Should Nonalcoholic Fatty Liver Disease Be Renamed?

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Key Words

Definitions · Fibrosis · Hepatic steatosis · Insulin resistance · Leptin · Metabolic syndrome · NASH · Pathogenesis

Abstract

Background: None of the synonyms of nonalcoholic fatty liver disease (NAFLD) include clinical correlates nor do they mention insulin resistance, a recognized determinant of the etiopathogenesis and natural history of NAFLD. **Method:** The literature concerning the pathogenesis and definition of NAFLD is reviewed. **Results:** The reasons why NAFLD should be renamed are: (a) clinically meaningful hepatic steatosis could be present at less than 5% triglyceride hepatic content; (b) steatosis is usually no longer observed in the most advanced forms of NAFLD ('cryptogenic cirrhosis'); (c) the concurrence of metabolic derangements could be more important than alcohol in the pathogenesis of alcoholic liver disease; (d) a concurrent metabolic etiology might worsen the course of chronic HCV and autoimmune hepatitis; (e) in NAFLD the liver is a target organ of the metabolic syndrome, a systemic subclinical inflammatory state. **Conclusion:** The introduction of a positive criterion also mentioned in its definition would benefit the diagnosis of NAFLD and of steatohepatitis observed in the setting of other liver diseases, help to estimate the risk of its progression and aid the treatment of metabolic (fatty) liver disorders.

There is a compelling need for an experts' agreement on a new definition of insulin resistance/metabolic-related liver disease.

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'Nomina sunt consequentia rerum'
Names are the consequences of things
Iustinianus, Institutiones, Book II, 7, 3

Background

According to the 'hyperactive fork coupled with the hypoactive foot' theory, body fat represents an energetic reservoir which accumulates owing to an imbalance between an increased availability of food and a decreased energetic expenditure necessary to get foodstuffs [1]. The development of fatty liver might accordingly represent an adaptation which occurs when future unfavorable environmental conditions are expected and therefore, fatty liver syndromes might be considered as a liver counterpart of the 'thrifty genotype'. Alternatively, fatty changes might represent either a biologic response with which the host tries to cope with HCV infection [2] or else a mechanism through which the liver tends to limit the enlargement in its volume [3].

Nonalcoholic fatty liver disease (NAFLD), which includes nonalcoholic steatosis and nonalcoholic steato-

hepatitis (NASH), describes the clinicopathologic spectrum of alcohol-like liver disease in the nonalcoholic [4–8]. Although it may be observed as a iatrogenic complication (due to drugs or anti-obesity surgery) or secondary to various other conditions (toxins, lipodystrophic syndromes, hypobetalipoproteinemia), NAFLD most commonly occurs as a primary (idiopathic) disease [9, 10].

The clinical importance of primary NAFLD appears to rest on three main observations:

It commonly occurs in the general population worldwide [11–13] and among patients presenting with unexplained mild to moderate raised aminotransferase levels [14–16].

It is not a sign/symptom of disease but it is a pathological condition that has the potential to progress to advanced hepatic [17–21] and extrahepatic disease [22, 23], and to interact with other etiologies of liver disease [2, 24, 25].

It may recur following orthotopic liver transplantation [26–28] and poses a heavy burden of complications in the setting of major extrahepatic and liver-related surgery [29–31].

As our understanding of causes and mechanisms of diseases progresses, descriptive and eponymic diagnoses of liver disease have given way to etiologic diagnoses, e.g. alcoholic liver disease, viral liver disease, autoimmune liver disease, metal storage liver disease, impaired transport of endogenous substance liver disease, and so on [32]. In the past, what is now collectively referred to as NAFLD was likely to fall in the descriptive chapters of liver disease in the obese [33] or in the diabetic [34] or else to be defined as ‘transaminitis’ [35]. Such definitions used to imply the lack of a nosographic dignity of what is instead now deemed to be the most common liver disease [32]. Recently, various authors have independently reported that NAFLD should no longer be considered a disease of exclusion and that mention to its close linkage to the metabolic syndrome (MS) should be made in its very name [36–39]. There are, in fact, several reasons for NAFLD to be renamed, and the purpose of the present review is to discuss the reasons why this should be done according to our improved understanding of its etio-pathogenesis.

