Nonalcoholic fatty liver disease in patients with metabolic syndrome in primary care.

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Abstract

Objective: To analyse the relationship between Hepatic Steatosis, also known as Non-Alcoholic Fatty Liver disease (NAFLD) in patients with metabolic syndrome criteria and cardiovascular risk factors.

Method: A cross-sectional study was performed to study a sample of 100 patients attending Primary Care with 2 or more cardiovascular risk factors and no alcohol consumption. For those who were selected a complete analysis was carried out, and they were assigned to the outpatient clinics for an abdominal ultrasound exam. It was assessed whether they had Hepatic Steatosis or not, and if so, it was classified into 3 grades (mild-moderate-severe). Subsequently, the following qualitative (sex, personal and family history of diabetes, hypertension, dyslipidemia, etc.) and quantitative (age, weight, height, body mass index, drug treatment, figures of analytical parameters, blood pressure and waist circumference) variables were collected.

Results: 100 patients, 44 men and 56 women participated, with an average age of 61.84 ± 9.5 years. Men, 82% had Hepatic Steatosis: 28% Grade I, 38.7% Grade II and 16% Grade III. Women, 28.57% did not have Hepatic Steatosis. Of those who had Hepatic Steatosis: 30.35% were Grade I, 21.43% Grade II and 19.64% Grade III. 22% were overweight and 38% were obese. Only 22% and 18% had impaired systolic and diastolic blood pressure values respectively. 60% had impaired fasting glucose levels, but only 26% had altered glycosylated hemoglobin.

Regarding lipid parameters 36% had hypertriglyceridemia, 41% hypercholesterolemia, 65% High LDL cholesterol and 16% low HDL cholesterol. Of the total study subjects, 23% had no Non-Alcoholic Hepatic Steatosis, 29% had mild hepatic Hepatic Steatosis, 29% moderate Hepatic Steatosis and 19% severe Hepatic Steatosis. 83% of patients had two or more criteria of metabolic syndrome.

Conclusions: There is a close relationship between the incidence of Non-Alcoholic Hepatic Steatosis and cardiovascular risk factors in patients with metabolic syndrome. Therefore it is recommended that upon the appearance of these risk factors, liver should be tested.

Keywords: Metabolic syndrome, Hepatic steatosis, Cardiovascular risk factors, Alcohol consumption.

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Introduction

The term Non-Alcoholic Steatohepatitis (NASH) was first introduced in 1980 by Ludwig, to define a disease characterized by similar histological changes observed in patients with alcoholic hepatitis, but where alcohol consumption was of no or little significance. This term should be included in a larger entity, called Non-Alcoholic Fatty Liver disease (NAFLD).

NASH is associated with a syndrome of insulin resistance (IR) and related conditions thereof. It has been suggested that the hepatic manifestation of the metabolic syndrome was the presence of the IR, obesity, type 2 diabetes mellitus, hypercholesterolemia, hypertriglyceridemia and hypertension [1-3].

The mechanisms leading to the development of hepatic steatosis are partially known: it is accepted that the factors that determine the appearance of the steatosis are insulin resistance, increased flow of fatty acids to the hepatocytes, less elimination of triglycerides in the liver and less fatty acid oxidation [4-7].

Currently, it is accepted that adipocytes can have a central role in the development of insulin resistance and NAFLD. The adipocyte is an important endocrine organ that can trigger an inflammatory process that facilitates the evolution of the hepatic steatosis, being capable of secreting substances such as TNF-α, Leptin and Resistin, in addition to free fatty acids whose concentration is related to the insulin resistance [8-11].

Therefore, obesity should be considered as a pro-inflammatory

entity. And so, the liver and other tissues are exposed to cytokines produced in adipose tissue.

In the hepatic steatosis, it is accepted that increased fatty acids within the hepatocytes on one hand, is due to the increased blood flow derived from lipolysis; and on the other hand, is due to an increased De Novo synthesis of the hepatocyte itself. During fasting, the fatty acids that reach the liver originate as a result of the hydrolysis of triglycerides stored in adipose tissue [10-14].

Several circumstances influence the growing interest in this disease: the high prevalence of this disease in the Western world, its ability to progress into more aggressive histological forms and diseases associated with increased cardiovascular risk.

