November 21, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13979-REVIEW).

Title: Type 1 Diabetes: A Predictable Disease

Author: Kimber M Simmons, Aaron W Michels

Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 13979

To begin, we would thank the reviewers and editor for their efforts toward the review of this manuscript. We believe that their comments, when combined with our edits in response to them, have resulted in a markedly improved text. Underlined text in the response letter is now included in the manuscript.

1) Revision has been made according to the suggestions of Reviewer 00255973
Comment: In this brief review, the authors provide an overview of autoimmune type 1 diabetes with particular focus on serologically detectable autoantibodies against islet-derived auto-antigens. The authors build the argument that by large scale screening close relatives and genetically predisposed individuals for these auto-Ab, it will be possible to identify individuals at risk to develop T1D and initiate treatment. These treatments could be secondary interventions – different dose, route and regimen of insulin administration to prevent potentially fatal metabolic complications such as ketoacidosis, and tertiary interventions aimed at arresting/even reversing the autoimmune destruction of the remaining healthy islet mass. Even though these treatments are only being offered in clinical trials, Ab screening would allow more individuals to be enrolled, eventually leading to further progress in disease prediction and treatment selection. While the emphasis of this review is on auto-Ab, it does provide a clear background on the pathogenic process, genetic and environmental factors involved and the immunological mechanisms implicated. It is very well written for a larger audience.
Response: We appreciate the time that you took to review our manuscript and thank you for your kind response.

2) Revision has been made according to the suggestions of Reviewer 00503474
Comment: Introduction: Please note: The sentence : “To date, no trial has prevented the onset of T1D, but data indicates that the disease process may be delayed with oral insulin.” Can insulin be given orally !!! Please clarify this issue.
Response: We agree with the reviewer that mentioning oral insulin without providing its proposed mechanism or action would be very confusing for a general audience. Oral insulin is not metabolically active. However, studies show that oral administration of auto-antigens has the potential to induce protective immunity by upregulating T-regulatory cells in the gut that go on to secrete inhibitory cytokines and reduce inflammation in the pancreas. On page 3 we added, “To date, no trial has prevented the onset of T1D, but data indicates that the disease process may be delayed by administering oral insulin to induce insulin specific regulatory T-cells in the gut, resulting in decreased inflammation in the pancreas.” On page 12 we added the following with appropriate references: “Oral insulin has no metabolic effect; however, orally administered insulin does encounter mucosal gut-associated lymphoid tissue. The role

of this lymphoid tissue is to provide protection from orally acquired pathogens and to keep individuals from developing reactions to ingested proteins. By administering low doses of oral insulin, insulin-specific T-regulatory cells are produced which may release cytokines that inhibit the inflammatory cascade that leads to β-cell destruction.[88-90]"

Comment: Epidemiology: The authors stated that: Children born in the spring tend to be at a greater risk for developing T1D, while diagnosis is increased during climatically cold seasons: Please explain the link between T!DM and occurrence in spring.
Response: The link between birth in the spring and increased diagnosis is a purely epidemiological association born out of a study in Ukraine. One hypothesis is that children born in the spring were developing as a fetus during "nutritionally marginal" months and that maternal diet therefore affected T1D development. This hypothesis has never been studied and seems to be lacking given the rapid decrease in poverty that was occurring in Ukraine at the time this study was done. To clarify in our manuscript, on page 4 we added, "This is an epidemiological association that requires further investigation."

Comment: Risk Factors Genetic: this section is well explained. Environment: GAD, glutamic decarboxylase, (Please write in full before abbreviation). Natural History: This section is clearly explained. Screening and Prevention: This section explain how would patients of T1DM will gain from early and preclinical diagnosis to prevent DKA.
Response: On page 6 we made the following addition, "The molecular mimicry hypothesis proposes that because the P2-C protein sequence of enterovirus is similar to glutamic decarboxylase (GAD), which is expressed in islet cells, the immune system erroneously targets destruction of beta cells.[38]"

Comment: Novel Approaches to Prevent Type 1 Diabetes: Sentence "Preclinical studies have shown this is be a potential pathway for diabetes" , be should be being.
Response: On page 15 we corrected grammar as follows, "Preclinical studies have shown this to be a potential pathway for diabetes intervention.[115]"

