

# Clinical Aspects of Fatty Liver Disease at a Tertiary Medical Center in Bogotá from 2009 to 2013

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## Abstract

**Introduction:** Nonalcoholic fatty liver disease (NAFLD), or simply fatty liver, is a major cause of hepatic disease worldwide: its prevalence is approximately 30% in adults. In our environment the clinical characteristics of these patients are not known. **Methodology:** This was a descriptive and retrospective review of medical records from January 1, 2009 to May 31, 2013 of 266 patients diagnosed with fatty liver disease in the hepatology outpatient service at the Clínica Universitaria Colombia. **Results:** Of the 266 patients included in this study, 52.3 % were men and 47.7 % were women. The mean age at diagnosis was 51.6 years. The most frequently found antecedent of importance to the development of NAFLD was dyslipidemia which was found in 113 patients (42.5 %). 127 (47.8%) patients had nonalcoholic steatohepatitis (NASH), and 108 (40.6%) had simple steatosis. Thirty-one patients (11.6%) had cirrhosis which was classified according to CHILD scale: 22 (70.9%) were classified as A, 8 (25.8%) were classified as B, and one (3.2 %) was classified as C. Liver biopsies were taken from 31 patients (11.6%). **Conclusions:** Elements of metabolic syndrome, especially dyslipidemia, are often identified in our patients with FLD. Since most of these patients are in early stages of the disease with a low percentage of cirrhotic patients, it may be that the disease progresses more slowly in our environment than elsewhere. This is a hypothesis that should be validated in other studies.

## Keywords

Fatty liver, risk factors, NASH, NAFLD, hepatic steatosis, liver cirrhosis, fibrosis.

## INTRODUCTION AND DEFINITION

Fatty liver or non-alcoholic fatty liver disease (NAFLD) was originally described in the eighties by Ludwig (1). Its asymptomatic form is frequently found when a blood test reports elevated transaminases, but it is also one of the main causes of liver disease worldwide (2, 4).

### Definition

From a histological point of view the term fatty liver or NAFLD encompasses a spectrum ranging from simple fatty steatosis (benign condition) to fatty liver with transaminase elevation or NASH (nonalcoholic steatohepatitis)

in which steatosis is accompanied by the phenomenon of ballooning and inflammation. It also includes progressive fibrosis which can lead to cirrhosis with its inherent complications (2-6).

Fatty liver is defined as an ultrasound finding of hepatic steatosis with or without inflammation and/or a finding of fibrosis in the absence of the secondary causes listed below (5-6):

- Alcohol consumption greater than 20 g/day for men and 10g/day for women
- Use of hepatotoxic drugs such as glucocorticosteroids, isoniazid, methotrexate, amiodarone, and tamoxifen within the 6 months prior to the study
- Positive serology for hepatitis B or C
- Ferritin concentration > 1000 mg/L.

- Anti smooth muscle antibodies serum titers > 1:160 or anti mitochondrial antibodies > 1:140

## PREVALENCE

Worldwide the prevalence of NAFLD in adults has been estimated to be between 20% and 30%. Prevalence varies according to the population studied and the method used for diagnosis (ultrasonography, liver biopsy or elevated liver enzymes) (7-10). It is much more common in industrialized countries where most patients are diagnosed between the ages of 40 and 50 years, although it is being diagnosed more and more frequently in children (11).

NAFLD is associated with risk factors such as obesity and alcoholism in 30% to 100 % of cases, type 2 diabetes mellitus in 10% to 75 % of cases, dyslipidemia in 90% of cases, and metabolic syndrome (MS) in 25 % of cases. Fatty liver is the hepatic manifestation of this syndrome: 90% of patients with NAFLD have at least one characteristic of metabolic syndrome, and a third have all of the criteria (3, 4-6). It is important to note that NAFLD can occur in patients who are not overweight (12). and that fatty liver is associated with an increased risk of death from any cause. It is a predictor of future cardiovascular events regardless of the person's age, gender, LDL levels, smoking and metabolic syndrome (13-16). Several studies have demonstrated a link between fatty liver and the onset of diabetes regardless of the presence of conventional risk factors such as obesity, insulin resistance and metabolic syndrome. This suggests that fatty liver may have a causal relationship with the genesis of diabetes which is probably associated with insulin resistance in the liver (17-20). This entity's ethnic distribution shows that Hispanics are most affected (58 %) followed by Caucasians (44 %) and finally African Americans (35 %) (9, 13, 14). Recent data shows increasing incidence parallel to the worldwide increase in obesity and diabetes which are both elements of metabolic syndrome (9, 13, 17).

