Fatty Liver and Nonalcoholic Steatohepatitis

Where Do We Stand and Where Are We Going?

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Key Words
Atherosclerosis • Cancer • Diagnosis • Epidemiology • Fatty liver • Nonalcoholic steatohepatitis • Metabolic Syndrome • Natural history • Pathogenesis • Treatment

Abstract
Background: Fatty liver (FL) is the most common liver disease but its clinical significance remains elusive. Nonalcoholic steatohepatitis (NASH) is increasingly recognized as a cause of liver failure, sometimes recurring following transplantation. Recent data on both conditions are critically reviewed. ***Methods:*** A Medline search of the medical literature (1990 to September 1998) and cross-references was performed. ***Results:*** FL most commonly affects middle-aged men with obesity, altered glucose metabolism, hyperlipidemia, and hypertension. The link between biology of HCV, iron metabolism and FL should be addressed. Prospective studies should also quantify the rate and the factors involved in the progression of FL to NASH. The clinical spectrum of NASH is currently broader than it was initially recognized. Diagnosis of FL and NASH may involve ultrasonography, liver biopsy, and recognition of related conditions. Treatment of these conditions must be tailored according to patient's features. ***Conclusions:*** The clinical significance of FL is incompletely understood at present. The relationship, if any, of FL and the metabolic syndrome should be carefully investigated.

Introduction

Liver steatosis or fatty liver (FL) is the most common liver disease [1], accounting for abnormal liver function tests in the majority of asymptomatic subjects [2]. Furthermore, elevated body weight and/or GGT levels, which are often associated with FL [3, 4], may predict coronary heart disease [5], development of non-insulin-dependent diabetes mellitus (NIDDM) [6] and poor response to interferon treatment of chronic hepatitis C [7]. In addition, FL is a contraindication to the use of the liver for transplantation because of the high incidence of primary graft failure [8]. Finally, FL can evolve into its inflammatory counterpart steatohepatitis even in the non-drinker (nonalcoholic steatohepatitis, NASH) [9].
Interest in FL, once deemed to be 'a harmless symptom of disturbed lipid metabolism but not a disease' [10]. has grown in recent years, as has that in NASH [9, 11-19].

Aim and Method

This paper aims to critically review recently available data on FL. A thorough Medline search of the medical literature (1990 to September 1998) and cross-references was performed. Additional references derive from the author's personal archive. Relevant principles concerning NASH will also be reviewed in a separate section of this paper.

Definition of FL

There are two definitions for FL: a histological and an ultrasonographical one. According to the former, FL consists of lipid (usually triglycerides) storage within > 5% of the hepatocytes [11]. The histological distinction between macro- and microvesicular steatosis is a clue to its etiology. Indeed some of the most common etiologies (alcohol, obesity, diabetes mellitus) are associated with macrovesicular steatosis, whereas microvesicular steatosis is observed in more rare conditions (FL of pregnancy, Reyes' syndrome, drug-related) [11, 12]. Fatty droplets within the hepatocytes will in any case scatter ultrasound beams in such a way as to produce the so-called 'bright' echotexture where the liver is more echogenic (hence bright') than the adjacent kidney. Accordingly, ultrasonographic has been proposed and validated as a noninvasive approach to diagnose FL [20-26]. It is important to remember, however, that ultrasonographic screening is likely to pick up liver fat only when it exceeds 25-30% implying that such screening will possibly underestimate the prevalence of this condition.

In clinical practice liver biopsy is generally not proposed by the physicians and/or not accepted by patients when an ultrasonographic 'bright liver' is found in a subject with minor and transient liver function test alterations [27]. Such conduct, however, could be criticized because NASH cannot be predicted by noninvasive testing and requires liver biopsy [9], as discussed in the NASH section of this review.

Epidemiology of FL

Prevalence

The estimated prevalence of FL averages constantly around 14 - 25% both in eastern population studies and in Italian clinical surveys [28-34]. In Saudi Arabia the prevalence figure is around 10% in a radiological series [35].

Sex

CT-diagnosed FL and autopsy-found NASH are reported as being equally prevalent among men and women [35, 36]. In more modern ultrasonographic studies, however, males are affected more often than females in Japanese adults [30,31] and children [37]. In individuals without obesity and without hypertriglyceridemia, the prevalence of FL was significantly higher in males than in females [28]. Liver steatosis in obese subjects is associated with men [38]. The female sex, in contrast, is a possible risk factor for NASH [13]. The significance of these findings is presently unknown: it is interesting, however, that a sex difference also exists in some rat models of FL [39].

