PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Near-normoglycaemia prevents the development of neuropathy. A 24-year prospective study from the diagnosis of type 1 diabetes
AUTHORS	Dan Ziegler, Margarete Behler, Maria Schroers-Teuber, Michael Roden

VERSION 1 - REVIEW

REVIEWER	Rodica Pop-Busui University of Michigan, Ann Arbor, MI
REVIEW RETURNED	28-Sep-2014

GENERAL COMMENTS	The paper describes a prospective observational study which followed 32 T1D patients over 24 years and concluded that good glycemic control over 24 years prevents the development of DPN and CAN among those with better glycemic control (group 1, n= 11)as compared to those with poor glycemic control(group 2, n= 21). However the study does not add anything new to the available body of knowledge and reports from larger and longer trials. It is well accepted that tight glucose control early in the course of diabetes and maintain has favorable effects in preventing neuropathy and other complications In addition this study has important limitations given the very small sample size, that it was not a randomized trial, and that the potential selection bias in the participants who adhered to a better control or other confounders that could have contributed were not included in analysis or discussed. The main outcome measures are not clearly defined up front. The authors report a series of descriptive variable of DPN and CAN basically. The observational nature and posthoc analysis are further limitations. These should be more clearly acknowledged by the authors

REVIEWER	Petr Boucek Diabetes Centre Institute for Clinical and Experimental Medicine Prague, Czech Republic
REVIEW RETURNED	09-Dec-2014

GENERAL COMMENTS	Despite the rather low number of subjects included this is an important long-term observational study confirming the current goals of glycemic control for the prevention of clinical diabetic neuropathy. I have just a few minor points and would appreciate some clarifications from the authors.

	I am not sure if I understand what was the total number of drop-outs throughout the study - is that the sum of the numbers of patients lost to follow-up at the individual time points (page 10, paragraph 2) or were examinations missed in some patients at some time-point but done at later time points - i.e. did the patient numbers at individual time points vary? I suppose also that the examiners were not blinded to the HbA1c results at the individual time points. I think it would be helpful to clarify these issues in the text. Since not every reader would probably be familiar with all the procedures done and equipment listed, I think a confirmation that either same equipment was used throw-out this very long study or that examinations done with changed equipment were strictly comparable. Were C-peptide levels of both groups available at some time point? Were all patients C-peptide negative? Residual C-peptide levels could play some role in better glycemic control or even influence development of neuropathy. I would suggest the use "causative" instead of "permissive" for the role of glycaemia in the development of neuropathy and IU/BW instead of IU for daily insulin dose. Minor change: Page 10, paragraph 2, line 1 should be - ..Group 1 and Group 2

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Rodica Pop-Busui
Institution and Country University of Michigan, Ann Arbor, MI
Please state any competing interests or state 'None declared': None declared

1. The paper describes a prospective observational study which followed 32 T1D patients over 24 years and concluded that good glycemic control over 24 years prevents the development of DPN and CAN among those with better glycemic control (group 1, n= 11)as compared to those with poor glycemic control(group 2, n= 21).

2. However the study does not add anything new to the available body of knowledge and reports from larger and longer trials. It is well accepted that tight glucose control early in the course of diabetes and maintain has favorable effects in preventing neuropathy and other complications In addition this study has important limitations given the very small sample size, that it was not a randomized trial, and that the potential selection bias in the participants who adhered to a better control or other confounders that could have contributed were not included in analysis or discussed.

REPLY
We disagree with the statement that the study does not add anything new to the available body of knowledge. No study has hitherto described the long-term natural course of peripheral and autonomic nerve dysfunction in relation to glycaemic control from the diagnosis of type 1 diabetes onward. We assume that the reviewer alludes to DCCT/EDIC which was an RCT including type 1 diabetic patients with a diabetes duration of around 12 years at baseline.
We agree that the study has limitations which were acknowledged in the discussion section.

3. The main outcome measures are not clearly defined up front. The authors report a series of descriptive variable of DPN and CAN basically.

REPLY

We disagree with the statement that the main outcome measures are not clearly defined up front. It was clearly stated that nerve function (MNCV, SNCV, HRV, QST) and confirmed clinical polyneuropathy were assessed. All these measures are necessary to give comprehensive information

4. The observational nature and posthoc analysis are further limitations. These should be more clearly acknowledged by the authors

REPLY
We disagree with the statement that the observational nature and posthoc analysis should be more clearly acknowledged, since we did exactly this. The reviewer only repeated the limitations we acknowledged.
Altogether, we wish to emphasize that this reviewer's comments were little helpful.

Reviewer: 2
Reviewer Name Petr Boucek
Institution and Country Diabetes Centre
Institute for Clinical and Experimental Medicine
Prague, Czech Republic
Please state any competing interests or state 'None declared': None declared

REPLY TO REVIEWER #2 (Comments to the Authors are shown in italics):

This is an important observational study confirming that the current glycemic control treatment goals as established by the DCCT trial (HbA1c less than 7% - NGSP) indeed prevent the occurrence of clinically established diabetic neuropathy in the long-term. The duration of follow-up is also the major strength of study.
I have a only few minor points and would appreciate some clarifications from the authors, as outlined below.

Despite the rather low number of subjects included this is an important long-term observational study confirming the current goals of glycemic control for the prevention of clinical diabetic neuropathy. I have just a few minor points and would appreciate some clarifications from the authors.

