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# Prevalence and Risk Factors of Fatty Liver among Adults

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## ABSTRACT

**Background:** Non-alcoholic fatty liver disease (NAFLD) is a heterogeneous condition that contains steatosis and non-alcoholic steatohepatitis (NASH), in the nonexistence of significant alcohol consumption, reaching 30% of the populace. The most common risk features are: age, ethnicity, gender, obesity, drugs, diabetes mellitus (DM), insulin resistance (IR), predisposition, metabolic syndrome (MS), and polycystic ovary syndrome.

**Materials and Methods:** Patients with non-alcoholic fatty liver disease were evaluated, with medical and epidemiological data collected after informed consent at King Abdulaziz Hospital.

**Results:** Of the 124 patients evaluated, 75.8% were women, and 88 were aged between 49 and 70 years and had no symptoms. Ultrasonography results showed steatosis in 84%. NASH was diagnosed in 75 patients of the sample. 42 patients underwent liver biopsy, of which 36% had cirrhosis, 1 had liver cancer, and 1 pure steatosis (5% each). Risk factors were found in 70% of patients with metabolic syndrome, 87% with increased waist circumference, 63% with dyslipidemia, 61% (n=76) with high blood pressure (HBP), 28% with DM, 52% physically inactive, and 44% with insulin resistance (IR) (HOMA> 3.5). There was an association between IR and NASH (p=0.011), IR and obesity (p=0.031), IR and MS (p=0.007), and MS and steatosis on medical ultrasound (USG) (p=0.012).

**Conclusion:** The results indicated that the most frequent risk factors were MS and its variables: increased waist circumference, dyslipidemia and HBP. This highlights the significance of metabolic control in non-alcoholic fatty liver disease and confirms its role as the hepatic component of metabolic syndrome.

**Keywords:** fatty liver, obesity, diabetes mellitus.

## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) represents the spectrum of a heterogeneous condition that includes steatosis and non-alcoholic steatohepatitis (NASH), in the nonexistence of significant consumption of alcohol [(1)], which might progress into cirrhosis. Histologically, fatty liver disease is categorized predominantly by macrovesicular steatosis and NASH, and is familiar when, in association to the accumulation of fat. One or more of the following features were found: lobular inflammation, hepatocellular ballooning, Mallory's hyaline bodies and zone 3 perisinusoidal fibrosis [(2)]. Even though NAFLD can persist stable and stationary for long periods of time, the condition can progress to advanced stages of cirrhosis and liver cancer [(3-5)]. The predisposing factors to the progressive course of NAFLD remain unclear.

NAFLD prevalence is high, being stated in around 20 to 30% of the general population in studies based on imaging methods [(6)]. For histological studies, in selected groups of patients with risk factors for this disease, the prevalence may be higher, with steatosis found in 70% of obese patients and 35% of non-obese individuals, while NASH is seen in 18.5% of obese and 3% of non-obese patients [(7)]. In patients with type 2 diabetes mellitus (DM2), the frequency of fatty liver disease can reach 75% [(8)]. Several individual features or external conditions allied with NAFLD might play a role in the etiology, pathogenesis, natural history and progression of this disease, for example: age, gender, ethnicity [(9)], diabetes mellitus [(10)], obesity, family predisposition [(11)], metabolic syndrome and peripheral insulin resistance [(8)].

Some drugs, for example, tamoxifen, amiodarone, diltiazem, cortisone and HAART have been associated with NAFLD, and the induction of NASH is connected with prolonged treatment more than 6 months and medicine accumulation [(12-14)]. Processes such as total parenteral nutrition, jejunoileal or gastric bypass have been related to fatty liver disease. An association has been designated amid NAFLD and rare genetic disorders, for example, Mauriac syndrome, lipoatrophy, abetalipoproteinemia, Andersen disease and Weber-Christian disease [(15)]. Environmental factors such as numerous types of petrochemicals and solvents [(16)] are related to the appearance of NAFLD. Data from the literature, in the first few studies and more, showed the variability of the risk factors for NAFLD according to gender, race and ethnicity [(17)], demonstrate the multiplicity of clinical, genetic and environmental factors associated with the



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heterogeneous presentation of NAFLD. There is still no consensus on the optimal management for this disease and there are numerous studies focused on the utilization of drugs for insulin resistance and antioxidants. In this perspective, studies on clinical and epidemiological features of the disease can add significant information to the diagnostic and therapeutic administration of these patients.

