Longitudinal Trajectories of HbA_{1c} and Fasting Plasma Glucose Levels During the Development of Type 2 Diabetes

The Toranomon Hospital Health Management Center Study 7 (TOPICS 7)

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OBJECTIVE—To describe the trajectory of HbA_{1c} and glucose concentrations before the diagnosis of diabetes.

RESEARCH DESIGN AND METHODS—The study comprised 1,722 nondiabetic Japanese individuals aged 26–80 years. Fasting plasma glucose (FPG) and HbA_{1c} were measured annually for a mean of 9.5 (SD 1.8) years.

RESULTS—Diabetes occurred in 193 individuals (FPG ≥7.0 mmol/L, self-reported clinician-diagnosed diabetes, or HbA_{1c} ≥6.5%). Mean HbA_{1c} values were >5.6% each year before diagnosis in diabetes cases. Mean HbA_{1c} (5.69% [95% CI 5.50–5.88]) was higher in the 21 individuals who developed diabetes 10 years after the baseline examination than in nondiabetic individuals after 10 years (5.27% [5.25–5.28]). From 3 years to 1 year prediagnosis, HbA_{1c} increased 0.09% (SE 0.01)/year, reaching 5.90% (5.84–5.96) 1 year prediagnosis. In the entire group, marked increases in HbA_{1c} of 0.3% (SE 0.05%)/year and FPG of 0.63 (0.07) mmol/L/year predicted diabetes.

CONCLUSIONS—HbA_{1c} trajectory increased sharply after gradual long-term increases in diabetic individuals.

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Trajectories of plasma glucose concentrations, insulin resistance, and insulin secretion to reflect the pathogenesis of type 2 diabetes were studied (1–8). Although HbA_{1c} is used to diagnose diabetes or indicate a prediabetic state in some countries (9), the long-term trajectory of HbA_{1c} before diabetes is little known. We retrospectively examined 10-year longitudinal data on apparently healthy Japanese individuals to investigate prediabetic changes in HbA_{1c} and compare such changes with those of fasting plasma glucose (FPG).

RESEARCH DESIGN AND METHODS

From 1997 to 2000, 23,939 participants underwent a baseline health examination at the Health Management Center, Toranomon Hospital, Tokyo, Japan. For this study, we reviewed data for 1,795 individuals who had annual examinations for 10 years after a baseline examination. After 73 diabetic individuals were excluded, our cohort consisted of 1,722 individuals aged 26–80 years. Self-reported clinician-diagnosed diabetes, FPG ≥7.0 mmol/L, or HbA_{1c} ≥6.5% (9) indicated diabetes.

We first divided participants according to whether they had developed diabetes during the 10-year follow-up. The year of diagnosis of diabetes (incident cases) or final follow-up (noncases) was indicated by year 0. We assessed FPG and HbA_{1c} trajectories from the baseline examination to year 0. Because diabetes developed at various times among the participants, 10-year data were unavailable for all incident cases. Blood samples were collected after an overnight fast (12-h) and measured using an automatic clinical chemistry analyzer (Hitachi, LABOSPECT 008). During the 10 years (mean 9.5 [SD 1.8]), 18,044 measurements were performed for HbA_{1c} and FPG, respectively. HbA_{1c} was assessed by high-performance liquid chromatography (Tosoh, Tokyo, Japan). The intra-assay coefficient of variation was 0.74% (mean 4.29), and the interassay coefficient of variation was 0.74% (mean 4.29). HbA_{1c} was estimated as the National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) (HbA_{1c} [%] = HbA_{1c} [Japan Diabetes Society] [%] + 0.4%) (10).

Statistical analyses were performed using IBM SPSS Statistics version 19 software. Repeated measurements of FPG and HbA_{1c} were analyzed with linear mixed models to investigate time-dependent changes in FPG and HbA_{1c} (8). The institutional review board at Toranomon Hospital reviewed the study protocol.

RESULTS

We documented 193 incident cases during the observational period, comprising 49 by self-report and 144 by FPG and/or HbA_{1c}. Among the 144 screening-detected cases, the FPG was ≥7.0 mmol/L in 96 and HbA_{1c} was ≥6.5% in 73. Mean follow-up for incident

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cases was 5.4 (SD 3.0) years, and only 21 individuals had prediabetic data for 10 years. Supplementary Table 1 shows baseline characteristics of study participants.

