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SHORT COMMUNICATION

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Increased aortic stiffness is persistent in type 1 diabetic women: a follow-up study

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Abstract *Aims/hypothesis:* We have previously reported that women, not men, with type 1 diabetes have increased aortic stiffness. Increased arterial stiffness may explain why diabetic women have a particularly high risk of developing cardiovascular complications. We have now followed up our previously investigated patients after 7 years, with a view to evaluating whether the sex difference was persistent, and also evaluating the degree of progression with time and the relationship between stiffness versus intima media thickness of the aorta. *Methods:* Stiffness (β) of the abdominal aorta (echo-tracking sonography) and intima media thickness (B-mode ultrasound) were assessed in 23 women and 19 men with type 1 diabetes and compared with matched healthy individuals. *Results:* At follow-up, aortic stiffness was still higher (60%) (p=0.0016) in diabetic than in control women, whereas there was no similar difference (p=0.4) between diabetic and control men. No progression of stiffness had occurred over the 7 years. At follow-up, the intima media thickness was increased and the internal diameter of the aorta was decreased in diabetic men and women without any sex-related difference. *Conclusions/interpretation:* The increased aortic stiffness that affects type 1 diabetic patients seems to be an early event that soon reaches a plateau without any further increase. Increased aortic stiffness in type 1 diabetic women seems to be a sex-specific functional disorder unrelated to the degree of underlying atherosclerosis.

Keywords Arterial compliance · Arterial stiffness · Arterial wall distensibility · Echo-tracking sonography · Gender difference · Sex difference · Type 1 diabetes mellitus · Ultrasound

Abbreviations DC: distensibility coefficient · IMT: intima media thickness · MAP: mean arterial pressure

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Introduction

Diabetic patients show an increased risk of cardiovascular complications, particularly women patients. We have previously shown that women, but not men, with type 1 diabetes have increased aortic stiffness [1], which may contribute to the increased risk of cardiovascular complications among such women. The aims of this follow-up study were: (1) to evaluate whether sex-related differences in aortic stiffness were persistent 7 years after their first examination, and (2) to evaluate the relationship between intima media thickness, a marker of atherosclerosis, and aortic stiffness.

Subjects and methods

Subjects At baseline, 56 (30 women) patients with type 1 diabetes were investigated. Seven years later four had died. The remaining patients were invited for re-evaluation and 42 (23 women) accepted. All patients gave informed consent and the Ethics Committee, Lund University, Sweden, approved the study.

Age- and sex-matched reference values for aortic stiffness were available for 79 (39 women) healthy subjects aged 27–70 years; for abdominal aortic intima media thickness

83 healthy subjects served as controls (58 women, age range 25–69; 25 men, age range 30–65).

Ultrasonic measurements of arterial diameter and distensibility The pulsatile changes in vessel diameter of the abdominal aorta were registered with an ultrasound echo-tracking system (Diamove; Teltec, Lund, Sweden). In combination with non-invasive blood pressure measurements, the pulsatile diameter changes provided the basis for calculating vessel wall stiffness (β). The method has been previously described in detail [1]. In addition, we calculated the distensibility coefficient (DC) [2].

Ultrasonic measurement of intima media thickness The intima media thickness (IMT) and the lumen diameter of the abdominal aorta were evaluated at the same site as the measurement of the pulsatile diameter change, using a Philips P700 ultrasound device (Philips Ultrasound, Santa Anna, CA, USA) with either a 5- or a 3.5-MHz transducer. A longitudinal image was frozen in diastole, and a section of 10 mm was measured manually by tracing a cursor along the echo edges, as recently described in detail [3]. In 15 of the diabetic subjects, it was not possible to evaluate IMT because of problems visualising the aorta.

Statistics Non-linear regression with 95% confidence intervals defines the normal ranges for stiffness, DC and mean arterial pressure (MAP) in the control subjects according to age and sex. Covariance was used to compare stiffness, DC, MAP and the aortic diameter in diabetic women and men versus sex- and age-matched control subjects. Differences in clinical characteristics were tested with the Mann–Whitney *U*-test. A p value of less than 0.05 was taken as significant. Data are presented as the mean value±SD, unless otherwise stated. The stiffness values were also expressed as percentage of predicted normal values.

Results

Clinical features Apart from the expected differences in height and weight, there were no significant differences between diabetic women and men in age (women: mean age 43, range 27–69; men 44 years, range 33–63 years), duration (women: mean 26 years, range 17–43; men 24 years, range 16–45 years), HbA_1c (women: 7.2±1.4; men: 7.7±1.2%) or plasma cholesterol (women: 4.8±0.5, men 4.7±0.7 mmol/l). One woman and one man had albuminuria. Three men and three women were being treated for hypertension. Three men and four women had severe retinopathy. Smoking was reported in eight women and seven men.

Stiffness and distensibility coefficient of the aorta At follow-up, diabetic women still showed significantly higher aortic stiffness (Fig. 1a) than control women (p=0.00162), whereas diabetic men did not show any significant difference (Fig. 1b) versus control men (p=0.4). The DC showed the same differences (women p=0.0022; men p=0.7). Comparing the results with those obtained 7 years earlier (and correcting for the increase in age between the examinations), we found no progression in aortic stiffness in women or men. The correlation between individual stiffness values in the first versus the second examination was low (r=0.39, p=0.07) among women, but high among men (r=0.69, p=0.002). Accordingly, increased aortic stiffness among women was a feature of the group and not the individual.

