

## Should nonalcoholic fatty liver disease be regarded as a hepatic illness only?

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### Abstract

The highly increasing prevalence of obesity and type 2 diabetes mellitus in the general population makes nonalcoholic fatty liver disease the most common diagnosis in every-day practices. Lifestyle changes (mainly exercise withdrawal and weight gain) have probably heightened the prevalence of nonalcoholic fatty liver disease. Mortality in patients with Nonalcoholic Fatty Liver Disease is significantly higher when compared with that of the same age-gender general population. Hepatologists claim to bear a new burden, being Nonalcoholic Fatty Liver Disease strongly linked to systemic diseases.

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### SCENARIO

Nonalcoholic fatty liver disease (NAFLD) has recently emerged as the most common cause of abnormal laboratory liver tests (LLTs) seen in patients presented to practicing hepatologists, with the overall prevalence of NAFLD in the developed world estimated to be between 20% and 30%. Changes in lifestyle have resulted in a dramatic increase in the prevalence of NAFLD. Apoptosis and insulin resistance (IR) play an important

role in the disease development and progression. Our current knowledge of the natural history of NAFLD can be summarized as follows: elevated body mass index (BMI) plays a key role; simple steatosis NAFL (Fatty liver, FL) does not generally progress to Non-Alcoholic SteatoHepatitis (NASH); patients with NASH progress, in relatively many cases, to cirrhosis; older age and advanced fibrosis are risk factors for hepatocellular carcinoma (HCC) in NASH; up to a third of patients develop liver-related morbidity or mortality. It is extremely important that physicians diagnose NASH accurately and perform appropriate treatments, because it represents an illness mirroring a systemic process, and an adjunctive cardiovascular disease (CVD) risk<sup>[1]</sup>. A great deal of research highlight the need for surrogate serum markers for diagnosing NASH. Among them, serum cytokeratin 18 has captured certain interest<sup>[2]</sup>.

### COULD NAFLD BE CONSIDERED A FURTHER EXPRESSION OF METABOLIC SYNDROME?

NAFLD and NASH are conditions gaining increasing recognition, obesity being (mainly of high grade) one of the more important risk factors. But, do other aspects of metabolic syndrome (MS) play a role? To answer this question, a prospective study was conducted in 127 consecutive obese patients (62% female, mean age 40 ± 11 years, mean BMI 42 ± 6 kg/m<sup>2</sup>) undergoing gastric bypass over a 20-month period. The report highlighted that arterial hypertension was present in 52 patients (41%) and type 2 diabetes mellitus (DM) in 18 (14%). However, NAFLD was confirmed in 80 patients (63%). Of them, 47 (37%) had FL, and 33 (26%) had NASH. Cirrhosis was found in 2 patients corresponding to 1.6% of the total population. For multivariate analysis, elevated HOMA independently predicted only NASH, (OR 4.18, 95% Confidence Interval, CI, 1.39-12.49). That NAFLD was frequently found, it is easy to deduce that the NAFLD presence coupled with obesity (visceral) and hypertension could be used as criteria to label the patients with MS<sup>[3]</sup>.

### ARE PATIENTS' AGE OR LONGEVITY OF ILLNESS A CRITERION TO INFER NASH PRESENCE?

To characterize the spectrum of NAFLD in morbidly

obese adolescents, a cross-sectional study correlated in 41 adolescent subjects' (mean age, 16 years, 61% female, 83% non-Hispanic white, mean BMI 59 kg/m<sup>2</sup>, undergoing bariatric surgery) liver histology with clinical features and compared data with those of the adults. The Authors wondered if NAFLD would be less severe as a result of younger age and shorter duration of obesity and which grade of portal inflammation and fibrosis would be present. Eighty-three percent had NAFLD: 24% FL, 7% isolated fibrosis with steatosis, 32% non-specific inflammation and steatosis, and 20% NASH. Twenty-nine percent had fibrosis; none had cirrhosis. Abnormal ALT was more prevalent in NASH. Mean fasting glucose was higher in NASH, but the percentage of MS was not different. The researchers concluded that NAFLD was very prevalent in morbidly obese adolescents, but severe NASH was uncommon. In contrast to morbidly obese adults, lobular inflammation, significant ballooning, and perisinusoidal fibrosis were rare, whereas portal inflammation and portal fibrosis were more prevalent, even in those who did not meet criteria for NASH. Presence of MS in morbidly obese adolescents did not distinguish NASH from FL. Conclusively; the answer is... yes it is<sup>[4]</sup>.