## NATURAL HISTORY

We know that simple steatosis may progress to NASH and then to cirrhosis. The risk for progression to cirrhosis from simple steatosis after 10 to 20 years is 0% to 4 %, but 5% to 10% of patients with NASH can develop cirrhosis in approximately 5 years (2, 4, 5, 6, 13, 21, 22, 40). A study by Rahman concludes that approximately 20 % of cases progress from simple fatty steatosis to NASH, 20% of these progress to cirrhosis, and some develop into hepatocellular carcinoma (23). Hepatocellular carcinoma has even been described in patients with NASH but without cirrhosis

which establishes that fatty liver is a risk factor for this tumor (23, 24).

## PATHOGENESIS

Although the pathogenesis of fatty liver has not been fully elucidated, the best supported theory involves a sequence of two main events.

1. Insulin resistance and a progressive accumulation of fatty acids in hepatocytes. Lipids accumulating as glycerolipids, glycerophospholipids and sterols
2. Alterations of the mitochondrial function of the hepatocytes which generate accumulation of the aforementioned fatty acids and results in an inability to maintain the B- oxidation, reduction in VLDL secretion, increased oxidative stress, lipid peroxidation, apoptosis, increased inflammatory response mediated by the release of tumor necrosis factor (TNF) involved in ballooning, fibrosis and Mallory's hyaline (3-6, 25-26). Dysfunction of insulin signaling responsible for lipid peroxidation and oxidative stress which causes inflammation and apoptosis through transcription factors and kinase-dependent signaling pathways (27-29).

## CLINICAL AND LABORATORY FINDINGS

Most patients are asymptomatic although isolated cases have fatigue, weakness and pain in the right upper quadrant. In advanced stages NAFLD is associated with clinical complications of portal hypertension and cirrhosis (2, 4, 6, 13).

Elevation of transaminases is usually mild to moderate, but normal levels do not exclude a diagnosis of NAFLD. Elevation of ALT is clinically relevant as it has been proven to be a predictor of the genesis of insulin resistance, diabetes mellitus, cardiovascular disease and metabolic syndrome in patients with fatty livers (30, 40). Other relevant laboratory findings include alkaline phosphatase (ALP) three times or more than its normal value and elevated ferritin (31). Albumin, bilirubin and clotting times are only altered during cirrhosis (6, 13, 32-34).

## LIVER BIOPSIES

A liver biopsy is considered to be the best tool for confirming a diagnosis of NAFLD, for assessing inflammation and fibrosis, and for providing information about prognosis (6, 10, 32). Some authors suggest that liver biopsies should even be performed on patients in high-risk groups such as obese and diabetic patients, those over the age of 45 years, and patients with AST/ALT ratio > 1, insulin resistance, hypertension and/or hypertriglyceridemia (8, 22, 35, 36). Given

the limitations of liver biopsies and controversies about their use, various biomarkers have been studied as measures of the degree of fibrosis for diagnosis of fatty liver. These include alpha-fetoprotein, ALT, GGT, non-esterified fatty acids, and altered glucose levels. None of these provide the same level of information about a patient's prognosis as a liver biopsy which encourages continued systematic use of biopsies (32, 33, 35, 36). A histological finding of fatty liver disease on the basis of fat infiltration can be classified as mild when infiltration into hepatocytes is between 5% and 33 %, moderate when it is between 34% and 66 %, and severe when it is over 66 %. Other relevant histological findings include lobular inflammation, ballooning and fibrosis (36-39).

