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Diabetes Mellitus among Centenarians

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Abstract

OBJECTIVES—Describe prevalence of diabetes mellitus among centenarians.

DESIGN—Cross-sectional, population-based.

SETTING—44 counties in northern Georgia.

PARTICIPANTS—244 centenarians (aged 98-108, 15.8% men, 20.5% African-American, 38.0% community-dwelling) from the Georgia Centenarian Study (2001-2009).

MEASUREMENTS—Nonfasting blood samples assessed HbA_{1c} and relevant clinical parameters. Demographic, diagnosis, and diabetes complications covariates were assessed.

RESULTS—12.5% of centenarians were known to have diabetes. Diabetes was more prevalent among African-Americans (27.7%) than Whites (8.6%, p=.0002). There were no differences between men (16.7%) and women (11.7%, p=.414), centenarians living in the community (10.2%) or facilities (13.9%, p=.540). Diabetes was more prevalent among overweight/obese (23.1%) than non-overweight (7.1%, p=.002) centenarians. Anemia (78.6% versus 48.3%, p=.004) and hypertension (79.3% versus 58.6%, p=.041) were more prevalent among centenarians with diabetes than without and centenarians with diabetes took more nonhypoglycemic medications(8.6 versus 7.0, p=.023). No centenarians with hemoglobin A1c < 6.5% had random serum glucose levels above 200 mg/dl. Diabetes was not associated with 12 month all-cause mortality, visual impairment, amputations, cardiovascular disease or neuropathy. 37% of centenarians reported

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onset before age 80 (survivors), 47% between 80 and 97 years (delayers) and 15% age 98 or older (escapers).

CONCLUSION—Diabetes is a risk factor for cardiovascular disease and mortality, but is seen in persons who live into very old age. Aside from higher rates of anemia and use of more medications, few clinical correlates of diabetes were observed in centenarians.

Keywords

Centenarians; Type 2 diabetes mellitus; Hemoglobin A_{1c}

INTRODUCTION

Increases in life expectancy of 2.2 years per decade suggest that fully one-half of all children born today could reach their 100th birthday[1]. Epidemiologic studies have revealed a progressive increase in diabetes mellitus prevalence (predominantly type 2 diabetes) among older adults[2, 3], but little is known about prevalence among centenarians, especially when diabetes mellitus is defined bycurrently accepted measures such as hemoglobin A1c (HbA_{1c})[4, 5]. Increasing survival afteronset of diabetes may be due to improved therapeutic remedies (pharmacological, dietary treatments and physical activity) and general increasesin life expectancy[6]. There is considerable variation in estimates of diabetes prevalence in older adults (from 10% to 38%) as a function of the year of measurement, sample composition and the diagnostic criteria employed[7, 8].

Few studies have characterized the prevalence of diabetes among persons who have survived into very old age (exceptional survivors). The Danish Centenarian Study reports a 10% prevalence of diabetes in Danish centenarians, but provides nodescription of prevalence variations across characteristics such as sex, race, or risk variables[9]. The current study describes prevalence of diabetesin centenarians, examines variations by key demographic and health variables anddescribes the associations of HbA_{1c} with relevant clinical parameters.

Historically, diabetes has been diagnosed on the basis of plasma glucose levels. Individuals with fasting glucose levels ≥126 mg/dl (7.0 mmol/l) or non-fasting glucose levels >200 mg/dl (11.1 mmol/l) are considered to have diabetes[4]. These cut-points were established because retinopathy was found to be relatively absent in individuals with glucose levels below these levels. Above these levels, prevalent retinopathy increases in a linear fashion;there are no age differences in diagnostic cut-points,only in treatment[4, 5]. Many patients accurately self-report having a diagnosis of diabetes [10, 11],but it is estimated that up to 26% of diabetes cases are undiagnosed[2], making objective measures preferable. Recently, a longer-term measure of glucose levels, glycated hemoglobin (HbA_{1c}), has been used to assess glucose levels, and risk of diabetes-associated retinopathy. Current guidelines suggest that HbA_{1c} ≥6.5% indicates diabetes and this cut-point does not differ by age[4]. HbA_{1c}level is considered an important monitoring tool in treating patients with diabetes[12]. Several previous studies have analyzedthe relationship between blood glucoseand HbA_{1c} in different populations[13]. However, analysis of the relationship between HbA_{1c} and relevant clinical parameters is not currently available in the research literature.

