

An Overview of Nonalcoholic Steatohepatitis: Past, Present and Future Directions

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Abstract

Nonalcoholic steatohepatitis (NASH) emerged from an anecdotal disease first described in 1981 to the most common cause of incident chronic liver disease at the end of the current decade. This article describes, from a historical perspective, some of the landmark changes in our perception and understanding of this disease. Natural history studies have shown the potential for serious liver damage and ultimately increased overall and liver-related mortality. The recognition of insulin resistance as an almost universal underlying condition in patients with NASH, its role as a major determinant of steatogenesis and possibly liver disease progression contributed to the identification of a probable cause for this disease, one that is amenable to therapeutic intervention. Consequently, screening for liver injury in patients with metabolic risk factors entered clinical practice in hepatology and endocrine diseases. NASH can coexist with other frequent liver diseases and often aggravate the course of liver injury; therefore it should be seen as an independent disease and not as an entity diagnosed only by exclusion of other hepatopathies. Finally, steatosis can have systemic consequences as it worsens insulin resistance, predicts the emergence of metabolic complications and increases the risk for cardiovascular events. Priorities for future research are the optimisation of non-invasive screening strategies, the identification of patients at risk of liver disease progression, the understanding of the hepatic carcinogenic potential and testing innovative pharmacological targets for therapy.

Key words

Nonalcoholic steatohepatitis – steatosis – diabetes

– insulin resistance – hepatocellular carcinoma – fibrosis
– obesity – cirrhosis – non-invasive markers.

Introduction

Back in 1980, Ludwig et al first formally described non-alcoholic steatohepatitis (NASH). For the following 30 years, numerous studies contributed to our better understanding of the epidemiology, etiology, natural history and systemic complications of this disease. Starting from the mere description of a condition called NASH we ended up exploring a multi-faceted liver disease that should be best called metabolic steatohepatitis. The whole new horizon of insulin resistance and related metabolic complications, previously uncharted territory for the hepatogastroenterologist, expanded our clinical practice and research in liver disease. Here we will briefly overview the key advances behind this change in concepts and practice. The recognition of the metabolic origin of this disease, as well as the demonstration that when occurring in association with other liver diseases it might worsen the course of liver injury, justifies in our view to abandon the non-alcoholic epithet and the adoption of a new nomenclature. Metabolic steatohepatitis could thus refer to steatohepatitis occurring in the context of insulin resistance (NASH), while metabolic fatty liver disease could refer to the entire spectrum ranging from bland steatosis to metabolic steatohepatitis (non-alcoholic fatty liver disease, NAFLD).

Historical context

In 1980, Jurgen Ludwig described a series of patients with chronic liver disease and a steatohepatitis on liver biopsy [1]. All patients denied alcohol intake, but histology suggested the opposite, since all of them presented lesions typical of alcoholic liver disease. The series comprised only 20 subjects but in fact 3 were HBsAg carriers and probably some others HCV infected. The disease had no name [1] and its cause was unknown. Despite these unpromising premises, the condition that Ludwig coined by the name of “non-alcoholic steatohepatitis” was to become 30 years later a leading cause of liver disease.

Received: 04.09.2010 Accepted: 11.10.2010

J Gastrointestin Liver Dis

December 2010 Vol.19 No 4, 415-423

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Two important observations allowed further individualization of this disease. All but one of the patients described by Ludwig were obese or overweight and presented the manifestations usually associated with obesity. This reinforced previous observations showing an association between obesity and liver disease; hence a causal relationship with obesity and its complications was suspected. The second important observation is that this disease was distinct from alcoholic hepatitis: the clinical and biological profile was different [2-4], the evolution was slower [5], some histological lesions such as Mallory bodies and polymorphonuclear cell infiltrates were less conspicuous or even absent [2-4]. However, it will take a long time for this distinction to be widely accepted.

