Patients with Wegener's granulomatosis: a long-term follow-up study

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ABSTRACT

Introduction. *Atherosclerosis is accelerated in Wegener's granulomatosis (WG) patients. This study was aimed to assess which factors can predict progression of atherosclerosis in WG.*

Methods. *23 WG patients (14 men; age 47±9 years, mean±SD) and 21 controls (12 men; age 47±10 years) were included. Intima-media thickness (IMT) was determined by ultrasound, as measure for atherosclerosis. After median follow-up of 72 months (interquartile range: 66-76), IMT was repeated. Traditional risk factors for cardiovascular disease were determined, as well as levels of C-reactive protein (CRP) and endothelial activation markers, including thrombomodulin, vascular cell adhesion molecule-1 (VCAM-1) and von Willebrand factor (vWf). Disease-related factors were recorded from time of diagnosis until end of follow-up.*

Results. *Maximum IMT at both evaluations was increased in patients. Patients had an increased prevalence of hypertension and increased levels of vWf and CRP. IMT progression was not different. IMT at follow-up was positively associated with age, blood pressure, CRP and VCAM-1, and negatively with HDL. During follow-up, disease activity was lower compared to the period from diagnosis until the first evaluation, and blood pressure and prevalence of dyslipidemia decreased in WG patients. Change in IMT was not correlated to any risk factor measured.*

Conclusion. *Maximum IMT was increased in WG patients. Progression of IMT was not different between patients and controls, probably because disease activity was low and reduction of traditional risk factors was achieved during follow-up. We suggest that control of disease activity and treatment of traditional risk factors are important to prevent cardiovascular disease in WG.*

Introduction

Atherosclerosis is considered to result from an inflammatory process (1, 2), and various large prospective epidemiological studies have demonstrated that increased levels of inflammatory markers are predictive of future cardiovascular disease (CVD) (3, 4). Inflammation is also one of the hallmarks of systemic autoimmune diseases such as Wegener's granulomatosis (WG). (5) Therefore, accelerated atherosclerosis, as well as endothelial activation and dysfunction, one of the earliest steps in atherosclerosis, might be expected in WG. Indeed, endothelial activation occurs *in vivo* in this disease, as demonstrated by increased serum levels of soluble intracellular adhesion molecule-1, vascular cell adhesion molecule-1 (VCAM-1), and E-selectin. (6) Furthermore, endothelial dysfunction measured using different techniques, including flow-mediated dilatation, laser Doppler fluxmetry and pulse wave velocity, has been described in WG. (7-11) The prevalence of atherosclerosis, as assessed by intima-media thickness (IMT), is also increased in WG. (12) This increased IMT could not be fully explained by the presence of traditional cardiovascular risk factors. Therefore, non-traditional risk factors are probably involved, including disease-related factors such as disease activity. The question remains as to which disease-related factors in particular are contributing most to this increased IMT in WG. A follow-up study measuring progression of IMT in relation to disease-related factors might solve this question. However, at present, no follow-up studies measuring IMT have been performed in WG.

The aim of the present study was to assess the progression of IMT thickening of the common carotid artery (CCA) in WG patients and controls. In addition, we investigated the possible associations between this progression and

traditional and non-traditional risk factors, including disease-related factors, for atherosclerosis.

Patients and methods

Subjects

Of the 29 patients who participated in the study described previously (12), 23 patients were included. Six patients were lost to follow-up; two patients died (due to urothelial cancer and massive haemoptysis, respectively), two patients had moved, and two patients withdrew informed consent. Pregnancy and active disease, defined as Birmingham Vasculitis Activity score (BVAS)>1 (13), were exclusion criteria at both evaluations.

We recruited 21 age- and sex-matched volunteers as controls, who also participated in the study described previously (12). Five controls were lost to follow-up; two controls died (unknown causes) and three controls had moved. The local research ethics committee gave approval for the study, and informed consent was obtained from each participant.

