Nonalcoholic fatty liver disease: defining a common problem

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Abstract. – Non Alcoholic Fatty Liver Disease (NAFLD), with prevalence of 10-51% in general population involving all ages, is the major cause of elevation of ALT and a common finding by ultrasound screening and may range from simple steatosis, to Non Alcoholic Steatohepatitis (NASH) and its clinical consequences as cirrhosis and hepatocellular carcinoma. In this review will be analysed factors influencing the onset of the disease.

NAFLD, primarily associated with insulin resistance, is in fact considered the hepatic manifestation of the metabolic syndrome: a cluster of disorders that includes obesity, diabetes mellitus, dyslipidaemia, arteriosclerosis and hypertension. The increased incidence and prevalence of obesity and diabetes may explain growing interest in NAFLD. Racial, ethnic, environmental and behavioural models are also reviewed.

Key Words:
Non Alcoholic Fatty Liver Disease, Non Alcoholic Steatohepatitis, Obesity, Diabetes, Metabolic syndrome, Liver.

Introduction

Nonalcoholic fatty liver disease (NAFLD) has been increasingly recognized as an important public health problem over the past 20 years and the most common chronic liver disease with potential progression to cirrhosis and to cause liver related death in 20-25% of cases. The prevalence of NAFLD is expected to increase in concern with the rapidly growing prevalence worldwide of obesity and diabetes.

NAFLD consists of a wide spectrum of liver abnormalities, ranging from steatosis to nonalcoholic steatohepatitis (NASH), when steatosis is accompanied by necroinflammatory change, fibrosis and/or cirrhosis1-3. The diagnosis of NAFLD is in fact based on clinico-pathological criteria and so on liver biopsy as method of choice.

The term “non-alcoholic fatty liver” is first used in 1980, to describe a clinicopathologic syndrome that occurred in obese, diabetic females who denied alcohol use, but in whom the hepatic histology was consistent with alcoholic hepatitis4. Although there is no consensus regarding the definition of nonalcoholic in NAFLD patients, it seems reasonable to exclude patients from this diagnosis if current or past (within 5 years) daily alcohol intake has exceeded more than 20 g per day in women and 30 g in men. Because neither NAFLD or NASH can be distinguished from alcoholic fatty liver or alcoholic steatohepatitis on either ultrasonographical or histological grounds (without clinico-pathological correlation), its diagnosis relies heavily on the determination of the quantity of alcohol consumed by the subject5.

Hepatic steatosis is an infiltration of fat, mainly triglycerides, inside hepatocytes, usually exceeding 5% of the liver weight, in a patient without excessive alcohol consumption6,7. While simple steatosis is usually associated with a benign prognosis, steatohepatitis and fibrosis may progress to cirrhosis8. In fact, NASH, once considered as a disease with benign course, is currently thought to be a significant cause of cryptogenic cirrhosis; the hepatocellular carcinoma can be the final step in natural history of NAFLD3,8.

Demographics

NAFLD may affect persons of any age, including children. However, it is considered to occur most commonly in middle age (the
mean age ranged from 47 to 54 years) and these findings are corroborated by ultrasound screening: the prevalence of fatty liver increased with age. On the contrary, presumed NAFLD based on elevated ALT activity was most common in relatively young age.

Knowledge of the epidemiology and demographics of NAFLD is limited due to the lack of an accurate, non invasive measure for use in screening of the general population.

Both serum liver enzyme tests and imaging have limited sensitivity and specificity and lack the ability to measure the severity of disease, so accurate epidemiologic data are not available.

The prevalence of NAFLD, by using different methodologies (clinical series, imaging or autopsy studies, and general population screening) and by considering different countries, is differently estimated and ranges between 10 and 51%.

A correct estimation of NAFLD in Western Countries has been recently fixed around 20-30%, and that of NASH around 2-3%. NAFLD is also the most frequent liver disease and the major cause of elevation of ALT.

Around 70% of individuals with increased transaminase levels showed steatosis when underwent to hepatic ultrasonography. An ultrasound screening study for fatty liver in the general population was conducted in Japan and the prevalence was 19% among adults.

NAFLD was originally believed to be more common in women, with a high prevalence in both type 2 diabetes mellitus (T2DM) and obesity. Recent series have included approximately equal numbers of men and women or a high proportion of men. Among Italian general population men had, by ultrasound means, more than twice the prevalence of chronic liver disease compared with women: this was due to a male predominance among persons less than 50 years, while the sex differences diminished after age 50. In the US adult population men had a higher prevalence of NAFLD, based on elevated ALT activity than women within every age group.

**Racial and Ethnic Differences**

Racial/ethnic variation in NAFLD has been studied. Two of the strongest risk factors for NAFLD, obesity and T2DM, show racial/ethnic differences. These differences in NAFLD risk may result from variation in body fat distribution or metabolism. Preliminary data suggest an over representation of Caucasians and Hispanics, with a low prevalence among African Americans.

NAFLD is considered the hepatic manifestation of the metabolic syndrome, a cluster of disorders that includes obesity, diabetes mellitus, dyslipidaemia, arteriosclerosis and hypertension, and has been aetiologically associated with insulin resistance.

