Non Alcoholic Fatty Liver Overview

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Abstract

Fatty liver disease is one of the common liver diseases, could be alcoholic (AFLD) when there is significant alcohol intake or non-alcoholic (NAFLD), when other causes of liver steatosis are ruled out in particular significant alcohol intake and viral hepatitis. The course of NAFLD could have one of two extremes, either benign simple steatosis or steatohepatitis known as NASH that could lead to progressive liver inflammation, cirrhosis and even hepatocellular carcinoma HCC, and is believed to be important cause for liver cirrhosis in those labeled before as cryptogenic cirrhosis. NASH represents more than 10% of liver transplant cases in the USA and unfortunately there is risk of recurrence post-transplant. The underlying cause is multifactorial, related to genetic and acquired factors, the acquired factors are mostly modifiable, related to lifestyle particularly increased calorie intake with limited consumption in people leading sedentary life, and this leads to overweight / obesity, insulin resistance and triglycerides accumulation in the liver. And so the management will mainly rely on reversal of these lifestyle negatives, so stress on the triad: Diet, exercise and weight reduction. In this review will focus on non-alcoholic fatty liver disease in adults, giving comprehensive overview including the latest recommendations about the management in clinical practice.

Keywords: Nonalcoholic fatty liver; Cryptogenic cirrhosis; Triglycerides

Introduction

Fatty liver disease (FLD) refers to triglycerides accumulation in the liver cells. FLD is a spectrum of disease, could be Alcoholic (AFLD) or Nonalcoholic (NAFLD), but morphological features cannot distinguish between AFLD and NAFLD. The AFLD, is considered when significant alcohol intake, but still this statement to be defined, it was suggested to use CAGE questionnaire (need to Cut down drinking, Annoyed by criticism, feeling Guilty about drinking, use Eye opener) to elicit alcohol dependence, with some limitations of this approach [1]. Practically exceeding the amount of 21 units per week for men and 14 units per week for women is considered toxic to the liver, even some studies denote lower levels could also be toxic, especially those with metabolic risk factors such as DM and obesity [2]. This review will focus on non-alcoholic part of this wide spectrum of fatty liver disease in adults. NAFLD is considered once the patient meets criteria for fatty liver (radiologically and/or histologically) in absence of other secondary causes of liver steatosis, and no significant alcohol intake.

It is pointed to as the hepatic manifestation of the metabolic syndrome, closely related to insulin resistance and seems to be related to overlap of genetic and acquired factors [3]. The loss of balance between energy intake and output seems to play critical part in the inappropriate fat storage in the liver and this was demonstrated in animal studies which showed insulin resistance in liver and adipose tissue followed by skeletal muscles when energy substrates supply exceeded the actual consumption, and this observation draws our attention to the modern dietary habits that could play substantial role in the development of NAFLD [4,5]. Diet high in saturated fat, meat and soft drinks low in anti-oxidants and omega 3 containing fish, would modulate hepatic triglycerides accumulation and affect insulin sensitivity (lowering the insulin sensitivity index ) and post prandial triglyceride metabolism leading to higher post prandial triglycerides level [6].

These lifestyle negatives including the high calorie diet and sedentary lifestyle with predominant obesity -that reached epidemic levels in some countries, result in excess fat storage in the adipose tissues in the form of triglycerides with subsequent increased insulin resistance, this could explain the high incidence of NAFLD, which is believed to be the hepatic branch of the metabolic syndrome [4,7].

Epidemiology

NAFLD is the most common form of liver disease in western countries. It is estimated that excess fat in the liver in adults in the USA and western countries have prevalence of 20-30%, almost 10% of whom meet criteria for NASH, and in Japan was estimated about 14% of general population, which reflects the extent of this health problem [8,9]. With continued liver inflammation, almost one third will end up with cirrhosis [8].