Hypertension was defined as systolic arterial pressure above 140 mmHg and/or diastolic arterial pressure above 90 mmHg, or use of antihypertensive drugs. Dyslipidemia was diagnosed if plasma cholesterol exceeded 6.21 mmol/l, LDL cholesterol exceeded 3.36 mmol/l, triglycerides exceeded 2.26 mmol/l, or use of lipid-lowering drugs. Furthermore, body mass index, smoking status, diabetes and family history of CVD (considered positive if first-degree relatives suffered from CVD before 60 years of age) were recorded.

Retrospectively, we assessed disease-related factors that might influence the development of atherosclerosis from time of diagnosis until end of follow-up in retrospective analyses. Data of medical records were used. The frequency of visits to our out-patient clinic is at least once in three months. As a measure of overall disease activity, cumulative BVAS was calculated by summing BVAS-score of each relapse. Mean C-reactive protein (CRP) over a certain period was calculated and depicted as mg/l/day, as we divided the area under the curve by the time span involved. In addition, we recorded cumulative prednisolone dose, proteinuria and creatinine clearance.

All measurements recorded at entry (evaluation 1), including traditional and disease-related risk factors, were repeated after median follow-up (evaluation 2) of 72 months (interquartile range: 66-76) in patients and controls. None of the patients or controls had any CVD events during follow-up.

Blood analyses

Plasma lipid concentrations (cholesterol, HDL, LDL, and triglycerides) were measured by routine techniques.

Additional serum and plasma samples for determination of levels of markers of endothelial activation and inflammation were stored at -20°C until analysis. All measurements were performed in a single batch. Serum levels of VCAM-1 (R&D Systems, Abingdon, UK) and thrombomodulin (Diaclone, Besançon, France) were measured according to the manufacturer's instructions. Von Willebrand factor (vWf) and CRP were determined using in-house enzyme-linked immunosorbent assays as described previously (12).

Measurements of intima-media thickness

IMT was measured as described by de Groot *et al*. (14). At evaluation 1 and evaluation 2, IMT was determined at the far wall of the left CCA approximately 1 cm proximal to the bulb using an acuson 128XP ultrasound with 7 MHz linear array transducers (Acuson Corp., Mountain view, USA). A B-mode image was obtained after which a probe was positioned perpendicular to the far wall, showing an intima-media complex over approximately one centimetre. Mean IMT (mean of the segment studied) and maximum IMT (highest IMT value found among the segment studied) were calculated. Progression of mean IMT was determined at the left CCA and defined as mean IMT at evaluation 2 minus mean IMT at evaluation 1 divided by time of follow-up in years. Progression of maximum IMT was similarly calculated. The measurements of both evaluations were read by the same person. Coefficient of variation of IMT measurement of the CCA is approximately 5% (15).

Statistical methods

Except when stated otherwise, values were expressed as mean ± standard deviation when variables were normally distributed. In case of a non-normal distribution values were expressed as median and interquartile range. Comparisons between patients and controls were made by two-sample *t*-tests or Mann-Whitney tests for continuous variables and by chi-square analysis for categorical variables. The univariate correlation between IMT and other categorical variables was assessed by Spearman correlation coefficient. Comparisons between variables at evaluation 1 and evaluation 2 were made by paired-samples *t*-test or Wilcoxon signed ranks test for continuous variables and by McNemar analysis for categorical variables. Multiple linear regression analysis was not performed due to the small sample size. All analyses were performed using SPSS 12.0. A two-sided *p*-value <0.05 was considered to indicate statistical significance.

