Background: The development of abdominal aortic aneurysm (AAA) is probably influenced by many factors. The role of some of these factors, such as intraluminal thrombus (ILT) or cystatin C serum levels, remains controversial. Proving their influence could have therapeutic implications for some patients with AAA. Associations between the rate of increase in diameter of an aneurysm and ILT, as well as other factors, including biochemical factors (C-Reactive Protein – CRP, cystatin C), age, sex, and comorbidities, could predict disease progression in individual patients.

Material/Methods: Seventy patients with small AAA were included into the study. The patients were followed using ultrasound and CT imaging. We evaluated aneurysm dimensions and aneurysm wall thickness, as well as ILT and its dimensions, aneurysm wall morphology, CRP, and cystatin C.

Results: We observed significant growth of AAA and thinning of aneurysmal wall. Aneurysms over 4 cm grew significantly faster in the second year of observation. ILT grew together with AAA size. Age, sex, smoking, dyslipidemias, or controlled arterial hypertension had no influence on aneurysm progression rate. Changes in serum of CRP concentration did not reach statistical significance, but cystatin C levels did.

Conclusions: Presence and size of ILT, wall thickness, and cystatin C levels may be considered in prediction of AAA progression. ILT might exert a protective influence on the risk of aneurysm rupture. However, larger aneurysms containing larger thrombi grow faster and their walls undergo more rapid degradation, which in turn increases the risk of rupture. This matter requires further studies.

MeSH Keywords: Aortic Aneurysm, Abdominal • C-Reactive Protein • Cystatin C • Aortic Rupture

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Background

Atherosclerosis and arterial hypertension are diseases of modern civilization. Amongst other serious complications, these disorders lead to a tendency to form segmental arterial dilatations known as aneurysms. Most aneurysms develop after the 6th–7th decade of life, which coincides with the degeneration of structural components in arterial walls. The problem is increasingly prevalent in ageing populations. The aorta, its abdominal part in particular, is at greatest risk of aneurysmal dilatation.

The specific etiology of aneurysm of abdominal aorta (AAA) has not been yet determined. One of newer definitions describes AAA as a particular, localized form of thrombosis on an atherosclerotic background [1]. Inflammatory reaction to Chlamydia pneumoniae or Listeria monocytogenes infection within the aneurysmal wall is also implicated in development of some AAAs (due to proteolysis of the vascular wall mediated by proteases released by mastocytes) [2,3]. However, the relationship between AAA progression and abnormalities of matrix components, mainly elastin (its deficiency as well as structural defect) and collagen, is indisputable [4,5]. There is also a known correlation between AAA and changes in concentrations of metalloproteinase inhibitors [4,6–10].

Familial occurrence of this pathology is diagnosed in 25% of patients with AAA [11]. Many authors also underscore the influence of comorbidities such as hypertension or smoking on the development of aneurysms [12].

AAA is a potentially lethal disease due to the risk of spontaneous rupture and massive internal hemorrhage, which is the main and most serious complication. In such cases, mortality ranges between 70% and 80% according to various sources [11]. It seems particularly important to identify the natural course of this disease and influencing factors in order to offer optimal treatment at the most appropriate time.

This study aimed to analyze the influence of factors such as intra-luminal thrombus (ILT) and biochemical markers (including cystatin C and CRP), as well as demographics and comorbidities, on the natural history of small AAA. In this article we examine the usefulness of these factors in the prognosis of AAA growth.

Material and Methods

Seventy patients with abdominal aortic aneurysms of less than 5 cm in diameter were included in the study in the period 2005–2010. They were recruited in the Vascular Surgery outpatient clinic of the Department of General and Thoracic Surgery, Medical University of Warsaw. Each patient had a computed tomography examination performed once every three months. There were 58 patients (48 men and 10 women), who remained in follow-up and were examined no less than 3 times, with no indications for surgical intervention. The remaining patients were referred for surgery due to the aneurysm reaching an operable size (5 cm diameter) or rapid growth, or were excluded from the study for other reasons (illness, withdrawal of consent, etc.). Age of men ranged between 55 and 88 years (mean: 71.7 years).

Women were aged between 64 and 78 years (mean: 73.4 years). Ultrasound examination of abdominal aorta was the standard method for determining the following parameters: transverse and sagittal diameters of the aneurysm, wall thickness, presence of intra luminal thrombus (ILT) and its dimensions.

