Prevalence of risk factors, coronary and systemic atherosclerosis in abdominal aortic aneurysm: Comparison with high cardiovascular risk population

Alberto Palazzuoli
Maddalena Gallotta
Giuseppe Guerrieri
Ilaria Quatrini
Beatrice Franci
Maria Stella Campagna
Eugenio Neri
Antonio Benvenuti
Carlo Sassi
Ranuccio Nuti

Department of Internal Medicine and Metabolic Diseases, Unit of Aortic Surgery, University of Siena, Italy

Background: Abdominal aortic aneurysm (AAA) is considered a manifestation of atherosclerosis, however there are epidemiologic, biochemical, and structural differences between occlusive atherosclerosis and AAA. The pathogenesis of AAA involves several factors, first of all destruction of collagen and elastin in the aortic wall. Classical risk factors may influence the evolution and development of AAA, though no consistent association has been found. Aims of the study were to evaluate associations between risk factors and to establish the prevalence of carotid, peripheral vascular and coronary atherosclerosis in patients with AAA.
Methods: We studied 98 patients with AAA (Group 1) awaiting surgery compared with high cardiovascular risk population having two or more risk factors (n = 82 Group 2). We evaluated traditional risk factors and we studied by eco-doppler and echocardiography the presence of carotid peripheral and coronaric atherosclerosis in two groups.
Results: We found a higher incidence of AAA in males ($p < 0.01$). The prevalence of infrarenal AAA was significantly higher than suprarenal AAA (81 vs 17 $p < 0.001$). No differences in total cholesterol (199 ± 20 vs. 197 ± 25 mg/dl), low-density lipoprotein (142 ± 16 vs. 140 ± 18 mg/dl), triglycerides (138 ± 45 vs. 144 ± 56 mg/dl), glycemia (119 ± 15 vs. 122 ± 20 mg/dl), and fibrinogen (388 ± 154 vs. 362 ± 92 mg/dl) were found between groups. We demonstrated significant differences for cigarette smoking ($p < 0.002$), systolic and diastolic blood pressure (150 ± 15 vs. 143 ± 14 mmHg and 88 ± 6 vs. 85 ± 7 mmHg, $p < 0.0001$ and $p < 0.05$, respectively) and high sensititivity C reactive protein (2.8 ± 1.3 vs. 1.3 ± 0.7 mg/dl, $p < 0.001$). High-density lipoprotein (HDL) cholesterol levels were significant greater in Group 1 than Group 2 ($p < 0.003$). Subgroups of patients with AAA and luminal thrombus showed higher fibrinogen levels (564 ± 235 vs. 341 ± 83 mg/dl, $p < 0.001$) and lower HDL than in controls (46.6 ± 6.5 vs. 52.1 ± 7.8 mg/dl, $p < 0.01$). We did not find any difference in body mass index, or prevalence of coronary and peripheral atherosclerosis between groups. Conversely, we found higher prevalence of carotid atherosclerosis in Group 2 (9% vs. 25%, $p < 0.004$).
Conclusion: Our AAA patients had fewer and different risk factors respect to patients with atherosclerosis. Only elevated blood pressure, C reactive protein, and smoking showed a significant association with AAA. Atherosclerosis in other arterial districts did not differ respect to subjects with high cardiovascular risk. Our results confirm the hypothesis that AAA and atherosclerosis are two different pathological entities with different risk profiles.
Keywords: aortic aneurysm, risk factors, atherosclerosis, hsC-reactive protein

Correspondence: Alberto Palazzuoli
Department of Internal Medicine and Metabolic Diseases, University of Siena, Le Scotte Hospital, Viale Bracci 1, 53100 Siena, Italy
Tel +39 577 585 363
Fax +30 577 233 446
Email palazzuoli2@unisi.it

Introduction

Abdominal aortic aneurysm (AAA) has high prevalence in the cardiovascular disease and it is considered a manifestation of atherosclerosis. This view has been increasingly questioned in recent years. Although many AAA are associated with conventional risk factors, a causal relation with atherosclerosis has not been confirmed. Most patients

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with cardiovascular disease do not develop AAA, and many AAA patients do not have peripheral carotid or coronary disease (Reed et al 1992).