We performed a power analysis based on our previous study concerning IMT measurements in WG, in which mean IMT of 29 WG patients (0.72±0.16 mm) were compared to mean IMT of 26 controls (0.66±0.13 mm) (12) Mean difference of mean IMT between patients and controls was 0.06 mm. We hypothesised that this enhanced increase in IMT in WG is due to the disease itself. To estimate a rate of progression we divided this mean difference in IMT by the disease duration (mean 79 months), resulting in an estimated rate of progression of IMT of 0.009 mm/year in patients. Progression of IMT in controls was estimated at 0.001 mm/year (16). Power analyses revealed that at least 20 patients and 20 controls had to be included to detect a difference in progression of mean IMT of 0.008 mm/year with a standard deviation of 0.010 at a significance level of 0.05 with a power of 80%.

Results

Traditional risk factors and endothelial activation markers

The demographic characteristics and traditional cardiovascular risk factors at both evaluations are shown in Table I.

At both time points, patients and controls showed a comparable profile with respect to age, sex, body mass index, prevalence of diabetes, lipid levels, use of lipid-lowering drugs and positive family history of CVD. At evaluation 1, both systolic and diastolic blood pressure were higher in patients (p<0.001 and p=0.002, respectively), despite more frequent use of antihypertensive drugs (p=0.003). Renal function was reduced in patients compared to controls at evaluation 2 (p<0.001). Concerning endothelial activation markers, level of CRP and vWf were increased in patients at both evaluations (p=0.005 and p=0.02 at evaluation 1, p=0.02 and p=0.01 at evaluation 2, respectively). At evaluation 2, also levels of TM were elevated in patients compared to controls (p=0.002).

During follow-up, some traditional risk factors changed, especially in patients (Table 1). At evaluation 2 diastolic blood pressure was decreased compared to evaluation 1 (p=0.004). Furthermore, prevalence of dyslipidemia decreased (p=0.02), as levels of cholesterol and levels of LDL decreased (p=0.002, and p<0.001, respectively) and levels of HDL increased (p<0.001). Use of lipid-lowering drugs did not significantly change during follow-up.

Disease-related factors

The disease duration from diagnosis until the first evaluation was 43 (21-86) months. Disease-related factors are depicted in Table II. In addition, at evaluation 1, three patients used cyclophosphamide, and two used methotrexate. At evaluation 2, no patients used cyclophosphamide or methotrexate any longer, and three used mycophenolate mofetil.

Parameters of disease activity, including cumulative BVAS, cumulative prednisolone dose, and mean CRP levels, were higher in the period from diagnosis until evaluation 1 compared to the period of follow-up (Table II).

Intima-media thickness

At entry and after follow-up, IMT of the left CCA was determined. Data are shown in Table III and Figure 1A. At both evaluations, maximum IMT of the left CCA was increased in WG patients (p<0.05). Mean IMT over this segment did not differ between controls and patients.

As shown in Figure 1B, progression of mean IMT of the left CCA was 0.005 (0.001-0.023) mm/year in patients and 0.004 (-0.006-0.021) mm/year in controls (p=0.46). Progression of maximum IMT was also not different between patients and controls (0.014 (-0.001-0.025) mm/year *vs*. 0.013 (-0.013-0.030) mm/year, respectively, p=0.58).

Table I. Characteristics and endothelial activation in patients and controls.

