Glycated Hemoglobin Is Associated With the Growth Rate of Abdominal Aortic Aneurysms

A Substudy From the VIVA (Viborg Vascular) Randomized Screening Trial

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Objective—An inverse association between abdominal aortic aneurysms (AAAs) and diabetes mellitus exists; however, the cause remains unknown. This study aimed to evaluate whether the degree of glycemia is associated with aneurysm growth.

Approach and Results—The study was based on VIVA trial (Viborg Vascular), the randomized clinically controlled screening trial for abdominal aortic aneurysm in men aged 65 to 74 years in the Central Denmark Region. The screening included measurement of the abdominal aorta by ultrasound, analysis of glycated hemoglobin (HbA1c), and follow-up for ≤5 years for aneurysms <5 cm. Analyses were conducted using mixed-effect models. At baseline, VIVA screening identified 619 individuals (3.3%) with abdominal aortic aneurysms. A total of 103 individuals were referred for vascular evaluation, and after removal of additional individuals who were lost to follow-up or had missing blood samples, we were left with 319 individuals. Sixty-one individuals (19.1%) had diabetes mellitus. The median growth rate was 1.7 versus 2.7 mm/y in individuals with and without diabetes mellitus, respectively (P<0.001). We found a significant inverse association between aneurysmal growth rate and HbA1c in the total study population (P=0.002). Both crude and adjusted analyses identified slower growth for the group with the highest HbA1c tertile compared with the lowest HbA1c tertile. After 3 years, the mean difference was 1.8 mm (confidence interval, 0.98–2.64). Similar significant differences were observed in subgroup analysis of individuals without self-reported diabetes mellitus.

Conclusions—We found an inverse association between the growth rate of abdominal aortic aneurysms and the level of HbA1c, indicating that long-lasting elevated blood sugar impairs aneurysmal progression in individuals with and without known diabetes mellitus.

Visual Overview—An online visual overview is available for this article. **(*Arterioscler Thromb Vasc Biol*. 2017;37:730-736. DOI: 10.1161/ATVBAHA.116.308874.)**

Key Words: aortic aneurysm, abdominal ■ atherosclerosis ■ comorbidity ■ diabetes mellitus ■ hyperglycemia

Abdominal aortic aneurysm (AAA) is a common, asymptomatic condition with a prevalence of 1.2% to 4% in people >50 years of age.[1–4] If left untreated, AAA progresses to rupture unless death occurs for another reason. The risk of rupture is closely related to aneurysmal size[5,6] with a high short-term mortality rate of 76%.[7,8] The progression of AAA is characterized by degradation and remodeling of the arterial extracellular matrix. Known risk factors for AAA are age, male sex, smoking, family history of AAAs, and comorbidities such as hypertension, atherosclerotic disease, and hypercholesterolemia.[3,9–11] AAAs have traditionally been considered solely as a manifestation of atherosclerosis in the abdominal aorta, and it was believed that the usual risk factors, including diabetes mellitus, were involved. However, the Aneurysm Detection and Management screening study reported in 1997 the remarkable finding that diabetes mellitus reduced the prevalence of AAA by almost half,[1] and later studies confirmed this finding.[12–15] The mechanism underlying this paradoxical association is unknown but may be related to hyperglycemia,[16] other factors in the diabetic milieu, or the effects of antidiabetics.[17]

The pathology of the arterial wall in diabetes mellitus includes not only the occurrence of atherosclerotic plaques but also a series of generalized alterations, for example, endothelial dysfunction,[18] increased arterial stiffness,[19] medial calcifications,[20] and changes in the extracellular matrix.[21–24] In relation to the formation of aneurysms, it is of interest that the compensatory remodeling, which occurs in atherosclerotic arteries, is seemingly not functional in diabetes mellitus. Instead of compensatory enlargements because of remodeling, coronary arteries from individuals with diabetes mellitus showed shrinkage as a response to the appearance of atherosclerotic plaques.[25,26] It is likely that these generalized arterial changes are involved in the decreased risk of AAA among individuals with diabetes mellitus.