Though atherosclerosis plays some role in the pathogenesis of AAA, additional processes respect to occlusive atherosclerosis are probably involved, as suggested by histological and macroscopic differences. In comparison to atherosclerosis, vascular tissue in AAA is characterized by high proteolytic activity and greater infiltration of inflammatory cells. Family histories of AAA indicate that genetic factors are also involved (Brophy et al 1991; Mac Sweeney et al 1994).

Several studies have shown that AAA and atherosclerosis have got risk factors such as age, hypertension, smoking, and hypercholesterolemia (Vardulaki et al 2000). Others reports revealed epidemiological differences among coronary and carotid disease and AAA (Alcorn et al 1996; Coggon et al 1996). In line with this, many authors did not found any association with common risk factors except for smoking (Blanchard et al 2000; Vardulaki et al 2000; Singh et al 2001). However, these studies are limited by the short duration of follow-up, small sample size, different inclusion criteria, and little information on risk factors, and epidemiology (Lilenfeld et al 1987). Identification of risk indicators is important to improve stratification, to prevent aortic dilation, and to select appropriate medical or surgical therapy (Alcorn et al 1996; Bengtsson et al 1996). The aims of this study were to investigate the prevalence of AAA in high cardiovascular risk patients, the prevalence of risk factors and AAA, the distribution of infrarenal/suprarenal AAA in patients awaiting surgical treatment. A further aim was to compare cardiovascular risk pattern between AAA population and asymptomatic age-matched subjects having two or more high cardiovascular risk factors.

Materials and methods

A case-control study was performed at Siena University Hospital between June 2003 and December 2006. We recruited 98 patients with AAA (group 1) and 82 control subjects (group 2). The two groups were matched for age, race, and sex. All patients underwent cardiologic examination with electrocardiogram, weight and height measurement, X-ray, and routine blood chemistry including glucose, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, liver and renal function parameters, electrolytes, fibrinogen, hemochrome, and high sensitivity C-reactive protein (hsCRP). They underwent ultrasonographic examination of the abdominal, peripheral, and carotid arterial segments. To assess coronary disease subjects underwent echocardiography stress examination with dipyridamol (Picano 2004) Patients with AAA also underwent computed tomography (CT) examination to assess intraluminal thrombosis and aortic transverse diameter.

Biochemical laboratory assessment

All blood samples were taken after a minimum 4-hour fast. Venous blood was taken in ethylenediaminetetraacetic acid (EDTA) tubes. The plasma samples were snap-frozen within 1 hour to −20° C and stored at −80° C within a week. All EDTA plasma for analyses were thawed and analyzed at the same time. LDL and HDL cholesterol concentrations were measured by direct, homogeneous assays based on detergent treatment of the serum (N-geneous HDL-c and N-geneous LDL reagents, respectively, from Genzyme Corp, Cambridge, MA, USA). hsCRP was measured by a latex-enhanced immunoturbidimetry assay (Tina-quant CRP [Latex] HS, Roche Diagnostics GmbH, Mannheim, Germany). Plasma fibrinogen levels was measured by the Clauss modified method with coagulomether (Behring Diagnostics, Marburg, Germany).

Cardiovascular risk factors

Body mass index (BMI) was calculated as weight divided by the square of height (kg/m^2). Blood pressure was recorded during cardiological examination in a quiet room after five minutes rest in sitting position; three measures were made at 2 minute intervals (oscillometric method, Colin Meter, Germany). Hypertension was defined as systolic blood pressure 140 mmHg or higher and/or diastolic blood pressure 90 mmHg or higher in the absence of self-reported use of antihypertensive therapy, and treated hypertension was defined as self-reported physician-diagnosed hypertension under treatment.

Hyperlipidemia was defined as cholesterol total higher than 240 mg/dl; LDL cholesterol higher than 140 mg/dl, and HDL cholesterol lower than 35 mg/dl.

Diabetes mellitus was defined as nonfasting plasma glucose levels higher than 126 mg/dl or use of oral antidiabetic drug or insulin.

