Reduced Aortic Wall Stress in Diabetes Mellitus

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Objective. Most risk factors are similar for abdominal aortic aneurysm (AAA) and atherosclerosis, e.g. smoking, male gender, age, high blood pressure, hyperlipidemia. Diabetes mellitus however, is a risk factor for atherosclerosis, but diabetic patients seldom develop AAA. The reason for this discrepancy is unknown. Increased aortic wall stress seems to be an etiologic factor in the formation, growth and rupture of AAA in man. The aim of our study was to study the wall stress in the abdominal aorta in diabetic patients compared with healthy controls.
Methods. 39 patients with diabetes mellitus and 46 age − and sex matched healthy subjects were examined with B-mode ultrasound to determine the lumen diameter (LD) and intima-media thickness (IMT) in the abdominal aorta (AA) and the common carotid artery (CCA). Diastolic blood pressure (DBP) was measured non-invasively in the brachial artery. LaPlace law was used to calculate circumferential wall stress.
Results. Age, DBP, and LD in the abdominal aorta were not significantly different in the diabetic patients compared to controls. IMT in the AA was larger in the diabetic patients, 0.89 ± 0.17 vs 0.73 ± 0.11 mm (p < .001). Accordingly aortic wall stress was reduced in the diabetics, $7.8 \pm 1.7 \times 10^5$ vs $9.7 \pm 1.9 \times 10^5$ dynes/cm^2 (p < .001).
Conclusions. Wall stress in the abdominal aorta is reduced in diabetes mellitus. This is mainly due to a thicker aortic wall compared to healthy controls. The reduced aortic wall stress coincides with the fact that epidemiological studies have shown a decreased risk of aneurysm development in diabetic patients.

Keywords: Abdominal aorta; Diabetes mellitus; Intima-media thickness; Wall stress; Wall tension; Aneurysm.

Introduction

The mechanism behind pathologic dilatation of the abdominal aorta is multifactorial.[1] The abdominal aortic aneurysms (AAA) are often described as atherosclerotic,[2] despite the fact that aneurysms may develop in aortas free of atherosclerosis. AAA and atherosclerosis share, however, several risk factors, such as high age, male gender, smoking, hyperlipid-emia, inflammation and hypertension.[3−10] Despite this, patients suffering from diabetes, a disease with a preponderance of atherosclerotic manifestations, seldom develop AAA.[6,7,11] The reason for this discrepancy has caused limited attention, and the cause for the reduced frequency of AAA in the diabetic population is unknown. Wall stress has been implied as a pathological factor in the development of AAA and we have previously described increasing wall stress and a defective stress auto-regulation in the ageing abdominal aorta.[12] In this pilot study we hypothesized that the abdominal aorta in diabetic patients might be affected by a changed remodeling response, and thus changed arterial wall stress compared to healthy subjects.

Material and Methods

We studied 39 patients with type 1 diabetes (17 males and 22 females, range 27−69 yrs, mean 43.3 ± 10.6 yrs), and 46 healthy age- and sex-matched controls (17 males and 29 females, range 28−69 yrs, mean 44.4 ± 10.5 yrs). All were Caucasian.

The controls were non-smokers, without hereditary factors regarding aneurysmal disease. They had no history of cardio-pulmonary, cerebro-vascular disease or peripheral vascular disease. The ankle brachial index was ≥1 in all control subjects. None of the

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controls took any prescribed drugs. Informed consent was obtained, and the ethics committee in Lund, Sweden approved the study.

The abdominal aorta (AA) was examined at the midpoint between the renal arteries and the aortic bifurcation. The right common carotid artery (CCA) was examined 1–2 cm proximal to the bifurcation. All examinations were performed after at least 15 minutes rest, with the subjects in a supine position. At the beginning of the investigation, pressure was measured in the upper arm bilaterally non-invasively with a cuff and a sphygmomanometer. No significant difference in pressure between the arms was found and the right arm was used in the pressure measurements. Non-invasive brachial pressure has been shown to generate a slight overestimation of the aortic diastolic pressure, but without sex or age-related differences.[13]