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Nonstandard Abbreviations and Acronyms	
AAA	abdominal aortic aneurysm
CI	confidence interval
HbA1c	glycated hemoglobin
VIVA	Viborg Vascular

The aim of this study was to increase our understanding of the paradoxically protective role of diabetes mellitus on AAAs. Our hypothesis was that the growth of AAAs is associated with the glycemic status and not only with the presence of diabetes mellitus itself. We investigated the association between glycated hemoglobin (HbA1c) and the growth rate, maximal anterior–posterior diameter, and stiffness in screening-diagnosed small AAAs in both individuals with and without self-reported diabetes mellitus. We found an inverse association between the growth rate of AAAs and the level of HbA1c.

Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

The data were based on the VIVA (Viborg Vascular) randomized screening trial of men aged 65 to 74 years in the Central Denmark Region, where 319 individuals were identified with an AAA and with at least one follow-up.[27,28] Analyses were conducted using Mann–Whitney *U* test, Spearman correlation, and mixed-effect models.

Results

Demographics

At baseline, AAAs were diagnosed in 619 men, which corresponds to a prevalence of 3.3%. Of the identified AAAs, 103 AAAs (16.7%) were ≥50 mm and 62 AAAs (10.1%) were ≥55 mm, and these 103 individuals were referred for vascular intervention or surveillance.

Of the 619 individuals with AAAs, 319 were included in our study (Figure 1).

Sixty-one individuals (19.1%) had diabetes mellitus (33 self-reported and 28 defined by increased HbA1c). HbA1c ranged from 28 to 77 mmol/mol. In all, 49 individuals had HbA1c >47 mmol/mol, with a range of 48 to 77 mmol/mol and a mean of 54 mmol/mol. The interpersonal coefficient of variation for HbA1c was (SD/mean %) 15.9% for the total population and 8.9% for individuals without (self-reported and defined) diabetes mellitus.

The median baseline aortic diameter was 35.0 versus 34.0 mm in individuals with and without diabetes mellitus, respectively (P=0.96). All demographic information are listed in the Table. Mean follow-up was 3.88 years (range, 0.47–5.86 years).

Association Between HbA1c and Calculated Aneurysmal Growth Rate

The median calculated growth rate was 1.7 versus 2.7 mm/y in individuals with and without defined diabetes mellitus, respectively (P<0.0001, Mann–Whitney *U* test). We found a statistically significant association between aneurysmal growth rate and HbA1c (Spearman ρ=−0.177; P=0.002) in the total study population.

Main Analysis Using Mixed-Effect Model

HbA1c was analyzed in tertiles in our mixed-effect model. Group 1 HbA1c ranged from 28 to 39 mmol/mol; group 2 from 40 to 43 mmol/mol; and group 3 from 44 to 77. We found a statistically significant difference between the change in aneurysmal diameter in individuals in the highest third HbA1c group compared with individuals in the lowest third HbA1c group in the crude model (P<0.000).

The following confounders were included in the mixed model adjusted analysis: (1) smoking status yes/no (former and never smoker were grouped as one in the analysis), (2) age, (3) body mass index, (4) baseline aortic measurement, (5) diastolic blood pressure, (6) level of total cholesterol, (7) presence of peripheral arterial disease, and (8) use of medication (self-reported) suspected to influence the growth rate (statins, aspirin, and β-blockers).

When adjusting for covariates, the decrease in growth was still statistically significant (P<0.000). After adjustment, aortas were 0.9 mm (confidence interval [CI], −1.71 to −0.03; P=0.04) smaller after 13 months in the highest HbA1c-tertile group compared with the lowest HbA1c-tertile group. After 3 years, the difference was a reduction of 1.8 mm (CI, 0.99–2.65; P<0.000) for the highest HbA1c-tertile group compared with the lowest HbA1c-tertile group (Figure 2).

In the subgroup analysis also using mixed-effect model, we analyzed individuals with and without self-reported diabetes mellitus. The HbA1c tertiles were for individuals without self-reported diabetes mellitus: group 1 HbA1c ranged from 28 to 39 mmol/mol; group 2 from 40 to 43 mmol/mol; and group 3 from 44 to 70 mmol/mol. Twenty-eight individuals (9.8%) had HbA1c >47 mmol/mol. For the group without self-reported diabetes mellitus, in which no one used antidiabetics, we found a statistically significant difference in growth between individuals in the highest and lowest HbA1c-tertile groups (P<0.000). Aortas were 0.9 mm (CI, 1.81 to −0.03; P=0.04) smaller after 21 months in the highest HbA1c-tertile group compared with the lowest HbA1c-tertile group. After 3 years, the difference was a reduction of 1.5 mm (CI, 0.59–2.42; P=0.001) for the highest HbA1c-tertile group compared with the lowest HbA1c-tertile group.

