Reviewer's report

Title: Impaired Mitochondrial beta-Oxidation in Patients with Chronic Hepatitis C: Relation with Viral Load and Insulin Resistance

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Reviewer: Hironori Mitsuyoshi

Reviewer's report:

In this manuscript, Sato et al. examined hepatic fatty acid oxidation in patients with HCV infection. They showed that hepatic oxidation was significantly decreased in HCV patients compared to healthy controls and that the decreased rate was associated with serum core antigen levels and the index of insulin resistance. The mechanisms by which HCV infection promotes hepatic steatosis would involve multiple steps. The findings are interesting. However, I have several questions regarding their results and discussion.

- Major Compulsory Revisions

1. The authors showed that hepatic fatty acid oxidation was decreased in HCV patients. However, the decrease in oxidation was not significantly associated with the grade of steatosis. What is the clinical implication of the impairment of fatty acid oxidation?

2. The authors speculated that the decrease in fatty acid oxidation was associated with insulin resistance (Discussion, 7th paragraph). This suggestion is seemingly curious, since insulin resistance generally results in the increase in serum fatty acid levels. The increased serum fatty acids may accelerate hepatic fatty acid oxidation as the authors showed in Figure 4B. The relationships between them should be discussed in more detail.

3. The authors discussed that "triglyceride accumulation in the hepatocytes due to the impairment of mitochondrial beta-oxidation leads to insulin resistance (Discussion, 7th paragraph)." However, it has been described that lipid accumulation in the liver does not necessarily cause the insulin resistance (Schonfeld et al. Trans Am Clin Climatol Assoc 2008; 119: 217–24). It should be discussed.

4. The authors described that the increase in the core protein levels leads to the decrease in the rate of hepatic oxidation (Discussion, 5th paragraph). Because HCV replication prefers lipid rich circumstances, it can be assumed that the increase in the core protein levels are the results, not cause, of decreased fatty acid oxidation. They should be discussed.

5. The authors evaluated hepatic fatty acid oxidation by the rate of change in ketone body concentration between 12h and 15h after the start of fasting (Methods, fasting test). Why did they measure ketone body levels at 2 times? Is this method more accurate than one point measurement? If so, it should be described.
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.