

## Risk Factors for Premature Atherosclerosis

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**Objectives:** to investigate the prevalence of risk factors in patients with premature atherosclerosis.

**Design:** retrospective controlled study.

**Materials:** 135 consecutive patients with premature atherosclerosis  $\leq 55$  years (group I) were investigated. A control group comprised 107 consecutive patients  $\geq 65$  years (group II) with atherosclerosis. Statistical analysis was performed with Chi-squared test and logistic regression analysis.

**Results:** group I versus group II: diabetes 11% vs. 27% ( $p=0.001$ ), smoking 84% vs. 67% ( $p=0.002$ ), hypertension 36% vs. 58% ( $p=0.001$ ), hypercholesterolaemia 47% vs. 34% ( $p=0.04$ ), family history of cardiovascular disease 53% vs. 42% ( $p=0.08$ ). In group I hyperhomocysteinaemia was present in 24 of the 108 patients tested, anticardiolipin antibodies were present in four of the 34 tested and coagulation abnormalities were found in four of the 22 patients tested.

**Conclusion:** the difference in the prevalence of the different risk factors between the two groups suggests that either certain risk factors are more likely to cause premature atherosclerosis, or that other risk factors must be present in addition to the known risk factors in order to induce premature atherosclerosis.

### Introduction

Only 1 to 7% of the patient population with atherosclerosis are young adults, depending on the age limit used to determine premature atherosclerosis. Premature atherosclerosis tends to follow a more virulent course than atherosclerosis in the elderly.<sup>2,3</sup> This leads us to believe that there must be risk factors other than the common known cardiovascular risk factors which induce premature atherosclerosis. Recently the presence of a hypercoagulable state, due to anticoagulant deficiencies or to antiphospholipid antibodies, has been identified as a risk factor for atherosclerosis, as well as hyperhomocysteinaemia.

The purpose of this study was to investigate the prevalence of risk factors in patients with premature atherosclerosis compared to elderly patients with atherosclerosis.

### Methods

A retrospective review was performed of 135 consecutive patients of 55 years of age and younger (group

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I), undergoing angiography for arterial occlusive disease, during the period from January 1993 until December 1996. A control group consisted of 107 consecutive patients of 65 years and older (group II), also admitted during the same period for angiography for atherosclerosis. In the control group the first symptoms of atherosclerosis had not occurred before the age of 60 years. We excluded patients between the age of 56 years and 64 years to avoid age overlap, so that the assessment of the different risk factors compared with age would be more meaningful. Patients with aneurysmal disease, trauma or other non-atherosclerotic disease, e.g. arteritis, were excluded from the study.

The angiograms of the patients of both groups were reviewed and the extent and distribution of atherosclerotic lesions were noted. The distribution of the lesions were categorised as aortoiliac, femoropopliteal, crural or multi-level when more than one region was afflicted. Carotid lesions and lesions in the intestinal and renal arteries and upper limb were also reviewed. The medical records were examined for medical history, age at onset of ischaemic symptoms and risk factors for cardiovascular disease. The risk factors evaluated were: smoking, hypertension, diabetes, hyperlipidaemia and family history of cardiovascular disease. Hypertension, diabetes or hyperlipidaemia

**Table 1. Univariate and multivariate analysis of risk factors for atherosclerosis in patients with premature atherosclerosis ( $\leq 55$  years of age) and elderly patients with atherosclerosis ( $\geq 65$  years of age)**

Risk factors	$\leq 55$ years	$\geq 65$ years	<i>p</i> -value	Odds ratio	95% confidence interval
Diabetes	11%	27%	0.001	0.44	0.21–0.93
Hypertension	36%	58%	0.001	0.41	0.23–0.71
Smoking	84%	67%	0.002	2.39	1.24–4.62
Hypercholesterolaemia	47%	35%	0.004	1.94	1.11–3.41
Family history	53%	42%	0.008 N.S.	0.87	0.44–1.71

Statistical analysis was performed by the Chi-squared test,  $p < 0.05$  was considered statistically significant.