Current situation

The past decade has witnessed significant advances resulting in the identification of NASH as a distinct, frequent and potentially severe disease [6]. Maybe the most important advance is the formal demonstration that NASH is strongly associated with insulin resistance. By using a hyperinsulinemic euglycemic clamp, the gold-standard for assessing insulin sensitivity *in vivo*, Sanyal and Marchesini proved that NASH is associated with both peripheral [7] and hepatic [8] insulin resistance. This translates into an increased prevalence and severity of phenotypic complications of insulin resistance, mainly the clinical and biological features defining the metabolic syndrome [9]. It is further strengthened by additional data showing that overweight and obesity could lead to fibrotic [10] and inflammatory [11] hepatic injury, with insulin resistance being an independent predictive factor. The association between steatohepatitis and insulin resistance is present even in individuals with no obvious overweight or glycemic dysregulation; thus steatosis /steatohepatitis might well be one of the earliest manifestations of insulin resistance. The major discovery here was the observation that the liver can be damaged in patients with insulin resistance and the metabolic syndrome.

Since most patients with steatohepatitis displayed some degree of insulin resistance, a cause-effect relationship was suspected. In favor of this hypothesis was the fact that patients with steatohepatitis had a more pronounced degree of insulin resistance than those with bland steatosis, which, themselves, are more insulin resistant than controls [12]. Thus, the degree of insulin resistance could correlate with the progression of liver disease. Longitudinal studies have confirmed a temporal relationship between the progression of clinical features of the metabolic syndrome and the occurrence of ultrasonographically defined steatosis [13]. Likewise, long-term follow-up of large cohorts of diabetic patients documented the occurrence of chronic liver disease unrelated to alcohol or viral hepatitis [14]. These seminal observations opened new perspectives as NASH was recognized as a distinct disease and not as a syndrome based on the exclusion of alcohol intake, or by that matter any other

cause of liver disease. Simultaneously, hepatology enriched itself with a semiology (Table I) which was not previously part of our clinical practice.

Table I. Metabolic risk factors

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- Overweight [body weight, body mass index (body weight Kg/height m²) > 25 Kg/m²]
 - Visceral adiposity (waist circumference > 102 cm for men; 88 cm for women)
 - Type 2 diabetes
 - Arterial hypertension (blood pressure > 130/85)
 - Fasting plasma glucose > 6.1 mmol/l, fasting insulinemia, HOMA index*
 - Triglycerides > 1.7 mmol/l
 - HDL cholesterol < 1 mmol (for men); 1.3 mmol/l (for women)
 - Family history of diabetes, overweight, cardiovascular complications
 - Atherosclerosis – coronary artery disease
 - Hyperferritinemia (with or without increase of the transferrin saturation but without C282Y homozygosity)
 - Obstructive sleep apnea, polycystic ovary syndrome
-

* calculated as: plasma glucose (mmol/l) x insulinemia (μUI/l)/22.5; a score > 3 signifies insulin resistance.

The identification of the probable cause of this new condition redefined the etiological framework consequences that ultimately changed to a large extent the way we diagnose chronic liver diseases. For instance, many studies have shown that NASH can worsen the natural course and, in particular, fibrosis progression in other liver diseases [15] such as chronic hepatitis C [16, 17], alcoholic liver disease [18, 19], hemochromatosis [20] and possibly chronic hepatitis B [21]. Hence, the very concept of NASH as an exclusion diagnosis became obsolete. A disease occurring in a well-defined epidemiological context (the presence of risk factors for the metabolic syndrome), with an identified etiology (insulin resistance), does not cease to exist when it occurs, as an incidental epidemiological association, in an excessive drinker or an HCV-infected patient. In our view, this justifies the recognition of morbid associations such as mixed metabolic and alcoholic or metabolic and viral liver disease; whether such an association will result in an additive or a synergistic effect on liver injury will need to be determined for each case. The logical next step will then be to change the name of this disease, abandoning the negative definition (NASH) while recognizing the possible association of the metabolic fatty liver disease with other causes of chronic liver disease.

