

Effect of Aging on A1C Levels in Persons without Diabetes: Evidence from the Framingham Offspring Study and NHANES 2001-2004.

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

Methods: We performed cross-sectional analyses of A1C across age categories in 2473 non-diabetic participants of the Framingham Offspring Study (FOS) and in 3270 non-diabetic participants from NHANES 2001-2004. In FOS, we examined A1C by age in a subset with NGT i.e. after excluding impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). Multivariate analyses were performed, adjusting for gender, BMI, fasting and 2-hr post-glucose (2hPG) values.

Results: In the FOS and NHANES cohorts, A1C levels were positively associated with age in non-diabetic subjects. Linear regression revealed a 0.014 and 0.010-unit increase in A1C per year in the non-diabetic FOS and NHANES populations, respectively. The 97.5th percentiles for A1C were 6.0 and 5.6 for non-diabetic persons aged <40 in FOS and NHANES, respectively, compared with 6.6 and 6.2 for persons 70 years or older (p for trend <0.001). The association of A1C with age was similar when restricted to the subset of FOS subjects with NGT and after adjusting for gender, BMI, fasting and 2hPG values.

Conclusions: A1C levels are positively associated with age in non-diabetic populations even after excluding subjects with IFG and/or IGT. Further studies are needed to determine if age-specific diagnostic and treatment criteria would be appropriate.

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 T2DM population (about 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.

Glycated hemoglobin (A1C) levels are used globally as an index of average glycemia over the preceding 8-12 weeks (3), as a marker for risk of developing diabetes complications, and to guide therapy (4). Some reports have demonstrated an association of A1C with age (5-13), while others have not (14-17). Higher A1C levels with advanced age may be a function of a higher prevalence of undiagnosed diabetes in older age persons. The non-diabetic range for A1C, used worldwide, and for all age groups, was established by the Diabetes Control and Complications Trial (DCCT) more than 20 years ago (18). A group of 124 non-diabetic healthy volunteers aged 13-39 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 people 40 years and older.

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 whether there are age-related differences in A1C. If so, current A1C targets may be too stringent for older T2DM patients, who are at 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 non-diabetic subjects and in subjects with no abnormality in glucose homeostasis using 2 large, diverse population-based cohorts, the community-based Framingham Offspring Study (FOS) and the nationally representative National Health and Nutrition Examination Study (NHANES 2001-2004) population. In subsidiary analyses, we assessed this relationship in FOS subjects with normal glucose tolerance (NGT), after exclusion of IFG and/or IGT determined by 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 rises with age.

METHODS

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

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

Study Design:

We performed a cross-sectional analysis of 2,473 non-diabetic FOS participants (age ≥ 25 years old) who attended their fifth exam 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, based on previous, treatment with anti-

diabetic medications, or fasting plasma glucose (FPG) ≥ 126 mg/dl, were excluded. The non-diabetic cohort was classified as having IFG if FPG was between 100-125mg/dl and IGT if 2-hr post load glucose (2hPG) was 140-199mg/dl (19). Participants with normal glucose tolerance had FPG <100 mg/dl and 2-hr post load glucose <140 mg/dl. Fifty-nine subjects who had missing 2hPG 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 a 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. ADA diagnostic criteria were used to categorize people 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 (NGSP) (26). The A1C assays used in both studies have inter- and intra-assay coefficient of variation (CV) less than 2.5%. Assay drift in the HPLC method used in FOS is prevented by the use of long-term stored reference samples.

Plasma glucose levels were measured with a hexokinase reagent kit (A-gent glucose test, Abbott, South Pasadena, California) in FOS, and with a hexokinase assay in NHANES (Cobas Mira Chemistry System, Roche Diagnostic Systems, Inc. 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, ≥ 70), 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 2hPG values on the association of A1C and age was also examined. The 97.5th percentile of A1C was measured in the FOS non-diabetic 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 if the increase in A1C with age was still evident. The effect of increasing age on A1C was examined in 1704 non-diabetic FOS participants who had A1C measured at Exam 5 and Exam 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 exams 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 non-response and planned over-sampling of certain subgroups. Again, the 97.5th percentile of hemoglobin A1C was computed incorporating appropriate weighting of the survey data (27). We used the method of Korn and Graubard (27) to compute 95% confidence intervals 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 (28) and with SUDAAN (version 9.01) for complex surveys.

RESULTS

The FOS sample (n= 2473) had a mean age of 54.7 ± 0.2 years, with 45.2% women, and a mean BMI of 27.15 ± 0.1 kg/m². The NHANES population included 3270 non-diabetic participants, mean age 47.1 ± 0.6 years, comprised of 52% women, with a mean BMI of 28.01 ± 0.14 kg/m². Of the 2473 non-diabetic 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 non-diabetic group met criteria for diabetes based on 2hPG ≥ 200 mg/dl but were included so that FOS and NHANES cohorts would be comparable. Of the 3270 non-diabetic NHANES participants, 31.6% had IFG. (See Table A1 available in the online appendix at <http://care.diabetesjournals.org> for the prevalence of IFG and IGT by age).

There was a significant positive association between mean A1C and age groups in the non-diabetic FOS and NHANES population (p for trend < 0.0001 for both) (Figures 1a and 1b). In the FOS population, a similar trend was observed even after excluding subjects with IFG and IGT (Fig 1c) (p for trend < 0.0001). In order to exclude diabetes using a more strict definition in the FOS cohort, we analyzed data from non-diabetic subjects who had both FPG <126 mg/dl and 2hPG < 200 mg/dl. We observed mean A1C results that were not different by more than 0.02 points in any age category compared to results obtained when FPG <126 alone was used to define diabetes. The trend remained significant at p < 0.0001.