#### **Could being overweight (not necessarily obese) be considered a risk factor for the NAFLD progression?**

The realization that a proportion of patients with NAFLD can progress through NASH and fibrosis to full-blown cirrhosis and HCC has recently focused the attention of the liver-disease scientific community on this condition, previously considered to be benign. Although several studies have been performed on risk factors (presented in a single or combined way) and natural course of NASH, it seems that NASH is inclined to be more than a disease confined to classic boundaries. The objective of a recent study was to assess the clinical features and risk factors for NASH patients in an Iranian population. Fifty three patients (21 female, mean age 37.8 ± 11.3 years) with histologically confirmed NASH entered the study. Twenty-six patients (55.3%) were overweight, 15 (31.9%) obese, 40 (75.5%) dyslipidemic, and three patients (5.7%) were diabetic. Liver histology showed mild steatosis in 35.7%, moderate steatosis in 53.6%, and severe forms in 10.7%. In 80.2% of patients, portal inflammation was present, and 9.4% had cirrhosis. The amount of increase in LLTs bore no relationship with fibrosis, portal inflammation, and degree of steatosis. The interesting point of this research dwells with the overweight, not the obese, as having a risk factor for NASH. Obviously, a careful history was taken regarding alcohol intake<sup>[5]</sup>.

#### **And what is the role of visceral fat?**

NAFLD is increasing rapidly in the population of the Asia-Pacific region, representing a good model of study. The aim of an up-to-date research was to define the anthropometric, metabolic and histological characteristics of patients with NAFLD in these countries. Seventy-five patients with persistently raised LLTs and/or FL detected on ultrasonography (US) with exclusion of other liver disorders were prospectively enrolled (39 men, mean

age 47.0 ± 12.2 years). Fifty eight patients (77.3%) had visceral obesity, 29 (38.7%) were diabetic and 15 (20.0%) had impaired glucose tolerance (IGT). Insulin resistance was diagnosed in 62 out of 64 (96.9%) patients. FL, NASH and cirrhosis were diagnosed in three (4.3%), 59 (84.3%) and eight (11.4%) of 70 patients, respectively. The complete histological spectrum of NAFLD was seen in these patients. The majority of them were characterized by IR, central obesity and had either type 2 DM or IGT<sup>[6]</sup>.

#### **Is isolated portal fibrosis the link between FL and NASH?**

NASH is a progressive form of NAFLD that can lead to hepatic fibrosis and cirrhosis. Until now, portal fibrosis in the absence of NASH, called isolated portal fibrosis (IPF), has received less attention and has not been classified as a spectrum of NAFLD, but, when found in patients with HCV-related chronic hepatitis it is considered to be a key feature of viral infection. Liver biopsies from 195 morbidly obese subjects who underwent bariatric surgery after excluding all other causes of liver disease were analyzed. The prevalence of fatty liver (FL) only, IPF, and NASH was 30.3%, 33.3%, and 36.4%, respectively. Again, hyperglycemia was the only metabolic parameter associated with NASH (OR, 5.4; 95% CI, 2.4-12) and IPF (OR, 2.8; 95% CI, 1.2-6.5). MS was identified in 78.5% of subjects, and a significant trend for the clustering of MS criteria was observed across the spectrum of FL, IPF, and NASH<sup>[7]</sup>.

#### **Is the exact prevalence of NASH in the severely obese known?**

NAFLD has been consistently associated with every grade of obesity and IR. As previously stated, NASH is a histological entity within NAFLD that can progress to cirrhosis. The prevalence of NASH in morbidly obese patients is a crucial point of study, because they represent a well-defined population. It is unclear whether differences in insulin sensitivity exist among subjects with NASH and FL. To evaluate the prevalence and correlates of NASH and consequently liver fibrosis in this distinctive cohort of ninety-seven subjects, a recent study was employed. Thirty-six percent of subjects had NASH and 25% had fibrosis. No cirrhosis was diagnosed on histology. Markers of IR and MS, but not BMI were associated with the presence of NASH. Forty-six percent of patients suffering from NASH had normal transaminases. Subjects with NASH had more severe IR when compared to those with FL. In conclusion, NAFLD is associated with MS rather than excess adipose tissue in the severely obese<sup>[8]</sup>.

