Non-Alcoholic Fatty Liver Disease: Cause or Effect of Metabolic Syndrome

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Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the most common liver disease in the world mainly because of the obesity pandemic [1]. It is assumed that the global prevalence of this disorder is similar to metabolic syndrome (MS) with around 25%. In 80% of affected subjects NAFLD is associated with obesity, although the disease may also develop in lean individuals. NAFLD may either present as simple steatosis (non-alcoholic fatty liver (NAFL)) or evolve in 10–20% towards its inflammatory complication, i.e. non-alcoholic steatohepatitis (NASH). Although the overall rate of NASH in the NAFLD population is unclear, certain studies propose that NASH may affect up to 5% of the general population. The disease further progresses towards liver cirrhosis and hepatocellular carcinoma, a complication which is increasingly observed also in the non-cirrhotic NAFLD population [2, 3]. The high rate of hepatocellular carcinoma in NAFLD requires special attention.

In the last decade, insulin resistance has been considered as the major underlying pathophysiological mechanism although it is not present in all affected individuals. Especially obesity-induced insulin resistance is a dominant pathophysiological factor underlying NAFLD. Inflammatory aspects are also of crucial importance particularly in NASH and NASH-associated fibrosis, which commonly develops subsequent to overwhelming inflammatory events in the liver [4]. Chronic inflammation characterizes many metabolic disorders such as obesity, MS, type 2 diabetes (T2D), or NAFLD. This so-called low-grade inflammation has also been termed metabolic inflammation as it has been initially observed in obesity and T2D [5, 6]. It is currently believed that, besides lipotoxic mechanisms, inflammatory pathways contribute substantially to insulin resistance observed in NAFLD.

Whereas NAFLD is commonly associated with insulin resistance and MS, the presence of MS or T2D should encourage every physician to search for accompanying NAFLD as all these disor-
obesity, and different immune cells and tissue macrophages con-
tribute to metabolic inflammation and associated insulin resist-
ance. Besides inflammation, lipid metabolism abnormalities have
been demonstrated in insulin-resistant states, and certain lipids
such as free fatty acids might interfere with insulin signaling,
thereby contributing to insulin resistance [17, 18]. The gut micro-
biota has evolved as another key player in insulin resistance, as rec-
ognized recently [19]. Importantly, hepatic steatosis is not unam-
biguously associated with insulin resistance, and situations might
exist where hepatic steatosis is associated even with increased insu-
lin sensitivity [20].

Pathophysiological Aspects: Regulation of Insulin
Resistance

Hepatic Steatosis and Insulin Resistance

NASH patients commonly present with metabolic inflamma-
tion which is mirrored by elevated levels of high-sensitivity C-
reactive protein, ferritin, or interleukin (IL)-1 receptor antagonist
serum levels. It is currently not understood why certain NAFLD
patients exhibit an inflammatory phenotype and progress towards
fibrosis and cirrhosis while most do not. Evidence is increasing
that systemic, i.e. metabolic inflammation, besides being prognos-
tically highly relevant, is also a driver of hepatic insulin sensitivity.
Research from the last decade has clearly shown that NAFLD is a
multisystem disorder which is caused by multiple parallel hits [15].
It is currently believed that besides lipotoxicity, insulin resistance,
 innate immunity, mitochondrial dysfunction, endoplasmic retici-
 lum stress, and the intestinal microbiota are involved in the disease
 process.

Insulin acts in all cells by means of binding to its specific recep-
tor and activating a cascade of intracellular signaling events. After
binding, the insulin receptor phosphorylates itself as well as several
members of the insulin receptor substrate family. The primary
pathophysiological mechanisms of insulin resistance induced by
inflammatory mediators are very likely due to interference at the
signaling level [16]. Proinflammatory cytokines and transcription
factors are highly expressed in the adipose tissue or liver in case of
obesity, and different immune cells and tissue macrophages con-

