Editorial

Touching some firm ground in the epidemiology of NASH

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Anyone trying to understand the burden of disease of NAFLD in our societies might feel like they are trapped in a labyrinth, under a dim light. A labyrinth, because there are many ways to look for NAFLD and not just one straightforward diagnostic method. Under a dim light, because all these imperfect procedures and tests do not allow us to see far enough, given their limited sensitivity and specificity. Yet, for all these uncertainties, the sense of facing a real problem is overwhelmingly present. Just as it should be when you are trapped in a labyrinth.

Because of the absence of a simple and readily available marker of NAFLD, data from the general population has been slow to emerge. The report from Armstrong *et al.* in this issue of the *Journal of Hepatology* is therefore an important addition to the literature. The authors studied NAFLD in the setting of a large, primary care practice in the UK. This is a step closer to the general population although not yet as close as screening for NAFLD in factory workers [1] or through City Hall records [2]. The overall design was to identify individuals with increased liver function tests, but without a past history of liver disease, known alcohol-related health problems, past or present intravenous drug use or current symptoms of liver disease. Increased LFTs were therefore diagnosed in asymptomatic individuals with a low risk of liver disease. But this does not mean that those individuals were otherwise healthy. Most of them had chronic health problems which actually prompted testing for LFTs. In fact 40% of participating individuals were obese, 43% had arterial hypertension, and 24% had type 2 diabetes (Table 2), all conditions epidemiologically associated with NAFLD. While this is far from the end-of-spectrum seen in tertiary referral centers, it still concerns a population enriched with risk factors for NAFLD, albeit less so than reports from specialized academic centers. With these entry criteria, 1118 individuals were included. The strength of the study is that almost all of them underwent a thorough work-up including ultrasound and specialized hepatological tests, to diagnose the underlying liver disease.

The results come as a surprise to anyone that first learned what causes liver disease, a bare 20 years ago. In today's clinical landscape, 26% of these cases are related to NAFLD, 25% to alcohol consumption, and 45% have no clear cause, while all classical causes of liver diseases (HCV and HBV infection, hemochromatosis, primary biliary cirrhosis, alpha1 anti-trypsin deficiency, etc.) account for less than 1% each! Thus, NAFLD is nowadays the main player in hepatology and probably here to stay. Worse, considering how the diagnosis was ascertained, there is a fair chance that the prevalence of NAFLD might have been underestimated by a good margin. Ultrasound is notoriously unable to diagnose excess fat in the liver when this is less than 20–30% on liver biopsy. Thresholds for alcohol were conservative at best (more than 20 g/day for females and 30 g/day for males); this is in line with expert recommendations [3] but totally misses the epidemiological reality of a large segment of the population which is exposed to both metabolic risk factors and moderate amounts of alcohol (<50 g/day). Studies in the French general population have shown that almost two-thirds of patients attending a routine examination in Social Security Health Care centers have metabolic risk factors but also consume alcohol higher than 10 g/day for females and 20 g/day for males [4]. Because of their exposure to metabolic risk factors, there is no reason why these individuals should not be considered as having NAFLD (with or without alcoholic liver disease) until proven otherwise. In some large epidemiological studies, only daily amounts >30 g/day were associated with steatosis [5]. Note that in the study by Armstrong *et al.*, 87% of the subjects with alcoholic liver disease (diagnosed with the liberal thresholds mentioned above) also happened to be overweight. On the other hand, more than half of these patients with "excessive" alcohol consumption did not have steatosis detectable by ultrasound. Despite the insufficient sensitivity/specificity of ultrasound, this questions whether the thresholds for the diagnosis of alcoholic liver disease might have been too low. Unsurprisingly, older studies establishing associations between alcohol intake and risk of alcoholic liver disease did not adjust for BMI, diabetes, or other metabolic risk factors. The lines are thus blurred until comprehensive studies of the association between exposure to metabolic risk factors and moderate alcohol consumption *vs.* hard outcomes become available. Meanwhile, it is reasonable to assume that the prevalence of NAFLD in asymptomatic patients with altered LFTs and no suspicion of other causes of chronic liver disease is even higher than that presented by Armstrong *et al.*

To their credit, Armstrong *et al.* avoided to some extent the usual limitations of this type of study. The vast majority of blood samples (1029/1118) were assayed in a central lab and the results of the others were standardized to the central lab refer-

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ence range. The upper limit of normal was close to 40 IU/L, higher than ideal but still acceptable and in line with that used by most labs. Ultrasound was performed by senior radiologists with good inter-observer reproducibility. Nonetheless, the study was based on a single time-point instead of persistently elevated LFTs. Many subjects with increases in aminotransferases could have normal values upon retesting. This could be accounted for by transient infectious episodes, drug intake, or other circumstantial events. The proportion of cases with an unknown cause of altered LFTs could have been lower, and that of cases due to NAFLD or alcohol consumption higher than what was ultimately found by Armstrong *et al.* Interestingly, an increased level of serum gamma glutamyl transpeptidase appeared to have higher sensitivity than increased aminotransferases, the usual test for screening patients at risk for NASH.