Characteristics evaluation 1	Evaluation 1		Evaluation 2	
	WG (n=23)	Controls (n=21)	WG (n=23)	Controls (n=21)
Age, years	51 ± 13	47 ± 11	56 ± 14	52 ± 11
Male sex, n (%)	14 (61%)	12 (57%)		
Body mass index, kg/m^2	26 ± 4	25 ± 3	26 ± 5	25 ± 3
Hypertension, n (%)	9 (39%)**	0	13 (57%)**	1 (8%)
Blood pressure, mm Hg				
Systolic	129 ± 16**	110 ± 15	124 ± 15	120 ± 11
Diastolic	78 ± 9**	68 ± 8	71 ± 9##	76 ± 8
Antihypertensive drugs, n (%)	8 (35%)**	0	13 (57%)**	0
Smoking, n (%)	1 (4%)*	6 (29%)	2 (9%)	2 (14%)
Diabetes, n (%)	1 (4%)	0	1 (4%)	0
Cholesterol, mmol/l				
Total	5.6 ± 1.0	5.5 ± 0.9	4.9 ± 0.7##	5.0 ± 0.8
LDL	3.8 ± 0.8	3.6 ± 0.9	3.0 ± 0.8##	3.3 ± 0.8
HDL	1.1 ± 0.3	1.1 ± 0.3	1.4 ± 0.4##	1.5 ± 0.3
Dyslipidemia, n (%)	19 (83%)	11 (53%)	11 (48%)#	12 (57%)
HMG-CoA inhibitors, n (%)	2 (8%)	0	5 (22%)	1 (8%)
Family history CVD, n (%)	6 (26%)	9 (43%)	6 (26%)	9 (43%)
Creatinine, µmol/l	101 (89-114)	ND	93 (78-112)**	75 (68-80)
Creatinine clearance, ml/min	92 (80-107)	ND	78 (71-98)**	112 (99-126)
TM, ng/ml	5.6 (4.8-8.1)	5.5 (4.5-6.5)	5.1 (4.3-7.6)**	4.1 (3.7-4.6)
VCAM-1, ng/ml	277 (234-333)	278 (223-330)	315 (255-398)	285 (253-318)
vWf, %	115 (85-194)*	79 (60-120)	93 (77-199)**	68 (45-107)
CRP, mg/l	2.2 (1.5-8.6)**	0.6 (0.4-3.1)	4.5 (2.5-22.4)**	1.9 (0.8-4.8)

LDL: low density lipoprotein; HDL: high density lipoprotein; CVD: cardiovascular disease; ND: not determined; TM: thrombomodulin; VCAM-1: vascular cell adhesion molecule-1; vWf: von Willebrand factor; CRP: C-reactive protein.
*p<0.05, **p<0.01 compared to controls, #p<0.05 compared to WG patients at evaluation 1, ##p<0.01 compared to WG patients at evaluation 1.

Table II. Disease-related factors of WG patients (n=23).

	Evaluation 1	Evaluation 2	Change during follow-up
Disease duration, months	43 (21-86)	117 (90-161)*	71 (61-75)
Proteinuria, mg/l	0.2 (0-0.5)	0.2 (0-0.5)	
Patients with relapse, n (%)	14 (61%)	15 (65%)	
Number of relapses	1 (0-2)	2 (0-4)	
Cumulative BVAS	27 (21-49)	37 (26-66)**	0 (0-18)**
CRP, mg/l/day	7.1 (1.9-11.7)	5.0 (1.9-7.6)	3.8 (1.5-6.8)*
Current prednisolone use, n (%)	11 (48%)	8 (35%)	
Daily dose, mg	7.5 (5-11.3)	6.25 (5-8)	
Ever prednisolone use, n (%)	22 (96%)	22 (96%)	
Cumulative dose, g	16 (9-25)	21 (13-34)**	5 (0-9)**
Azathioprine use, n (%)	8 (35%)	9 (39%)	
Daily dose, mg	63 (50-94)	100 (75-125)	

Values are depicted as median (interquartile range), unless stated otherwise
BVAS: Birmingham Vasculitis Activity Score; CRP: C-reactive protein;
*p<0.05; **p<0.01 compared to evaluation 1.

Table III. Intima-media thickness of patients and controls.

	Evaluation 1		Evaluation 2	
	WG (n=23)	Controls (n=21)	WG (n=23)	Controls (n=21)
IMT				
Mean, mm	0.67 (0.54-0.77)	0.64 (0.57-0.75)	0.69 (0.63-0.86)	0.68 (0.57-0.80)
Maximum, mm	0.85 (0.73-0.93)*	0.73 (0.66-0.85)	0.85 (0.81-1.01)*	0.77 (0.66-0.85)

Values are depicted as median (interquartile range). IMT: intima-media thickness; CCA: common carotid artery. *p<0.05 compared to controls.