Definition of NAFLD

Liver steatosis is commonly diagnosed by ultrasonography,
which is an acceptable screening tool to suggest the presence of
NAFLD. A more accurate diagnosis of steatosis is possible when
using proton magnetic resonance spectroscopy, which is, however,
not readily available. NASH with features of inflammation, bal-
looning, and fibrosis can only be diagnosed by liver biopsy. Fibro-
sis has been demonstrated to reflect the most important prognostic
factor as the degree of fibrosis directly correlates with the prognosis
of liver disease [7, 8]. Unfortunately, definite diagnosis of the
presence of fibrosis and NASH can only be made by liver histology
which is rarely performed in NAFLD patients except in selected
situations and/or clinical trials [9–13]. Besides ultrasonography,
the use of transient elastography is recommended to discover ad-
vanced fibrosis; however, in the case of severe obesity this method
has certain shortcomings [14]. Although there might exist a typical
profile of elevated liver enzyme values with increased serum ala-
nine aminotransferase (ALT) and/or γ-glutamyl transferase (GGT)
levels, many NAFLD patients exhibit normal values.

Inflammation: The Key Driving Force in NASH

 Fibrosis is commonly considered the net end result of over-
whelming and uncontrolled chronic inflammation. This is also
the case in NASH, although it has been speculated that fibrosis might
also evolve independent from inflammation in a small number of
subjects. Importantly, even simple fatty liver may progress towards
NASH and fibrosis [21], suggesting that either intermittent inflam-
ination exists and/or the disease itself exhibits an undulating
course. This is difficult to prove in humans because of the short-
comings of noninvasive diagnostic possibilities. Nevertheless, the
importance of proinflammatory cytokines in NASH has been re-
peatedly demonstrated.

The liver plays a fundamental role in insulin resistance and
T2D. Various inflammatory pathways involving proinflammatory
cytokines such as TNF-α or IL-6 are activated in the liver in states
of insulin resistance [22, 23]. Activation of the transcription factor
nuclear factor-kappa B (NF-xB) and its associated inflammatory
signaling pathways are involved in hepatic insulin resistance. The
IkB kinase (IKK) complex plays a crucial role in the activation of
NF-xB by triggering phosphorylation and degradation of the inhi-
bitory molecule IkBa. Two studies have shown a role for IKKβ
expression in the liver and in insulin resistance [24, 25]. Cai et al.
[24] generated chronic, NF-xB-driven hepatic inflammation in
mice constitutively expressing low levels of IKKβ in the liver. These
mice exhibited a T2D-like disease with moderate systemic insulin
resistance. Arkan et al. [25] investigated mice lacking IKKβ either
in hepatocytes or the myeloid compartment. Mice with liver-spe-
cific deletion of IKKβ retained their liver insulin responsiveness
after consumption of a high-fat diet but developed insulin resist-
ance in muscle and fat. Overall, elevated NF-xB activity in the
hepatocyte is associated with insulin resistance, suggesting a key
importance of the hepatocyte in the regulation of hepatic insulin
sensitivity. We have shown that receptor activator of NF-xB
(RANKL), a prototypic activator of NF-xB, also regulates hepatic
insulin sensitivity [26]. All these studies clearly underline the im-
portance of inflammatory pathways in NASH and suggest that tar-
geting these cascades at various steps might constitute an attractive
treatment approach (fig. 1).

Adiponectin: The Key Adipocytokine Controlling Metabolic
Processes

Adiponectin is a prototypic anti-inflammatory adipocytokine
mainly produced by the adipose tissue [27]. It suppresses inflam-
Adiponectin also inhibits endothelial NF-κB signaling and controls macrophage function [29]. Adiponectin KO mice exhibit evidence of increased local and systemic TNF-α production [30]. Anti-inflammatory mechanisms of adiponectin also involve the induction of other anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonists [31]. Another anti-inflammatory pathway controlled by adiponectin involves regulation of heme oxygenase-1 [32]. Weight loss is a very potent inducer of adiponectin synthesis [23, 33]. Plasma levels of adiponectin are markedly diminished in visceral obesity and in states of insulin resistance such as NASH, atherosclerosis, and T2D [34].
Adiponectin exerts anti-inflammatory effects in various animal models of liver inflammation. We have observed that the protective effect of adiponectin in concanavalin A-induced hepatotoxicity is mainly mediated by induction of IL-10, suggesting that adiponectin-induced regulation of various anti-inflammatory mechanisms throughout the body contributes to its beneficial metabolic functions [35]. Overall, evidence is overwhelming to suggest that adiponectin reflects a master adipocytokine in health and that dysregulation drives metabolic inflammation, as observed in NAFLD, MS, and T2D.

