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Effects of Cardiorespiratory Fitness on Aging-glucose Trajectory in a Cohort of Healthy Men

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Abstract

PURPOSE—We modeled the age-related trajectory of glucose and determined if cardiorespiratory fitness altered the trajectory in a cohort of men from the Aerobics Center Longitudinal Study.

METHODS—10,092 men free of diagnosed diabetes, CVD, and cancer, aged 20 to 90 years, completed from 2 to 21 health examinations between 1977 and 2005. Cardiorespiratory fitness was measured by a maximal treadmill exercise test and normalized for age. The covariates included waist circumference, hypertension, elevated cholesterol, smoking behavior and physical activity.

RESULTS—Linear mixed models regression analysis showed that fasting glucose increased at a linear rate with aging. Glucose increased at a yearly rate of 0.17 mg/dL (95% confidence interval: 0.16, 0.19). Fitness had little influence on the aging glucose trajectory below age 35, but significantly influenced the trend after age 35 (P for interaction <0.001). The aging-related glucose increases in low fit men (0.25 mg/dL per year) was higher than average fit (0.15 mg/dL per year) and high fit (0.13 mg/dL per year) men.

CONCLUSIONS—The aging-related glucose increases in low fit men was nearly double that of high fit men. Our results may suggest that it is possible to delay the age-related glucose impairment through increasing one's fitness.

Keywords

Fasting glucose; aging; physical fitness

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INTRODUCTION

With the U.S. population aging, chronic non-communicable diseases such as heart disease and diabetes are becoming major public health problems. In 2010, an estimated 25.8 million Americans had type-2 diabetes and another 79 million of them had blood glucose readings that placed them at risk for type-2 diabetes (1). Studies have shown that advancing age is associated with impaired glucose handling (2–8). Elevated fasting glucose is not only one of the most important predictors of subsequent deterioration to diabetes (9–11), but also associated with various cardiovascular disease (CVD) outcomes (12–16). Substantial evidence suggests that changes in diet and physical activity are among the major causes of age-related glucose impairment (6).

Previous research has linked physical activity with incidence of type-2 diabetes (17). A few studies have reported associations between cardiorespiratory fitness (hereafter as ‘fitness’), an objective measure of habitual physical activity, and type-2 diabetes (18–20). The 15-year longitudinal results of the Coronary Artery Risk Development in Young Adults (CARDIA) study showed that fitness measured with a maximum treadmill test was inversely associated with developing type-2 diabetes and metabolic syndrome (18). The investigators reported that risk of developing type-2 diabetes was double for low fit participants compared with high fit young adult men and women. Improving fitness over the 7 years significantly reduced the risk of developing type-2 diabetes and metabolic syndrome. One treatment goal for type-2 diabetes is to maintain an optimal glucose (21). Being physically active is viewed as an important lifestyle determinant in maintaining a healthy glucose level (22). To date, longitudinal studies on effects of age-associated glucose changes with accurate measures of fitness are lacking. Defining the age-related glucose trajectory and identifying the factors that alter the trajectory is an important public health topic.

The Aerobics Center Longitudinal Study (ACLS) includes a large number of individuals who vary in age and have serial health examinations that include objectively measured fitness, percent body fat and fasting plasma glucose (hereafter as ‘glucose’). Findings from our previous research document that elevated glucose is associated with both obesity and low fitness in men (20). The influence of aging and fitness on the longitudinal change of fasting glucose is complex and not clearly defined because fitness declines with age (23;24) and percent body fat increases with age (25). The purposes of the current study were to 1) define the longitudinal, aging glucose trajectory; and 2) determine if fitness altered the trajectory independent of percent body fat.