was considered present if a patient was receiving treatment for this condition. Furthermore, hyperlipidaemia was considered present if the fasting level of cholesterol was  $>6.5$  mmol/l or HDL  $<0.9$  mmol/l or triglycerine  $>2.0$  mmol/l or LDL  $>5.0$  mmol/l, diabetes was considered present if two fasting venous plasma glucose levels were  $>7.8$  mmol/l and hypertension was considered present when the diastolic blood pressure was  $>105$  mmHg on more than three occasions. The family history for cardiovascular diseases was considered positive if one or more first degree relatives were also afflicted. If patients with premature atherosclerosis were evaluated for the presence of hyperhomocysteinaemia, antiphospholipid antibodies or a hypercoagulable state, the results of these tests were also noted.

#### Statistical analysis

Statistical analysis was performed by Pearson Chi-squared test. The Fisher exact test was applied where appropriate. Combinations of parameters were tested by logistic regression analysis. The odds ratios with 95% confidence intervals were calculated. A  $p$ -value of  $<0.05$  was considered statistically significant.

#### Results

The mean age of the 135 younger patients (group I) was 46.2 years with a mean age of onset of atherosclerotic symptoms of 43.1 years. The mean age of the older patients (group II) was 72.6 years, with a mean age of onset of 69.3 years. Table 1 shows the presence of the different risk factors in group I and group II. In both groups an average of 2.3 risk factors per patient was present. The distribution of the atherosclerotic lesions

in both groups is shown in Table 2. Significantly more patients in the older group were admitted for stenotic lesions of the cerebrovascular arteries (32% vs. 8%  $p < 0.0001$ ). When the younger and elderly patients with arterial lesions in the lower extremities were compared, the presence of the different risk factors did not differ from the percentages shown in Table 1. Significantly more younger patients had only lesions at the aortoiliac level (20% vs. 6%  $p < 0.01$ ). Even so, 67% of them had multi-level disease compared to 94% of the elderly.

Since 1994 a methionine loading test has been regularly performed. In 24 (22%) of the 108 patients with premature atherosclerosis the test was positive, indicating the presence of hyperhomocysteinaemia. Hyperhomocysteinaemia was more often associated with hyperlipidaemia ( $p = 0.07$ ) and with hypertension ( $p = 0.09$ ), although this did not reach statistical significance (Fisher exact test). In 1996 testing of the presence of anticardiolipin antibodies in patients with premature atherosclerosis was introduced. In total, 34 patients with premature atherosclerosis were tested, in four patients (12%) either IgG or IgM antibodies were present. Two patients were male and two female. Only one patient (female) did not have a history of smoking. Two of the four patients had a positive family history of cardiovascular diseases. The atherosclerotic lesion was located in the upper extremity in two patients and in the cerebrovascular arteries in one. The fourth patient had an ulcer in the abdominal aorta with stenosis of the coeliac artery and the superior mesenteric artery.

Since 1996 testing for clotting abnormalities was performed; the presence of deficiencies of protein C, protein S and antithrombin III and resistance to activated protein C (APC resistance) were evaluated. Twenty-two patients, in whom a thrombotic component was suspected, were tested. In total a hypercoagulable state was found in four (18%) of the 22 patients tested. One patient had protein S deficiency, a non-smoking male who presented with digital ulceration on his left hand due to occlusion of the ulnar

**Table 2. Distribution of the arterial lesions, stenosis greater than 50%.**

Location	Group I ( $\leq 55$ yrs)	Group II ( $\geq 65$ yrs)	<i>p</i> -value
Aortoiliac	22 (16%)	4 (3.7%)	<0.01
Femoropopliteal	7 (5%)	0	
Crural	8 (6%)	0	
Multi-level	74 (55%)	65 (60.7%)	<0.001
Intestinal	3 (2%)	1 (1%)	
Carotid	12 (9%)	35 (30.7%)	<0.0001
Proximal extremity	9 (7%)	2 (2%)	

Statistical analysis is performed by Chi-squared test. For comparison of the patients with multi-level disease, only patients with peripheral vascular disease were taken into consideration.

artery. There were three patients with APC resistance; in all three patients the lesions were located in the lower extremities. No patients had antithrombin III deficiency or protein C deficiency. None of the patients with a hypercoagulable state had a history of venous thrombosis. Three of the four patients had a positive family history of cardiovascular disease.