3) Revision has been made according to the suggestions of Reviewer 00504224
Comment: Overall, this is a well written article suggesting that Type I Diabetes has become a predicable disease and suggesting that general screening of the population for islet autoantibodies should now be considered as a goal. Whilst admirable and certainly worthy of publication, I feel that some of the issues of such a screening strategy have not been discussed in great enough detail. For example there are no costings suggested. In addition, some of the issues arising from other large scale at risk screening (as an example consider the US National Lung Screening Trial based on low dose computerised tomography screening. This trial showed a 20% reduction in lung cancer mortality and a 6?7% decrease in all-cause mortality. THowever, a significant area of concern remains the issue of overdiagnosis, as estimates indicate that at least 20% of the detected lung cancers may in fact be indolent . This has significance "because it incurs unnecessary treatment, morbidity (and mortality in rare cases), follow-up, cost, and anxiety and labels a patient with a disease that otherwise would never have been detected". What are the sensitivity/specificity fro each of the autoantibodies top be used? Is there any risk of overdiagnosis. Admittedly, this may not necessarily be the case for Type I diabetes, but it should be addressed even as a discussion at the end of the article as to how such issues could be overcome in a large scale setting of the general populace.
Response: We agree with the reviewer that there are many considerations when proposing large scale

screening. At this time, there is not a cost effective or technically feasible way to conduct population wide screening, and screening will not be possible until a cheaper and more generalizable method can be designed without greatly altering the specificity and sensitivity of the current gold standard serum autoantibody measurements. On page 10-11 we added the following to elaborate of the risks of generalized screening for T1D: "Islet autoantibodies can be reliably measured in serum, with each antibody assay having a specificity of 99% when measured by radioimmunoassay in tertiary referral centers such as the Barbara Davis Center for Diabetes. The sensitivity for each autoantibody assay ranges from 70-80%. We view these radioimmunoassays as a confirmatory tests for T1D. A desired screening test needs to be reliable with high sensitivity, cost effective, and technically feasible, likely as a multiplex assay in which all four autoantibodies are measured in a single well of an assay plate. Currently, to measure islet autoantibodies a blood draw is required with subsequent shipping of venous or capillary blood samples to a reference laboratory. This is not feasible for population wide screening due to technical requirements of sample collection and high cost. Screening large populations of infants for metabolic diseases and other congenital disorders has been successfully done using dried blood spots.[84] To establish an accepted screening program for T1D, the sensitivity and specificity of islet autoantibodies, specifically insulin autoantibody, needs to be established using a feasible collection method such as dried blood spots on filter paper, which would be a simplified collection method and more cost effective. Overall, T1D would not be over diagnosed with general population screening as diagnosis of the disorder requires both the presence of islet autoantibodies and metabolic abnormalities."

4) Revision has been made according to the suggestions of Reviewer 00629064

Comment: The paper represents a clear overview on type 1 diabetes and the possibilities to improve prevention in genetically predisposed subjects.

Response: Thank you for your kind response.

5) Revision has been made according to the suggestions of Reviewer 02520738

Comment: We have read through the manuscript and we think that some lacking news should be better re-evaluated: 1) The author should describe the key words adopted, the scientific research motor adopted (PUBMED; SCOPUS; etc).

Response: We completed a PubMed search in September of 2014 using the following Medical Subject Headings (MeSH) terms: Diabetes Mellitus, Type 1, Type 2, Autoimmunity, Prevention, and Complications. The limits on our searched included those within the last 10 years in English and containing abstracts.

Comment: 2) What is the number of articles included for the final analysis? How many article were excluded? 3) A table resembling the characteristics of the considered studies should be provided.

Response: Given that this is a review article and not a meta-analysis, we do not believe it is necessary to add information regarding all potential literature that we examined for this review. We have paid special attention to referencing all articles that we reviewed, and believe that there is a good breadth of literature cited, especially after the reviewer's insightful comments below.

Comment: 4) Please discuss the paper from Ciccone MM et al. Ciccone MM, et al. 2014;5:364. doi: 10.4172/2155-6156.1000364 5) Please consider the value of revascularization therapy in diabetic foot for this patients. The authors can consider the work from Ciccone MM et al. Pak J Biol Sci. 2012 Aug 15;15(16):789-94.

Response: Thank you for providing reference to this important work. We have incorporated references into the manuscript. On page 9 the following text with references have been added: "Once T1D is clinically diagnosed, individuals must commit to lifelong blood glucose monitoring and intensive insulin administration via multiple daily injections or an insulin pump to achieve good glycemic control. With improved diabetes management, the risk for long-term complications such as renal failure, myocardial infarctions, stroke, and lower extremity amputations has

decreased over the last two decades.[62] However despite the decreasing prevalence of complications in diabetes, the need still exists to understand the underlying pathogenesis of complications such as diabetic cardiomyopathy and novel approaches for treating complications such as neovascularization in diabetic foot disease.[63,64]"

6) Figures were all made as decomposable images in PowerPoint as required.

7) We believe that the deleted citations are relevant and important to this manuscript. We kept them in this manuscript.

Thank you again for the opportunity to publish our manuscript in The World Journal of Diabetes.

Sincerely Yours,

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