METHODS

Study Population

The current analysis included 10,092 men who completed at least two comprehensive medical examinations at the Cooper Clinic in Dallas, Texas between 1977 and 2005. The men completed from 2 to 21 tests (mean: 3.9) for a total of 38,947 observations. All participants included in this study had normal resting and exercising electrocardiograms (ECGs), a body mass index (BMI) ≤ 35 , and were able to reach 85% of his age-predicted maximal heart rate during the exercise tests. Those who reported a history of myocardial infarction, stroke, or cancer were excluded. We also excluded men with physician-diagnosed diabetes or those who used insulin, but not those with undiagnosed diabetes (e.g., fasting glucose ≥ 126 mg/dL (7.1 mmol/L)) during any visit in order to remove treatment effects on fasting glucose levels. The comparison of baseline characteristics between the ACLS population and the present population was shown in the Appendix 1.

Participants came to the clinic for periodic preventive health examinations and for counseling regarding diet, exercise, and other lifestyle factors associated with increased risk of chronic diseases. Many were sent by their employers for the examination, some were referred by their physicians, and others were self-referred. Participants were predominantly white, well-educated, and belonged to middle and upper socioeconomic strata; all had access to health care. Participants signed an informed consent for the clinical examinations and follow-up, and the study was reviewed, approved and had ethical approval from the Institutional Review Board of the Cooper Institute.

Clinical Measurements

The clinical examinations were completed after an overnight fast of at least 12 hours and included a physician examination; clinical evaluations such as blood chemistry analyses and blood pressure measurements; questionnaires on personal health history and habits; and a maximal treadmill exercise test. Resting blood pressure was measured in the seated position and was recorded as the first and fifth Korotkoff sounds by auscultatory methods after at least 5 min of sitting quietly. Two or more readings separated by 2 min were averaged. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, or a history of physician diagnosis. High cholesterol was defined as serum cholesterol ≥ 240 mg/dL (6.2 mmol/L). Smoking status (current smokers or not) was obtained from a standardized questionnaire. Physical activity habits were assessed by self-reported leisure-time or recreational activities during the past three months. The questionnaire has been validated previously (26;27). Participants were classified as inactive or active based on previous reports from our group (24;28).

Percent body fat was measured by either hydrostatic weighting(29) or skinfold thickness (30), and in some instances, both. The hydrostatic weighing method measured body density and the skinfold method estimated body density from the sum of seven skinfolds and age. The reported multiple correlation for the skinfold equation(30) with hydrostatic weighing was 0.90 (SEE = 0.008 g/cc, 3.4% fat). The two-component Siri model (31) converted the underwater measured and skinfold estimated body density to percent fat. When a man had both the skinfold and underwater weighing measures, the underwater weighing method (54%) was used. BMI (kg/m^2) was computed from measured height and weight. Waist circumference was measured level with the umbilicus.

Cardiorespiratory fitness was quantified as the duration of a symptom-limited maximal treadmill exercise test using a modified Balke protocol (32). Patients were encouraged to give a maximal effort, and the test endpoint was volitional exhaustion or termination by the physician for medical reasons. The mean (standard deviation, SD) percentage of age-predicted maximal heart rate achieved during exercise was 103.6 (6.5) in the current study. The speed and elevation of the final minute of the treadmill test was used to convert treadmill performance to METs (33). One MET is an oxygen uptake of 3.5 ml/kg/minute, the energy expenditure at resting. Exercise treadmill duration on this protocol is highly correlated ($r = 0.92$) with measured peak oxygen uptake in men (34). Abnormal ECG responses were broadly defined as rhythm and conduction disturbances and ischemic ST-T wave abnormalities as described in detail elsewhere (35).

It has been shown that the fitness declines at a non-linear rate with aging and the rate of decline accelerates after age 45 (24). To control for the aging effect, fitness was normalized for age (AN-Fitness). The equations (24) used to compute AN-Fitness were:

$$\text{AN-Fitness} = \text{Measured Fitness (METs)} - \text{Estimated Fitness (METs)}$$

Where Estimated Fitness was estimated by:

$$\text{Estimated Fitness} = 10.46381 + (\text{Age} \times 0.13626) - (0.00205 \times \text{Age}^2)$$

AN-Fitness is a continuous variable representing the patient's fitness level in METs for his age. We also classified men below the 33rd percentile as low fit and those above the 66th percentile as high fit. The men between the 33rd and 66th percentile were classified as average fit.

