Effect of Aging on A1C Levels in Individuals Without Diabetes

Evidence from the Framingham Offspring Study and the National Health and Nutrition Examination Survey 2001–2004

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OBJECTIVE — Although glycemic levels are known to rise with normal aging, the nondiabetic A1C range is not age specific. We examined whether A1C was associated with age in nondiabetic subjects and in subjects with normal glucose tolerance (NGT) in two population-based cohorts.

RESEARCH DESIGN AND METHODS — We performed cross-sectional analyses of A1C across age categories in 2,473 nondiabetic participants of the Framingham Offspring Study (FOS) and in 3,270 nondiabetic participants from the National Health and Nutrition Examination Survey (NHANES) 2001–2004. In FOS, we examined A1C by age in a subset with NGT, i.e., after excluding those with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). Multivariate analyses were performed, adjusting for sex, BMI, fasting glucose, and 2-h postload glucose values.

RESULTS — In the FOS and NHANES cohorts, A1C levels were positively associated with age in nondiabetic subjects. Linear regression revealed 0.014- and 0.010-unit increases in A1C per year in the nondiabetic FOS and NHANES populations, respectively. The 97.5th percentiles for A1C were 6.0% and 5.6% for nondiabetic individuals aged <40 years in FOS and NHANES, respectively, compared with 6.6% and 6.2% for individuals aged ≥70 years ($P_{trend} < 0.001$). The association of A1C with age was similar when restricted to the subset of FOS subjects with NGT and after adjustments for sex, BMI, fasting glucose, and 2-h postload glucose values.

CONCLUSIONS — A1C levels are positively associated with age in nondiabetic populations even after exclusion of subjects with IFG and/or IGT. Further studies are needed to determine whether age-specific diagnostic and treatment criteria would be appropriate.

Diabetes Care **31:1991–1996, 2008**

Glycemia is recognized to change with age. The prevalence of diabetes and impaired glucose homeostasis (impaired fasting glucose [IFG] and impaired glucose tolerance [IGT]) is increased among older individuals (1). Given the large size of the elderly type 2 diabetic population (approximately 15.3% diagnosed and 6.9% undiagnosed) (2), it is important to consider the effects of aging on glycemic measures, particularly as targets are set for diabetes management.

A1C levels are used globally as an index of average glycemia over the preceding 8–12 weeks (3), as a marker for risk of development of diabetes complications, and to guide therapy (4). Some reports have demonstrated an association of A1C with age (5–13), whereas others have not (14–17). Higher A1C levels with advanced age may be a function of a higher prevalence of undiagnosed diabetes in older individuals. The nondiabetic range for A1C, used worldwide and for all age-groups, was established by the Diabetes Control and Complications Trial (DCCT) >20 years ago (18). A group of 124 nondiabetic healthy volunteers aged 13–39 years was drawn from local DCCT clinics to generate the A1C distribution. The volunteers did not have an oral glucose tolerance test (OGTT) to exclude undiagnosed diabetes and were not representative of individuals aged ≥40 years.

Current A1C targets for diabetes treatment set by the American Diabetes Association (A1C <7%) (19) or the American College of Endocrinology (A1C ≤6.5%) (20) are not age specific. The central role played by A1C in the management of diabetes (4) and possibly in its diagnosis (21) raises the question of whether there are age-related differences in A1C. If so, current A1C targets may be too stringent for older type 2 diabetic patients, who have an increased risk of hypoglycemia and medication side effects (22,23).

Our aim was to examine the relationship between A1C and age using current diagnosis criteria for diabetes in nondiabetic subjects and in subjects with no abnormality in glucose homeostasis using two large, diverse population-based cohorts, the community-based Framingham Offspring Study (FOS) and the nationally representative National Health and Nutrition Examination Survey (NHANES) 2001–2004 population. In subsidiary analyses, we assessed this relationship in FOS subjects with normal glucose tolerance (NGT), after exclusion of

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Received 20 March 2008 and accepted 9 July 2008.
Published ahead of print at http://care.diabetesjournals.org on 15 July 2008. DOI: 10.2337/dc08-0577.
J.B.M. is currently receiving research grants from GlaxoSmithKline and sanofi-aventis and has consulting agreements with GlaxoSmithKline, sanofi-aventis, Interleukin Genetics, Kalypsis, and Outcomes Science.

those with IFG and/or IGT determined by an OGTT. Finally, in a subset of FOS participants with longitudinal A1C data, we determined the annual rate of change in A1C as an alternate approach to test the hypothesis that A1C increases with age.

