Modification of the Effect of Glycemic Status on Aortic Distensibility by Age in the Multi-Ethnic Study of Atherosclerosis

R. Brandon Stacey, Alain G. Bertoni, John Eng, David A. Bluemke, W. Gregory Hundley, David Herrington

Abstract—Elevated serum glucose from diabetes mellitus (DM) or impaired fasting glucose shares many mechanisms with aging that decrease aortic distensibility (AD), such as glycation of the extracellular matrix. However, few data compare the simultaneous effects of elevated serum glucose and aging on AD. To study this, we examined the relationship among fasting glucose status, age, and AD in the Multi-Ethnic Study of Atherosclerosis: a multiethnic cohort of individuals aged 45 to 84 years without clinical cardiovascular disease. In the Multi-Ethnic Study of Atherosclerosis, participants with normal fasting glucose (n=2270), impaired fasting glucose (n=870), and DM (n=412) underwent MRI assessment of proximal thoracic aortic distensibility. This sample was 46% male, 42% white, 30% black, 11% Asian, and 17% Hispanic. The relationship among glucose status, age, and AD was analyzed with general linear models by adjusting for factors influential on AD. An interaction term was used to determine whether age modified the effect of glucose status on AD. AD was lowest among those with DM. The interaction term was significant (P=0.024). Comparing participants <65 years of age, AD was different between normal fasting glucose and DM (P<0.01) and between normal fasting glucose and impaired fasting glucose (P=0.02). In those >65 years of age, the fasting glucose group was no longer a significant predictor of AD. Our data indicate that there are overall differences in AD among DM, impaired fasting glucose, and normal fasting glucose. However, age modified the effect of glucose status such that differences between the groups diminished with advancing age. (Hypertension. 2010;55:26-32.)

Key Words: aging ■ aorta ■ diabetes mellitus ■ glucose ■ MRI

The aging population will present difficult challenges for health care providers in the coming decades. By 2040 in the United States, individuals who are ≥65 years old will double from 40 million to >80 million people.1 This age group accounts for >80% of deaths related to coronary artery disease in the United States, as well as 75% of the total population diagnosed with heart failure.2

One well-described change that occurs with aging is aortic stiffness. Aortic stiffness is a strong, independent predictor of cardiovascular mortality in elderly patients.3 Aging and diabetes mellitus (DM) affect the vasculature through glycation of the vascular wall.4-7 Previous researchers have described an interaction between age and DM in which increasing age decreased the difference in pulse wave velocity between diabetics and nondiabetics.8 However, this has not been replicated. In addition, no major studies have addressed whether impaired fasting glucose also modifies this relationship.

With ≈3500 MRI scans measuring aortic distensibility, the Multi-Ethnic Study of Atherosclerosis (MESA) provides an opportunity to revisit these relationships with more precise imaging techniques and a larger study population. The purpose of this study was to determine whether age modifies the effect of DM on aortic distensibility. In addition, we also sought to determine whether age modifies the effect of impaired fasting glucose on aortic distensibility.

Methods

Study Participants

The recruitment criteria of participants in MESA has been published previously.9 The MESA study is a population-based cohort of 6814 men and women aged 45 to 84 years from 4 ethnic groups (white, black, Hispanic, and Chinese) who were free of clinical cardiovascular disease when recruited from the years 2000 to 2002. Of these, we excluded 1810 who did not have cardiac MRI. We further excluded 1443 participants without aortic distensibility measures and 9 participants with missing diabetes status.