Clinical Aspects: NAFLD, Metabolic Syndrome and Type 2 Diabetes – a Cluster of a Single Disease?

NAFLD: Commonly Associated with Insulin Resistance

Obesity and related insulin resistance is the major risk factor for NAFLD. A landmark observation by Marchesini et al. [36] defined this association for the first time, describing the presence of insulin resistance in a high percentage of NAFLD subjects. Numerous reports have proven this association, and it is currently believed that more than 80% of subjects with NAFLD including lean patients exhibit insulin resistance. Insulin resistance involves various tissues, including liver, adipose and muscle tissue. It is commonly defined in non-diabetic NAFLD subjects by the product of fasting glucose (in mmol/l) and insulin (in mU/ml), divided by 22.5 (homeostatic model assessment of insulin resistance (HOMA-IR)), and reflects an accepted parameter for insulin resistance [37]. During follow-up of NAFLD patients, HOMA-IR and worsening of metabolic risk factors might identify patient groups at risk for NASH or fibrosis progression in selected cases [9–13]. Another clinically relevant aspect is the proper interpretation of elevated liver function tests. Several large studies have convincingly shown that elevated serum ALT and/or GGT levels are associated with an increased incidence of T2D even after adjustment for several risk factors [38, 39]. Ultrasonography-defined NAFLD exhibits a more than 2- to 5-fold risk of developing T2D over time [40]. This underlines a role for clinical surveillance of patients with ‘only’ liver steatosis because of their high likelihood of developing MS and/or T2D. Furthermore, each patient with liver steatosis needs a careful investigation to rule out MS/T2D either by fasting or random blood glucose or HbA1c, or standardized 75-g oral glucose tolerance testing. However, some genetic forms of NAFLD with mutations in PNPLA3 and TM6SF2 are not associated with insulin resistance or features of MS or an increased risk of T2D [41]. It has been postulated by some authors that this group accounts for potentially 20–30% of the NAFLD population.

Metabolic Syndrome: Commonly Associated with NAFLD

Subjects with MS with additional insulin resistance exhibit increased liver fat and frequently elevated ALT levels [42]. NAFLD is highly prevalent in patients with MS, and indeed, all components of MS correlate with the amount of liver steatosis. This results in the important clinical recommendation to evaluate the risk of NAFLD and vice versa the presence of NAFLD in all subjects with any component of MS. Although it is well accepted, as stated before, that the degree of fibrosis is the key prognostic factor, earlier investigations have demonstrated by using follow-up liver biopsies that a substantial proportion of patients with NAFLD progress towards NASH and fibrosis, especially if metabolic risk factors worsen and T2D develops [43].

T2D: Search for NAFLD

T2D patients commonly exhibit increased liver enzymes and show a rate of NAFLD of up to 50–70%, as assessed by ultrasonography [44–46]. Magnetic resonance elastography demonstrated high rates of both NAFLD and advanced fibrosis [47]. NAFLD in T2D might exert a much higher incidence of NASH compared to non-diabetic NAFLD populations, and rates between 20 and 50% have been reported [48, 49]. Furthermore, other prognostically relevant features such as fibrosis are much more prevalent [50]. It has also been shown that the presence of T2D in NAFLD patients is an independent predictor of moderate-to-severe fibrosis [51]. Therefore, it is suggested that every T2D should be screened for NAFLD by at least liver chemistry (although 50% of patients will exhibit normal ALT levels) and ultrasonography.

NAFLD: A Multisystem Disease

Importantly, we have learned in the last decade that NAFLD is a mirror of many potential entities and can be considered more as a ‘symptom’ of a complex disease. In line with this, data have accumulated that NAFLD is not only associated with a significantly increased risk of T2D but also with an increased prevalence and incidence of cardiovascular and chronic kidney disease [52]. NAFLD per se may also play a role in the pathogenesis of these extrahepatic chronic complications. This clearly implies that NAFLD patients need counseling regarding these associations to decrease the risk for cardiovascular and kidney complications.

