

## Fatty liver in lean patients: is it a different disease?

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Nonalcoholic fatty liver disease (NAFLD) has widely been considered a manifestation of metabolic syndrome in close relation to obesity [1]. In fact, although obesity is undoubtedly one of the main risk factors for fatty liver, since its first description it is known that it can also occur in lean subjects. Studies in the Occident, with liver histology performed in subsets representative of the general population, as for example liver donors and automobile crash victims, among others, have roughly found hepatic steatosis in 15% of non-obese subjects, as opposed to 65% and 85% in obese and morbid obese, respectively [2,3]. In fact, the majority of patients with steatosis are either overweight or obese [4]. The reality of developing countries seems to be different, with a recent study in India showing that in a rural population with low prevalence of NAFLD, 75% of NAFLD patients had a body mass index lower than 25 kg/m<sup>2</sup> and 54% had neither overweight nor abdominal obesity [5]. Furthermore, it is believed that not all excessive body fat is relevant, rather visceral obesity seems to be the metabolically dangerous one, being the main source of fatty acids, and pro-steatogenic, pro-inflammatory and pro-fibrogenic mediators [6]. Unexpectedly, recently, Fracanzani et al suggested that among patients with hepatic steatosis, the presence of visceral obesity does not seem to be a major determinant for having nonalcoholic steatohepatitis or advanced fibrosis [7].

The paper by Margariti et al. in this issue of *Annals of Gastroenterology* [8] highlighted the fact that a percentage of NAFLD patients in a tertiary care are lean. They studied 162 consecutive patients with hepatic steatosis and found that one in every eight patients with NAFLD, followed in a specialized unit, had normal body mass index. As compared with overweight or obese, lean patients had less metabolic disturbances, but higher aminotransferase levels. Correlation with histology data is missing. The present study raises several important issues regarding lean NAFLD patients; whether this is a different disease with other risk factors and a different progression eventually to more severe disease,

or just the same disease with a similar metabolic profile but in the absence of excessive weight. It is also possible that NAFLD may be more frequently unnoticed in normal weight populations.

One explanation for the existence of ectopic fat in the liver of lean subjects, could reside in the concept of metabolically obese normal weight subjects, which corresponds to 5% of the occidental population [9]. These are subjects with normal weight that usually became slightly heavier during adult life, with a 2 to 10 kg increase in weight, which was almost entirely due to an increase in adiposity [10]. They are frequently sedentary, with a low peak oxygen uptake, reduced insulin sensitivity, metabolic disturbances and increased cardiovascular risk [11]. In fact, one third of the lean patients in Margariti's paper had increased waist circumference, one fifth had metabolic syndrome and more than half at least one criterion of the metabolic syndrome. One could wonder whether these patients have subclinical metabolic disease, with ectopic fat being the first manifestation. It would be interesting to follow these patients in order to evaluate their risk of metabolic disturbances, insulin resistance/diabetes mellitus, cardiovascular events and liver disease progression. It would also be of interest to know if a family history of diabetes was present in this sub-group of lean NAFLD, thus increasing the possibility of future appearance of diabetes. Actually, excessive liver fat content is considered an independent risk factor for metabolic disturbances, after adjustment to body mass index, body fat percentage and visceral fat mass [2].

The lean population with ectopic liver fat could also unravel a different physiopathology. There are several well known animal models and genetic diseases that can lead to hepatic steatosis and are not associated with obesity or insulin resistance. A paradigm of that is the methionine and choline-deficient diet (MCD) mouse model, the most widely used to study NAFLD. Mice submitted to the MCD diet do not become insulin resistant or obese, on the contrary they even lose weight [12], and liver fat accumulates as a consequence of a decrease in the beta-oxidation of fatty acids and a decrease in very low density lipoproteins (VLDL), and hence triglycerides export from the cell [13]. Another example is the genetically modified mice that over express acyl-CoA:diacylglycerol acyltransferase 2 (DGAT2), which catalyzes the final step in triacylglycerol biosynthesis. These mice develop hepatic steatosis with increased amounts of triglycerides, diacylglycerol, ceramides and unsaturated long-chain fatty acyl-CoAs, without developing insulin resistance or disturbances in the metabolism of glucose [14]. In humans, genetic polymorphisms associated with NAFLD may also dissociate hepatic steatosis from obesity

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and insulin resistance. The widely studied PNPLA3 gene, encoding for adiponutrin, is one such case. The most relevant polymorphism, I148M is associated with a decreased lipolytic activity. It is also associated with higher aminotransferases levels, but not with insulin resistance [15]. Regarding human disease, the most well studied is probably hypobetalipoproteinemia, which is associated with severe forms of NAFLD, but not with increased metabolic risk [16]. Also, diseases that lead to malabsorption can cause hepatic steatosis, namely celiac disease [17], cystic fibrosis [18] and inflammatory bowel disease [19]. Alcohol and over-the-counter drugs are extremely difficult to exclude, even after a detailed questionnaire. In this particular sample, alcohol intake is unlikely, since history of alcohol consumption was taken from the patients, but also confirmed by relatives and/or friends. However, traditional markers of alcohol consumption, like increased  $\gamma$ -glutamyl-transferase, were higher in lean *versus* overweight/obese patients, although without statistical significance. Lastly, unknown risk factors and secondary causes of NAFLD should be further investigated.

The study by Margariti et al [8] has, however, some limitations. The diagnosis of NAFLD was not done uniformly among patients, with some being diagnosed through ultrasonography and others through liver biopsy, the gold standard. In fact, ultrasonography is accurate only in patients with moderate to severe steatosis, and even in that setting it is not perfect, with a reported sensitivity of 85% and specificity of 94% [20]. It could be that hepatic steatosis was less severe in lean patients that in obese, since in obese a positive ultrasonography could be sufficient to establish the diagnosis and in lean the threshold to perform liver biopsy could be lower. It would also be of interest to know the dietary patterns in those patients with normal body mass index, as well as some information regarding physical activity. In fact, we have recently highlighted that former athletes who become sedentary may be at increased risk of developing insulin resistance and metabolic complications, such as NASH in the absence of the usual risk factors [21].

In conclusion, NAFLD should not be neglected in normal weight subjects with altered liver enzymes. It could indicate a higher risk for metabolic disturbances and/or cardiovascular morbidity, or it could unravel a different entity of non-metabolic, non-alcoholic fatty liver disease. Accordingly, a deeper diagnostic investigation for secondary causes of hepatic steatosis, like hypobetalipoproteinemia and malabsorption diseases is required in lean NAFLD patients. Follow-up studies specifically in this set of patients is necessary in order to better understand the association with other diseases and the real prognosis of liver disease. Also, a difficult unsolved issue is how to treat these patients who already have normal weight and whether diet and exercise are useful.

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