RESEARCH DESIGN AND METHODS

— The FOS, a community-based population study in Framingham, Massachusetts, was described previously (24). This predominantly white population has been studied every 4–8 years since 1971: interim histories are obtained, and clinical examinations are performed.

NHANES is a national population-based study based on household sampling with oversampling for minority groups. NHANES 2001–2004 data were used for this analysis. Detailed descriptions of the sample design, interviewing procedures, and physical examinations have been published (25,26).

We performed a cross-sectional analysis of 2,473 nondiabetic FOS participants (aged ≥25 years) who attended their fifth examination between January 1991 and September 1995, during which fasting glucose and A1C were measured and a 75-g OGTT was performed. FOS subjects with diabetes, determined on the basis of previous treatment with antidiabetic medications or fasting plasma glucose (FPG) ≥126 mg/dl, were excluded. The nondiabetic cohort was classified as having IFG if FPG was between 100 and 125 mg/dl and IGT if 2-h postload glucose was 140–199 mg/dl (19). Participants with NGT had FPG <100 mg/dl and 2-h postload glucose <140 mg/dl. Fifty-nine subjects who had missing 2-h postload blood glucose measurements were excluded from the NGT analyses.

Of the 2001–2004 NHANES sample, we limited our eligible study population to the 3,272 individuals aged ≥25 years who did not have diagnosed diabetes and had an FPG <126 mg/dl (OGTT was not performed). Two individuals were not included because they did not have an A1C test available. Diagnosed diabetes was defined as a self-reported history of diabetes. American Diabetes Association diagnostic criteria were used to categorize individuals with previously undiagnosed diabetes (FPG ≥126 mg/dl) (19).

Laboratory measurements

A1C was measured in FOS and NHANES study subjects using high-performance liquid chromatography (HPLC) assays standardized to DCCT values by the National Glycohemoglobin Standardization Program (27). The A1C assays used in both studies have inter- and intra-assay coefficients of variation (CVs) <3%. Assay drift in the HPLC method used in FOS is prevented by the use of long-term stored reference samples. In NHANES, the boronate affinity HPLC method was used.

Plasma glucose levels were measured with a hexokinase reagent kit (A-gent glucose test, Abbott Laboratories, South Pasadena, CA) in FOS and with a hexokinase assay in NHANES (COBAS MIRA Chemistry System; Roche Diagnostic Systems, Montclair, NJ). The intra-assay CV was <3% for both assays.

Statistical analysis

Framingham offspring study. We categorized age into groups of 5 years (i.e., <40, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, and ≥70 years) with the age-groups collapsed for adequate sample size in the youngest and oldest bins. A1C levels were analyzed by age and by sex. Differences in mean A1C by age-group were examined by ANOVA. Tests for trend were performed using linear regression analysis. Secondary analyses considered sex-specific age-A1C associations. The sex-by-age interaction on A1C levels was tested with a first-order multiplicative interaction term. The effect of fasting and 2-h postload glucose values on the association of A1C and age was also examined. The 97.5th percentile of A1C was measured in the FOS nondiabetic sample to estimate the upper limit of A1C by age-group. A subset of FOS subjects with no evidence of IGT and IFG was analyzed to examine whether the increase in A1C with age was still evident. The effect of increasing age on A1C was examined in 1,704 nondiabetic FOS participants who had A1C measured at examinations 5 and 7 (1998–2001) to determine whether the A1C differences by age observed in the cross-sectional analysis corresponded to changes observed longitudinally. Change in weight between examinations 5 and 7 was included as a potential confounder in multivariable regression analysis.

