Gastrointestinal complications of obesity: Non-alcoholic fatty liver disease (NAFLD) and its sequelae

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Obesity is a major risk factor for malign and non-malign diseases of the gastrointestinal tract. Non-alcoholic fatty liver disease (NAFLD) is an outstanding example for the complex pathophysiology of the metabolic system and represents both source and consequence of the metabolic syndrome. NAFLD has a growing prevalence and will become the leading cause of advanced liver disease and cirrhosis. Obesity has a negative impact on NAFLD at all aspects and stages of the disease. The growing epidemic will strain health care resources and demands new concepts for prevention, screening and therapeutic approaches. A better understanding of the interplay of liver, gut and hormonal system is necessary for new insights in the underlying mechanisms of NAFLD and the metabolic syndrome including obesity. Identification of patients at risk for progressive liver disease will allow a better adaption of treatment strategies.

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Introduction

Overweight and obesity have a growing incidence worldwide and are a major challenge for health care systems. According to the World Health Organization about 1.4 billion adults were classified as overweight in 2008. Among them, 500 million have a body mass index (BMI) >30 kg/m\(^2\) fulfilling the definition of obesity.\(^1\) In the United States and Western European countries more than one third of the adult population is overweight or obese.\(^2,3\)

In gastroenterology, obesity related complications are frequent and comprise both non-malignant and malignant diseases in all parts of the digestive system (Table 1).\(^3\) In addition to specific symptoms of the listed gastroenterologic diseases, obese patients frequently suffer from unspecific complaints like upper belly pain and dyspepsia and functional disorders like foregut-related nausea or hindgut associated diarrhoea or constipation.\(^4,5\)

The following review focuses on the consequences of obesity for the liver, because the liver is the central organ of metabolism and thus a key player in the pathogenesis of obesity related complications (Fig. 1). Non-alcoholic fatty liver disease (NAFLD) can be taken as the hepatic manifestation of the metabolic syndrome and is particularly associated with insulin resistance, obesity, and abnormalities of glucose and lipid metabolism.\(^6\) However, NAFLD may precede weight gain, and the resulting fundamental metabolic derangement in association with diabetes mellitus type 2 reflects its potential causality for obesity. The spectrum of NAFLD displays a wide range from simple hepatic steatosis to chronic non-alcoholic steatohepatitis (NASH) which can result in progressing fibrosis, liver cirrhosis, and ultimately hepatocellular carcinoma in a significant number of patients.\(^7\)

Therefore, NAFLD will be discussed in detail as a paradigm of obesity related gastrointestinal complications and clinical challenges.

Definitions

Non-alcoholic fatty liver disease (NAFLD) is defined by evidence of hepatic steatosis, either by imaging or by histology, without any causes for secondary hepatic fat accumulation (e.g. significant alcohol consumption, steatogenic medication, hereditary disorders).\(^25\) NAFLD is histologically further categorized into non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH), depending on the absence or presence of hepatocellular inflammatory injury with or without fibrosis.\(^25\)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Overview over gastrointestinal complications of obesity.</th>
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<tbody>
<tr>
<td>Upper gastrointestinal tract</td>
<td>GERD: increased risk of gastro-oesophageal reflux disease, especially related to the amount of visceral adipose tissue.(^8,9) IBD: higher incidence of perianal disease, requirement for more aggressive medical therapy, higher risk for postoperative complications.(^12) Risk for complications may increase in the future, because one third of children with IBD are overweight or obese.(^13)</td>
</tr>
<tr>
<td>Lower gastrointestinal tract</td>
<td>Gallstones: increased incidence of symptomatic gallstones and higher rate of perioperative complications of laparoscopic cholecystectomy.(^17,18) Pancreatitis: higher risk for acute biliary pancreatitis and a severe course of the disease.(^19,20)</td>
</tr>
<tr>
<td>Hepatobiliary system</td>
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</table>

GERD – gastro-oesophageal reflux disease, IBD – inflammatory bowel disease.
Incidence and prevalence of non-alcoholic fatty liver disease

NAFLD is the most common cause of chronic and advanced liver disease both in adults and in children in industrialized countries and affects up to 30% of the general adult population. Its prevalence is increased in diabetic and obese patients (60–80%) and may be as high as 100% in morbidly obese individuals. Changes in life style and dietary habits lead to a growing number of affected patients and thus fatty liver is epidemic in western countries. In addition, NAFLD is affecting at least 10% of the general population in Asia with a prevalence of up to 27.2% in urban areas comparable to European countries.

