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# "Nonalcoholic Fatty Liver and Metabolic Syndrome in a Population of Southeastern Mexico"

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***Abstract:***

***" NASH (Non alcoholic steato hepatits) disease and metabolic syndrome in Mexico´s southeastern population***

***Introduction:*** *The nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease associated with an accumulation of fat that can lead to steatosis, steatohepatitis, cirrhosis, carcinoma and in cases more severe end-stage liver failure. The prevalence of this disease is unknown in the Mexican population; They have reported recent studies where it occurs up to 30% of the general population, being more frequent in subjects with central obesity, insulin resistance, hypertension and dyslipidemia, considered as criteria for diagnosis of metabolic syndrome (MS). Nonalcoholic fatty liver is the only hepatic manifestation of the metabolic syndrome.*

***Materials and Methods:*** *This is a descriptive study in which subjects with an ultrasonography report of NASH were admitted, integrating cases with metabolic syndrome as its prevalence variable confirmed by at least 3 different diagnostic criteria for MS. Staging and categorization of MS and NASH components were ensamble as well a determine the differences between Chi-square test and Anova of a factor according to the variable, the correlation level between these was determined by the Spearman test.*

***Results:*** *A population of 200 patients were included with an ultrasonography diagnosis of NASH, 39% with Metabolic Syndrome (MS) criteria. 7 out of 10 patients with MS presented mild steatosis with a correlation value of 54.4% in female patients and 45.5% in male patients, reporting a male/female trust interval ratio of 0.989 (Trust interval ratio to 95% (IC95%):33.7 - 46.2)). As well a correlation between obese patients and steatohepatic disease stages was made, getting a Rho: 0.11 value.*

***Conclusions:*** *Four out of ten patients with Non alcoholic steato hepatic disease (NASH) are Metabolic syndrome carriers.*

***Keywords:*** ***Metabolic Syndrome (MS), Non alcoholic steato hepatic disease (NASH), Obesity, Hypertension.***

## Introduction

The epidemiological transition within last years, has reveal an increment in MS prevalence in the population, NASH disease is a pathologic syndrome related to MS and obesity, however overweight patients could be affected as well.


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The excessive accumulation of adipose tissue within the liver tissue is call Non alcoholic steato hepatic (NASH) disease, identified as an infiltration of more than 5% of the hepatocytes in the histopathological report. Besides the adipose tissue increment, a subgroup of patients with NASH could progress to damage and inflammation of hepatocytes (steato hepatitis), which, histologically, is undeniable compared to an alcoholic hepatitis. Untreated NASH disease will develop steato hepatitis and with it the risk of cirrhosis, hepatic failure and hepato celular carcinoma, increasing mortality due to liver damage in NASH carrier patients. NASH comorbidity correlation with cardiovascular pathologies is considered the second most common cause of hepatic transplant after cirrhosis secondary to an hepatitis C infection.

Even though NASH is not considered as part of MS criteria, several health professionals do include it and suggest that the increase in adipose tissue deposit within the liver correlates significantly with every criterion on MS regardless if the patient is obese or not. The reason why NASH has not been approved within the definition of MS is still unknown.

Some authors suggest that NASH is the expression of MS linked to diseases such as Diabetes mellitus type II and insulin resistance, central obesity, hyperlipidemia and hypertension. MS is considered as an important NASH predictor, being the steatosis generally secondary to an insulin resistance metabolic state, present in subjects with one or more component of MS.

It is estimated that males and women with MS are at high risk of developing NASH (4 times and 11 times more respectably) than patients without any of MS criteria. It is the main cause of chronic liver disease and its global prevalence fluctuates between 2.8% and 46%associated to obesity and Diabetes Mellitus type II. Ethnicity plays an important role in NASH development, being the hispanic community at a higher risk for developing it, followed by white subjects and african american patients, being these more frequently in male subjects. There is a global prevalence of NASH reporting values from 15% to 30% in countries like Asia and the US, reaching numbers up to 50% of patients with diabetes mellitus type II. Several studies had been done in the center and south of Mexico, reporting un matching prevalence between 4.54% and 82.9% of NASH in subjets with MS, due to that fact, the main objective of this study is to asses the correlation and related factors between MS and NASH disease.