### Discussion

In our study the common known risk factors for atherosclerosis were also present in the patients with premature atherosclerosis. An equal number of risk factors was present in patients with premature atherosclerosis and elderly patients with atherosclerosis. This is in contrast to what one might expect, that is that, to develop premature atherosclerosis, more risk factors must be present. However, the prevalence of the different risk factors was significantly different in the two groups. Diabetes and hypertension were significantly more common in the elderly population. This could be expected, as the prevalence of both risk factors increase with age. Patients with premature atherosclerosis tended to have a positive family history for cardiovascular disease. Smoking was significantly associated with premature atherosclerosis. This might be a risk factor that has more effect than others on the progression of atherosclerosis. Our results are consistent with other studies in which smoking has been mentioned as a major risk factor for premature atherosclerosis.<sup>1,3,14</sup> However, this can not explain why 67% of the elderly smoke, yet did not develop symptoms due to atherosclerosis at a younger age. Dyslipidaemia has also been associated with the development of premature atherosclerosis<sup>10,11</sup> and our results support this. Dyslipidaemia can be exacerbated by smoking,<sup>11</sup> which makes the combination of smoking and dyslipidaemia a significant risk factor for the early onset of atherosclerosis. Homocysteinaemia causes atherosclerosis through damage to the vascular wall by the

sulphydryl group of homocystein, which facilitates the formation of hydrogen peroxide, which in its turn facilitates the uptake of low-density lipoprotein by smooth muscle cells.<sup>5,15,29,30</sup> In our study 22% of the tested patients had hyperhomocysteinaemia. This is consistent with the 30% which is noted by Griend *et al.*<sup>15</sup> and the 23% noted by van de Berg *et al.*<sup>31</sup>

An incidence of 30–90% of hypercoagulable states has been reported in patients with premature atherosclerosis, depending on which tests were performed.<sup>2,12–14</sup> It is unlikely that the presence of a hypercoagulable state in itself enhances the progression of atherosclerosis, but one can imagine that an arterial thrombosis is more readily formed in an atherosclerotic artery, which leads a patient with atherosclerosis and a hypercoagulable state to present with symptoms at a younger age. In this study only 22 patients were tested for the existence of a hypercoagulable state, yet 4 (18%) had at least one positive test. Other studies have shown the main abnormalities to be deficiencies of protein S, C and antithrombin III, resistance to activated protein C (APC resistance), mainly due to a mutation in the factor V gene, and the presence of anticardiolipin antibodies. In our study, anticardiolipin antibodies were present in 4 (12%) of the 34 patients tested. The prevalence of all causes of hypercoagulability in a population with premature atherosclerosis is four- to nine-fold higher than in the general population.<sup>2,4,8,12,14</sup> Deficiencies of certain coagulation factors in patients with premature atherosclerosis can be due to consumption of these factors, if the patients are tested in an acute phase of their disease. Only APC resistance has not been associated with premature atherosclerosis. On the contrary, Ouriel *et al.* described the patient population with peripheral vascular disease and APC resistance to be older than the patients without APC resistance, although there was a higher incidence of graft failure in patients with APC resistance.<sup>7</sup> Eldrup *et al.*<sup>14</sup> showed 47% of patients with peripheral vascular disease to have hyperaggregable platelets, yet no incidence in the

general population was reported. As this percentage is extremely high, it calls for further investigation. Until now we have found no other reports on this coagulation defect in patients with premature atherosclerosis.

In conclusion, premature atherosclerosis is significantly associated with smoking and dyslipidaemia. There is a higher incidence of hypercoagulability in patients with premature atherosclerosis compared to the general population, and possibly also a higher incidence of a positive family history of cardiovascular disease. The former seems up until now the most likely cause of a premature onset; however, if hypercoagulability is associated with premature atherosclerosis, it is clinically relevant to know whether a hypercoagulable state is present, as these patients could then be treated with anticoagulants to prevent thrombosis, thus preventing early presentation. A prospective study is therefore necessary.

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