Aetiology

Fat accumulation in the liver is a multifactorial process with underlying several genetic and acquired factors involved [3]. Fatty liver disease could be:

- Primary- this is our target in this review, when no underlying cause could explain hepatic steatosis and no significant alcohol intake.
- Secondary- that needs to address the underlying cause, as the management is different from that of the primary type.
- Secondary causes include- excess alcohol intake, viral hepatitis HCV and HBV which are the common causes. Other less common
causes include- Protein calorie malnutrition, rapid weight reduction, parenteral nutrition, gastric by-pass surgery (with some controversies), lipodystrophy, dysbetailoproteinemia, small bowel diverticulosis with bacterial overgrowth, inflammatory bowel disease, HIV infection. Acute fatty liver of pregnancy and Rye syndrome (would cause microvesicular steatosis where the mitochondrial dysfunction plays the major role). Drugs-such as steroids, synthetic estrogens, tamoxifen, methotrexate and antimicrobials such as zidovudine and tetracycline, others such as valproic acid, cocaine, didanosine, fialuridine and petrochemicals. Amiodarone (that would cause hepatic phospholipidosis) [3,10-14].

Pathology

The morphological features cannot distinguish AFLD from NAFLD, so it is presumed that both forms could at certain point share a common pathway ending in the FLD. So will review -in brief- the alcohol induced FLD followed by the NAFLD pathology.

In alcohol induced FLD- the peroxisome proliferator-activated receptor – PPAR-a is pivotal for regulation of hepatic fatty acid metabolism, as fatty acids act as ligand for PPAR-a, with increased levels of fatty acids, the PPAR-a activates a series of fatty acid metabolizing enzymes to lower the fatty acids to normal level. Ethanol intake elevates Fatty acid level but on the other hand it also inhibits PPAR-a binding to DNA, inhibits activation of reporter genes, so increases free fatty acid levels, which are highly reactive, damaging biological membranes and so potentially cytotoxic [15,16].

Coming to the NAFLD, things are not so clear, Insulin resistance was shown to be clearly correlated with NAFLD to the level that severity of insulin resistance is related to the extent of fatty liver infiltration, even in lean normo-glycemic subjects, so other underlying mechanisms including genetic factors could play role in its pathogenesis [15,17].

The insulin resistance is believed to be multifactorial, with several molecular factors could be implicated, including mutations of nuclear receptor PPAR-gama, the gene of Rad (Ras associated with diabetes ) which was shown to be overexpressed in diabetes mellitus type2 (DM II), also overexpression of PC-1,which is a membrane glycoprotein that acts as an inhibitor of insulin receptor tyrosine kinase, and the inflammatory insult with subsequent overexpression of IKK-B resulting in insulin resistance in obesity and DM II [18-21]. Insulin resistance leads to increased lipolysis and increased free fatty acid delivery to hepatocytes [15]. A possible role of gut microbes in NAFLD/NASH development was also raised, and it was shown in animal and human studies that gut microbes could eventually play a role in progression of NAFLD, a relation known as gut-liver axis [22,23].

As the gut commensal bacteria are modulated by diet ,so it is expected to go same direction of the effect of unhealthy diet habits , giving negative effects demonstrated in the form of fat deposition in the liver (NAFLD) as well as its effect on other components of the metabolic syndrome such as glucose homeostasis and central obesity.

A correlation was demonstrated between increased gut permeability (such as in celiac disease ) and presence of small intestinal bacterial overgrowth ( both conditions represent increased risk of bacterial access to the portal circulation ) and hepatic fat deposition .

The underlying mechanism could be attributed to an inflammatory process, as these microbes/microbe products - in case of incompetent tight junctions of small intestinal mucosal cells - could gain access to the portal circulation ,and drive an inflammatory process contributing to insulin resistance and hepatic fat deposition [22,23,24].

The fat accumulation within hepatocytes, oxidative stress, mitochondrial dysfunction and dysregulation of various cytokines, expected to play important role in liver cell injury, apoptosis and progression to NASH [15,7]. The AOX gene (acyl-CoA oxidase) was shown to be essential for regulation of PPAR-a system activity,and its deficiency was shown (in mice) to contribute to overreaction of PPAR-a with subsequent microvesicular metamorphosis of hepatocytes, steatohepatitis and hepatocellular tumors (adenomas and carcinomas) [25].

The end point is triglycerides accumulation within hepatocytes, but why some remain quiescent with just simple steatosis and others may get more aggressive course into steatohepatitis and its sequelae - cirrhosis and even HCC (this is not fully explored).

