Author’s response to reviews

Title: Assessment of endogenous insulin secretion in insulin treated diabetes predicts postprandial glucose and treatment response to prandial insulin

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Version: 2 Date: 30 March 2012

Author’s response to reviews: see over
Dear Editors,

Many thanks for considering this article. We than the reviewers for their helpful comments and feedback. We have detailed our response to the reviewer’s comments below with the original comments in italics. In our accompanying revised manuscript we have highlighted changes in red and scored through any deletions.

Best Wishes

Angus Jones

**Reviewer’s report**

**Title:** Assessment of endogenous insulin secretion in insulin treated diabetes predicts postprandial glucose and treatment response to prandial insulin

**Version:** 1  **Date:** 11 March 2012

**Reviewer:** Klaus-Dieter Kohnert

**Reviewer’s report:**

In this manuscript, the authors address the important issue of guiding insulin therapy by measurement of C-peptide as a marker of endogenous insulin secretion. They demonstrated in their cross-sectional study for the first time a significant relationship between C-peptide levels and the impact of prandial insuline. This is a beautiful piece of work.

I have only to recommend a few minor essential revisions:

**Minor essential revisions**

1. **Methods**

- The authors note that participants fasted overnight without taking their morning insulin or OHAs. As far as sulfonylureas are concerned, for example glimepiride, it can not be expected that the effects of this agent tail off within a few hours after treatment discontinuation. Thus C-peptide levels prior to the MMT might be higher and C-peptide increments lower in these cases so that they fall into upper C-peptide tertiles. Was this taken into consideration? I recommend that the authors briefly consider this point in their discussion.

This is an important point we partly addressed in our study design by randomising the order of the two mixed meal tests - we apologise as we forgot to include this in the paper! We have now added to the methods section ‘Mixed meal tests were conducted in random order using a randomization list generated in StatsDirect (StatsDirect Ltd, UK), between 48 h and 2 weeks apart’. We have also added the following to our discussion (page 12, final paragraph): ‘It is possible that results could have been influenced by differences in participant’s oral hypoglycaemic agents. While diabetes treatments were withheld on the morning of mixed meal tests, residual levels of treatment taken the previous day could potentially still affect both glucose and C-peptide. However this is unlikely to systematically differ between mixed meal tests (which were conducted in random order) and a longer period without medication might have made results less applicable to clinical practice.’
2. Results

-In Table 1, diabetes duration should additionally be included, because it appears plausible that the longer the disease, as in tertile 1, the lower the C-peptide levels.

We have added diabetes duration to Table 1. As is expected, patients with longer diabetes duration have the lowest C-peptide levels.

-Furthermore, I recommend to indicate the proportion of patients with type 1 and type 2 diabetes within the tertiles.

We have added this information to Table 1.

-It is not clear why 102 patients were recruited but data for only 80 are shown (Table 1 and 2).

We apologise if this is unclear. We attempted to explain this in the methods section (paragraph 2) - 'In a subgroup of 80 patients treated with prandial breakfast insulin (rapid analogue 61 (4 via insulin pump), rapid analogue/basal mixed 9, human prandial soluble 2, human soluble/basal mixed 8) a further morning MMT was performed with participants’ normal morning insulin dose given’. We have also specified in the table legend that the table includes ‘Participants completing both MMT and MMTI only’.

3. Discussion

-When interpreting the results, the authors should take into account that elevated endogenous insulin levels represent a compensatory response to insulin resistance. The observation that in those study participants with the highest endogenous insulin secretion prandial exogenous insulin had little effect despite similar insulin doses can best be explained by greater insulin resistance.

We have added this explanation to paragraph 3 page 11 (final sentence).

Discretionary Revisions

1. Results

-It would be interesting to know the carbohydrate content of the participants’ home meal compared to the MMT.