The intima-media thickness (IMT) and the lumen diameter (LD) were measured with aid of a Philips P700 ultrasound device (Philips Ultrasound, Santa Ana, California, United States) using a 7.5 MHz linear transducer for scanning of the CCA. For aortic imaging either a 5 MHz or a 3.5 MHz transducer was used. A longitudinal perpendicular image of the vessel was insonated and recorded on a video monitor, two images of good quality were frozen in diastole, according to the prevailing standard of IMT measurements. The IMT of the far wall as well as the LD were measured manually by tracing a cursor along the echo edges on a section of 10 mm with the aid of the digitizer.[14−16] This provides approximately 100 boundary points from which the mean value of IMT and LD is automatically calculated (VAP version 2.0, Dept of Appl Electronics, Chalmers University of Technology, Gothenburg, Sweden). The accuracy of the technique was studied by Pignoli et al. (1986)[16] who showed a good correlation between ultrasound and histology both on the carotid and the aortic wall. In our lab inter- and intra-observer variability are 6–8% and 10–11% regarding IMT and 2–3% and 4–6% regarding LD in CCA and AA respectively.[14] The success rate of visualizing carotid IMT was 100% and aortic IMT 90% in healthy individuals.[14] It is evident that the major part of the total wall thickness is included in the IMT measurements.[17,18] Further, the relation between adventitial thickness and IMT is unaffected by gender and age.[19] Accordingly, IMT has during recent years been used as a surrogate to arterial wall thickness in arteries in the calculation of wall stress.[20−22]

It may be argued that the exclusion of the adventitial layer of the wall give erroneous results since it contributes to the strength of the wall. The wall stress, however, is not affected by the histology but wall thickness only, in contrast to wall strength that is defined by the constituents of the wall.

Stress is the force per unit cross-sectional area. In the arterial wall, stresses are present along the circumferential, longitudinal and radial axes. Since arteries elongate little during the cardiac cycle and the wall is considered incompressible, we have focused on the circumferential wall stress (dyne/cm^2), calculated according to the law of LaPlace.[23,24]

$$\text{Wall stress} = \frac{\text{DP} \times \text{LD}/2}{\text{IMT}} \tag{1}$$

Diastolic pressure (DP, dyne/cm^2) was used since IMT measurements were performed in diastole. 1 mm Hg equals 1333 dyne/cm^2. LD, lumen diameter (cm). IMT, intima-media thickness (cm). All subjects were examined twice consecutively by one experienced ultra-sonographer regarding IMT, LD and blood pressure.

Statistics

For calculating the difference in IMT, LD, Wall stress, age, height, weight, BSA (body surface area), BMI (body mass index), and blood pressures between diabetic patients and controls, we used unpaired students t-test. For calculating differences in smoking habits, albuminuria, and retinopathy between diabetic patients and controls we used Chi-square test with Yates correction and Fishers exact test. For analyzing differences between the group of diabetic patients in whom it was not possible to examine the aorta, and the group possible to examine the aorta, we used Mann-Whitney-U test, Chi-square test with Yates correction and Fishers exact test. Linear regression and forward stepwise multiple regression was used to analyze correlations between different variables.

Results

For baseline clinical characteristics of the study population, see Table 1. A high incidence of retinopathy was found among the diabetic patients, 18 had background retinopathy and eight had proliferative retinopathy. Smoking was reported in 14 diabetic patients. The ankle brachial index was ≥1 in all diabetic patients. Two diabetic patients suffered from albuminuria (>0.5 g/24 h) and eight from microalbuminuria (30−300 mg/24 h).

Five were treated for hypertension, four with ACE-inhibitors and one with β-blocker. All diabetic

Table 1. Baseline clinical characteristics

	Controls $n = 46$	Diabetes Type 1 $n = 39$	P value
Age (yrs)	44.4 ± 10.5	43.2 ± 10.6	ns
Height (cm)	171 ± 8	172 ± 10	ns
Weight (kg)	70 ± 11	72 ± 12	ns
Body Surface Area (m^2)	1.81 ± 0.17	1.84 ± 0.19	ns
Body Mass Index (kg/m^2)	23.6 ± 2.7	24.3 ± 3.3	ns
Diastolic Blood Pressure (mm Hg)	76 ± 8	76 ± 9	ns
Systolic Blood Pressure (mmHg)	124 ± 15	122 ± 22	ns
Pulse Pressure (mm Hg)	48 ± 12	46 ± 22	ns
Mean Arterial Pressure (mm Hg)	92 ± 9	92 ± 10	ns

Mean $\pm$ SD.

patients were treated with insulin. The diabetic patients had mean diabetes duration of 26 ± 8 years, range 15–45 years. Their mean HbA1c was $7.4 \pm 1.3\%$ and their mean creatinine level was 76 ± 36 micromol/l.

It was possible to measure the carotid IMT in all 39 diabetic patients. However, in 12 of the diabetic patients it was not possible to obtain high enough sonographic image quality to measure aortic IMT. The 12 did not differ significantly from the successfully examined diabetic patients regarding blood pressure, carotid wall stress, carotid IMT, carotid LD, BMI (body mass index), BSA (body surface area), diabetes duration, HbA1c, smoking habits, degree of albuminuria or retinopathy. The intraobserver variability was 6% for carotid IMT and 10% for aortic IMT in the diabetic patients.