Compared with noncases, the 21 participants who developed diabetes after a 10-year follow-up had elevated baseline values for FPG (5.57 [95% CI 5.28–5.85] mmol/L) and HbA_{1c} (5.69% [5.50–5.88]) (Fig. 1*A* and *B*). Mean (SE) FPG and HbA_{1c} values throughout the observational period were higher at 1.022 (0.035) mmol/L and 0.471% (0.024), respectively, in incident cases than in noncases ($P < 0.001$). From 3 years to 1 year before diagnosis, incident cases experienced a 0.09% (0.01)/year increase in HbA_{1c}, reaching 5.90% (95% CI 5.84–5.96) 1 year before diagnosis. The FPG trajectory was similar and was elevated by 0.11 (0.02) mmol/L/year within the same time period. In the year before diagnosis, sudden increases in HbA_{1c} of 0.3% (0.05) and FPG of 0.63 (0.07) mmol/L occurred in incident cases.

The HbA_{1c} slope between cases and noncases significantly differed only in the year before diagnosis, although the slope for FPG differed significantly at each time point before diagnosis ($P < 0.001$) (Fig. 1*C*). Analysis of available data for FPG and HbA_{1c} for more than 2, 3, 4, 5, or 6 consecutive years before the development of diabetes showed that trajectories were fundamentally the same (data not shown).

When incident cases were diagnosed by the HbA_{1c} 6.5% criterion alone, the increase in HbA_{1c} from 1 year before diagnosis was sharp at 0.64% (SE 0.06)/year. Findings were similar when only the FPG criterion was used at 1.14 (0.09)/mmol/L/year. However, overall trajectories for both markers over 10 years were similar to results shown in the Figs., regardless of diagnostic criteria (Supplementary Figs. 1 and 2).

CONCLUSIONS—HbA_{1c} was >5.6% throughout the observational period in incident cases, with trajectories steeply elevated in the year before diagnosis after long-term gradual increases. We found that trajectories of FPG during development of diabetes were comparable to those reported previously (7,8). There is evidence that rapidly increasing glucose concentrations, rather than gradual increases, occur late in the disease process (2,5–8). However, those studies provided no data on repeated assessments of HbA_{1c} before the diagnosis of diabetes; thus, changes in HbA_{1c} during diabetes development are