As part of the baseline examination, participants submitted fasting blood samples. Samples were collected at each clinical site and sent to the central laboratory for analysis. Glucose was measured in serum at the University of Minnesota Central Laboratory using thin
film adaptation of the glucose oxidase method on the Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Inc). Total cholesterol and high-density lipoprotein cholesterol (HDL) cholesterol were measured in EDTA plasma on the Roche/Hitachi 911 Automatic Analyzer (Roche Diagnostics Corporation) using a cholesterol esterase-glucose oxidase reaction (Chol R1, Roche Diagnostics Corporation). Before measurement of HDL cholesterol, the non-HDL cholesterol fractions were precipitated with magnetic 50 000 MW dextran sulfate and magnesium chloride. Triglycerides were measured using a glycerol blanked enzymatic method (Trig/GB, Roche Diagnostics Corporation). Low-density lipoprotein (LDL) cholesterol was calculated in specimens having a triglyceride value <400 mg/dL using the Friedewald equation.

Individuals in this study were classified into 1 of 3 groups using criteria based on the fasting glucose level established by the American Diabetes Association.29 These groups included normal fasting glucose (NFG; fasting glucose level <100 mg/dL), impaired fasting glucose (IFG; fasting glucose level 100 to 125 mg/dL), and DM (fasting glucose level >126 mg/dL). Individuals with a history of DM were classified into the DM group without regard to their fasting glucose level.

Resting, seated systolic and diastolic blood pressures were measured 3 times using a Dinamap automated oscillometric sphygmomanometer (Model pro100l, Critikon); the last 2 measures were averaged for analyses. Hypertension was defined on the basis of use of antihypertensive medications or blood pressure ≥140/90 mm Hg. Use of lipid-lowering medication was used as an indicator of being diagnosed with high cholesterol. Cigarette use was divided into 3 groups: never, former, and current, which was defined as having smoked within the past 30 days.

Magnetic Resonance Imaging (MRI)

Images of the proximal thoracic aorta were acquired axially at the level of the main pulmonary artery identified on a sagittal scout image. Participants were scanned in a supine position using a torso phased array coil placed anteriorly and posteriorly. Images of the proximal thoracic aorta were acquired axially at the level of the main pulmonary artery identified on a sagittal scout image. Imaging parameters included a phase-contrast gradient-echo sequence. Imaging parameters were as follows: repetition time, 10 ms; echo time, 1.9 ms; field of view, 34 cm; section thickness, 8 mm; matrix size, 256×224; 2 signal averages; temporal resolution, 20 ms; velocity encoding gradient, 150 cm/s in the superior-to-inferior direction; and receiver bandwidth, ±32 KHz. Blood pressure was measured in the supine position at the beginning and end of the 45-minute MRI session; the 2 results were averaged for the final blood pressure measurement.

**Ascending Aortic Stiffness**

To determine ascending thoracic aortic stiffness, aortic distensibility was calculated by using the following validated formula:10,11

\[
\text{aortic distensibility} = \frac{[\text{maximum aortic area} - \text{minimum aortic area}]}{\text{minimum aortic area}} \times \frac{\text{pulse pressure} - \text{diastolic blood pressure}}{\text{systolic blood pressure} - \text{diastolic blood pressure}}
\]

**Statistical Analyses**

Baseline characteristics were described for each fasting glucose group (NFG, IFG, and DM). We performed t-tests and χ² tests to identify statistical differences in baseline characteristics between the groups, with NFG serving as our reference. Next, we compared aortic distensibility between the fasting glucose groups through ANCOVA. From this point, multiple linear regression lines of aortic distensibility for each fasting glucose group on age were generated by the PROC GLM in SAS Enterprise Guide 4.1 (SAS Institute, Inc).

We first included the fasting glucose group and age, as well as an interaction term between the 2 in the model to predict aortic distensibility (model 1, see below). Next, additional covariates were adjusted for their influence on the relationship between fasting glucose level and age (model 2, see below). Graphs depicting these relationships were generated with GraphPad Prism version 4.00 for Windows (GraphPad Software, www.graphpad.com).

There were 2 models fit to describe aortic distensibility. These models included the following: model 1, which included age, fasting glucose group, and age*fasting glucose group (interaction term); and model 2, which included model 1 plus adjustment for sex, race, body mass index, mean arterial pressure, use of antihypertensive medication, LDL, HDL, triglycerides, use of lipid-lowering medications, smoking history, pack years, creatinine, and C-reactive protein levels.

