Author’s response to reviews

Title: Non-alcoholic fatty liver disease

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The reviewers’ thoughtful input is much appreciated.

Reviewer #1: The author should be congratulated for this comprehensive and well-written review on NAFLD, covering the many uncertainties related to its natural history, diagnosis and treatment. Key aspects are discussed and current controversies highlighted, making it a "must-read" for all clinicians interested in a brief up-to-date in NAFLD.

Thank you.

Two minor suggestions are included:

1. Natural history: the true prevalence of NASH has been a challenge to establish since systematic population-wide liver biopsies cannot be ethically justified. In addition, no plasma biomarker or imaging study is currently good enough to this end. However, many suspect that the prevalence of NASH is higher than the 2-5% quoted from ref. 4 (from Goh & McCullough, Dig Dis Sci. 2016). A recent review by Younossi et al (Hepatology 2016) suggested that the prevalence of NASH among NAFLD patients without an indication for liver biopsy was 6.67% (95%CI:2.17-18.73) in studies from Asia and 29.85% (95%CI:22.72-38.12) in those from the United States.

The recent Younossi paper estimating the economic burden of disease is now included.
A higher rate is very likely in patients that are obese and/or have type 2 diabetes mellitus (T2DM). In the Dallas Heart study (Browning et al, Hepatology 2004), the prevalence of NAFLD among obese patients was ≥60% or about 2-fold higher than in the general population. Diabetes is another major factor, based on our own experience (Portillo-Sanchez et al, JCEM 2015) and that of others (Targher et al, Diabetes Care 2007; Leite et al, Liver Int 2009; Prashanth et al, J Assoc Physicians India 2009; Williamson et al, Diabetes Care 2011; Doycheva et al, Aliment Pharmacol Ther. 2016). In the small study by Portillo-Sanchez et al (JCEM 2015) the prevalence of NAFLD by 1H-MRS in 103 diabetics with ALT ≤40 U/L was 50%, with 26% of those biopsied having NASH. A limitation of all of these studies is that they are from tertiary academic institutions, and as such, coming from somewhat selected populations. Finally, two recent large population-based studies (by Kwok et al, Gut 2015 and Koehler et al, Hepatology, 2016) have reported that up to 17% of patients with T2DM may have significant fibrosis when assessed by VCTE (vibration controlled transient elastography; Fibroscan®), presumably from NASH. I am sure the author agrees with the above view and would welcome adding a comment regarding a higher prevalence rate of NASH among patients with obesity or T2DM.

Agree. Screening high risk patients such as those with T2DM is an important message to disseminate. Space constrains preclude having a full description of the data, but the Kwok and Koehler papers are now cited.

2. Treatment: the author should include vitamin E and pioglitazone in this section, the only two treatments recommended in the current AASLD guidelines (Gastroenterology 2012). In patients with prediabetes or T2DM, pioglitazone has been highly effective in RCTs as shown in a short-term proof-of-concept 6-month study (Belfort et al, NEJM 2006), and more recently, in 101 patients treated for up to 3 years (Cusi et al, Annals of Internal Medicine 2016). In PIVENS (Sanyal et al, NEJM 2010) 247 patients without diabetes were treated with pioglitazone, vitamin E or placebo. Both agents improved histology. Pioglitazone led to remission of NASH in 47% of patients (p=0.001 vs. placebo) while vitamin E did so in 36% (p=0.05 vs. placebo). Including this information would be of value to the readers as both agents are low-cost generic drugs with efficacy equal or greater than others under investigation for the treatment of NASH.

The PIVENS trial of pioglitazone or vitamin E and the more recent Cusi trial of pioglitazone are now cited.
Reviewer #2: - Background: non-alcoholic fatty liver disease (NAFLD) is an umbrella term that range from simple fatty liver to cirrhosis and its complications. Non-alcoholic steatohepatitis (NASH) is the part of the disease that include hepatocellular injury. Please report this concept and the acronym of NASH in the text.

- Natural history: report the acronym of ALT

The requested acronyms are reorganized for clarity.

- Pathogenesis: NAFLD is the liver border of metabolic syndrome. The natural history of NAFLD is linked with many metabolic features (Abenavoli et al. World J Gastroenterol. 2016)

The text was modified to highlight the association of metabolic disease with NASH. Space constraints do not allow for a review of the extensive clinical literature on this association.

- Treatment: lifestyle changes, and in particular a diet rich in fibers, vegetables with antioxidant properties is efficacy and scheduled in the treatment of NAFLD (EASL guidelines J Hepatol 2016). In particular, the benefit of Mediterranean diet was been collected (Abenavoli et al. World J Gastroenterol. 2014; Godos Int J Food Sci Nutr. 2016)

The EASL guidelines and Abenavoli paper are now mentioned and cited.