EDITORIAL

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CAP: a Novel Era to Better Quantitate Fatty Liver?

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Hepatic steatosis is one of the most popular findings in patients with liver injury and it has been considered by most textbooks as the first sign of all chronic liver diseases. Fatty liver has long been appreciated as symptomatic for patients who consume alcohol [1] and it is seen more frequently with the epidemic rise of NASH. In the now classical Dionysos study, Bellentani et al. were able to demonstrate that almost all obese people who consumed alcohol had fatty liver [2].

The liver is the central metabolic organ located at the cross roads of many physiological pathways and its response towards environmental, nutritional, hormonal and metabolic changes is rather complex (Fig. 1). Theodor Frerichs recognized in his famous classical 'Klinik der Leberkrankheiten' in 1858 that liver fat can be stored reversibly upon feeding a high fat diet and that hibernating mammals store fat in the liver during winter periods [3]. It is not widely conceived that the liver responds with fat accumulation both in the fasting state due to peripheral lipolysis and under conditions of excess nutritional fat (Fig. 1). In the 19th century, infectious diseases were the most common causes of fatty liver due to peripheral lipolysis. Today, apart from nutritional causes, toxic conditions due to drugs or viral hepatitis are very common. These conditions typically cause microvesicular steatosis by impairing the mitochrondrial ß-oxidation. Ethanol consumption as most popular reason for steatosis causes fatty liver via multiple pathways [4]. In patients with non-alcoholic steatohepatitis (NASH), insulin resistance is certainly the most reproducible factor. Patients usually have elevated fasting insulin and C-peptide levels. Insulin resistance leads to hepatocyte fat accumulation by, first, enhanced peripheral lipolysis with increased circulating free fatty acids, and, second, hyperinsulinemia.

On the other side, the high prevalence of steatosis in most liver diseases has cast serious doubt on the causal role of hepatic fat, which is considered by some authors rather as a bystander (Fig. 2) [5]. Indeed, only a minority (15%) of patients with non-alcoholic fatty liver (NAFLD) will progress to advanced end stage liver disease despite the abundance of liver fat in the remaining patients. Moreover, the recently discovered new genes involved in NAFLD and alcoholic liver disease (ALD) progression such as *PNPLA3* [6] seem to primarily cause hepatocyte damage rather than steatosis [7]. In line with this, alcoholic steatohepatitis (ASH) rather than steatosis seems to be the major risk for cirrhosis development in patients who consume alcohol [8].

One of the major obstacles in better defining the role of liver fat has been an easy noninvasive and quantitative method to measure steatosis. The invasive liver biopsy is not only prone to mild and severe complications, but has an unacceptable high sampling error of cca. 30% [9]. This is a major challenge for following-up hepatic steatosis over time. It should also be mentioned that fat can change rapidly not only in response to drugs, but also alcohol or dietary changes [7]. Conventional screening tools for steatosis have been ultrasound, and to some extent CT and MRI, especially proton MRI spectroscopy [10]. Unfortunately, the widely used ultrasound has a poor analytical sensitivity and specificity in detecting steatosis, while MRI and MR technique are limited by the lack of established standardization of sequence characteristics and their high cost [11]. Recently, CAP (controlled attenuation parameter) has been introduced, which is run on the Fibroscan platform (Echosens, Paris, France). It measures the attenuation of the shearwave induced by the 50 Hz vibration probe and results are expressed as decibels per meter (dB/m) and range from 100 to 400 dB/m. While first only available on the M probe, it now can be used with the XL probe. First studies indicated that CAP is reproducible and quantitative with an AUROC up to 90% for

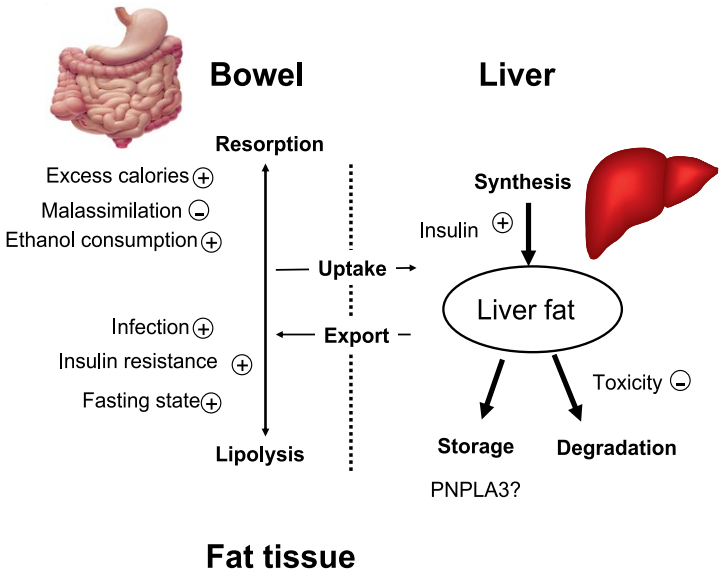

Fig. 1. Liver fat is modulated by various environmental and genetic factors both at the systemic and cellular level. The scheme roughly depicts the complexity between steatosis and clinical entities and it is far from beeing complete. CAP will help to better understand the role of liver fat in all these conditions.

fatty liver [12]. However, biopsy proven studies from various geographic regions are urgently required to better validate CAP, to learn more about regional differences of the prevalence of steatosis and to address the major problems mentioned above.

