# A1C to Detect Diabetes in Healthy Adults

## When should we recheck?

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**OBJECTIVE** — To evaluate the optimal interval for rechecking A1C levels below the diagnostic threshold of 6.5% for healthy adults.

**RESEARCH DESIGN AND METHODS** — This was a retrospective cohort study. Participants were 16,313 apparently healthy Japanese adults not taking glucose-lowering medications at baseline. Annual A1C 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 ($\pm$SD) of participants was 49.7 $\pm$ 12.3 years, and 53% were male. Mean A1C at baseline was 5.4 $\pm$ 0.5%. At 3 years, for those with A1C at baseline of <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 A1C <6.0%, rescreening at intervals shorter than 3 years identifies few individuals ($\sim\leq$1%) with an A1C $\geq$6.5%.

Since fasting and post-glucose challenge blood glucose levels were found to predict the risk of diabetic retinopathy, they have been the international standard for diagnosis (1). Recently, a shift to A1C for diagnosis has been proposed because A1C integrates longer-term glucose levels and has better preanalytic stability (2). The proposed diagnostic threshold of 6.5% was based on retinopathy risk at different levels of A1C (2). However, optimal frequency for repeating A1C has not been determined (3). We used a large, longitudinal dataset to explore the value of repeating A1C at different intervals to identify subjects who might progress above the threshold ($\geq$6.5%).

## RESEARCH DESIGN AND METHODS

— Between January and December 2005, we consecutively enrolled all adults (aged >20 years) attending the Center for Preventive Medicine at St. Luke's International Hospital in Tokyo, Japan, for the health check program. The program promotes early detection of chronic diseases and disease risk factors. We excluded people who took glucose-lowering medications at baseline.

### Data collection

We extracted data from records of people undergoing annual health checks from January 2005 to December 2008. We excluded those without health checks in years 1, 2, or 3. St. Luke's International Hospital Institutional Review Board approved the study.

### Measurements

The annual health check collected demographic information and medical history with an initial evaluation (vital signs and laboratory data). Laboratory data included A1C, fasting plasma glucose (FPG), and lipids (total cholesterol, LDL cholesterol, and HDL cholesterol). Venous blood was drawn after an overnight fast and analyzed at the Central Laboratory at St. Luke's International Hospital. A1C assays were performed by an automated glycohemoglobin analyzer (HLC-723G; Tosoh, Tokyo, Japan), with a coefficient of variation (CV) of <1.34%, and certified by the National Glycohemoglobin Standardization Program (4). We classified subjects with either a single measured A1C $\geq$6.5% (5,6) or self-reported commencement of glucose-lowering treatment as diabetic. As a sensitivity analysis, we used FPG $\geq$126 mg/dl as one of the diagnostic criteria.