Fasting blood samples were obtained using venipuncture with minimal stasis and were analyzed by automated techniques in a laboratory certified by the Centers for Disease Control and Prevention Lipid Standardization program. Glucose was enzymatically determined. Participants were considered to have an abnormal glucose level if a glucose reading was ≥ 100 mg/dl (5.6 mmol/L, to convert to mmol/L, multiply by 0.0555) on any of his examinations (36).

Statistical Analyses

Linear mixed model (LMM) regression random intercept growth model (37;38) was used to analyze the longitudinal data. The patient's age was the measure of time for the growth model. The major advantage of LMM is that it accommodates unbalanced, unequally spaced observations over time making it an ideal method to model longitudinal data. Stata[®] version 10 xtmixed program was used for all LMM analyses (www.stata.com). The dependent variable for each LMM analysis was fasting glucose. We first examined the longitudinal change in fasting glucose associated with aging. Both linear and quadratic models were examined. We then evaluated the influence of percent body fat on the age-glucose association. Next, we investigated the independent influence of AN-Fitness and percent body fat on the age-related changes in glucose. Finally, we accounted for the time-varying covariates including waist circumference (cm), smoking status (current or not), physical activity habits (inactive or active), hypertension (yes/no) and high cholesterol (yes/no). A log likelihood ratio test was used to determine if the model improved the fit (37;38). Each regression coefficient was tested with a z-statistic to determine if it was significantly different from 0. Statistical tests were two-sided: $P < 0.05$ was accepted to indicate statistical significance.

RESULTS

Table 1 gives the descriptive statistics for all observations and contrasted by AN-Fitness group. Provided are the number of observations, means and SD for the continuous variables, percentages for categorical variables and the P values for a linear trend of the continuous variables. The age range for all men was 20 to 90 years. The mean difference in age among fitness groups varied by less than a year. Mean body weight, percent fat, BMI, waist circumference and glucose were inversely related to AN-Fitness. The proportion of men who currently smoked, were inactive, and found to be hypertensive and have elevated cholesterol was inversely related to fitness level.

Table 2 provides the LMM analyses that define the longitudinal change in glucose with aging and percent fat. Model I defines the aging glucose trajectory of all men. Adding a quadratic term did not increase the accuracy of the model ($X^2 = 1.43$, $P = 0.23$) confirming that the glucose longitudinal aging trajectory was linear. Glucose changed at a yearly linear rate of 0.22 mg/dL (95% confidence interval (CI): 0.20, 0.23). Model II combined percent fat with age. A log ratio test confirmed that the model improved fit ($X^2 = 605.78$, $P < 0.001$). Age Model II demonstrated that with percent fat controlled, the aging glucose trajectory was

slightly reduced to 0.17 mg/dL per year (95% CI: 0.16, 0.19). The significant regression weight for percent fat showed there was a positive association between changes in glucose and percent fat. The rate of change in glucose, per unit change in percent fat, was 0.26 mg/dL (95% CI: 0.24, 0.28) independent of aging.

