Reviewer’s report

Title: Combining Glycosylated Hemoglobin A1c and Fasting Plasma Glucose for Diagnosis of Type 2 Diabetes in Chinese Adults

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Reviewer: Zhiheng He

Reviewer’s report:

In the manuscript “Combining Glycosylated Hemoglobin A1c and Fasting Plasma Glucose for diagnosis of Type 2 Diabetes in Chinese adults”, Mo and colleagues conducted a cross sectional study to evaluate a novel diagnostic approach for T2DM in 6661 Chinese adults who lives in Shanghai, China in 2009. They aimed to test the hypothesis that combinational use of FPG and HbA1c can potentially replace WHO’s diagnostic criteria for T2DM in Chinese. The authors concluded that FPG (#7 mmol/L) plus HbA1c (#6.1%) confers adequate sensitivity (83.7%) and specificity (89.35) in the diagnosis of type 2 diabetes in the studied cohort.

This is a very interesting study that provides substantial information that may potentially advance our knowledge on T2DM in Asians. Such information is in urgent need since consensus lacks regarding an optimal cut-off threshold to diagnose T2DM in this growing population. It has been reported that using HbA1c #6.5% alone as a diagnostic test has high specificity but might miss substantial diagnosis in Asians (Hsu et al. Diabetes Care, 2012, 35:1189). An optimal threshold is yet to be established in Asian population but several different cut-off points were proposed in the literature. Ethnicity-specific cutoff should be established (Tsugawa et al. Annals of Internal medicine, 2012; 157:153).

The strength of this study consists of 1) large sample size; 2) the novelty of combinational use of FPG and HbA1c; & 3) well performed statistical analysis with clinically relevant stratifications. However, the quality of the study was offset by the following weaknesses: 1) lack of direct correlation to the presence of complications such as retinopathy, which was used to establish the diagnostic criteria in the US. Therefore, a comparison to OGTT is suboptimal since it was really indirect; 2) the authors spear to have not decided what to use the combined FPG and HbA1c for, is it a screening test or a diagnostic test. It will be an expensive screening test but will not be appropriate for a conformational diagnosis unless they are performed on separate days; 3) The authors failed to put the current study into the context of many previous relevant reports suggestive of different cutoffs. A comparison to those studies are highly suggested and should be clearly discussed.

I have the following critiques:

#1. The authors concluded that “The combing use of FPG and HbA1c is a potential alternative to the 1999 WHO diagnostic criteria of T2DM.” This was provocative. While using HbA1c as a diagnostic criterion, positive results on 2
separate days are accepted for making the diagnosis. There is no clear evidence to support that abnormal results within one day can substitute the established diagnostic criteria.

#2. It was not clear from the manuscript whether the simultaneous use of FPG and HbA1c will be for screening test or for diagnosis confirmation.

#3. In the methods section, the description of "physically disabled" were elusive and should be clearly defined. I was not able to know whether the authors have considered other conditions that might affect the results of HbA1c, e.g. hemoglobinopathy such as thalassemia, which is common in China; or renal insufficiency which is frequently associated with anemia that may underestimate HbA1c. What about those subjects who have received blood transfusion shortly prior to the test? These should be clearly defined and probably should be excluded from the study.

#4. Hemoglobin levels for the different groups should be listed in the Table 1 if available.

#5. In page 15, table 1, Information should also include the percentage of subjects on anti-hypertensive medication and lipid lowering medications. Statin use should also be listed given its effect on diabetes.

#6. Additional table should be provided to list and compare sensitivity, specificity, PPV, and NPV for by FPG alone, by 2HPG alone; by HbA1c alone; and by FPG+HbA1c.

#7. Table 5 was very confusing and should be reformatted for clarity. Sensitivity, specificity, PPV, and NPV can be listed and compared in a separate table.

#8. In the background section, it should be noted that lack of standardized HbA1c was probably another major reason why HbA1c has not been adopted as the diagnostic criteria in China, in addition to the lack of knowledge about racial-specific standard. In the United States, it took a long time before HbA1c was standardized and adopted as a diagnostic criteria.

#9. Since HbA1c measurement is the core of the study, detail information regarding its measurement should be provided including the machine and protocol used. The reported CV for HbA1c was reported as <6.13%, which appears to be less stringent than those reported in the literature. Please explain and discuss about it.

#10. In page 9, it was not clear why the authors chose WC about 85 cm in male and 80 cm in females. Appropriate literatures should be cited to give the rationals. This also applies to the other parameters such as HW (hypertriglycerideremic waist phenotype), which is not a conventional measure and reported with different cutoff in the literature.

#11. Many of the references were not properly cited. For example, in Page 9, reference 23 was not a representative study to back up author's argument. I am
under the impression that the authors lack the understanding of up-to-date litterateurs in diabetes and randomly select reference without really reading the contents. All references should be re-examined before used.

#12. The language of this manuscript needs to be significantly improved. The authors might need editorial assistance from someone who use English as a native language.

**Level of interest:** An article of importance in its field

**Quality of written English:** Not suitable for publication unless extensively edited

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I have no competing interests in relation to this paper I reviewed. I have no disclosure of financial interest relevant to the content of the paper I reviewed.