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The Role of The Spleen in Atherosclerosis

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ABSTRACT

Objective: Atherosclerosis is a chronic inflammatory process characterized by the accumulation of lipid and inflammatory cells in the walls of medium and large arteries. Metabolic effects of splenectomy are less known, especially the effects on lipid metabolism is a debate. In this study, we aimed to investigate the effects of splenectomy on atherosclerosis in humans.

Methods: The data of 280 patients who underwent a splenectomy at a tertiary center between 2009-2016 were analyzed. The 50 patients were included in the study as a splenectomy group. In addition, 50 patients who applied to our outpatient clinic between January 2021 and August 2021 with similar characteristics to those in the splenectomy group except for splenectomy were included in the study as a non-splenectomy group. Atherosclerosis was evaluated by measuring the right, left, and the mean carotid artery intima-media thickness (CAIMT).

Results: All measurements were significantly higher in the splenectomy group (p=0.010 for left CAIMT, p=0.011 for right CAIMT and p=0.008 for mean CAIMT).

Conclusion: The CAIMT measurements were higher and therefore atherosclerosis risk was increased in patients with splenectomy. For this reason, it should be kept in mind that these patients may develop cardiovascular and cerebrovascular problems due to atherosclerosis and should be followed up in this respect.

Keywords: lipoprotein; carotid artery; vessel; lipid

Research Article

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INTRODUCTION

Atherosclerosis is a chronic inflammatory process characterized by the accumulation of lipid and inflammatory cells in the walls of medium and large arteries (1). It is the main cause of myocardial and cerebral infarctions and related deaths (2). Plasma cholesterol and low-density lipoprotein (LDL) levels are associated with atherosclerosis (3).

The spleen has many functions and effects on different systems. As the functions of the spleen are better understood, the indications for splenectomy have decreased, and spleen-sparing surgeries have become more common. However, splenectomy is still one of the most frequently performed surgeries for such reasons as trauma, hematological diseases, and malignancies.

Hematological and immunological side effects of splenectomy are well-known, besides there are also lesser known metabolic effects. Especially the effects of splenectomy on lipid metabolism is a debate, in addition, there is no human study about atherosclerosis after splenectomy in literature. In this study, for the first time, we aimed to investigate the effects of splenectomy on atherosclerosis in humans.

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MATERIAL and METHODs

The study is a cross-sectional cohort study and the data were obtained from a retrospective database. The data of 280 patients who underwent a splenectomy at a tertiary center between 2009-2016 were analyzed. The inclusion criteria were the age between 20-50 years, having a body mass index (BMI) between 19-30 kg/m^2, being a non-smoker, not using drugs that would affect the lipid profile, having splenectomy for benign reasons, and having passed five years after splenectomy. Finally, 50 patients were included in the study as a splenectomy group. In addition, 50 patients who applied to our outpatient clinic between January 2021 and August 2021 with similar characteristics to those in the splenectomy group except for splenectomy were included in the study as a non-splenectomy group.

Atherosclerosis was evaluated by measuring the right, left, and the mean carotid artery intima-media thickness (CAIMT). The mean CAIMT was determined by dividing the sum of the right and left CAIMT by two. The CAIMT was measured at the carotid artery bifurcation level using Vivid E95 ultrasound system (GE Healthcare, Oslo, Norway) and 11-LD Linear Array Transducer (4.5-12 MHz). Ethical approval was obtained from the institutional Ethical Committee (2906-2021).

Statistical Analysis: The Shapiro-Wilk test was used to assess the normality of the distribution of numerical variables. Numerical variables were given as median (minimum-maximum). Categorical variables were defined as frequency (percentage).

The Mann-Whitney U test was used in between-group comparisons for numerical variables. Categorical variables were analyzed with the Chi-Square or the Fisher's Exact tests. A p value<0.05 was considered significant. The IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) was used for statistical analyses.

RESULTs

Demographics and medical features of patients are summarized in Table 1. The median age of whole study group was 38 years (20-50). The splenectomy group had higher median age (41 vs 38) but the difference was not significant. Almost half percent of the patients in both groups and in the whole study group were male. The BMI values were similar between the groups. Only three patients had comorbidities and all were in the splenectomy group (one patient with asthma, one patient with multiple sclerosis and one patient with von Willebrand disease). In addition there was only one patient using medication (the patient with asthma used bronchodilator).

Table 2 shows the indications for splenectomy. The most common indication was trauma (n=25, 50%) followed by immune thrombocytopenic purpura and iatrogenic splenic injury. Comparisons and results of CAIMT are given in Table 3. All measurements were significantly higher in the splenectomy group (p=0.010 for left CAIMT, p=0.011 for right CAIMT and p=0.008 for mean CAIMT).