Patient had CRP and cystatin C levels measured every six months. Serum levels of those proteins may be used for monitoring of disease course. Ultrasound examinations were performed at three-month intervals on average, interims not exceeding six months (TOSHIBA SSA-340A and TOSHIBA NEMIO SSA-550A device, convex probe). Whenever ultrasound gave equivocal results, the aneurysm was found to reach a diameter over 5 cm or growth rate exceeded 1 cm/year, the patient underwent a computed tomography examination. Other than assessment of morphological changes, we also took into consideration the data on vascular comorbidities and risk factors for their development (arterial hypertension, diabetes, dyslipidemia, and smoking) as well as medication administered to patients at the time. Among 70 patients included in the study, 19 subjects were referred for surgery at the Department of General and Thoracic Surgery. Out of this group, 18 patients underwent an endovascular aneurysm repair and one patient had an open surgery.

Among all patients included in the program we did not observe any deaths in the course of follow up, either during surgery or due to spontaneous rupture. It was necessary to narrow the study group down to 25 for the purpose of performing a proper statistical analysis of variance for such parameters as maximal transverse diameter of an aneurysm, ILT thickness or thickness of diseased vessel, as only in this group of patients we could use the same time intervals for control visits (both ultrasound and biochemical).

Follow-up time was 2 years and results of control examinations performed at 6-month intervals were selected for analysis.

Distributions of variables were analyzed with a Lilliefors test. Depending on the results, the further analysis applied parametric tests for repeated measures based on analysis of variance (ANOVA) or their nonparametric counterparts. A Chi square test corrected for subgroup size was used for percentage data.
For analysis between groups we used nonparametric U-Mann-Whitney test. Correlation and regression analysis was performed using Spearman or Pearson coefficient depending on a distribution of the data. In all cases \( p < 0.05 \) was considered statistically significant.

**Results**

In the analyzed group of 25 patients, the initial maximal transverse diameter of the aneurysm ranged between 31 and 46 mm (mean: 39 mm). The greatest final diameter (after 24-month follow-up period) transverse ranged from 31 mm to 55 mm (mean: 43 mm).

Increase in aneurysm diameter in time was significant \( (p < 0.0001) \) as depicted in Figure 1.

Thickness of diseased aortic wall changing over time with increasing transverse diameter of an aneurysm was another parameter subjected to analysis \( (p = 0.004) \). Figure 2 represents these changes in the study population.

ILT size changes over time were highly significant over the course of the study \( (p < 0.008) \). Values noted in initial measurements oscillated between 0 and 26 mm (mean: 9.7 mm). However, after 24 months ILT growth within aneurysmal sac was apparent (values ranged from 0 to 29 mm, mean: 14.3 mm). Figure 3 depicts observations described above.
Age of patients had no influence on dynamics alterations such parameters like wall thickness (p=0.08) and size of ILT (p=0.48) Figure 4.

In order to examine the dynamics of changes depending on aneurysm diameter patients were divided into two groups: with aneurysm diameter not exceeding 4 cm and over 4 cm. These groups were compared with respect to thickness of diseased aortic wall and growth of ILT. Statistical analysis revealed that aortic wall loses its thickness to the same extent (no significant differences in aneurysmal wall thickness) regardless of the degree of aortic dilatation. A trend was also noted for larger thrombus in patients with aneurysms larger than 4 cm, without reaching statistical significance.

We also compared changes with regard to increase in aneurysm maximal transverse diameter and aneurysmal wall thickness in the first and the second year of observation, noting no significant difference. Similar observations are true for aneurysmal wall thickness.

Comparison of changes in the above-discussed parameters (diameter, wall thickness, and ILT) in the first and the second year of study was also performed for aneurysms with maximal diameter less than and over 4 cm. We saw a rapid increase in transverse diameters of larger aneurysms (over 4 cm in diameter) in the second year of follow-up (Student’s t-test p=0.04).