Although the actual prevalence rate of NAFLD is not yet known, there is a general consensus that it is significantly increasing in the recent years. The estimated prevalence ranges between 3% and 46% of the population tested, so the prevalence rates may fluctuate considerably [14-19].

There are limited data about the natural history of patients with NAFLD due to the indolent nature of the process and the rare existence of prospective studies. Patients with simple steatosis have a benign course in contrast to about 23% of patients with NASH who progress to cirrhosis over a period of 10 years to15 years. Furthermore, 30% to 40% of patients with NASH have advanced fibrosis upon diagnosis. Some of the patients with cirrhosis due to NAFLD develop hepatocellular carcinoma in a 10 year period. In addition to death due to liver damage, life expectancy is lower than the control population of equal sex and age due to increased cardiovascular mortality.

The diagnosis of NAFLD should be based on the combination of the data from the clinical history and non-invasive diagnostic methods [20-24]. A proper diagnosis process should include the following basic aspects:

1. Suspected diagnosis of NAFLD, including verification of no alcohol consumption and excluding the potential causes of hepatic steatosis and diagnosis of possible associated diseases.
2. Diagnosis of insulin resistance.
3. Assessment of cardiovascular risk of these patients.
4. Assessment of the severity of hepatic steatosis by non-invasive techniques, such as ultrasound.

For all of the above we propose this work with the following objectives:

Primary objective

To estimate the prevalence of hepatic steatosis in population with metabolic syndrome or multiple cardiovascular risk factors.

Secondary objective

1. Assessment of the epidemiological characteristics of these patients, including sex, age and/or several cardiovascular risk factors.
2. Classification of the degree of steatosis in mild, moderate or severe based on the ultrasound criteria.
3. Assessment whether there is a correlation between the ultrasound results and serum triglycerides, aminotransferase (ALT, AST) and BMI.

Material and Methods

A cross-sectional descriptive study. During the period of 12 months, 100 patients with 2 or more cardiovascular risk factors and low or no alcohol consumption, attending Primary Care were selected in the Health Care of Casas de Haro (Cuenca-Spain).

A sample size with a 24% prevalence of metabolic syndrome in the general population and 30% prevalence of non-alcoholic fatty liver disease in those was estimated, and the selection was made by systematic random sampling technique where one of every two patients was selected.

The target population meets the following criteria (inclusion criteria):

1) No or low alcohol consumption (<20 g/day in women and <30 g/day for men) proven and tested.

2) Normal or altered liver function tests, not due to viral hepatitis or other hepatobiliary or systemic diseases, nor due to drug causes (glucocorticoids, synthetic estrogens, amiodarone, aspirin ...).

Once selected the following demographic and biochemical variables were analyzed:

Age, gender, alcohol consumption, history of diabetes, hypertension, weight, height, body mass index (BMI) (defined as weight/height^2), systolic and diastolic blood pressure, glucose, glycated hemoglobin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, criteria for Metabolic syndrome ATP III ≥ 150 mg/dL), AST, ALT, bilirubin and alkaline phosphatase. Fasting glucose, cholesterol, triglycerides, transaminases, bilirubin and alkaline phosphatase were analyzed in the laboratory of the Hospital of Villarrobledo (Spain). Other variables such as family history of diabetes, hypertension and hyperlipidemia, pharmacological treatment, and personal history.

Metabolic syndrome was defined according to the presence of three or more of the ATP III criteria:

1. Abdominal obesity: circumference >102 cm in men and >88 cm in women.
2. Hypertriglyceridemia: ≥ 150 mg/dL.
3. HDL cholesterol < 40 mg/dL in men and <50 mg/dL in women.
4. Hypertension: ≥ 130/85 mmHg.
5. Basal glucose: ≥ 110 mg/dL.

The clinical history and laboratory tests were used to rule out other causes of liver disease and to support the diagnosis of NASH. The excessive consumption of alcohol should be discarded carefully. It is therefore necessary questioning the patient and their families, and to evaluate some analytical tests such as mean corpuscular volume of red blood cells or the Aspartate Aminotransferase/Alanine Aminotransferase (AST/ALT) ratio.

Once the diagnosis is suspected clinically and analytically, the study must be completed by an imaging test such as ultrasound, sometimes it is even necessary to complete the study with

Computed Tomography (CT) or magnetic resonance (MRI), especially in specialized areas. It is a very sensitive technique. By comparing the echogenicity of the hepatic parenchyma with other neighbouring structures such as the gallbladder or kidney, semi-quantitative estimation of the degree of steatosis may be performed. The usefulness of the ultrasound decreases in cases where steatosis is less than 30% or when there is morbid obesity.