NHANES. Age was categorized into 5-year groups to match the age distribution of the FOS and to provide reasonable sample size in each age bin. All analyses took into account differential probabilities of selection and the complex sample design. Sampling weights adjust for unequal probabilities of selection resulting from nonresponse and planned oversampling of certain subgroups. Again, the 97.5th percentile of A1C was computed, incorporating appropriate weighting of the survey data (28). We used the method of Korn and Graubard (28) to compute 95% CIs around the percentiles. Differences in mean A1C by age-group were examined by ANOVA.

Analyses of FOS and NHANES data were performed using SAS (version 9.1) (29). SUDAAN (version 9.01) was used for complex surveys.

RESULTS

— The FOS sample (n = 2,473) had a mean ± SD age of 54.7 ± 0.2 years with 45.2% women and a BMI of 27.15 ± 0.1 kg/m^2. The NHANES population included 3,270 nondiabetic participants aged 47.1 ± 0.6 years, 52% female, and with a BMI of 28.01 ± 0.14 kg/m^2. Of the 2,473 nondiabetic FOS subjects at visit 5, 65.6% had NGT, 20.3% had IFG only, 5.5% had IGT only, and 6.8% had both IFG and IGT. Approximately 2% (n = 44) of FOS subjects in the nondiabetic group met the criteria for diabetes on the basis of 2-h postload glucose ≥200 mg/dl but were included so that FOS and NHANES cohorts would be comparable. Of the 3,270 nondiabetic NHANES participants, 31.6% had IFG. (For the prevalence of IFG and IGT by age, see supplemental Table A1, available in an online appendix at http://dx.doi.org/10.2337/dc08-0577.)

There was a significant positive association between mean A1C and age-groups in the nondiabetic FOS and NHANES populations (P_{trend} <0.0001 for both) (Figs. 1*A* and *B*). In the FOS population, a similar trend was observed even after subjects with IFG and IGT were excluded (Fig. 1*C*) ($P_{trend} < 0.0001$) (Table 1). To exclude diabetes using a more strict definition in the FOS cohort, we analyzed data from nondiabetic subjects who had both FPG <126 mg/dl and 2-h postload glucose <200 mg/dl. We observed mean A1C results that were not different by >0.02 points in any age category compared with results obtained when FPG <126 mg/dl alone was used to define diabetes. The trend remained significant at $P < 0.0001$.

To determine whether FPG and 2-h postload glucose contribute to the increase in A1C observed with age, we analyzed FPG and 2-h postload glucose by age categories (supplemental Table A2, available in the online appendix). In nondiabetic subjects, we noted an ~8 mg/dl