Definitions and Synonyms

While the histological features of what we now call NASH were described as early as 1962 by Heribert Thaler from Vienna [40], Ludwig coined the definition of

nonalcoholic steatohepatitis (NASH) in 1980 [4]. Over the time, this condition has also been named *diabetic hepatitis* [41], *nonalcoholic steatonecrosis* [42], *alcohol-like liver disease in the non-alcoholic* [5], *nonalcoholic fatty hepatitis* [43], *fatty liver hepatitis* [44], *bright liver syndrome* [45–47] and *non-alcoholic steatosis syndromes* [10] by authors emphasising various facets of this common clinico-pathological syndrome. Most of these definition allude to the histological similarity with alcoholic liver disease though observed in the absence of a significant alcohol intake. However, none of the synonyms includes obesity nor is reference made to hyperlipidemia or hypertension, which are common clinical correlates of NAFLD [48–50]. Furthermore, none explicitly mentions insulin resistance (IR), though this is presently deemed to be its key pathogenic factor [51, 52].

There are several reasons for NAFLD to be renamed.

Although hepatic steatosis is defined as a triglyceride content exceeding 5% of the liver weight [53], normal values have not been determined precisely [54]. Recent studies indicate that in normal subjects there is no liver fat [55, 56] and clinically meaningful hepatic steatosis could be present even at less than 5% triglyceride content [54].

Steatosis is usually no longer observed in the most advanced forms of NAFLD (so-named ‘cryptogenic cirrhosis’) [57, 58].

Even in alcoholic liver disease the concurrence of metabolic derangements could be more important than alcohol itself [59, 60].

A concurrent metabolic etiology appears to be able to worsen the course of chronic liver disease due to other origins, such as hepatitis C and autoimmune liver disease [2, 25].

The liver appears to be a target organ of a disease (the MS) which is systemic in nature and therefore carries implications for both hepatic and extrahepatic manifestations and complications [51, 61] (fig. 1).

Is NAFLD a Liver Manifestation of Insulin/Leptin Resistance and Lipotoxicity?

IR describes the reduced tissue response to the many actions of the hormone with ensuing hyperinsulinemia. IR secondary to biological stress may be a transient state aimed at saving glucose utilization in times (such as sepsis, puberty and pregnancy) when supply and assimilation of exogenous nutrients are jeopardized [62]. Primary IR in otherwise healthy subjects, in contrast, is an irrevers-

Fig. 1. The link between NAFLD and hepatic and extrahepatic disease states.

ible phenomenon [62, 63] and the ensuing clinical phenotype or IR syndrome or MS, formerly referred to as ‘the deadly quartet’, is the constellation of hyperlipidemia, obesity, hypertension and altered glucose metabolism observed in subjects with IR [1]. Additional components of the MS are hypercoagulability (increased plasminogen activator inhibitor), hyperferritinemia and hyperuricemia (fig. 2). A recent estimate places the number of Americans with the MS at 47 million [64].

The physiopathology of IR was initially closely linked to the concepts of glucose intolerance and type 2 diabetes mellitus (T2DM). The ‘glucotoxicity’ theory, though, has recently been challenged on the grounds that it might actually be a protective mechanism that, by excluding glucose from cells, decreases glucose-derived lipogenesis [65]. Unger [65] has emphasised that resistance to insulin-stimulated glucose metabolism is not a primary event but, in obesity, it is secondary to lipid accumulation. For the development of the MS, failure to confine the lipid overload to the cells specifically designed to store surplus calories, the white adipocytes, appears to be more important than the total amount of body fat stored [66]. The evolution of adipocytes served the purpose of extending survival by allowing surplus fuel to be stored as triglycerides during caloric abundance for subsequent retrieval during periods of caloric need [67].

Storage of even a modest caloric surplus in lean tissue, though, would ultimately be conducive to organ dysfunction [66]. Therefore, to protect nonadipocytes from lipid

Fig. 2. The expanding galaxy of the insulin resistance syndrome. Beyond the deadly quartet (dark satellites) NAFLD as one of the additional components (light satellites) of the IR syndrome (or MS).

overload, adipocytes evolved a hormone, leptin, which plays a vital antisteatotic role [68]. Just as insulin regulates intracellular glucose homeostasis and thereby prevents glucotoxicity, leptin regulates intracellular fatty acid homeostasis and prevents lipotoxicity [69]. Lipotoxicity – a term originally used to describe the lipid-induced dysfunction in the rodents’ lean tissues – defines cellular dysfunction or cell death of nonadipose tissues resulting from excess lipid storage [70]. Triglycerides stored within the cells are probably inert but once hydrolyzed, are precursors to free fatty acids (FFA), particularly saturated ones, which are believed to be the culprits for the synthesis of ceramide-induced apoptosis, mitochondrial damage, increased oxidative stress and up-regulation of inducible nitric oxide synthase [70]. The organs where lipotoxicity occurs include the heart, muscle, pancreas and kidney, resulting in relevant diseases such as heart failure, T2DM and renal failure [68, 70].