### Statistical methods

For the analyses, we used SPSS software 15.0J (SPSS Japan, Tokyo, Japan), except with 95% CIs, which were based on an exact binominal (7) using Stata version 10 (Stata, 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 ($\pm$SD) of participants was 49.7 $\pm$ 12.3 years, and 53% were male. Mean BMI was 22.5 $\pm$ 3.2 kg/m$^2$; fasting plasma glucose was 99.2 $\pm$ 12.7 mg/dl; A1C at baseline was 5.4 $\pm$ 0.5%; total cholesterol, LDL cholesterol, and HDL cholesterol levels at baseline were 204.3 $\pm$ 33.8 mg/dl, 117.6 $\pm$ 29.7 mg/dl, and 62.4 $\pm$ 15.8 mg/dl, respectively; and systolic and diastolic blood pressure was 119 $\pm$ 18 mmHg and 73 $\pm$ 11 mmHg, respectively. The trends of mean A1C levels for the entire cohort from 2005 to 2008 slightly increased over 3 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 A1C. At 3 years, for those with A1C of <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 $\geq$126 mg/dl to the diagnostic criteria showed similar results (Fig. 1). Logistic regression suggested that only BMI (odds ratio 1.14/kg/m$^2$) and FPG (1.06/mg/dl) added to the baseline A1C; age, sex, sys-
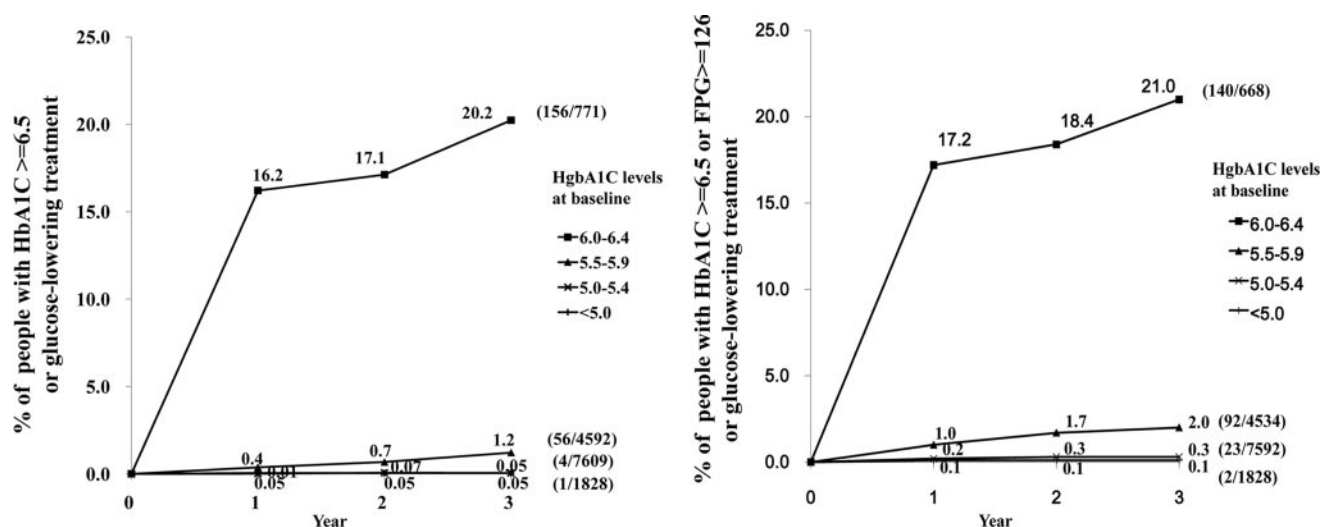
**Figure 1**—*Percent of patients at annual rechecks with A1C >6.5% or FPG >126 mg/dl (by baseline A1C).*

tolic blood pressure, and LDL were not significant. The average CV of A1C stratified by baseline A1C was 2.7% and did not differ among these subgroups.

**CONCLUSIONS** — This study confirms that the rise in A1C in a nondiabetic population is slow. Participants who are well under the diagnostic threshold of A1C 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 A1C was at 1 year and may be attributable to measurement error and short-term variation in A1C. The CV (including within-subject variation) varies between 2 and 5% (8); a CV of 5% would mean that a 95% measurement interval of a single A1C 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 A1C found in trials with diabetic patients. For example, in the UK Prospective Diabetes Study, the patients on diet alone had a rise of <0.2% per year (9). Our nondiabetic cohort had an even lower average change in A1C of 0.05% per year.

This study has several limitations. First, the follow-up is incomplete because 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 favor those developing diabetes to reattend. 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, and might not generalize to other populations. For example, adult mean BMI levels of 22–23 kg/m$^2$ are found in Africa and Asia, while levels of 25–27 kg/m$^2$ are prevalent across North America and Europe, and then BMI level could be related to the cumulative incidence of diabetes. Finally, although the American Diabetes Association criteria recommend a repeat A1C test to confirm the diagnosis of type 2 diabetes (2), our study included only a single measurement of A1C.

In conclusion, for the purpose of detecting new cases of diabetes, in those with an initial A1C <6.0%, rescreening at intervals shorter than 3 years identifies few individuals (~≤1%) with an A1C ≥6.5%. At A1C ≥6%, rescreening even at a 1-year interval would be reasonable strategy to identify disease.

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