Age

Using ultrasonography, FL can be observed from childhood, where it affects 1.8-3.4% of subjects in the 4 - l2-year-old age group [37]. However, it peaks in the 40- to 59-year-old age group [28]. In our series age was found to be an independent predictor of FL [34].

High-Risk Groups

There is a close relationship between FL and each of the following: obesity; altered glucose metabolism; hyperlipidemia, and hypertension [3, 4, 4042]. For instance, 53% of obese children [43] and up to 84% of obese adults [28, 44] will have a bright liver. It is noteworthy that even subjects with a normal body mass index (BMI) and a high waist/height ratio have been shown to have an increased prevalence of FL [45] in agreement with the observation that the abdominal distribution of fat is a predictor of FL, independent of body weight or body fat [46]. Fifty percent of patients with mixed hyperlipidemia [47] have a bright liver. The frequency of FL is also increased in impaired glucose tolerance and diabetes mellitus [48, 49]. Finally, both systolic and diastolic blood pressure are significantly higher in subjects with hepatic steatosis, independent of their BMI and due to the association of FL with hyperinsulinemia [32]. The significance of such epidemiologic findings will be discussed later.

Etiology of FL

Since most heavy drinkers develop steatosis, alcohol is widely considered to be a classic cause of FL. The pathogenesis of alcoholic steatosis involves a redox shift resulting from ethanol metabolism *[50]*. However, if one focuses on an unselected series of patients who have FL (such as seen in the general population or in clinical practice in Europe), one wonders whether alcohol per se is hepatotoxic [51]. It has been known for many years that obesity is a risk factor for alcoholic liver disease *[52]*. Recent and preliminary data from Italy tend to suggest that obesity is a more relevant etiology of FL than alcohol [34, 53, 54]. In a large cohort of 1,666 French alcoholics, being overweight for at least 10 years was the only independent risk factor of steatosis, again suggesting the possible potentiation of ethanol and excess weight [55]. It is

Table 1. Etiology of fatty liver [4, ll~14, 17, 32, 5~59, 72]

Common associations
Obesity
Hypertension
Adult-type diabetes mellitus
Hyperlipidemia
Alcohol abuse
Less common etiology
Genetic or congenital
Abeta- and hypobetalipoproteinemia
Wilson's disease
Congenital portosystemic venous shunt
Environmental
Viral (HCV, HIV, yellow fever)
Starvation or protein malnutrition
Occupational hazard (e.g. solvents, metals)
Secondary to extra hepatic conditions
Altered endocrine function (thyroid/surrenal)
Chronic heart failure
Chronic intestinal conditions (celiac disease, inflammatory bowel disease, Whipple's disease)
Tuberculosis
Cancer
Pregnancy
Iatrogenic
Hepatotoxicity due to drugs (e.g. antiviral agents, aspirin, sodium valproate, amiodarone, perhexilene maleate, tetracycline antibiotics, amineptine, pirprophene. vitamin A, hormones, cancer chemotherapy)
Total parenteral nutrition
Jejunoileal bypass

presently unknown whether such data specifically reflect the pattern of alcohol drinking in southern Europe (preferentially daily drinking of wine as opposed to weekend spirits). As shown in table 1, there are basically 2 groups of conditions that are associated with FL: the most common of them fall within the domain of the metabolic syndrome (obesity, type-Il diabetes, hyperlipidemia, hypertension) [4, 11-14, 32, 56-59]. An uncommon etiology should be suspected in teetotallers who do not fit in the stereotype of hyperinsulinism.

Pathogenesis of FL

The following steps affecting hepatic availability, consumption and export capacity of fatty acids are acknowledged as being critical in the development of FL [11, 13, 60]: (a) increased availability of fatty acids to the liver (due to increased delivery to the liver and/or increased synthesis in the liver) can be seen in obesity. starvation, dietary indiscretion, total parenteral nutrition (b) decreased mitochondrial β-oxidation of fatty acids is observed in carnitine deficiency and mitochondrial dysfunction, and (c) reduced capacity to export triglycerides (due to decreased incorporation of triglycerides into VLDL and/or to impaired export of VLDL from the hepatocyte) is seen in a- and hypobetalipoproteinemia. impaired cholesterol esterification, choline deficiency and protein malnutrition.

