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SHORT COMMUNICATION

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Mean HbA_1c over 18 years predicts carotid intima media thickness in women with type 1 diabetes

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Abstract *Aims/hypothesis:* Intima media thickness (IMT) of the common carotid artery (CCA) is a validated surrogate marker of early atherosclerosis. The aim of our study was to assess the association between IMT in CCA and long-term mean HbA_1c in type 1 diabetes. We also elucidated the association between carotid IMT and preclinical coronary atherosclerosis. *Methods:* In 39 individuals with type 1 diabetes, HbA_1c was measured prospectively over 18 years. The IMT examinations were performed with high-resolution ultrasound. The association between carotid IMT and preclinical coronary atherosclerosis (assessed by intravascular ultrasound [IVUS]) was tested in 29 of the patients. *Results:* Mean HbA_1c over 18 years was 8.2% (range: 6.6–11.3%). Mean age at follow-up after 18 years was 43 years and mean duration of diabetes was 30 years. IMT was significantly higher in diabetic patients than in an age- and sex-matched reference population. The IMT values were at the same level as for controls who were 20 years older. In women, HbA_1c was significantly associated with mean average CCA IMT (r^2=0.77, p<0.0001 when adjusted for age), whereas there was no significant association for men. Among women, a significant association was also found between carotid IMT and the percentage of coronary vessel area stenosis (r=0.65, p=0.03). *Conclusions/interpretation:* The present findings suggest an important role of long-term hyperglycaemia in the development of atherosclerosis, especially in women with type 1 diabetes.: Type 1 diabetes patients have earlier development of, and more advanced, atherosclerosis compared with an age- and sex-matched reference population. In women, carotid IMT reflects preclinical coronary atherosclerosis.

Keywords Coronary artery disease · Glycaemic control · Intima media thickness · Macrovascular disease · Type 1 diabetes

Abbreviations IMT: intima media thickness · IVUS: intravascular ultrasound · CCA: common carotid artery

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Introduction

Intima media thickness (IMT) of the carotid arteries is associated with coronary atherosclerosis and is a predictor of coronary events [1]. Improved blood glucose control obtained by intensive insulin treatment of type 1 diabetes is associated with lower carotid artery IMT than that found with conventional insulin treatment [2, 3].

We aimed to evaluate the IMT and its association with mean HbA_1c measured longitudinally over the previous 18 years in people with type 1 diabetes. The diabetic patients in the present study were also examined for early coronary atherosclerosis by intravascular ultrasound (IVUS) [4]. As carotid IMT measurements are easier to perform than IVUS examinations of the coronary arteries and as, to our knowledge, a comparison of these methods has never been done, we assessed any association between carotid IMT and early coronary atherosclerosis as observed by IVUS.

Subjects and methods

Subjects Thirty-nine patients from the Oslo study on type 1 diabetes participated in the present study. They were followed prospectively for 18 years (1982–2000). The protocol and results are given in detail elsewhere [5]. In the original study 45 patients were included. Two of these patients died, one of lung disease and the other of breast cancer, and four

declined further participation. The Governmental Regional Ethics Committee approved the study. Twenty-nine patients agreed to coronary IVUS examination. All patients gave their written consent. The reference population is the fourth survey of the Tromsø Study [6].

Ultrasonography Ultrasound studies were performed according to a standard protocol. High-resolution B-mode ultrasonography of the right carotid artery was performed with a 7-MHz ultrasound scanner (Acuson 128 Computed Sonography System, Mountain View, CA, USA) equipped with a linear array transducer. All examinations were performed by the same sonographer. Patients were examined in the supine position with the head turned 45° contralaterally with the help of a cushion that had been specially designed for this purpose. IMT of the far wall of the CCA and the carotid bulbous was examined. The images were stored on high-resolution S-VHS videotape for offline analysis. For repeated measurements in individual patients the mean coefficient of variation was 5.6% for CCA IMT.

The ultrasonic images were analysed offline by a computerised technique for automated ultrasonic image analysis. This was undertaken by an experienced investigator from the Tromsø study who had no knowledge of the patients [7]. The different layers with their interfaces of the carotid artery wall were defined automatically. A 10-mm wall segment on both sides of the demarcation arrow separating the CCA and the bifurcation of the carotid artery was measured. The computer program estimated the maximum, minimum and average IMT along the 10-mm segment. The mean of the average IMT and the mean of the maximum IMT of three to four measurements were calculated and used in the analyses.