For these models, the interaction term was examined. If significant at the level of 0.05, specific pairwise comparisons of the slopes of the regression lines on age were performed.

From this point, age was divided into 2 groups (45 to 64 years versus 65 to 84 years) as a categorical variable to use for both a main effect and as a part of an interaction term with the fasting glucose

| Table 1. Baseline Characteristics of Participants |
|-----------------------------|-----------------------------|-----------------------------|
| Variable                    | Normal (n = 2270)            | IFG (n = 670)                | DM (n = 412)               |
| Age, y                      | 59.4 ± 10.0                 | 62.2 ± 9.9*                 | 63.5 ± 9.4*                |
| Body mass index, kg/m²      | 27.1 ± 4.7                  | 28.8 ± 5.1*                 | 29.8 ± 5.3*                |
| HDL, mmol/L                 | 3.0 ± 0.8                   | 3.1 ± 0.8                   | 3.0 ± 0.9                  |
| Triglycerides, mmol/L       | 1.4 ± 0.4                   | 1.3 ± 0.4*                  | 1.2 ± 0.4*                 |
| Glucose, mmol/L             | 5.0 ± 0.3                   | 5.9 ± 0.3*                  | 8.4 ± 2.8*                 |
| SBP, mm Hg                  | 122.1 ± 20.3                | 128.2 ± 21.1*               | 132.7 ± 22.4*              |
| MAP, mm Hg                  | 73.1 ± 10.2                 | 73.4 ± 10.4*                | 72.8 ± 10.4*               |
| Creatinine, μmol/L          | 83.1 ± 17.7                 | 85.7 ± 17.8*                | 85.7 ± 51.3                |
| Lipid medication use        | 278 (12)                    | 315 (18)*                   | 116 (28)*                  |
| Hypertension medication use | 623 (27)                    | 377 (43)*                   | 258 (63)*                  |
| Race                        | *                           | *                           | *                          |
| White                       | 1061 (47)                   | 337 (39)                    | 98 (24)                    |
| Hispanic                    | 233 (10)                    | 111 (13)                    | 49 (12)                    |
| Black                       | 605 (27)                    | 267 (31)                    | 189 (46)                   |
| Chinese                     | 372 (16)                    | 156 (18)                    | 77 (19)                    |
| Sex                         | *                           | *                           | *                          |
| Male                        | 939 (41)                    | 475 (55)                    | 209 (51)                   |
| Female                      | 1332 (59)                   | 396 (45)                    | 204 (49)                   |
| Smoking                     | *                           | *                           | *                          |
| Never                       | 1188 (52)                   | 429 (49)                    | 202 (49)                   |
| Former                      | 767 (34)                    | 326 (37)                    | 167 (40)                   |
| Current                     | 308 (14)                    | 111 (13)                    | 43 (10)                    |

Data are mean ±SD or n (%). SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; GFR, glomerular filtration rate.

*Data show the difference with NFG with a P < 0.05.
group to interpret the interaction. First, the adjusted means of aortic distensibility were compared using model 1. Next, ANCOVA analyses were performed using model 2.

**Results**

After exclusions, our study population consisted of 3552 participants. Their characteristics by glycemic status are shown in Table 1. Both the IFG and DM groups had higher body mass index, higher systolic blood pressure, and higher C-reactive protein levels than the NFG group. In addition, the IFG and DM groups had lower HDL cholesterol levels than the NFG group. In comparing demographic features, the NFG group was younger and composed of more women and white participants. A box plot of aortic distensibility was compared using model 1. Next, ANCOVA analyses were performed using model 2.

Adjusting for additional covariates in model 2, the overall interaction term was statistically significant ($P=0.04$). Individually assessing the glucose status comparisons, the slope of age was different between the DM group and the NFG group ($P=0.031$), but there were no differences in the slopes of age between the DM group and the IFG group ($P=0.39$). There was a trend toward a difference in the slope of age between the IFG group and the NFG group ($P=0.088$). These comparisons are shown in Table 2 and are presented graphically in Figure 2.