Smoking history was defined as greater than or equal to 100 cigarettes/year. Patients were considered to have hypertension, hypercholesterolemia, or diabetes if they had been given these diagnoses by a physician or were treated for these conditions.

Examinations

Abdominal ultrasonographic examination of the abdominal aorta was performed by two blinded physicians. Subjects

lay in supine position and/or in their left side if necessary. A 3.5 MHz sector probe (5500 SONOS Hewlett-Packard) was used. The abdominal aorta was first visualized in the longitudinal plane from the diaphragm to the iliac bifurcation. The aorta was studied in the axial plane with scans perpendicular to the previous ones. Longitudinal and transverse aortic diameter was measured at the renal arteries, 5 cm distally, and at the bifurcation. Transverse wall thickness and endoluminal diameter were measured. In the case of AAA with mural thrombus true and false lumen diameter were also measured. All AAA patients were also submitted to abdominal CT to evaluate vessel lumen and parietal thining.

Echocardiographic examination was performed under baseline conditions and during infusion of dipyridamol, atropine according to American Society of Echocardiography criteria (Schiller et al 1989). Stress echocardiography was performed by dypiridamol and atropine infusion at standard doses with electrocardiogram (ECG) recording; it was stopped if clinical, echographic, or electrocardiographic alterations occurred. All scans were evaluated in apical, four and two chambers, and longitudinal and short parasternal views by two experienced physicians.

The vascular and carotid ultrasonographic examinations were performed using either an ATL HDI 3000 or 5000 (Philips Medical Systems, Monza, Italy). Information obtained from color-flow/B-mode imaging and Doppler spectral waveform analysis from the distal aorta to the pedal arteries was used to draw a schematic color-coded map of the arterial tree. The arteries were scanned in cross and longitudinal sections using scanheads of 3–2, 5–2, 7–4, and 10–5 MHz extended operating frequency range. The arterial segments evaluated were classified as normal or mildly diseased (less than 50% narrowing), significantly stenosed (greater than 50%), occluded, or not visualized. Focal stenosis was graded based on B-mode imaging of the plaque and residual lumen in cross section, whenever applicable, presence of color flow disturbances, and velocity spectral waveform analysis. A peak systolic velocity (PSV) ratio greater than 2 was used to tell hemodynamically significant (>50%) from hemodynamically insignificant stenosis. Long arterial narrowing (residual lumen <50% of the actual artery diameter) in diffusely diseased arterial segments was also observed based on B-mode/color-flow imaging. Presence of intraluminal echoes and absence of color flow confirmed artery occlusion. Iliac disease was assessed by direct ultrasonographic visualization and by observation of common femoral artery (CFA) waveform abnormalities in the spectral window, number of phases, and acceleration time (>140 ms considered abnormal). For the scanning protocol, the test starts with femoral arteries scanning and is followed by the popliteal artery examination. The popliteal artery is scanned both from the medial and posterior approaches. The tibioperoneal trunk, peroneal, and anterior tibial arteries are examined in lateral decubitus. The aorta, iliac, posterior tibial, dorsalis pedis, and common plantar arteries are scanned after returning the patient to the supine position.

B-mode real-time ultrasound was performed in blind, evaluating the arterial stenosis in the carotid arteries with a probe of 7.5–10.0 MHz. Patients were examined in the supine position and each carotid wall or segment was examined. Each scan of the common carotid artery began just above the clavicle, and the transducer was moved until the carotid bifurcation and along the internal carotid artery. Three segments were identified and measured in antero and posterior planes on each side: the distal 1.0 cm of the common carotid proximal to the bifurcation, the bifurcation itself, and the proximal 1.0 cm of the internal carotid artery. At each of these sites we detected any possible plaque. Carotid lesions were considered pathological if they were higher than 50% of the vascular lumen or have peak velocity more than 100 cm/sec. Intra-observer coefficience of variance was 5% and inter-observer coefficience of variance was 10%.

