Author's response to reviews

Title: Low fat intake is associated with pathological manifestations and poor recovery in patients with hepatocellular carcinoma

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Author's response to reviews:

Dear Dr. Hiromichi Kumagai,

I appreciate your laborious work of reviewing twice our manuscript, MS: 2126761805878423, entitled "Low fat intake is associated with pathological manifestations and poor recovery in patients with hepatocellular carcinoma". I understood that we need to response only to the reviewer 3 in this second round of review. In accordance with the Reviewer’s comments, the manuscript has been revised. A point-by-point response to the comments has been prepared and follows this cover letter. The corrections in the revised version were indicated in red for the first revise and in blue for the second revise in the text and figures. We are very grateful if the second revision is judged to be suitable for publication in your prestigious journal, Nutrition Journal, now.

Sincerely,

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Reply to the Reviewer #3
R3-2-Q1: RQ depends on substrate oxidation- when the only substrate that is oxidized (theoretically). Carbohydrate – 1.0
Fat – 0.68
Protein/amino acids – 0.85
However, when only ketogenesis happens, then the RQ is <0.68 since partial oxidation of fatty acids results in ketogenesis, but when ketones are completely oxidized, then the RQ increases to 1.0. When there is ketogenesis but only some of the ketones are oxidized, then the RQ decreases below 0.68.

Gluconeogenesis, on the other hand is a very interesting phenomenon. It is due to incorporation of carbon dioxide into a basic carbon skeletal provided either from pyruvate or from gluconeogenic amino acids. Gluconeogenesis, therefore can theoretically result in an RQ <1.0. To state that gluconeogenesis results in an increase in RQ is difficult to reconcile given these. The authors are referred to a number of excellent references on RQ in cirrhosis including some recent papers that have specifically focused on this. Studies by Muller’s group (Germany) et al would be instructive in this regard as would papers by the group from Italy (Manuela Merli and others). More recently, a publication of very low RQ in hospitalized cirrhotics also addresses these issues in the discussion section. The authors need to consider this before the response and the appropriate modifications in the discussion section can be accepted. Reviewer 3 question 1 and 7, the responses and the relevant Discussion need to address these.

R3-2-A1: I appreciate the reviewer’s critical reading and suggestions. Based on the reviewer’s comment, I understood that our discussion is not an appropriate expression of what we really want to advocate. What we want to reconcile in terms of npRQ increase and fat intake is not gluconeogenesis itself, but rather the activation of sugar metabolism in a whole body due to the gluconeogenesis, which takes place in the liver. It is also the case for ketogenesis and the oxidation of ketones. Because we evaluated npRQ in a whole body, npRQ would increase even under the situation where npRQ decreases in the liver as peripheral tissues oxidizes glucose and ketone, which are provided from the liver. The manuscript that the reviewer suggested support this notion, that a 72-hr fasting leads to the increase of NEFA uptake accompanied with the increase of glucose output from the liver and the increase of ketone body production. In cirrhotic patients, a less glycogen storage makes one night fasting affect the body in a similar way with a 72-hr starvation leading to a teleological increase of NEFA uptake. In order to make our hypothesis clear, the discussion was added with additional references in the revised version. I believe that the discussion also can be our additional response to the previous questions 1 and 7.

R3-2-Q2: Stating that ketogenesis is responsible for possible differences in mechanisms of cerebral energy expenditure in MHE vs overt HE is also difficult to reconcile.

R3-2-A2: We did not discuss anything about the differences in mechanisms of cerebral energy expenditure between MHE and overt HE in this manuscript.