Mean serum leptin levels are increased in NASH [71, 72]. Leptin levels correlate with C peptide levels but not with BMI [71, 72]. In multivariate analysis, serum leptin was one of the independent predictors of hepatic steatosis but not of inflammation or fibrosis [72]. These findings are compatible with the hypothesis that in NAFLD patients, leptin serum levels increase secondary to blunted response in peripheral tissues.

Fig. 3. Prevalence of metabolic alterations/diseases in NAFLD. Data from the POLISTENA study [81]. Number of subjects enrolled 161, mean age (years $\pm$ SE): 48.6 ± 1.23 , males/females (n) = 96/65. Cut-off values from the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) [87].

In conclusion, leptin resistance is conceptually similar to insulin resistance in NAFLD, which should probably be considered the hepatic manifestation of lipotoxicity pointing to another metabolic pathogenetic mechanism of liver damage.

Evidence for IR as the Key Pathogenic Factor in the Development of NAFLD

If primary NAFLD is to be universally considered to be associated with IR, several findings are anticipated.

First, on the grounds of an impressive body of evidence [73–86], it is expected that all NAFLD patients have IR. As a matter of fact, though, the vast majority of – but not all – patients with NAFLD have demonstrable IR. In our unselected series including 161 patients with a clinical-ultrasonographic diagnosis of NAFLD – histologically confirmed in 61 – we observed IR (assessed through HOMA-IR >2) in 86.5% of cases (fig. 3) [13, 81, 87]. This finding may be accounted for by at least 2 different explanations: (a) the methods (and cut-off values) used for the evaluation of IR. Evidence for this comes from the paper by Marchesini et al. [79], who have reported that IR can be shown through the euglycemic clamp technique even in lean subjects with normal fasting glucose; (b) it could well be that NAFLD antedates the development of IR/MS in a subset of patients. The development of T2DM in subjects with fatty liver followed up for 10 years has been recently reported

[23]. Therefore, the requirement of IR appears to be fully satisfied in the vast majority of cases of primary NAFLD.

Second, that patients with one or more of the components of the syndrome are at a high risk for NAFLD is widely supported by data of the literature: the prevalence of NAFLD in obesity [50, 88–91], T2DM [34, 88, 92], patients with arterial hypertension [93], and hypertriglyceridemia [49] is more elevated than in the general population. Furthermore, in our series we found a 74.5% prevalence of hyperlipidemia, a 57.2% of patients with arterial hypertension, 17.0% of subjects with T2DM; the prevalence of the MS defined according to ATP III criteria [87] was: 36.2% [Loria P., unpubl. obs.]. Furthermore, the number of components of the MS in patients with NAFLD associates with higher IR as assessed through HOMA-IR values [Loria P., unpubl. obs.].

Third, independent predictors of NAFLD on multivariate analysis correlate with the degree of MS and overlap with the components of the MS. Earlier studies not including direct indexes of IR showed that independent predictors of a ‘bright’ liver echopattern were apoB, plasma lipid values and BMI [94]. However, more recent observations disclose that fasting insulin serum levels (a more straightforward index of IR) are more important than BMI in differentiating NAFLD from controls [81, 82]. Similarly, in the NHANES study overweight accounts for the otherwise unexplained increase of ALT in the American population through its correlation with central adiposity, hyperinsulinemia and hyperleptinemia

Table 1. Impact on liver histology of therapeutic interventions aimed at reducing IR in NAFLD patients