## Method:

This was a descriptive, prevalence case analysis report study, which included outpatients from the radiology department of a second level hospital within September 2014 and September 21. Inclusion factors for this study were patients with an ultrasonographic report and diagnosis of NASH (in any of its stages) for the resulting correlation with Metabolic syndrome disease. (Inclusion criterium for MS was used from the 3rd National report on education of cholesterol patients (NCEP-ATPIII)) with at least 3 of the following: Abdominal circumference >102cm in males and >88cm in females, Triglycerides of <150mg/dl (with or without pharmacologic treatment), High Density Lipoproteins “HDL” levels of <40 mg/dl in males and <50 mg/dl in females, blood pressure of >130/85 mmhg (with or without treatment) and a fasting glucose of >100 mg/dl. Patients with Diabetes mellitus type II being treated pharmacologically were excluded from the study. Nevertheless some changes had been taken in some of the criterium in regards ethnicity and geographic location as in the Latin American Diabetes Association in which defines a specific abdominal circumference for the Latin American community, being the same reference for waist circumference for the south asian population, which goes between >90cm in males and >80cm in females compared to other study group as Europeans with values of >94 cm in males and >80 cm in females. It also excluded patients taking hepatotoxic medication, immunocompromised subjects and post op By-pass patients; Additionally BMI data was obtained to classify the weight amount vs. heigh of each patient and sort them as normal with a BMI of 19-24 kg/ m2, obesity a BMI of > 30 kg/m2, overweight BMI 25-30 kg/m2 and morbid obesity when above 40 kg/ m2.

Sample size is estimated thanks to a population infinite proportion formula with a likelihood occurrence of 50% a confidence interval of 95% and a 7.5% accuracy value; A sample size of 171 subjects with measurement adjustments of dropping out patients by 15% was used; A final sample size of 200 patients was used.

Sampling method was aleatory and 200 subjects were included every one with an ultrasonographic diagnosis of NASH; Where 50 of these had at least 3 out of 5 inclusion criteria for MS (Previously described).

NASH severity staging classification was according to the following criteria based on imaging and NASH staging done with an GE LOGIQ x200 ultrasound adapting a convex 3.5 Mhz transducer, manufactured by the same radiologist.

**Nash staging criteria described as followed:**

**Mild:** minimum diffuse increase of the hepatic echogenicity, normal visualization of the diaphragm and intra hepatic blood vessels edge.

**Moderate:** Moderate rise in hepatic echogenicity, mild reduction of the intra hepatic blood vessels edge and diaphragm.


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**Severe:** Noticeable rise in hepatic echogenicity and poor hepatic posterior lobe display as well as decreased or lacking of the intra hepatic blood vessels edge and diaphragm.

**Statistic Analysis:** Prior construction and data base clean up with study variables, A descriptive analysis was employed to determine frequencies and proportions. Chi-square and T Students were applied according to the type variable. A multivariate analysis assessed with ANOVA factor was made. a $P<0.05$ was considered to be a significant trust value.

**Table 1: Description of the population**

| Variable | n | % | IC 95% |
|---|---|---|---|
| **Age** | 48.7 | 30 - 50 | |
| **Gender** | | | |
| • Male | 91 | 45.5 | 38.59 - 52.4 |
| • Female | 109 | 54.5 | 47.59 – 61.40 |
| **NAFLD** | | | |
| • Mild | 144 | 72.0 | 65.77 – 78.22 |
| • Moderate | 54 | 27.0 | 20.84 – 33.15 |
| • Severe | 2 | 1.0 | 00.03 – 00.23 |
| **Metabolic Syndrome** | | | |
| • With MS | 79 | 39.7 | 03.29 – 04.64 |
| • Without MS | 120 | 60.3 | 05.35 – 06.70 |
| **Comorbilities** | | | |
| • Without comorbilities | 108 | 54 | 04.70 – 06.09 |
| • HIV | 43 | 21.5 | 01.58 -02.71 |
| • DM2 | 37 | 18.5 | 01.31 – 02.38 |
| • Crónico Alcoholism | 8 | 4.0 | 03.32 – 04.67 |
| • Others | 4 | 2.0 | 01.44 – 02.54 |
| **Blood Pressure** | | | |
| • With treatment | 50 | 25.0 | 01.89 -03.10 |
| • Without treatment | 150 | 75 | 06.89 – 08.10 |

