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ORIGINAL ARTICLE

Aortic aneurysm associated with rheumatoid arthritis: a population-based cross-sectional study

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Abstract There is substantial evidence that aortic aneurysm (AA) may be a manifestation of several systemic rheumatic disorders. However, only several studies have assessed the association between rheumatoid arthritis (RA) and AA. The aim of this study was to evaluate the incidence of AA in RA patients in a case-control study. A retrospective case-control study was performed utilizing the database of Clalit Health Services (CHS), a large healthcare provider organization in Israel. Data available from the CHS database included age, sex, socioeconomic status (SES), and diagnoses of chronic diseases, including AA. Patients over the age of 20 years who were diagnosed with RA ("cases") were compared with a sample of age- and gender-matched enrollees without RA ("controls") regarding the prevalence of AA. Chi-square and *t* tests were used for univariate analysis, and a logistic regression model was used for multivariate analysis. The study included 11,782 RA patients and 57,973 age- and gender-matched controls. The proportion of AA was significantly higher in RA patients (0.72 %) compared to the control group 0.49 % (odds ratio (OR) 1.48, 95 %; confidence interval (CI) 1.15–1.88; $p = 0.002$). A multivariate analysis that evaluated covariates associated with AA revealed an independent association of AA and RA after adjustment for different factors including age, gender, SES, and smoking status (OR 1.406, 95 %; CI 1.094–1.789; $p = 0.006$). Our study has demonstrated that AA is more prevalent in patients with RA in comparison with general population. Future large randomized studies are important to identify cardiovascular- and disease-related risk factors for AA formation in RA patients.

Keywords Aortic aneurysm · Atherosclerosis · Autoimmune disease · Rheumatoid arthritis

Ora Shovman and Shmuel Tiosano are the two first authors who shared equal contribution.

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory immune system disorder primarily affecting the joints yet often targets other organs as well including the cardiovascular system. Overall, diverse cardiac manifestations have been described in RA such as pericarditis, myocarditis, cardiac amyloidosis, coronary vasculitis, arrhythmias, and valvular disorders. In addition, RA is a risk factor contributing to the pathogenesis of atherosclerosis leading to higher rates of ischemic heart disease and congestive heart failure resulting in increased higher mortality rate [1–3].

Higher cardiovascular (CV) risk in RA patients is partially mediated by traditional CV comorbidities such obesity, dyslipidemia, type 2 diabetes mellitus (T2DM), metabolic syndrome, hypertension, physical inactivity, advanced age, male

gender, family history of CVD, and tobacco use [2, 4, 5]. Nowadays, the importance of RA-specific factors, such as ongoing and long-term inflammation has been recognized to be an additional significant disease-related risk factor [2, 4, 5].

Some studies and isolated case reports demonstrate that aortic involvement may occur as an unusual complication of RA. The described manifestations of aortic involvement in RA consist of aortitis, sometimes to be found only at autopsy, asymptomatic aortic regurgitation, and AA [6–12]. Generally, AA and aortic dissection are rare vascular complications occurring most commonly in elderly men with systemic hypertension and atherosclerosis [13]. Nevertheless, the increased prevalence of cardiovascular risk factors along with the accelerated arthrosclerosis in RA patients raises the hypothesis that these patients may have a higher incidence of AA than previously reported. Studies of AA and aortic dissection in RA patients are scant, and the true incidence of AA in RA patients has not been definitively determined.

The aim of our study is to investigate the coexistence of AA in RA patients in comparison with the general population using the medical database of the largest health maintenance organization in the country, the Clalit Health Services (CHS).

Patients and methods

Study design and participants

This study is a retrospective case-control study that incorporates data mining techniques and utilizes the Clalit Health Services (CHS) database. CHS is the largest public health insurance organization in Israel, and it provides medical care for approximately 4,400,000 enrollees. The large computerized database of this organization provides unique opportunities for population-based estimates of the incidences of rare events such as AA in RA patients. The potential of this database in population-based studies has been previously described [2, 13–17]. This system ensures virtually complete ascertainment of all clinically recognized cases of RA among the residents of Israel registered in CHS. All diagnosed cases of RA were identified using the computerized diagnostic index. Patients were defined as having RA when there was at least one documented diagnosis of RA in the medical records registered by CHS rheumatologists or CHS physicians in patients diagnosed during hospitalization. Unfortunately, we had no available data regarding the disease activity scores of the RA patients.

The diagnosis of AA was extracted from the CHS chronic diseases registry which is based on data withdrawn from hospital and primary care physicians' reports. Patients who were diagnosed with RA ("cases") and enrollees without RA ("controls") were matched based on age and sex. The prevalence of AA was compared between the study groups in the entire study sample as well as in age, sex, and SES subgroups. Chi-square and *t* tests were used for univariate analysis. A logistic regression model was used to estimate the association between RA and AA in a multivariate analysis. Statistical analysis was performed using R Statistical Software (version 3.0.3; R Foundation for Statistical Computing, Vienna, Austria).