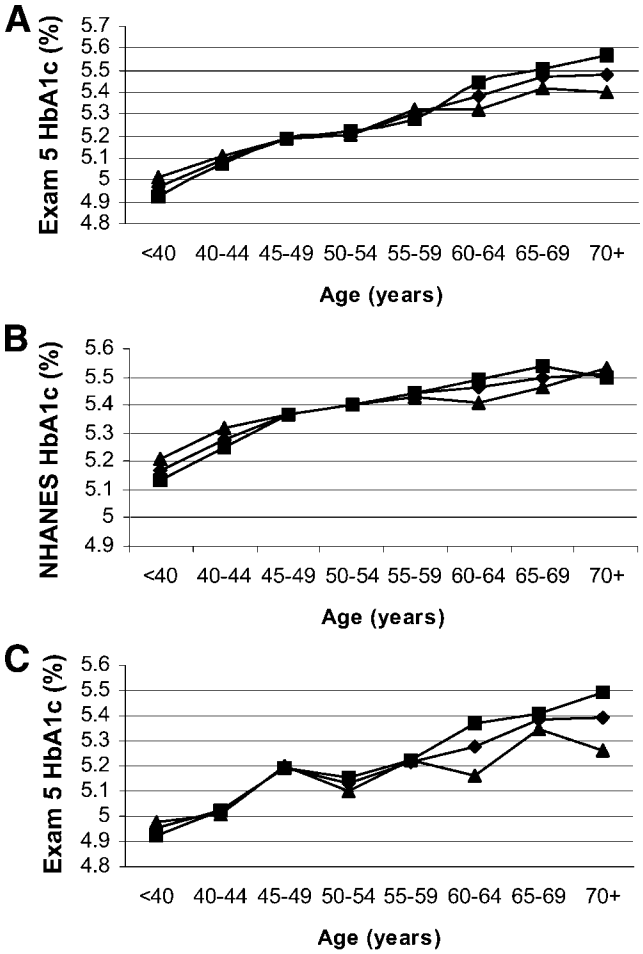

Figure 1—*Mean A1C by age categories in the FOS nondiabetic population* (A)*, the NHANES 2001–2004 nondiabetic population* (B)*, and the FOS NGT population* (C)*. The number of subjects in each age-group is shown in Table 1. Tests for trend were significant at* $P < 0.0001$ *for both the FOS and NHANES 2001–2004.* ♦*, All;* ■*, women;* ▲*, men.*

rise in FPG in both FOS and NHANES and a 35 mg/dl rise in 2-h postload glucose in FOS. In FOS subjects with NGT, FPG increased minimally and 2-h postload glucose increased by 15 mg/dl with age.

There was no difference in BMI noted across different age categories in either FOS or NHANES. In both the FOS and NHANES samples, there was a sex difference in the relationship between A1C and increasing age. We performed multivariate analyses to adjust for differences in sex, BMI, fasting glucose, and 2-h postload glucose. In FOS nondiabetic and NGT populations, the relationship between age and A1C remained unchanged in models adjusting for sex, BMI, fasting glucose, and 2-h postload glucose (supplemental Table A3a in the online appendix). Models adjusted for sex, BMI, and FPG in NHANES resulted in similar findings (supplemental Table A3b in the online appendix). From the above-mentioned multivariable linear regression models, every 1-year increase in age was associated with a 0.012-unit increase in A1C per year in the FOS and a 0.010-unit increase in the NHANES ($P < 0.001$ for both) nondiabetic sample. Analyses of the FOS NGT subgroup (IFG and/or IGT excluded) showed a similar relationship between age and A1C (0.012-point A1C increase per year, $P < 0.0001$).

The longitudinal analysis in FOS included a mean follow-up period of 6.7 years. An increase in A1C was observed in every age-group between examinations 5 and 7 in both the nondiabetic subjects and subjects with NGT (Table 2) (paired *t* tests $P < 0.0001$). Mean increases in A1C of 0.024–0.043/year in each of the age-groups in nondiabetic subjects and 0.020–0.045/year in subjects with NGT over the 6.7-year period were observed.

The 97.5th percentiles for A1C by 5-year age-groups are shown for FOS and NHANES in Table 1. Although the absolute values are different for each cohort, they rise with age, with the 97.5th upper limits for <40 years being 6.1 and 5.7 for FOS and NHANES, respectively, compared with 6.61 and 6.20 for those aged ≥70 years. We explored whether the differences in race distribution of the two populations might explain the differences in absolute A1C levels by analyzing data from only non-Hispanic white NHANES participants (74.7%). The 97.5th percentile A1C remained similar to that of the total NHANES population, with no more than a 0.1-unit difference in 97.5th percentile A1C in each age category.

Table 1—*A1C and 97.5th percentile A1C among FOS and NHANES participants*

	FOS subjects with NGT			FOS nondiabetic subjects			NHANES nondiabetic subjects		
Age (years)	*n*	Mean ± SE	97.5th percentile	*n*	Mean ± SE	97.5th percentile	*n*	Mean ± SE	97.5th percentile
<40	119	4.95 ± 0.05	6.10	141	4.97 ± 0.04	5.99	1,037	5.2 ± 0.01	5.7
40–44	192	5.02 ± 0.04	6.05	234	5.08 ± 0.04	6.28	330	5.28 ± 0.02	5.8
45–49	313	5.19 ± 0.03	6.63	443	5.19 ± 0.03	6.61	322	5.37 ± 0.02	6.0
50–54	295	5.13 ± 0.03	6.05	450	5.20 ± 0.02	6.26	261	5.40 ± 0.02	6.0
55–59	216	5.22 ± 0.04	6.53	356	5.28 ± 0.03	6.51	198	5.44 ± 0.02	6.0
60–64	196	5.28 ± 0.04	6.60	372	5.40 ± 0.03	6.83	283	5.46 ± 0.03	6.1
65–69	138	5.38 ± 0.05	6.44	280	5.46 ± 0.03	6.56	198	5.50 ± 0.03	6.1
≥70	97	5.39 ± 0.05	6.60	197	5.50 ± 0.04	6.61	641	5.51 ± 0.02	6.2