Inclusion criteria

AAA subjects were enrolled if they had transverse aortic dilation >4.5 cm and no history of cardiovascular disease. All were elegible for surgery due to aneurysm dimensions. This group also underwent computed tomography. The control group consisted of age-matched subjects referred to the Cardiology Laboratory of our Department with at least two risk factors but without clinical evidence of atherosclerosis diseases such as coronary heart disease, peripheral arterial disease. Subjects gave written informed consent and the study was approved by the Ethical Committee.

Exclusion criteria

Patients with previous vascular or cardiac events such as myocardial infarction, angina, claudicatio intermittens or stroke, aortic dissection or dissecting aneurysm were excluded. Subjects with neoplastic, immunological, liver, or kidney disease were also excluded. Patients with Marfan syndrome were excluded.

Results

Of the 98 patients in group 1, 76 were males and 22 females. Of these patients, 81 had infrarenal and 17 suprarenal AAA ($p < 0.001$). 45% had endoluminal thrombus. Mean

transverse diameter of aneurysms was 5.4 cm (4.8 for suprarenal and 5.9 for infrarenal) (Table 1). Of the 82 patients in group 2, 50 were males and 32 females (mean age in both group 74 ± 8, range 62 to 87 years).

The frequency of peripheral vasculature disease was similar in the two groups: 15 (19%) controls and 19 (20%) AAA patients.

The incidence of coronary disease evaluated by stress-echo test was similar in both groups: 17 (23%) in controls, 25 (26%) in AAA patients (NS). Patients with AAA showed less evidence of carotid atherosclerosis than controls: Group 1 9 patients (9%), 18 controls (25%), ($p < 0.004$) (Figure 1). Two patients in the control group had recruited AAA (mean diameter infrarenal 4.5 cm).

No significant differences in BMI was found, both groups showing high frequency of first degree obesity (Controls 28 ± 3.6, Group 1 29 ± 3.8 kg/m^2). The percentage of patients with cholesterol over 200 mg/dl was 33% in Group 1 and 35% in controls (199 ± 20 and 197 ± 25 mg/dl, respectively NS). Likewise no differences were found for LDL cholesterol (Group 1 142 ± 16 vs. Group 2 140 ± 18 mg/dl NS), or blood glucose (Group 1 119 ± 15 vs. Group 2 122 ± 20 mg/dl NS). Significant differences regarding hsCPR were found: Group 1 2.8 ± 1.3 vs. Group 2 1.3 ± 0.7 mg/dl ($p < 0.001$).Triglyceride levels were not significantly different in the two groups (Group 1 138 ± 45 vs. Group 2 144 ± 56 mg/dl NS). HDL cholesterol levels were significantly greater in Group 1 than in controls (Group 1 52.1 ± 7.8 vs. Group 2 47.5 ± 6.5 mg/dl, $p < 0.003$). On the contrary HDL level was significantly less in AAA subgroup associated with wall thrombosis than in AAA without thrombosis (46.6 ± 6.5 vs. 52.1 ± 7.8 mg/dl, $p < 0.01$) (Figure 2).

Significant differences in systolic and diastolic blood pressure were found: Group 1 150 ± 15 vs. Group 2 143 ± 14 mmHg ($p < 0.001$) and Group 1 88 ± 6 vs. Group 2 85 ± 7 mmHg ($p < 0.05$). When patients were divided into two groups according to blood pressure cut-off of 140/90 mmHg, 42% of controls and 71% of AAA patients had hypertension ($p < 0.0006$). Past or present cigarette smoking was more frequent in AAA patients: Group 1 59(66%) Group 2 31 (40%) ($p < 0.002$) (Table 2).

Fibrinogen levels was similar in both groups (Group 1 388 ± 154, Group 2 362 ± 92 mg/dl, NS). When Group 1 was divided into two subgroups, with wall thrombosis (n = 46) and without, the thrombosis subgroup demonstrated higher fibrinogen levels (564 ± 235 vs. 341 ± 83 mg/dl, $p < 0.0001$) (Figure 3).