To forward our understanding of the clinical significance of FL we addressed the issue of clinico-metabolic correlations of an ultrasonographic 'bright liver', namely the so-called 'bright liver syndrome' [14, 27, 34, 61, 62]. In short, we postulate the existence of 2 different types of FL: the 'ordinary type' and the rare etiologies. The former's independent predictors (univariate analysis) are BMI, age, total cholesterol, triglycerides, apolipoprotein (apo) B, albumin and HDL cholesterol. The last 2 variables dropped out when logistic regression analysis was applied. It seems likely that the pathogenesis of FL in these patients involves failure in the hepatocyte's capacity to export lipids into the bloodstream due to hyperlipidemia (lipidic overcharge in subjects with apo B in the normal-elevated range). The occurrence of otherwise unexplained FL in hypolipidemic patients should raise the suspicion of a rare condition such as familial heterozygous hypobetalipoproteinemia [63]. Contrasting with the former category, the pathogenesis of the latter type of FL involves primary failure of the hepatocytes' capacity to export triglycerides into the bloodstream (genetic hypobetalipoproteinemia with apo B in the subnormal range). It should be noted that, in a recently observed case, such a condition evolved into extra hepatic primary malignancy and hepatocellular carcinoma in a non-cirrhotic liver [64].

FL and HCV Infection

Since the early 1990s it has been reported that fatty changes are present in a significant percentage of liver biopsies of HCV-infected patients [65, 66] and, therefore. it has been suggested that steatosis may represent the expression of a likely HCV-induced 'cytopathic' change [66]. Though, when controlled for diabetes, obesity, hyperlipidemia and alcohol, HCV infection turned out to be an irrelevant risk factor for FL in an Italian study [67]. In our series there was no statistical difference in the prevalence of anti-HCV positivity in patients with FL vs. controls [14].

However, in a study from Taiwan the prevalence of anti-HCV positivity in patients with FL is 5.4%, a proportion allegedly slightly higher than in the general population [68]. Furthermore, HCV core has been shown to be cytoplasmic and localized on the endoplasmic reticulum and on lipid droplets [69]. It is speculated that steatosis could arise, at least in part, from direct effects of HCV proteins on lipid metabolism [69]. The suggested relationship between the expression of the HCV core protein and cellular lipid metabolism is also based on additional lines of evidence. For instance, the levels of apolipoprotein Al and high-density lipoprotein are independent predictive factors for response to interferon-α in patients with chronic hepatitis C [70]. Furthermore, in multivariate analysis HCV infection is independently related to a significantly lower serum cholesterol level in patients with chronic hepatitis [71]. Recently Czaja et al. [72] concluded that fat deposition in chronic hepatitis C is mainly a viral effect that is potentiated by host-related metabolic factors.

The relationship, if any, between the biology of HCV and hepatic lipid metabolism deserves further assessment.

FL and the Metabolic Syndrome

First proposed by Reaven [73] in 1988, the metabolic syndrome is an intriguing entity postulating the concurrence, in the same individual, of common conditions (such as hypertriglyceridemia, low HDL cholesterolemia, hypertension, diabetes mellitus and obesity) to share a pathophysiologic basis in insulin resistance [74 - 78]. This is defined by a biological suboptimal response to a given insulin concentration and is widely acknowledged as a major

risk factor for premature atherosclerosis [79]. Given the systemic nature of the metabolic syndrome and the pivotal role of the liver in physiological and deranged metabolic processes, it would theoretically appear unlikely that the liver is not involved in the insulin resistance syndrome. As a matter of fact, however, the precise role of the liver, if any, in the metabolic syndrome is presently unknown. On the grounds of the confounding influence of obesity and/or hypertriglyceridemia on insulin resistance, FL (of the ordinary type) tends not to be included as a component of the insulin resistance syndrome [Ferrannini E, personal commun., 14]. Nevertheless, a few reports have envisaged a possible role for FL in the metabolic syndrome highlighting areas of overlapping and similarities between these two conditions [32, 34, 42, 80, 81]. Such similarities can be summarized as follows: both FL and the insulin resistance syndrome are common in the general (particularly in the elderly) population; both are associated with central (as opposed to gynoid) body fat distribution; they share common metabolic derangements such as hyperinsulinemia and its correlates (hypertension, obesity, hyperlipidemia and NIDDM); both may be associated with coronary heart disease and are amenable to treatment with restricted diet and physical training; the animal model for the experimental induction of atherosclerosis also develops FL such as shown in table 2 [14, 82, 83]. According to preliminary data, it is also likely that the same biological mediators (namely tumor necrosis factor-α and ferritin) are involved both in FL or its inflammatory counterpart [84] and in the metabolic syndrome [85].

