Reviewer’s report

Title: The effects of metformin in type 1 diabetes mellitus

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Reviewer: Steven K. Malin

Reviewer's report:

Manuscript ID Ref: BEND-D-17-00059; Metformin reduces insulin requirement by improving metabolic syndrome in type 1 diabetes mellitus

Overview: The study by Beysel et al. was retrospective and investigated the effect of metformin on pharmacological insulin dose in type 1 diabetics on insulin therapy, compared with patients on insulin therapy alone, 1 year after treatment. The results suggest that metformin decreased glucose concentrations more than control, lowered metabolic syndrome prevalence as well as insulin dose. Interestingly these results were independent of blood lipid improvement or weight loss, although on average weight maintained/decreased with metformin+insulin whereas insulin on average increased. While the work merits attention in type 1 diabetic patients, there are several concerns that require attention.

Title:

This title is too strong. The study doesn't show amelioration of metabolic syndrome causes insulin dose via metformin. There is simply an association. Importantly, the association is not statistically significant (page 7). If it not significant then the title needs further refining.

Abstract:

Replace "sparing" with "sensitizing" to be more accurate.

Is the p-value regarding metabolic syndrome reduce (p=0.37) a typo? If so, it should be corrected.

Introduction:

Might want to point out that metformin has been shown to reduce metabolic syndrome incidence (e.g. Orchard 2005, Malin 2012) in people without type 1 diabetes. This would allow the reader
to identify why metformin may help people with type 1 diabetes. In particular since metabolic syndrome correlates with not only insulin resistance but also beta-cell function.

Methods:

It needs to be more clearly stated that IRB approval was given to conduct such retrospective analysis.

It's not clear how long the study is for. In the discussion, it mentions 12 months of metformin. Is this true? Does this mean all people started metformin and remained for 12 months.

How often were measures made throughout the study? Would be of interest to know if any changes occurred early (e.g. 3 or 6 months) but not later at 12 months.

The methods section may be helped if broken apart more. For instance, page 4, line 53, "Metabolic syndrome, etc…” make a new paragraph and label "Clinical outcomes".

Were patients on other medications, e.g. lipid or blood pressure lowering? This is important as 40% had metabolic syndrome. If on other drugs, it is of interest to identify if there were drug-to-drug interactions that enhanced the ability of metformin to lower insulin dose or possibly even blunt this response.

Was waist-circumference measured? If so, how? This should be reported.

Was blood pressure recorded? If so, when and how?

Was dietary control provided prior to clinical blood work or measures? Alterations in acute diet could influence results, particularly since metformin reduces appetite and caloric intake.

PPG was measured. How? Was a 75g OGTT used. Or is this the estimated glucose level from clinical labs based on HbA1c?

Results:

The results section should be broken apart into sub-sections. For instance, Demographics: weight, drug and metabolic syndrome, then Glycemia and Lipids. Then have a correlation paragraph. Otherwise, the results are hard to follow lumped together.

If the correlation on page 7, ln 15 is correct, then it is inappropriate to say there is really a relationship given it lacks statistical significance. Verify the p-value please. If there is a typo and the p-value is significant, this would be an interesting data point to graph.
When was the last metformin and insulin dose provided before clinical tests were performed? How do the authors know the results were do to the chronic vs. acute effect of the medication?

Is it known how many ATPIII risk factors people had? Could this be reported for table 2?

Body weight should also be reported.

There are 2 "HDL" listed in Table 2. Perhaps one is LDL?

Other medications should be listed in Table 1 and others if changed.

It's not really clear how helpful Table 2 is for the most part. Table 3 is critical in showing the change in parameters relative to baseline. It would seem from Table 1 that several outcomes related to blood glucose are higher in T1D patients treated with metformin+insulin than insulin alone. This is likely then the reason why in Table 2 there is no difference in blood glucose, but Table 3 shows greater change. As a result, Table 3 provides insight that metformin likely improved glycemic control more than insulin alone and this also contributed to metabolic syndrome reductions.

Blood pressure and waist circumference are really needed to help understand how metabolic syndrome was reversed.

Discussion:

Lots of the discussion needs to be rewritten to place proper emphasis on Table 3 data vs. that of table 2. For instance, it is stated that insulin dose decreased without improving glucose control. Table 3 clearly shows this isn't the case.

Does the change in glucose parameters correlate with the change in insulin?

Have the authors considered calculating the metabolic syndrome z-score as an indicator of disease severity? The z-score correlates with insulin resistance and beta-cell function across the glucose continuum in obese adults at risk for type 2 diabetes.

Page 7, ln 35 suggests that BP may be important. Can the authors comment?

Page 8, ln 44 suggests no study has systematically tested metformin in metabolic syndrome patients with T1D and that this study addressed the gap. While up to 40% of people had metabolic syndrome, this current report does not either test metabolic syndrome patients per se. It would be stronger to break down each group of metformin+insulin vs. insulin only into T1D vs. T1D+metabolic syndrome. In this analysis, it could then be directly compared how metformin impacts metabolic syndrome compared to non-metabolic syndrome controls.
Page 9, ln 35, it says that metformin improves glycemic control by improving metabolic syndrome and insulin resistance. It would be fair to be more direct here to highlight that metformin reduces hepatic glucose production, stimulates glucose uptake in muscle as well as improves blood flow for nutrient utilization.

Page 9, ln 40, it suggests lipids improve in other studies. Why not this one? Because values are relatively normal?

The limitation section is weak. The study wasn't randomized or placebo controlled. Sex differences were not adequately accounted for, nor was age. Diet doesn't appear to be standardized prior to testing.

Page 10, conclusions should be toned down regarding metabolic outcomes.

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.

No

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.

Not relevant to this manuscript

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