and non-drinker patients. However, the prevalence of liver disease should also be calculated in light of moderate drinkers with psoriasis (consuming $\leqslant$2 drinks and 3–4 drinks, respectively) in order to analyze the contribution of these groups in achieving a total NAFLD prevalence of 47% in psoriatic patients.

Co-morbidities in psoriasis have been deeply investigated in the last years. The relationship between psoriasis and comorbidities is probably related to the underlying chronic inflammatory process. In this regard, emerging co-morbidities of psoriasis include cardiovascular disease and metabolic syndrome, notably obesity, dyslipidemia, and insulin resistance. Therefore, it is plausible that chronic systemic inflammation, as observed in psoriasis, may also be responsible for NAFLD [3] and this association should be considered when dealing with patients affected by psoriasis, as reported by Gisondi et al. However, the prevalence of this association is probably overestimated and we believe that an accurate evaluation of the daily alcohol intake using the world-wide established alcoholic unit (corresponding to 8 g of EtOH) may improve the selection of patients in which NAFLD prevalence has to be calculated.

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.

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