Table 3 provides the models that included fitness. Adding AN-Fitness and the age $\times$ AN-Fitness interaction terms improved fit over the model with age and percent fat (Model III, $X^2 = 125.98$, $P < 0.001$). We also added the age $\times$ percent body fat interaction to the model, but it did not improve fit ($P = 0.07$). Figure 1 graphically shows the interaction of age and fitness. Provided in the figure are the age trends for the total sample and the low, average and high fitness groups assuming a constant percent body fat of 20.5%, the mean of all observations. Separate LMM regression models were used to define the age trends using the observations for the total sample and the data for each fitness group and assuming a percent body fat of 20.5%. The interaction shown in Figure 1 documents that the glucose trajectories differed by age and fitness group. Below age 35, the glucose estimates of the fitness groups were similar, but after age 35 years, fitness progressively influenced the aging glucose trajectory. These data show that the yearly increase in glucose for the total sample was 0.17 mg/dL (95% CI, 0.16, 0.19) and increased at a yearly linear rate of 0.25 (0.16, 0.19) mg/dL for the low fit group and 0.13 (0.11, 0.15) mg/dL for the high fit group. The yearly change in glucose for average fit was 0.15 (0.13, 0.17) mg/dL.

Model IV in Table 3 included the covariates. The AN-Fitness and age by AN-Fitness interaction term remained significant and did not change much. Model IV regression coefficients for waist circumference, smoking behavior, hypertension and elevated cholesterol were significant correlates of aging glucose trajectory, while the physical inactivity covariate was not. Being hypertensive and having elevated cholesterol were both associated with higher glucose levels independent of age, percent fat and fitness, however being a current smoker was associated with lower glucose levels. The significant waist circumference regression weight indicated that glucose variation was associated with changes in abdominal visceral fat. Adding waist circumference to Model IV reduced the regression weight for percent fat from 0.23 mg/dL to 0.09 mg/dL.

DISCUSSION

The principal findings from these longitudinal analyses were that with percent body fat statistically controlled, glucose increases at a linear rate with aging and the trajectory was strongly influenced by fitness level. We found that fitness had little influence on the aging glucose trajectory below age 35 years, but significantly influenced the trend above age 35. While the general trend was for glucose to increase with aging, the level of fitness influenced the rate of change with aging.

The relationship between aging and worsening of fasting glucose has been documented in the literature (2;3;5–8). The age-associated impaired glucose handling is mainly due to increased insulin resistance (2;3;5). However, the small sample size and short follow-up time were the major limitations of these previous studies. The Framingham Heart Study reported a similar age trajectories with fasting glucose in both men and women and the curves increase with age until about 80 years (8). Our results agree with these data showing a longitudinal increase of 0.22 mg/dL (0.01 mg/dL) in glucose per year across the age group studied for these serial data with a large healthy cohort of ACLS men. In an occupational cohort study with men and women, Tabak et al. reported that the aging-glucose trajectory of the patients free of diabetes was linear with a slight 0.07 mg/dL (0.004 mmol/L) increase per year over the follow-up period. In contrast, the aging trend for the diabetic group was non-linear (7). Like these ACLS men, all of the subjects studied by Tabak et al. were free of type

2 diabetes at baseline. We found that the age-glucose trajectory in the ACLS men was linear, however we were not able to separate men who developed diabetes from those who did not because all men in the current study were free of physician diagnosed diabetes not only at baseline but also during follow-up and their fasting glucose was untreated.

Glucose values ≥ 100 mg/dL increase the risk of type 2 diabetes (36). The influence of fitness on the glucose values is illustrated in Figure 1. Assuming a constant percent fat of 20.5% (mean value of the current study sample), low fit men can be expected to reach the high risk level of 100 mg/dL at age 50 years compared to about age 61 for high fit men. The fitness effect was independent of percent fat, waist circumference, smoking behavior, hypertension and elevated cholesterol. Self-reported physical activity was not related to longitudinal glucose variation suggesting that the objectively measured fitness provided a more accurate indication than the self-reported activity data. To the best of our knowledge, this study is the first one to investigate the role of fitness on the longitudinal aging-glucose trajectory in a healthy group of men with serial untreated glucose measurements. Findings from this study suggested that individual's fasting glucose value is not fixed for the entire adult lifespan but increases with aging and can be altered with changes in body composition and fitness.

