To Dr. Ying Dou

Science Editor

World Journal of Diabetes

Dear Dr. Ying Dou

Thank you for reconsidering our paper "*Numbers of comorbidities affects physical, but not mental health related quality of life in type 1 diabetes with confirmed polyneuropathy*" for publication in World Journal of Diabetes. The helpful reviewer comments have allowed us to improve our manuscript. We replied to each of the reviewer's comments in detail in a point-by-point fashion, with appropriate cross-referencing to the text. The associated revisions in the manuscript are highlighted in yellow.

On behalf of all authors,
Anne-Marie L. Wegeberg

Response to Reviewer #1

Thank you for the opportunity to review this well-written study on the effects of DN on QoL of people with T1D. The topic is interesting and the results have indeed some useful clinical implications.

Thank you for taking the time to thoroughly review our manuscript.

I have some comments on the study:

1. It is accurate that the majority of previous studies that examined the impact of DN on QoL have included mixed (T1D and T2D) populations; however, the negative impact of DN on QoL exclusively in people with T1D has been previously highlighted in the literature [please see Jacobson et al., Diabetes Care 2013;36(10):3131-38]. It would be useful this research to be cited in the relevant part of the discussion.

We thank you for transferring our attention to this publication. We agree that this is relevant information to include in the discussion and have done so.

Page 9, section 2 "*In contrast, a study by Jacobsen et al. studied HRQoL in people with type 1 diabetes over an average of 23 years and found no decrease in HRQoL scores over time. The present study we looked into HRQoL in patients with type 1 diabetes compared to healthy and we found numerically decreased and clinically relevant declines in HRQoL for all sub-scores, except social functioning and a most significant decrease in the physical components. This finding, related to the mixed cohorts, is possibly because people with type 1 diabetes are found in all social groups, and hence also in all social groups with larger psychological resources in comparison to people with type 2 diabetes. Contrary, compared with the study by Jacobsen et al., we only had a cross-sectional look at HRQoL and therefore do not know the long-term ramifications for our patient group.*"

And Page 10, section 1 "*Additionally, a study over 17 years in people with type 1 diabetes showed that develop-ment of microvascular complications significantly decreased HRQoL.*"

2. To assess the impact of DN on QoL, it would be more reasonable to recruit as controls people with T1D but without DN, and not healthyindividuals, in order to diminish the effects of diabetes itself,on QoL. This may be a confounder amplifying the impact of DN on QoLand I think it's appropriate this aspect to be included and discussed in the article.

This is a pivotal angle and we agree that a comparison with people with diabetes without neuropathy could be very interesting as well. We have added this to the limitations part of the discussion.

Page 11, section 2 "*Additionally, these were compared with healthy individuals, and therefore the effects measured may be skewed due to the effect of diabetes alone on SF-36.*"

3. The other limitations of this study are already mentioned and discussed by the authors, therefore there is no need in repeating them. Some more minor suggestions:

- **Please clarify whether the study protocol was approved by the ethics committee of the institute conducted in.**

We agree this needs clarification within the manuscript. This study was performed in Denmark, where institutional ethical committees does not exist. All studies must however be approved by the regional ethics committees, which this study have been. This has been clarified in the manuscript and the ethics approval number has been added.

Page 6, section 2 "*The local ethics committee approved the study protocols (N-20130077).*"

- **Which was the method used for HbA1C assessment?**

Thank you for this clarifying question. We used the standardized International Federation of Clinical Chemistry standards (IFCC) measured in mmol/mol. This has been added in the text and in table 1

Page 7, section 1: "*A blood sample was taken for measurement of HbA1c (IFCC)….*"

- **The results section is very short and unbalanced compared to introduction and discussion. It could be more extended and informative.**

We agree that the result section is a bit short and refer this to great importance we attach to our tables and graph. Though we believe short and concrete is best for at result section, we have tried to elaborate a bit on the section to increase the informative yield and understanding without needing reference to the graphs and tables.

Page 8 "*A total of 48 people with type 1 diabetes and 21 adult heathy volunteers were included in and completed the study. The demographic distribution is shown in Table 1 and display no notable difference in demographic characteristic between the two groups.*

Comparison between type 1 diabetics and healthy controls
As seen in figure 1, when diabetes was present, a numerical decline was observed in every SF-36 domain, compared to healthy subject. Significant differences were found on physical functioning (78.6 ±27.7 vs. 96.7 ±6.2, p=0.005), role limitation due to physical problems (82.4 ±31.7 vs. 100 ±0, p=0.01), general health (64.4 ±24.5 vs. 85.3 ±13.1, p<0.001), vitality (65.5 ±23.9 vs. 78.1 ± 13.9, p=0.03), role limitations due to personal or emotional problems (87.0 ± 27.3 vs. 100 ± 0, p=0.03) and the physical composite score (46.3 ± 11.7 vs. 54.6 ± 3.3, p=0.002). However, no significance was found lookig at bodily pain (76.2±24.34 vs. 87.3 ±17.7, p=0.07), social functioning (91.9±13.9 vs. 95.2±15.0, p=0.39), mental health (81.2±16.9 vs. 86.7±13.6, p = 0.20) and the mental composite score (51.9 ±8.9 vs. 53.1 ±5.5, p = 0.56).

Associations
There was a negative association between the physical composite score of SF-36 and number of comorbidities (r=-0.62, p<0.001), both diabetes (r=-0.53, p=0.018) and non-diabetes related(r=-0.51 p<0.001), and HbA1c level (r=-0.41, p=0.005), as can be seen in figure 2. However, one of these were associated with the mental composite score of SF-36 (p>0.05).
Additionally, physical parameters of physical function, role limitation due to physical health, bodily aim and general health were all associated to and number of comorbidities (p<0.01), both diabetes (p<0.03) and non-diabetes related (p<0.02), while only physical function and bodily pain were associated to HbA1c (p<0.02). More detail can be found in table 2."

Revision made based on Editors suggestion

Journal name, manuscript number and Manuscript type has been added on the front page.

Corresponding author information have been updated with full address.

The abstract have been edited to contain background and specific aim.

All authors abbreviation names and manuscript title have been added below core tip.

Citation style has been edited and references have been updated with all authors, PMID and DOI and checked for repeated references.

Article highlights have been added before References in the manuscript file.