Univariate analyses of risk factors

In controls mean IMT of the CCA as measured at evaluation 1 was correlated with the following variables at evaluation 1: age (r=0.67, p=0.001), diastolic blood pressure (r=0.57, p=0.02), and levels of total cholesterol (r=0.56, p=0.008). In patients, mean IMT at evaluation 1 was associated with age (r=0.53, p=0.005), diastolic blood pressure (r=0.41, p=0.04) and levels of VCAM-1 (r=0.46, p=0.02). Maximum IMT showed the same significant correlations with these variables (data not shown). Although cumulative CRP values during follow-up tended to correlate with progression of IMT (r=0.37, p=0.1), no significant correlations were found between progression of IMT and all other risk factors included, such as cumulative prednisolone dose and cumulative BVAS.

Mean IMT at evaluation 2 was correlated to variables at evaluation 1 to investigate predictive factors of increased IMT after follow-up. Mean IMT at evaluation 2 was correlated with age (r=0.53, p<0.001), systolic (r=0.24, p=0.03) and diastolic (r=0.45, p=0.004) blood pressure, levels of HDL (r=-0.44, p=0.003), levels of VCAM-1 (r=0.39, p=0.02) and levels of CRP (r=0.36, p=0.03) using data of controls and patients together. Also, maximum IMT at evaluation 2 was significantly correlated to these variables (data not shown). Furthermore, univariate analyses were performed between IMT at visit two and changes in risk factors during follow-up, for example blood pressure. No significant correlations were found (data not shown).