There was no difference between diabetic patients and controls in aortic LD (13.29 ± 2.20 mm vs 13.73 ± 2.10 mm, ns), nor in carotid LD (6.17 ± 0.96 mm vs 6.02 ± 0.61 mm, ns).

Fig. 1 shows the aortic IMT in diabetic patients and controls. The aortic IMT was 22% larger in the diabetic patients (0.89 ± 0.17 mm vs 0.73 ± 0.11 mm), $p < .001$.

Fig. 2 shows the calculated aortic wall stress in diabetic patients and controls. The aortic wall stress was 20% lower in the diabetic patients ($7.8 \pm 1.7 \times 10^5$ dynes/cm^2 vs $9.7 \pm 1.9 \times 10^5$ dynes/cm^2), $p < .001$.

Fig. 3 shows the carotid IMT in the diabetic patients and controls. The carotid IMT was 11% larger in the diabetic patients (0.61 ± 0.11 mm vs 0.55 ± 0.09 mm), $p < .05$.

Fig. 4 shows the calculated carotid wall stress in diabetic patients compared to controls. No difference between diabetic patients and controls was found ($5.3 \pm 1.2 \times 10^5$ dynes/cm^2 vs $5.6 \pm 0.9 \times 10^5$ dynes/cm^2), NS.
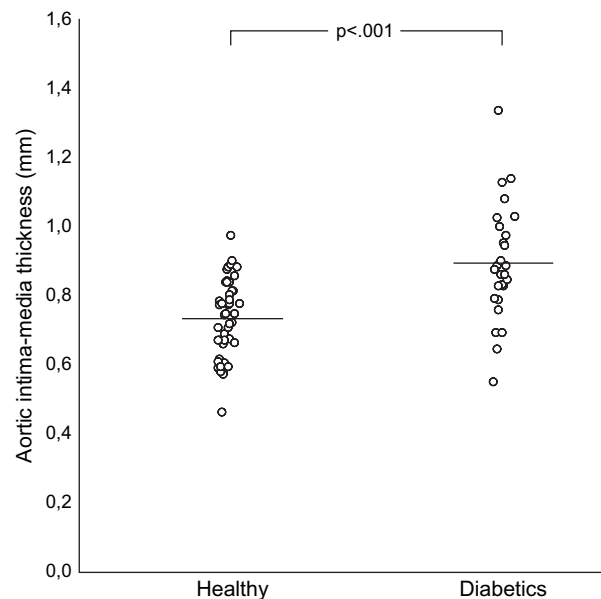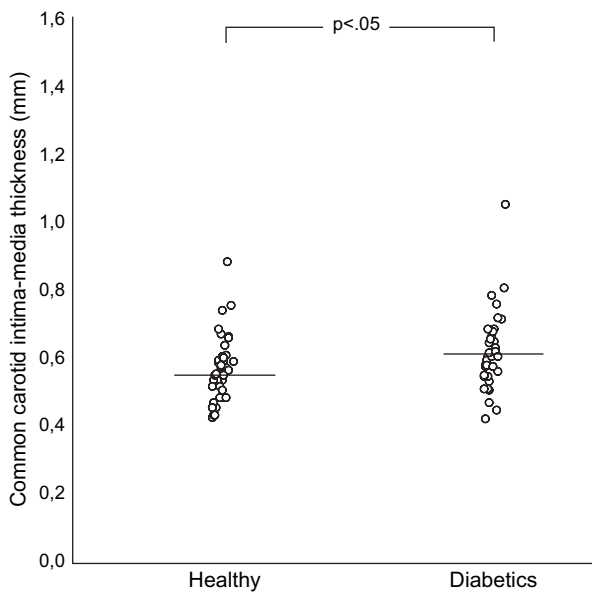
Fig. 1. Intima-media thickness (IMT) in the abdominal aorta (AA). Each circle represents an individual. Solid lines represent mean IMT. Increased IMT in diabetic patients was found ($p < .001$).

The smoking diabetic patients did not differ from the non-smoking diabetic patients regarding aortic and carotid wall stress, IMT, LD and blood pressure.