Changes in smaller and larger aneurysms with respect to the remaining parameters in the first and the second year of study were not statistically significant. Interestingly, no statistically significant relationship was noted between age, sex, presence of arterial hypertension (controlled), abnormalities of lipid metabolism or smoking and size of the aneurysm (diameter less than or over 4 cm). Thus, AAA growth was the same in both groups independently of the above-mentioned factors. Aside from AAA morphological parameters we also examined selected biochemical factors, which could potentially be of significance for disease progression. Serum concentrations of CRP – one of acute phase proteins, and cystatin C – one of cysteine protease inhibitors, were measured in all patients from the study group. Changes in CRP levels did not reach statistical significance; therefore one cannot draw any prognoses with regard to natural course of the disease based on this parameter. On the other hand serum cystatin C levels clearly increase in time in correlation with aneurysm growth (p=0.04), Figure 5. There was also noticed significant relation between changes of cystatin C levels and patient’s age. The older patient the greater increasing of cystatin C concentration (p=0.04) Figure 6. Moreover, it was noted that increase in serum cystatin C level in the second year of observation is greater in case of rapidly growing aneurysms (increase in diameter 5–9 mm per year) Figure 7.
Discussion

The relationship between maximal aneurysm diameter as well as increase in its transverse diameter and risk of rupture is a widely accepted fact, which does not raise any controversies [11–16]. Average rate of growth in a population ranges between 2.5 to 4 mm per year depending on the source. Untreated aneurysm increases in diameter, which may result in spontaneous rupture and pose an immediate threat to life. The role of ILT and its significance for natural history of AAA is not clear. Ene et al. undertook this matter in their publication [17]. Pressures and diameters were considered for silicone models with and without ILT, which was located at various sites within an AAA. Thrombi reduced wall compliance (depending on ILT characteristics). Reduced wall strain and compliance was observed in AAA areas of maximal ILT thickness (beside soft ILTs). Shifting of maximal strain and compliance to proximal part of aneurysmal neck resulted in increased ILT stiffness, leading to development of potential rupture site. Our premises did not include analysis of AAA wall compliance and strain values depending on the presence and morphology of ILT. There were no observed cases of spontaneous aneurysm rupture. Relationship between ILT and risk of AAA rupture was also emphasized by Stenbaek et al. [16], who analyzed the correlation between maximal aneurysm diameter, ILT surface area in small (up to 5 cm in diameter) AAAs and relative risk of rupture (rupture itself or threatening rupture). The authors suggest that rapid increase in ILT thickness is a good, or even better predictor of AAA rupture than transverse and sagittal diameter alone. Material gathered by the authors of this publication did not include any cases of spontaneous rupture and it would be difficult to document such correlation. However, there is a tendency for increase in ILT thickness over the course of the disease. It is significantly bigger in aneurysms over 4 cm in diameter. Geogakarakos et al. studied the influence of ILT on maximal values of peak wall stress (PWS) in abdominal aortic aneurysm [18]. It was determined that patients with larger AAAs were characterized by greater PWS values than those with smaller AAAs. However, the sole occurrence of ILT resulted in reduction of PWS value. Moreover, a strong correlation between ILT volume and degree of PWS reduction was apparent in a group of smaller AAAs. It was not observed for larger aneurysms. The above mentioned results indirectly indicate a protective role of ILT in the natural course of the disease, particularly in small aneurysms. In this work, results indicate that the size of ILT increases in aneurysms of greater diameters. Moreover, no cases of AAA rupture were noted and all surgeries were elective. Therefore, it supports the hypothesis regarding protective role of ILTs, although not unequivocally. Speelman et al. [15] studied the mechanical role of ILT and its correlation to the rate of AAA growth. They calculated wall strain with or without a thrombus. Moreover, they compared the rate of increase in diameter of AAA containing small or large ILTs. Presence of ILT decreased AAA wall strain. The greater the ILT the more apparent was the effect. However, presence of larger ILT was related to significantly faster increase in AAA diameter. Authors conclude that weakening of AAA wall by thrombus may play a greater role in AAA growth than wall strain. Results obtained by the authors of this publication may corroborate the observation that AAAs with large ILTs grow faster (ILTs were significantly larger in larger AAAs).