Table 1. Demographics and medical features of patients

	Whole study group (n=100)	Splenectomy group (n=50)	Non-splenectomy group (n=50)	P value
Age (year)	38 (21-50)	41 (21-50)	38 (21-50)	0,249
Gender (male)	51 (51%)	25 (50%)	26 (52%)	0,841
BMI (kg/m^2)	24,30 (19,10-29,60)	24,45 (19,10-29,60)	24,00 (19,00-28,00)	0,233
Comorbidity (yes)	3 (3%)	3 (6%)	-	0,242
Drug use (yes)	1 (1%)	1 (2%)	-	1

BMI: Body mass index

Table 2. Indications for splenectomy of the splenectomy group

	Splenectomy group (n=50)
Trauma	25 (%50)
ITP	13 (26%)
Iatrogenic	4 (8%)
Pancreatic cyst	3 (6%)
Splenic cyst	2 (%4)
Hereditary spherocytosis	1 (2%)
Splenic abscess	1 (2%)
Hemangioma	1 (2%)

ITP: Immune thrombocytopenic purpura

Table 3. Comparisons and results of CAIMT

	Whole study group (n=100)	Splenectomy group (n=50)	Non-splenectomy group (n=50)	P value
Left CAIMT (mm)	0,07 (0,03-0,37)	0,08 (0,04-0,37)	0,06 (0,03-0,37)	**0,010**
Right CAIMT (mm)	0,07 (0,03-0,22)	0,08 (0,04-0,22)	0,06 (0,03-0,16)	**0,011**
Mean CAIMT (mm)	0,07 (0,03-0,24)	0,08 (0,04-0,24)	0,06 (0,03-0,24)	**0,008**

CAIMT: Carotid artery intima–media thickness, Bold values denote statistical significance at the p < 0.05 level

DISCUSSION

The role of the spleen and the side effects of splenectomy on different systems are well known, but their effects are not clear on the development of atherosclerosis. To the best of our knowledge, this is the first study in the literature to investigate the effect of splenectomy on atherosclerosis in humans. In this study, atherosclerosis was evaluated using CAIMT and was found to be significantly higher in patients with splenectomy.

The main pathological process in atherosclerosis is the accumulation of LDL in the subendothelial space. Subendothelial LDL is oxidized by reactive oxygen species, and oxidized LDL (ox-LDL) occurred (4). Hypertension, diabetes mellitus, smoking, and dyslipidemia increase ox-LDL by activating the NADPH-oxidase system (5). Ox-LDL induces the development of atherosclerosis by causing inflammation in the arterial wall (6). B cell-mediated and T cell-mediated inflammation, which is effective in the occurrence of atherosclerosis, is mostly activated by plasma LDL (7). For these reasons, the main strategy in the treatment of atherosclerosis is to reduce blood LDL levels and reduce inflammatory responses.

The spleen is a component of the reticuloendothelial system. Splenectomy has hematological, immunological, and metabolic side effects, but the metabolic ones have not yet been fully elucidated. Many possible mechanisms have been described that explain the effects of the spleen on lipid metabolism. The most popular of these is to be a reservoir for lipids (8). Another theory argues that the spleen produces anti-ox-LDL antibodies via B-lymphocytes (9). In addition, the spleen has a role in LDL metabolism too (10,11). Consequently, different studies presented different results about the effects of spleen and splenectomy on lipid metabolism and atherosclerosis. Some of them found changes in blood lipid levels (12–16) and some of them did not (9,17–21). But almost all of which were experimental. Similarly, some of them found increased atherosclerosis incidence (9,18,19) and some of them did not (20,21). Conversely, a study by Li and Stone stated a lower atherosclerosis incidence (17). Robinette and Fraumeni Jr. found a higher mortality rate due to cardiovascular diseases in veterans with splenectomy, and they argued that this may due to the effect of splenectomy on lipid metabolism (10). In another study, although cardiovascular diseases were found to be higher in veterans with splenectomy, this difference was not observed when those with autoimmune diseases were excluded from the study (22).

In this study, CAIMT measurement via ultrasound was used to evaluate atherosclerosis. It is a cheap, non-invasive, and easily accessible method to evaluate atherosclerosis. While intimal thickening in the carotid artery is associated with atherosclerosis, the thickening of the medial layer is usually related to hypertension-related smooth muscle hypertrophy (23). CAIMT is accepted as a marker for early-stage atherosclerosis (24). In a meta-analysis, it was reported that cardiovascular events may be reduced by reducing the occurrence and progression of CAIMT (24).

While the risk factors for atherosclerosis (such as age, BMI, drug usage, comorbidities, smoking status) were similar between the groups, we found higher CAIMT measurements in the splenectomy group. This indicates splenectomy increases the risk of atherosclerosis. We think that this may be due to the effects of splenectomy on lipid metabolism and inflammatory processes, but further studies (especially molecular levels) are needed to understand the underlying mechanism clearly. In addition, CAIMT measurement via ultrasound after splenectomy may be used as a good option in follow-up for patients, especially those with a high risk of atherosclerosis, cardiovascular and cerebrovascular diseases.

Limitations

The study has certain limitations. First, this is a cohort study. Second, approximately half of the splenectomy group had splenectomy due to autoimmune disease, and this may be a weakness of the study. However, these patients were in remission and were not using any drugs that were effective on atherosclerosis. Third, the number of patients is relatively small. Fourth, we could not analyze the laboratory findings (such as the blood levels of cholesterol, triglyceride, and glucose) that may affect atherosclerosis occurrence. Fifth, we could not examine the underlying mechanism of how splenectomy increases the atherosclerosis process.

CONCLUSION

The CAIMT measurements were higher and therefore atherosclerosis risk was increased in patients with splenectomy. For this reason, it should be kept in mind that these patients may develop cardiovascular and cerebrovascular problems due to atherosclerosis and should be followed up in this respect.

Informed Consent: The aim and content of the research were clarified to the individuals included in the study, and voluntary consent forms were signed.

Author Contributions: OG, MEC, EC, YMB, ET, NTB, CA, CK: Study Design, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Search- OG: Manuscript Preparation, revisions

Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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