Intravascular coronary ultrasound examinations The IVUS system used in this study consisted of the Clear View Ultra with Automatic Pullback Device and the Ultra Cross 3.2 F30-MHz catheter (Boston Scientific, Sunnyvale, CA, USA). The ultrasound images were recorded on S-VHS videotape for offline analysis. Percentage of vessel area stenosis, defined as plaque area divided by vessel area multiplied by 100 [4], was used to study the statistical association between IMT and HbA_1c.

Laboratory methods Lipid profiles were measured by conventional methods in the fasting state. The first HbA_1c measurement of each year was used for analyses. Further details are described elsewhere [4]. Microalbuminuria was defined as urinary albumin excretion above 30 mg/24 h in at least two of three samples, and overt nephropathy as albumin excretion above 300 mg/24 h in two of three samples [4].

Statistical methods To allow for adjustment for age when studying the relation between HbA_1c and IMT in the CCA, multivariate linear regression analysis was performed. All significance tests were two tailed, and p values of less than 0.05 were considered significant. All calculations were performed using SPSS version 10.0 (SPSS, Chicago, IL, USA).

Results

Demographic characteristics of the 39 patients at the time of the IMT measurements are presented in Table 1. Mean age was 43 (range: 35–58) years, and mean duration of disease was 30 (23–39) years. The mean HbA_1c over 18 years was 8.2% (6.6–11.3%). Table 2 shows the mean IMT values according to age and sex for the average and maximal common carotid and the carotid bulb. A comparison with a large age-matched reference population is also shown. The mean CCA IMT of the far wall was 0. 86 (0.62–1.35) mm for men and 0.83 (0.65–1.09) mm for women. Compared with the control population, IMT values in the patients were at the same level as those in people more than 20 years older.

Carotid IMT was significantly correlated with age in females (r=0.68, p<0.004) but not in males (r=0.21, p=0.33). Furthermore, multivariate linear regression analysis with age and HbA_1c as independent variables demonstrated that in females, both age and HbA_1c were significantly related to mean IMT (r^2=0.77; age: p<0.0001, HbA_1c: p<0.0001) whilst in males, no significant associations were found (r^2=0.07; age: p=0.71, HbA_1c: p=0.32). According to the regression analyses, an increase of HbA_1c of 1% over 18 years corresponded in women to a 0.10-mm increase in

Table 1 Demographic and putative risk factors for atherosclerosis according to sex

	Men (n=23)	Women (n=16)
Age (years)	44 (38–58)	42 (35–53)
Duration of diabetes (years)	31 (23–39)	30 (23–39)
Mean HbA_1c (%)	8.3 (6.6–11.3)	8.1 (6.6–10.5)
Systolic BP (mmHg)	130 (100–150)	127 (108–185)
Systolic BP 1982 (mmHg)	125 (110–170)	125 (105–150)
Diastolic BP (mmHg)	81 (60–109)	79 (70–100)
Diastolic BP 1982 (mmHg)	78 (65–90)	78 (60–90)
Total cholesterol (mmol/l)	5.4 (3.6–6.3)	5.3 (3.7–6.8)
Total cholesterol 1982 (mmol/l)	4.8 (3.3–6.3)	5.2 (4.2–7.3)
HDL cholesterol (mmol/l)	1.7 (0.9–2.4)	1.8 (0.9–2.0)
HDL cholesterol 1982 (mmol/l)	1.3 (0.8–3.8)	1.3 (0.5-1.4)
Total cholesterol:HDL cholesterol ratio	3.3 (1.7–6.4)	3.1 (2.1–4.2)
LDL cholesterol (mmol/l)	3.1 (1.3–4.5)	3.1 (2.1–4.5)
Triglycerides (mmol/l)	1.2 (0.4–6.8)	0.8 (0.5–1.3)
Triglycerides 1982 (mmol/l)	0.8 (0.3–2.1)	0.8 (0.5–1.4)
BMI (kg/m^2)	25 (20–41)	24 (19–30)
BMI 1982 (kg/m^2)	23 (19–26)	22 (19–26)
Number of patients with microalbuminuria (%)	5 (22)	1 (6)
Number of patients on antihypertensive treatment (%)	6 (26)	1 (6)
Number of patients on lipid-lowering treatment (%)	4 (17)	1 (6)
Number of patients who have smoked (%)	9 (39)	8 (50)
Number of current smokers (%)	5 (22)	5 (31)

