European Journal of Internal Medicine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Liver steatosis: The new epidemic of the Third Millennium. Benign liver state or silent killer?

Claudio Puoti [a,b,*], Maria Giuseppa Elmo [c], Daniela Ceccarelli [d], Michela Ditrinco [b]

[a] Liver Unit, INI Research Institute and Clinics, Grottaferrata, Rome, Italy
[b] N. Cusano University, Rome, Italy
[c] Mental Health Department, ASL Rome 1, Rome, Italy
[d] Department of Radiology, CTO Hospital, Rome, Italy

ARTICLE INFO

Article history:
Received 19 June 2017
Accepted 29 June 2017
Available online xxxx

Keywords:
Diet
Metabolic syndrome
Non alcoholic
NAFLD
NASH
Steatosis

ABSTRACT

Until the end of the 90′s of the last century, rather little attention was paid to the issue of the non-alcoholic fatty liver disease (NAFLD), perhaps due to the fact that the newly discovered hepatitis C virus did attract a paramount interest of hepatologists and researchers.
On the other side, fatty liver was considered a relatively uncommon cause of liver damage, occurring almost exclusively in obese females, often associated with non-insulin dependent diabetes mellitus (NIDDM), and with a relatively benign prognosis.
Due to the complexity of international available guidelines, we decide to approach the main unsolved issues on this topic in the form of a dialog between a hepatologist and a man suffering from NAFLD, trying to give evidence-based answers to the more frequently asked questions from patients and their GPs. This is the third instalment of the Trilogy of Dr. Calm, a skilled hepatologist who will try to clearly explain to his patient Mr. Frightened the natural history of NAFLD, the diagnostic workup, indications for liver biopsy and suggested medical treatments, advicing him on the importance of dietary intervention and lifestyle modifications.

1. Introduction

Until the end of the 90′s of the last century, rather little attention was paid to the issue of the non-alcoholic fatty liver disease (NAFLD), perhaps due to the fact that the newly discovered hepatitis C virus did attract a paramount interest of hepatologists and researchers. On the other side, fatty liver was considered a relatively uncommon cause of liver damage, occurring almost exclusively in obese females, often associated with non-insulin dependent diabetes mellitus (NIDDM), and with a relatively benign prognosis [1]. Thus, very few position papers and international guidelines were available up to the beginning of this decade. Only recently the medical community became aware of three issues: i) liver steatosis is the hepatic counterpart of a more complex metabolic syndrome, ii) the natural history of the disease is not always as benign as previously thought, ranging from “simple” fatty liver to steatohepatitis and to cirrhosis and hepatocellular carcinoma (HCC), and iii) liver steatosis is becoming the first cause of chronic liver disease (CLD), at least in developed Industrialized countries [2].

The increasing prevalence of the liver steatosis among general population has been paralleled by an ever increasing and huge number of practice guidelines on NAFLD diagnosis and management issued by Scientific Societies, which may probably add to the uncertainties concerning the best conduct to follow in clinical practice [2].

Thus, due to the complexity of international available guidelines, we wish to approach the main unsolved issues on this topic in the form of a dialog between a hepatologist and a man suffering from NAFLD, trying to give evidence-based answers to the more frequently asked questions from patients and their GPs. This is the third instalment of the Trilogy of Dr. Calm [3,4], a skilled hepatologist who will try to clearly explain to his patient Mr. Frightened the natural history of NAFLD, the diagnostic workup, indications for liver biopsy and suggested medical treatments, advicing him on the importance of dietary intervention and lifestyle modifications.

Patient: Good morning, Doctor Calm.

Doctor: Good morning, Mr....?

P.: May I introduce myself, Doctor? My name is Frightened, Mr. John Frightened. I′m a friend of Ms. Worry and Mr. Concern [3,4], they spoke very well of you. They said you are a very skilled hepatologist.

D.: Oh thank you, Mr. Frightened. Very nice to meet you. What is your problem? How are you?

P.: Not very well Doc, I'm afraid I'm severely ill, I'm very scared.

D.: Calm yourself, Mr. Frightened, and tell me everything.