The prevalence of NAFLD is not precisely known as we lack sensitive and specific diagnostic markers for this disease. Studies using aminotransferases as a screening test found that 3% to 6% of the general population has unexplained elevations of aminotransferases; this would rank steatohepatitis first or second among causes of increased aminotransferases depending on whether the prevalence of obesity is high [22] or low [23] in the different studied countries. Most of these individuals with unexplained increases of aminotransferases have NAFLD since there is a

strong cross-sectional [24] and longitudinal [25] correlation between an increase in aminotransferases and the presence of metabolic risk factors. However, this is believed to be largely an underestimation as the majority of individuals with steatosis have in fact normal aminotransferases. Hepatic ultrasound, a more sensitive procedure than liver function tests for detecting liver fat, has consistently shown a 20% to 30% prevalence of NAFLD in Western countries, the Near-East and Japan [26, 27]. Finally, studies using magnetic resonance spectroscopy to measure hepatic triglyceride content have found that a third of the general United States population has excessive liver fat [28]. Importantly, however, we do not know how much histological steatosis corresponds to the threshold value defining the abnormal elevation of liver triglycerides with this procedure: liver biopsy was indeed unavailable in these series [28]. These figures indicate nonetheless that metabolic steatohepatitis has the potential to become a real public health problem. Hospital-based hepatological practice was also transformed by the increased prevalence of this condition, rising from the third most frequent cause of chronic liver disease in the early 90's [29], to the first place one decade later and the top cause of incident chronic liver disease. Currently, in the United States, NAFLD amounts to 39% of the newly diagnosed cases of chronic liver disease [30]. In France, metabolic steatohepatitis has been diagnosed histologically in 55% of patients with otherwise unexplained increases in aminotransferases [31]. Obesity is a stronger predictor of steatosis than alcohol in people drinking less than 30-50 g of alcohol per day [27, 32].

While the epidemiological burden of steatohepatitis is now widely recognized its severity is still debated, partly because of its historical perception as a benign condition. The past decade has provided a wealth of data that helped us gain a better insight in the natural course of the disease. Several retrospective series have shown that 25-30% of patients with steatohepatitis had advanced fibrosis (bridging fibrosis) upon diagnosis, including 10-15%

with cirrhosis. Fibrosis progression on serial biopsies has been documented in 25-33% of cases [33, 34] although numerous methodological issues limit the interpretation of these results [35, 36]. Cirrhosis occurrence during follow-up has also been documented. Because quite often the histological signs of steatohepatitis are no longer present at the cirrhotic stage [37], the cirrhotic potential of this disease was underestimated until Caldwell et al noted that a large proportion of patients with « cryptogenic » cirrhosis had been exposed to metabolic risk factors [38]. This proportion was comparable to that of patients with well documented non-cirrhotic steatohepatitis and significantly higher than that of viral or autoimmune cirrhosis [38]. Hence, almost half of the cases of « cryptogenic » cirrhosis could ultimately be traced to the end-stage evolution of NASH [39]. Another observation that reinforced the association between overweight and liver cirrhosis was the parallel increase in liver transplant candidates of body mass index and cryptogenic cirrhosis as the underlying diagnosis [40].

Hepatocellular carcinoma (HCC) can occur in patients with metabolic steatohepatitis [41] albeit its diagnosis can be seriously delayed. Because it is usually asymptomatic and because there is insufficient awareness of steatohepatitis in patients with metabolic risk factors, the diagnosis of HCC is made at an advanced stage, outside of monitoring programs and hence is less often amenable to curative treatments [39]. Akin to cryptogenic cirrhosis, the link between HCC and NASH has been inferred from studies documenting a high prevalence of metabolic risk factors in patients with HCC lacking an identifiable underlying liver disease [42]. Again, data from the hepatological series grossly underestimate the epidemiological reality of large cohorts of diabetic or obese patients. In diabetic patients, there is a 2 to 3 fold increase in the risk of HCC in countries of either low [43] or high endemicity [44, 45] for viral hepatitis. Some studies found a significant increase in risk with increasing levels of fasting insulin [46] or serum glucose [47, 48], thus suggesting a dose-effect relationship which reinforces the epidemiological