Table 1 Clinical and structural characteristics of patients with abdominal aortic aneurysm (AAA) and controls

	Group 1	Group 2
Number of patients	98	82
Male/Females	76/22	50/32
Age	74 ± 8	74 ± 8
Infrarenal AAA	81	2
Suprarenal AAA	17	
Mean transverse diameter (infra/super-renal)	5.4 (5.9/4.8)	4.5 ± 0.3
% of endo luminal thrombus	45%	

Discussion

Occlusive vascular disease and AAA are considered manifestations of the same atherosclerotic process, however there are many differences in pathophysiology and morphology between the two diseases (Louwrens et al 1993; Patel et al 1995). Traditionally, atherosclerosis is characterized by increase in plaque volume due to growth of the lipid core into the vessel lumen and migration of smooth muscle cells and macrophages, leading to endothelial dysfunction, increase in intima-media thickness, and wall thickness. On the other hand, aneurysm involves dilation of all layers of the artery wall: parietal deterioration is due to loss of elastin and smooth muscle cells. Biochemical studies of possible genetic causes have focused on structural defects in aorta matrix proteins, overactive proteolysis and impaired homeostasis of collagen (Cannon and Read 1982; Brophy et al 1991; Cohen et al 1992). Steinberg and colleagues (2000) recently demonstrated different inflammatory responses in the two diseases with elevated cytokine levels in AAA. There have been large prospective studies about the relationships between cardiovascular disease risk factors and AAA, and most of them are limited by small statistical samples, short follow-up, different inclusion criteria, and different definitions of AAA (Lilienfeld et al 1987; Blanchard et al 2000; Singh et al 2001). All these problems could explain the different results reported by observational studies. Several population-based studies have established male gender, age, smoking, and a family history of AAA as independent risk factors for AAA (Louwrens et al 1993; Blanchard et al 2000; Jamrozik et al 2000; Singh et al 2001). Although several studies revealed a strong association between AAA and atherosclerotic diseases (Simoni et al 1995; Blanchard et al 2000; Jamrozik et al 2000; Singh et al 2001), reports on possible associations between AAA and established risk factors for atherosclerosis such as hypercholesterolemia and hypertension have shown different results (Patel et al 1995; Simoni et al 1995; Jamrozik et al

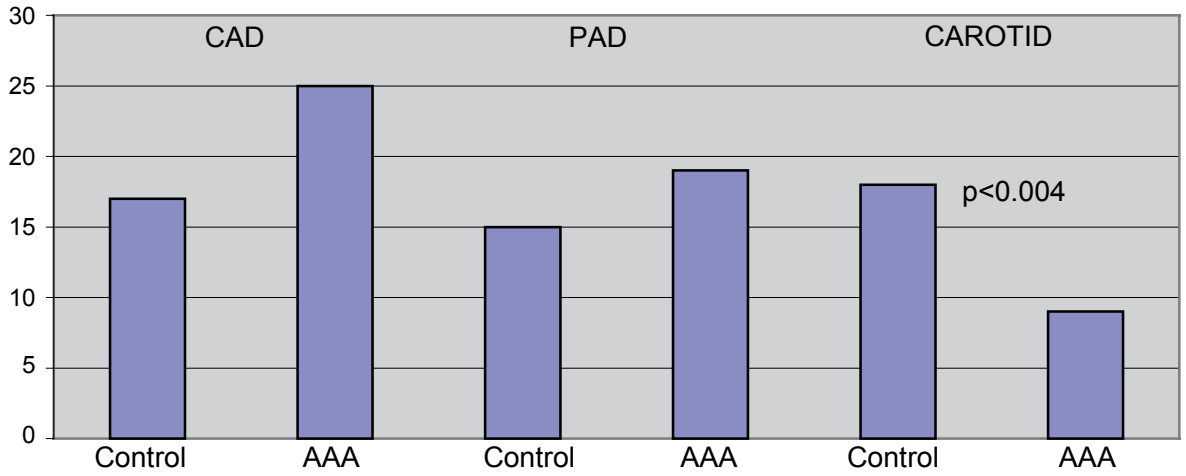

Figure 1 Prevalence of carotid disease (CAROTID), peripheral arterial disease (PAD), and coronary artery disease (CAD) in the two groups.

2000; Singh et al 2001). Histological and epidemiological differences between AAA and atherosclerosis have further challenged the traditional theory that AAA is a manifestation of atherosclerosis (Lilienfeld et al 1987; Louwrens et al 1993; Satta et al 1998; Singh et al 2001).