To determine whether these results differed by race or sex, 3-way interaction terms were used. Using model 2, age, fasting glucose group, and race were used for the interaction term but failed to reach statistical significance ($P=0.15$). In a separate analysis using model 2, age, fasting glucose group, and sex were used for the interaction term, but, likewise, the term failed to reach statistical significance ($P=0.2$). Next, we stratified the cohort according to race and sex, separately. The absolute values in the differences between the fasting glucose groups in the 2 age categories for each ethnic group and sex paralleled those of the entire cohort.

To determine whether the variables in the numerator (percent-age of change in aortic area for proximal thoracic aorta) or the

**Table 2. Comparison of Regression Coefficients**

<table>
<thead>
<tr>
<th>Fasting Glucose Group</th>
<th>Model 1, Standardized Regression $\beta$ Coefficient for Age</th>
<th>Model 2, Standardized Regression $\beta$ Coefficient for Age</th>
<th>Aortic Distensibility Comparisons</th>
<th>Model 1, $P$</th>
<th>Model 2, $P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NFG</td>
<td>$-0.43$</td>
<td>$-0.38$</td>
<td>Age</td>
<td>$&lt;0.001$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>IFG</td>
<td>$-0.36$</td>
<td>$-0.30$</td>
<td>Overall interaction term</td>
<td>$0.0412$</td>
<td>$0.038$</td>
</tr>
<tr>
<td>DM</td>
<td>$-0.32$</td>
<td>$-0.26$</td>
<td>NFG age $\beta$ vs IFG age $\beta$</td>
<td>$0.088$</td>
<td>$0.057$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFG age $\beta$ vs DM age $\beta$</td>
<td>$0.39$</td>
<td>$0.38$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NFG age $\beta$ vs DM age $\beta$</td>
<td>$0.031$</td>
<td>$0.022$</td>
</tr>
</tbody>
</table>

NFG is the reference group, except for IFG vs DM, in which IFG serves as the reference group.
denominator (pulse pressure) of aortic distensibility were more influential in accounting for the results, additional analyses using model 2 were performed. Overall, the interaction term continued to be significant ($P=0.002$). After adjusting for the cardiac cycle–dependent percentage of change in aortic area, aortic distensibility before age 65 years was $2.18\times10^{-3}$ mm Hg$^{-1}$ for NFG, $2.11\times10^{-3}$ mm Hg$^{-1}$ for IFG ($P=0.01$ from NFG), and $2.00\times10^{-3}$ mm Hg$^{-1}$ for DM ($P<0.001$ from NFG), and after age 65, aortic distensibility was $1.75\times10^{-3}$ mm Hg$^{-1}$ for NFG, $1.78\times10^{-3}$ mm Hg$^{-1}$ for IFG ($P=0.32$ from NFG), and $1.75\times10^{-3}$ mm Hg$^{-1}$ for DM ($P=0.4$ from NFG). In separate analyses adjusting for pulse pressure, the interaction term was less significant ($P=0.054$). After adjustment for pulse pressure, aortic distensibility before age 65 years was $2.18\times10^{-3}$ mm Hg$^{-1}$ for NFG, $2.06\times10^{-3}$ mm Hg$^{-1}$ for IFG ($P=0.06$ from NFG), and $1.86\times10^{-3}$ mm Hg$^{-1}$ for DM ($P<0.001$ from NFG), and after age 65, aortic distensibility was $1.71\times10^{-3}$ mm Hg$^{-1}$ for NFG, $1.76\times10^{-3}$ mm Hg$^{-1}$ for IFG ($P=0.5$ from NFG), and $1.67\times10^{-3}$ mm Hg$^{-1}$ for DM ($P=0.6$ from NFG). Because of the patterns noted between the groups in model 2 remain, the results of these adjustments suggest that both values in the numerators and denominators are important for influencing the differences or similarities in aortic distensibility noted between the groups assessed in this study.