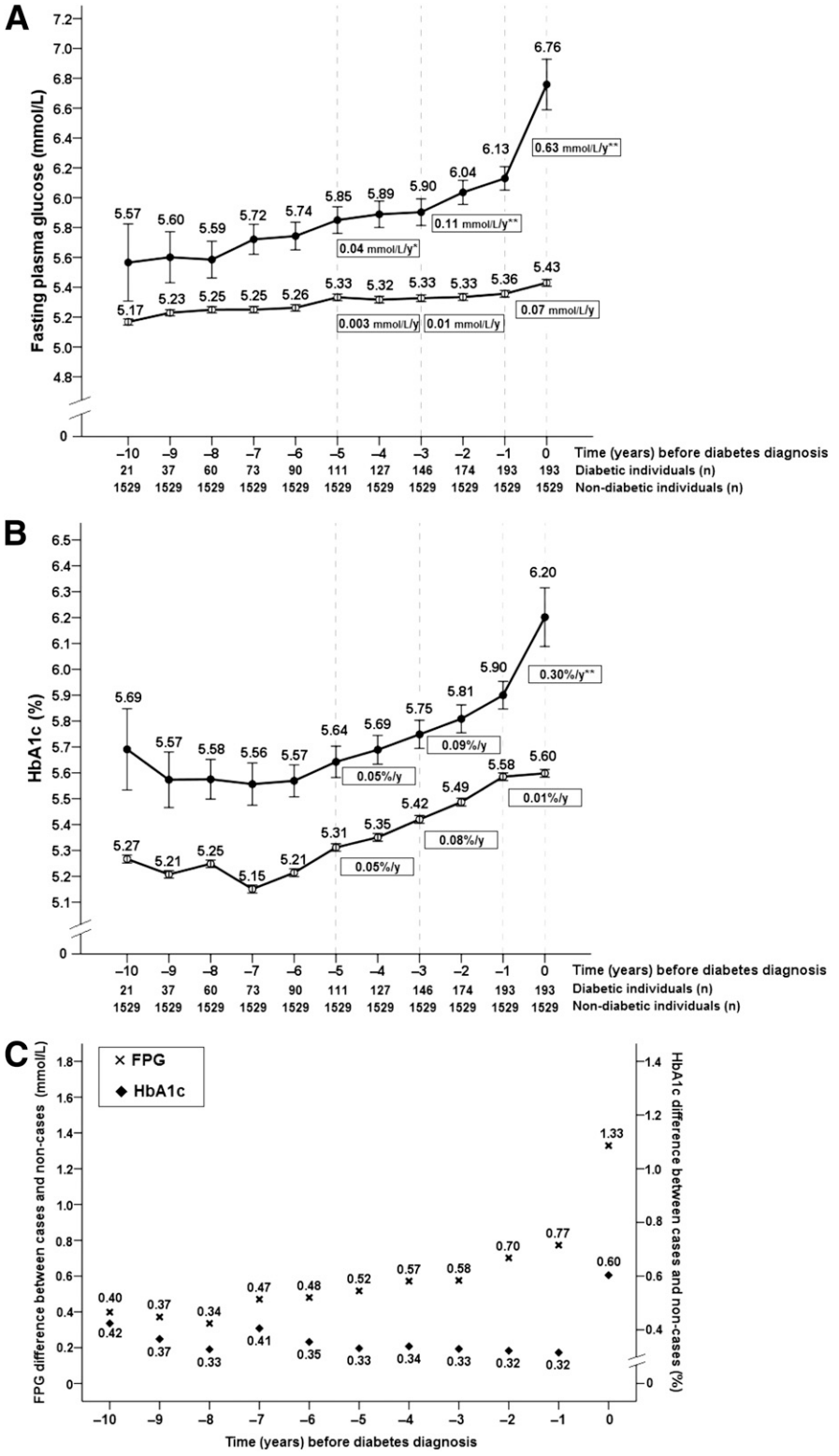

Figure 1—*Trajectory of values for FPG* (A)*, HbA_{1c}* (B) (●*, individuals who developed diabetes;* ○*, individuals who did not develop diabetes), and differences in FPG and HbA_{1c} values between cases and noncases* (C) *before the diagnosis of type 2 diabetes. Data in the boxes show annual increases in FPG or HbA_{1c} values during –5 to –3, –3 to –1, or –1 to 0 years before the diagnosis of diabetes. Slope difference vs. nondiabetic individuals: **P < 0.001, *P < 0.01. The value for HbA_{1c} (%) was estimated as the NGSP equivalent value (%) calculated by the formula [HbA_{1c} (%) = HbA_{1c} (Japan Diabetes Society) (%) + 0.4%].*

little known. Our results indicated that the year before diagnosis, when the FPG was 6.1 mmol/L, HbA_{1c} levels reached 5.9% and then further increased.

We observed that noncases had increasing HbA_{1c} values without elevated FPG concentrations. Although we could not determine the mechanism for these differences in patterns, several explanations may be considered. Tabák et al. (8) reported that individuals who did not develop diabetes over 13 years had stable FPG concentrations while postprandial glucose levels were increasing and insulin sensitivity was decreasing. Higher HbA_{1c} was positively associated with age independently of FPG or postprandial glucose levels in cross-sectional studies (11,12). Nonetheless, mean HbA_{1c} values did not exceed 5.6% in noncases during the 10-year observational period.

The large number of individuals with annual data on HbA_{1c} and FPG over a rather long period was a strength of our study, as was the standardization nationwide in Japan of HbA_{1c} (10). Study limitations were *1*) unavailability of data on oral glucose tolerance tests; *2*) the possibility of selection bias because study subjects may have paid more attention to their medical care than those who did not have such checkups; and *3*) the number of diabetic individuals diagnosed at various time points was not sufficiently consistent to draw trajectories, although we confirmed that trajectories for glycemia and the discontinuous rise from 1 year before diagnosis were equally apparent regardless of the difference in assessable years. To confirm our findings, further investigations are needed that include participants of other ethnicities.

In conclusion, trajectories for HbA_{1c} rapidly increased in the late stage before diagnosis following a gradual increase in the early stage of disease development.

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