In my perception the relationship between FL and insulin is twofold. On the one hand, portal vein hyperinsulinism is, in most conditions, a prerequisite for the development of FL [13, 46, 86); on the other hand, once FL is established, it is a reason for further insulin resistance via decreased insulin clearance or pancreatic insulin hypersecretion [14, 46, 87-90], so leading to a vicious circle. Ueno et al. [83] recently reported that in obese subjects following adequate life-style alterations, FL is a reversible condition. It is reasonable to postulate that caloric restrictions and increased energy expenditure have led their cases (but not the controls) to an increased insulin sensitivity and therefore to reduced insulin plasma levels. Therefore, in addition to its therapeutic implications, the article by Ueno et al. [83] is further, albeit indirect, evidence that FL is more a systemic than a liver-restricted condition. Their report highlights the similarity with the metabolic syndrome, which is itself amenable to exercise treatment [91]. Also the data of Hsieh et al. [92] show that the frequency of physical activity is inversely related to the prevalence of FL (and of coronary risk factors) in a sample of 3,331 adult Japanese men with normal BMI [92]. Patients with central-type body fat distribution may have FL even though they have normal BMI [Hsieh SD, personal commun.] and so they could be considered 'metabolically obese, normal-weight' individuals [93].

Future research should address the mechanisms through which diet and aerobic exercise reverse FL in obese subjects. If reversal of insulin resistance is involved this will provide the rationale for more pathogenic treatment such as discussed later in this review.

Table 2. Similarities between fatty liver and the metabolic syndrome

	Fatty liver	Metabolic syndrome
Epidemiologic		
Common in general population	up to 25% in adults	epidemic in elderly people
Prevalence raising with age	yes	strongly age-related
Prevalence of the male sex	both in children and in adults	yes
Anthropometric		
Association with central adiposity	abdominal fat is an independent predictive factor	visceral fat is correlated with insulin and lipid metabolism alterations
Metabolic		
Hyperinsulinemia	documented	pathogenetic mainstay
Associations with		
Hypertension	both in drinkers and in nondrinkers	yes
Obesity	yes	yes
Hypertriglyceridemia	yes	yes

Low HDL cholesterol	preliminary evidence	yes
Clinical		
Multisystemic condition	yes	yes
Accelerated atherogenesis and its complications	circumstantial evidence	yes
Response to a restricted diet and/or physical exercise	in obese people	yes
Experimental pathology		
Animal models	atherogenic diet induces fatty liver in rats	3 models of hypertension in rats resistance and hypertriglyceridemia

Modified from Lonardo [14].

NASH

This syndrome was first described by Ludwig et al. [94] in 1980 as a histological alcohol-like liver damage affecting middle-aged women with obesity-related conditions in the absence of a history of excessive alcohol drinking. According to modern criteria [9, 13] NASH is diagnosed in the presence of the following.

(1) A liver biopsy specimen that shows moderate-to-gross macrovesicular fatty degeneration with inflammation (lobular or portal) with or without Mallory hyaline bodies, fibrosis, or cirrhosis. Substantial inflammation of portal triads and bile duct injury, however, must be absent.

(2) Convincing evidence of negligible alcohol consumption (<20 g ethanol/day) that includes a detailed history taken by 3 physicians independently and interrogation of family members and local medical practitioners. Results of random blood assays for the estimation of ethanol levels should be negative. If done, assays for the presence in serum of desialylated transferrin, a marker of alcohol consumption, should also be negative.

(3) Absence of antibodies to HCV, of evidence of ongoing HBV infection, of markers of autoimmunity (anti-nuclear, anti-smooth muscle, anti-LKM antibodies), and of Wilson's disease.

Since the I980s clinical syndromes accounting for large numbers of patients with chronic liver injury, have now been better defined by the identification of specific causes, such as HCV infection and autoimmune hepatitis [13]. Paradoxical though it may appear, as a result of this process, the clinical spectrum of NASH is currently broader than was initially recognized. Bacon et al [60] first showed that NASH may occur in men also in the absence of diabetes and/or hyperlipidemia. Also Italian contributions confirm this shift in the clinical spectrum *[95]* and point to the presence of features typical of the metabolic syndrome in subjects with NASH [27]. Covert alcohol abuse is a recognized pitfall in the diagnosis of NASH in adults. Such a pitfall, however, is nonexistent in children. It is of interest, therefore, that NASH exists predominantly or exclusively in obese peripubertal children, where it represents a frequent reason for liver biopsy [96].