We agree that this would be interesting information however while we roughly recorded participants usual breakfast in the study for use in deciding on any necessary adjustment of insulin dose to prevent hypoglycaemia (in the infrequent case of the study mixed meal containing less carbohydrate than the participants usual breakfast) we did not have measurements (such as weight of breakfast cereal/volume of milk) therefore this would be a very rough estimate. We have reported that in the carbohydrate was estimated to be similar or more than participants home meals in the vast majority of participants (first paragraph page 7) and commented on this in the final paragraph of the results section.

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.

Reviewer's report

Title: Assessment of endogenous insulin secretion in insulin treated diabetes predicts postprandial glucose and treatment response to prandial insulin

Version: 1 Date: 11 March 2012
Reviewer: Fernando Guerrero-Romero

Reviewer's report:

In this study authors assess the relationship between endogenous insulin secretion as measured by 90 minute post mixed meal serum C-peptide and the postprandial glucose increment in a standardized mixed meal test and the response to exogenous prandial insulin by change in mixed meal glucose increment when exogenous prandial insulin is given. They conclude that endogenous insulin secretion is predictive of postprandial hyperglycemia and response to prandial exogenous insulin.

Major concerns

Data about methodological design, target population, sampling strategy, inclusion- and exclusion criteria, matching criteria, sample size estimation are missing.

We apologise that this was insufficiently detailed and have now expanded details on recruitment strategy and inclusion criteria in the methods section, added a subheading to make this clearer and referred to papers using the first part of this study (MMTT without insulin) to validate UCPCR where further details can be found.

We did not provide a power calculation as the results of this study are statistically significant. There was no attempt to match participants in any way and we apologise if this was not clear. We are happy to include any further details the editors or reviewers think appropriate.

Analysis stratified by gender is mandatory.
We have now added information about stratification by gender which did not alter the results. We have added to the results section (final sentence page 9): ‘Results did not differ when analysing by gender’

Because the physiopathology of Type 1 and Type 2 diabetes is not the same, the response to insulin differs between these patients; so, an analysis stratified by type of diabetes is required.

We agree this is a very important point and apologise if our analysis of this was not made sufficiently clear. We had included an analysis in the original article results section on Page 9 ‘In those with the same type of diabetes the correlations (type 1 diabetes r=-0.49 (p<0.001, n=54), type 2 diabetes r=-0.41 (p=0.037, n=26)) and the relationship across tertiles (Table 2) were also maintained.’ and had also included this in the discussion (page 12, second paragraph).

We have now added a new subheading to the relevant results paragraph to make this clearer: ‘These associations remain in those with the same type of diabetes and similar insulin treatment’. In addition we have now included the proportion in each tertile of insulin secretion with type 1 diabetes in Table 1.
Anthropometric and biochemical characteristics of subjects in study are necessary. We have described characteristics of the study population in paragraph one of the methods section (page 9). Characteristics are also described by C-peptide tertile in Table 1. We can include these details in a further table on combined participant characteristics if the editorial team feel appropriate.

*Which was the age of diagnosis for the type 2 diabetic individuals?* We have added age of diagnosis and BMI by type of diabetes to the methods section.

*One way ANOVA test (or Friedman analysis) with post-hoc test should be used to compare more than two groups.* We have sought the advice of a statistician regarding this. In this study we are comparing a single variable (e.g. glucose increment or change in glucose increment when insulin is given) across tertiles of C-peptide production. We have been advised that the one-way ANOVA approach (or Kruskal-Wallis, the non-parametric equivalent) is appropriate for detecting differences between more than two groups, however, we were more interested in whether there were increasing or decreasing trends across the tertiles, rather than differences between the three groups which could indicate the middle tertile being lower or higher than the other two. The non-parametric statistic (appropriate as our data is not normally distributed even after log transformation) for this purpose is the Jonckheere test. If we use Kruskal-Wallis, the results are not altered.

**Level of interest:** An article of insufficient interest to warrant publication in a scientific/medical journal

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:** I declare that I have no competing interests’