Elevated Hemoglobin A_{1c} Is Associated With Incident Diabetes Within 4 Years Among Normoglycemic, Working-Age Individuals in an Employee Wellness Program

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Assessment of hemoglobin A_{1c} (HbA_{1c}) levels in addition to fasting glucose (FG) levels and other risk factors can improve diabetes risk assessment (1). Employee wellness programs (EWPs) are common in the U.S. (2), providing opportunities to identify working-age individuals at risk for diabetes (3) and to offer risk-reduction programs targeted to those at most risk. Based on the records of one large laboratory testing provider for EWPs, 25% of those offered FG testing were also offered HbA_{1c} testing (4). Here we investigated whether the addition of HbA_{1c} to FG testing for EWP participants with apparently normal FG (<100 mg/dL) would identify those at elevated risk for incident diabetes.

The analysis was based on a cohort of 34,676 employees and spouses who participated in an EWP in 2012. Those with baseline FG ≥100 mg/dL, HbA_{1c} ≥6.5% (48 mmol/mol), or a self-reported physician diagnosis of diabetes (n = 8,837), with missing baseline data (n = 244), or who failed to participate in the EWP at least once during 4 years of follow-up (n = 4,256) were excluded, leaving 21,339 participants. The association between baseline HbA_{1c} level and incident diabetes (FG ≥126 mg/dL or a self-reported physician diagnosis of diabetes in any annual follow-up EWP) was assessed in regression models that adjusted for age, sex, FG, triglyceride–to–HDL cholesterol ratio, serum creatinine, alanine aminotransferase, BMI, and blood pressure.

In this population of working-age individuals without diabetes with normal FG, 513 participants had incident diabetes during 4 years of follow-up. Those with incident diabetes were older (46.1 ± 9.9 years) than those without incident diabetes (43.7 ± 11.0 years; $P = 3 \times 10^{-7}$). Of the 85% of participants who reported their ethnicity, 49% reported white, 17% Asian, 13% African American, 12% Hispanic, and 9% other. The cumulative rate of incident diabetes after median follow-up of 3.96 years was 0.74 (95% CI 0.68 to 0.80) per 100 person-years (cumulative incidence of 3.0%, 95% CI 2.7 to 3.2, at 4 years of follow up). Baseline HbA_{1c} levels were associated with incident diabetes (adjusted odds ratio [OR] 2.2, 95% CI 2.0 to 2.5, per SD; $P = 4 \times 10^{-62}$). Similar results were observed after further adjustment for ethnicity (OR 2.2, 95% CI 2.0 to 2.5).

Those with the highest 5% of HbA_{1c} values had 8.4-fold greater risk of diabetes (adjusted OR 8.4, 95% CI 6.6 to 10.8) (Fig. 1) than those with normal HbA_{1c} levels. At the end of follow-up, the diabetes-free survival rate was 0.84 (95% CI 0.81 to 0.87) for those with HbA_{1c} >5.9% (41 mmol/mol) but <6.5% (48 mmol/mol), and 0.98 (95% CI 0.98 to 0.99) for those with normal HbA_{1c} levels.

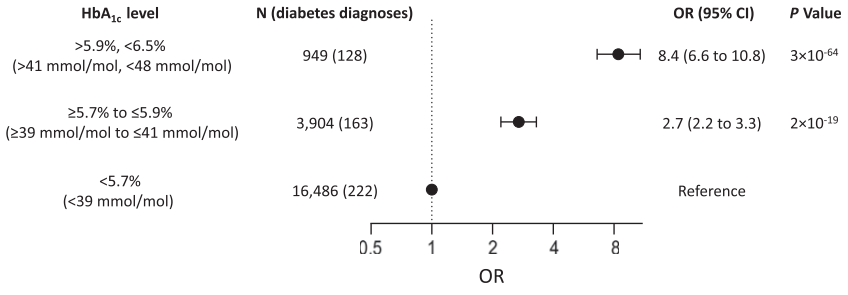

Figure 1—Odds of incident diabetes according to HbA_{1c} level. ORs and 95% CIs for incident diabetes among EWP participants who were free of diabetes and who had FG <100 mg/dL at baseline. The ORs were estimated in models that adjusted for age, sex, FG, triglyceride–to–HDL cholesterol ratio, serum creatinine, alanine aminotransferase, BMI, and blood pressure.

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Potential limitations include basing incident diabetes events on either FG testing or self-reported physician diagnoses of diabetes during annual EWP testing. About a third of the events were based on self-reported diagnosis alone, without support by an EWP blood test result, which could lead to either an over- or undercounting of events. Despite this, the observed ORs were large and the CIs were small. Furthermore, although EWP data were available for those who participated at baseline or during follow-up, no effort was made to contact the ~16.6% of participants who did not participate in any follow-up EWP. We note that because a variety of genetic, ethnic, behavioral, or medical factors can disrupt the correlation between average blood glucose levels and HbA_{1c} (5), the possibility of false-negative risk assessment can be reduced by using both HbA_{1c} and FG levels to assess diabetes risk. Although this analysis focused on the use of HbA_{1c} to identify diabetes risk among those with normal FG levels, recently HbA_{1c} levels have been combined with BMI and other modifiers of diabetes risk in risk prediction models that have been developed in two large community-based, U.S.-based population studies (1).

We conclude that among those with normal FG levels, some will progress to diabetes within 4 years, but HbA_{1c} levels can be used to identify some of those at the highest risk of progression so that appropriate prevention efforts can be directed to this small but important group.

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