METHODS

Sample and Design

A population-based sample of 244 centenarians (n=135) and near-centenarians (n=109) from Phase III of the Georgia Centenarian Study[14] (GCS, 2001-2008) was employed,

representing over 19% of that total estimated population from a 44 county region of northeast Georgia[15]. Ages ranged from 98 to 108 years, 15.8% were men, 20.5% were African-American, and 38.0% lived in community settings. The study was approved by the University of Georgia Institutional Review Board on Human Subjects. Inclusion criteria for the GCS were verified age-eligibility and consent to blood draw, with no exclusions.

Procedures

The multidisciplinary nature of the GCS required that a data collection team meet centenarians at their residence. Data collection was divided into four sessions, each of which could be completed within two hours. On the first visit, after explaining the study aims and obtaining informed written consent, demographics, family longevity and mental status information was collected. A second session included a blood draw and a physical examination. The third and fourth sessions focused on neuropsychological and physical functioning, respectively[16].

Measures

Outcomes—Individuals were considered to have diabetes if their HbA_{1c} levels were ≥6.5%[4] or they were currently taking hypoglycemic medication. Only five centenarians were taking insulin,all at low dose. Information about disease diagnoses across a variety of organ systems, including diabetes, was obtained. Multiple sources could be consulted to obtain this information including self-report (n=38, 15.6%), proxy report (n=119, 48.8%), healthcare professionals (n=12, 4.9%), and medical records (n=138, 56.6%).

Covariates—Demographic covariates included sex (men/women), race (White/AfricanAmerican) and residential status (community/facility). Age was calculated based on interview and birth dates. Education was recorded in years. Information was obtained regarding lifetime alcohol and tobacco use. Based on low frequencies of current use, these values were dichotomized as current/ever=1 versus never=0. Number of medications, excluding those for hyperglycemia, was recorded. Using American Hypertension Association guidelines, the pulse pressure method was used to measure sitting systolic (SBP) and diastolic blood pressure (DBP) in the right arm with proper cuff size, unless participants were not able to sit or right-arm measurement was precluded. Supine BP measurement was employed if participantswere confined to bed or could not sitcomfortably. There were no differences in BP values, systolic or diastolic, based on sitting (n=215) or supine (n=26) measurement classification (p=.644 and .799 for systolic and diastolic, respectively) and all findings were the same when controlling statistically for sitting or standing measurement in preliminary analyses. Presence of hypertension was determined by presence ofSBP≥140mmHg, DBP≥90, current reported hypertension diagnosis, or current treatment with antihypertensive medications (any=1 versus none=0). Body weight and height were directly measured by interviewers, obtained from charts or via self-report. If the centenarian was bedbound or had kyphosis, height was estimated from knee height using standard formulas[17]. Body mass index (BMI) was calculated as weight (pounds)/height $(\text{inches})^2 \times 703$. BMI categories were based on the National Institutes of Health[18] guidelines, and focused on non-overweight ($\leq 25 kg/m^2$) or overweight/obese ($>25 kg/m^2$). There were insufficient numbers of obese centenarians (n=13) to consider finer distinctions as a function of BMI. Extent of visual impairment was coded based on acuity on a Snellen chart (mild=at least 20/60, moderate=between 20/60 and 20/160, severe=less than 20/160 or unable to complete task due to vision problems). Presence of any amputations was noted during the examination and coded dichotomously (yes=1, no=0). Sensory testing was conducted on left and right feet using a 10g monofilament and evidence of neuropathy in either foot was coded dichotomously (yes=1, no=0). Diagnoses of peripheral artery disease and congestive heart failure were determined as part of the medical examination. Cognitive functioning was

assessed using the Global Deterioration Rating Scale[19]Presence of an apolipoprotein-E-*ε4* allele (*APOE-ε4*, yes=1, no=0) was also recorded. Anemia was determined by hemoglobin status (<13g/dl for men and <12g/dl for women). All-cause mortality was recorded for the 12-month period following interview. .

Blood samples were collected at the centenarians' residences at the time of the physical examination. Due to varying times of collection and the frail nature of some participants, blood was collected in the non-fasted state. Blood samples were assessed(Lab Corp, Inc., Burlington, NC) for HbA_{1c}, glucose, creatinine, blood urea nitrogen (BUN), alanine aminotransferase (AST) aspartate aminotransferase (ALT), ferritin, and c-reactive protein (CRP, mg/l). HbA_{1c} values were not obtained for 13 participants for the following reasons: (1) insufficient blood draw volume (n=9), (2) lab did not return HbA_{1c} value without explanation given (n=3), and (3) sample too hemolyzed for HbA_{1c} analysis (n=1).