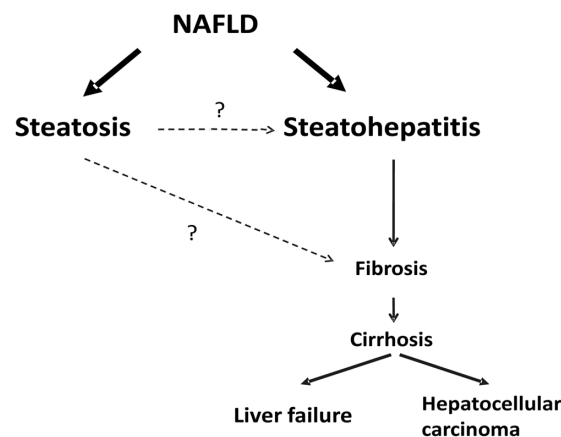
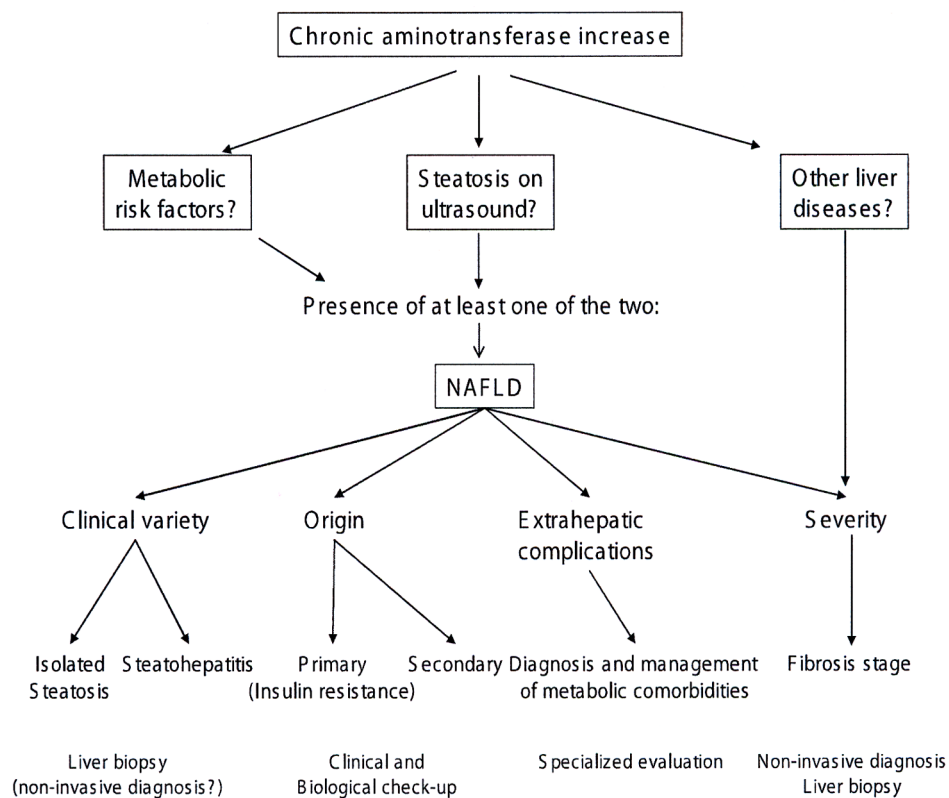


Fig 1. Current paradigm of the natural history of NAFLD.