Liver evaluation by ultrasonography

Sonographic studies were carried on by the ultrasound apparatus *"*ESAOTE mylab20plus*"*. Abdominal ultrasound is a safe, inexpensive technique with a high diagnostic value in abdominal pathology. For these reasons it has become the first procedure to be performed in patients with chronic liver disease, both in its initial assessment and follow-up.

The fundamental ultrasound feature of fatty infiltration of the liver is the increased echogenicity due to fat deposition (steatosis) in hepatocytes. Depending on the number of hepatocytes with fat accumulation, this fat deposition can be mild (<33%), moderate (33% to 66%) or severe (>66%). This hyperechogenicity is composed of very dense fine grains which give the liver a "bright" appearance, matching or even exceeding the echogenicity of the pancreatic parenchyma, and slightly increased echogenicity relative to the renal cortex. This increased echogenicity due to the fatty infiltration of the liver causes posterior sonic attenuation, which makes the assessment of the deep parts of the liver difficult.

Based on these characteristics we can distinguish three grades:

Grade I or Mild steatosis: Discrete diffuse increased echogenicity, with normal assessment of the diaphragm and the intrahepatic vessels edges.

Grade II or Moderate steatosis: Moderate diffuse increased echogenicity, with difficult assessment of diaphragm and the intrahepatic vessels.

Grade III or Severe steatosis: Marked increased echogenicity, with little or no visualization of the intrahepatic vessels walls, diaphragm and the right hepatic lobe posterior portion due to the poor penetration of the ultrasound waves.

Fatty infiltration of the liver typically has a homogeneous distribution (diffuse steatosis), although in some cases can cause irregular fat deposition (focal steatosis):

Diffuse pattern: It affects the whole parenchyma, although within this pattern it is quite common to observe hypoechoic areas representing "areas of normal parenchyma" with more defined boundaries (they seem to be continuous with fatty parenchyma) without mass effect (space-occupying lesion). It's often localized in the hepatic hilum or in the area next to the bladder.

Focal pattern: Corresponds to regions of increased echogenicity on the top of a normal parenchyma. This pattern is especially common in right hepatic lobe. It is easy to diagnose and easy to distinguish from the space-occupying lesion by the absence of mass effect. It does not displace or compress the hepatic vessels, neither does it alter the liver contour, and it usually has geographic margins. While the ultrasound image is often characteristic, diagnostic doubts sometimes arise with other processes such as hemangiomas (multifocal nodular steatosis), liver metastases, hematoma or abscess. If so, performing a CT or an MRI might be necessary, and sometimes ultrasound-guided biopsy.

To evaluate the degree of fatty infiltration of the liver, we can use the measuring scale proposed by DF Chan.

This scale classifies the hepatic steatosis in 3 grades: normal liver or grade 0 (0 points), mild hepatic steatosis or grade 1 (1 points to 3 points), moderate hepatic steatosis or grade 2 (4 points to 6 points) and severe hepatic steatosis or grade 3 (7 points to 9 points) [15-17].

The study proceeded according to the regulations of the Helsinki Declaration of 1983, and in all cases the study participants signed an informed consent.

Statistical analysis

This is an observational, descriptive and analytical cross-section study.

The variables recorded in the case report were included and sorted in the Excel database.

The qualitative variables are represented as an exact value and percentage, the quantitative variables as mean and standard deviation (SD).

Comparisons between means were performed using Student's-t test for independent groups or the Mann-Whitney if normal conditions were not met (Kolmogorov-Smirnoff and Shapiro Willks tests). As for the qualitative variables, the chi-square test was used.

Using these criteria, the average sensitivity of ultrasound test for the diagnosis of NAFLD is 87% (60 to 100), and the specificity is 86% (56% to 95%). The higher the fat deposition, the higher sensitivity and specificity of the ultrasonography.

Results

100 patients, 44 men and 56 women have participated, with an average age of 61.84 years ± 9.5 years. Of the men, 82% had hepatic steatosis: 28% of them Grade I, 38.7% Grade 2 and 16% Grade III. Women, 28.57% of them did not have fatty liver disease. Of those who had steatosis, a 30.35% were Grade I, 21.43% Grade II and 19.64% Grade III (Table 1).