For the group with known diabetes mellitus, we analyzed HbA1c as a continuous variable because there were few observations (33 individuals). The difference in growth was not statistically significant (P=0.086). Furthermore, we found no statistically significant association between the growth after adjusting for the number of years with diabetes mellitus (P=0.093) or for the treatment for diabetes mellitus (tablets, insulin, and diet; P=0.079).

Our mixed-effect model did also show statistical significance and an inverse association when analyzing HbA1c as a continuous variable for the total population (P<0.000 for both crude and adjusted models).

Association Between HbA1c and Maximal Aneurysmal Size and Stiffness

We found no significant association between the largest anterior–posterior diameter measurement and HbA1c (Spearman ρ=−0.09; P=0.13).

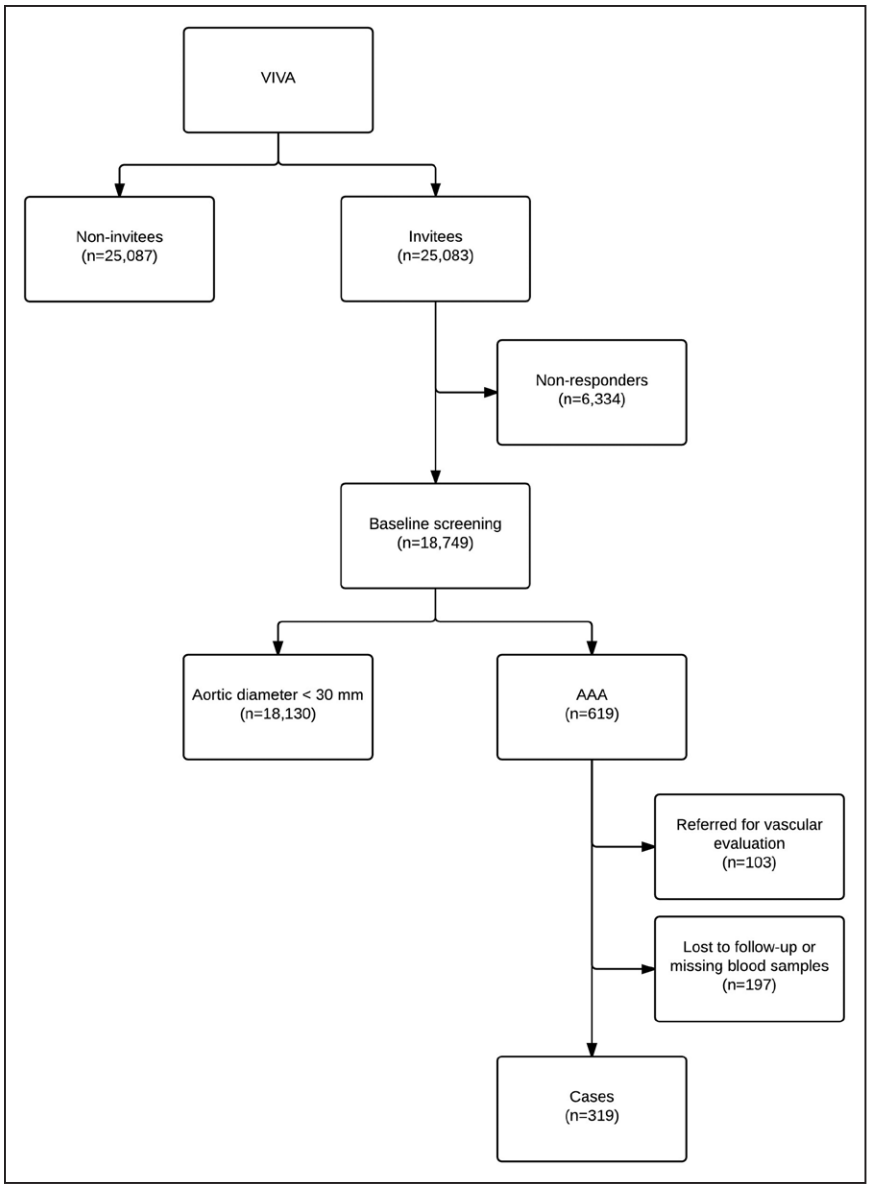

Figure 1. Flow chart of cases and controls in the VIVA (Viborg Vascular) randomized screening trial. This study is based on the 319 cases with abdominal aortic aneurysms (AAAs).

We also found no significant associations between HbA1c and stiffness (ρ=−0.0001; *P*=0.999) or pressure strain elastic modulus (ρ=−0.002; *P*=0.97), nor between growth rate and stiffness (ρ=−0.06; *P*=0.33) or pressure strain elastic modulus (ρ=−0.06; *P*=0.34).

Discussion

In this prospective cohort study investigating the association between AAA and the average blood sugar level, we found that elevated levels of HbA1c were inversely associated with the aneurysmal growth rate both in the total study population and in the subgroup analysis of individuals without self-reported diabetes mellitus. However, we found no association between HbA1c and aneurysmal size or stiffness.

In the total population (self-reported diabetes mellitus+unknown (HbA1c>47) diabetes mellitus+no diabetes mellitus), we observed statistically significant relation between aneurysmal growth and HbA1c—this may be because of the effect of diabetes mellitus and antidiabetics and glycemic status itself. In the above-mentioned population minus self-reported diabetes mellitus, we observed statistically significant relation between aneurysmal growth and HbA1c—this may be because of glycemic effect (or factors related