Reviewer’s report

Title: Insulin resistance and systemic metabolic changes in oral glucose tolerance test in 5,340 individuals: An interventional study

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Reviewer: Timo Müller

Reviewer's report:

In this manuscript, Wang and colleagues assessed a number of metabolic measures of glycemic control in a large cohort of patients with a varying degree of glycemic dysregulation. The patient subgroups include Insulin-Resistant- normal glucose tolerance (IR-NGT), Insulin-Sensitive- normal glucose tolerance (IS-NGT), Impaired fasting glucose (IFG), and new diabetes (NDM). The results show profound differences in these well selected groups in various measures of glucose handling, implying that careful diagnosis of patients is key for the successful therapy.

The manuscript is well written, easy to understand and deals with an important and innovative research question. The study is considered as of importance for its field.

The authors measured here 76 metabolites. The statistical analysis is based on a simple t-test in which the metabolite at each time point is compared to the baseline measure. I recommend having this checked by a statistician. This approach neglects that data have been obtained longitudinally at multiple time points (0, 60, 90, 120min after the glucose load). Thus, a 2-way ANOVA with a bonferroni post-hoc analysis for the individual time points or the area under curve taking into account the entire dataset seem required. In my view a t-test can't be used if there are longitudinal data and thus there are more than 2 groups and time effects to consider. I recommend having this seen by a statistician. Figures should ideally then also show the bonferroni post-hoc p-values for the multiple time points.

Figure 2. what is the rational for showing only one group (NGT) in this figure? Wouldn't it be better to compare all groups for one measure per graph? This would allow the comparison of metabolic measures among the treatment groups. The current Figure 2 raises more questions than it solves. I wonder how the other groups compare to the NGT in these measures?

Figure 3. Why does Figure 3 show only 2 groups (IS-NGT vs IR-NGT)? This figure is valuable but it should show all groups to allow the most optimal comparison. The authors are underselling their data here by showing only 2 groups. Another caveat is that the graph shows just changes (%), neglecting the information whether the changes are beneficial or detrimental. So in addition to the % change, showing absolute changes is required to appreciate the true value of the data.

Figure 4. Same here, why did the authors show IS-NGT vs IR-NGT in Fig 3 and IR-NGT vs IGT or NDM in Figure 4? This should be all in one Figure. Also, why does it say IGT or NDM? This looks as if the authors show only selected data while neglecting others. The authors have to show all data in an
unbiased manner.

Assessment of metabolic changes in response to a real meal would have added value to the presented data and would have allowed conclusions that go beyond a simple glucose challenge.

Something worth being mentioned in the discussion is that insulin resistance itself is heterogenous and thus patients in the IR groups might differ in the reason and tissues corresponding to insulin resistance. This makes this group a bit harder to analyze and also limits a bit the conclusions drawn from this group.

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

No

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?
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