Table 2—*Change in A1C per year in FOS participants between examinations 7 and 5*

Age at examination 5 (years)	Nondiabetic subjects		NGT subjects	
	n	Mean ± SE	*n*	Mean ± SE
<40	104	0.027 ± 0.006	87	0.028 ± 0.007
40–44	182	0.032 ± 0.005	153	0.026 ± 0.006
45–49	337	0.037 ± 0.004	253	0.037 ± 0.004
50–54	343	0.043 ± 0.005	238	0.045 ± 0.007
55–59	258	0.024 ± 0.005	165	0.020 ± 0.006
60–64	239	0.024 ± 0.006	144	0.025 ± 0.007
65–69	184	0.030 ± 0.005	98	0.031 ± 0.007
≥70	100	0.026 ± 0.007	59	0.024 ± 0.009

Mean duration between the two examinations was 6.7 years (range 4.3–9.4). Paired *t* test for the difference in A1C between examinations 7 and 5: $P < 0.0001$.

CONCLUSIONS — We examined whether A1C increases with age in several ways: by examining two large and racially different nondiabetic populations, by studying a subset of subjects with no evident abnormalities of glucose metabolism, and finally by examining a cohort of nondiabetic subjects over time. The studies that have failed to demonstrate an association between age and A1C used diagnostic criteria to exclude diabetes that are now outdated (14–17) or were small and possibly underpowered (15–17). In our study we used the most recent criteria for diabetes diagnosis and large population-based cohorts.

We found a consistent increase in A1C with age in the cross-sectional analyses of both FOS and NHANES 2001–2004 nondiabetic populations. Our longitudinal analysis of FOS nondiabetic subjects confirmed an increase in A1C with aging. The 0.03-point increase per year in subjects with no abnormality in glucose homeostasis was greater in magnitude than expected from FOS examination 5 cross-sectional analysis, perhaps related to the relative increase in obesity among individuals of the FOS by the time of examination 7. An increase in BMI was noted in all age-groups, except for the ≥70 years age-group during that period (data not shown). It is also possible that subjects who returned for visit 7 may have been different from subjects who did not return. Results of our longitudinal analysis are comparable with those for a previous analysis of the original Framingham Heart Study, comprising parents of the FOS population, in which a 0.28% point increase in A1C over a 4- to 6-year period was observed, with a greater increase observed with increasing age (30). Even though we found a small increase in FPG and a more significant increase in 2-h postload glucose values across age categories, we could not translate these into mean blood glucose values to estimate the corresponding rise in A1C across age categories. However, we accounted for variation with age of FPG and 2-h postload glucose levels by performing multivariate analyses. None of these adjustments materially affected the association of age category with change in A1C.

In the current study, the upper limit (97.5th percentile) of A1C could be as high as 6.83% in older nondiabetic subjects and 6.60% in older subjects with no detectable abnormality of glucose homeostasis on standard testing. Despite using similar methodology to determine the 97.5th percentile A1C in the FOS and NHANES nondiabetic populations, the 97.5th percentile A1C was slightly higher in the FOS population than in the NHANES population, even though statistically significant increases with age were noted in both populations. Differences in assays and in the study populations, including their different racial compositions, and differences in the proportion of subjects with dysglycemic states (supplemental Table A1) may have contributed to the difference observed. The similar relative increase with age in both cohorts strengthens the conclusion that A1C levels increase with age. Moreover, the data from both the NHANES and the FOS enhance the generalizability of our results.