These high epidemiological numbers are backed up by a few other converging reports. Earlier this year in a study performed in middle-aged, US Army personnel seeking medical care for unspecified medical conditions (but unrelated to NAFLD), the prevalence of ultrasonographically defined and histologically confirmed fatty liver was an intriguing 48% [6]. This is double the previous estimates from Western countries based on similar ultrasound detection. It may be explained by particulars of the population under study (mean BMI of 30 kg/m^2 and a 45% prevalence of obesity) but, remarkably and contrary to the report by Armstrong *et al.*, patients were included irrespective of abnormal LFT values. Even more concerning are data of incidental findings of NAFLD and NASH in candidates for living-donor liver transplantation. Because of the selection process, these individuals are at lowest risk for liver disease. Yet, histological verification shows that the prevalence of steatosis alone ranges from 12–51% and that of steatohepatitis from 2% to 15% [7–12]. It should come as no surprise that the initial reports in the 90's [13] were largely confirmed a decade later: nowadays NAFLD has become the most frequent cause of newly diagnosed cases of chronic liver disease [14].

While this study shows that NAFLD is exceedingly common in today's practice, it is also a reminder that all patients with increased LFTs and no alcohol consumption do not, necessarily, have NAFLD. In this series, 45% of patients with a single-time increase in LFTs did not have an identifiable chronic liver disease, including NAFLD. In another series of patients with persistently elevated aminotransferases and no identifiable cause of liver disease, including alcohol consumption, only 55% had histologically documented NAFLD [15]. Twenty percent had normal or near normal liver biopsy and 25% had miscellaneous pathological conditions that did not qualify for NAFLD. Population-based surveys such as NHANES III asserting *de facto* that any patient with an unexplained increase in ALT has NAFLD, thus most likely have some significant margin of error.

Granted that now everyone accepts NAFLD as the front-runner in the epidemiology contest, the next question is: to what extent does it induce significant liver damage? Most available series, heavily biased by tertiary-care referral, tend to overemphasize the end-of-severity spectrum of the disease. The current report by Armstrong *et al.*, as well as the earlier report by Williams cited above, provide some insights from a more global perspective, closer to the general population.

Two issues require consideration: (1) the frequency of NASH, the progressive form of the disease and (2) the frequency of advanced fibrosis, including cirrhosis. When performing liver biopsy in 134 unselected patients with ultrasound suggestive of hepatic steatosis, Williams *et al.* showed that 30% of patients with NAFLD (at least 12% of the entire adult population that was screened) had NASH [6]. This is much higher than the conventional estimate drawn from studies performed in the 80's and early 90's, that showed that only 10% of patients with fatty liver have steatohepatitis. A few other recent studies with liver histology are rather in the high range found by Williams *et al.*: 43–55% in patients with increased aminotransferases [15,16], and as high as 49% in morbidly obese patients [17]. Considering that steatohepatitis is the main histological factor driving fibrosis progression, this means that at least one-third of patients with NAFLD are at risk of progressive disease. How many of these patients will actually develop advanced fibrosis depends on contingent factors, not all related to NAFLD: length of follow-up, inter-individual variability for susceptibility to fibrosis and competing risks from co-morbid associations. But the point here is that, even in unselected populations, a significant proportion of patients with NAFLD are at risk of disease progression and thus should be monitored and treated accordingly.