## MATERIALS AND METHODS

This clinical and epidemiological study was first submitted to the approval of the local ethics committee. Adult patients with a definitive diagnosis of NAFLD (as defined below) were assessed. The medical records of these patients with NAFLD, acquired throughout its examination and repetitive follow-up throughout the period from February 2016 to March 2017, were reviewed with the objective of completing a form created for collection of epidemiological, clinical and laboratory data and results from imaging and histological examinations. NAFLD was defined in patients as steatosis proven by biopsy or imaging examination, such as medical ultrasound (USG) and/or computed tomography (CT) and magnetic resonance imaging (MRI), related with known risk factors, in the nonexistence of alcohol intake greater than 20 g per day. The diagnosis of probable NASH was defined as persistent and unexplained increase in transaminases accompanied by steatosis on USG and/or CT and/or MRI examinations of the upper abdomen, without any history of significant alcohol consumption (<20 g per day) and associated with one of the following risk factors: metabolic syndrome, overweight or obesity, *diabetes mellitus*, peripheral insulin resistance, drugs, environmental and other factors demonstrably associated with NAFLD. Definitive diagnosis of NASH was based on the presence of steatohepatitis on biopsy and in the absence of significant consumption of alcohol (<20 g per day).

We excluded patients previously submitted to stomach reduction surgery such as jejunoileal or gastric bypass, along with liver diseases, for example, hepatitis B and C, Wilson's disease, hemochromatosis and autoimmune hepatitis. Patients with incomplete or inconsistent mandatory information were excluded.

SPSS software was used to evaluate the descriptive data, which was expressed as the mean and median with their variations and standard deviation, as appropriate. Student's t-test or Mann-Whitney U tests were applied to compare continuous variables, and chi-squared test and Fisher's exact test were used for categorical variables. P value was considered significant as less than 0.05.

## RESULTS

Demographic, clinical and some of the laboratory data of the 124 patients with NAFLD are represented in Table 1. 94 of the 124 patients were women (75.8%).

**Table 1** Demographic, clinical and laboratory data of 124 patients with NAFLD

| | | | |
|---|---|---|---|
| Age (years) | 49.5 | - | 13.54 |
| Weight (kg) | 82.74 | - | 16,8 |
| Height (m) | 1,59 | - | 0.09 |
| BMI (kg/m2) | 31.02 | - | 5,97 |
| SBP (mmHg) | 130 | 110-200 | - |
| DBP (mmHg) | 80 | 60-120 | - |
| Blood sugar (mg/dL) | 93 | 72-204 | - |
| HOMA | 3,42 | 0.81-12.0 | - |
| Cholesterol (mg/dL) | 198 | - | 40.98 |
| HDL (mg/dL) | 47.1 | - | 11,87 |
| LDL (mg/dL) | 116.2 | - | 35.2 |
| Triglycerides (mg/dL) | 137 | 41-788 | - |
| AST (U/L) | 34 | 16-255 | - |
| ALT (U/L) | 36 | 13-295 | - |
| GGT (U/L) | 37 | 7.8-270 | - |

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HOMA: homeostatic model assessment; HDL: high-density lipoprotein; LDL: low-density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transpeptidase.

The main symptoms reported by the patients were: abdominal pain: 10 patients (8%); dyspepsia: 4 (3%); diarrhea: 4 (3%); postprandial fullness: 4 (3%); increased abdominal volume: 4 (3%); jaundice: 2 (2%); borborygmus: 2 (2%); asthenia: 2 (2%); and bitterness in the mouth: 2 (2%). 88 patients (71%) referred to themselves as being asymptomatic.

There were changes to the physical examination in 56 patients (45%), with hepatomegaly evident in 42 patients (34%), telangiectasia in 14 (11%), palmar erythema in 14 (11%), splenomegaly in 8 (6%), jaundice in 6 (5%), edema of the lower limbs in 6 (5%) and ascites in 4 (3%). AST and ALT values above the reference values were found in 70% and 34% of patients, respectively. Abnormal AST/ALT ratio was found in 47% of patients. 30 patients (24%) did not have changes to ALT and AST. The risk factors found for NAFLD are listed in Table 2.

**Table 2:** Risk factors for NAFLD

| | | |
|---|---|---|
| Dyslipidemia | 76/122 | 62,30% |
| High blood pressure | 76/124 | 61,29% |
| Physical inactivity | 64/124 | 51,61% |
| Obesity | 56/124 | 45,16% |
| Overweight | 48/124 | 38,71% |
| Increased abdominal waist (AW) | 82/94 | 87,23% |
| Type 2 diabetes mellitus | 34/120 | 28,33% |

There were 48 (39%) overweight patients. 28 (23%) of 56 obese patients were classified as grade I obesity, 20 (16%) as grade II, and 8 (6%) as grade III obesity. The waist was measured in 94 of 124 patients and found compatible with metabolic syndrome in 82 cases (87%).