Values are given as means (range) unless stated otherwise

Table 2 IMT in diabetic and reference populations according to sex and age

Localisation of ultrasound examination	Age groups (years)	Diabetic population IMT (mm)	Reference population IMT (mm)	*p* values
Mean CCA IMT (SD)	Men			
	35–45	0.860 (0.164) (*n*=15)	0.605 (0.082) (*n*=131)	<0.0001
	45–55	0.923 (0.193) (*n*=7)	0.704 (0.155) (*n*=464)	<0.0001
	Women			
	35–45	0.773 (0.134) (*n*=10)	0.586 (0.065) (*n*=173)	0.002
	45–55	0.928 (0.094) (*n*=6)	0.658 (0.107) (*n*=202)	<0.0001
Max. CCA IMT (SD)	Men			
	35–45	1.005 (0.169) (*n*=15)	0.749 (0.193) (*n*=131)	<0.0001
	45–55	1.071 (0.238) (*n*=7)	0.876 (0.209) (*n*=464)	0.015
	Women			
	35–45	0.930 (0.182) (*n*=10)	0.709 (0.102) (*n*=173)	0.004
	45–55	1.06 (0.121) (*n*=6)	0.799 (0.154) (*n*=202)	<0.0001
Mean bulb IMT (SD)	Men			
	35–45	1.104 (0.200) (*n*=10)	0.811 (0.207) (*n*=131)	<0.0001
	45–55	1.163 (0.015) (*n*=5)	0.935 (0.298) (*n*=464)	0.015
	Women			
	35–45	0.947 (0.191) (*n*=9)	0.732 (0.174) (*n*=173)	0.0004
	45–55	1.213 (0.403) (*n*=6)	0.845 (0.223) (*n*=202)	0.075
Max. bulb IMT (SD)	Men			
	35–45	1.455 (0.362) (*n*=10)	1.088 (0.366) (*n*=131)	<0.003
	45–55	1.478 (0.220) (*n*=5)	1.271 (0.523) (*n*=464)	0.10
	Women			
	35–45	1.252 (0.167) (*n*=9)	0.990 (0.346) (*n*=173)	0.001
	45–55	1.724 (0.670) (*n*=6)	1.125 (0.346) (*n*=202)	0.089

mean IMT, whereas a 10-year increase in age resulted in a rise of 0.15 mm. We found no association between HbA_1c and IMT in the carotid bifurcation. The crude associations between IMT and the factors: family history of cardiovascular disease, family history of type 2 diabetes, BMI, microalbuminuria, total cholesterol, smoking or systolic blood pressure were not statistically significant. For the whole group there was a significant association between mean CCA IMT and the percentage of vessel area stenosis as found by IVUS (r=0.43, p=0.034). When the men and women were examined separately, this correlation was high for women (r=0.65, p=0.032) and low for men (r=0.07, p=0.78). Similar results were obtained when mean CCA IMT was replaced with maximal IMT.

Discussion

In the present study we found a strong association between carotid IMT and HbA_1c in women but not in men. This result indicates an important role of glycaemic control in the development of preclinical atherosclerosis in women with type 1 diabetes. Considering the low p values in this analysis for women, our results suggest that age and HbA_1c have a strong impact on CCA IMT in diabetic females.

In the Epidemiology of Diabetes Interventions and Complications (EDIC) study, where IMT was measured 18 months after the Diabetes Control and Complications Trial (DCCT), mean HbA_1c during the DCCT did not significantly correlate with carotid IMT. However, when the measurements in the EDIC were repeated 6 years later, IMT for both men and women was associated with mean HbA_1c during the DCCT [3]. Considering that our results refer to 18 years of follow-up, the strong association found between HbA_1c and IMT for diabetic women in our study is in accordance with the findings of the EDIC study in women. The implication of these studies might be that elevated long-term plasma glucose is not only a risk factor for the progression of atherosclerosis in type 1 diabetes but may be causally related to the atherosclerotic process.