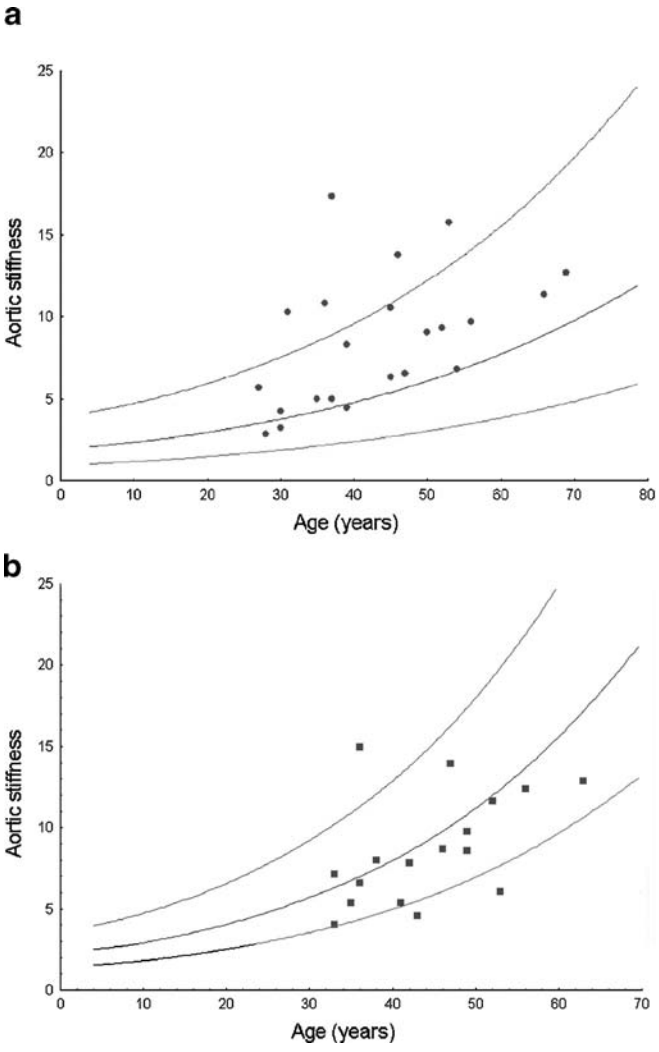

Fig. 1 Aortic stiffness (β) in women (**a**) and men (**b**) with type 1 diabetes. The *solid lines* represent mean, upper and lower 95% confidence interval for control women (**a**) and control men (**b**) (86 women, age range 4–87 years; 84 men, age range 4–74 years; in the statistical analyses only control subjects in the age range of the patients are included as stated in "Subjects and methods"). Note the significantly increased stiffness in diabetic women versus control women (p=0.00162). There was no significant increase in stiffness in diabetic men versus control men (p=0.4)

Intima media thickness and diameter of aorta IMT was significantly increased in diabetic women and men versus corresponding control subjects (women p=0.0049, men p=0.000016; Fig. 2a, b). Similarly, the aortic diameter was significantly decreased in diabetic women and men, whether corrected for body surface area or not (women: p=0.002 and p=0.003 respectively; men p=0.01 and p=0.04 respectively).