Abnormal high-density lipoprotein (HDL) cholesterol and triglycerides (TG) results were found in 52% and 44% of the 124 patients, respectively. The results showed changes to both HDL and TG values in 38 patients. 26 patients (21%) exhibited changes in HDL alone, and 16 patients (13%) showed alterations of the TG values. Assessing the blood pressure (BP) measurement of 118 patients, 51% were classified as having some degree of hypertension: 32 patients with mild hypertension (grade 1); 26 patients with moderate hypertension (grade 2); and 2 patient with severe hypertension (grade 3). Amongst the normotensive patients, 8 (7%) were classified as having optimum BP, 32 (27%) as having normal BP and 18 (15%) as borderline BP. Regarding medication, a total of 94% of the patients reported use of at least one type of medication. The use of medication known to be associated with NAFLD occurrence was noted in 21% of patients and these drugs are listed in Table 3.

**Table 3:** Medications associated with occurrence of NAFLD used by the 124 patients.

| | | |
|---|---|---|
| Estrogens | 14 | 11,29% |
| Tamoxifen | 6 | 4,84% |
| Acetylsalicylic acid (ASA) | 4 | 3,23% |
| Chloroquine | 2 | 1,61% |

44 patients (35%) underwent liver biopsy, with steatosis described in all of them. Non-alcoholic steatohepatitis (NASH) was found in 42 patients. Other findings in the biopsies were: hepatocellular ballooning in 32 patients, fibrosis in 32 patients, iron overload in 26 patients, presence of Mallory bodies in 22 patients and the presence of a tumor in 2 patients.

Amid the 72 patients in whom metabolic syndrome could be studied, the condition was found in 70%. In 52 (42%) of the 124 patients, assessing metabolic syndrome was not possible due to incomplete data. 3 or more criteria indicating metabolic syndrome were found in 50 patients (70%), with 3 criteria found in 28 patients (39%), 4 criteria in 18 patients (25%) and 5 criteria in 4 patients (6%). Among the 22 patients (31%) that did not have 3 or more criteria, 10 patients (14%) had only 2 criteria, 10 patients (14%) had only 1 criterion, and 2 patients (3%)were free of all. Regarding dyslipidemia, 52 (55%) of the 94 women studied and 12 (40%) of the 30 men studied were found to have abnormal HDL cholesterol values. With respect to the values for triglycerides, 54 (44%) of the 124 patients evaluated had abnormal values for the parameters of metabolic syndrome. Regarding mean arterial pressure (MAP) a value compatible with metabolic syndrome was evident in 42 (36%) of the 118 patients, with the maximum values for systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 200 and 120 mmHg, respectively, and minimum values for SBP and DBP at 140 and 90 mmHg, and a median of 150 x 100 mmHg.

There was an association between metabolic syndrome and steatosis on USG (p=0.012). Metabolic syndrome was estimated in 69% of patients with steatosis on USG (95CI 53-79%) and there was evidence that the syndrome affects the majority of these patients (p=0.005).

76 of the 124 patients studied (61%) were classified as having NASH according to one of the criteria adopted. Of these 76 patients, 60/124 (48%) were classified as having probable NASH and 42/124 (34%) as having definitive NASH.

## DISCUSSION

NAFLD has enlarged epidemiological relevance in recent years, demonstrating one of the leading reasons of chronic liver disease in the 21st century, and can apparent itself in different age ranges, ethnic groups and gender. The true commonness of NAFLD is undervalued in the overall population, as the sickness is asymptomatic and the common of patients start examination as a result of accompanying findings on USG, increased liver enzymes or check-ups. Recent studies indicated prevalence at around 20 to 30% in the general population. In obese patients or with diabetes mellitus it can reach up to 50% of the population [18]. Most of the available studies on NAFLD comprise patients in hospital environments and, consequently, their characteristics might not precisely represent those estimated in the general population. In the current study, there was a prevalence of NAFLD in middle-aged women, as revealed in previous studies [19].

Nevertheless, the actual participation of gender as a determining factor in the improvement of NAFLD has not yet been recognized, given that some studies showed a higher pervasiveness in men or an equal distribution amid the genders [18, 20]. With respect to medicines used by the examined population sample, about 21% of the patients reported using drugs known to be associated with the induction of hepatic steatosis, such as estrogens, tamoxifen, ASA and chloroquine. Despite these patients having risk factors for metabolic syndrome, we cannot rule out the possibility that the use of these drugs is correlated with the progression of NAFLD. Regarding NASH, less than 2% of the causes were due to drug induction. The mechanisms of action can be divided into direct hepatoxicity and action on metabolic processes in the liver, such as mitochondrial ATP production and the metabolism of fatty acids ([13]. Tamoxifen, a drug used in patients with breast cancer to inhibit estrogen receptors in this organ alone, was found in almost 5% of the patients. Studies showed that tamoxifen raises the risk of increasing NAFLD/NASH only in overweight and obese females with risk factors related with metabolic syndrome. Studies revealed that 43.2% of patients advanced steatosis within two years of use and had their tests return to normal one year afterward end of therapy [21, 22].