If the gender variable is associated with hepatic steatosis=no statistical significance.

The mean age was 61.84 years ± 9.5 years with a minimum range of 33 and maximum of 87 years. The highest incidence of NAFLD and metabolic syndrome was observed in patients who were under thirty years old 54% and 40% in those whose age was between 31 and 65 years old.

Overweight (defined as BMI ≥ 26 to 30 kg/m^2) was found in 24 (24%) patients and obesity (defined as BMI ≥ 30 kg/m^2) in 70 (70%) patients, with an average total weight 86.59 ± 16.13 kg and an average BMI of 33.33 kg/m^2 ± 4.31 kg/m^2 (Table 2).

Table 1: *Hepatic steatosis grade according to sex.*

Steatosis Grade	0	I	II	III
Man	18	28	38.7	16
Women	28.57	30.35	21.43	19.54

Grade 0: no hepatic steatosis

Of patients diagnosed with NAFLD, 38 (38%) of them had history of diabetes mellitus and 41 (41%) history of hypertension, with an average serum fasting glucose level 115.31 mg/dL ± 33.38 mg/dL and average level of HgbA1C 6.26 ± 5.1. The average readings for systolic blood pressure were at 135.68 ± 14.87 and at 78.29 mmHg ± 10.92 mmHg for the diastolic one. 83% of patients had two or more Sd. Metabolic criteria (Table 3).

As for the lipid parameters 34% had hypertriglyceridemia, 48% hypercholesterolemia, 24% high LDL cholesterol and 24% high HDL cholesterol (Table 4). Of the total study subjects, 23% had no NAFLD, 29% had mild hepatic steatosis, 29% moderate hepatic steatosis and 19% severe hepatic steatosis.

The average abdominal circumference was 109.29 cm ± 12.10 cm. 79% of the study subjects had pathological levels, with 32% women and 58% men (Table 5).

Of these, 79% had hepatic steatosis, of which 29% steatosis is grade 1, 50% grade 2 and 20.6% grade 3.

Transaminases levels (AST and ALT) were normal in 94%, while AGT was elevated in 66.6% of them.

Of patients with normal ALT and AST, 72% had hepatic steatosis in different degrees, and 63.3% of the patients with normal AGT.

When making a statistical correlation of the observed variables:

Table 2: *Patients classification according to body mass index.*

S.No	Body Mass Index	Frequency	Percentage
1	Normal Weight	4	8%
2	Overweight	10	20%
3	Obesity I	19	38%
4	Obesity II	17	34%

Table 3: *Distribution of patients according to metabolic syndrome criteria.*

Numbers criteria for metabolic syndrome	Frequency	Percent
0	4	4%
1	13	13%
2	27	27%
3	33	33%
4	16	16%
5	7	7%

Table 4: *Lipid parameters and liver transaminases.*

	Average	Maxim	Minimum	Incidence of Hyperlipidemia or Diabetes
Cholesterol	199.50	305	124	48%
HDL cholesterol	54.78	137	25	24%
LDL Cholesterol	116.79	200	52	28%
Triglycerides	155.57	727	42	34%
Glucose	115.31	202	62	38%
AST	24.98	89	12	
ALT	32.19	94	9	
AGT	55.65	314	7	

Table 5: *Classification of patients according to the abdominal circumference.*

Abdominal Circumference	Frequency	Percent
0 (minor 80 cm)	5	10%
1 (81-104 cm)	16	32%
2 (major de 104 cm)	29	58%

1. Obesity especially when measured by the BMI is closely related to NAFLD (p=0.02).
2. Lipid parameters especially hypertriglyceridemia (p=0.02) are associated with NAFLD and has also shown the protective role of HDL (p=0.01). The higher HDL, the lower incidence of NAFLD.
3. Also being diabetic has shown a strong relationship with the incidence of NAFLD (p=0.02).
4. Patients treated with metformin have shown little connection with NAFLD incidence (p=0.01).
5. Patients treated with fibrates have also shown a relationship regarding the incidence of NASH (p=0.045).
6. On the other hand the appearance of metabolic criteria has also shown a relationship with NASH incidence (p=0.000). The more criteria the patient has, the more likelihood of the disease incidence.