Author, year, reference	Study type	Experimental therapy	Control treatment	Cases	Time months	Effects on biopsy
<i>Weight loss and lifestyle interventions</i>						
Andersen, 1991 [98]	case series	diet	–	41	4–23	variable
Vajro, 1994 [99]	case series	diet, exercise	–	9	30	improved
Ueno, 1997 [100]	open label	diet, exercise	no treatment	25	3	improved
Franzese, 1997 [101]	case series	diet, exercise	–	58	6	n.d.
Harrison, 2003 [102]	case series	orlistat	–	3	6	improved
Hickman, 2004 [103]	case series	diet, exercise	–	14	15	improved
Dixon, 2004 [104]	case series	bariatric surgery	–	36	9–51	improved
<i>Insulin-sensitising agents</i>						
Coyle, 1999 [105]	case series	metformin	–	2	4–11	improved
Marchesini, 2001 [106]	open label	metformin	–	20	4	n.d.
Caldwell, 2001 [107]	case series	trogliatone	no treatment	10	<6	variable
Neuschwander-Tetri, 2003 [108]	case series	rosiglitazone	–	30	12	improved
Uygun, 2004 [109]	open label	metformin	diet	36	6	no difference
Promrat, 2004 [110]	case series	pioglitazone	–	18	12	improved
n.d. = Not determined. Modified from [111].						

(discussed in the paragraph of lipotoxicity); moreover, the correlation between hyperinsulinemia and (surrogate) indexes of NAFLD was independent of BMI and fat distribution [95].

Fourth, NAFLD recurs in patients submitted to liver transplantation for NASH cirrhosis [26–28, 96] attesting to the systemic nature of the metabolic derangements underlying NASH [97].

Fifth, life-style and drug interventions restoring insulin sensitivity appear to cure NAFLD [98–111]. Table 1 shows that those (medical or surgical) treatments that are capable to induce weight loss and the use of drugs that improve insulin sensitivity (acting on the liver or adipose tissue) also improve histologic changes in NAFLD patients. Some authors feel evidence-based on some of these issues to be uncertain [112] and the methodology of the therapeutic studies (limited sample size, often nonrandomized, noncontrolled trials) might be criticized. However, the overall trend disclosing a clear-cut benefit for a variety of heterogeneous treatment schedules sharing the same mechanism of action, namely reduced IR, represents a solid proof that insulin resistance is the cause and not the effect of NAFLD and may lead the clinician's practice.

In conclusion, a large body of evidence [8, 38, 39, 51, 52, 61, 113–116] definitely supports the pathogenic role of IR in NAFLD and includes this condition within the boundaries of the MS.

Role of IR in the Progression of NAFLD

On the accounts that it predicts liver-related deaths, fibrosis represents the most significant feature in the biopsies of patients with NASH [7]. It is of interest, therefore, that fibrosis is found in 15–50% of patients and cirrhosis in 7–26% of cases when they receive the first diagnosis of NASH [4, 5, 7, 44, 57, 117–122]. What is the evidence for IR to have any role in the progression of NASH?

None of the factors associated with likelihood of finding more advanced disease on the initial biopsy has been studied adequately as predictors of progression over time: nevertheless they are deemed likely to carry long-term prognostic significance [38]. Eight studies have addressed the risk factors for fibrosis in NAFLD [50, 89, 90, 123–127]. In four studies, age – which probably represents a longer duration of disease or a more marked IR – turned out to be an independent predictor of fibrosis [90, 123, 124, 128]. Also the entity of inflammatory changes – estimated on the grounds of an isolated increase of ALT values [50] and histologically [124] – associates to fibrosis. It is of interest that indexes belonging to the domain of the MS, namely BMI/obesity, diabetes [123, 129], arterial hypertension and increased C peptide [50] represent other independent predictors of fibrosis in these studies [50, 123]. Several studies support that IR plays a key-role not only in the etiology but also in the progression of

Table 2. Evidence that factors associated with the presence of steatosis also affect its inflammatory and fibrotic evolution

	Steatosis	Inflammation/NASH	Fibrosis
BMI/central body fat distribution	large body of evidence [50, 89, 90, 123]	preliminary evidence [51]	large body of evidence [90, 123, 124]
T2DM/peptide c/insulin resistance/	large body of evidence [50, 89, 90, 125]	preliminary evidence [50, 127]	large body of evidence [50, 90, 91, 123, 125–127]
Leptin	preliminary evidence [72]	not addressed	not addressed
Hypertension	preliminary evidence [50]	preliminary evidence [50]	preliminary evidence [50]
Hyperlipidemia	preliminary evidence [89]	not addressed	preliminary evidence [124]
Steatosis	–	not addressed	preliminary evidence [90]
Metabolic syndrome	not addressed	preliminary evidence [84]	preliminary evidence [84]

Preliminary evidence: reported by few/single human studies. Large body of evidence: confirmed by at least 3 authors in human studies.