It might be argued that rather than counting the number of patients at risk for progressive disease, a better estimate of the potential severity of NAFLD would be the proportion of patients that actually have advanced disease, i.e. significant (bridging) fibrosis and cirrhosis. Armstrong *et al.* used a serum fibrosis marker, the NAFLD fibrosis score (NFS) [18], and found a high score, suggestive of advanced fibrosis, in almost 8% of patients with NAFLD. The diagnostic performance of the NFS was confirmed *vs.* biopsy in a small series of patients [19] with an acceptable but rather low positive predictive value for ruling in fibrosis (79%) and a higher more satisfying negative predictive value for ruling it out (92%). Considering that the PPV may be reduced in unselected patients with lower prevalence of advanced fibrosis (as in the cohort studied by Armstrong *et al.*), the actual proportion of patients with advanced fibrosis may be lower. Poynard *et al.*, when screening the general population with Fibrotest, found a prevalence of advanced fibrosis of 3% [4]. The results of these two studies are difficult to compare, as Armstrong *et al.* did not provide the total number of patients screened for increased LFTs, nor did they study NAFLD patients with normal LFTs. However, with a rather conservative estimate of 25% of the adult Western population having NAFLD, and only half of them with increased LFTs, between 1% and 2% of the general population might have advanced fibrosis due to NAFLD. These figures are supported by the findings of Williams *et al.* [6] (admittedly in a population with a high level of obesity), which used histology instead of serum markers: 2.7% of the total population and 7% of those with NAFLD had advanced fibrosis.

Of course, these estimates will be magnified in populations biased by referral patterns to specialist care. Large studies of selected NAFLD patients have shown a prevalence of advanced fibrosis (F3, F4 Kleiner) ranging between 17% and 27% and cirrhosis between 8% and 14% [18–21]. But perhaps the closest study to the one of Armstrong *et al.* is the French multicentric study, mentioned above [15], in which patients with unexplained increases in LFTs underwent liver biopsy. Nine out of 263 patients were found to have cirrhosis; all nine had NASH as the underlying histological diagnosis. Seventeen were found to have advanced bridging fibrosis (F3 METAVIR); all but one had NASH.

How then one can disagree with these findings of increased prevalence and fibrotic severity in patients with NAFLD and their overall impact? Simply by stating that while cirrhosis is linked to

increased liver-related mortality, bridging fibrosis will not kill anyone; therefore, the high numbers of NAFLD patients with bridging fibrosis will in fact not experience liver-related morbidity or mortality. While this makes sense today, tomorrow might be different. Liver fibrosis does progress, although, admittedly, at a different pace in different individuals. Patients with bridging fibrosis have reached this stage because of active fibrogenesis; this will not stop once the diagnosis has been made, provided that the underlying disease is still present (in fact it might even be that with increasing age, fibrosis will progress faster). There are long-term prognostic data that support this contention, as they show an increase in liver-related mortality or complications of cirrhosis even in patients with bridging fibrosis but without cirrhosis. For instance, patients with NAFLD and bridging fibrosis had an independent 5.7-fold increase in liver-related mortality over those without bridging fibrosis [22]. In chronic hepatitis C, the HALT-C trial demonstrated an association between fibrosis stages and liver-related clinical outcomes [23], already starting at the advanced bridging fibrosis stage. In a Japanese long-term follow-up study, patients with early bridging fibrosis (F2 META-VIR) had an independent 8-fold increased risk of liver-related death over those with no or mild fibrosis (F0, F1 METAVIR) [24]. That clearly shows that in the mid-term, bridging fibrosis is not benign. Granted, the individual predisposition to fibrosis might be different between NAFLD and HCV, in the sense that a lesser proportion of patients with NAFLD than with HCV have advanced fibrosis. However, for those who already have bridging fibrosis, the prognosis should be the same. Micromorphometry studies have indeed shown that for a given histological stage and after adjustment for all main cofactors of fibrosis, patients with NAFLD have the same amount of fibrosis than those with HCV [25].

NAFLD is increasingly frequent in the general population, and the number of those at risk of disease progression and of those having advanced disease is clearly a concern. The next chapter is to determine what is best to do about it, as far as screening efforts, therapy and cost effectiveness. Fortunately, we are taking on this new task based on a firm ground provided by these epidemiological studies. So much the better that the labyrinth is not built on moving sands...

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.

References

[1] Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, et al. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. Ann Intern Med 2005;143:722–728.

[2] Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysus nutrition and liver study. Hepatology 2005;42:44–52.

[3] Ratziu V, Bellentani S, Cortez-Pinto H, Day CP, Marchesini G. A position paper on NAFLD/NASH based on the EASL 2009 special conference. J Hepatol 2010;53:372–384.

[4] Poynard T, Lebray P, Ingiliz P, Varaut A, Varsat B, Ngo Y, et al. Prevalence of liver fibrosis and risk factors in a general population using non-invasive biomarkers (FibroTest). BMC Gastroenterology 2010;10:40.