#### **Are laboratory liver tests worth using to screen NAFLD?**

A fascinating study was conducted to determine whether the current liver screening program for NAFLD has sufficient evidence to justify its continued implementation. The LLTs program to detect NAFLD was performed on 411 Japanese workers utilizing serum ALT, AST, and gammaglutamyl transpeptidase (GTP). Subjects with viral and alcohol hepatitis were excluded from the evaluation. The diagnosis of NAFLD was based on US findings. The program was evaluated by efficacy and effectiveness in comparison with the BMI. Effectiveness, based on

the efficacy determinations, was assessed by means of the positive predictive value (PPV) test performance, the disease characteristics, and the program cost. The diagnostic performances of ALT and BMI were far from excellent. The areas under the curves of the two indices were 0.69 and 0.63, respectively. The PPV ranged from 15 to 28% where the prevalence of fatty liver was 12.3%. The cost of the program was estimated at \$4 U.S. dollars per person based on the medical reimbursement fee rate. The efficacy of the liver screening program was found to be insufficient and, therefore, revealed that BMI monitoring may provide a more suitable and inexpensive alternative. The authors challenge the effectiveness of the LLTs, considering the high price of the program<sup>[9]</sup>.

#### **What is the risk of cancer in patients with NAFLD?**

The relation between NAFLD and cancer risk is poorly understood. Using the population-based National Registry of Patients, some Authors examined the incidence of cancer in 7326 patients discharged with a diagnosis of NAFLD from a Danish hospital during 1977-1993. Overall, 523 cancers were diagnosed during 47 594 person-years of follow-up, yielding a 1.7-fold increased risk (95% CI, 1.6-1.9) compared with the Danish general population. The risk of primary liver cancer was markedly elevated in patients with alcoholic liver disease (ALD) as well as NAFLD with a standardized incidence ratio of 9.5 (95% CI, 5.7-14.8) and 4.4 (95% CI, 1.2-11.4), respectively. Patients with ALD also had substantially increased risks of several types of cancer associated with alcohol and tobacco use (cancers of the lung, pharynx, larynx, esophagus, and stomach) and a moderately increased risk for cancers of the colon and breast. Among patients with NAFLD, an increased risk of some alcohol- and tobacco-related cancers was seen, and there was also an increased risk of colon and pancreas cancer<sup>[10]</sup>.

#### **Then, what is the natural history of NAFLD in the community?**

Authors sought to determine survival and liver-related morbidity among community-based NAFLD patients. Four hundred twenty patients diagnosed with NAFLD in Olmsted County, Minnesota, between 1980 and 2000 were identified using the resources of the Rochester Epidemiology Project. Overall survival was compared with the general population of the same age and sex. Overall, 53 of 420 (12.6%) patients died. Survival was lower than the expected survival for the general population ( $P = 0.03$ ). Higher mortality was associated with age (hazard ratio per decade 2.2; 95% CI 1.7-2.7) and impaired fasting glucose (hazard ratio 2.6; 95% CI 1.3-5.2). Liver disease was the third leading cause of death (as compared with the thirteenth leading cause of death in the general population), occurring in 7 (1.7%) subjects. Twenty-one (5%) patients were diagnosed as being affected by cirrhosis, and 13 (3.1%) developed serious complications<sup>[11]</sup>.

#### **And what about NAFLD in atopic/non-atopic children?**

NAFLD in non-obese Japanese children was observed in 3.2% of non-atopic children and in 17.6% of patients

with atopic dermatitis or suffering from bronchial asthma, allergic rhinitis, in 2000. NAFLD was studied by abdominal US scans. The prevalence of NAFLD was increasing annually, and it reached 12.5% in non-atopic children, 13.1% in patients with bronchial asthma, 13.7% in patients with allergic rhinitis, or 33.9% in patients with atopic dermatitis, in 2003. Since NAFLD in childhood may be a risk factor for lifestyle-related diseases in future, care should be taken to prevent it<sup>[12]</sup>.

It would have been interesting to know how many of those subjects were on steroid therapy.

