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# INCREASED ACCUMULATION OF ADVANCED GLYCATION ENDPRODUCTS IN PATIENTS WITH WEGENER'S GRANULOMATOSIS

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Dear editor,

Wegener's granulomatosis (WG) is a systemic autoimmune disease characterized by an increased risk for cardiovascular disease due to accelerated atherosclerosis, which cannot be fully explained by traditional risk factors.<sup>1</sup> Therefore, non-traditional risk factors are probably involved. Among these, accumulation of advanced glycation endproducts (AGEs) might be important. AGEs are implicated in vascular pathology<sup>2</sup> and are independent predictors of cardiovascular mortality in diabetic and hemodialysis patients.<sup>3,4</sup>

In this study, AGE accumulation, atherosclerosis, and levels of the receptor for AGEs (sRAGE) were measured in 24 consecutive WG patients, fulfilling the American College of Rheumatology criteria<sup>5</sup>, with inactive disease and 21 controls (table 1). AGE accumulation was assessed as previously described<sup>6</sup> and intima-media thickness (IMT) in both carotid arteries was determined with ultrasound.<sup>7</sup> IMT could not be assessed in all subjects due to technical problems (n=4) or due to the presence of plaque, defined as a localized IMT >1 mm (n=12). Serum levels of sRAGE were measured using a commercially available enzyme-linked immunosorbent assays (R&D systems, Minneapolis, MN, USA).

Traditional risk factors were not different between groups (table 1). Patients used more often antihypertensive drugs compared to controls (14 (58%) vs. 0,  $p < 0.01$ ). Furthermore, levels of creatinine were increased in patients (median (interquartile range): 94 (78-112)  $\mu\text{mol/l}$  vs. 75 (68-80)  $\mu\text{mol/l}$ ,  $p < 0.01$ ). Disease duration was 115 (88 - 157) months. Sixteen patients had generalized disease. Eight patients used prednisolone (daily dose 6.3 (5 - 8) mg), 9 used azathioprine (100 (75-125) mg), and 3 used mycophenolate mofetil. Fifteen patients had experienced one or more relapses after diagnosis.

WG patients had increased AGE accumulation (figure 1A). In diabetes mellitus and systemic lupus erythematosus increased AGE accumulation has previously been demonstrated, which correlated to age and blood pressure.<sup>4,8</sup> Also in our WG patients, AGEs were correlated to age and blood pressure ( $r = 0.61$ ,  $p < 0.001$ , and  $r = 0.50$ ,  $p = 0.001$ , respectively). There were no correlations found between AGEs and all other included factors, for example levels of creatinine or use of medication.

Furthermore, IMT and plaques were measured (table 1). In contrast to our previous study<sup>1</sup> no increased IMT was found in WG, however, increased prevalence of plaques still indicates accelerated atherosclerosis. Interestingly, AGEs and IMT were positively correlated (mean IMT including all subjects:  $r = 0.42$ ,  $p = 0.02$ , maximum IMT:  $r = 0.44$ ,  $p = 0.01$ , figure 1B).

The increased AGE accumulation in WG patients might result, in part, from decreased sRAGE levels, whereas these levels tended to be decreased in patients (1239 (826-1582) pg/ml vs. 1440 (1283-1666) pg/ml,  $p = 0.1$ ). Furthermore, sRAGE correlated negatively to AGE accumulation ( $r = -0.33$ ,  $p = 0.04$ ) and mean and maximum IMT in the bulb ( $r = -0.65$ ,  $p = 0.01$ , and  $r = -0.66$ ,  $p = 0.01$ , respectively). No significant correlations between sRAGE and other parameters were found.

In conclusion, AGE accumulation is increased and associated with IMT in WG. As accelerated atherosclerosis in WG cannot be fully explained by traditional risk factors and AGEs are involved in vascular pathology, these AGEs may accelerate the development of atherosclerosis. Also, lower levels of sRAGE, which can act as a decoy receptor for AGEs<sup>9</sup>, might contribute to accelerated atherosclerosis in WG.

*Conflict of Interest*

Dr. A.J. Smit is a founder of Diagnostix Technologies BV, The Netherlands, manufacturing autofluorescence readers ([www.diagnostix.com](http://www.diagnostix.com)).

*Statement*

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**Table 1. Characteristics and ultrasound measurements in patients and controls**

	Controls (n = 21)	WG (n = 24)	P value
Age, years	56 ± 14	51 ± 11	NS
Male sex, n (%)	17 (63%)	12 (57%)	NS
Body mass index, kg/m <sup>2</sup>	26 ± 5	25 ± 3	NS
Blood pressure, mm Hg			NS
Systolic	127 ± 20	120 ± 11	
Diastolic	70 ± 9	74 ± 8	
Smoking, n (%)	3 (12%)	2 (10%)	NS
HbA1c, %	5.4 ± 0.6	5.4 ± 0.4	NS
Cholesterol, mmol/l			
Total	4.9 ± 0.7	5.0 ± 0.8	NS
LDL	3.0 ± 0.8	3.3 ± 0.8	
HDL	1.4 ± 0.4	1.5 ± 0.3	
Family history for CVD, n (%)	9 (38%)	9 (43%)	NS
IMT, mm			
CCA			
Mean	0.67 (0.59-0.79)	0.72 (0.62-0.81)	NS
Maximum	0.81 (0.73-0.92)	0.85 (0.75-1.00)	NS
Bulb			
Mean	0.85 (0.79-1.10)	0.82 (0.74-1.29)	NS
Maximum	1.04 (0.93-1.37)	1.04 (0.87-1.65)	NS
ICA			
Mean	0.67 (0.52-0.77)	0.68 (0.55-1.04)	NS
Maximum	0.84 (0.63-1.00)	0.82 (0.69-1.20)	NS
All segments			
Mean	0.73 (0.65-0.81)	0.75 (0.67-1.00)	NS
Maximum	0.88 (0.80-0.98)	0.92 (0.78-1.23)	NS
Plaque, n (%)			
All segments	3 (14%)	9 (38%)	0.08
CCA	1 (5%)	1 (4%)	NS
Bulb	2 (11%)	8 (33%)	0.06
ICA	1 (5%)	6 (25%)	0.06

Abbreviations: LDL; low density lipoprotein, HDL; high density lipoprotein, CVD; cardiovascular disease, IMT; Intima-media thickness, CCA: common carotid artery, ICA; internal carotid artery.

### Legend to the figure

**Figure 1.** AGE accumulation reflected as skin autofluorescence in patients and controls

**A.** Accumulation of AGEs is increased in WG compared to controls. Horizontal line represents the median.

**B.** AGE accumulation is associated with IMT. The line represents the correlation between skin autofluorescence and mean of maximum IMT of all segments studied ( $r = 0.44$ ,  $p = 0.01$ )