to this), but not antidiabetic treatment, because none of the individuals received diabetes mellitus–related treatment. In the population consisting of individuals with self-reported diabetes mellitus, no statistically significant relation between aneurysmal growth and HbA1c has been observed, but the reason is probably because of the small number of individuals in this group; hence, we do not focus much on results from this group.

Strengths and Limitations

Our study has several strengths. This was a unique study because we had prospective data on the level of HbA1c and the growth rate from 319 AAAs performed by specially trained nurses using a strict standardized method of

Table. Demographics of the Individuals With AAA

Characteristics	Individuals With AAA	Individuals With AAA and Without Diabetes Mellitus	Individuals With AAA and Defined Diabetes Mellitus
Number	319 (100)	258	61 (19.1% of all patients)
Sex, men	319 (100)	259 (100)	61 (100)
Age*	(67.8) 70.1 (72.4)	(68.0) 70.2 (72.6)	(67.1) 69.3 (71.7)
Body mass index*	(24.7) 27.1 (29.4)	(24.4) 26.5 (28.8)	(27.1) 28.7 (31.6)
Systolic blood pressure, mm Hg*	(142) 155 (169)	(142) 156 (169)	(141) 152 (169)
Diastolic blood pressure, mm Hg*	(79) 86 (94)	(79) 86 (95)	(77) 85 (91)
AAA measure, mm*	(31.7) 34 (38.6)	(31.7) 34 (38.9)	(32) 35 (38)
Smoking	133 (41.7)	112 (43.4)	21 (34.4)
Diabetes mellitus (self-reported)	33 (10.3)	0	33 (54.1)
Diabetes mellitus (defined)	61 (19.1)	0	61 (100)
Comorbidity†			
Previous AMI	61 (19.9)	47 (19.0)	14 (23.7)
Angina	44 (14.4)	32 (13.0)	12 (20.3)
Peripheral arterial disease	80 (25.5)	60 (23.7)	20 (32.8)
Hypertension	175 (54.9)	130 (50.4)	45 (73.8)
Medicine			
Antidiabetic per oral‡	18 (5.7)	0	18 (30.0)
Insulins	6 (1.9)	0	6 (10.0)
Statins	173 (54.8)	130 (50.8)	43 (71.7)
ACE inhibitor	80 (25.4)	54 (21.3)	26 (42.6)
Angiotensin II antagonists	39 (12.4)	24 (9.5)	15 (24.6)
β-Blocker	88 (27.9)	69 (27.2)	19 (31.2)
Aspirin	158 (49.7)	119 (46.3)	39 (63.9)
NSAIDs	10 (3.2)	8 (3.2)	2 (3.3)
Blood samples			
HbA1c, mmol/mol*	(38) 41 (44)	(37) 40 (42)	(48) 51 (55)
Total cholesterol, mmol/L*	(4.2) 4.7 (5.4)	(4.2) 4.7 (5.4)	(4.1) 4.4 (5.0)
Hemoglobin, mmol/L*	(8.4) 8.9 (9.4)	(8.5) 9.0 (9.4)	(8.4) 8.9 (9.5)
Nonfasting glucose, mmol/L*	(6.4) 6.8 (7.2)	(6.2) 6.6 (6.9)	(7.8) 8.2 (8.8)

