Reviewer's report

**Title:** Increment of plasma glucose by exogenous glucagon is associated with present and future renal function in type 2 diabetes a retrospective study from glucagon stimulation test.

**Version:** 0  **Date:** 13 Aug 2019

**Reviewer:** Edward Janus

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The glucagon stimulation test assesses the insulin reserve of the pancreatic beta cells by measuring the increment in plasma C peptide. There is also an increment in plasma glucose. There is existing evidence that the glucose increment results from increased hepatic glucose output from gluconeogenesis and glycogenolysis and that in addition renal gluconeogenesis contributes. The authors hypothesised that the glucose increment reflects gluconeogenesis in both liver and kidney and would be influenced by liver and kidney function.

In a cross sectional study they measured C peptide and glucose increments following glucagon stimulation in 209 well characterised patients with T2DM patients and corelated the glucose increments with a range of parameters of liver and kidney function. The key new findings were a positive correlation between the glucose increment and renal function with a decrease in the case of renal impairment. In addition there was a positive correlation between the glucose increment at the base line test and renal function a year later it had predictive value. A number of other baseline characteristics (BMI, HBA1c, total, LDL and HDL cholesterol) were not entirely unexpectedly also independent determinants of eGFR at one year. A range of liver disease parameters did not show any such relationships.

This is a very interesting and overall well conducted and comprehensive study with new findings about kidney disease. There are a number of points for the authors to address:

1. Renal function/impairment is clearly related to eGFR, creatinine and cystatin C however the "liver function" tests included are less clearly measures of actual liver function so this makes it harder to test for a relationship between liver function and glucose increment. In addition there was a wide eGFR range but seemingly a narrower ALT, AST, INR and albumin range. There is brief mention of this in the discussion but it should be more specifically addressed as a limitation of the study. It ultimately makes it hard to dissect the respective roles of the liver and kidney in gluconeogenesis and to fully address the hypothesis.

2. The patients with diabetes had a high mean HbA1c. This may reflect attendees. Is there any way to comment on the results for those with better controlled diabetes or does this require a further study?

3. Please clarify insulin therapy prior to the test. It is stated that short acting insulins were not give. What specifically was done about any long acting insulins.
4. Figures 1a, 1B and 1C don't correlate well with the text

There is a comprehensive discussion but this should be expanded as above.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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