Suspicion of NAFLD is based on the ultrasonographic demonstration of steatosis and/or the presence of metabolic risk factors. The absence of either of these does not rule out NAFLD (ultrasound has suboptimal sensitivity and NASH has been documented in patients without full-blown metabolic syndrome).

Fig 2. Diagnostic flow-chart in patients with increased aminotransferases and suspicion of NAFLD.

association. Finally, longitudinal studies favor a causal relation as diabetes precedes the diagnosis of HCC [14]. Obesity also increases the risk of HCC and even liver cancer mortality in males [49]. Studies performed in European [50, 51], Asian [52] or American [49] populations with variable prevalences of obesity and chronic liver disease all reinforce the validity of the epidemiological association; this was also demonstrated by some meta-analyses [53], although the risk appears higher in men than in women [52].

The most convincing demonstration of the potential severity of a disease is without doubt an increase in mortality [54]. NASH patients have increased overall and liver-related mortality [54]. While patients with steatosis alone have a survival identical to the age and sex-matched reference population [55, 56], those with metabolic steatohepatitis have a significant increase in overall mortality [56-59]. Of note, excess mortality is still significant even after adjustment for different metabolic syndrome components [58]. The magnitude of excess risk ranges from 11% [58] to 260% [59], mostly dependent on criteria used for diagnosing steatohepatitis and the length of follow-up. Here again, large population based studies using an “unexplained increase” in aminotransferases as the diagnostic criteria for steatohepatitis grossly underestimate the risk since most patients with metabolic steatohepatitis at large have normal

aminotransferases. Nonetheless these studies robustly showed that cirrhosis is an independent cause of death ranking third most frequent cause after cardiovascular disease and neoplasia. This contrasts with data from the general control population of the same studies, where cirrhosis is only the 13th cause of death. All these studies have also shown that liver related mortality is increased 10 to 20 fold [56, 58, 59]. This is all the most remarkable given the high competitive mortality in patients with the metabolic syndrome.

Perspectives

A major challenge for reducing future liver-related morbidity and mortality will be the large scale diagnosis of liver injury in patients with insulin resistance and related pathological conditions. Currently, most of these patients are not seen by a liver disease specialist, for several reasons including insufficient awareness of the hepatic disease, concurrent endocrine or cardiovascular co-morbidities, asymptomatic liver disease or normal aminotransferase values. Therefore, a critical aspect will be to develop multidisciplinary collaborative networks for clinical care and research including specialists in the hepatology, endocrinology, diabetes, nutrition and cardiology fields.

A simple, sensitive and specific marker of liver injury related to insulin resistance will also help screening the patients at risk. Unfortunately, no such marker yet exists, as neither insulin resistance nor the corresponding liver damage have a unique mechanism. The determinants of insulin resistance are multi-factorial (polygenic factors and numerous environmental determinants) hence no single test reliably predicts the risk in an individual patient. Multiple pathogenetic mechanisms also concur for liver damage. Steatogenesis is accounted for by an excessive supply of free fatty acids to the liver, by an inappropriate increase in hepatic *de novo* lipogenesis, by a reduction in fatty acid disposal through beta-oxidation and possibly by a reduction in the hepatic export of lipoproteins. The occurrence and progression of steatohepatitis is driven by numerous complex mechanisms: increased oxidative stress due to a variety of causes, mitochondrial dysfunction, apoptosis, altered innate immunity, vulnerability of steatotic hepatocytes to injury, increased endotoxemia, altered adipocytokine balance, activation of the renin angiotensin system, inflammatory cytokines, etc. Finally, the mechanisms of fibrogenesis operating within the context of insulin resistance are mostly unknown. This long list of multiple mechanisms makes it improbable that a single diagnostic marker could be used for diagnosing and monitoring this disease.