[5] Bellentani S, Saccoccio G, Masutti F, Croce LS, Brandi G, Sasso F, et al. Prevalence of and risk factors for hepatic steatosis in Northern Italy. Ann Intern Med 2000;132:112–117.

[6] Williams CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology 2011;140:124–131.

[7] Kim KM, Choi WB, Park SH, Yu E, Lee SG, Lim YS, et al. Diagnosis of hepatic steatosis and fibrosis by transient elastography in asymptomatic healthy individuals: a prospective study of living related potential liver donors. J Gastroenterol 2007;42:382–388.

[8] Minervini MI, Ruppert K, Fontes P, Volpes R, Vizzini G, de Vera ME, et al. Liver biopsy findings from healthy potential living liver donors: reasons for disqualification, silent diseases and correlation with liver injury tests. J Hepatol 2009;50:501–510.

[9] Nadalin S, Malago M, Valentin-Gamazo C, Testa G, Baba HA, Liu C, et al. Preoperative donor liver biopsy for adult living donor liver transplantation: risks and benefits. Liver transpl 2005;11:980–986.

[10] Ryan CK, Johnson LA, Germin BI, Marcos A. One hundred consecutive hepatic biopsies in the workup of living donors for right lobe liver transplantation. Liver transpl 2002;8:1114–1122.

[11] Tran TT, Changsri C, Shackleton CR, Poordad FF, Nissen NN, Colquhoun S, et al. Living donor liver transplantation: histological abnormalities found on liver biopsies of apparently healthy potential donors. J Gastroenterol Hepatol 2006;21:381–383.

[12] Lee JY, Kim KM, Lee SG, Yu E, Lim YS, Lee HC, et al. Prevalence and risk factors of non-alcoholic fatty liver disease in potential living liver donors in Korea: a review of 589 consecutive liver biopsies in a single center. J Hepatol 2007;47:239–244.

[13] Byron D, Minuk GY. Clinical hepatology: profile of an urban, hospital-based practice. Hepatology 1996;24:813–815.

[14] Weston SR, Leyden W, Murphy R, Bass NM, Bell BP, Manos MM, et al. Racial and ethnic distribution of nonalcoholic fatty liver in persons with newly diagnosed chronic liver disease. Hepatology 2005;41:372–379.

[15] de Ledinghen V, Ratziu V, Causse X, Le Bail B, Capron D, Renou C, et al. Diagnostic and predictive factors of significant liver fibrosis and minimal lesions in patients with persistent unexplained elevated transaminases. A prospective multicenter study. J Hepatol 2006;45:592–599.

[16] Soderberg C, Stal P, Askling J, Glaumann H, Lindberg G, Marmur J, et al. Decreased survival of subjects with elevated liver function tests during a 28-year follow-up. Hepatology 2010;51:595–602.

[17] Campos GM, Bambha K, Vittinghoff E, Rabl C, Posselt AM, Ciovica R, et al. A clinical scoring system for predicting nonalcoholic steatohepatitis in morbidly obese patients. Hepatology 2008;47:1916–1923.

[18] Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45:846–854.

[19] McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut 2010;59:1265–1269.

[20] Guha IN, Parkes J, Roderick P, Chattopadhyay D, Cross R, Harris S, et al. Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: validating the European liver fibrosis panel and exploring simple markers. Hepatology 2008;47:455–460.

[21] Neuschwander-Tetri BA, Clark JM, Bass NM, Van Natta ML, Unalp-Arida A, Tonascia J, et al. Clinical, laboratory and histological associations in adults with nonalcoholic fatty liver disease. Hepatology 2010;52:913–924.

[22] Younossi ZM, Stepanova M, Rafiq N, Makhlouf H, Younoszai Z, Agrawal R, et al. Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. Hepatology 2011;53:1874–1882.

[23] Everhart JE, Wright EC, Goodman ZD, Dienstag JL, Hoefs JC, Kleiner DE, et al. Prognostic value of ishak fibrosis stage: findings from the HALT-C trial. Hepatology 2009;51:585–594.

[24] Imazeki F. Favorable prognosis of chronic hepatitis C after interferon therapy by long-term cohort study. Hepatology 2003;38:493–502.

[25] Charlotte F, Naour GL, Bernhardt C, Poynard T, Ratziu V. A comparison of the fibrotic potential of nonalcoholic fatty liver disease and chronic hepatitis C☆. Human Pathol 2010;41:1178–1185.