Statistical Analysis

All analyses were performed using STATA11[20]. Fisher's exact test was used to evaluate associations between diabetes status and dichotomous variables, and Mann-Whitney test used was to evaluate associations between diabetes status and ordinal variables. Independent-samples t-tests were used to evaluate associations between diabetes and continuous variables (with equal or unequal variances as indicated by a robust Levene'stest of homogeneity of variance). James's test was used to evaluate omnibus differences in predictors by diabetes status. A Mantel-Haenzel test was used to determine whether the association between diabetesand race persisted when controlling for overweight status. Ordinary least squares (OLS)regression with robust standard errors was used to model the associationsbetween predictor variables and HbA_{1c}.

RESULTS

Diabetes Prevalence

Overall, 29 of 232 (12.5%) of centenarians had diabetesas indicated by HbA_{1c} levels ≥6.5% and/or use of hypoglycemic medications, and no centenarians with HbA_{1c} levels <6.5% had random plasma glucose levels ≥200 mg/dl. In order to determine the morbidity profiles for diabetes[21], those with a known diagnosis of diabetes (n=21) were asked to provide information about year of onset. Ten participants were on only oral hypoglycemics, three were on oral hypoglycemics and low dose insulin, and two were on low dose insulin only. All five individuals on low-dose insulin were diagnosed in their 70s or 80s. Based on 19 (of 21 diagnosed) cases with complete data for this question, 7 reported age of onset before 80 years (survivors), 9 reported onset between 80 and 97 years (delayers), and 3 reported onset at 98 years or older (escapers). Mean disease duration for centenarians with diagnosed diabeteswas 16.8 years (SD=13.5).

Zero-Order Associations with Diabetes

Table 1 presents descriptive statistics by diabetes status. James's test[22], an extension of Hotelling's T^2 allowing for heterogeneous variances used as a protection scheme for testing multiple variables was statistically significant ($F(30,33.4)=2.47$, $p=0.006$). There was no difference in prevalence between men (16.7%) and women (11.7%, p=.414) or by community (10.2%) versus institutional residence (13.9%, p=.540), but African-Americans (27.7%) were more likely than Whites (8.6%, p=.002) to have diabetes, and diabetes was more prevalent among overweight/obese centenarians (23.1%) than those who were not overweight/obese (7.1%, p=.002). A Mantel-Haenzel test indicated that the relative risk (odds ratio) of diabetes remained higher among African-Americans than Whites controlling for overweight status (OR=3.30, p=.006).Two additional analyses (not presented) were

performed to examine potential differences in the association between HbA_{1c} levels between Whites and African-Americans. First, we evaluated effect modification with a race×HbA_{1c} interaction term (p=.331). Second, as suggested by previous work investigating whether HbA1c is equally useful as a criterion across ethnic groups[23, 24], we estimated a pair of logistic regression models predicting diagnosis of diabetes from HbA_{1c} levels separately for Whites and African-Americans. Solving for the values of HbA_{1c} at which an individual was predicted to be more likely than not to have diabetes yielded predicted values of 7.40% for Whites and 7.35% for African-Americans, suggesting that the associations between HbA_{1c} and diagnosed diabetes appear robust across Whites and African-Americans.

Anemia was more prevalent among centenarians with (78.6%) than without (48.3%) diabetes (p=.004), as was hypertension (79.3% versus 58.6%, p=.041). There were no differences in diabetes prevalence as a function of lifetime alcohol or tobacco use, or the presence of *APOE-ε4*. Diabeteswas not associated with 12-month all-cause mortality, extent of functional visual impairment, amputations, neuropathy of the feet, or global cognitive functioning. Age was not associated with diabetes, but more educated centenarians were less likely to have diabetes. Diabetic centenarians took significantly more non-hypoglycemic medications than non-diabetic centenarians, but there were no differences in the probability of NSAID use.

Non-fasting serum glucose levels were higher among diabetic centenarians compared to those without diabetesand hemoglobin levels were significantly lower among diabetic centenarians with diabetes compared to those without diabetes. There were no differences between centenarians with and without diabetes in levels of serum creatinine, CRP, ferritin, BUN, AST, or ALT(Table 1).

Multivariate Predictors of HbA_{1c}

In order to identify the multivariate predictors of HbA_{1c}status among centenarians, an OLS regression model with bootstrapped standard errors was used including age, sex, race, institutional residence, educational attainment, BMI, lifetime use of alcohol, tobacco, hypertension, APOE-*ε4*, and CRP (Table 2). Further model building and trimming procedures did not alter the substantive conclusions. The full model (Wald $\chi^2(11)=38.92$, p<.001) accounted for 22.3% of the variance in HbA_{1c} and indicated that African-Americans had higher HbA_{1c}than Whites (b=0.400, p=.022),individuals with higher BMIs had higher HbA_{1c}(b=0.044, p<.001), and individuals who had ever used tobacco had lower HbA_{1c} (b= −0.237, p=0.015). Only a small proportion of the sample (28.2%) reported ever having used tobacco and just 2.9% were current users. Those who reported ever using tobacco were roughly evenly split between <10 years of tobacco use (51.5%) and 10+ years of tobacco use (48.5%). When years of tobacco use (none, <10 years, 10+ years) was included in the model, the coefficients remained negative. There was no evidence of effect modification for lifetime tobacco use.