To determine if FPG and 2hPG contribute to the increase in A1C observed with age, we analyzed FPG and 2hPG by age

categories. In non-diabetic subjects, we noted approximately an 8mg/dl rise in FPG in both FOS and NHANES, and a 35mg/dl rise in 2hPG in FOS. In NGT FOS subjects FPG increased minimally and 2hPG increased by 15mg/dl with age (Online appendix Table A2).

There was no difference in BMI noted across different age categories) in both FOS and NHANES. In both the FOS and NHANES sample, there was a gender difference in the relationship between A1C and increasing age. We performed multivariate analyses to adjust for differences in gender, BMI, fasting and 2hPG. In FOS non-diabetic and NGT populations, the relationship between age and A1C remained unchanged in models adjusting for gender, BMI, fasting glucose and 2hPG (Online appendix Table A3a). Models adjusted for gender, BMI and FPG in NHANES resulted in similar findings (Online appendix Table A3b). From the above 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) non-diabetic 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 exams 5 and 7 in both the non-diabetic and NGT subjects (Table 2) (paired t-tests p < 0.0001). A mean increase in A1C of 0.024-0.043/year in each of the age groups in non-diabetic subjects and 0.020-0.045/year in NGT subjects over the 6.7-year period was observed.

The 97.5th percentiles for A1C by 5-year age groups are shown for FOS and NHANES in Table 2. 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 70 years or older. 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.

DISCUSSION

We examined whether A1C increases with age in several ways: by examining two large and racially different non-diabetic populations, by studying a subset of subjects with no evident abnormalities of glucose metabolism, and finally by examining a cohort of non-diabetic subjects over time. The studies that have failed to demonstrate an association between age and A1C used now outdated diagnostic criteria to exclude diabetes (14-17), or have been small and possibly underpowered (15-17). Our study has utilized 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 non-diabetic populations. Our longitudinal analysis of FOS non-diabetic 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 Exam 5 cross-sectional analysis, perhaps related to the relative increase in obesity among individuals of the FOS by the time of exam 7. An increase in BMI was noted in all age groups, except for the ≥ 70 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 to a previous analysis of the original Framingham Heart Study, comprised of parents of the FOS population, in which a 0.28% point increase in A1C over a 4-6 year period was observed, with a greater increase observed with increasing age (29). Even though we found a small increase in FPG and a more significant increase in 2hPG values across age categories were observed, we could not translate these into mean blood glucose values these to estimate the corresponding rise in A1C across age categories. However, we accounted for variation with age of FPG and 2h PG 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 non-diabetic 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 non-diabetic populations, the 97.5th percentile A1C was slightly higher in the FOS population than in the NHANES, 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 (online appendix 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 US (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 post-challenge 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 2hPG with age, an increase in A1C with age was still observed.

A possible explanation for the observed association of higher A1C with increasing age in persons 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 due to decreased clearance with ageing as a possible explanation. A 2-hr OGTT test may not adequately capture post-prandial glycemic excursions in the elderly. 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), gender differences were noted in the relationship between A1C and age. It is possible that this is related to lower hemoglobin levels in menstruating women with more rapid red blood cell turnover, as previously suggested (9). Women in peri- and post-menopausal age groups had a steeper slope than men.

Even though the association of A1C with complications is well established in people with diabetes (30), and in non-diabetic subjects (31, 32), the clinical significance of increased A1C in the subset of older people

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 target would be necessary to determine if 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 NGSP (26), different laboratories performed the FOS and NHANES assays, and comparing 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 or greater in order 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 populations, 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 non-diabetic population.

CONCLUSIONS

In the current study, the uniform results between FOS and NHANES establish clearly that A1C increases with age even after multivariate adjustments for gender, fasting and 2hPG. The finding of higher upper limits of normal A1C in older people suggests that non-glycemic factors may contribute to the relationship of A1C with age. Bearing in mind that the elderly are at increased risk for hypoglycemia and other medication side

effects (22, 23), adopting A1C targets that are lower than age-appropriate non-diabetic 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.

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Table 1: Mean A1C and 97.5th percentile A1C among FOS and NHANES participants

Age (years)	FOS NGT Subjects			FOS Non-diabetic Subjects			NHANES Non-diabetic Subjects		
	n	Mean (SE)	97.5 th percentile	n	Mean (SE)	97.5 th percentile	n	Mean (SE)	97.5 th percentile
<40	119	4.95 (0.05)	6.10	141	4.97 (0.04)	5.99	1037	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

*Means and standard errors are reported

Table 2: Change in A1C per year in FOS Participants between Exams 7 and 5*

Age at Exam 5 (years)	Non-diabetic 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)

* Results are expressed as Mean A1C change/year and Standard Error

Mean duration between the two exams: 6.7 years; range 4.3 – 9.4 years. Paired T-test for the difference in A1C between exam 7 and 5, P<0.0001

Figure 1: Mean A1C by age categories in (A) FOS non-diabetic population (B) NHANES 2001-2004 non-diabetic population and (C) FOS normal glucose tolerance population. The number of subjects in each age group is shown in Table 1. Test for trend significant at $p < 0.0001$ for both the FOS and NHANES 2001-2004.