Treatment of NASH: Only Effective If Interfering with Insulin Resistance?

NAFLD and T2D share some common pathophysiological features; therefore, it is not surprising that several therapies used in the treatment of T2D also show efficacy in the treatment of NAFLD. Although several treatments have so far been studied in NAFLD, especially targeting insulin resistance such as thiazolidinediones [53], still no medical therapy is currently approved for this disorder. Although thiazolidinediones improve insulin resistance, they result in weight gain and, importantly, were not able to reduce liver fibrosis in clinical studies [54]. The increase in adiponectin secretion and the decrease in free fatty acid release likely underlie the beneficial effect of peroxisome proliferator-activated receptor-gamma (PPARγ) agonists on NAFLD. Independent of the efficacy of thiazolidinediones in liver disease, several other aspects require attention. Fluid retention with the risk of congestive heart failure and also atypical bone fractures in women have been reported. Vitamin E also demonstrated some efficacy in large clinical trials, in-
cluding histological improvements, but again could not improve liver fibrosis [53]. Importantly, vitamin E is a prototypic example of a therapeutic with a certain efficacy in NASH without affecting insulin resistance. Incretin mimetics, such as glucagon-like peptide-1 agonists, primarily stimulate glucose-dependent insulin secretion. They lead to reductions in body weight, insulin resistance, and liver transaminases. In a recently reported pilot trial, subcutaneous administration of liraglutide (1.8 mg/day) resulted in significant decreases in liver fat content and histological resolution of NASH [55]. Bile acids have recently been shown to control metabolic and immune functions, signaling through two major receptor pathways: farnesoid X receptor (FXR), a member of the nuclear hormone receptor superfamily, and TGR5, a G protein-coupled bile acid receptor [56]. A large placebo-controlled randomized study suggested that obeticholic acid, an FXR agonist, shows promising effects in NASH with histological improvement of steatosis, lobular inflammation, and especially fibrosis [57]. One of the caveats regarding this potential therapy, however, remains the fact that it caused itching in a significant number of patients and worsened the lipid profile. Another recent approach focused on targeting PPARα/δ. Here, Ratziu et al. [58] showed that elafibranor induces resolution of NASH without worsening fibrosis. Overall, all these studies support the notion that not only most therapies used to treat NASH come from the diabetes field but also that, more importantly, targeting insulin resistance and inflammation remains the cornerstone of therapeutic avenues. However, a detailed discussion of this aspect is beyond the scope of this article.

**Conclusion**

In this review article, we presented evidence that NAFLD, MS, and T2D are highly interconnected clinical entities. This results in the very important clinical consequence that the presence of either entity should immediately result in searching for the other. The question of ‘What comes first?’ is difficult to answer as we have learned that (i) NAFLD is frequently accompanied by insulin resistance, (ii) diagnosis of NAFLD is commonly followed by later diagnosis of MS/T2D, and (iii) MS/T2D is extremely frequently associated with NAFLD. Therefore, we can conclude that these three entities are part of a syndrome sharing mechanisms and pathophysiology. We need to educate practitioners, internists, diabetologists, and hepatologists to share this knowledge and to look at NAFLD what it is: a complex metabolic, multisystem disease.

**Highlights**

- NAFLD is the most common liver disease worldwide; 10–20% of patients exhibit NASH.
- Degree of fibrosis is the most relevant prognostic marker.
- Inflammation, lipotoxicity, insulin resistance, and gut dysbiosis reflect hallmarks of NAFLD.
- NAFLD, MB, and T2D are part of a syndrome sharing pathomechanisms and treatment targets.
- Recent studies suggest that thiazolidinediones, vitamin E, obeticholic acid, and elafibranor demonstrate some efficacy in NASH, although they are currently not approved for this indication.

**Disclosure Statement**

No conflict of interest exists.

**References**


41 Yki-Jarvinen H. Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. Lancet Diabetes Endocrinol 2014;2:901–910.


