HbA1c to Detect Diabetes Mellitus in Healthy Adults: When Should We Re-check?

Osamu Takahashi, MD, MPH 1,2; Andrew J. Farmer, D.M., F.R.C.G.P.1; Takuro Shimbo, MD 3; Tsuguya Fukui, MD, MPH 2; Paul P. Glasziou, MBBS, PhD 1

1Department of Primary Health Care, University of Oxford, Oxford, UK; 2Division of General Internal Medicine, Department of Medicine, St. Luke’s International Hospital, Tokyo, Japan; 3Department of Clinical Research and Informatics, International Medical Centre of Japan, Tokyo, Japan

Correspondence to:
Osamu Takahashi, MD, MPH
E-mail: otakahas@luke.or.jp

Submitted 31 March 2010 and accepted 12 June 2010.

This is an uncopyedited electronic version of an article accepted for publication in Diabetes Care. The American Diabetes Association, publisher of Diabetes Care, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of Diabetes Care in print and online at http://care.diabetesjournals.org.
Objective: To evaluate the optimal interval for re-checking HbA1c levels below diagnostic threshold of 6.5% for healthy adults.

Research Design and Methods: Retrospective cohort study. Participants were 16,313 apparently healthy Japanese adults not taking glucose-lowering medications at baseline. Annual HbA1c measures from 2005 to 2008 at the Center for Preventive Medicine, a community teaching hospital in Japan, estimated cumulative incidence of diabetes.

Results: Mean age (SD) of participants was 49.7 (12.3) years and 53% were male. Mean (SD) of HbA1c at baseline were 5.4 % (0.5). At three years, for those with HbA1c at baseline of less than 5.0 %, 5.0-5.4%, 5.5-5.9%, and 6.0-6.4%, cumulative incidence (95%CI) was 0.05% (0.001- 0.3), 0.05% (0.01 – 0.11), 1.2% (0.9 – 1.6), and 20% (18 – 23), respectively.

Conclusions: In those with an HbA1C under 6.0%, rescreening at intervals shorter than three years identifies few individuals (~1% or less) with an HbA1C ≥ 6.5%.
Annual repeated hba1c measurement is not needed

commencement of glucose-lowering treatment. As a sensitivity analysis, we used FPG≥126 mg/dl as one of the diagnostic criteria.

**Statistical methods.** Analyzes used SPSS software 15.0J (SPSS Japan, Tokyo, Japan), except 95% confidence intervals (CI) which were based on an exact binominal (7) using Stata version 10 (STATA Corp, College Station, TX).

**RESULTS**

From January 2005 to July 2008, 16,313 people of the enrolled population of 39,284 underwent annual checks. Mean age (SD) of participants was 49.7 (12.3) years; 53% were male. The mean (SD) body mass index was 22.5 (3.2) kg/m²; fasting plasma glucose was 99.2 (12.7) mg/dl; HbA1c at baseline was 5.4 (0.5) %; total, LDL cholesterol, and HDL cholesterol level at baseline were 204.3 (33.8) mg/dl, 117.6 (29.7) mg/dl, and 62.4 (15.8) mg/dl, respectively; and systolic blood pressure 119 (18) mmHg and diastolic blood pressure 73 (11) mmHg. The trends of mean HbA1c levels for the entire cohort from 2005 to 2008 slightly increased over the three years (0.05% per year). The demographic characteristics of nonparticipants and participants were similar.

At 3 years the cumulative incidence of diabetes was 3.2 % (95%CI: 3.0 – 3.4). However, this varies greatly by initial level of HbA1c. At three years, for those with HbA1c of less than 5.0 %, 5.0-5.4%, 5.5-5.9%, and 6.0-6.4% at baseline, cumulative incidence (95%CI) was 0.05% (0.001- 0.3%), 0.05% (0.01 – 0.11%), 1.2% (0.9 – 1.6%), and 20% (18 – 23%), respectively and adding FPG≥126 mg/dl to the diagnostic criteria showed the similar results (Figure). Logistic regression suggested that only BMI (Odds Ratio 1.14/kg/m²) and FPG (Odds Ratio 1.06/mg/dl) added to the baseline HbA1c; age, gender, SBP, and LDL were non-significant. The average coefficient of variation (CV) of HbA1c stratified by baseline HbA1c was 2.7% and did not differ among these subgroups.

**DISCUSSION**

This study confirms that the rise in HbA1c in a non-diabetic population is slow. Participants who are well under the diagnostic threshold of HbA1c of 6.5% are unlikely to exceed this within several years of follow-up. Much of the increased detection of diabetes in those with a higher baseline HbA1c was at one year, and may be attributable to measurement error and short term variation in HbA1c. The CV (including within subject variation) varies between 2 and 5 % (8); a CV of 5% would mean a 95% measurement interval of a single HbA1c in this range would be +/- 0.6%. This degree of variation would lead to some individuals having sequential tests from just below to just above 6.5%. Although the variation could occur at all time points, this is much less likely in the 5.0-5.9% range.

Our findings echo the slow rise of HbA1c found in trials with diabetic patients. For example, in the UKPDS study the patients on diet alone had a rise of less than 0.2% per year (9). Our non-diabetic cohort had an even lower average change in HbA1c of 0.05% per year.

This study has several limitations. First, the follow-up is incomplete as not all participants came back every year. This could be addressed by other analysis, such as a linear mixed model. However, any bias would be likely to favour those developing diabetes to re-attend. Second, a few participants (1.1%) began taking glucose-lowering drugs, but this is unlikely to make a large difference to our conclusions. Third, our data are from one institution in Tokyo, Japan, might not generalize to other populations. For example, adult mean BMI levels of 22-23 kg/m² are found in Africa and Asia, while levels of 25-27 kg/m² are prevalent across North America.
and Europe and then BMI level could be related to the cumulative incidence of diabetes. Finally, although the ADA criteria recommend a repeat HbA1c test to confirm the diagnosis of type 2 diabetes (2), our study included only a single measurement of HbA1c.

In conclusion, for the purpose of detecting new cases of diabetes, in those with an initial HbA1c under 6.0%, rescreening at intervals shorter than three years identifies few individuals (~1% or less) with an HbA1c ≥ 6.5%. At HbA1c ≥ 6%, rescreening even at a 1-year interval would be a reasonable strategy to identify disease.

Author Contributions: O.T wrote manuscript, AF wrote manuscript, PG wrote and reviewed manuscript and, TS and FT contributed discussion.

ACKNOWLEDGMENT
This work was supported in part by a UK National Institute for Health Research program grant and by a grant from the Ministry of Health, Labour, and Welfare of Japan. We would like to thank the following people: Sachiko Ohde, St. Luke’s Life Science Institute, and Gautam A. Deshpande, St. Luke’s Life Science Institute and University of Hawaii, for their helpful comments.

Conflict of Interest: None

REFERENCES
Annual repeated hba1c measurement is not needed

Legends
Figure: Percent of patients at annual re-checks with HbA1C above 6.5% or FPG above 126 mg/dl (by Baseline HbA1c)

Abbreviations: HbA1c, haemoglobin A1c, FPG, fasting plasma glucose