Data in the literature regarding the relationship between AAA and cholesterol levels are contradictory. In a large screening study, the ADAM study (Lederle et al 2000), high cholesterol levels were independently associated with AAA in a multivariate analysis including atherosclerosis. Simoni and colleagues (1995) showed a relationship between lower HDL cholesterol levels and AAA, but no difference was observed in LDL cholesterol or total cholesterol levels. In the Tromso study, a highly significant relation between low HDL cholesterol and the risk of AAA was found (Singh et al 2001). We did not show a significant association with serum lipids (LDL cholesterol and triglycerides), which may be due to the high risk comparison group: indeed, we analyzed AAA in a late stage when alterations in serum lipids could not be directly involved in the pathogenesis (Lee et al 1997). Curiously, low HDL levels were significantly associated to thrombotic aneurysms, probably due to elevated lipoprotein consumption and turnover. Our findings appear in accordance with Simoni and colleagues (1995) and ADAM study data, which reveals an association with HDL cholesterol. Patients with AAA and parietal thrombus also had high fibrinogen levels in respect

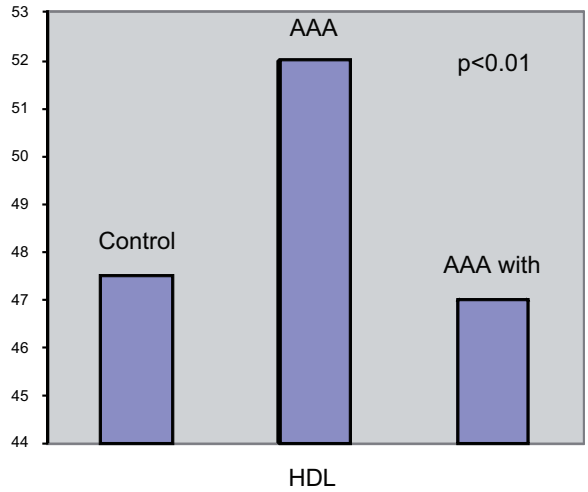

Figure 2 HDL cholesterol difference in AAA with and without thrombus and in controls.
Abbreviations: AAA, abdominal aortic aneurysm; HDL, high-density lipoprotein.

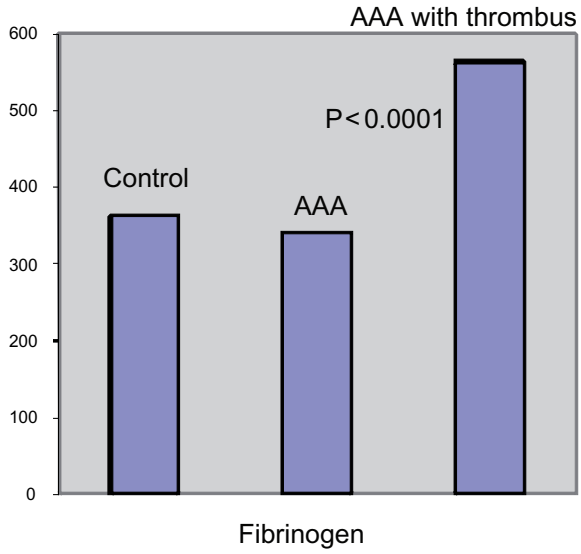

Figure 3 Different levels of fibrinogen in AAA with and without thrombus and in controls.
Abbreviation: AAA, abdominal aortic aneurysm.

Table 2 Association between classical risk factors in abdominal aortic aneurysm (AAA) subjects and in controls with two or more risk factors