DISCUSSION

This study provides the first estimates of diabetes prevalence among centenarians using current standards of HbA_{1c} measurement in a population-based sample. It is interesting to note that the distinction between type 1 and type 2 diabetes was not recognized until the current cohort of centenarians had reached adulthood[25]. Findings indicate that diabetesis prevalent, even among extreme survivors. Several factors associated with risk for diabetes in younger populations appear inthe second century of life, specifically differences by race, overweight status, and educational attainment[2]. In contrast to younger populations[12, 26], relatively fewerdiabetes-related complications were seenin centenarians.

Prevalence of anemia is higher (and correspondingly, hemoglobin levels are lower) among centenarians with diabetes than those without, a finding observed with younger populations[27]. These differences seem not be attributed to medications, as use of non-steroidal anti-inflammatory medications between individuals with and without diabetes was similar and only two diabetic individuals were taking glitazones, One plausible mechanism may be related to the effects of diabetes on renal functioning and development of chronic kidney disease. Serum creatinine levels did not differ significantly between individuals with and without diabetes, however, although creatinine levels also vary as a function of age, sex, race, and BMI, and so are unlikely to be a reliable indicator of kidney disease in this age group. Direct measurement of creatinine clearance such as through 24-hour urine collection was not available, and standard formulas to estimate creatinine clearance have either been standardized using individuals selected for kidney disease[28] or in much younger populations[29, 30].

Prevalence of hypertension and total number of medications were higher among centenarians with diabetes than those without. However, no differences were observed in 12-month all-cause mortality, functional vision impairment, amputations, neuropathy of the feet, or cognitive functioning, despite the fact that, on average, the diagnosedcentenarians have lived with diabetes for more than 15 years, and in onecase for more than 50 years.

Sample size is small. However,the current population of centenarians also is very small, and we recruited nearly 20% of the entire estimatedpopulation in this targeted geographic area. Our study employed numbers of centenarians which are comparable with the Health and Retirement Study (n=143) and the 2004 wave of the National Long Term Care Survey (n=253) which oversampled individuals 95 years of age and older. Use of a single measure of BP is a limitation, but other indices of hypertension were also employed and results were not affected by different operationalizations (SBPor DBP, unadjusted or adjusted for treatment, and mean arterial pressure), nor were there associations of diabetes with peripheral artery disease or congestive heart failure. Prevalence of other cardiovascular disease variables was too low to include them in meaningful analyses. These included angina (n=0), coronary artery disease (n=4), and cardiomegaly (n=1). Prevalence of cognitive impairment in this aged population is high[16], rendering self-report data suspect for many individuals. Further, many individuals have outlived many of the most reliable potential sources of proxy information. To reduce these potential problems, more objective measures (e.g., observed height, BP, serum values, and recording medication information from prescription bottles) were used to the fullest extent possible.

CONCLUSION

A substantial proportion of centenarians have diabetes, most commonly with age of onset in their 80s. Given the typically long duration of diabetes for this rapidly growing population, future research should carefully address potential consequences of diabetes among centenarians. In younger populations, these includephysical disability, cognitive impairment, and indicators of cardiovascular and renal functioning. It is notable that in this study we found relatively few complications associated with diabetes. It will be important to replicate these findings as larger samples of centenarians become available in order to disentangle several possibilities. It can be difficult to distinguish between complications related to one specific disease in a group of centenarians characterized by multimorbidity. Centenarians typically reach this age with considerable burden of disease, such that the additional consequences of diabetes may be less important than for younger, less impaired persons. Alternatively, because diabetes is associated with both older age and mortality, there may be important selective forces at work such that the only centenarians who are able to attain this age in the presence of diseases such as diabetes are, by definition, those with relatively

fewer complications.This kind of selective mortality may also explain the finding of lower HbA_{1c} levels among former smokers. Centenarians who smoked, did so relatively little. Thus, it is possible that many smokers with diabetesdied at a younger age. Paradoxically, we may need to direct attention to younger individuals with diabetes to address these questions raised with centenarians, and we may need to do so within the context of longitudinal studies. For example, one simple hypothesis is that individuals with diabetes whose physicians make more effective decisions with regard to treatment and monitoring of risk factors are able to live with diabetes free of complications for longer periods.