REPLY
We thank the reviewer for this comment.

I am not sure if I understand what was the total number of drop-outs throughout the study - is that the sum of the numbers of patients lost to follow-up at the individual time points (page 10, paragraph 2) or were examinations missed in some patients at some time-point but done at later time points - i.e. did the patient numbers at individual time points vary? I suppose also that the examiners were not blinded to the HbA1c results at the individual time points. I think it would be helpful to clarify these issues in the text.

REPLY
This point has been made clear on p7, last para: The numbers of patients lost to follow-up at the individual time points in Group 1 and Group 2 varied and were 2 and 3 at 5 years, 1 and 4 at 12 years, 1 and 6 at 20 years, and 2 and 10 at 24 years, respectively (p10, para 3). The examiners were not blinded to the HbA1c results at the individual time points.

Since not every reader would probably be familiar with all the procedures done and equipment listed, I

think a confirmation that either same equipment was used throw-out this very long study or that examinations done with changed equipment were strictly comparable.

REPLY
This is point now addressed on p7, para 4: The NCV, TPT, and HRV parameters were measured in the same way using equipment from different manufacturers and were comparable throughout the study.

Were C-peptide levels of both groups available at some time point? Were all patients C-peptide negative? Residual C-peptide levels could play some role in better glycemic control or even influence development of neuropathy.

REPLY
We agree that measurement of C-peptide levels would have been useful during the study, but unfortunately these were measured in only a few patients precluding useful analysis.

I would suggest the use "causative" instead of "permissive" for the role of glycaemia in the development of neuropathy and IU/BW instead of IU for daily insulin dose.

REPLY
"Permissive" was changed to “causative” on p4, first para and p13, last para as suggested.
We agree that it would be more precise to give the daily insulin dose as IU/BW, but unfortunately data on weight during was missing for some at several time points patients.

Minor change: Page 10, paragraph 2, line 1 should be - ..Group 1 and Group 2...

REPLY
Thank you; this was corrected.

VERSION 2 – REVIEW

REVIEWER	Rodica Pop-Busui University of Mcihigan
REVIEW RETURNED	05-Mar-2015

GENERAL COMMENTS	This is an interesting study, Paper is well written and patients are very carefully characterized. My main concerns are the very small sample size, the fact that there was no randomized design and the potential for bias of the results due to group allocation. The authors acknowledge this somewhat, but I would make it more clear. The authors also state that the patients were treated according to the standard of care . However, it looks this study was initiated several years before the DCCT trial was published, and as far as I am aware, an intensive glucose control to target A1c < 7% was not the standard of care before DCCT. Perhaps authors could clarify what treatment criteria were applied and what rationale was used to reach such a tight glucose control in the intensive group? What was the incidence of hypoglycemia in the groups? How about weight gain in the intensive treatment group? What was the change in other neuropathy risk factors over time in these groups. Table 2 , what are the units of the changes? Suggest to add p values for change over time in table 2 to better understand which DSPN and HRV measured significantly changed over time

	I would add the information about other medication such as statins, ACEi, beta blockers

REVIEWER	Petr Boucek Diabetes Centre Institute for Clinical and Experimental Medicine Prague, Czech Republic
REVIEW RETURNED	11-Jan-2015

GENERAL COMMENTS	The points suggested have been dealt with in a satisfactory manner, I have no additional comments.

VERSION 2 – AUTHOR RESPONSE

REPLIES TO REVIEWER'S COMMENTS

This is an interesting study, Paper is well written and patients are very carefully characterized.
My main concerns are the very small sample size, the fact that there was no randomized design and the potential for bias of the results due to group allocation. The authors acknowledge this somewhat, but I would make it more clear.

REPLY
The study limitations are discussed on p 13. In addition, we now also list the drop-outs as a potential source of bias.

The authors also state that the patients were treated according to the standard of care . However, it looks this study was initiated several years before the DCCT trial was published, and as far as I am aware, an intensive glucose control to target A1c < 7% was not the standard of care before DCCT. Perhaps authors could clarify what treatment criteria were applied and what rationale was used to reach such a tight glucose control in the intensive group?

REPLY
As stated in the Methods on p 6, the post-hoc analysis was based on the current ADA recommendations: "To establish whether the development of neuropathy is related to the long-term degree of glycaemic control, patients were grouped according to their mean HbA1c levels during the 24 years of follow-up (excluding baseline HbA1c) in line with the current recommendations by the American Diabetes Association (11)."
Thus, there was no "intensive group" and no "rationale" for such a treatment but rather different standards of care relevant over the period of 24 years which applied to all the patients studied.

What was the incidence of hypoglycemia in the groups? How about weight gain in the intensive treatment group?
What was the change in other neuropathy risk factors over time in these groups.

REPLY: We agree that this information would be useful. Unfortunately, these data is not available.

Table 2, what are the units of the changes? Suggest to add p values for change over time in table 2 to better understand which DSPN and HRV measured significantly changed over time.

REPLY:
As suggested, the units are now given in Table 2 for the absolute changes, and % stands for the

relative changes.
We prefer not to give the P values in Table 2, since the P values for the differences in outcome measures between the groups at the different time points are given in Figs. 1 and 2.

I would add the information about other medication such as statins, ACEi, beta blockers

REPLY:
This information is given on p 9.