Although it is considered a relatively benign nonprogressive condition, FL serves as a necessary precursor lesion to NASH: this suggests that a FL is more vulnerable to insults than a normal liver [13]. The usually slow progression of FL to NASH is held to be the precursor of cryptogenic cirrhosis. In one such case of NASH cirrhosis undergoing liver transplantation, the disease was complicated by hepatocellular carcinoma [15). Subfulminant NASH has become exceedingly rare because many clinicians are now aware of the hazards of sudden weight loss, particularly in morbid obesity [15]. Recent views propose NASH as a tale of two 'hits'. The first 'hit' being steatosis and the second one a source of free radicals capable of inducing oxidative stress [17). Accordingly one of the most critical issues to be ascertained will be the magnitude of the risk and the precise pathogenesis involved in the progression of FL to its inflammatory counterpart NASH. Such factors include obesity, viral infections, alcohol use, uncontrolled diabetes, hyperinsulinemia, hypertriglyceridemia, protein malnutrition, exposure to drugs, herbal or chemical hepatotoxins [13]. Since some of these are acknowledged risk factors for FL itself it remains to be ascertained whether a threshold effect exists in the development of NASH or a proportionality between the degree of such conditions (e.g. obesity, hyperinsulinemia, etc.) and that of liver inflammatory changes.

Approach to the Patient with FL and NASH

Diagnosis

FL is usually revealed through altered liver function tests in the asymptomatic subject. The most common laboratory alteration in patients with a FL will be an isolated slight GPT increase or GPT alteration> GOT. In our series there was no statistically significant difference in the mean values of transaminases between cases with a 'bright liver' and control subjects who did not have such an ultrasonographic appearance [34]. Significant transaminase alterations should prompt the search for necroinflammatory agents (viruses, alcohol, autoimmunity, metabolic disease, NASH, hepatotoxins). GGT, and AP alterations are often observed [13].

The etiology of FL will usually be obvious in the single patient following history and physical examination. It may remain elusive in individual cases that should therefore be further investigated for covert alcohol abuse, exposure to hepatoxins, altered glucose metabolism or thyroid function [97]. Otherwise unexplained low plasma levels of triglycerides and cholesterol are a clue to the diagnosis of hypobetalipoproteinemia [63].

FL will evolve into NASH in a subset of patients. Whenever NASH is suspected on the grounds of compatible anagraphic and clinic laboratory data, the decision for liver biopsy should be done early. Indeed, the histological features span a wide spectrum from uncomplicated FL (not NASH in a strict sense) to a slowly progressive FL with inflammation and fibrosis, to steatohepatitis with submassive hepatic necrosis, which may run a subfulminant fatal course [15, 98]. No clinical, laboratory, or histological features can predict progression or distinguish patients with or without worsening liver disease [9]. It has been estimated that 54% of patients with NASH remain unchanged, 43% have histological progression during a 1- to 7-year period and 3% improve [9]. After a similar follow-up period, the rate of progression to cirrhosis of patients with NASH would be 8-17% compared with 38-50% of patients with alcoholic hepatitis
[9].

Recognition of Related Conditions

High-fat diets used to produce atherosclerotic lesions in mice cause accumulation of fat in the liver and gallstone formation [99]. Such an FL-atherosclerosis-gallstone association was found to affect approximately 15% of patients in a preliminary report from our group [27]. In a survey involving 2,584 healthy residents in Japan, it was shown that FL was a strong factor associated with gallstone disease [100].

In addition, several authors have highlighted the relationship between risk factors for premature atherosclerosis and/or its complications and FL [5, 27, 31, 32, 34, 42, 80, 92]. The finding of hypercoagulability in patients with FL is also relevant to this issue. Alterations typical of FL (hypertriglyceridemia and hyperinsulinism) are held responsible for altered plasma hemostatic factors, namely increased plasminogen-activated inhibitor, factor VII clotting activity and decreased tissue-type plasminogen activator [80]. Taken together, these alterations in FL could theoretically contribute to the risk of mortality and morbidity for coronary artery disease similar to that seen in overweight and hyperlipidemic subjects [101, 102]. The relationship, if any, between hemostatic alterations and the decrease of elcosapentaenoic acid found in FL of diabetic subjects [103] deserves investigation. If these observations are further confirmed, it could be wise to screen patients with FL for gallstones and atheroclerosis.