Discussion

The disease NAFLD is an inflammatory chronic liver disease of great relevance today because of its strong association with increasingly prevalent diseases like obesity and Type 2 Diabetes, we can see that our results confirm this with a strong relationship between NAFLD incidence and suffering these diseases (p=0.02) [1-5].

The metabolic syndrome is a combination of risk factors of high prevalence, especially in patients with a cardiovascular condition. Most of the studies agree that the prevalence is to be found around 24% in the general population and nearly 50% in patients with ischemic heart disease or other vascular condition. The prevalence increases proportionally with age and overweight. The prevalence in Spain is somehow less analysed and early studies show prevalence rates similar to those of the international studies [6-11].

In our study, 46% of the subjects have met the criteria of the metabolic syndrome, the prevalence of steatosis in our study is 72%, 34% being obese. We can see a close relationship between the incidence of NAFLD and the number of the metabolic syndrome criteria (p=0.000). Obesity is a leading cause of this liver disease. A study found that among people who had no known liver disease, 76% of people who did not consume alcohol but were obese, had a fatty liver; while this proportion was much lower, at16%, among those who were of normal weight. These data demonstrate the importance of obesity as a cause of the fatty liver disease. 70% of the obese subjects of our study had steatosis: the degree of the steatosis is related to the BMI; the higher the BMI, the more advanced grade of esteatosis [12-18].

Adult-onset diabetes or Type 2 diabetes is the second cause of NAFLD, in terms of frequency; it can be found in "34% to 75%" of diabetic patients and is often associated with obesity. Patients with type 2 diabetes and obese patients have a common metabolic disorder, known as "insulin resistance" which can predispose to hypertension and changes in blood lipids such as cholesterol and triglycerides. All these metabolic disorders, type 2 diabetes, abdominal obesity prevalence, hypertension and alterations in blood lipids or dyslipidemia form what is now called "metabolic syndrome," which is considered as the

leading cause of liver fat disease in the developed world. The metabolic syndrome contributes decisively to the accumulation of fat in the liver [19-23].

The NAFLD is associated with insulin resistance and metabolic syndrome. About the half develop liver fibrosis and 17% progress to cirrhosis in periods of up to 7 years, 71% progress to diabetes over a period of 13.7 years [22,23]. Randomized and diagnosed by liver biopsy trials have been evaluated; where the effects of metformin was associated with improved levels of (AST-ALT) liver function, sensitivity to insulin, C-peptide, plasma glucose, plasma cholesterol and BMI. Our study also confirms that patients treated with metformin have a lower incidence probability of NAFLD than the non-treated patients [24-28].

Lipid-lowering therapy with statins and fibrates has shown mixed results, although they tend more to benifit, two small studies studied the effects of fibrates in these patients. Gemfibrozil was able to reduce the transaminases enzymes levels and Clofibrate decreased the level of alkaline phosphatase, but neither of the two drugs could improve the histological appearance of the steatosis. And so, we cannot allow ourselves to widely recommend them as a treatment option for the liver steatosis. Our study shows a statistically weak association between intake of fibrates and the incidence of NAFLD [26-29].

While the study for the diagnosis of certainty of NAFLD is the hepatic biopsy. Different studies have showed that a complete medical history and ultrasound performed by an experienced radiographer have high rates of sensitivity and specificity. In our study all ultrasounds were performed by the same radiologist with extensive experience in the field.

While included in the history of each patient, results of vitamin-E intake through herbs or other compounds, diet and regular exercise were not conclusive and were not included in the study.

With the results of our study we can recommend that patients with metabolic syndrome of primary care should be evaluated at an early stage to detect hepatic steatosis as soon as possible [21].