Histopathology

Hepatic steatosis is accumulation of large (macrovesicular) or small (microvesicular) intracytoplasmic fat droplets within the hepatocytes [4,12]. Hepatocytes near the central veins are at higher risk of metabolic stress, so during the process of fat infiltration, these cells start accumulating fat earlier than cells at the periphery near the portal triads, then at later stages the infiltrate would be diffuse [26]. In the macrovesicular form the hepatocytes contain single large vacuole, occupying large area of cytoplasm pushing the nucleus to the periphery giving signet ring appearance and these manifests in zone 3 and in more severe cases could be panacinar [4]. In the microvesicular form, small fat droplets accumulate in the cytoplasm, with still centralized nucleus, and this form is more aggressive, could be attributed to mitochondrial dysfunction and abnormal B oxidation of fatty acids. The macrovesicular form is the most common form in both AFLD and NAFLD while some cases show mixed picture [4].

The histological features of AFLD and NAFLD both share some features of hepatic steatosis/steatohepatitis that have the potential to progress to cirrhosis and hepatocellular carcinoma, so AFLD versus NAFLD cannot be differentiated histologically. NAFLD could be benign (non-inflammatory ) hepatic steatosis, that seems not to be associated with adverse sequelae, but also could have the other extreme with steatohepatitis (NASH nonalcoholic steatohepatitis), that could lead to cirrhosis, end stage liver disease and accounts for about 14% of liver transplant recipients in the USA [10]. NAFLD is defined as fat deposition exceeding 5-10% by weight of hepatocytes, and is estimated practically as the percentage of fat-laden hepatocytes observed by light microscopy, provided no significant alcohol intake [8].

The term NASH first introduced by Ludwig et al. in 1980 to describe liver biopsy findings in cases with no significant alcohol intake, they found lobular hepatitis, mixed inflammatory infiltrate, fatty infiltrate, focal necrosis, fibrosis and in most cases Mallory bodies and cirrhosis in some patients [27].

Histologic abnormalities associated with NAFLD include- Simple steatosis (no hepatic injury) and the more injurious pattern NASH [27].
NAFLD (steatosis and steatohepatitis) is graded as:

- Steatosis alone (type 1).
- Steatosis plus inflammation (type 2).
- Steatosis plus hepatocyte injury or ballooning degeneration (type 3).
- Steatosis plus sinusoidal fibrosis, Mallory bodies (type 4), or both.[28,29].

So NAFLD is diagnosed when hepatic steatosis without evidence of hepatic cellular inflammatory infiltrate while NASH when there is evidence of hepatic injury (inflammation with or without fibrosis) [30].

Clinical Presentation

Usually the fatty liver is diagnosed accidentally during imaging such as US study or LFTs done usually for other reasons; these patients may have some nonspecific symptoms such as fatigue, malaise and sense of abdominal heaviness in the right upper quadrant.

Laboratory work up

First work up will include liver function (enzymes and albumin), but Liver enzymes are not reliable to establish diagnosis or stage extent of fibrosis [8]. Then work up for other causes of liver injury. It is of paramount importance to rule out other causes of liver steatosis/fibrosis such as HCV, HBV infection, metabolic causes such as Wilson disease, and medications such as amiodarone among others that can also cause liver steatosis and if clinically appropriate to consider rare causes such as alpha one antitrypsin deficiency [31].

The level of recommendation for clinical practice is limited because of predominant obesity factors (namely obesity, DM, hyperlipidemia) with elevated liver enzymes have histologically hepatic steatosis and also other patients with no comorbidities could have histologically hepatic steatosis/NASH, so liver biopsy can sort out if hepatic steatosis is there and also to diagnose NASH and assess the extent of liver injury (simple steatosis, inflammation or fibrosis) [35,39]. Also plays a prognostic role, as it was demonstrated that absence of periportal fibrosis at baseline had a negative predictive value of 100% in predicting liver-related complications, after mean observation period of 13 years [40]. The liver biopsy on the other hand is liable for some limitations including cost, being invasive procedure so impractical on the wide scale of patients putting in mind the high prevalence of this liver entity, also sampling error and risk of complications [28,41].