P.: Ok, Doc. Well, a few weeks ago I did perform by chance routine lab examination, and I found that my liver is severely ill!

* Corresponding author at: Liver Unit, INI Research Institute and Clinics, Via Sant' Anna, 00046 Grottaferrata, Rome, Italy.
E-mail address: puoti@epatologia.org (C. Puoti).

http://dx.doi.org/10.1016/j.ejim.2017.06.024
0953-6205/

D.: Keep cool, my dear. I haven't still understood what we are talking about.

P.: You're right, Sir. Would you please just evaluate my medical report?

D.: Yes, of course. Well, in first you've raised aminotransferase levels, although not marked, 1.5–2 times the upper limit of normal values. Alanine aminotransferase (ALT) levels are higher than those of aspartate aminotransferase (AST), and γ-glutamyltranspeptidase levels are slightly elevated (no more than 2 times the normal values). Blood count, alkaline phosphatase, bilirubin, albumin levels, total/HDL cholesterol, and blood glucose are all within the normal range. By contrast, your triglycerides values are strikingly elevated, up to twice the upper limit of the normal.

P.: Please Doc, tell me: do I have chronic hepatitis or cirrhosis? Will I spread the disease to my relatives? How sick will I become?

D.: Just a moment please, Mr. Frightened. There are here several other data.

P.: Yes, my GP did prescribe many other blood tests.

D.: Yes, I see. Well, serum markers of chronic viral hepatitis (HBsAg, HBcAb, anti HCV antibodies) are negative. Serum ferritin levels and transferrin saturation are normal and serum markers of coeliac disease are negative. Finally, non-organ specific autoantibodies (NOSA) are negative. Did you perform also ultrasound liver scan?

P.: Yes Doc, here it is.

D.: There are here four very interesting sonographic findings: (i) a diffuse hyperechoic echotexture (the so-called bright liver), (ii) increased liver echotexture compared with the kidneys, (iii) vascular blurring, and (iv) deep attenuation [5].

P.: Then, Doctor Calm? Your conclusions?

D.: Keep calm, please. I have some important questions to ask you. First of all, tell me something about you and your lifestyle. How old are you? Did you have important diseases in the past? Do you usually drink wine or alcoholics?

P.: I'm 68 year-old, I had no important illness, I'm retired. My wife is a housewife, and we have two sons. I'm a teetotaler, my blood pressure is persistently normal and I don't take any medication. I'm 1.73 m tall and my weight is 96 kg.

D.: OK, and are you engaged in some physical activity? Or do you lead sedentary life?

P.: No physical activity, Doc, I'm almost sedentary.

D.: Dear Mr. Frightened, have you ever heard of steatosis?

P.: Oh my God Doc, what did you say? Cirrhosis? Can I be cured? Is liver biopsy needed? Can I have a normal life? Is liver transplantation urgently needed?

D.: No, I said steatosis, not cirrhosis at all. The term steatosis means "fatty liver", i.e. a condition characterized by excessive fat accumulation [6]. Traditionally, fatty disorders of the liver have been classified as alcoholic or nonalcoholic [5]. As you are teetotaler, in your case we can use the term non-alcoholic fatty liver disease (NAFLD). When steatosis coexists with liver-cell injury and inflammation, the term steatohepatitis (NASH) should be used [7].

P.: If I have correctly understood, NAFLD and NASH are not the same entity, isn't it Doc?

D.: You are right, Sir. More precisely, NAFLD includes two pathologically distinct conditions with different prognoses: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH); the latter covers a wide spectrum of disease severity, including fibrosis, cirrhosis and hepatocellular carcinoma (HCC) [6].

P.: It seems so distressing, Doc! Thus, I'm a very unusual case for you?

D.: Not at all. NAFLD is the most common liver disorder in Western countries, affecting 17–46% of adults [8]. NAFLD is also present in 7% of normal-weight (lean) persons, more frequently in females, at a younger age and with normal liver enzymes [9]. More in detail, the prevalence of NAFLD in the general population assessed by ultrasonography is 20–30% in Europe and the Middle East, 15% in the Far East, and 16% in some studies of normal weight subjects without metabolic risk factors [10].