The prevalence of NAFLD depends on the population studied and varies widely according to the definition used. The general prevalence of NASH in apparently healthy individuals ranges from 3% to 16% in Europe and from 6% to 15% in the US. In otherwise healthy individuals like living liver donors histological evidence of NAFLD occurs with prevalence between 15% in Europe and 30% in the United States. One Italian study reported even a prevalence of up to 50% in living liver donors and identified increased body weight and obesity as predictive parameters for clinically unapparent NASH.

However, screening studies in large populations where biopsy is not feasible apply non-invasive diagnostic criteria which result in different estimates for NAFLD and NASH prevalence. Conventional ultrasound tends to overestimate NAFLD prevalence. Diagnosis based on elevated aminotransferase levels can lead to false low prevalence estimations as patients with persistently normal alanine-aminotransferase (ALT) may have progressive liver disease. The issue of ALT-defined NAFLD estimations is complicated by the elusiveness of normal ALT values.

Data on the annually incidence NAFLD and associated predictive factors are scarce. Recently, a cumulative 7-year incidence of 19% has been reported among the general population in Israel.

Pathophysiology of obesity and NAFLD

Hepatic steatosis is the result of increased hepatocellular incorporation and the novo synthesis of lipids exceeding oxidation and export via very low density lipoproteins (VLDL). NAFLD encompasses a wide spectrum of histopathological changes of liver tissue induced by complex interactions between glucose and lipid metabolism, genetic predisposition, environmental conditions, and modulation of the intestinal microbiota.
Impact of insulin resistance and obesity

Body weight excess and liver fat content show a nearly linear relationship and are linked by impaired insulin action. In obese individuals, adipose tissue promotes insulin resistance and diabetes type 2 by release of non-esterified fatty acids, hormones and pro-inflammatory cytokines. In turn, impaired hepatic insulin sensitivity correlates with increased blood concentration of free fatty acids and inhibits their hepatic beta-oxidation which finally results in increased hepatic fat content. This is probably promoted by deregulation of intracellular second messenger systems which increase hepatic de novo lipogenesis and impair inhibition of adipose tissue lipolysis. The resulting impaired hepatic insulin effectiveness reflects a causal role of NAFLD in the genesis of insulin resistance and explains why NAFLD may precede the manifestation of diabetes and associated cardiovascular complications. Therefore, NAFLD must be considered as a keystone in the multiorgan system derangement of insulin sensitivity and is thus associated with all other components of the metabolic syndrome.

Progression from steatosis to steatohepatitis

Not all patients with NAFLD develop progressive liver disease. While some individuals have merely increased hepatic fat content without histological evidence of hepatic inflammation or significant fibrosis, more than half of patients present with any degree of steatohepatitis (NASH) and up to 20% will develop fibrosis. Diabetes is strongly associated with risk of NASH and advanced fibrosis in NAFLD patients and even a family history of diabetes is associated with an increased risk for progressive disease. Moreover, adipose tissue dysfunction in obese individuals alters adipokine response to fat ingestion which has recently been identified as a modulating factor of liver injury. Thus, considering that NAFLD is a continuum from simple steatosis to NASH, a ‘multiple-hit’ model has been proposed: Due to insulin resistance and its associated metabolic disturbances (the ‘first hit’), the liver becomes vulnerable to oxidative damage and hepatocyte apoptosis and fibrogenic pathways are deregulated (further ‘hits’). This may finally result in progressive hepatocyte injury and fibrosis.

However, there are only few documented cases with proven progression from simple pure fatty liver to NASH and underlying causal mechanisms remain questions of on-going research. Therefore, NASH and pure fatty liver may also be regarded as two independent conditions which have distinct pathogenic characteristics and different aetiological mechanisms.

Genetic predisposition for NAFLD

In addition to metabolic and life style factors genetic variants have been identified as risk parameters for NAFLD. Variants in the patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene are involved in fat accumulation in hepatocytes and are associated with risk of advanced liver disease. The G allele of rs738409 in PNPLA3 is associated with increased odds of histologic NAFLD irrespective of body mass index, triglyceride levels, or diabetes. In-vitro studies have demonstrated that this polymorphism modulates triglyceride hydrolase and acylglycerol transacylation activity of PNPLA3, but its definite role in triglyceride metabolism has not yet been defined.