Values in parentheses are percentage unless otherwise indicated. AAA indicates abdominal aortic aneurysm; ACE, angiotensin-converting enzyme; AMI, acute myocardial infarction; HbA1c, glycated hemoglobin; and NSAID, nonsteroid anti-inflammatory drug.

*Values are median ((p25) p50 (p75)).

†Comorbidity is self-reported except from peripheral arterial disease (measured by ankle-brachial index at screening).

‡Antidiabetics are not specified.

measurement with reported low interobserver variability.[29] We had high-quality information about the participants because the study was conducted as a screening trial with standardized continual visits, measurements of AAAs, and questionnaires regarding medication use (although self-reported), smoking, previous illnesses, etc. Although blood samples were taken at numerous sites, HbA1c was measured at the same laboratory, thereby minimizing the risk of information bias. Furthermore, the risk of selection bias was minimal because the study was based on a randomized population-based screening trial. This is in contrast to many patient-based studies in which the slowest expanding aneurysms are under observation longer than the more rapidly expanding ones that require repair within a short time.

Our study also has some potential limitations. Although we used HbA1c, which is the telltale blood sugar measurement for the average level of blood sugar within the past 3 months, we only had one measurement per individual. Measurements from blood samples taken at each visit could have further strengthened the association between AAA growth rate and HbA1c. Furthermore, a study has shown that the within-subject biological variation of HbA1c does not only show low intraindividual variation (1.7% in individuals with and 1.2% in individuals without diabetes mellitus).[30] In contrast,

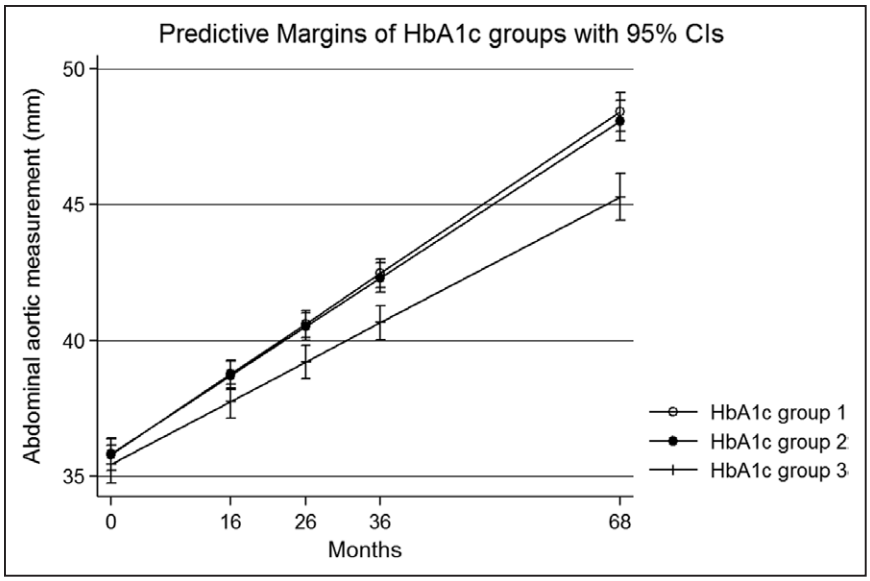

Figure 2. Slopes for linear estimate for growth using the mixed-effect model according to glycated hemoglobin (HbA1c)-tertile groups, with group 1 having the lowest third of HbA1c. A statistically significant difference becomes visible after 26 mo.