A legitimate question as far as screening and diagnosis of this disease is, what features are important to predict? In most chronic liver disease mortality is exclusively determined by liver fibrosis and its progression to cirrhosis and therefore fibrosis detection is of paramount importance. The diagnosis of advanced (bridging) fibrosis by different serum fibrosis markers seems to be as performant in metabolic steatohepatitis as in other liver diseases [60]. Several panels or algorithms have been proposed with variable degrees of analytical and independent validation: Fibrotest [61], Fibrometer [62], Angulo [63] score, ELF [64] score or BARD [65]. Ultrasound-based transient elastography using Fibroscan also provides encouraging results [66, 67] although much progress remains to be made to reduce the failure rate of signal acquisition due to obesity. A study performed in a large cohort of apparently healthy controls has shown a failure rate of 25% for individuals with a BMI between 30 and 35 kg/m², 41% between 35 and 40 kg/m² and 88% for a BMI higher than 40 kg/m² (morbid obesity) [68]. Newer probes specifically designed for obese patients are currently under investigation. However, if one considers that predicting steatohepatitis, mainly for identifying patients at risk of fibrosis progression [69] or selecting those in need for pharmacological therapy, is equally important, then the choice of non-invasive markers is considerably limited [70-73]. Finally, one may as well argue for the need of a non-invasive quantification of steatosis. Extrahepatic complications of liver fat, mainly cardiovascular and metabolic are now well established. Moreover, in treated patients whether with diet and lifestyle measures or with pharmacological agents, the reduction in liver fat is a good indication of treatment efficacy. Several

serum based biochemical panels are now available [74-76], some of them with some degree of independent validation [77, 78]. Imaging techniques based on magnetic resonance spectroscopy can also quantify liver fat [79] but availability, standardization and cost limit their use in clinical practice.

While waiting for these new markers, current diagnostic tools and strategies need optimization. Despite important progress in the systematization of the histological definition and the assessment of histological changes on therapy [80], more work is necessary before creating and validating consensual and reproducible histological definitions for diagnostic, staging or follow-up on therapy purposes. Despite its shortcomings, first and foremost sampling variability [81], liver biopsy is currently unavoidable for the diagnostic distinction between steatosis and steatohepatitis and will be required for current and future therapeutic trials. In clinical practice, the indications for liver biopsy need to be redefined according to the availability of non-invasive diagnostic methods and the predictably discordant results they will provide. Considering the large number of patients with normal aminotransferases, a key point will be the extension of indications for biopsy in these patients. This will amount to a radical change of practices in our discipline which will need to be accepted by patients and referring physicians.

Our understanding of the natural history of metabolic steatohepatitis is still quite limited and future, multicentric, collaborative studies will need to shed light on many aspects. For instance, long-term prognosis of patients with bland steatosis is good in studies with a median follow-up of 15 years or less. However, does this change with longer follow-up? Also, do patients with bland steatosis have no risk of fibrosis progression as these series have shown (in which case the few observations stating the contrary might have simply missed lesions of steatohepatitis on the initial biopsy) or is the risk lower than for steatohepatitis, but not entirely absent?

Another unsettled question is whether the transition between steatosis and steatohepatitis is a mandatory step or whether these distinct entities evolve independently early in the course of the disease. Longitudinal studies on larger cohorts should assess liver fibrosis progression and predictive factors thereof, but also reversibility for different fibrosis stages. Of particular interest in that respect will be the placebo groups of future randomized trials. Finally, the mechanisms of fibrogenesis operating in the context of insulin resistance are yet to be unraveled.