So, it indicates that NAFLD with increased risk of progression to steatohepatitis and cirrhosis and if other diagnoses cannot be sorted out except with biopsy, so that definite diagnosis and treatment can be planned [14]. And in those with indeterminate score in NAFLD fibrosis score and still high risk for progressive course of NASH [14,42].

Non-invasive evaluation

Some models have been developed trying to establish a non-invasive method for diagnosing NASH or at least to identify patients risky for progressive fibrosis that should take more attention, but apart from the NAFLD fibrosis score, not yet these models came to the level of recommendation for clinical practice [35,14].

NAFLD fibrosis score

Consists of variables (age, BMI, IGF/DM, platelet count, albumin, AST/ALT ratio) and it is calculated using (http://nafldscore.com) [14,42]. This score can be used to evaluate presence or absence of significant fibrosis, or indeterminate. This scoring system was evaluated in several trials and sounds reliable to identify those with advanced fibrosis in a noninvasive way to reserve biopsy for those in the indeterminate range. NAFLD Fibrosis Score has an AUROC (area under the receiver operating curve) of 0.85 for predicting advanced fibrosis (i.e., bridging fibrosis or cirrhosis) and a score < 1.455 had 90% sensitivity and 60% specificity to rule out advanced fibrosis whereas a score > 0.676 showed 67% sensitivity and 97% specificity to identify presence of advanced fibrosis [14,43].

Transient elastography

Although it was valuable to elucidate fibrosis in viral hepatitis cases, its validity in NAFLD cases is limited because of predominant obesity in such cases which limits sensitivity of this technique [14,42].

Biomarkers

A good example of these suggested biomarkers, the CK 18 (cyto keratin 18) which is released via effect of caspases on hepatocytes inducing apoptosis, which is claimed to be the underlying mechanism of liver cell injury in NASH, a value of 395 U/L was shown to have a specificity of 99.9%, a sensitivity of 85.7%, and positive and negative predictive values of 99.9% and 85.7%, respectively, for the diagnosis of NASH [44].
Imaging Studies

The fat content ideally exceeds 33% fat on liver biopsy (in wet weight) to be radiologically detectable [13,45]. The imaging techniques despite great advantage to pick up fatty liver infiltrate, they cannot differentiate simple steatosis from NASH, so it is part of the evaluation but not all [46].

Ultrasound

It is one of the most commonly used imaging modalities for liver disease, as mostly fatty liver disease is picked up during this study, as the liver appears enlarged and hyperechogenic as compared to kidneys and spleen. The pattern of fat accumulation in the liver could be diffuse, diffuse with focal sparing areas or focal accumulation areas. Also, could be mimic inflammatory or neoplastic processes such as multinodular and perivascular patterns, so precaution should be exercised to avoid unnecessary work up [13,47]. At US, fatty liver shows echogenicity higher than renal cortex and spleen, with attenuated US wave and Loss of delineation of the diaphragm, and poor delineation of intrahepatic architecture [13].

CT scan

In the unenhanced CT study normally liver has less attenuation than spleen and blood, while in fatty liver the attenuation is more marked, exceeding 10 HU (Hounsfield units) from spleen or less than 40 HU [23,48]. While in contrast enhanced CT study, the study is not so reliable due to overlap between attenuation values in normal and fatty liver cases also the study results will vary according to timing and injection rates which limit its utility in clinical practice [49].

MRI

MRI is also valid imaging modality for diagnosing fatty liver infiltrate with quantitative evaluation of fat component in the liver tissue, different modalities available such as: chemical-shift imaging, frequency- selective imaging and MR spectroscopy, with variable degrees of accuracy between different modalities to elicit fat infiltrate. Further details about imaging in Fatty liver disease are beyond scope of this article [41].