There was a significant correlation between **aortic IMT** and diabetes duration (r = 0.57, $p < .01$), age
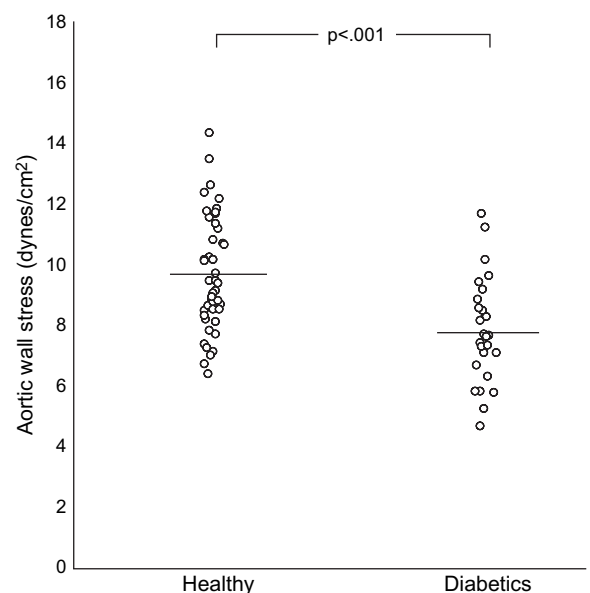
Fig. 2. Wall stress in the abdominal aorta (AA). Each circle represents an individual. Solid lines represent mean wall stress. Reduced wall stress in diabetic patients was found ($p < .001$).

Fig. 3. Intima-media thickness (IMT) in the common carotid artery (CCA). Each circle represents an individual. Solid lines represent mean IMT. Increased IMT in diabetic was found ($p < .05$).

($r = 0.43$, $p < .05$), systolic blood pressure (SBP), ($r = 0.40$, $p < .05$), but not with aortic LD, diastolic blood pressure (DBP), body mass index (BMI), body surface area (BSA) and HbA1c in diabetic patients. A multiple regression analysis of factors affecting aortic IMT, including diabetes duration, age and SBP
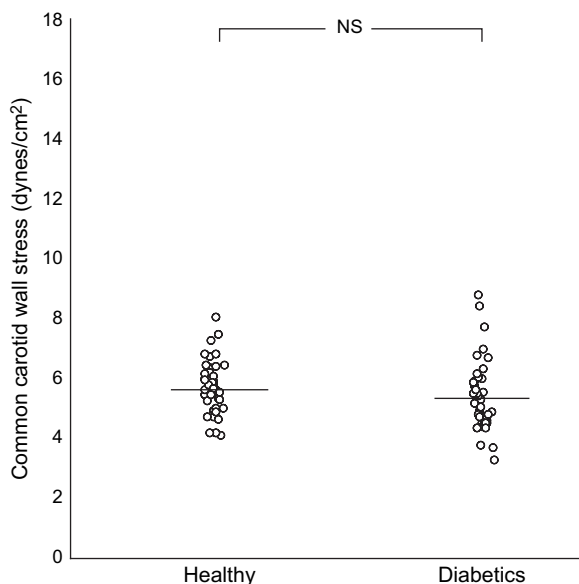

Fig. 4. Wall stress in the common carotid artery (CCA). Each circle represents an individual. Solid lines represent mean wall stress. No changed in wall stress in diabetic patients was found compared to healthy individuals.

showed borderline significance for diabetes duration ($\beta = 0.48$, $p = .06$). Since only 27 diabetic patients was included in the model it is likely that better significance would have been achieved in a larger cohort of patients. The annual growth rate of IMT was 0.007 mm/y in diabetic patients.

There was a significant correlation between **aortic IMT** and age ($r = 0.55$, $p < .001$), aortic LD ($r = 0.45$, $p < .01$), SBP ($r = 0.36$, $p < .05$), DBP ($r = 0.30$, $p < .05$), but not with BMI and BSA in healthy matched controls. When performing stepwise multiple regression analysis, only age stayed significantly correlated with aortic IMT in the healthy controls ($\beta = 0.36$, $p < .05$). The annual growth rate of IMT was 0.006 mm/y.

Discussion

The abdominal aorta (AA) in man is of interest both from a physiological and patho-physiological perspective, because of the predilection for pathological dilation and aneurysm formation. The possibility of an imbalance between wall stress and wall strength, being an underlying factor responsible for pathological dilatation, has been emphasized by the found relation between high blood pressure and increasing aneurysm diameter, as well as aneurysm diameter and risk of rupture.[1,25,26] Further, a direct relation between increased wall stress and risk of aneurysmal rupture has been proposed.[27−29] Remodeling of the arterial wall is an important physiological response to changes in wall stress, and mechanical stimuli seem to play a major role.[30] Despite an increase in both diameter and pressure in ageing arteries, wall stress is unchanged due to a compensatory increase in wall thickness, and may thus be an important determinant for vessel wall remodeling during ageing in man. Increased wall stress seems to activate smooth muscle cell production of connective tissue components, with an increase in matrix and thickness of the wall.[30−33] In the remodeling process metalloproteinases (MMP's) seem to play an important role with ability to degrade extra-cellular matrix.