Recently, more hepatic steatosis associated variants including polymorphisms in the lysophospholipase-like 1 and peroxisome proliferator activated receptor-gamma genes have been identified. These are, however, not uniformly associated with NASH or fibrosis. Moreover, Interleukin 28B variants (rs12979860, rs8099917), which have already been described as predominant factor in genetically determined hepatitis C immunity, seem to affect the severity of histological liver damage in NAFLD patients.

Functional studies on NAFLD progression are required for the understanding of underlying mechanisms which are influenced by these genetic risk factors. Perspective, genomic risk assessment may help identifying patients at risk for rapid progression of NAFLD.

“Gut-liver axis”

The liver is the first-pass organ for portal blood which carries highest concentrations of digestive system products. There is growing evidence that modulation of the intestinal microbiota influences
hepatic fat accumulation and NAFLD progression. In addition, obesity has been linked to a specific gut microbiota pattern, probably caused by fat enriched diet.

The intestinal epithelia provide homeostasis between bacteria and host derived signals and barrier disturbances can result in increased endotoxinaemia. Recently, genetic determined activity changes of inflammasomes, which are cytoplasmic multi-protein complexes involved in the regulatory cleavage of pro-inflammatory cytokines, have been described as a factor for host-related gut dysbiosis. The resulting abnormal accumulation of bacterial products in the portal circulation was associated with progression of NAFLD in different mice models. This reflects the complex and potentially outstanding role of microbiota in the pathogenesis of NAFLD and other metabolic disorders and may help to further understand clinically observed associations between nutrition patterns and the course of NAFLD.

**Diagnosis of NAFLD and NASH**

The diagnosis of NAFLD requires evidence of hepatic steatosis without causes for secondary hepatic fat accumulation. This implicates the necessity to exclude any other chronic hepatic disease like viral hepatitis, hereditary metabolic disorders, and in particular alcoholic liver disease or therapy with steatogenic medication.

The wide clinical spectrum of NAFLD demands a careful assessment with respect to additional risk factors for the presence of NASH and associated complications. Table 2 summarizes the advantages and limitations of invasive and non-invasive diagnostic approaches.

**Liver biopsy**

Liver histology is considered as the current reference standard for diagnosis of NAFLD. The degree of steatosis can be quantified according to the number of affected hepatocytes. Steatosis is defined by lipid deposition exceeding 5% of hepatocytes, while involvement of more than 50% defines “fatty liver”. In addition, tissue analysis allows grading of associated inflammation and staging of the degree of liver fibrosis. The NAFLD activity score (NAS) is the current standard for histopathological diagnosis of NAFLD: it comprises a semi-quantitative classification for steatosis, lobular inflammation, hepatocellular ballooning (enlarged cells with fat droplets), and fibrosis. However, liver biopsy is an invasive procedure with potential complications, and sampling errors may lead to underestimation of

<table>
<thead>
<tr>
<th>Method</th>
<th>Assessment of</th>
<th>Advantages</th>
<th>Limitations</th>
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<tr>
<td>Liver biopsy</td>
<td>+</td>
<td>- Established scoring systems&lt;sup&gt;59&lt;/sup&gt;</td>
<td>- Sampling errors and interobserver variability&lt;sup&gt;60&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>- Diagnosis of accompanying diseases&lt;sup&gt;58&lt;/sup&gt;</td>
<td>- Invasive procedure: potential complications, limited repeatability&lt;sup&gt;61&lt;/sup&gt;</td>
</tr>
<tr>
<td>MRI</td>
<td>+</td>
<td>- High accuracy for steatosis quantification&lt;sup&gt;64&lt;/sup&gt;</td>
<td>- Contraindications (e.g. pacemaker, claustrophobia, morbid obesity)</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Significant steatosis</td>
<td>- Assessment of whole liver volume&lt;sup&gt;65&lt;/sup&gt;</td>
<td>- Costs and availability</td>
</tr>
<tr>
<td>Elastography</td>
<td>Fibroscan with CAP&lt;sup&gt;70&lt;/sup&gt;</td>
<td>- Non-invasive and repeatable assessment of liver structure</td>
<td>- Depends on operator skills&lt;sup&gt;64&lt;/sup&gt;</td>
</tr>
<tr>
<td>Biomarker panels</td>
<td>Designated to risk assessment in NAFLD: detection of NASH and fibrosis&lt;sup&gt;77&lt;/sup&gt;</td>
<td>- Highly standardized</td>
<td>- Feasibility and validity limited in obese patients&lt;sup&gt;76,77&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- High accuracy for detection of advanced fibrosis/cirrhosis&lt;sup&gt;77,81&lt;/sup&gt;</td>
<td>- Inflammation can affect fibrosis assessment&lt;sup&gt;81&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>- Immediate results</td>
<td>- Availability</td>
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<tr>
<td></td>
<td></td>
<td>- No contraindication</td>
<td>- Majority of scores not liver specific</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Combination with other techniques&lt;sup&gt;81&lt;/sup&gt;</td>
<td>- Costs and availability</td>
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fibrosis in up to 30% of patients.60,61 Therefore, biopsy indication remains confined to individual cases after careful risk consideration.25,26