The mean CCA IMT in the present study is significantly higher than in the sex- and age-matched reference groups and corresponds to what was found in subjects around 20 years older, even though mean blood pressure, mean cholesterol and BMI were lower in the diabetic group [6]. In middle-aged non-diabetic subjects the risk of coronary artery disease is two to five times higher in men than in women [8]. Diabetes is an independent risk factor for cardiovascular disease, greater in women than in men; the usual lower risk in women does not seem to be the case here [9]. Interestingly, an association between HbA_1c and cardiovascular disease was found in women but not in men in the Pittsburgh Epidemiology of Diabetes Complications Study although the researchers were not convinced by this result [10]. In earlier studies, poor glycaemic control did not explain the increased risk of the early development of coronary artery disease in either sex [11, 12]. However, IMT measurements reveal atherosclerosis at an earlier stage than

coronary angiography and our findings indicate that long-term hyperglycaemia is a stronger risk factor for the development of atherosclerosis in women than in men. We do not know why this is the case but it is plausible that diabetes-related risk factors have a stronger atherosclerotic effect in women.

We also identified an association between IMT and preclinical coronary atherosclerosis (by IVUS) in women but not in men. This suggests that IMT is an indirect measure of coronary atherosclerosis in asymptomatic type 1 diabetes, at least in women. However, considering that the low sample size of this study does not allow adjustment for several confounders, our results must be interpreted with caution until further long-term results from larger studies are available.

Concluding remarks

In women with type 1 diabetes there is an association between long-term HbA_1c and carotid IMT. Individuals with type 1 diabetes have higher carotid IMT than age- and sex-matched controls. Carotid IMT in women with type 1 diabetes reflects preclinical coronary atherosclerosis as shown by IVUS.

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References

1. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH et al (1998) The role of carotid arterial intima-media thickness in predicting clinical coronary events. Ann Intern Med 128:262–269
2. Jensen-Urstad KJ, Reichard PG, Rosfors JS, Lindblad LE, Jensen-Urstad MT (1996) Early atherosclerosis is retarded by improved long-term blood glucose control in patients with IDDM. Diabetes 45:1253–1258
3. Nathan DM, Lachin J, Cleary P, Orchard T, Brillon DJ, Backlund JY et al (2003) Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. N Engl J Med 348:2294–2303
4. Larsen J, Brekke M, Sandvik L, Arnesen H, Hanssen KF, Dahl-Jorgensen K (2002) Silent coronary atheromatosis in type 1 diabetic patients and its relation to long-term glycemic control. Diabetes 51:2637–2641
5. Dahl-Jorgensen K, Brinchmann-Hansen O, Hanssen KF, Ganes T, Kierulf P, Smeland E et al (1986) Effect of near normoglycaemia for two years on progression of early diabetic retinopathy, nephropathy, and neuropathy: the Oslo study. Br Med J (Clin Res Ed) 293:1195–1199
6. Stensland-Bugge E, Bonaa KH, Joakimsen O (2001) Age and sex differences in the relationship between inherited and lifestyle risk factors and subclinical carotid atherosclerosis: the Tromso study. Atherosclerosis 154(2):437–448
7. Stensland-Bugge E, Bonaa KH, Joakimsen O (1997) Reproducibility of ultrasonographically determined intima-media thickness is dependent on arterial wall thickness. The Tromso study. Stroke 28:1972–1980
8. Krolewski AS, Kosinski EJ, Warram JH, Leland OS, Busick EJ, Asmal AC et al (1987) Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus. Am J Cardiol 59:750–755
9. Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR et al (2003) Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. Diabetologia 46:760–765
10. Orchard TJ, Stevens LK, Forrest KY, Fuller JH (1998) Cardiovascular disease in insulin dependent diabetes mellitus: similar rates but different risk factors in the US compared with Europe. Int J Epidemiol 27:976–983
11. Pajunen P, Taskinen MR, Nieminen MS, Syvanne M (2000) Angiographic severity and extent of coronary artery disease in patients with type 1 diabetes mellitus. Am J Cardiol 86:1080–1085
12. Lloyd CE, Kuller LH, Ellis D, Becker DJ, Wing RR, Orchard TJ (1996) Coronary artery disease in IDDM. Gender differences in risk factors but not risk. Arterioscler Thromb Vasc Biol 16:720–726