NASH: Marchesini et al. [84] have shown that the presence of components of MS carries a 3.5-fold increase in the risk of fibrosis in NAFLD subjects. The same group also showed that IR (but not iron burden and HFE mutations) is a major, independent risk factor for advanced fibrosis in NAFLD [130]. This finding is also confirmed by our own data (fig. 4) [131, 132] and by other authors' experience [133]. Steatosis itself is a risk factor for fibrosis in NAFLD [90]. Interestingly, atherogenic anomalies in the lipid plasma profile, such as a decrease of apo AI and an increase in LDL-cholesterol and of Lp(a), have been reported to correlate to fibrosis in NASH [134]. Such changes might evoke the premature atherogenesis which is commonly observed in MS.

IR syndrome is often perceived to be a subclinical inflammatory state [25, 135]. What is (are) the target organ(s) of such systemic inflammation? The endothelium is often presented as the target organ, but the liver of NAFLD patients has the potential not to be just an innocent bystander but also a guilty party of this inflammatory process on the grounds that it is involved in the synthesis of procoagulant factors [47, 61].

In conclusion, these findings confirm the hypothesis that IR plays a key role not only in the development (first hit) but also in the progression (second hit) of NAFLD (table 2) and suggest that subjects with MS and NAFLD are at increased risk for cirrhosis and cardiovascular complications.

Fig. 4. Evidence that IR associates with more advanced NAFLD types. Indices of IR in patients from the POLISTENA study are significantly more elevated in advanced (types 3 and 4) as compared to early (types 1 and 2) NAFLD [131].

Conclusions

IR has gained a universally accepted importance in the etiopathogenesis and in the natural history of NAFLD [136–139]. Owing to genetics and lifestyle, asymptomatic metabolic forerunners develop as a result of *periph-*

Fig. 5. Overview of the interactions between metabolic alterations, target organs and clinical manifestations/complications. NAFLD as a key manifestation in the natural history of IR.

Table 3. Clues to the diagnosis of IR

Clinical

Personal/familial history

Full metabolic syndrome or its components/complications

Physical findings

BMI (kg/m²)

Waist

Waist/hip ratio

Waist/height ratio

Blood pressure

Biological

Fasting glucose/OGTT

Fasting insulin

HOMA/QUICKI

Triglycerides

HDL cholesterol

TG/HDL cholesterol ratio (in the obese)

Uric acid

Ferritin

BMI = Body mass index; OGTT = oral glucose tolerance test; HOMA = homeostasis model assessment; QUICKI = quantitative insulin check index.

eral IR and increased availability of FFA that affect both lipid [136] and glucose metabolism [137] resulting in fatty changes within the liver and the muscle (leptin resistance and lipotoxicity). Steatosis and *hepatic IR* [138, 139], in particular, appear to have a central role in the development of NASH and other hepatic and extrahepatic complications. Additional factors involved in the development of inflammatory/fibrotic complications of NAFLD may also result from the action of other factors linked to persistent hepatic insulin/leptin resistance, such as increased production of reactive oxygen species (ROS), pro-inflammatory cytokines and lipid peroxidation products, that further worsen peripheral IR so closing the pathogenic circle linking peripheral and hepatic IR (fig. 5). Therefore, IR does deserve mention in the very name of this condition. The metabolic nature of its pathogenesis is further supported by the finding that primary NAFLD appears to be one in several examples of organ manifestation of IR (MS) and leptin resistance (lipotoxicity).

Similar to what happened with nAnB hepatitis when HCV was discovered, in our opinion the time has come to abandon the NAFLD acronym. Nowadays NASH is

best defined as a *critical link in the chain of metabolic fatty liver disorders that spans steatosis to cryptogenic cirrhosis* [38]. On the grounds of previous suggestions [36–39], we fully agree that there is a compelling need for international agreement on terminology in MS-related liver disease. In the new terminology of NAFLD, the difference between the two terms often used interchangeably of ‘insulin resistance’ (a term more dedicated to illustrate a physiopathologic mechanism) and ‘metabolic’ syndrome (a term emphasizing obesity and its clinical correlates) [140] should also be remembered.

The introduction of a positive criterion would undoubtedly benefit the diagnostic process. Simple clinical

and biological indexes (table 3) should routinely be introduced in hepatological practice. These tests of IR appear to be sensitive but relatively nonspecific and capable – together with histologic findings – to lead to a positive diagnosis of NAFLD, help to estimate the risk of its progression and to target its treatment.

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