Author's response to reviews

Title: Delayed beta-cell response and glucose intolerance in young women with Turner syndrome

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Author's response to reviews: see over
Dear Tim Shipley

We have now revised our manuscript according to yours and the reviewers comments and suggestions, and feel that the manuscript has improved in the process. We hope that the manuscript now meets the standards of BMC Endocrine Disorders and we therefore resubmit our paper: “Delayed β-cell response and glucose intolerance during dynamic testing in young and normal weight women with Turner syndrome” by Britta Eilersen Hjerrild, Jens Juul Holst, Claus B. Juhl, Jens Sandahl Christiansen, Ole Schmitz, Claus Højbjerg Gravholt. In particular, we have responded to all queries brought forward by the reviewers; we have extended the Discussion of results and we have also omitted the sentence “results not shown” and now either present a p-value or results and a p-value. All changes are marked with yellow.

The manuscript or parts of the manuscript has not been published and is not under consideration for publication elsewhere.

Yours sincerely

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Reviewer 1 Romuald Stupnicki

1. We have changed the according to the reviewers suggestion.
2. Introduction changed as suggested.
3. We did indeed mean blood – has been corrected.
4. Table 1: we would actually like to keep it as is, because it illustrates quite nicely that TS women of course are much smaller in absolute terms, but have exactly the same percentage of body fat and muscle. We hope that this is acceptable for the reviewer.
5. The reviewer is course right in pointing out that replacement of SD’s with SE’s would make the figures more presentable, however, we feel in the interest of using appropriate statistics and not presenting data that some could think of as manipulated, that we would rather retain the SD’s. Our statisticians always keeps telling us that we should always present SD’s and not SE’s, for the sake of being as pure as possible in laying out data as they are. We hope this will be acceptable for the reviewer and the editor.
6. In response to your comments and the other reviewers, we have slightly expanded the Discussion with incorporation of the possible genetic background for the increased risk of diabetes in Turner syndrome. These changes in the Discussion have been marked with yellow.
7. We have included a discussion of recent findings with respect to the presence of possible genes on the X chromosome, and on the basis of our result and these considerations, we have now changed the conclusion and the abstract. Here we have included a recommendation of regular testing for diabetes.
8. We have done our best to improve the grammar and spelling. We hope that this is now satisfactory.
Reviewer 2 Ieda Verreschi

1. Missing legend: has been corrected.
2. We have corrected ref 6 with the appropriate ref. Thank you.
3. Reviewer 3 – Valeria Calcaterra

Sample size: we have previously studied one of the largest group of women with Turner syndrome ever published (n=26), and other groups looking in detail at glucose homeostasis (and not just reporting fasting glucose and insulin and then calculating some sort of index for insulin resistance) have reported from studies of similar size. Other studies have used considerably larger sample sizes, but have then only applied a 2 hour OGTT with subsequent calculation of the QUICKI or other indexes of insulin resistance. Here, we have attempted at answering the enigmatic question of why diabetes is so frequent in Turner syndrome, and to that end we designed a very laborious and time consuming study consisting of 3 entire study days where participants (both TS and controls) had to use 3 entire workdays (in other words – all had to take time of from work, and indeed all participants were fully employed) – this is of course in addition to the substantial cost for running the study. We also employed all the most sophisticated methods for studying glucose homeostasis in absolute detail. In addition, we have previously in our own lab, but also shown by others, in other study groups shown that a sample of down to 8 individuals in each study group would normally be enough to show significant differences between groups, due to the elaborate nature of the methodology. We have also already included power analyses with different outcome to show that the current sample size of 13 would be sufficient to show clinically significant differences between groups. We therefore feel confident that the current sample size was both sufficient and scientifically sound.

Birth weight: in light of the Barker theory and the fact that birth weight is lower in females with TS, at least when studying large groups of TS (Carel et al, JCEM, 2005), it could have been interesting to take a closer look at birth weight in the current study. However, the current study aimed at studying glucose homeostasis in the greatest possible detail and therefore the size of the study group was restricted, and we felt that inclusion of birth weight as an additional variable might cloud our primary messages, and that the study group would be too small to see any correlations with the other variables. Unfortunately we did not collect the information on birth weight from our participants.

“Data not shown”: we now present actual p-values and have omitted the term “data not shown”.

We now discuss the results in the Discussion in additional detail. We have included a discussion of the possible genetic background for the increased risk of diabetes and we have expanded the discussion of our results. These changes have been marked with yellow.