**Imaging techniques**

Ultrasound is a save and inexpensive technique for liver assessment. Hepatic steatosis can be classified according to the intensity of ultrasound signal attenuation.62 When combined with serologic markers ultrasound is a useful tool not only for diagnosis, but also for further risk stratification in NAFLD: in case of increased gamma glutamyl-transferase levels a hyperechogenic liver structure is associated with increased risk of mortality in men.63

Alternatively, the amount of fat in the liver can be estimated with magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS).64,65 Moreover, MRI based techniques allow assessment of liver volume and fat distribution over the whole liver and may thus be regarded as a potential new reference standard for hepatic fat quantification.66,67 However, widespread clinical use of MRI in NAFLD patients will be limited due to restricted availability and economic aspects. Furthermore, all imaging techniques are not suitable for grading of hepatic inflammation and have a limited value for the estimation of fibrosis.26,57

**Elastography**

Tissue stiffness measurement represents a potential non-invasive alternative to estimate the degree of liver fibrosis. Transient elastography (Fibroscan®) and Acoustic Force Radiation Impulse (ARFI) can be used to identify NAFLD patients with significant risk for advanced liver fibrosis or cirrhosis who should undergo liver biopsy to optimize their clinical prognosis.68,69 Recently, an additional software module incorporated in the Fibroscan® system – the Controlled Attenuation Parameter (CAP) – has been developed for non-invasive quantification of hepatic steatosis.70 First data show a high correlation between CAP and the histological stage of liver steatosis comparable to MR-based techniques.69,71

**Non-invasive diagnostic scores**

Several clinical scores based on metabolic factors and biomarker panels have been proposed for risk assessment in NAFLD patients.57 Among them, the NAFLD fibrosis score is based on six readily available variables (age, BMI, hyperglycaemia, platelet count, albumin, AST/ALT ratio) and has a high predictive value for detection of advanced fibrosis.57,72 Biomarker panels show good accuracy for fibrosis detection comparable to elastography methods.57 In addition, increased serum ferritin levels have recently been recognized as an independent predictor of histologic severity and advanced fibrosis in NAFLD patients.73

**NAFLD screening and diagnostics in the context of obesity**

Despite of recent advances in non-invasive liver assessment a general screening for NAFLD is currently not recommended even for high risk populations (e.g. obese or diabetic patients).25,26 However, in patients with evidence of hepatic steatosis the presence of obesity and the metabolic syndrome are associated with steatohepatitis and thus may be used for risk stratification and decision for liver biopsy indication.25,26 Furthermore, PNPLA3 genotyping may help to identify patients with high risk for progressive liver disease.51

Obesity is not only a major risk factor for advanced liver disease but also limits feasibility and accuracy of different non-invasive diagnostic approaches for NAFLD assessment. Pure fatty liver and NASH may not correctly be discriminated by NAS grading in obese patients and thus refined histology scores are needed for this patient group.60 Ultrasound is affected by obesity which hampers steatosis differentiation.74 Morbid obesity can represent a technical contraindication for MRI due to the narrow gantry aperture.75 Fibroscan applicability is reduced in obese individuals with a BMI > 30 kg/m² and is associated with measuring failure in at least one of six cases and with higher liver stiffness after adjusting for fibrosis stage.76,77 A special XL-probe has been developed to overcome these
limitations. However, although this device exhibits an accuracy for fibrosis detection comparable to the standard M-probe, it deserves further evaluation due to lower liver stiffness cut-off values.