**Table 2: Anova a factor for AFL**

| | | N | Mean | Confidence interval for the mean value of 95% | | value p |
|---|---|---|---|---|---|---|
| | | | | Lower Limit | Upper Limit | |
| Weight of each patient | Mild | 144 | 75.51 | 73.09 | 77.93 | 0.7 |
| | Moderate | 54 | 79.55 | 75.41 | 83.68 | |
| | Severe | 2 | 92.50 | -91.74 | 276.74 | |
| | Total | 200 | 76.77 | 74.68 | 78.85 | |
| Age of each patient | Mild | 143 | 50.43 | 47.97 | 52.88 | 0.26 |
| | Moderate | 54 | 44.78 | 41.73 | 47.83 | |
| | Severe | 2 | 39.00 | 13.59 | 64.41 | |
| | Total | 199 | 48.78 | 46.81 | 50.75 | |
| Size of each patient | Mild | 144 | 1.58 | 1.5702 | 1.6030 | 0.1 |
| | Moderate | 54 | 1.60 | 1.5833 | 1.6334 | |
| | Severe | 2 | 1.68 | 1.5529 | 1.8071 | |
| | Total | 200 | 1.59 | 1.5798 | 1.6070 | |
| Abdominal Circumference | Mild | 98 | 94.39 | 92.04 | 96.73 | 0.6 |
| | Moderate | 39 | 95.44 | 91.22 | 99.65 | |
| | Severe | 2 | 102.50 | -56.33 | 261.33 | |
| | Total | 139 | 94.80 | 92.77 | 96.83 | |
| Triglycerides | Mild | 91 | 190.47 | 170.80 | 210.15 | 0.07 |
| | Moderate | 40 | 251.88 | 215.30 | 288.45 | |


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| | | | | | | |
|---|---|---|---|---|---|---|
| | Severe | 1 | 205.00 | . | . | |
| | Total | 132 | 209.19 | 191.27 | 227.10 | |
| Impaired Glucose in fasting | Mild | 116 | 136.23 | 117.30 | 155.17 | 0.38 |
| | Moderate | 48 | 117.04 | 106.63 | 127.45 | |
| | Severe | 2 | 95.50 | -63.33 | 254.33 | |
| | Total | 166 | 130.19 | 116.62 | 143.77 | |
| High density cholesterol | Mild | 26 | 63.50 | 35.28 | 91.72 | 0.86 |
| | Moderate | 17 | 59.88 | 26.99 | 92.77 | |
| | Severe | 0 | . | . | . | |
| | Total | 43 | 62.07 | 41.50 | 82.64 | |

** ANOVA test of a factor CI 95%.*

**Table 3: Differences between NAFLD and Degree of Obesity according to BMI BODY MASS INDEX**

| Degree of NAFLD | % | Normal Weight | Overweight | Obesity | Morbid Obesity | Total |
|---|---|---|---|---|---|---|
| **Mild** | % of NAFLD | 22 (15.3%) | 49 (34.0%) | 62 (43.1%) | 11 (7.6%) | 144 100%) |
| | % de NAFLD | 10 (18.5%) | 15 (27.8%) | 24 (44.4) | 5 (9.3%) | 54 (100%) |
| **Moderate** | % of BMI | 31.2% | 23.1% | 27.6% | 31.2% | 27% |
| | Total | 5.0% | 7.5% | 12.0% | 2.5% | 27.0% |
| **Severe** | % of NAFLD | 0 (0.0%) | 1 (50.0%) | 1 (50.0%) | 0 (0.0%) | 2 (100%) |
| | % of BMI | 0.0% | 1.5% | 1.1% | 0.0% | 1.0% |
| | %Total | 0.0% | 0.5% | 0.5% | 0.0% | 1.0% |
| **Total** | % of NAFLD | 32 (16.0%) | 65 (32.5%) | 87 (43.5%) | 16 (8.0%) | 200 (100%) |
| | % of BMI | 100% | 100% | 100% | 100% | 100% |

** Chi test square p>0.05*

**Table 4: Differences according to Metabolic Syndrome**

| Variable | With syndrome n(%) μ | Without syndrome n(%) μ | BI | | p |
|---|---|---|---|---|---|
| **Age‡** | 45.51 | 50.77 | 9.235 | 1.299 | 0.01 |
| **Weight** | **81.79** | **73.68** | **3.999** | **12.217** | **0.00** |
| **BMI** | 32.72 | 28.74 | 2.519 | 5.425 | 0.11 |
| **Gender†** | | | | | |
| Male | 36 (39.6%) | 55 (60.4%) | | | |
| Female | 43(39.8%) | 65 (60.2%) | | | |

† *Chi square test*
‡ *T Student test*
n*: number of subjects %: proportion de subjects 95% CI: Confidence Interval at 95%, p= statistical significance.*

200 patients with a previous diagnosis of NASH disease were evaluated; Within the sample, 79 (39.5% (IC95%:32.72-46.27)) subjects presented at least 3 out of 5 inclusion criteria for MS diagnosis, age fluctuated among 30 - 50 years old, with a mean value of 48.7 years old (IC95%:46.81-50.75). A correlation of 54.4% in males and 45.5% in females in the prevalence of MS was obtained; 72% of NASH cases were at a mild stage (Described in table #1).