References

1. Veronica MV, Rosario GC, Jorge MJR, et al. Etiopathogenesis, diagnosis and treatment of non-alcoholic fatty liver disease. Rev Esp Enferm Dig. 2013;105:409-20.
2. Milie S, Lulie D, Stimac D. Nonalcoholic fatty liver disease and obesity: biomechical, metabolic an clinical presentations. World J Gastroenterol. 2014;20:9330-7.
3. Alves de C, Coelho CP, Arruda KG, et al. Risk factors associated with hepatic steatosis: a study in patients in the Northeast. Brazil Nutr Hosp. 2012;27:1344-50.
4. Carolina L, Alejandro MA, Carmen C, et al. Hepatic steatosis : prelude to type 2 diabetes in the pediatric population? Nutr Hosp. 2014;29:350-8.
5. Buque X, Aspichuetay P, Ochoa B. Molecular basis of hepatic steatosis associated with obesity. Rev Esp Enferm Dig. 2008;100:565-78.
6. Powell EE, Cooksley WGE, Hanson R, et al. The natural history of nonalcoholic steatohepatitis: A follow-up study of forty–two patients for up to 21 years. Hepatology. 1990;11:74-80.
7. Ludwig J, Viggiano RT, McGill DB. Non-alcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc. 1980;55:342-8.
8. Bellentani S, Saccoccio G, Masutti F, et al. Prevalence of and risk factors for hepatic steatosis in northern Italy. Ann Intern Med. 2000;132:112-7.
9. Jick SS, Stender M, Myers MW. Frequency of liver disease in type 2 diabetic patients treated with oral antidiabetic agents. Diabetes Care. 1999;22:2067-71.
10. Hulcranzt R, Glaumann H, Lindberg G, et al. Liver investigation in 149 asymptomatic patients with moderately elevated activities of serum aminotransferases. Scand J Gastroenterol. 1986;21:109-13.
11. Rosety-Rodríguez M, Fornieles G, Rosety I, et al. Central obesity measurements predict metabolic syndrome in a retrospective cohort study of postmenopausal women. Nutr Hosp. 2013;28:1912-7.
12. Dixon JB, Bhathal PS, OBrien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology. 2001;121:91-100.
13. Kemmer NM, McKinney KH, Xiao SY, et al. High prevalence of NASH among Mexican American females with type II diabetes mellitus. Gastroenterology. 2001;120:117.
14. Francisco JVL, Cristina CM, Maria JAG, et al. Very low calorie (BVC) diets in the clinical management of morbid obesity. Nutr Hosp. 2013;28:275-85.
15. Kopelman PG. Obesity as a medical problem. Nature. 2000;404:635-43.
16. Matteoni CA, Younossi ZM, Gramlich T, et al. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology. 1999;116:1413-9.
17. Lee RG. Non-alcoholic steatohepatitis: a study of 49 patients. Hum Pathol. 1989;20:594-608.
18. Dyson JK, Anstee QM, McPherson S. Nonalcoholic fatty liver disease: a practical approach to treatment. Frontline Gastroenterol. 2014;5:277-86.
19. Gomez RM, Cuenca MB. Hepatopatía difusa e hipertension portal Ecografia digestiva Jose Maria Segura Cabral Cap.
20. El-Hassan AY, Ibrahim EM, Al-Mulhim FA, et al. Fatty infiltration of the liver: analysis of prevalence, radiological and clinical features and influence of patients management. Br J Radiol. 1992;65:774-8.
21. Martin AA, Castellano TG. Echographic follow-up of patients with chronic liver disease. Rev Esp de Eco Dig. 2006;1-10.
22. Teran A, Crespo J. Screening of hepatic disease by fat deposition: how and to whom. Gastroenterologia y Hepatologia. 2011;34:278-88.

23. Moreno MA, Baluja PR. Sindrome metabolico Educacion Continuada en el Laboratorio Clinico.

24. Alegria E, Cordero A, Laclaustra M, et al. Prevalence of metabolic syndrome in Spanish labor population: MESYAS registry. Rev Esp Cardiol. 2005;58:797-806.

25. Perez AF, Benlloch S, Berenguer M, et al. Non-alcoholic steatohepatitis: physiopathological, clinical and therapeutic implications. Rev Esp Enferm Dig. 2004;96:628-48.

26. Lazo M, Hernaez R, Bonekamp S, et al. Non-alcoholic fatty liver disease and mortality among US adults: prospective cohort study. BMJ. 2011;343.

27. Gill HK, Wu GY. Non-alcoholic fatty liver disease and the metabolic syndrome: effects of weight loss and a review of popular diets Are low carbohydrate diets the answer? World J Gastroenterol. 2006;12:345-53.

28. Uygun A, Kadayifci A, Isik AT, et al. Metformin in the treatment of patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2004;19:537-44.

29. Malnick SDH, Beergabel M, Knobler H. Non-alcoholic fatty liver: A common manifestation of a metabolic disorder. QJM. 2003;96:699-709.

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