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Patients with Abdominal Aortic Aneurysm Demonstrate Higher Levels of Non-cholesterol Sterol Markers of Endogenous Cholesterol Synthesis

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MP and JH designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors FP and LD managed the analyses of the study. Authors Petr Sedivy and Petr Stadler managed the classification of patients. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To establish the levels of selected non-cholesterol sterols in patients with abdominal aortic aneurysm (AAA) and to compare them with levels in non-AAA patients treated for lipid metabolism disorder. To compare the levels of high-sensitivity C-reactive protein (hs-CRP) and Lp-PLA 2 – inflammation markers in the same group of patients.
Study Design: A total of 58 AAA patients indicated for elective surgical procedure and 20 non-AAA patients in the control group treated for lipid metabolism disorder were examined.
Methodology: Lathosterol (Lat), desmosterol (Des), lanosterol (Lan), campesterol (Cam) and sitosterol (Sit) were analysed with the use of GC/MS in fasting plasma of patients with AAA and

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outpatients suffering from lipid metabolism disorder. hs-CRP and lipoprotein-associated phospholipase A2 were analysed in both groups.

Results: hs-CRP levels were significantly increased in patients with AAA compared to the control group (med. 3.6 mg/L, IQR 1.83 to 6.0 mg/L vs. 2.05 mg/L, IQR 0.99 to 3.0 mg/L, P = .007). Levels of non-cholesterol precursors of cholesterol synthesis – Lan, Des and Lat – were statistically significantly higher in the group of AAA patients compared to non-AAA patients (Lan: med. 0.28 µmol/L, IQR 0.24 to 0.32 µmol/L vs. 0.23 µmol/L, IQR 0.20 to 0.25 µmol/L, P = .004; Des: med. 3.69 µmol/L, IQR 3.12 to 4.66 µmol/L vs. 3.03 µmol/L, IQR 2.68 to 3.33 µmol/L, P = .0005; Lat: 5.95 µmol/L, IQR 5.18 to 6.9 µmol/L vs. 4.72 µmol/L, IQR 4.32 to 5.22 µmol/L, P = .0002) while there were no statistically significant differences in the absorption parameters of Sit or Cam in either group (Sit: med 6.29 µmol/L, IQR 5.02 to 9.37 µmol/L vs. 6.12 µmol/L, IQR 4.99 to 7.01 µmol/L, P = .65; Cam: med 8.6 µmol/L, IQR 7.31 to 10.71 µmol/L vs. 8.46 µmol/L, IQR 7.24 to 10.86 µmol/L, P = .96).

Conclusion: The markers of endogenous cholesterol synthesis in AAA patients are higher compared with those in non-AAA patients treated for lipid metabolism disorder. Higher hs-CRP levels in AAA patients show increased inflammatory activity compared with the control group.

Keywords: Aortic abdominal aneurysm; non-cholesterol sterols; high-sensitivity C-reactive protein; statins.

1. INTRODUCTION

Abdominal aortic aneurysm (AAA) is a serious disease with unclear aetiopathogenesis and in the case of its most significant complication – aneurysm rupture – also a disease with high mortality [1]. Arteriosclerosis is one of the discussed aetiopathogenetic factors involved in its development. Standard parameters – cholesterol, HDL cholesterol, LDL cholesterol and triglycerides – do not bring about any significant benefits in terms of determining the disease activity – aneurysm progression [2]. Precursors of endogenous cholesterol synthesis and phytosterols (collectively referred to as non-cholesterol sterols) are newer parameters which monitor endogenous synthesis and absorption of cholesterol. Campesterol and sitosterol are markers of cholesterol absorption while lathosterol, lanosterol and desmosterol are markers of its synthesis. Their monitoring is used to determine the correct therapy for patients with lipid metabolism disorder. AAA is also associated with arterial wall inflammation. So far, there has been no parameter which can identify patients with intense inflammation and who are thus at a high risk of disease progression and aneurysm rupture. High-sensitivity C-reactive protein (hs-CRP) is a marker associated with chronic inflammation of the arterial wall. Lipoprotein-associated phospholipase A2 (Lp-PLA 2) is an enzyme produced in inflamed arteries which binds to lipoprotein particles when released into the blood. It is a relatively new biomarker indicating the presence of inflammation in the arterial wall and its increased levels are associated with a higher incidence of cardiovascular events [3,4]. Our study aimed to examine selected non-cholesterol sterols and biomarkers associated with arterial wall inflammation in AAA patients and in a control group of non-AAA patients with lipid metabolism disorder.