Awareness of the group of treatment utilized by these patients was likewise relevant, as it presented that 40% of the patients utilized at least one type of anti-hypertensive and 28% used at least one anti-diabetic medicine, suggesting the occurrence of diseases directly connected with metabolic syndrome, and likewise associated to NAFLD [6]. Metabolic syndrome is signified by a set of risk factors, mostly associated to a central deposition of fat and insulin resistance, which were found in nearly 70% of patients in the investigated sample. Consistent with an earlier study, the attendance of 3 or more criteria for metabolic syndrome raised the hazard of developing severe fibrosis, chronic liver sickness and cardiovascular sickness by 3.5 times [23]. In the current study, six or more criteria for metabolic syndrome were found in 50 patients (70%).

Being overweight or obese was found in the vast majority of the patients (84%). This result is compatible amid the patients with NAFLD and is reliable with the literature [24]. Obesity, estimated using the BMI, was found in 45% of patients studied. Previous studies have estimated NAFLD at 57.5% to 74% of the obese population; displayed the significance of calculating the BMI and the intense association between obesity and NAFLD, in addition to presenting that there is a direct correlation between obesity and the severity of steatosis [7]. Waist circumference relates to the amount of visceral adipose tissue and is predictive of comorbidities, for example, obesity, hypertension and diabetes mellitus, about the pathogenesis of insulin resistance and glucose intolerance. Abnormal WC values were found in 66% of the 124 patients, and were higher than those found in the literature (42-47%) [7]. Nevertheless, if considering the abnormal WC values merely in those cases where this datum could be measured, the percentage increased to reach 87%. This datum can be linked to the point that the measurements were carried out on the vast majority of the obese patients, highlighting the significance of anthropometric measurements, which is frequently neglected in the physical exam.

In earlier studies, NAFLD was diagnosed on USG in 20 to 40% of the patients [12]. In the current study, steatosis was current in 104 (84%) of the 124 patients studied. Even though the assessment of NAFLD using USG has proven itself to be beneficial as an initial test in patients with suspected NAFLD, it is inadequate in defining the presence of inflammation and fibrosis, and it is unable to assess the stage of hepatic impairment. Furthermore, if absent on USG, this does not except the possibility of NAFLD. In the literature it is accepted that the

mere occurrence of fat without inflammation in the liver might have a benign course, even though the suggestion of steatosis, inflammation, ballooning degeneration, Mallory bodies and fibrosis characterizes NASH, which can develop into cirrhosis and subsequent complications, such as hepatocarcinoma [25].

The progression from steatosis to cirrhosis and death as a result of its complications only arises in less than 5% of cases; nevertheless, when steatohepatitis is current, that incidence of progression can reach up to 25% [26]. Data about the speed of the progression of this disease is uncommon. 76 of the 124 patients studied (61%) were classified as having NASH. Of these 76 patients, 60/124 (48%) were classified as having probable NASH, that is, abnormal USG associated with increased transaminases and risk factors for metabolic syndrome, while 42/124 (34%) had definitive NASH, that is, with a biopsy proving NASH.

## CONCLUSION

Bearing in mind the epidemic of metabolic syndrome in the modern world, the examination of other components of this syndrome is needed. Metabolic syndrome summarizes a large part of the systemic manifestations of insulin resistance. As well as the classic components of the syndrome, new components of great clinical relevance, such as NAFLD, have been validated. Present studies specify a growing occurrence of this disease in relation with metabolic syndrome risk factors, meaning that better diagnostic and prognostic examination of NAFLD is necessary.

As there was a significant relationship between NAFLD and metabolic syndrome, this highlights a need to control their component factors and corroborates the concept that NAFLD might be a hepatic component of metabolic syndrome.

As an deceptive and progressive disease with nonspecific symptoms, NAFLD can induce a malignant course, progressing to NASH, cirrhosis of the liver and hepatocellular carcinoma. Consequently, liver biopsy becomes an indispensable inspection for appraising the course of the disease. We recognized NAFLD in all of its clinical forms, predominantly steatohepatitis. The most frequent risk factors were metabolic syndrome and its variables: increased waist circumference, dyslipidemia and hypertension. This underscores the significance of metabolic control in NAFLD and confirms its role as the hepatic component of metabolic syndrome.

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