The study by Lupsor and coworkers [13] is stepping in by presenting a large monocenter cohort from Romania. They prospectively analyzed 201 consecutive patients with various liver diseases all of whom have underwent CAP measurements and liver biopsy. This study confirms earlier reports that steatosis is the only histopathological factor independently influencing CAP. Maximal values for diagnostic accuracy of >80% could be obtained for the prediction of S2 and S3 steatosis. The prediction of S1 still reached an acceptable accuracy of 76.1%. The study thus confirms the usefulness of noninvasive steatosis assessment by CAP, rendering it especially helpful to follow up individual patients, e.g. with NASH, over time and for clinical multicenter studies on liver steatosis. Thus, the study of Lupsor et al. is a further important piece of work in paving the road for a better understanding of the role of steatosis in liver disease progression.

However, many questions remain open that should be addressed in future studies: How does CAP changes in response to fast kinetics such as alcohol detoxification, binge drinking, after nutrition and the intake of certain drugs? The

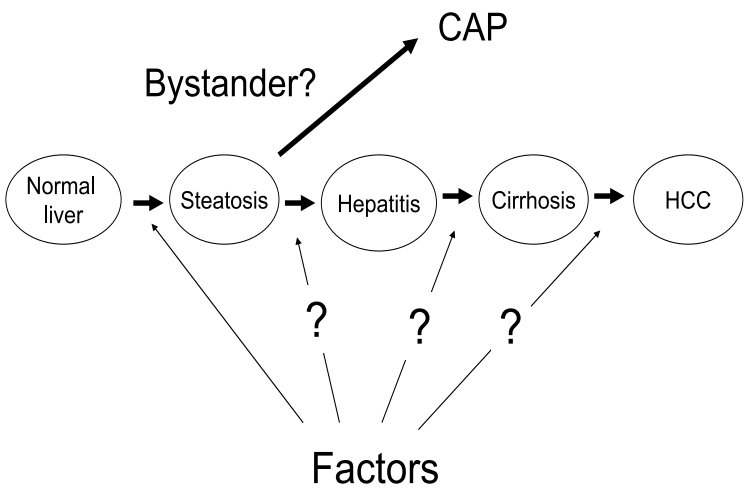

Fig. 2. All liver diseases ultimately lead to liver cirrhosis with hepatocellular carcinoma (HCC) as major complication. Whether steatosis is a causal event or a mere bystander is an actual controversial debate. Novel non-invasive diagnostic means such as CAP are urgently needed to unravel the role of steatosis in liver disease progression.

first recent data seem to indicate that CAP rapidly decreases within 5 days by 30 dB/m after alcohol detoxification [7]. How does CAP compare to ultrastructural features such as microvesicular or macrovesicular steatosis? Does CAP-assessed steatosis depend on disease etiology?

At the moment, clinical and translational hepatology has a great momentum and CAP is only one of the many technical and innovative givers. It is expected that non-invasive methods such as CAP will permit many more studies in the future that will enhance our knowledge on steatosis avoiding the bias of invasive, biopsy-dependent studies.

Conflicts of interest: No conflict to declare.

REFERENCES

1. Seitz HK, Mueller S. Alcoholic liver disease. In: Dancygier H, ed. *Clinical Hepatology: Principles and Practice of Hepatobiliary Diseases*. Heidelberg, Dordrecht, London, New York: Springer, 2009: 1111-1152.
2. Bellentani S, Saccoccio G, Costa G, et al. Drinking habits as cofactors of risk for alcohol induced liver damage. The Dionysos Study Group. Gut 1997; 41: 845-850. doi: 10.1136/gut.41.6.845
3. Frerichs TF. *Klinik der Leberkrankheiten*. Braunschweig: Vieweg, 1858.
4. Seitz HK, Mueller S. Ethanol metabolism and its consequences. In: Anzenbacher P, Zanger U, eds. *Metabolism of Drugs and Xenobiotics*. Weinheim: Wiley, 2011.
5. Day CP, James OF. Hepatic steatosis: innocent bystander or guilty party? Hepatology 1998; 27: 1463-1466. doi: 10.1002/hep.510270601
6. Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2008; 40: 1461-1465. doi: 10.1038/ng.257
7. Rausch V, Straub BK, Peccerella T, et al. Primary hepatocellular damage lowers alcohol consumption and suppresses fat mobilization in heavy drinkers with PNPLA3 G genotype (submitted), 2015.
8. Mathurin P, Beuzin F, Louvet A, et al. Fibrosis progression occurs in a subgroup of heavy drinkers with typical histological features. Aliment Pharmacol Ther 2007; 25: 1047-1054. doi: 10.1111/j.1365-2036.2007.03302.x
9. Mueller S, Seitz HK, Rausch V. Non-invasive diagnosis of alcoholic liver disease. World J Gastroenterol 2014; 20: 14626-14641. doi: 10.3748/wjg.v20.i40.14626
10. Schwenzer NF, Springer F, Schraml C, Stefan N, Machann J, Schick F. Non-invasive assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. J Hepatol 2009; 51: 433-445. doi: 10.1016/j.jhep.2009.05.023
11. d'Assignies G, Ruel M, Khiat A, et al. Noninvasive quantitation of human liver steatosis using magnetic resonance and bioassay methods Eur Radiol 2009; 19: 2033-2040. doi: 10.1007/s00330-009-1351-4
12. Sasso M, Beaugrand M, de Ledinghen V, et al. Controlled attenuation parameter (CAP): a novel VCTE guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes. Ultrasound Med Biol 2010; 36: 1825-1835. doi: 10.1016/j.ultrasmedbio.2010.07.005
13. Lupșor-Platon M, Feier D, Stefănescu H, et al. Diagnostic accuracy of controlled attenuation parameter measured by transient elastography for the non-invasive assessment of liver steatosis: a prospective study. J Gastrointestin Liver Dis 2015; 24: 35-42.