**Treatment strategies for NAFLD and NASH**

The standard treatment for patients with any grade of NAFLD is life style intervention with the purpose of weight loss. Additional pharmacologic therapy is indicated in the presence of comorbidities, especially for components of the metabolic syndrome (e.g. diabetes mellitus type 2, dyslipidaemia), but cannot be recommended solely for NAFLD treatment.

**Life style intervention**

There is evidence for the positive effect of weight reduction and physical exercise on NAFLD severity and progression. Generally, the degree of hepatic fat reduction is directly related to the intensity of life style change. This reflects the dominant role of visceral adipose tissue in the pathogenesis of NAFLD. Reduction of more than 5% of baseline weight can induce NAFLD remission in 75% of patients in the long term. Moreover, weight loss results in significant improvement of steatosis and inflammation, but not fibrosis. A recent meta-analysis on the effect of exercise on NAFLD revealed a benefit on liver fat which may even become apparent with minimal weight loss and at low exercise intensity.

However, individual reports of life style interventions often have insufficient power and high risk of bias which affects detection of meaningful hepatic benefits. Moreover, most studies are based on non-invasive NAFLD assessment and lack data on modulation of associated liver lesions like inflammation and fibrosis. Randomized controlled trials with follow-up liver biopsies are needed to define the best composition of diet and the required intensity of physical activity for NAFLD patients. The impact of life style intervention on NAFLD related mortality still deserves evaluation in long term studies. Nevertheless, the overall positive effects of physical activity and – in case of obesity – moderate weight reduction on the metabolic system and cardiometabolic risk factors legitimate the recommendation of life style intervention for all NAFLD patients.

Besides weight reduction patients with NAFLD should not consume heavy amounts of alcohol (more than one drink per day) while the impact of occasional alcohol drinking remains controversial. In NASH, coffee caffeine consumption is associated with a significant reduction in risk of fibrosis. Therefore, moderate coffee intake can complement the dietary management of NASH patients.

**Impact of different pharmacological options**

There is a growing need for specific and targeted treatments other than weight loss, because weight loss has a poor long-term success rate in the majority of patients. Potential targets for NAFLD treatment mainly comprise modulation of associated metabolic disturbances, e.g. insulin resistance and dyslipidaemia. However, the complex and still not completely elucidated pathophysiology of NAFLD gives major drawbacks to successful therapeutic approaches. Although impressive amelioration of different aspects of NAFLD has been detected in single studies, there is still insufficient evidence to recommend any pharmacologic intervention as general treatment. The failure of large clinical trials on promising compounds call for a critical reflection of current clinical dogmata and new diagnostic endpoints for clinical research in NAFLD.

**Table 3** gives an overview of common pharmacologic approaches which may become relevant for subgroups of NAFLD patients in the coming years. Further treatment strategies include anti-TNF-α agents (pentoxifylline) and other lipid lowering drugs. Future directions for NAFLD therapy will focus on incretin analogues, probiotics and drug combinations.

**Therapeutic approach in obese NAFLD patients and impact of bariatric surgery**

Patients with morbid obesity should be transferred to a structured nutrition counselling with regular follow-up visits to achieve weight loss maintenance. In case of failure of dietary measures, bariatric surgery is an effective treatment option for severe obesity (BMI > 35 kg/m²) which provides
significant long-term weight loss and improvement of obesity-related complications in most patients.\textsuperscript{96} NAFLD or NASH without cirrhosis do not affect the safety of bariatric surgery and weight loss after bariatric surgery is associated with histologic improvement of NASH.\textsuperscript{97} However, no prospective randomized trials are available assessing NAFLD related outcomes after bariatric surgery and fulminant steatohepatitis in selected cases with excessive weight loss have been reported.\textsuperscript{97} Therefore, the indication for bariatric surgery may be emphasized by the presence of NASH but remains restricted to patients with morbid obesity.\textsuperscript{25,97}

### Complications of NAFLD

Simple hepatic steatosis has a benign nature in the majority of affected individuals. However, a significant number of patients has progressive disease and suffers from associated complications.\textsuperscript{25} The risk of NAFLD complications increases with disease progression from simple steatosis over NASH and fibrosis to liver cirrhosis\textsuperscript{26}. Typical complications of NAFLD are summarized in Fig. 2.