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Table 1

Descriptive Statistics by Type 2 Diabetes Status

	HbA_{1c}< 6.5 and no hypoglycemics			**HbA_{1c}≥ 6.5 and/or hypoglycemics**			
Variable	N	M/%	SD	N	M/%	SD	p value
HbA_{1c} (%)	203	5.7		28	7.0		---
Female*	203	85.2%		29	79.3%		0.414
African-American*	203	16.7%		29	44.8%		0.002
Institutional Residence*	203	61.1%		29	69.0%		0.540
Ever used alcohol*	201	19.4%		29	31.0%		0.150
Ever smoked*	200	29.0%		29	20.7%		0.507
Hypertension (observed, diagnosed, treated)*	203	58.6%		29	79.3%		0.041
Any APOE ε4*	203	17.7%		29	24.1%		0.444
Anemia*	201	48.3%		28	78.6%		0.004
Overweight/Obese*	193	25.9%		26	57.7%		0.002
Visual Impairment†	192						0.668
Mild	192	9.4%		26	15.4%		
Moderate	192	46.9%		26	42.3%		
Severe	192	43.8%		26	42.3%		
All-Cause Mortality within 12 Months*	203	27.6%		29	20.7%		0.508
Amputations*	203	2.0%		29	6.9%		0.165
Neuropathy*	187	2.7%		24	0.0%		1.000
Peripheral Artery Disease*	204	21.2%		28	10.7%		0.310
Congestive Heart Failure*	204	16.7%		28	14.3%		1.000
Non-Steroidal Anti-Inflammatory Medication*	203	38.4%		29	41.4%		0.839
Age (Years) ‡	203	100.6	2.0	29	100.5	2.2	0.870
Education (Years) ‡	197	10.9	3.8	29	9.1	4.0	0.020

	HbA_{1c}< 6.5 and no hypoglycemics			HbA_{1c}≥ 6.5 and/or hypoglycemics			
Systolic Blood Pressure (mmHg)[§]	200	127.8	16.2	29	128.5	11.0	0.765
Global Deterioration Rating Scale[†]	201	4.0	1.6	24	3.8	1.9	0.357
Diastolic Blood Pressure (mmHg)[‡]	200	73.7	9.6	29	73.3	9.2	0.831
Body Mass Index (kg/m^2)[‡]	193	22.6	4.3	26	25.2	4.5	0.004
Number of non-hypoglycemic medications[†]	203	7.0	3.8	29	8.6	3.7	0.023
Serum glucose (non-fasting, mg/dl)[§]	194	103.7	24.9	28	139.4	49.6	0.001
Serum creatinine (mg/dl)[‡]	194	1.1	0.5	28	1.2	0.3	0.177
Hemoglobin (g/l)[‡]	201	121.2	14.5	28	113.8	12.9	0.011
Ferritin (ng/ml)[‡]	190	117.8	171.8	28	154.0	155.1	0.293
BUN (mg/dl)[‡]	194	25.0	10.8	28	25.4	9.1	0.840
AST (iu/l)[‡]	194	21.3	5.8	28	20.4	5.5	0.452
ALT (iu/l)[‡]	194	13.6	5.4	28	14.4	4.9	0.444
C-reactive protein (mg/l)[‡]	183	9.7	18.6	27	10.4	17.5	0.854

HbA_{1C} = Hemoglobin A_{1C}

APOE = Apolipoprotein E

BUN = Blood urea nitrogen

AST = Alanine aminotransferase

ALT = Aspartate aminotransferase

[*] Fisher's Exact Test

[†] Wilcoxon Signed Rank Test

[‡] t-test for equal variances

[§] t-test for unequal variances

Table 2

Ordinary Least Squares Regression Model Predicting HbA_{1c} Status

Variable	b*	SE(b)	p value
Age (Years)	−0.023	0.024	0.338
Female	0.022	0.112	0.841
African-American	0.400	0.178	0.024
Institutional Residence	0.016	0.090	0.859
Education (Years)	−0.002	0.014	0.866
Body Mass Index (kg/m^2)	0.044	0.012	0.001
Ever used alcohol	0.163	0.110	0.138
Ever smoked	−0.237	0.093	0.011
Hypertension	0.081	0.083	0.333
Any APOE ε4	0.054	0.133	0.685
C-reactive protein (mg/l)	0.002	0.003	0.432
Intercept	7.046	2.401	0.003

$\chi^2(11)=39.61$, $p<.001$

HbA_{1c} = Hemoglobin A_{1c}

APOE = Apolipoprotein E

* Entries are regression coefficients.