The multifactorial nature of fatty liver disease is important: fatty liver may be the end result of numerous diverse causes that may have different mechanisms, natural histories and response to therapy.

**Obesity**

Obesity has been the factor most strongly associated with NAFLD, independently of alcohol drinking and has been found in 30% to 95% of NAFLD patients. The prevalence of fatty liver on ultrasound was much higher in obese Italian adults (76%) compared with 16% of controls. NAFLD may occur in as many as three-quarters of obese people and close to 20% may have NASH. There is, however, a significant proportion of NAFLD cases with a normal body weight: this means that obesity and NAFLD are common consequences of a shared disorder, or that obesity increases the risk of developing NAFLD only in presence of additional events.

Whether the higher risk of NAFLD among the obese can be attributed to conditions that frequently coexist with excess weight, such as diabetes and hyperlipidemia, is less clear. BMI is the only independent predictor of the degree of fat infiltration of the liver and the likelihood of developing NASH increase with the degree of obesity, especially among morbidly obese patients. There is also evidence that obesity has a significant long-term clinical impact on liver disease. Especially central obesity, has been shown to be associated with NAFLD in normal weight, obese, and diabetic individuals: among normal-weight, middle-aged men, those with a high waist-to-hip ratio had a great prevalence of fatty liver (30%), compared with those with a low one (16%).

**Dyslipidemia**

Hypertriglyceridemia, reported in 20% to 81% of NAFLD patients and independently
of obesity, and mixed hyperlipidemia most commonly associated with NAFLD, but also the presence of low levels HDL-cholesterol, expression of insulin resistance, doubles the risk of NAFLD. The prevalence of fatty liver on ultrasound was much higher in persons with hypertriglyceridemia (> 250 mg/dl) compared with those with normal triglycerides among both men and women.

**Diabetes**

T2DM has been the factor most commonly associated with NAFLD and was reported in 10% to 55% of NAFLD patients. Similarly, any category of altered glucose regulation and even the sole family history of T2DM increase the risk of NAFLD. The predominance of steatohepatitis and the extent of steatosis among diabetics was independent of the degree of obesity. The HOMA method and the euglycemic clamp technique have shown that NAFLD patients have a reduced sensitivity to both endogenous and exogenous insulin, similar to that observed in T2DM, also in presence of normal glucose.

**Insulin resistance and metabolic syndrome**

Metabolic syndrome (MS) has been defined as a combination of 5 risk factors: (a) visceral obesity (waist circumference > 102 cm for males and > 88 cm for female); (b) hypertension (> 130/85 mmHg); (c) high triglycerides (> 150 mg/dl); (d) low HDL-cholesterol (< 40 mg/dl in males, < 50 mg/dl in females); (e) high glucose (> 110 mg/dl) or treated for diabetes. Insulin resistance has come to be regarded as central in the pathogenesis of both NAFLD and MS and was an independent predictor of the degree of hepatic steatosis. The recent hypothesis for NAFLD pathogenesis considers that insulin resistance may be involved in both onset of fatty liver and in disease progression. NAFLD had been proposed as the liver manifestation of the MS in non-obese patients, the increased prevalence of fatty liver reported, appears to be related to insulin resistance.

**Diagnosis**

**Liver Biopsy**

Liver biopsy remains the method of choice for confirming or excluding the diagnosis in a patient with clinical features of NAFLD, image-detected steatosis and elevated liver enzymes. Evaluation of liver histology in NASH, is required for characterization and quantification of parenchymal necroinflammatory injury, determination of the presence and type of fibrosis and assessment of architectural changes thus providing significant prognostic information.

Currently, almost 25 years after the introduction of the term “NASH” by Ludwing, it was accepted that a constellation of histological findings is required for the identification of adult NASH:

- **Steatosis:** steatosis (ranging from “any amount” to 15-30% of the parenchymal cells) is the hallmark of NAFLD and is more commonly macrovesicular, with a single large fat droplet displacing the nucleus or with smaller intracytoplasmic droplets.

- **Hepatocyte ballooning:** in the form of enlarged, swollen hepatocytes with rarified cytoplasm. It may represent not only a feature of cellular injury, but also an adaptation phenomenon in NASH.

- **Lobular inflammation:** the common feature is the presence of mild chronic inflammation without evidence of acute inflammation.
• **Perisinusoidal fibrosis**: is not required for the diagnosis of NASH, but it was generally a common or helpful finding.

• **Zone 3 predominance** of the characteristic acinar lesions was considered a necessary or common feature by the majority of hepatopathologists.

Others common findings for the diagnosis of NASH, are the presence of Mallory’s hyaline bodies, an intracytoplasmic inclusion, commonly found in zone 3 ballooned hepatocytes and in areas of perisinusoidal fibrosis; megamitochondria with crystalline inclusions distributed randomly among acinar zones; glycogenated nuclei.

There is no uniformity among hepatopathologists regarding the minimal necessary criteria for the diagnosis of NASH, however, it is clear that steatosis and inflammation alone, cannot justify the diagnosis of NASH.