#### Liver fibrosis and cirrhosis

Simple steatosis progresses to NASH in around 10–20% of patients.\textsuperscript{58} Of these, 25–30% develop progressive liver fibrosis.\textsuperscript{57} Older age, male gender, and the presence of the metabolic syndrome are risk factors for a higher prevalence of NAFLD related fibrosis.\textsuperscript{7} More than 10% of patients with milder stage of fibrosis and up to 25% of patients with advanced fibrosis ultimately develop liver cirrhosis which is associated with a significant liver related mortality and a median survival of 6 years.\textsuperscript{57} Notably, steatohepatitis can resolve once cirrhosis is established and many cases classified as “cryptogenic liver cirrhosis” are believed to be the result of NASH.\textsuperscript{58,98} Liver cirrhosis associated portal hypertension is a severe late sequela of NASH: affected patients have a high risk for bleeding complications, spontaneous bacterial peritonitis and other infections, encephalopathy and liver failure with an overall reduced survival.\textsuperscript{26}

Today, data on regression of advanced NASH fibrosis are rare and liver cirrhosis is considered as an irreversible end-stage of NASH.\textsuperscript{26,99} However, improvement of liver histology and function is frequently observed in chronic liver diseases of other origin once treatment is initiated.\textsuperscript{100} In NASH patients, the impact of new treatment strategies on fibrosis modulation remains to be defined.\textsuperscript{47}

### Table 3

Pharmacologic treatment approaches in NAFLD.

<table>
<thead>
<tr>
<th>Drug (class)</th>
<th>(Potential) effect on NAFLD</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin\textsuperscript{82}</td>
<td>- Reduces gastrointestinal glucose absorption and modulates insulin sensitivity</td>
<td>- Decreases elevated liver enzymes</td>
</tr>
<tr>
<td></td>
<td>- Can induce weight-loss</td>
<td>- No effect on NAFLD histology</td>
</tr>
<tr>
<td>Glitazones\textsuperscript{90,91}</td>
<td>- Improve insulin sensitivity</td>
<td>- Decrease steatosis and inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Role on fibrosis not defined</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Concerns about cardiovascular safety</td>
</tr>
<tr>
<td>Gliptines\textsuperscript{92}</td>
<td>- Enhance the effect of incretin on insulin synthesis</td>
<td>- Limited data show improved metabolic parameters associated with NAFLD</td>
</tr>
<tr>
<td>Antioxidants (vitamins C and E)\textsuperscript{24,82,83,91}</td>
<td>- Reduction of oxidative stress</td>
<td>- Vitamin E can improve liver histology in non-diabetic adults with NASH</td>
</tr>
<tr>
<td>Vitamin D\textsuperscript{91}</td>
<td>- Immunomodulatory, anti-inflammatory and antifibrotic properties</td>
<td>- Ongoing research on vitamin D supplementation in NAFLD</td>
</tr>
<tr>
<td></td>
<td>- Association of Vitamin D deficiency with chronic liver diseases</td>
<td>- No significant effect on liver histology of NASH patients</td>
</tr>
<tr>
<td>Ursodeoxycholic acid (UDCA)\textsuperscript{94}</td>
<td>- Modulates biliary cholesterol secretion and intestinal cholesterol uptake</td>
<td>- Phototherapy and vitamin D supplementation improves liver histology in animal models</td>
</tr>
<tr>
<td></td>
<td>- Assumed anti-inflammatory effects</td>
<td></td>
</tr>
<tr>
<td>Statins\textsuperscript{82}</td>
<td>- Decrease cholesterol synthesis</td>
<td>- Improve aminotransferase levels and steatosis in hyperlipidaemic NAFLD</td>
</tr>
<tr>
<td></td>
<td>- Potential anti-inflammatory effect</td>
<td>- No effect on liver histology</td>
</tr>
</tbody>
</table>
Liver failure

Acute-on-chronic liver failure is characterized by an acute clinical condition in case of a pre-existing chronic liver disease and is characterized by sudden and severe hepatic injury leading to encephalopathy and coagulopathy associated with a high risk of progressive multiorgan failure. In NAFLD patients, it is the first clinical manifestation of previously unrecognized NASH cirrhosis in up to 50% of cases. Especially middle aged obese women with unremarkable medical history are at risk for NASH-related liver failure. Moreover, more than one third of cirrhotic patients will suffer from liver failure within 10 years after diagnosis is established.