## TREATMENT

Treatment is based on modification of lifestyle and risk factors including encouragement of exercise, weight loss, a healthy low-calorie diet, and continuous monitoring for early detection of fibrosis and/or cirrhosis. In addition, effective therapies with minimal side effects have been developed to control the progression of the disease. These include administration of antioxidants such as vitamins E and C which have been shown to reverse high levels of transaminases, cholesterol and hyaluronic acid although they do not reverse elevated levels of cytokines and inflammation does not improve (4, 6, 18, 41). Weight loss, even when it is the sole factor, is associated with histological improvement (41, 42). The Greek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) demonstrated that lipid-lowering agents such as statins can benefit patients with NAFLD as well as reducing cardiovascular risks (43).

Other interventions such as administration of angiotensin II receptor (ARB ) inhibitors, ursodeoxycholic acid, and L-carnitine which carries lipids in the mitochondria can also be useful. Peripheral insulin sensitizers such as biguanides and thiazolidenediones have been shown to normalize transaminase levels, inflammatory response and hepatic steatosis. Probiotics reduce the intestinal bacterial translocation and decrease the inflammatory response in the liver (44-50). Surgical interventions such as the specific combination of restrictive and malabsorptive bariatric surgery using the technique of Roux-en-Y gastric bypass (RYGBP) and a modified Fobi- Capella technique have shown benefits and improvements of inflammation demonstrated by liver biopsies (51).

Clinical characteristics of patients diagnosed with fatty liver disease and their relation to metabolic diseases were unknown in our environment and we did not have proper statistics. Consequently, the epidemiological data presented here is based on international literature, but this study

describes the clinical features of fatty liver in a series of 266 patients at the Clinica Universitaria Colombia.

## OBJECTIVE

The objective of this study is to describe the clinical characteristics of 266 patients diagnosed with fatty liver disease in the hepatology service at the Clinica Universitaria Colombia in Bogotá, Colombia during the study period.

## METHODOLOGY

All medical records of patients diagnosed with fatty liver disease attending the outpatient department of hepatology at the Clinica Universitaria Colombia during the period from January 1, 2009 to May 31, 2013 were reviewed. A descriptive analysis of each of the variables studied was made. For continuous variables means and standard deviations were estimated, for categorical variables proportions were estimated and presented in text, tables and/or graphs employing EXCEL and SPSS.

Design, population and definition of variables: A descriptive, retrospective study with review of the medical records of adult patients diagnosed with fatty liver who attended the department of hepatology of Clinica Universitaria Colombia. The study only included patients with a fatty liver diagnosis based on ultrasound findings and/or increased transaminases and/or liver biopsy. Data from the physical examination and laboratory test, demographic characteristics, reason for patient referral, background information regarding the clinical history were pooled and tabulated.

## Ethical Considerations

This is a retrospective study using data from the medical records of patients. No intervention or intentional modification of the biological, physiological, psychological or social variables of individuals was performed. It was conducted according to the principles stated in the Eighteenth World Medical Assembly (Helsinki, 1964). The identification data of the patients and their diagnoses were not entered in the publications and the investigators handled all medical history data with complete confidentiality.

## RESULTS

The average age of the 266 patients diagnosed with fatty liver disease was 51.6 years. The age range was 13 to 86 years. Age distribution was as follows: 13 to 29 years - 15 patients, 30 to 45 years - 61 patients, 46 to 65 - 126 patients, and 66 to 86 years - 38 patients (Figure 1). There were 139 male patients

(52.3 %) and 127 female patients (47.7%) The main reasons for referral to the hepatology department were diagnoses of fatty liver disease (129 patients, 48.5%), elevated transaminases (59 patients, 22.2%), cirrhosis (17 patients, 6.4%), jaundice (9 patients 3.4%), variceal bleeding (4 patients, 1.5%), liver masses (3 patients, 1.1%) and other reasons (45 patients, 16.9%) (Table 1). Laboratory parameters during patient admission are presented in Table 2. Average transaminase levels should be highlighted. Average ALT was 65 U/L and average AST was 46 U/L while the highest ALT level was 290 U/L and the highest AST was 272 U/L. Cholesterol and triglycerides had mean levels of 208 and 196 with maximum values of 373 and 640 mg/dl respectively. The average fasting blood glucose value was 108.2 mg/dl while the highest level was 369 mg/dl. Demographic characteristics of patients are presented in Table 1.