One of the pathways between aging and glucose impairment is physical activity (6). The benefit of exercise or physical activity on glucose metabolism is well established (39;40). Progressive changes with age and variability in physical activity (41) in an individual can significantly modify the age-related glucose curve. However, previous studies on glucose trajectories among normal and abnormal glucose individuals do not usually consider the impact of physical activity change during follow-up (7;42;43). In the current study, we evaluated the influence of fitness on the age-related glucose trajectories and found that the aging trajectories of men who were low fit for their age was steeper compared with higher fit men. The aging trends provided in Figure 1 are the regression lines for fitness normalized for age. Since AN-Fitness is a continuous variable, Model III (Table 3) can be used to define longitudinal trajectories of men for any level of AN-Fitness and different levels of percent body fat. The regression lines shown in Figure 1 were the means for the low, average and high fit groups (Table 1). The principal strength of this study is the large population under observation who varied in age across the adult life span. A broad array of clinical and behavioral variables has been assessed in baseline and follow-up exams. The objective data from patients' usual examinations on fasting glucose, body composition, and fitness, blood lipids, and blood pressure collected at multiple exams, are other strengths. Another important strength of the study was the use of percent body fat to measure body composition rather than the weight-height ratio BMI. A limitation of BMI is that changes in weight can be due to changes in fat weight and fat-free weight and we have shown that fat weight and fat-free weight have different longitudinal aging trends (25).

Limitations of the study include those common to prospective epidemiological investigations. Attrition bias is a concern in studies involving serial measurements (repeated clinical visits). We have studied this issue and it is not a serious problem in the ACLS (44). Generalization of results must be done with caution. Many epidemiological studies involve nonrandom, opportunistic samples, as does ours. However, the use of nonrandom samples is not a major problem in terms of internal validity of the study. We did not have either the oral glucose tolerance test or HbA_{1c} test but fasting plasma glucose test. However, screening with either of those tests is unlikely to appreciably change our results, since the threshold for detection of diabetes corresponds closely for all three tests (45). The growing awareness of the value of blood glucose monitoring warrants further studies. We do not have information on the antihypertensive and lipid lowering medication. Finally, the current study contains

relatively healthy men with untreated fasting glucose data. Therefore, generalization of our findings should be made in caution.

In summary, fasting glucose increases with aging at a linear rate in ACLS men who were relatively healthy. A higher level of fitness played an important role in slowing the age-associated glucose trajectory, which is independent of percent body fat. The consensus physical activity guideline (46) to obtain 150 minutes per week of moderate-intensity physical activity such as brisk walking for 30 minutes or more on five days of the week will move most individuals out of the low fitness category. The potential fitness or activity consequences on longitudinal associations between fasting glucose and aging highlight the need for replication and further studies in other ethnic groups.

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Selected Abbreviations and Acronyms

ACLS	Aerobics Center Longitudinal Study
AN-Fitness	cardiorespiratory fitness normalized by age
BMI	body mass index
CI	confidence interval
CARDIA	Coronary Artery Risk Development in Young Adults
CVD	cardiovascular disease
ECG	electrocardiogram
LMM	linear mixed model
MET	metabolic equivalent
SD	standard deviation

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FIGURE 1.

Modeled longitudinal trajectories in glucose of men associated with aging and fitness. Provided are the aging glucose trajectories of the total sample (dashed line), low (triangle), average (circle) and high fit men (square), assuming a constant percent body fat of 20.5%. The solid line represents the cutpoint for an abnormal glucose level of 100 mg/dL.

TABLE 1

Descriptive statistics of men for all observations and according to fitness groups – Aerobics Center Longitudinal Study, 1977–2005.