Disease activity and intima-media thickness

To investigate whether disease activity would influence progression of IMT,

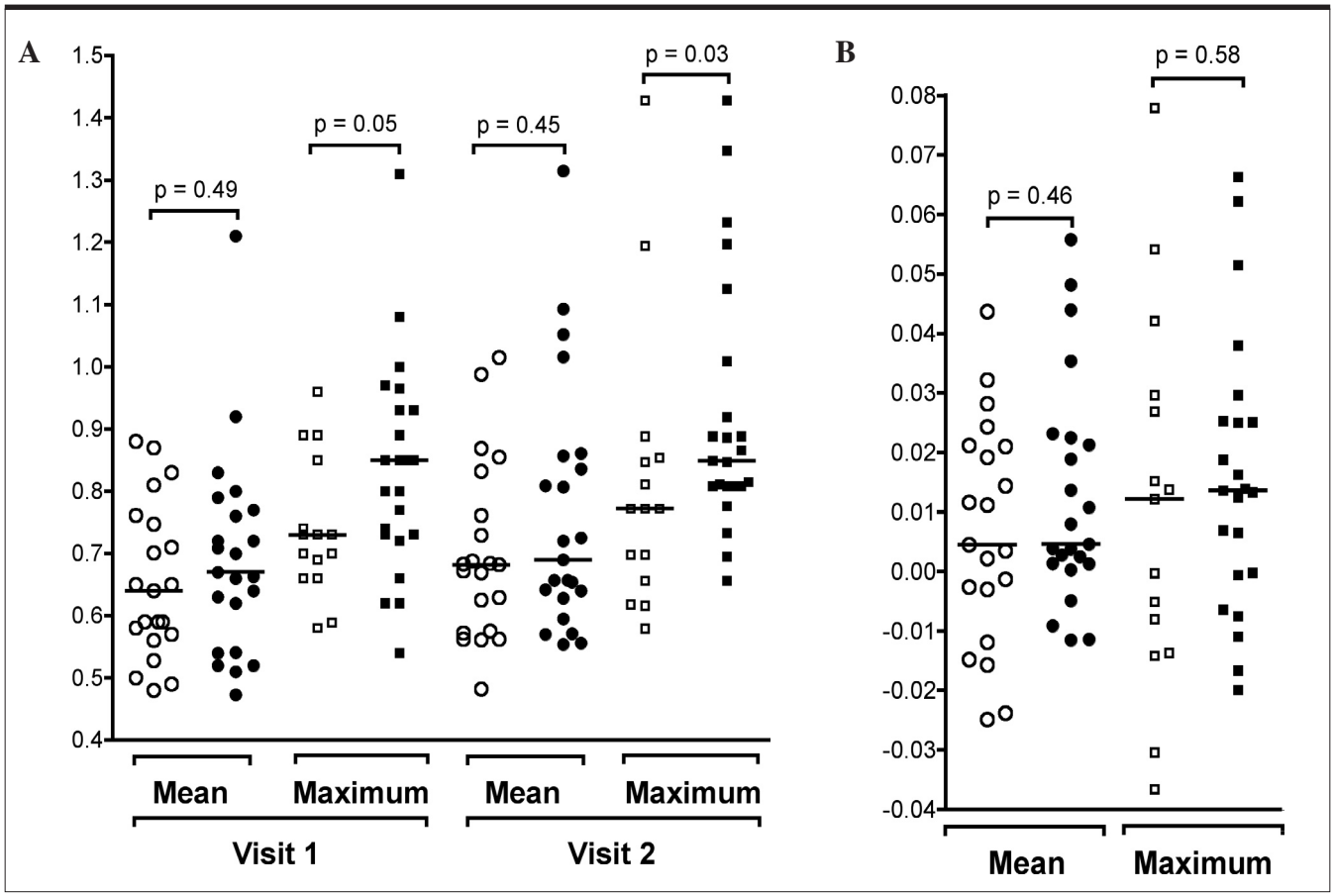

Fig. 1. Intima-media thickness (IMT) in patients and controls.
Maximum IMT of the left common carotid artery (CCA) is increased in Wegener's granulomatosis (WG) patients compared to controls at both evaluations. No differences in mean IMT of the left CCA are found (**A**).
Progression of mean IMT and maximum IMT after a follow-up period of approximately six years did not differ between WG patients compared to controls (**B**). Open symbols represent controls and closed symbols represent WG patients. Circles represent mean values of IMT, squares represent maximum values of IMT.

we compared patients who experienced one or more relapses during follow-up (n=11) to those patients without relapses (n=2). Twenty relapses occurred during follow-up. Median BVAS score of these relapses during follow-up was lower compared to BVAS score of relapses in the period from diagnosis until evaluation 1 (9 (8-12) *vs*. 16 (9-18), p=0.02). No differences were found in traditional or non-traditional risk factors, including EC activation markers between patients with relapses during follow-up compared to patients without relapses (data not shown). Progression of IMT was not different between both patient groups (change in mean IMT: 0.004 (-0.005-0.019) mm/year *vs*. 0.012 (0.002-0.042) mm/year, p=0.21, and, change in maximum IMT: 0.006 (-0.006-0.025 mm/year *vs*. 0.015 (0.008-0.048) mm/year, p=0.17, in patients with and without relapses, respectively).

Discussion

This study is the first to measure IMT longitudinally in WG patients. At entry, patients had an increased maximum IMT of the left CCA compared to controls. After follow-up, maximum IMT was still increased in patients. However, progression of IMT among patients and controls was similar.

We performed a follow-up study to investigate whether WG patients are prone to accelerated progression of IMT. This hypothesis could not be confirmed, as no increased progression of IMT could be detected in WG. In addition, we compared patients who had one or more relapses during follow-up to those without relapses, expecting that patients with relapses would have an increased progression of IMT. However, no such increased IMT was found in these patients.