Obese individuals have a high risk for delayed diagnosis, liver failure and other complications of NAFLD-related cirrhosis. In these patients, liver injury can be associated with non-steroidal anti-inflammatory drugs (e.g. acetaminophen) which are frequently used for symptomatic treatment of other obesity related symptoms like joint pain. Hepatotoxic slimming aids and other herbal medication can further contribute to liver injury. Therefore, obese individuals need a careful clinical assessment before initiation of a potentially hepatotoxic medical therapy.

Hepatocellular carcinoma

A growing incidence of HCC has been recognized in recent years resulting in a rapidly increasing number of liver-related cancer deaths. NASH cirrhosis is considered as an important contributing factor to this development. Both diabetes and obesity promote the development of HCC in NASH patients and hepatic iron deposition may be an additional carcinogenic risk. These factors can cause HCC development independently of the presence of advanced fibrosis or cirrhosis. Up to 40% of NAFLD patients have no evidence of cirrhosis at the time of HCC diagnosis. In a recent analysis of 2863 of NAFLD-related HCC cases, only 64% of patients had cirrhosis and remarkable 18% had simple fatty liver without steatohepatitis. These findings identify NAFLD and the metabolic syndrome as emerging independent risk factors for HCC and demonstrate the need for new preventive and diagnostic implications.

Compared to hepatitis C, patients with NASH-associated HCC have a less severe liver dysfunction at diagnosis and a better chance of survival after curative treatment. However, presence of the metabolic syndrome augments complications and mortality of surgical HCC treatment and overweight is associated with technical difficulties of percutaneous loco-regional treatment approaches.
Impact on liver transplantation

The epidemic of obesity and metabolic syndrome has increased the frequency of liver transplantation for NASH by 5-fold during the last decade requiring increased resource utilization. Although long-term data are limited, cardiovascular comorbidities seem to have a negative impact on the outcome of liver transplantation in NAFLD patients. Higher rates of postoperative complications and mortality are most likely caused by obesity and diabetes. NAFLD and NASH recurrence are frequent in transplanted patients and up to 10% will progress to bridging fibrosis or cirrhosis within 10 years. In one study evaluating patients with HCC, a BMI >30 kg/m² predicted microvascular tumour invasion, a higher rate of tumour recurrence and hence a poor overall survival after liver transplantation regardless of the underlying liver disease.

Conclusion

Obesity is a major risk factor for both malign and non-malign diseases of the gastrointestinal tract. NAFLD is an outstanding example for the complex pathophysiology of the metabolic system and represents both source and consequence of the metabolic syndrome. Obesity has a negative impact on NAFLD and NASH at all aspects and stages of the disease. The growing epidemic of NAFLD will strain health care resources worldwide and demands urgent action for preventive measures.

A deeper understanding of the interplay between liver, gut, and the endocrine system is necessary for new insights in the underlying molecular mechanisms of NASH on other manifestations of the metabolic syndrome including obesity. Identification of patients at risk for progressive disease will allow implementation of screening strategies and may improve effects of pharmacologic NAFLD treatment.

Practice points

- Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome. Therefore, the liver is a key player in the pathogenesis of obesity related complications.
- NAFLD has a high prevalence and is a growing epidemic worldwide.
- Body weight excess and liver fat content have a strong association and are linked by impaired insulin action.
- NAFLD is defined by evidence of hepatic steatosis in the absence of any other causal chronic liver disease. The presence of non-alcoholic steatohepatitis (NASH) increases the risk for progressive liver disease.
- Non-invasive diagnostic methods provide helpful information for the clinical practice while liver histology remains the reference standard for grading and staging of NAFLD and NASH.
- Life style intervention is the standard treatment for NAFLD. Patients should be screened and treated for associated manifestations of the metabolic syndrome.

Research agenda

- Data on true prevalence and incidence of NAFLD, associated risk factors and course of the disease are required.
- Functional studies on NAFLD progression are essential for a better understanding of the underlying mechanisms and associated genetic risk factors.
- Non-invasive diagnostic methods require further evaluation in histologically well defined, large patient cohorts.
• New definitions for differentiation of simple steatosis from non-alcoholic steatohepatitis are needed for better characterization of patients at risk for disease progression. Promising pharmacological agents should be evaluated in these patients in histology controlled trials.
• Screening algorithms are needed for early diagnosis of NAFLD associated complications, especially HCC.

Acknowledgements

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