	All (n=38,947) (mean (SD) or %)	Level of Fitness			P for linear trend
		Low (n=9,142) (mean (SD) or %)	Average (n=13,792) (mean (SD) or %)	High (n=16,013) (mean (SD) or %)	
Age, years	48.3 (9.7)	47.7 (9.0)	48.4 (9.6)	48.5 (10.1)	<0.001
Height, cm	179.0 (6.4)	178.6 (6.5)	179.2 (6.4)	179.0 (6.4)	0.02
Weight, kg	82.4 (11.5)	88.6 (13.7)	83.2 (10.4)	78.0 (8.8)	<0.001
BMI, kg/m ²	25.7 (3.1)	27.7 (3.8)	25.9 (2.7)	24.3 (2.2)	<0.001
Waist circumference, cm	92.0 (9.1)	98.4 (10.0)	92.9 (7.9)	87.6 (7.0)	<0.001
Percent body fat, %	20.5 (5.6)	24.7 (5.2)	21.5 (4.6)	17.3 (4.8)	<0.001
Treadmill time duration, minutes	20.2 (4.5)	14.5 (2.3)	19.1 (1.9)	24.3 (2.8)	<0.001
Maximal METs	12.7 (2.3)	10.0 (1.1)	12.1 (0.9)	14.8 (1.7)	<0.001
AN-Fitness, METs	0.3 (2.2)	-2.1 (0.9)	0.1 (0.6)	2.7 (1.5)	<0.001
Fasting plasma glucose, mg/dL	98.6 (10.0)	100.8 (11.8)	98.6 (9.7)	97.5 (8.9)	<0.001
Current smoker, %	11.4	19.2	11.7	6.6	<0.001
Physically inactive, %	17.9	38.4	16.7	7.2	<0.001
Hypertension, %	25.4	31.5	25.2	20.8	<0.001
High cholesterol, %	17.1	22.9	18.1	12.9	<0.001

BMI= body mass index; AN-Fitness= cardiorespiratory fitness normalized by age.

Maximum likelihood estimates for age and percent body fat models including the random intercept of the men – Aerobics Center Longitudinal Study, 1977–2005.

TABLE 2

Variable	Model I			Model II		
	Est.	SE	P	Est.	SE	P
Fixed Part						
Constant	88.64	0.33	<0.001	85.25	0.35	<0.001
Age	0.22	0.007	<0.001	0.17	0.007	<0.001
Percent body fat				0.26	0.01	<0.001
Random Part						
SD Intercept Est (95% CI)	7.27 (7.14, 7.41)			7.12 (6.99, 7.25)		
SD Error Est (95% CI)	6.87 (6.82, 6.93)			6.84 (6.79, 6.89)		

SD= standard deviation; CI= confidence interval; SD Intercept= standard deviation of the individual variance of the random part of the model; SD Error= standard error of the LMM model.

TABLE 3

Maximum likelihood estimates for fitness models including the random intercept of the men – Aerobics Center Longitudinal Study, 1977–2005.

Variable	Model III			Model IV		
	Est.	SE	P	Est.	SE	P
Fixed Part						
Constant	85.08	0.38	<0.001	73.20	0.75	<0.001
Age	0.19	0.007	<0.001	0.18	0.007	<0.001
Percent body fat	0.23	0.01	<0.001	0.09	0.01	<0.001
AN-Fitness	0.92	0.12	<0.001	0.96	0.13	<0.001
Age × AN-Fitness	−0.02	0.003	<0.001	−0.02	0.003	<0.001
Waist circumference				0.16	0.009	<0.001
Current smoker				−0.44	0.16	0.007
Physically inactive				0.13	0.12	0.22
Hypertension				0.84	0.11	<0.001
High cholesterol				0.58	0.12	<0.001
Random Part						
SD Intercept Est (95% CI)	7.09 (6.96, 7.22)			7.04 (6.91, 7.17)		
SD Error Est (95% CI)	6.84 (6.78, 6.89)			6.83 (6.78, 6.89)		

AN-Fitness = cardiorespiratory fitness normalized by age; SD= standard deviation; CI= confidence interval; SD Intercept= standard deviation of the individual variance of the random part of the model; SD Error= standard error of the LMM model.