P.: And among people with NAFLD, how many persons suffer from NASH?

D.: This is a very proper question. Recent studies in tertiary-care centers, using current histological definitions, have shown a surprisingly high prevalence of NASH among NAFLD cases: 43–55% in patients with increased aminotransferases [11,12] as high as 49% in morbidly obese patients [13,14], and 67% in a subset of patients with incident chronic liver disease [15]. In apparently healthy, living liver donors, the prevalence of NASH ranges from 3% to 16% in Europe and from 6% to 15% in the US [10].

P.: Dr. Calm, you've been very clear, but let me resume my condition. I'm a 68 year-old man, I'm a teetotaler, I have only mild elevation of liver enzymes, I have no other biochemical abnormalities except for high triglyceride values. Finally, my US liver scan shows some abnormalities.

D.: … and you are clearly an obese person. Indeed, your BMI is 32.1 kg/m^2. Let me now spend some more words on the NAFLD. The excessive accumulation of fat into liver cells seen in persons with NAFLD might be secondary to several causes, such as obesity, diabetes, hypertrygliceridemia, disorders of lipid metabolism, drugs, and so on [16]. Furthermore, a high-calorie diet, excess (saturated) fats, refined carbohydrates, sugar-sweetened beverages, a high fructose intake and a Western diet [17] have all been associated with weight gain and obesity, and with NAFLD. In your case, your unhealthy lifestyles and your sedentary behaviour [18] certainly worsen your liver's health.

P.: In other words, you say that I should modify my lifestyle…

D.: Yes, of course. Unhealthy lifestyles are of paramount relevance in the development and progression of NAFLD. The dietary and physical activity habits play a key role in the treatment of NAFLD [7]. But let me continue my explanation.

P.: Please Doc, I apologize for my repeatedly interruptions of your speech.

D.: What I want to say is that NAFLD is often associated with metabolic risk factors, that are component of the so-called Metabolic Syndrome (MS) [6]. This is a complex syndrome, characterized by the following features: central/visceral obesity, hyperinsulinemia, peripheral insulin resistance, diabetes, hypertriglyceridemia, and hypertension [5]. The current definition of MS implies: waist circumference > 94 cm for men and >80 cm women, arterial pressure > 130/85 mmHg or treated for hypertension, fasting glucose > 100 mg/dL (5.6 mmol/L) or treated for Type 2 diabetes (T2DM), and finally serum triglycerides > 150 mg/dL and HDL cholesterol < 40 mg/dL for men and <50 mg/dL for women [6].

P.: In conclusion Doc, I suffer from this Metabolic Syndrome …

D.: No Mr. Frightened, probably I did not clearly explain this issue. You show only two features of the MS (elevated waist circumference and abnormal serum triglycerides), thus in your case we cannot diagnose a MS, at least at present.

P.: Lovely!

D.: However, we cannot anticipate whether in the future you will develop a full MS, becoming an hypertensive or a type 2 diabetic patient.

P.: I hope this will not happen, Doctor Calm! But I have a doubt of great relevance, at least for me. How can you distinguish between NAFL and NASH in clinical practice?

D.: This is not only an excellent question, Mr. Frightened, but also a very critical issue. From a clinical point of view, it is not possible to differentiate between NAFL and NASH merely on the basis of non invasive tools (e.g., biochemistry, imaging, etc.) [5–7]. Liver biopsy is essential for the diagnosis of NASH and is the only procedure that reliably differentiates NAFL from NASH, despite limitations due to sampling variability [19]. NAFL encompasses: a) steatosis alone, b) steatosis with lobular or portal inflammation, without ballooning, or c) steatosis with ballooning but without inflammation [20]. The diagnosis thus requires the joint presence of steatosis, ballooning and lobular inflammation [20,21]. Steatosis is a prerequisite for the diagnosis of NAFL, and the minimal

Please cite this article as: Puoti C, et al, Liver steatosis: The new epidemic of the Third Millennium. Benign liver state or silent killer?, Eur J Intern Med (2016), http://dx.doi.org/10.1016/j.ejim.2017.06.024