Prognosis

Survival in NAFLD (simple steatosis) patients was shown to be comparable with matched control population of same age and gender, but this was challenged in one review, it was shown that simple steatosis also carries small risk of complication with cirrhosis and liver related mortality [35]. While in NASH patients survival was reduced, with the most common cause of death being cardiovascular causes and this could be attributed to the metabolic syndrome in those patients, and liver related disorders such as liver cell failure and hepatocellular carcinoma [40]. Also, recently it is acceptable that NASH is one of the major causes of cryptogenic cirrhosis, representing advanced stage with lost necroinflammatory and steatotic features [50]. Almost 88% of NAFLD patients will develop DM/impaired glucose tolerance [50].

The risk of HCC in NASH-related cirrhosis is comparable to that in cirrhosis associated with alcohol or hepatitis C. This could be in part secondary due to obesity and its metabolic sequelae of insulin resistance and DM. As obesity was shown to be an independent risk factor for HCC (hepatic cell carcinoma) in alcoholic and cryptogenic cirrhosis and in one review there was positive linear trends in death rates with increasing body-mass index for all cancers, including HCC [51-53].

Management

Lifestyle

As NAFLD/NASH is considered the hepatic manifestation of a larger disease spectrum known as the metabolic syndrome particularly after defining insulin resistance as core pathology in NAFLD, so it is logic to consider the management of metabolic syndrome as crucial part in NAFLD management.

Several studies addressed this proposal, and came up with conclusion that lifestyle including diet adjust, exercise and weight reduction could limit progression of NAFLD and this was also shown in other studies, like the study done by Huang et al. and Ueno et al., that showed promising results with positive impact of nutritional counseling and weight reduction on liver biochemistry and liver histology in NAFLD patients [36,54-56]. As regard the exercise, in one study, aerobic exercise 30-45 minutes for three times per week for 6-12 weeks was assessed and showed significant reduction of liver fat content independent on weight loss [14,57]. This could be at least in part related to reduction of insulin resistance that was shown in other studies to be significantly reduced with exercise, as insulin resistance is a core part of the pathogenesis of fatty liver disease. As the incidence of NIDDM (non-insulin independent diabetes mellitus) was reduced by 6% annually for every 500 Kcal energy expenditure/week in physical activity, this can be obtained by sustained physical activity (jogging, bicycling, etc.) for one hour [58]. Actually till now, lifestyle measures are the only evident therapeutic approach to NAFLD.

The target weight loss was defined in overweight and obese patients (BMI 25-40 ) to be, 5% weight reduction to improve steatosis but more than 7% is required to improve necro-inflammation [14,59]. Here we need to stress on the negative impact of rapid weight loss that could exacerbate liver status and precipitate decompensation, but the underlying mechanism is not clear [29]. Weight reduction is proven to be effective in reducing fatty infiltrate and improving LFTs, and weight reduction may be with lifestyle measures or bariatric surgery. After bariatric surgery significant histopathological improvement was demonstrated despite rapid weight loss and baseline significant histopathological changes that would otherwise predict progression of liver disease and worse prognosis, but also deterioration was demonstrated in other studies with about 24% of patients showed more inflammatory changes, this is particularly shown in patients with higher fatty infiltrate at the start point, and in severely obese patients with NAFLD after bariatric surgery [60-63].

So patients after bariatric surgery show improvement of liver biochemistry and histology but some have the other extreme with worse histology and more necro-inflammation, although this was demonstrated in those with greater fat burden in the liver at the start, the mechanism is not fully understood, at least we need to be more cautious in planning weight reduction either way lifestyle or bariatric surgery. The ideal rate of weight loss has to be determined, the rate of 1600 gm/wk in adults, has been suggested, but still candidate for further assessment [11].
Medical Treatment

Apart from vitamin E (alpha tocopherol) there is no clear evidence that any medication could be of significant help in NAFLD/NASH, although some medications have been evaluated and showed promising results (but in small trials).