the interindividual coefficient of variation was 15.9% in our total population and 8.9 for individuals without self-reported or defined diabetes mellitus. A single measurement of HbA1c can, therefore, be assumed to be representative of each individual's glycemic level during the follow-up time in our study, although it would have been optimal to be able to include serial measurements. Blood samples were only possible in 9 out of 13 screening locations. We referred individuals with an aneurysmal diameter >5 cm for surgical evaluation, and individuals who did not undergo aneurysmal repair received continued surveillance by the vascular department, as the shorter surveillance intervals requested made it impossible to handle these individuals in the VIVA trial organization. Although this left us with only small-to-moderate aneurysms, we have no reason to think that large aneurysms react differently to hyperglycemia than smaller aneurysms. We analyzed the individuals with or without diabetes mellitus according to their baseline status. We did not have data on new onset of diabetes mellitus during the follow-up, but we assume the number is low. This leaves us with a potential small risk for overestimating the reduction in growth in the group of individuals without self-reported diabetes mellitus. Finally, we do not have any data on exercise, which leave us with a small risk of residual confounding.

Hyperglycemia and AAAs in Humans

In our study, we found a statistically significant association between aneurysmal growth rate and the level of HbA1c. Furthermore, we found a reduced change in AAA measurement for individuals in the highest HbA1c-tertile group compared with the lowest HbA1c-tertile group; after 3 years, the difference was 1.8 mm (CI, 0.99–2.65; P<0.000). When stratifying by diabetes mellitus and analyzing only individuals without self-reported diabetes mellitus, hence avoiding antidiabetic treatment as a confounder, we still noticed a statistically significant reduction of 1.5 mm (CI, 0.59–2.42; P=0.001) after 3 years for the highest HbA1c-tertile group compared with the lowest HbA1c-tertile group. This is an observational study, so we cannot conclude anything about causality. However, these findings suggest that hyperglycemia or metabolic/hormonal factors closely related to glucose levels are protective.

Our mixed-effect model did also show statistical significance and an inverse association when analyzing HbA1c as a continuous variable (P<0.000 for both crude and adjusted models).

The analysis of individuals with self-reported diabetes mellitus did not show any statistical significance. However, the numbers were small, and this analysis was probably underpowered.

To the best of our knowledge, only one study has previously investigated the association between hyperglycemia and aneurysmal growth rate. Our results are in disagreement with this study. Golledge et al[31] studied 198 individuals, of whom 20 had diabetes mellitus, and they found no association between fasting serum glucose and AAA progression. The discrepancy between our results and those of Golledge et al could be because of their use of fasting glucose rather than HbA1c. Although both of the studies only include one measurement of the level of blood sugar, HbA1c is a more accurate measurement being the average level of blood glucose over 3 months. In addition, their study included fewer participants and used less-sensitive statistics. Additionally, the standardized training and validation of the nurses making ultrasound measurements in this study showed a rather low interobserver variability of the measurements.[29]

The reduced growth in relation to elevated HbA1c could be because of the formation of cross-links in the extracellular matrix after hyperglycemia,[32] although we did not find any statistically significant associations between stiffness and growth rate or HbA1c.

Experimental Hyperglycemia

A few experimental studies have attempted to explain the association between hyperglycemia and AAAs. Dua et al[16] showed that hyperglycemia was associated with reduced experimental AAA diameter in a murine model. These findings are consistent with the study by Miyama et al[33] on hyperglycemic mice with induced AAAs, which showed that hyperglycemia

reduced the experimental AAA diameter compared with normoglycemic mice. Furthermore, insulin-mediated reductions in serum glucose levels partially reversed the protective effects of hyperglycemia on aneurysm progression.[33] These and the present findings suggest that hyperglycemia, rather than its treatment, retards aneurysmal progression.