Work by Coutard et al. presents a different view on the ILTs, describing biological activity of aneurysmal wall, which is stimulated by ILT through release of, among other things, matrix metalloproteinase – 9 (MMP9) and MMP2 into AAA wall [19]. After conducting detailed studies it was shown that ILT secreted significantly more MMP9 than the wall itself. Secretion of MMP2 remained at the same level. Authors suggest that ILT may contribute to AAA progression through its influence on proteases within aortic wall. No evidence of protective role of ILT in the natural history of the disease was noted in our material. Presence of ILT did not reduce the rate of AAA diameter growth (progression of wall degradation). In larger (>4 cm) aneurysms there was a larger increase in diameter over time than in those not exceeding 4 cm. Larger ILTs were seen in larger aneurysms. An interesting study on the influence of ILT on AAA wall, its relationship to local oxygen deficiency in particular, was presented by Vorp et al. [20]. They performed quantitative assessment of oxygen-regulated protein (ORP) expression (a marker of cellular hypoxia). Measurements of PO2 in subjects with large ILTs and augmented ORP expression in comparison to patients with small ILTs provide the evidence of wall hypoxia, as does the presence of wall inflammation and neovascularization in the first group. As previously mentioned, there were no cases of aneurysm rupture in our study material, while increase in AAA diameter was accompanied by increased ILT thickness with simultaneous acceleration of aneurysm growth in its transverse diameter. That would suggest lack of protective role of ILT on the risk of rupture. Another study implying a relationship between presence of ILT and weakening of aneurysmal wall, thus disease progression is the work by Koole et al. [21]. Authors based their assumptions on results of earlier in vitro experiments showing that ILT connected with vascular wall releases proteolytic enzymes, leading to local hypoxia and destruction of aortic wall structure. Obtained results indicate that with increasing ILT thickness decreases the number of smooth muscle cells and elastin fibers in middle layer of the aorta. It is the evidence for severe apoptosis of myocytes and degradation of elastin fibers that, together with increased metalloproteinase 2 activity, that implies AAA wall destruction by ILT contributing to disease progression. As previously emphasized, topic of this work focused on the correlation between selected biochemical parameters, such as CRP and cystatin C, and the disease. At the background was the assumption that cystatin C deficiency facilitates AAA wall proteolysis, contributing to its degradation and thus,
disease progression. However, the direct role of this cysteine protease inhibitor in progression of AAA has not been confirmed. Schulte et al. created a murine model of AAA (induced by angiotensin II) with cystatin C deficiency [22]. In this case transverse diameters of aneurysms were increased compared to control mice (without protease inhibitor deficiency). Cystatin C deficiency augmented cysteine protease activity and inflammatory processes. In this study, cystatin C levels in peripheral blood increased with aneurysm growth. It could have been due to increased synthesis of this inhibitor in response to augmented activity of cysteine protease and thereby, disease progression. Significance of the equilibrium between cysteine proteases and their inhibitors (cystatin C) in the process of aneurysm development was also noted by Sukhova et al. [4]. They created a murine model characterized by cystatin C and apolipoproteinase E deficiency. Increased fragmentation of elastin fibers in tunica media leading to loss of its thickness was noted in the absence of cystatin C. Abdominal and thoracic aortic dilatation in comparison to control group was also noted. In conclusion, one may infer that low cystatin C level is one of the factors facilitating the process of aortic dilatation. In this study serum cystatin C levels were also rising with increasing transverse diameter of the aneurysm. It might be explained by enhanced production of this inhibitor in order to prevent aortic wall degradation. Studied patients were most likely not suffering from congenital cystatin C deficiency. Lindholt et al. drew similar conclusions as Sukhova et al. [23]. Blood samples were obtained from 142 men aged 65–73 years with small AAAs over a period of approximately 2.9 years. Levels of CRP, creatinine and cystatin C were measured. It was determined that cystatin C levels correlate negatively with mean rate of AAA growth. This dependence was not noted for creatinine and CRP. In our publication these relationships were similar for CRP and opposite for cystatin C. In their project, Tambyraja et al. examined preoperative serum levels of CRP, white blood cells (WBC), platelets, fibrinogen and albumin in 112 patients undergoing elective or urgent surgery for AAA [24]. Significantly higher CRP and WBC levels were noted in a group of patients with ruptured or symptomatic aneurysms (higher fibrinogen levels were noted in this group of patients as well) compared with asymptomatic patients. Interestingly, significantly elevated CRP levels with low WBC were observed in symptomatic patients, but not in patients with ruptured aneurysms. Authors conclude that symptomatic and ruptured AAAs are associated with early elevation of markers