Treatment

There is no single treatment of FL and NASH. Different subsets of patients are likely to be responsive to different options.

Management of FL includes ascertainment and control of the predisposing etiology. Although difficult to achieve [15], diet and exercising are among the best documented options for FL in obese people [83]. Whether or not an individual must achieve near ideal body weight to attain an effect has not been established [13]. Sudden weight loss, however, is hazardous owing to the risk of subfulminant NASH [15].

Glycemic control is an important consideration in diabetic patients with ongoing liver injury [104]. In patients with prolonged total parenteral nutrition specific supplementation with polymixin, or choline has been advocated [13].

It is of interest that a diminution of eicosapentaenoic acid in hepatic triglycerides is associated with lipid accumulation in the liver cells of diabetic subjects [103]; and conversely that feeding a structured emulsion containing fish oil prevents sepsis in the FL of rats [105]. We are not aware of any trials involving co-3 fatty acids in the treatment of FL in humans.

NASH associated with altered lipid metabolism will typically be responsive to ursodeoxycholic acid and not to clofibrate [106]. The significance of this finding could be that once triggered, the necroinflammatory liver response is ongoing even following removal of the offending hypertriglyceridemia. In cases where insulin resistance is shown to be associated with FL it would appear logical to use insulin-action-enhancing drugs such as thiazolidinediones [107-110]. Trials of nonhepatotoxic insulin-enhancing drugs in FL are therefore needed.

Unsettled Issues

Iron Metabolism

Moirand et al. [111] reported on a seemingly new syndrome of liver iron overload with normal transferrin saturation. Their series consist of 65 cases, 95% of them having one or more of the following conditions: obesity; hyperlipidemia; abnormal glucose metabolism, or hypertension. The authors argue that it is tempting to add iron excess to the insulin resistance syndrome [111]. It is unknown whether their cases showed (non-alcoholic) FL/NASH and what, if any, the nature of the relationship is between FL and hepatic iron overload in nondrinkers with the metabolic syndrome. However, a recent paper described serum ferritin as a component of the insulin resistance syndrome [112]. It is of interest that abnormal iron metabolism was reported by Bacon et al. [60] in 54'/i of 31 patients with NASH. Four patients in their series also had elevated hepatic iron concentrations but none had a hepatic iron index in the range of homozygous hereditary hemochromatosis [60]. The authors conclude that the mild iron storage in their patients was likely to result from the underlying necroinflammatory condition with release of tissue iron and ferritin into the blood, similar to what is seen in chronic viral hepatitis [60, 113].

Cancer

Hayashi et al. [114] recently reported that patients with FL tend to have a reduced rate of liver metastasis from colorectal cancer and, when compared to patients without FL of the same Dukes class, have longer survivals [114]. The first finding can be accounted for by FL's hypothetical 'local' protective effect against the various steps that ate deemed necessary for a metastasis to take place and to thrive in the FL. However, the second observation obviously implies a 'systemic' activity through which the presence of FL is associated with a prolonged survival. whatever their Dukes classification. If we assume that patients with FL are in a better nutritional status than the controls without FL [34], we should probably address the relationship between nutritional status and cancer. Such a relationship is both close and complex and the serum cholesterol level could be one of the various factors involved. Indeed some cholesterol-lowering drugs are carcinogenetic agents in the animal [115-117]. In addition 2 epidemiologic studies [116, 117] reported an excess non-cardiovascular mortality (including cancer mortality) in the general population with low-cholesterol levels. While the overall interpretation of available epidemiologic studies remains controversial [118, 119], it is of interest that in our personal unselected series [34] the prevalence of digestive tract cancer was 2/92 (2.17%) in patients with FL and 27/291(9.27%) in patients without FL ($p<0.05$).

Conclusions

While generally reversible and nonprogressive, FL is not a paraphysiological condition but it is the most common of liver diseases. It renders the liver less responsive to interferon treatment in chronic hepatitis C and less vital as a graft for transplantation. FL is a complex marker of the general health, nutrition, and metabolic status of

patients. Its clinical significance is connected with the hyperinsulinemic state by which it is usually generated. Hence, the ultrasonographic diagnosis of FL could be a useful clinical marker of the metabolic syndrome.

The link between the biology of HCV, iron metabolism and FL should be addressed. Prospective studies should also quantify the rate and the factors involved in the progression of FL to NASH and the relationship, if any, between FL, atherosclerosis, and cancer.

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