Finally, to determine the influence of aortic size on aortic distensibility, additional analyses using model 2 adjusted for minimum aortic area were performed. The interaction term was no longer significant ($P=0.18$). After adjusting for the minimum aortic area, aortic distensibility before age 65 years was $2.27\times10^{-3}$ mm Hg$^{-1}$ for NFG, $2.14\times10^{-3}$ mm Hg$^{-1}$ for IFG ($P=0.039$ from NFG), and $1.85\times10^{-3}$ mm Hg$^{-1}$ for DM ($P<0.001$ from NFG), and after age 65, aortic distensibility was $1.67\times10^{-3}$ mm Hg$^{-1}$ for NFG, $1.68\times10^{-3}$ mm Hg$^{-1}$ for IFG ($P=0.8$ from NFG), and $1.44\times10^{-3}$ mm Hg$^{-1}$ for DM ($P=0.02$ from NFG). Although the pattern persists, after age 65 years, NFG and DM become statistically different. This suggests that the lack of difference seen previously may be related to aortic size.

**Discussion**

The relationship between aging and aortic stiffness has been described for many years.\cite{14,15} In this study, we sought to determine whether increasing age modified the effect of DM on aortic distensibility and to determine whether the effect of IFG on aortic distensibility would also be modified by increasing age. From this study, several relationships can be described. First, increasing age decreases the differences in aortic distensibility between fasting glucose groups. Second, at younger ages, IFG decreased aortic distensibility when compared with NFG, and, as expected, it behaves as an intermediate between DM and NFG.

**Table 3.** Model 1 and Model 2 Means for Aortic Distensibility by Age

<table>
<thead>
<tr>
<th>Age Group and Model</th>
<th>NFG AD, $10^{-3}$ mm Hg$^{-1}$</th>
<th>IFG AD, $10^{-3}$ mm Hg$^{-1}$</th>
<th>DM AD, $10^{-3}$ mm Hg$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age $&lt;65$ y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>2.42 (2.35 to 2.48)</td>
<td>2.22 (2.1 to 2.33)$^*$</td>
<td>1.91 (1.74 to 2.08)$^*$</td>
</tr>
<tr>
<td>Model 2</td>
<td>2.31 (2.22 to 2.39)</td>
<td>2.16 (2.03 to 2.28)$^*$</td>
<td>1.88 (1.71 to 2.07)$^*$</td>
</tr>
<tr>
<td>Age $\geq65$ y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.47 (1.38 to 1.57)</td>
<td>1.47 (1.35 to 1.6)</td>
<td>1.24 (1.05 to 1.41)$^*$</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.52 (1.41 to 1.63)</td>
<td>1.57 (1.43 to 1.7)</td>
<td>1.38 (1.03 to 1.40)</td>
</tr>
</tbody>
</table>

Means and 95% CIs between fasting glucose group stratified by age 65 years. For comparisons, NFG serves as the reference group.

$^*$Data are statistically different at $P<0.05$.\footnote{14}
Multiple mechanisms describe how aging affects aortic distensibility. Glycation of the extracellular matrix, including both elastin and collagen, occurs even at normal levels of glucose as a consequence of aging. Glycation of collagen results in less flexibility, greater strength, and an increased resistance to proteolysis. Although not as well studied as collagen, glycation of elastin results in fragmentation and loss of elasticity. These same nonenzymatic glycation processes occur with increased frequency to both collagen and elastin in hyperglycemic states. In addition to glycation, age and DM also affect the vasculature through formation of atherosclerosis, inflammation, and decreased endothelial function.