In conclusion, exploring the association between AAA and diabetes mellitus, we found an inverse association between the growth rate of AAAs and the level of HbA1c, indicating that long-lasting elevated blood sugar impairs aneurysmal progression. Importantly, we extend previous findings, because we observe that this association is also present among individuals without diabetes mellitus. Specific aspects related to diabetes mellitus as, for example, treatment with antidiabetic drugs, which may influence growth rates, does of course not play a role in the group of individuals without diabetes mellitus, and our observation, therefore, strongly support the notion that the glycemic level itself (or factors related to it) is a determinant of the growth rate of AAA. The exact mechanism remains to be discovered. Elucidating the mechanism may lead to the discovery of novel medical treatments for AAA and may provide a better understanding of the arterial damaging consequences of type 2 diabetes mellitus.

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Disclosures

None.

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Highlights

- In the total population (self-reported diabetes mellitus+unknown (HbA1c>47) diabetes mellitus+no diabetes mellitus), we observed statistically significant relation between aneurysmal growth and HbA1c—this may be because of effect of diabetes mellitus and antidiabetics and glycemic status itself.
- In the above-mentioned population minus self-reported diabetes mellitus, we observed statistically significant relation between aneurysmal growth and HbA1c—this may be because of glycemic effect (or factors related to this), but not antidiabetic treatment, because none of the individuals received diabetes mellitus–related treatment.

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Glycated Hemoglobin Is Associated With the Growth Rate of Abdominal Aortic Aneurysms: A Substudy From the VIVA (Viborg Vascular) Randomized Screening Trial

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Supplemental material

Materials and Methods

In this study, we investigated the association between the growth rate of AAAs and HbA1c using mixed effect models. The data were based on the Viborg Vascular (VIVA) randomized screening trial of men aged 65-74 in the Central Denmark Region, where 319 individuals were identified with an AAA and had at least one follow-up and an available blood sample[1,2].

Data source

The VIVA trial is a randomized clinically controlled screening trial that was launched in October 2008 and included only men aged 65-74 living in the Central Denmark Region, one of five regions in Denmark. Study participants were subjected to a triple screening or to the usual Danish practice of no systematic screening (n=50,170 with an attendance of 74.7%). Randomization was stratified by municipality as the prevalence of the disease was expected to differ across this relatively large region. The region consists of 19 counties covering more than 13,000 km^2, which includes some of the largest Danish cities in the eastern part of the region as well as rural areas in the western part of the region. The triple screening included evaluation of hypertension, AAAs and peripheral arterial disease, and we investigated whether the screening was beneficial regarding mortality and cost-effectiveness. The VIVA trial is a registered clinical trial with the registration number NCT00662480[1,2].
The screening consisted of, among other things, a questionnaire (lifestyle parameters along with current medications, smoking status, and previous illnesses, etc.), an ankle brachial index measurement, and an ultrasound scan of the abdominal aorta, which were performed by specially trained nurses. The interobserver variation of the diameter measurements was 2 mm^3. Using the cinematic function, the maximal systolic inner-to-inner diameters were identified and measured in the right-angled anterior-posterior (AP) view. A maximal aortic diameter ≥30 mm was considered to be an AAA. Dilatations <50 mm were monitored annually with ultrasound for up to five years, and dilatations > 50 mm were referred for consultation by a vascular surgeon. Furthermore, at follow-up, arterial blood samples were drawn and tested, i.a. for HbA1c. Only one blood sample was drawn per individual in the entire follow-up, it was drawn at baseline. Blood samples were only possible in 9 out of 13 screening locations. The individuals were not informed about results of blood samples; it was used simply for a bio bank with the individuals' informed consent. The blood samples were analyzed at the Department for Clinical Biochemistry of Viborg Hospital using ion-exchange chromatography on a TOSOH G8 instrument.

Inclusion

We defined our study population based on the source population. Inclusion criteria were a) an aortic AP-diameter ≥30 mm, b) at least one follow-up, and c) a blood sample with HbA1c (figure 1).

Definitions

Individuals were classified as having defined diabetes if they had self-reported diabetes or had an HbA1c over 47 mmol/mol according to the World Health

Organization classification[4,5]. If the individuals were diagnosed with diabetes during the follow-up period, then we analyzed them according to their status at baseline.