- Vitamin E (alpha tocopherol) - was investigated as an antioxidant and did have positive effects on NASH histology, so it is recommended in dose of 800 IU/D for non-diabetic, biopsy proven NASH [14,64,65].
- Metformin (dose of 500 mg tds for 4 months ) which improves hepatic cell sensitivity to insulin, showed reduction of mean transaminases and liver volume by almost 20%, but the study volume was small [66].
- Gemfibrozil showed reduction of transaminases in NASH patients with persistently elevated enzymes (for more than 6 months), and this was demonstrated even in absence of hypertriglyceridemia, but again the study volume is small [67].
- Pravastatin showed also positive results on liver histology in NASH patients (non-obese, non-diabetic), and this was confirmed by biopsy findings, these patients showed significant reduction of cholesterol level but not triglycerides, this could be related to anti-oxidant and anti-inflammatory effect of statins, but still the study volume is small [68].
- Rosuvastatin was evaluated in hyperlipidemic, NASH group of patients, and showed normalisation of transaminases and GGT with significant reduction of total cholesterol, LDL cholesterol, triglycerides and elevation of HDL, but again the observation period was relatively short (8 months ) and the study volume is small [69].

In another study with larger volume (68 NAFLD patients) and longer duration (10.3 to 16.3 years), statins treated group showed less steatosis and are less likely to progress to fibrosis, even it was demonstrated that statins have good safety profile -liver wise -even with elevated liver enzymes due to NAFLD [70]. Ursodeoxycholic acid UDCA (dose 13-15 mg/kg/d) was evaluated in NASH patients with histological and biochemical abnormalities, and showed improved histological findings with persistance of AMK phosphatase, ALT, GGT and hepatic steatosis after 12 months treatment, but again in need for further larger scale studies to validate this effect [71]. While TZDs use in NAFLD patients showed reduction of transaminases but did not show promising histological effects [72]. (NB: the study was run before withdrawal of troglitazone with concern about its hepatotoxicity).

Surgery

Patients progressing to end stage liver disease, are candidates for liver transplantation, but unfortunately NAFLD could recur in the allograft, and the incidence was determined about 60% steatosis recurrence in NASH patients receiving liver transplant (post-transplant ), steatohepatitis in up to 33% and again progression to cirrhosis in 12.5% [73].

Summary and Recommendations

Fatty liver disease represents a spectrum of disease including alcohol induced or non-alcohol induced liver cell infiltrate with triglycerides. The NAFLD represents a major health problem with high prevalence among general population particularly in view of lack of effective medical treatment. First, no recommendations for screening either those having risk factors or family members of patients with established diagnosis. If the diagnosis is made accidentally during imaging study for some other reasons, apart from liver related symptoms or signs, it is recommended to assess further for cardio-metabolic risk: obesity, impaired glucose tolerance/DM, dyslipidemia, lifestyle such as dietary habits particularly high calorie intake and level of exercise. Also to rule out other causes of secondary FLD, so proper history taking, particularly alcohol intake (asking about details including amount and frequency), also other common causes that may mimic fatty liver such as HCV, HBV infection and if clinically appropriate to consider other causes such as hemochromatosis, autoimmune hepatitis, alpha one anti trypsin deficieny- putting in mind the limitations of some findings such as high ferritin or ANA (as described before).

If no liver related symptoms or signs and normal liver biochemical profile, biopsy is not indicated, taking into consideration the limitations of liver enzymes (as described before). But if liver related manifestations with persistently abnormal liver biochemical profile, biopsy is indicated for accurate diagnosis and guide management. The only proven benefits shown are clearly linked to lifestyle measures, particularly in those with obesity or leading unhealthy life style (high calorie intake with lack of regular exercise), as it is well recognized that regular aerobic exercise, would decrease insulin resistance, which plays a major role in pathogenesis of fatty liver, in addition to control of other metabolic issues such as blood glucose and lipids [74]. But medical treatment - apart from vitamin E - despite having some promising effects with some medications aiming basically to control other metabolic associations (insulin resistance, DM, hypertriglyceridemia and hypercholesterolemia), yet candidate for further larger volume trials to validate its benefits coming to the level of recommendations to be part of our standard of care.

In my practice, I stress on lifestyle measures: Diet, exercise and weight reduction (for overweight and obese patients), recommending patients to increase fruit and vegetable intake (rich in anti-oxidants) and low fat and carbohydrate, also to do regular exercise, about 150 minutes physical activity per week which is 30 minutes per day for five days per week, and regular follow up, in addition to control of any comorbidities particularly metabolic issues such as DM and hyperlipidemia [75].

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