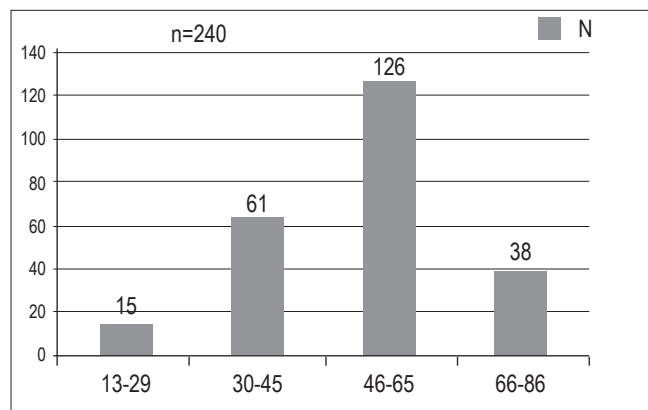
Patients' medical histories related to fatty liver disease and metabolic syndrome showed dyslipidemia in 113 patients (42.5%), hypertension in 56 (21.1%), diabetes mellitus in 46 (16 %), obesity in 38 (14.3%), and coronary artery disease in 4 (1.5%) (Figure 2). Some patients had more than 1 factor. The average Body Mass Index (BMI), a measure of whether and how much patients are overweight and/or obese, was 27kg/m<sup>2</sup>. The highest BMI was 45 kg/m<sup>2</sup> (Figure 2).

**Table 1.** Distribution of demographic variables of patients diagnosed with NAFLD and reasons for referral to hepatology

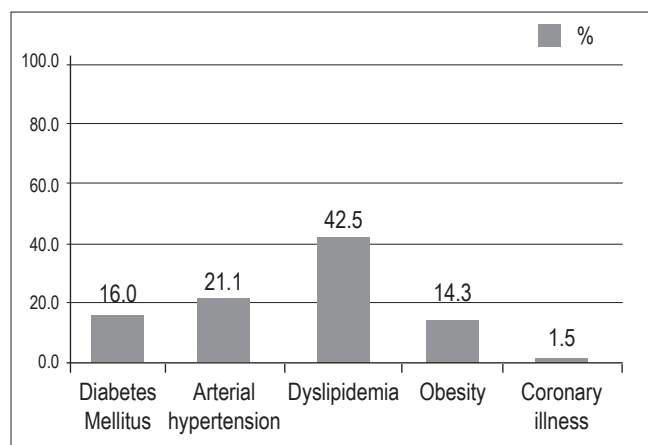
Variables	n	%
Gender		
Male	139	52,3
Female	127	47,7
Reason for referral to hepatology		
Referred because of diagnosis of NAFLD	129	48,5
Cirrhosis	17	6,4
Jaundice	9	3,4
Variceal Bleeding	4	1,5
Liver mass	3	1,1
Elevated transaminase	59	22,2
Other	45	16,9

Of 266 patients diagnosed with NAFLD, 127 presented NASH (47.8 %), 108 simple steatosis (40.6%) and 31 cirrhosis (11.6%). The latter were classified according to the CHILD scale: 22 classified as A (70.9%), 8 classified as B (25.8%) and 1 classified as C (3.2 %).