The wall stress in the aorta appears to be greater than that found in other elastic arteries.[14] Furthermore, during ageing the AA dilates about 25−30% in healthy subjects, and to a larger extent than in other arterial regions.[34] Wall stress auto-regulation seems to be defective in males despite increasing wall thickness. Thus wall stress increase with age and points to the fact that the aorta is a vulnerable artery.[12] Since MMP's are activated by wall stress, a more proteolytic profile may be found in the aorta than in other arteries

which forms a background to the preponderance for aneurysm formation in the AA.[35–40] Especially MMP-2 and MMP-9 have been shown to be involved in the degradation of the vessel wall during development of abdominal aortic aneurysms (AAA), and the levels of MMP are related to the AAA enlargement, suggesting that the enzymatic activity varies with aortic diameter.[41,42]

The AAA are often described as atherosclerotic although aneurysms sometimes develop in aortas free of atherosclerosis.[2] One reason to describe AAA as atherosclerotic is the occasional co-localization of diffuse aortic atherosclerosis and AAA. Another reason might be shared risk factors, such as increased age, male gender, smoking, hyperlipidemia, inflammation and hypertension.[3–10] Despite this, patients suffering from diabetes, a disease with a preponderance of atherosclerotic manifestations, exhibit a low prevalence of AAA.[6,7,11] Furthermore if diabetic patients develop AAA's, the expansion rate of those AAA's is only 30% compared to non-diabetic patients.[43] The reason for this discrepancy has caused limited attention, and the cause for the reduced frequency of AAA in the diabetic population is unknown. Diabetic patients might however be affected by changed remodeling response in the abdominal aorta compared to healthy subjects, leading to a protection from aneurysmal disease. We measured intima-media thickness (IMT) as a surrogate to arterial wall thickness with aid of B-mode ultrasound technique according to Pignoli _et al_. (1986),[16] and used the law of LaPlace to calculate wall stress.[14] This technique has recently been shown to have acceptable reproducibility (CV 11%) also in deep lying arteries such as the abdominal aorta.[14] Wall stress was significantly reduced in the aorta of diabetic patients, mainly due to an increased wall thickness (Figs. 1 and 2). High glucose-levels induce altered MMP expression in cell cultures,[44] and a down regulation of MMP seems to be the reason for the matrix accumulation in diabetic nephropathy.[45] Furthermore, carotid IMT is increased in diabetic patients, and there is an association between IMT in non-diabetic patients and the level of postprandial hyperglycemia.[46–48]

A down regulation of MMP activity has been shown in the internal mammary and tibial arteries of diabetic patients as well as the coronary arteries of diabetic rats,[49–51] and a reduced MMP activity would fit well with our findings of markedly increased aortic wall thickness in the diabetic patients. Thus high glucose levels inactivating metalloproteinases responsible for aortic wall degradation might be the mechanism behind reduced aortic wall stress, decreased aneurysm prevalence, and reduced rate of increasing aneurysmal size found in the diabetic population.[6,7,11,43]

It was only possible to examine 69% of the diabetic patients regarding aortic IMT. The reasons for this are not known. A factor of importance might be the amount of intra-abdominal fat influencing the possibility to perform ultrasound scans. However, BMI (body mass index) and BSA (body surface area) did not differ between the diabetic patients that were possible to study and the rest. Neither did diabetes duration, blood pressure, carotid IMT, carotid LD, wall stress, HbA1c, smoking habits, degree of albuminuria or retinopathy indicating that the two groups were comparable. The vessels in diabetic patients are commonly known to be more difficult to examine with ultrasound, although the reason is unknown. An alternative technique would have been CT or MRI. However, these techniques offer less resolution. We used the diastolic pressure in the calculation of circumferential wall stress since the IMT measurements were performed in diastole according to prevailing standard. A weakness with the study was that we did not measure local pressure in the abdominal aorta, but instead used auscultatory brachial pressure. This means a slight overestimation of the aortic diastolic pressure, but without sex or age-related differences.[13]

In conclusion, our study shows that patients with diabetes mellitus have increased wall thickness in the abdominal aorta compared to healthy controls, generating lesser wall stress. This coincides with the fact that diabetic patients have lesser risk of developing abdominal aortic aneurysms (AAA). Future studies examining wall stress in risk-populations for AAA are warranted in order to elucidate the protective influence of diabetes on AAA formation.

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