A semi-quantitative system for **grading** (grade 1-mild, grade 2-moderate, grade 3-severe) and **staging** is the basis for many histopathologists. A classification system correlating histological features of NAFLD with disease outcome has been drawn up by Matteoni et al. According to this system, NAFLD may be separated into four histologic subgroups based on the presence of steatosis (type 1), steatosis and lobular inflammation (type 2), steatosis and hepatocellular ballooning (type 3), steatosis with ballooning and either Mallory’s hyaline or fibrosis (type 4), NAFLD histologically and clinically resembles NASH (type 3 and 4).

Liver biopsy is therefore considered the gold standard for diagnosis and is the only method for differentiating NASH from steatosis with or without inflammation.

Disagreement exists, however, regarding the necessity for performing liver biopsy in NASH patients, considered the generally good prognosis, the lack of effective therapy, the uncertain benefit to asymptomatic patients and the risk and costs associated with this procedure. Therefore, radiologic and serum chemistries have been investigated as alternative noninvasive methods for diagnosis of NAFLD.

**Imaging**

Ultrasound, computer tomography (CT) and magnetic resonance imaging (MRI) can be used to detect fatty liver: however, all are insensitive to identify fibrosis, the degrees of steatosis and evaluate the severity of disease.

**Ultrasonography**, due to its lower costs and lack of known risks, has been considered the most common imaging modality used for evaluating hepatic steatosis and for performing epidemiologic studies. Several studies have used similar criteria for the detection of fatty liver by ultrasonography, the more subjective of them is the increased parenchymal echogenicity or “bright liver”.

The sensitivity for detecting steatosis was 94% and the specificity was 84%. These values ranged from 60% to 100% and from 66% to 100% respectively in other studies of patients who underwent both liver biopsy and ultrasonography.

**Clinical and Serum Chemistries**

A large proportion of patients with NAFLD (45% to 100%) are asymptomatic. Fatigue, malaise, and vague right upper quadrant abdominal discomfort bring some patients with NASH to medical attention. These symptoms are reported to antedate the diagnosis in about one third of patients. Typically, NAFLD patients, are incidentally found to have abnormal liver function tests or hepatomegaly; this latter condition occurring in up to 75% of patients and may increase to 85% when assessed by ultrasound.

**Liver enzymes** are not considered to be sensitive or specific either for diagnosing NAFLD or judging the severity of disease and the degree of steatosis and may also be in the normal range despite significant liver injury, including fibrosis and cirrhosis.

Increased aminotransferase activities are the most common abnormality reported in patients with NASH, however the true sensitivity and specificity of liver enzyme elevations for detection of NAFLD are unknown. Usually, AST or ALT are elevated only mildly to moderately in the range of a two-to fivefold elevation.

Serum ALT has been most widely used to screen for NASH, although other enzymes, such as AST and gamma-GT, have sometimes been used. Alkaline phosphatase(ALP) may be abnormally elevated two to threefold, in fewer than half of patients.
For a histologic diagnosis of steatosis, the sensitivity of a single ALT > 40 U/ml was 45% and the specificity was 100%. For NASH, the sensitivity was 44% and specificity was 64%. Recently a lower cut-off levels for ALT (> 30 U/l) have been proposed! Using a definition based on an elevated ALT, ALP or gamma-GT, only modestly increased the sensitivity to 55% and decreased the specificity to 75% for steatosis. For NASH sensitivity was 53% and specificity was 50%. Prevalence estimates of presumed NAFLD ranged from 3.1% using ALT alone, to 5.4% using ALT and AST to as high as 23% using gamma-GT, as well as ALT and AST. The AST/ALT ratio is reported to be less than 1 in 65% to 90% of NAFLD patients. The positive predictive value, estimated from series of patients with chronically elevated transaminases, is of about 90% for NAFLD, and of 34% for NASH.

Hematologic measurements are usually normal, unless cirrhosis has led to hypersplenism. Many studies, however, have reported elevated serum ferritin in approximately 50% of NAFLD patients without evidence of hepatic iron overload. Two studies noted that heterozygosity for the HFE gene is increased in NAFLD patients with a trend toward more severe hepatic fibrosis in NASH patients. Persistent elevation levels of liver enzymes would be more likely to indicate chronic disease, in fact, as has been recently reviewed. It is important for diagnosis to exclude other diseases associated with increased fat, such as drug-induced disease (corticosteroids, estrogens, amiodarone, nifedipine), occupational toxins, bacterial contamination of the small bowel, autoimmune liver diseases, Wilson’s disease, inherited metabolic disorders and surgical procedures (bilio-pancreatic diversion, jejunostomy bypass, gastrectomy). It is particularly important to exclude alcohol and HCV-associated disease: these combinations have prognostic and therapeutic implications. It is in these situations that a liver biopsy gains clinical importance.

Furthermore, for future research, the accuracy of the combination of abnormal enzymes and radiographic techniques versus histology for the detection of fatty liver disease needs to be performed in a systematic manner among populations of sufficient size.

References


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