An important challenge will be to determine the morbidity and mortality associated with metabolic steatohepatitis in diabetic patients. Both hepatic and extrahepatic complications of liver fat will need to be taken into account. When compared to the age and sex-matched general population, diabetics have an increased mortality by cirrhosis [82]. Since competitive causes of mortality are now better controlled (in particular cardiovascular mortality) it is possible that in the near future the liver might emerge as a major cause of morbidity and mortality. In this case screening, monitoring and management of liver injury

in diabetic patients will become a priority akin to other complications such as diabetic micro or macroangiopathy. Numerous studies are now available showing that steatosis worsens atherosclerotic disease and increases cardiovascular events. It remains to be seen if this is independent of other linked risk factors such as the degree of insulin resistance and the amount of visceral adiposity. It will also need to be established if the main determinant is the amount of steatosis or the presence of steatohepatitis. Remarkably, some studies have shown that the amount of steatosis not only worsens insulin resistance but also is the main determinant of daily amounts of insulin required to control serum glucose in diabetic patients [83]. If confirmed, the development of anti-steatogenic agents might become a priority in the management of diabetic patients.

Because NASH is frequent and potentially severe, developing specific treatments is a major unmet need. Bariatric surgery provided the proof of principle that correcting excessive weight will improve the hepatic condition, if only an improvement in insulin sensitivity also occurs [84]. Both steatosis, steatohepatitis and even advanced fibrosis can be reversed when massive weight loss occurs [85]. However, the minimal amount of weight loss associated with histologic improvement is not well determined. Nine % weight loss might be required for short-term reversal of hepatic lesions although for inflammation and fibrosis a greater weight loss is probably needed [86]. Whether beyond weight loss, the type of diet (low carbohydrate vs. low fat, vs. hypocaloric diet, etc.) has any additional impact on liver histology needs to be determined. Moreover, specific nutrient deficits have been described in the diet of patients with metabolic steatohepatitis [87], therefore the role of micronutrient supplementation such as, for instance, omega 3 polyunsaturated fatty acids, needs to be studied. Finally the effect of physical activity independent of diet should be studied. Some studies have shown a higher deficit in aerobic than in non-aerobic exercise in NAFLD patients hence the optimal exercise program is yet to be determined [77].

Since diet and lifestyle measure often fail or cannot be implemented efficiently there is clearly a need for pharmacological agents in this condition, designed and studied with the aim of improving hepatic histology. Whether non-invasive surrogates could ultimately replace the histological assessment in terms of drug efficacy remains to be proven [73] and therefore should be tested early in drug development programs. As far as therapeutic classes, one can logically envision two distinct avenues in terms of NASH treatment: 1) insulin-sensitizing agents that correct the underlying, presumably causal, mechanism, and 2) "hepatoprotective" agents directly targeting liver inflammation and/or fibrosis [88].

Among insulin sensitizing agents, a growing body of data suggest some efficacy of glitazones. These drugs induce a strong biochemical and anti-steatogenic response, most probably improve necroinflammation and clear steatohepatitis but have no efficacy on fibrosis [89-92]. Future studies should test whether there is increased

efficacy with longer exposure [93], and long-term safety and durability of response. It will also be important to understand the correlation between the insulin sensitizing effect (metabolic improvement) and the improvement of the liver condition (histological and biochemical response). Metformin and orlistat have no proven efficacy [86, 94]. No other insulin-sensitizing drug has been tested in human NASH while registration trials and the development program of rimonabant, a type1 cannabinoid receptor blocker have been stopped as a consequence of the withdrawal of the drug from the market.

As far as hepatoprotectants, so far very few seem to be viable candidates. High dose ursodesoxycholic acid (28-32 mg/kg) has an undeniable biochemical efficacy, possible metabolic effects and is still to be proven, histological effects [95]. Anticaspases have provided promising preliminary results [96, 97] worth pursuing. Earlier small studies of vitamins (E or C) were negative but recently the PIVENS trial unexpectedly demonstrated good histological efficacy of vitamin E [92].

Future studies of those most promising pharmacological agents will need to test an integrated approach between drugs and diet and lifestyle modifications in order to determine the benefit of a drug beyond what can be expected from non-pharmacological measures and the best timing for this association. Finally, because of the frequency of metabolic steatohepatitis, the risk benefit of future pharmacological agents will have to be carefully assessed for each stage of the disease.

Conflicts of interest

None to declare.

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