According to the NASH staging scale data was obtained as followed: HIV patients with mild NASH disease 23 (11.5%), diabetes mellitus type II 33 (16.5%), HIV infection with moderate NASH disease 19 (19.5%), diabetes mellitus type II 4 (2%) and severe HIV and NASH stage 1 (0.5%). Subjects under hypertension treatment were a total of 50 (25%) in which 39 presented mild NASH disease, moderate 10 and severe stage just 1.

Patients showing altered fasting glucose with less than 125mg/dl were a total of 40 (20%), 126 - 200 mg/dl a total of 114 (57%) and subjects with more than 200 mg/dl were a total of 11 (5.5%); Just 79 (39.5%) presented with MS and NASH. Differences regarding NASH stages are shown in table #2. A statistically significant value for triglyceride levels only existed in moderate NASH stage (p<0.05) even


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though clinically positive correlation does exist among steatosis and variables discussed previously.

Regarding NASH disease and obesity, the study reports that obese subjects present a 51% vs. 24% relation with mild and moderate steatosis, on the other hand compared to patients with a normal weight and NASH showing a 69% value to mild staging and 31% value to moderate staging (detailed in table #3).

Setting differences according to patients with a prevalence of MS, women had a 3.8% value compared to males, regarding weight, the value was more in patients with MS than non carriers 8.11 kg (p=0.0001), as well as the relationship between age and MS, showing they are 5.76 years younger (p=0.01) Table #4. The risk of MS vs. non MS carriers showed an OR=1.004.

## Discussion:

The prevalence of NASH in patients with MS found in this study was 39%; Similar to data found in reference studies, within this study, age ranked between 30´s and 50´s with an average of 48 years old primarily in women 54.5%.

MS is considered as an important predictor factor for NASH due to the steatosis generally secondary to an insulin resistance state present in subjects with one of the components of MS, MS and obesity are directly related to life style changes.[6]

Currently NASH has become a major public health problem in Mexican population, the study shows a connection between MS and BMI with a prevalence of obesity of 67%. In this study 100% of the patients presented with NASH in any of its stage, however, almost 4 out of 10 patients were MS carriers. The correlation between overweight-obesity and MS was directly proportional to the fact that for every 8.11 kg (p=0.001) of weight, MS prevalence increase. In the US population the prevalence of NASH goes from 3% to 25% in obese subjects. ranking between 15% to 30% of the population and more than 50% in patients with Diabetes Mellitus type II and MS. In México, according to the national health and nutrition system inquiry from 2006, reports a prevalence of MS of 36.8% and 49.8%, being more frequent in women rather than male subjects and patients with a lower socioeconomic status.[12]

A study done in Mexico city reported that, the prevalence of NASH in individuals with MS rises up to 82.9%, being higher in male population with a 86.9% value than women with a 76.1% value; Nevertheless giving a higher proportion regarding the severity of NASH staging: mild 52.3%, moderate 22.3% and severe 8.3%.[3]

Another study performed in the state of Oaxaca, where NASH´s prevalence together with MS showed a 4.54% value (38.1% males and 61% women) with a mean age ranking from 30´s to 50´s; 79% presented dyslipidemia of which: 24.5% had hypertriglyceridimia, 12.7% had hypercholesterolemia and 40.9% had both of them; In obese patients, 4 out of 5 patients were positive for NASH without a correlation between abdominal circumference considered for males and females.[10]

Identifying the relationship between NASH in MS carrying subjects, which is more often found just as a radiologic diagnosis for some other concomitant pathologies sometimes not associated with it, could anticipate hepatic and cardiovascular complications. Lifestyle and nutritional changes are crucial to reverse hepatic changes, for which our role as first contact medical doctors is to provide information and aware patients.

Other Studies referring to NASH and MS related factors, at least for now, had not been yet diffused among the population as it should among southeastern mexico´s population, for which this study shows results among ranking values reported previously around the globe as well as within the country, therefore, supporting the presence of a clinical relationship between hepatic damage and metabolic disorders such as obesity, overweight and MS.

The study belongs to an incipient line of investigation of metabolic disorders in southeastern adult patients in Mexico, which will offer a diagnostic criteria as well as a treatment approach on this patients.

One of the weak points of this study was not including non NASH carrier patients to correlate the results, which suggest other studies in the subject to add this criteria.

Prevalence of MS in patients with NASH is similar to values in other places around the globe and Mexico, however, the relationship between obesity and the severity of NASH could not be proved with this study, it is necessary for next studies regarding the subject to include a larger sample to proof the hypothesis.

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