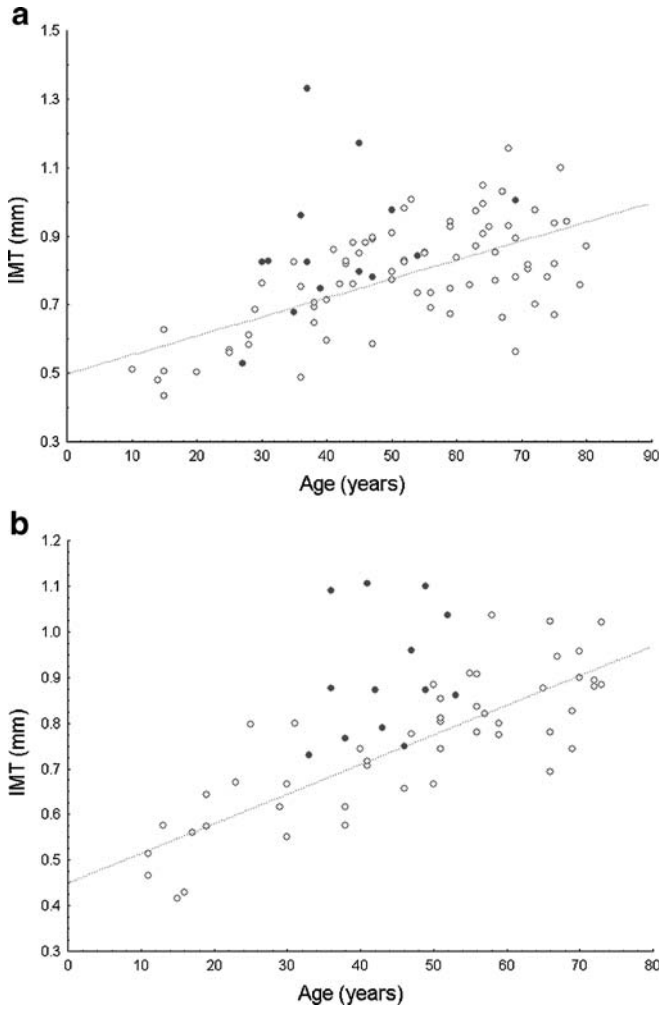

Fig. 2 **a** Intima media thickness (*IMT*) of the abdominal aorta in women with type 1 diabetes (*closed symbols*) and control women (*open symbols*). IMT was significantly increased in diabetic women compared with control women (p=0.0049). **b** IMT of the abdominal aorta in men with type 1 diabetes (*closed symbols*) and control men (*open symbols*). IMT was significantly increased in diabetic men compared with control men (p=0.000016)

Deaths Since the first examination, four patients had died. One 34-year-old woman and one 56-year-old man died from myocardial infarction. At baseline, this woman had the highest aortic stiffness value (257% of predicted normal value for age and sex) of all patients, and the man the second highest value among the diabetic men (160% of predicted normal value). Of the remaining deaths, a 34-year-old woman had died from intoxication and a 26-year-old man of excessive alcoholic intake. The aortic stiffness in these patients was 81 and 123% of the predicted normal value respectively.

Discussion

The present study shows that 7 years after the initial investigation, there is still a marked sex-related difference in aortic distensibility, with an increase in aortic stiffness among diabetic women compared with control women, but without a similar difference among men. Interestingly, the follow-up study demonstrated that the increased aortic stiffness in women with type 1 diabetes was not based on individual test results. Hence, factors related to the female sex in general seem to explain the increased stiffness in aorta among diabetic women. In contrast to stiffness, aortic intima media thickness was increased to a similar extent in diabetic men and women. Hence, it is unlikely that atherosclerosis caused the proved sex-related difference in aortic stiffness among our type 1 diabetic patients.

Increased arterial stiffness is an independent risk marker for cardiovascular mortality [4]. Our initial finding of a sex-related difference in the stiffening of elastic arteries in type 1 diabetes [1] has recently been supported by another study [5]. In other studies of type 1 diabetes, however, the possibility of sex-related differences in changes of arterial wall properties has not been taken into account. One confounding factor might be that superficial arteries such as the common carotid artery have been studied despite the fact that most marked changes in arterial wall mechanics are found in the abdominal aorta [1]. Our finding of a sex-related difference with more decreased distensibility in central arteries in diabetic women than in diabetic men may be important for the particularly increased risk of cardiovascular complications in diabetic women, including their poor prognosis after myocardial infarction with increased incidence of congestive heart failure, reinfarction and death [6].

IMT is considered as a valuable marker of atherosclerosis. The current study is the first showing that aortic IMT is increased in diabetic patients without differences between the sexes. The IMT-data fit well with the decreased aortic inner diameter found in both sexes amongst our diabetic patients. Increased thickness of the arterial wall may increase the arterial wall stiffness, linking the atherosclerotic process to arterial wall elasticity. However, the relation between early atherosclerosis and arterial stiffening is unclear. In our study diabetic women and men had a similar increase in aortic IMT. Hence, atherosclerosis does not explain the selective increase in aortic wall stiffness in diabetic women (Fig. 1). Further, the sex-related difference found in aortic stiffness could not be explained by differences in duration of diabetes, frequency of complications, HbA_1c concentrations or smoking habits between women and men.

When correcting for the increase in age between the two investigations no progression of stiffness has occurred over the 7 years. Giannattasio et al. [7] recently reported a reduction in arterial distensibility in type 1 diabetic patients during a short two-year follow-up. These patients had a considerably shorter duration of diabetes than our patients. Indeed, we previously reported a correlation between aortic stiffness and the duration of type 1 diabetes in a study including patients with a short disease duration [8]. These observations, together with the lack of progression of aortic stiffness in the current follow-up study, favour the hypothesis that the increase in arterial wall stiffness in diabetic

women is rather an early event in the disease process, soon reaching a plateau and then not increasing any further.

The lack of increment in aortic stiffness in this study makes it unlikely that accumulation of advanced glycation end products contributes to the increased aortic stiffness. In fact, the individual variation in aortic stiffness among diabetic women, together with the relation between aortic stiffness and autonomic nerve dysfunction found earlier [8], suggests a functional background to the increase in aortic stiffness. Factors of importance might be insulin resistance, or hormonal factors. Women with type 1 diabetes have a delayed menarche, increased prevalence of menstrual and hyper-androgenic disorders [9], and earlier age at menopause than non-diabetic women [10].

In conclusion, the increased aortic stiffness that affects type 1 diabetic women seems to be an early event soon reaching a plateau and not increasing any further. Increased aortic stiffness in type 1 diabetic women seems to be a sex-specific functional disorder unrelated to the degree of underlying atherosclerosis.

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Duality of interest: None

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