

June 4th, 2015

Dear Mr Fang-Fang Ji,

Science Editor:

Please find enclosed the revised manuscript as word document (File name: Epigenetic MS for WJD revised - June 4th 2015).

Title: Epigenetic profiles of Pre-diabetes transitioning to Type 2 Diabetes and Nephropathy

Author: Thomas A. VanderJagt, Monica H. Neugebauer, Marilee Morgan, Donald W. Bowden, Vallabh O. Shah.

Name of the Journal: World Journal of Diabetes

ESPS Manuscript NO: 17289

We appreciated the **helpful and constructive** comments from the reviewers. The manuscript has been revised accordingly, and our responses to reviewers are provided below.

Response to reviewer 1

a. The reviewer questioned the use of two subjects as controls. We have revised the description of the methods section to point out that these should not be considered as controls, which was a poor use of terminology. These are merely used to establish a baseline methylation so that both the Pre-DM subject samples and the T2DM time point samples can be normalized to the same baseline, which then allows for determination of differences in the cohort at each time point in progression of T2DM.

b. The reviewer points out limitations in a study with a small sample size, as we pointed out. We have expanded upon this at the end of the discussion to point out how the results of this study will guide future studies.

c. The issue of only using male subjects was raised. We now address this in the methods section to point out that with a small sample size of materials that are difficult to obtain, the restriction to non-Hispanic males was considered as appropriate in order to limit confounding variables such as ethnicity and gender. The discussion again raises this issue in describing how future studies will allow ethnicity and gender to be addressed.

d. The reviewer pointed out that there were grammatical errors in the original submission. These errors were address during the editing process for resubmission.

Response to reviewer 2

a. The reviewer questions the inclusion of results or discussion related to CKD. We wish to point out that the samples for this study were specifically taken from subjects who eventually developed diabetic nephropathy in order to address the possibility that the epigenetic profiles identified when the subjects developed T2DM may include markers that will predict future development of nephropathy. We now

address this in the discussion to include future studies that may address the concerns of the reviewer, such as obtaining DNA samples from subjects when they develop nephropathy as well as samples from subjects who never develop nephropathy. We will then be able to test whether the results from this preliminary study, which was limited by the availability of hard to obtain materials, can be confirmed in other populations. As mentioned in the revised discussion, this study is important in that it raises questions that can be addressed in future studies.

Response to reviewer 3

a. The reviewer is concerned with the limits of a study with a small sample size. We address this issue in the discussion to point out that the material for a study such as ours is especially difficult to obtain. However, the results of this study raise numerous questions that can now be addressed in future studies, some of which are now suggested in the discussion.

Response to reviewer 4

a. The reviewer questions the use of only two controls. We have revised the description of the methods section to point out that these should not be considered as controls, which was a poor use of terminology. These are merely used to establish a baseline so that both the Pre-DM subjects and the T2DM subjects can be normalized to the same baseline, which then allows for determination of differences in the two populations.

b. The reviewer points out limitations in a study with a small sample size, as we pointed out. We have expanded upon this at the end of the discussion to point out how the results of this study will guide future studies.

c. The issue of only using male subjects was raised. We now address this in the methods section to point out that with a small sample size of materials that are difficult to obtain, the restriction to non-Hispanic males was considered as appropriate in order to limit confounding variables such as ethnicity and gender. The discussion again raises this issue in describing how future studies will allow ethnicity and gender to be addressed.

Thank you again for reviewing and considering our manuscript for publication in the World Journal of Diabetes.

Sincerely,



Vallabh "Raj" Shah, PhD, FASN

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