2. PATIENTS AND METHODS

2.1 Study Design

This was a prospective observational trial performed at the Na Homolce Hospital in 2014–2015. A total of 58 AAA patients indicated for an elective surgical procedure and 20 non-AAA patients in the control group who were treated for lipid metabolism disorder were examined.

2.2 Methodology

Clinical assessment of each case, including a thorough history and physical examination, followed by investigations including basic haematological and biochemical tests, was performed. In addition, the following parameters were examined: campesterol, sitosterol, lanosterol, desmosterol and lathosterol, using the method of mass spectrometry – plasma GC/MS by a Finnigan SSQ 700, modified according to Theuniss [4]. Plasma levels of hs-CRP (K-Assay, Kamiya Biomedical Company) and Lp-PLA 2 (Diazyme) by means of turbidimetry using a UnicelDxC 800 analyser (Beckman Coulter) were determined in both groups. Baseline demographics included age and gender; data

were also collected with regard to lipid metabolism parameters – cholesterol and triglycerides – and the presence of diabetes (DM), hypertension (HT), coronary heart disease (CHD) and smoking (Table 1).

2.3 Statistical Analysis

Results were expressed as the median and interquartile range (IQR) for non-continuous variables and relative frequency. Comparisons between groups were made using one-way analysis of variance and chi-square tests for both types of data, respectively. A P value < .05 was considered statistically significant.

All protocols and informed consent forms were approved by the Na Homolce Hospital Ethics Committee. Informed consent for participation was provided by all patients.

3. RESULTS

No statistically significant differences were found in Lp-PLA 2 levels between the two groups. hs-CRP levels were statistically significantly higher in the AAA patient group (med. 3.6 mg/L, IQR 1.83 to 6.0 mg/L) compared to the control group (med. 2.05 mg/L, IQR 0.99 to 3.0 mg/L, P = .007). No statistically significant differences were detected between the two groups for markers of cholesterol absorption – campesterol and sitosterol (P = .96 and .65, respectively). On the other hand, cholesterol synthesis markers – lanosterol, desmosterol and lathosterol – were significantly higher in the AAA patient group compared to the control group (lanosterol: med. 0.28 µmol/L, IQR 0.24 to 0.32 µmol/L vs. 0.23 µmol/L, IQR 0.20 to 0.25 µmol/L, P = .004; desmosterol: med. 3.69 µmol/L, IQR 3.12 to 4.66 µmol/L vs. 3.03 µmol/L, IQR 2.68 to 3.33 µmol/L, P = .0005; lathosterol: 5.95 µmol/L, IQR 5.18 to 6.9 µmol/L vs. 4.72 µmol/L, IQR 4.32 to 5.22 µmol/L, P = .0002; Fig. 1).