of systemic inflammation. Results of our study do not corroborate these observations. No significant increase in CRP level was noted in the course of the study, thus there was no correlation between level of this protein and increase in transverse AAA diameter. Domanovits et al. produced a consolidative publication on the relationship between acute phase factors and progression of AAA [25]. They compared inflammatory markers, such as CRP and WBC, in patients with asymptomatic, symptomatic and ruptured aneurysms. Statistical analysis revealed that patients with symptomatic and ruptured AAAs levels of CRP and WBC were significantly higher compared to asymptomatic subjects. In our work, on the other hand, statistical analysis examining the association between CRP and increase in transverse diameter of AAA did not corroborate such correlation. Sweeting et al. conducted a meta-analysis of factors individual for each patient, other than maximal transverse diameter, such as demographics, medical history, or patient medication, which might be related to or influence growth and rupture of small aneurysms (3.0–5.4 cm). Mean increase in aneurysm diameter was independent of patient sex. Rate of growth was faster among smokers and slower among diabetics. Mean blood pressure did not influence AAA growth and neither did antihypertensive medication. Risk of spontaneous rupture was fourfold higher in women, twofold higher in smokers and increased with blood pressure elevation. Our analysis also did not confirm the influence of sex on the course of the disease. Smoking did not produce a difference with respect to the rate of disease progression in both groups of patients (less than 4 cm and over 4 cm). Due to the fact that the majority of patients smoked (51 patients in the analyzed group of 58 patients) analysis of the influence of smoking on AAA progression among smokers and non-smokers was not performed. Influence of factors, such as smoking, sex, race or presence of diabetes on progression of an aneurysm was also studied by Lederle et al. [26]. Effect of smoking on aneurysm progression increased significantly with the number of pack-years. On the other hand, correlation decreased significantly with number of years free of the addiction. Among patients with aneurysm equal to or larger than 3 cm in diameter as much as 78% were smokers and this factor exerted the greatest impact on progression of AAA. Female sex, black race and diabetes showed no correlation with the disease. Our results show that influence of smoking on progression of AAA is not statistically significant. There are a number of publications regarding correlation and influence of comorbidities on progression of AAA. For example, the association between hypertension and AAA has not been unequivocally confirmed. Naydeck et al. performed ultrasound examination on 266 patients [27]. In that group, 143 patients had isolated arterial hypertension. Following statistical analysis of all data, factors such as: male sex, high LDL concentration, rapid heart rate and smoking were considered independent risk factors for AAA growth. sole presence of arterial hypertension was not correlated and did not influence AAA progression. Likewise, in our study we did not find a correlation between arterial hypertension and its influence on progression of AAA neither in a group of patients with aneurysms smaller than 4 cm, nor larger than 4 cm (provided that blood pressure was well-controlled). Mofidi R et al., on the other hand, analyzed sex-dependent differences in AAA progression [28]. Mean yearly increase in AAA diameter was significantly greater in women (3.67 mm) compared with men.
(2.03). Authors conclude that larger initial transverse diameter and female sex are significant factors influencing more rapid aneurysm growth. No significant differences with respect to increase in aneurysm diameter in men and women were noted in our work. It was true for aneurysms smaller and larger than 4 cm in diameter. Solberg et al. also addressed the question of AAA progression in both sexes [29]. The study was based on ultrasound examinations performed in 185 men and 49 women. In this publication, prognostic factors for AAA progression included initial transverse diameter of an aneurysm and female sex as well. Data acquired from our study also indicate maximal transverse diameter of an aneurysm as a key prognostic factor for disease progression, as opposed to sex, which did not exhibit such correlation.

Conclusions

Analysis of results obtained in the present study shows that the presence of ILT is correlated with AAA growth in transverse and sagittal diameters. The nature of this correlation requires further studies. Based on the acquired results, it cannot be unequivocally concluded whether ILT stabilizes or facilitates growth of an aneurysm. Similar conclusions are true for AAA wall thickness. Moreover, we observed positive correlation between increase in cystatin C concentration and AAA diameter in transverse and sagittal planes. We did not find any evidence of correlation between CRP level and AAA growth. The above relationships between ILT presence and size, wall thickness, or serum cystatin C levels and transverse and sagittal diameters of an aneurysm may be useful for predicting AAA progression. Age, sex, treated dyslipidemias, hypertension, and smoking do not exert significant influence on AAA growth.

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