#### **Could polyunsaturated fatty acids be used to improve an immunological disease and an apparently distant illness of liver, i.e., NAFLD?**

The higher incidence of inflammatory diseases in Western countries might be related, in part, to a high consumption of saturated fatty acids and n-6 polyunsaturated fatty acids (PUFA) and an insufficient intake of n-3 fatty acids. In an intriguing study, Balb/C mice were fed for 3 wk either n-6 or n-3 PUFA-fortified diets. After inducing a contact or an atopic dermatitis, immunological parameters were analyzed by the authors to evaluate the anti-inflammatory potential of these n-3 PUFA. Accordingly, n-3 PUFA lessened innate and specific immune responses through inhibition of TH1 and TH2 responses, increase of immunomodulatory cytokines such as IL-10, and regulation of gene expression. Furthermore, reduction in edema, leukocyte infiltration, and enhancement of antioxidant defenses in the inflamed ears of mice from both models proved n-3 PUFA efficacy. Authors' data suggest that dietary fish oil-derived n-3 fatty acids could be useful in inflammatory disorders<sup>[13]</sup>.

On the other hand, is obesity a chronic low-grade inflammatory process or not? Because eicosapentaenoic acid, docosahexaenoic acid, and gamma-linolenic acid have anti-inflammatory, as well as lipid-modifying properties, the effects of supplement mixtures of these PUFA should have received much more attention by researchers in the field of NAFLD treatment.

#### **What have two peculiar syndromes to do with NAFLD?**

NAFLD and polycystic ovary syndrome (PCOS) are both associated with IR. Thus, women with PCOS may have an increased prevalence of NAFLD, including NASH. To determine the prevalence and characteristics of NASH and abnormal ALT in women with PCOS were retrospectively studied 200 women with PCOS, diagnosed with irregular menses and hyperandrogenism. Fifteen percent (29 out of 200) had AST and/or elevated ALT. Women with aminotransferase elevations had lower high-density lipoprotein (HDL),  $P = 0.006$ , higher triglycerides ( $P = 0.024$ ), and higher fasting insulin ( $P = 0.036$ ) compared with women with normal aminotransferases. Six women had NASH with fibrosis. The authors concluded that abnormal aminotransferase activity is common in women with PCOS and suggest a reflection of whether to screen PCOS women for liver disease at an earlier age than is currently recommended for the general population<sup>[14]</sup>.

Recently, obstructive sleep apnea (OSA) has been proposed as an independent risk factor for IR. The

objectives of this study were to document the prevalence of SOSA in patients with NAFLD and to determine whether prevalence rates for SOSA differ in NAFL versus NASH patients. The prevalence of OSA was similar in both biochemically ( $P = 0.66$ ) and histologically ( $P = 0.11$ ) defined NAFL and NASH patients. Other risk factors for NAFLD such as BMI, cholesterol and triglyceride levels, and prevalence of diabetes were also similar in the two groups. Approximately one-half of NAFLD patients, whether NAFL or NASH, have OSA<sup>[15]</sup>.

### Could abnormalities in the estradiol to testosterone ratio (increased androgens and decreased estrogens) lead to insulin resistance and NASH?

Recently, the fourth case has been presented of an adult man (29 years old) affected by aromatase deficiency resulting from a novel homozygous inactivating mutation of the CYP19A1 (P450-aromatase) gene. The patient showed also a complex dysmetabolic syndrome characterized by IR, type 2 DM, acanthosis nigricans, NASH, and signs of precocious atherogenesis. The analysis of the effects induced by the successive treatment with high doses of testosterone, alendronate, and estradiol allows further insight into the roles of androgens and estrogens in several metabolic functions. High doses of testosterone treatment resulted in a worsening of IR and type 2 DM. Estrogen treatment resulted in an improvement of acanthosis nigricans, IR, and NASH, coupled with a better glycemic control and the disappearance of two carotid plaques. Data from this case provided new insights into the role of estrogens in glucose, lipid, and liver metabolism in men<sup>[16]</sup>.

## CONCLUSION

For many years, research concerning acute and chronic liver diseases have been mostly confined to few areas of Medicine, i.e., virology and immunology. Vice versa, for the first time in decades, the liver comes back to have a pivotal role in Health Sciences, embracing endocrine, cardiovascular and oncological diseases, so the answer to the initial question, "Should nonalcoholic fatty liver disease be regarded as a hepatic illness only?," is... It should not!

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