4. DISCUSSION

AAA is a serious disease with an increasing prevalence [5]. Its rupture is associated with high mortality [6]. Aetiopathogenesis has not been satisfactorily established. It has a clearly multifactorial aetiology, with arteriosclerosis as one of the factors involved in the development of the disease. However, at present, it is not considered as the most significant aetiopathogenetic factor [7,8]. It has to be mentioned, though, that histological findings of AAA are, in the vast majority of cases, associated with arteriosclerosis and AAA is considered to be its equivalent. Therefore, the same treatment is recommended for AAA patients as for those with arteriosclerosis [9]. However, no correlation has been found between classic arteriosclerosis and AAA progression [10]. There are also other biomarkers which are used to predict the correct treatment of patients with arteriosclerosis. Recently, works by Miettinen and Gylling [11,12], Nissinen et al. [13] and Hamilton et al. [14] have demonstrated, similarly to the study of Hyanek et al. [15] in children, the importance of non-cholesterol sterols for effective treatment of lipid metabolism disorder. Individuals have different possibilities to regulate cholesterol synthesis and absorption [16]. In some, synthesis is dominant while in others absorption takes precedence over synthesis. Lathosterol is the largest source for cholesterol synthesis [17]. Approximately 80% of cholesterol is derived from lathosterol while 20% of synthesis is associated with desmosterol. Sitosterol and campesterol represent markers of cholesterol absorption. Patients with increased cholesterol absorption also have increased levels of these sterols. The treatment method is governed by the balance between cholesterol synthesis and absorption. While patients with high levels of lathosterol react best to statin treatment, patients with high levels of sitosterol and campesterol react well to ezetimibe treatment. Recently, articles on the effect of statins on AAA and the risk of its rupture have been published [18-20]. It was demonstrated that the use of statins reduces the speed of aneurysm growth and the risk of its rupture. On the other hand, Fergusson et al. [21] did not confirm this association. In our study we established increased levels of non-cholesterol precursors – markers of endogenous cholesterol synthesis in AAA patients compared with the control group – in our study. On the other hand, there were no significant differences between levels of absorption markers compared with the control group. AAA patients were also treated with statins and there were no statistically significant differences between cholesterol and triglyceride levels in non-AAA patients treated in the outpatient department for disorders of lipid metabolism. These results indicate that, in AAA patients, there are primarily higher levels of cholesterol synthesis markers while cholesterol absorption in these patients was the same as in control group patients. These findings lead to the conclusion that statin treatment should be set in such a way as to reach levels of cholesterol

precursors which would be comparable to those in non-AAA patients with lipid metabolism disorder. It could be a possible method for affecting AAA progression. In connection with our study, we did not find any article dealing with determination of cholesterol precursors in AAA patients. Based on our experience from monitoring the success in treatment of patients with the lipid metabolism disorder we know that lathosterol, desmosterol and lanosterol exhibit a long-term mutual correlation. For the time being, we plan to continue monitoring of all the three parameters and find out if some of them will have priority concerning the illness progression.