HbA1c is the average level of blood sugar for the past three months and the measurement is independent of the individuals fasting status at the time of the blood sample.
The primary outcome was mean annual aneurysmal growth rate of maximal systolic AP-diameter.
In all analyses except for the mixed effect models, we used the calculated growth rate = (last-first max AP measurement)/follow-up time. Secondary outcomes were maximal aneurysmal AP diameter and aneurysmal wall stiffness expressed as pressure strain elastic modulus and stiffness of the AAA wall calculated as: pressure strain elastic modulus ($10^5 Nm^{-2}$) = 133.3*(systolic-diastolic blood pressure)/ ((Dmax systolic – Dmin diastolic diameter)/(diastolic diameter)) and stiffness (arbitrary units) = natural log(systolic/diastolic blood pressure)/((Dmax systolic – Dmin diastolic diameter)/(diastolic diameter)). Stiffness represents the entire deformation of the arterial wall without pressure dependence.
In the mixed effect model, HbA1c was categorized in tertiles; in group 1 HbA1c ranged from 28-39 mmol/mol; group 2 40-43 mmol/mol; and group 3 44-77. In our sub group analysis we analyzed individuals with and without self-reported diabetes. The HbA1c tertiles were for individuals without self-reported diabetes: group 1 HbA1c ranged from 28-39 mmol/mol; group 2 40-43 mmol/mol; and group 3 44-70 mmol/mol. For individuals with self-reported diabetes: group 1 HbA1c contained only 39 mmol/mol; group 2 41-43 mmol/mol; and group 3 45-77 mmol/mol. Dividing a population based on tertiles of the variable of interest for the study of associations to other parameters is common practice. Relations to glycemic status are not always linear and may even form U-shaped connections [6]. To have the opportunity to look for non-linear associations and even U-shaped relations, we chose to separate our population into categories of HbA1c. Three groups were chosen to keep a reasonable number of individuals in each group.

Sample size calculation

We are planning a study of a continuous response variable from independent individuals with and without diabetes, respectively, with ten controls without diabetes per individual with diabetes. In a previous study the response within each subject group was normally distributed with standard deviation 2.5. If the true difference in the individuals with and without diabetes means is 1.25, we will need to study 35 individuals with diabetes and 350 individuals without diabetes to be able to reject the null hypothesis that the population means of two groups are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

Main analysis

The association between the overall calculated aneurysmal growth rate and HbA1c was calculated using the Mann-Whitney U test and Spearman's correlation. For the main analysis, we used mixed effect models because we had continuous

measurements on each individual, and each measurement was dependent on the previous measurement. The assumption of normality of continuous measurements was confirmed by visual inspection of residual log-log plots. This supported the use of normal methods. In the main analysis, the whole group was analyzed. In the subgroup analyses, individuals with and without self-reported diabetes were analyzed. We conducted both crude and adjusted analyses where we adjusted for potential confounders.
Finally, the associations between HbA1c and aneurysmal maximal diameter and stiffness were analyzed using Spearman's correlation.

Potential confounders

The questionnaire provided us with information about the individuals' medical histories along with current medications. In the analysis, current medications and comorbidity were self-reported, with the exception of peripheral arterial disease, which was defined by 0.9 > ankle brachial index > 1.4 at screening. Medications were grouped according to the Anatomical Therapeutic Chemical classification system developed by the World Health Organization[7]. Medications included oral blood glucose-lowering medications (A10B), insulins (A10A), statins (C10AA), angiotensin-converting enzyme inhibitors (C09AA, C09BA, C09BB, C02EA, and C02LM), angiotensin II antagonists (C09C), beta blockers (C07), calcium antagonists (C08), low-doses of aspirin (B01AC06), non-steroidal anti-inflammatory drugs (M01AB), oral corticosteroids (H02), and inhaled corticosteroids (R03BA).

The following confounders were included in the mixed model adjusted analysis: a) smoking status yes/no (former and never smoker were grouped as one in the analysis), b) age, c) body mass index, d) baseline aortic measurement, e) diastolic blood pressure, f) level of total cholesterol, g) presence of peripheral arterial disease, and h) use of medication (self-reported) suspected to influence the growth rate (statins, aspirin, and beta blockers).

Other

All analyses were performed using Stata® Release 13.0 (StataCorp, College Station, TX, USA). This project was approved by the Danish Data Protection Agency (1-16-02-1-08). Ethical approval was provided by the Ethical Committee of the Central Region of Denmark (M20080028).

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