Increased ascending aortic distensibility greatly reduces the energy cost of cardiac work. As such, therapeutic options to improve aortic distensibility may be an attractive option, particularly in heart failure. One such option, collagen cross-link breakers, failed to improve aortic distensibility. In the ascending aorta, elastin is at its highest concentration and organization, whereas collagen is uniformly distributed throughout the vascular tree. Hence, in describing aortic distensibility from MRI measurements of the ascending aorta, the effects of age and DM on elastin may account for the behaviors seen in our study, and, as such, may serve as a target of future therapy.

The interaction seen in this study is attributable to a greater association between the fasting glucose group and aortic distensibility at younger ages than at older ages. Aortic distensibility started at a lower level in the DM and IFG groups than the normal group. As such, both DM and IFG had lower slopes than the normal group, with the differences among the 3 groups decreasing with increasing age. If this study were performed prospectively, one would expect a steep decline in aortic distensibility during the time of IFG and early DM that would be followed by the lower slopes observed in our analysis. In addition, studies in younger populations are needed to further describe the relationship between different measures of vascular stiffness and fasting glucose level. One issue that may have influenced our analysis is that many of our participants already had stiff vessels as a result of aging alone.

The shared mechanisms of action between DM and aging enable us to consider a previously published concept. DM may act by increasing the physiological age of the cardiovascular system. From our study, this influence can be described quantitatively from the regression models (see Table 4). This provides us with an additional perspective to consider how DM often leads to conditions at younger ages, such as diastolic dysfunction, that otherwise are not encountered until later in life. In addition, it provides us with a vehicle to explain to patients how DM affects their vasculature.

The MESA provided us with the unique opportunity to pursue these questions. Because of a balanced recruiting of individuals from major ethnic groups, our results are more generalizable to diverse populations. In addition, the MESA afforded us the opportunity to investigate aortic stiffness using area measurements derived from MRI scans, a technique validated by previous research studies. Likewise, with 3500 MRI scans describing aortic distensibility, the MESA provided us with enough statistical power to develop and test more directed hypotheses.

There are several limitations of this study. First, noninvasive blood pressure measurements were used to calculate aortic distensibility. Although not ideal, previous studies have indicated that noninvasive measures are adequate approximations and that they do predict cardiac mortality. In addition, our results are consistent with previous invasive studies that demonstrated that central pulse pressure is different between those with NFG and those with IFG. Second, a selection bias may be present in our study. The MESA specifically recruited individuals without cardiovascular disease, and, as such, our participants may have more resistance or fewer risk factors than the general population to cardiovascular disease. Likewise, this limits the generalizability of this study to individuals without cardiac disease. Third, our analysis is limited by the cross-sectional nature of our data.
As such, temporality cannot be assessed. Another weakness of cross-sectional data is trying to determine whether covariates are confounders or mediators. Fourth, one measurement of fasting glucose was used to identify participant glycemic status, which may have resulted in misclassification.

Conclusions

There are differences in aortic distensibility between fasting glucose groups. However, increasing age decreases the differences in aortic distensibility between the fasting glucose groups.

Perspectives

In many societies, the proportion of elderly individuals in the population is increasing. Parallel to this trend, there is a rapid expansion of individuals with IFG and DM. To help assess the potential burden of these trends, this study described the interaction between age and fasting glucose status on aortic distensibility. A growing body of literature recognizes the significant roles that aortic stiffness and its associated measures have on the development and progression of cardiovascular disease. This study demonstrated that, at younger ages, those individuals with IFG had significant less aortic distensibility than those with NFG. With 25% of the adult population having IFG, even a small increase in cardiovascular risk can have significant public health ramifications. As such, further studies are needed to see whether correction of mild hyperglycemia at younger ages can prevent premature morbidity and mortality from aortic stiffness. DM has long been recognized as a significant risk factor for cardiovascular disease, and, as a result, guidelines have been developed to help clinicians to manage their patients’ risk. More data need to be collected to develop guidelines that can assist clinicians in managing the cardiovascular risk in patients with IFG.

Acknowledgments

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Disclosures

None.

References


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