The age-related increase in A1C observed in our study is similar in magnitude to that in two previous studies: one in Japan (8) and one in a very small (n = 109) convenience cohort in the U.S. (10). Of the studies that have demonstrated an association between A1C and older age, many have been performed in selected samples (6–9,12). Some have inadvertently included subjects with diabetes by not screening the populations for diabetes with fasting or postchallenge glucose levels (6,8,10). Inclusion of subjects with IGT and/or IFG in previous studies may have contributed to the rise in A1C observed. In the current study, even after excluding subjects with the categorical dysglycemic states of IGT and IFG and controlling for the rise in FPG and 2-h postload glucose with age, we still observed an increase in A1C with age.

A possible explanation for the observed association of higher A1C with increasing age in individuals with NGT is that factors unrelated to glucose metabolism are affecting A1C levels. One such explanation may be changes in the rate of glycation associated with aging (12,13). There is no evidence for decreased red cell turnover owing to decreased clearance with aging as a possible explanation. A 2-h OGTT may not adequately capture postprandial glycemic excursions in elderly individuals. It is possible that other factors such as worsening kidney function with aging or anemia could be playing a role; however, these are less likely to play a significant role in healthy aging adults.

As in other studies (9), sex differences were noted in the relationship between A1C and age. It is possible that this finding is related to lower hemoglobin levels in menstruating women with more rapid erythrocyte turnover, as suggested previously (9). Women in peri- and postmenopausal age-groups had a steeper slope than men.

Even though the association of A1C with complications is well established in individuals with diabetes (31) and in nondiabetic subjects (32,33), the clinical significance of increased A1C in the subset of older individuals who have no evidence of glucose intolerance is unknown. Current treatment targets for patients with diabetes are similar regardless of age. A study designed to address the question of age-specific treatment targets would be necessary to determine whether treatment targets should be different.

There are several limitations of this study. First, the differences in sampling strategies for the two studies precluded combining the data from both. Second, although both studies used an A1C assay that was standardized by the National Glycohemoglobin Standardization Program (27), different laboratories performed the FOS and NHANES assays and

a comparison of the absolute A1C values may be problematic. Furthermore, the age distribution and prevalence of dysglycemic states in the two studies differed, and this may also have affected the absolute A1C levels in the two studies. Our sample size was smaller at the extremes of age, and we therefore combined all subjects who were ≥70 years old to have an analyzable sample size in all age categories. Finally, we did not account for the prevalence of other conditions that could affect A1C in either study population, including anemia and its treatment and kidney dysfunction; however, their effect is likely to be small overall. Despite these limitations, the similar impact of increasing age on A1C in both populations provides confirmation of the relationship between age and A1C in the nondiabetic population.

In summary, in the current study, the uniform results between FOS and NHANES establish clearly that A1C increases with age even after multivariate adjustments for sex, fasting, and 2-h postload glucose. The finding of higher upper limits of normal A1C in older individuals suggests that nonglycemic factors may contribute to the relationship of A1C with age. If we bear in mind the fact that elderly individuals have an increased risk for hypoglycemia and other medication side effects (22,23), the adoption of A1C targets that are lower than age-appropriate nondiabetic values may be associated with more medication-associated complications; however, a clinical study directly addressing the question of whether A1C should be age adjusted is needed. We recommend that further studies be undertaken to determine whether the increase in A1C associated with age in subjects with normal glucose tolerance is of clinical significance and to clarify whether age-specific diagnostic and treatment criteria would be appropriate.

Acknowledgments— This work was supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (National Heart, Lung and Blood Institute/National Institutes of Health Contract N01-HC-25195) and Boston University School of Medicine. J.B.M. is supported by an American Diabetes Association Career Development Award and National Institute of Diabetes and Digestive and Kidney Diseases Grant K24 DK080140D.M.N. is supported in part by the Earl P. Charlton Fund for Innovative Diabetes Research. L.P. is supported by an institutional National Research Service Award (T32).

We thank Peter Shrader and Sharon Saydah for assistance with statistical analyses. For contribution to the study, we thank Deborah Wexler, Diana Berger, Randie Little, Eran Bellin, and Curt Rohlfing.

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