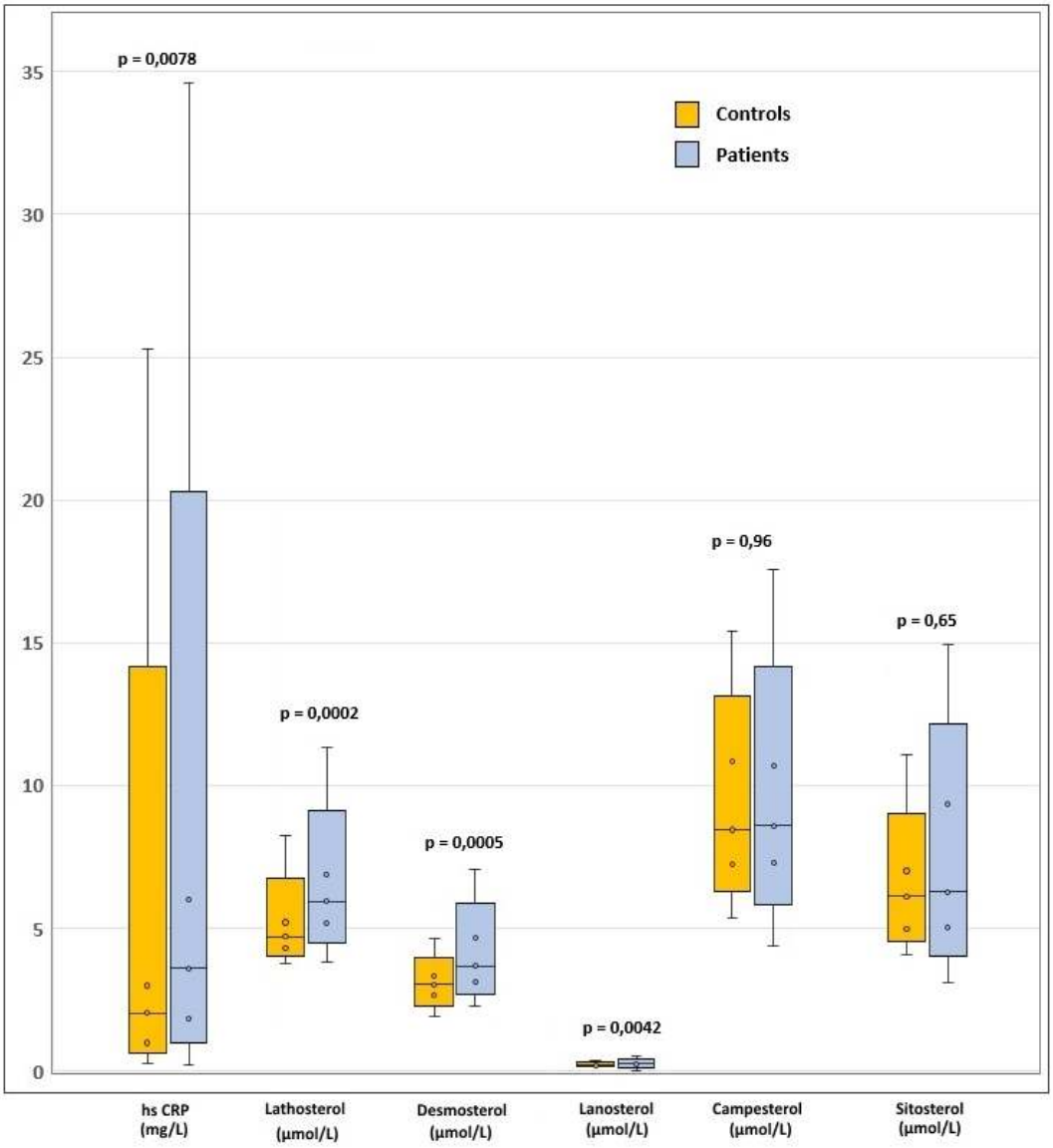

Fig. 1. Levels of hs CRP, lathosterol, desmosterol, lanosterol, campesterol and sitosterol

Table 1. Demographic and clinical characteristics of patients

	n	m	f	Age	CHOL (mmol/L)		TGL (mmol/L)		DM	HT	IHD	Smoking
				(Mean)	Mean	95% CI	Mean	95% CI				
Patients	58	47	11	71	5.38	5.21-5.49	1.78	1.65-1.95	9	49	26	52
Controls	20	10	10	62	5.25	5.01-5.41	1.81	1.69-2.01	5	9	1	6

Identifying patients with a high risk of aneurysm growth is one of unresolved issues in AAA patients. Imaging methods such as ultrasonography and CT-AG when patients are regularly followed up (every 3 or 6 months) are routinely used in clinical practice. Finding a parameter which could identify these patients would be extremely useful for clinical practice. Finding biomarkers which could predict the risk of AAA growth has been a long-term aim of studies. One of these markers is hs-CRP. Its importance for determining the risk of AAA progression was studied in the past. A study performed by De Haro et al. [22] showed a correlation between the speed of aneurysm growth and hs-CRP levels. Similar results were achieved in a study performed by Qin et al. in which hs-CRP and cathepsin S predicted active inflammation [23]. Higher hs-CRP levels in our patients compared with the control group can prove a higher intensity of arterial wall inflammation and, again, probably the insufficient efficacy of statin treatment. However, such an increased concentration is likely to be connected with a higher comorbidity of these patients in comparison with the control group. To confirm these findings, more studies are required. Levels of Lp-PLA 2, another parameter indicating active arterial wall inflammation, were not significantly different in both groups.

5. LIMITATION OF THE STUDY

Our results refer to a small group of patients and do not contain their long-term follow-up. The patients were assessed once at the time when surgical treatment became a necessity. It would be advisable to perform a long-term study in patients with AAA and determine its development based on preselected markers – lanosterol, desmosterol, lathosterol and hs-CRP.

6. CONCLUSION

Statistically significant differences were found in the levels of non-cholesterol precursors of cholesterol synthesis – lanosterol, desmosterol and lathosterol – in AAA patients while no statistically significant differences were established for absorption parameters – sitosterol and campesterol – in either group. This indicates an imbalance in cholesterol synthesis in AAA patients which is not sufficiently corrected by statin treatment. AAA patients had higher hs-CRP levels compared with non-AAA patients with lipid metabolism disorder.

CONSENT

All authors declare that written informed consent was obtained from the patients for collecting blood samples.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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