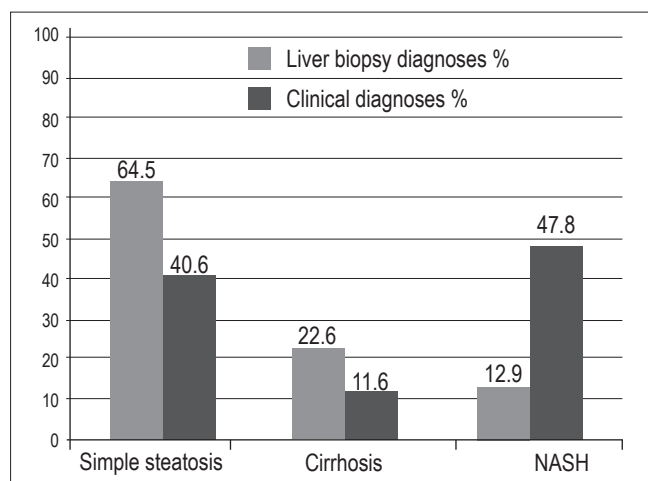
Liver Biopsies were performed on 31 patients (11.6%), of whom 20 (64.5%) were diagnosed with non-significant fatty alterations or simple steatosis (<5 %), 4 with NASH (12.9%), and 7 patients with cirrhosis (22.6%). All data is presented in Figure 3.



**Figure 1.** Age distribution of patients diagnosed with NAFLD



**Figure 2.** Patients' History related to metabolic and cardiovascular diseases and NAFLD



**Figure 3.** Distribution of clinical diagnoses and liver biopsy diagnoses

## DISCUSSION

The average age of all patients was 51.3 years and the age range in which NAFLD was most commonly diagnosed

**Table 2.** Laboratory results of patients diagnosed with NAFLD plus normal reference values

Variables	Minimum	Maximum	Mean	Median	25 <sup>th</sup> percentile	75 <sup>th</sup> percentile
ALT (U/L) VN= up to 41	11	290	65,021	46,5	36	83
AST (U/L) VN= up to 38	16	272	46,5	35	26	54
Total Bilirubin mg/dl (VN up to 1)	0,2	4	0,82	0,68	0,5	1
Alkaline Phosphatase (U/L)	11	351	102,8	91	71,7	117,2
GGT	9	981	106,1	55	29	109
Total Cholesterol mg/dl Optimum: Less than 200 mg/dl Mid High: 200 - 239 mg/dl High: More than or equal to 240 mg/dl	115	373	208,8	201	177	237
Triglycerides mg/dl Normal: Less than 150 mg/dl Medium High: 150 - 199 mg/dl High: 200 - 499 mg/dl Very high: Greater than or equal to 500 mg/dl	45	640	196,3	165,5	123	233,7
TSHuU/ml	0,01	33	3,62	2,7	1,7	4,23
Blood sugar mg/dl (VN=70-100)	79	369	108,2	97	90	110
Leukocytes /uL (VN = 4500-11300)	2750	18 640	6554	6370	5300	7390
Platelets /uL VN= 150,000-450,000	24 000	454 000	243 713	241 000	198 000	287 000

was 46 to 65 years. This is consistent with international studies in which the average age of diagnosis is between 40 and 50. The distribution by gender behaved similarly: NAFLD diagnoses were more common among men (52.3%) than among women (47.7 %) (5, 6, 10). Dyslipidemia was found in 42.5% of the patients, hypertension in 21.1 %, diabetes in 16%, obesity in 14.3% and coronary heart disease in 1.5% of the patients. All of these are factors in metabolic syndrome consistent with the link in the literature between NAFLD and metabolic diseases (6-25, 26). Only 1.5 % of patients had a history of coronary heart disease. Transaminase and lipid values found in this study agree with those reported in the international literature (5, 30, 40).

Cirrhosis was clinically diagnosed in 31 patients (11.6%). Most of them were classified Child A. Of these 31 select patients, cirrhosis was confirmed histologically in 22.6%. Although this data might create an idea that the natural history of NAFLD is relatively benign, it should be remembered that it currently affects up to 30% of the world's population, and we should be alert to the possible of a late diagnosis. Measures must be taken to diagnose this condition early and to prevent it (4, 6, 13). As a final note, it should be pointed out that none of the patients were diagnosed with hepatocellular carcinoma despite the risk in this group of patients. Patients with cirrhotic fatty liver disease should be screened for this condition every 6 months.

In conclusion, a high frequency of factors involved in metabolic syndrome was found in our patients with NAFLD. Prospective studies need to be done in Colombia to provide guidelines for early detection and intervention against this disease.

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