Risk factor	Control group	AAA group	p
Peripheral vascular disease	15 (19%)	19 (20%)	n.s.
CAD	17 (23%)	25 (26%)	n.s.
Carotid atherosclerosis	18 (25%)	9 (9%)	<0.004
BMI	28 ± 3.6	29 ± 3.8	n.s.
Total cholesterol	197 ± 25	199 ± 20	n.s.
Cholesterol > 200 mg/dl	35%	33%	n.s.
LDL cholesterol	140 ± 18	142 ± 16	n.s.
HDL cholesterol	47.5 ± 6.5	52.1 ± 7.8	<0.003
Tryglicerides	144 ± 56	138 ± 45	n.s.
Diabetes	122 ± 20	119 ± 15	n.s.
hsCRP	2.8 ± 1.3	1.3 ± 0.7	<0.001
Systolic BP	143 ± 14	150 ± 15	<0.001
Diastolic BP	85 ± 7	88 ± 6	<0.05
BP > 140/90	42%	71%	<0.0006
Smoking	31 (40%)	59 (66%)	<0.002
Fibrinogen	362 ± 92	388 ± 154	n.s.

Abbreviations: CAD, Coronary Disease; BMI, Body Mass Index; hsCRP, high sensivity C-Reactive Protein; BP, Blood Pressure.

to controls groups. Both findings may explain at least in part the pathophysiological mechanism: fibrin binds to lipoproteins and sequesters more fibrinogen in the vascular intima, enhancing their accumulation. Fibrinogen is also an essential component of platelet aggregation, increasing plasma viscosity, and it is correlated with fibrin levels in clots (Heinrich and Assmann 1995).Many studies found hypertension to be associated with AAA (Jamrozik et al 2000; Vardulaki et al 2000). In line with this data, we found a correlation with both elevated diastolic and systolic blood pressure. The mechanism leading to the development of aortic enlargement is related to increased wall tension according to Laplace's law. Hypertension increases wall stress, altering elastin and collagen, causing wall thickening, and precipitating aneurysm formation (Naydeck et al 1999; Rodin et al 2003).

Smoking has consistently been associated with AAA (Lee et al 1997; Jamrozik et al 2000; Lederle et al 2000; Törnwall et al 2001) and several studies have found a dose-response relationship suggesting a causal role for smoking in the etiology of AAA. Smoking per se promotes atherosclerosis, and may also upset protease/antiprotease balance and occlude the vasa vasorum in this tract where the vascularization is reduced with respect to the district of the thoracic aorta (Cannon and Read 1982; Louwrens et al 1993; Lee et al 1997; Lederle et al 2000). Lawlor and colleagues (2008) emphasized the role of smoking as a major risk factor for cardiovascular diseases in populations with low cholesterol levels.

HsCRP has recently emerged as a strong independent risk factor for atherosclerosis and atherosclerosis-related complications in apparently healthy individuals and patients with cardiovascular disease (Ridker et al 1997; Lagrand et al 1900). Powell and colleagues (1987) showed that, among patients undergoing elective aortic reconstruction, serum hsCRP was elevated in AAA patients compared with patients with obstructive disease. The elevation of hsCRP was equally pronounced in small and large AAA, indicating an inflammatory process in the early pathophysiologic phase of AAA. These findings corroborate the notion that CRP up-regulation is a reaction to several types of tissue injury. Macrophages and smooth muscle cells might be the producers of 'vascular' CRP (Yasojima et al 2001).

No differences were found in carotid and peripheral atherosclerosis between groups: carotid disease seemed less frequent in the AAA group compared with the high risk group.

A similar study reveals that mean carotid intima-media thickness in AAA patients was similar to healthy subjects and significantly lower than patients affected to peripheral atherosclerosis. The findings support the notion that the formation of AAA is not fully atherosclerosis-dependent (Cheuk et al 2007).

These data appear consistent with those of SMART, which did not show a strict correlation between significant carotid stenosis in a large population study (Simons et al 1999).

AAA patients had fewer and different risk factors respect to patients with atherosclerosis. Only elevated blood pressure and smoking showed a significant correlation with AAA. Atherosclerosis in other districts appears similar respect to high cardiovascular population.

Conclusions

In conclusion, the present study demonstrates that AAA and atherosclerosis differ in certain pathophysiological aspects and risk factors. However risk factors such as hypertension and cigarette smoking and hsCRP, could negatively promote further dilation. Cardiac, peripheral, and carotid vascular ultrasonography study demonstrated different risk profiles in the two diseases. Further studies into other potential risk factors, such as inflammation, autoimmunity, and genetics, may be warranted.

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