Several explanations for these findings can be mentioned. First, disease-related factors might not have been sufficiently present to accelerate atherosclerosis. In general, vasculitis patients are nowadays treated more aggressively to prevent relapses, as described by Mukhtyar *et al*. (17). Also in the current study, disease activity was low during follow-up compared to the period from diagnosis until evaluation 1, as reflected by lower parameters of disease activity during follow-up, including cumulative BVAS, mean CRP levels and cumulative prednisolone dose. This might explain the fact that even in patients with relapses during follow-up no progression of IMT was found, because relapses during follow-up were less severe than relapses before evaluation 1, as demonstrated by lower BVAS scores during follow-up. Studies in patients with giant cell arteritis (GCA), a large and middle-sized blood vessel vasculitis, confirm the hypothesis that disease activity might influence the progression of atherosclerosis (18). IMT in patients with GCA who had been able to discontinue corticosteroid therapy tended to be decreased compared to IMT in patients who used corticosteroids longer than 2 years. This might indicate that patients with mild GCA have less progression of IMT compared to patients with more severe disease. Also, in patients with rheumatoid arthritis longitudinal evaluation of CRP levels, as measure of disease activity during that particular period, revealed to correlate directly with the presence of atherosclerosis (19).

Secondly, traditional risk factors were more adequately treated during follow-up, presumably because more attention is being paid to traditional risk factors in WG patients in recent years. At evaluation 2, blood pressure was better regulated. Also, lipid levels improved in patients, as levels of cholesterol and LDL significantly decreased and levels of HDL significantly increased. More awareness and treatment of traditional risk factors of CVD in WG is comparable to the trend seen in other systemic autoimmune diseases, for example systemic lupus erythematosus (20-22).

We also aimed to assess predictors of progression of IMT. No correlations could be detected between progression of IMT and risk factors included in this study. However, when we analysed which factors at evaluation 1 could predict increased mean IMT at evaluation 2, we found that IMT at evaluation 2 positively correlated to age and blood pressure at evaluation 1, and negatively to levels of HDL. This emphasises that traditional risk factors are of influence and should be adequately treated. Furthermore, positive correlations were found between IMT and levels of CRP and VCAM-1, indicating that inflammation and endothelial activation are implicated in atherosclerosis. Indeed, CRP has been found to be an independent prognostic marker for CVD (23), and levels of VCAM-1 have been demonstrated to be independent predictors of long-term clinical outcomes, including CVD in diabetic patients (24, 25).

Our study has some limitations. First, we included a limited number of patients. Therefore, no adjustments could be made for possible confounders, like smoking, and smaller differences in IMT progression between patients and controls could have been missed. However, whereas the coefficient of variation of IMT measurement is rather small (5%), significant differences can already be detected in relatively small groups. Furthermore, to detect possible differences in progression of IMT, we compensated for this relatively small number of patients by a long follow-up period of six years. Secondly, although measuring the CCA has a better reproducibility and should have made it easier to reliably detect small differences in increases in IMT between WG patients and controls, atherosclerotic lesions, especially plaques, often appear later in the CCA than in the ICA or bulb (26, 27). Therefore, measuring only the CCA has the risk of missing more accelerated progress in the other segments. Benedetto *et al*. recently showed that only new plaque formation in the bulbar area, and not IMT, was independently correlated to cardiovascular events in patients with end-stage renal disease (28). Furthermore, IMT at the CCA can be affected by blood pressure and is probably a more reliable index of vascular hypertrophy than of atherosclerosis (29). It might be suggested to measure progression of IMT in all segments, as well as to include plaque score in further studies. Third, we demonstrated that the period between diagnosis and the first evaluation was crucial, whereas in this period, accelerated atherosclerosis occurred in WG patients compared to controls. Un-

fortunately, clinical data were collected retrospectively. In order to draw stronger conclusions concerning the influence of the different disease-related factors, a prospective study from diagnosis onwards should be performed.

In conclusion, although IMT was increased in WG patients compared to controls at entry, no accelerated development of atherosclerosis in WG could be demonstrated during a follow-up of approximately six years. This might be explained by the fact that during follow-up disease activity was low and traditional risk factors were more adequately treated. These data suggest that control of disease activity and reduction of traditional risk factors may result in prevention of overt CVD in WG patients.

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