The study was approved by the institutional review board of the Clalit Health Services at the Soroka Medical Center, in Beer-Sheva.

Results

The study included 11,782 RA patients and 57,973 age- and sex- matched controls. Characteristics of the study population are presented in Table 1.

The proportion of AA was significantly higher in RA patients (0.72 %) compared to the control group 0.49 % (OR 1.48, 95 %; CI 1.15–1.88; $p = 0.002$). The prevalence of smokers in the RA group (32.8 %) was higher than in the control group (28.8 %).

OR for AA in patients with RA and controls in the entire study sample stratified by age, sex, smoking status, and SES is presented in Table 2. The association between AA and RA was statistically significant among females (0.51 versus 0.31 %; OR 1.64, 95 %; CI 1.16–2.27; $p = 0.006$). In addition,

Table 1 Descriptive characteristics of the study population ($n = 69,755$)

Variables	Controls $n = 57,973$	Patients with RA $n = 11,782$	p value
Gender: Female	44,589 (76.9 %)	9103 (77.3 %)	0.413
Age, Mean ± SD	60.8 ± 17.0	61.1 ± 17.0	0.174
SES:			
Low	22,657 (39.2 %)	4505 (38.3 %)	Ref.
Medium	22,831 (39.5 %)	4816 (41.0 %)	0.009
High	12,334 (21.3 %)	2438 (20.7 %)	0.831
Smoking	16,671 (28.8 %)	3865 (32.8 %)	<.001
AA	284 (0.49 %)	85 (0.72 %)	0.002

AA aortic aneurysm, *RA* rheumatoid arthritis, *SES* socioeconomic status, *n* number, *SD* standard deviation

Table 2 RA and AA: stratified analysis (n = 69,755)

Variable	Controls n = 57,973	RA patients n = 11,782	OR	p value
Aneurysm	284 (0.49 %)	85 (0.72 %)	1.48 (1.15;1.88)	0.002
Female	138 (0.31 %)	46 (0.51 %)	1.64 (1.16;2.27	0.006
Male	146 (1.09 %)	39 (1.46 %)	1.34 (0.93;1.90)	0.114
Age: 40–59	18 (0.10 %)	8 (0.23 %)	2.25 (0.91;5.05)	0.076
Age: 60–79	168 (0.64 %)	53 (0.98 %)	1.55 (1.13;2.10)	0.007
Age: 80+	98 (1.32 %)	24 (1.53 %)	1.17 (0.73;1.81)	0.498
SES: low	96 (0.42 %)	34 (0.75 %)	1.79 (1.19;2.63)	0.006
SES: medium	115 (0.50 %)	27 (0.56 %)	1.12 (0.72;1.68)	0.605
SES: high	72 (0.58 %)	24 (0.98 %)	1.70 (1.05;2.67)	0.033
Smoking	141 (0.85 %)	50 (1.29 %)	1.54 (1.10;2.12)	0.012

CI confidence interval, *OR* odds ratio, *SES* socioeconomic status, *AA* aortic aneurysm, *n* number

the age interval 60–79 was also a considerable risk factor for AA in RA population in comparison with controls (0.98 versus 0.64 %; OR 1.55, 95 %; CI 1.13–2.10; p = 0.007). The incidence of AA was higher in RA patients from low SES than in controls subjects (0.75 versus 0.42 %; OR 1.79, 95 %; CI 1.19–2.63; p = 0.006).

A comparison between RA patients with AA and RA patients without AA revealed that AA is more prevalent at older ages within the RA group (OR 1.06, 95 %; CI 1.04–1.08; $p < 0.001$). Furthermore, smoking was determined to be a risk factor for AA in RA patients (58.8 versus 32.6 %; OR 2.95, 95 %; CI 1.91–4.59; $p < 0.001$).

A multivariate analysis that evaluated covariates associated with AA revealed an independent association of AA and RA after adjustment for different factors including age, gender, SES, and smoking status (OR 1.406, 95 %; CI 1.094–1.789; p = 0.006) (Table 3).

Discussion

The present study is a case-control study, based on a large cohort of patients with AA and controls from the CHS database. RA was found to be associated with a higher coexistence rate of AA.

Table 3 Logistic regression—covariates associated with AA

	OR	CI	p value
Age	1.075	1.066–1.085	<.001
Male	2.727	2.194–3.389	<.001
SES:			
Medium vs. Low	0.803	0.630–1.022	.074
High vs. Low	0.968	0.738–1.264	.810
Smoking	2.285	1.834–2.849	<.001
RA	1.406	1.094–1.789	0.006

CI confidence interval, *OR* odds ratio, *SES* socioeconomic status, *RA* rheumatoid arthritis, *AA* aortic aneurysm, *n* number

To the best of our knowledge, only a small number of studies have addressed this issue and investigated the association between RA and AA. In a recent report, 18 cases of abdominal AA were identified from an AA database of over 1000 patients (prevalence of 0.18 %) [18].

Interestingly, this rate of comorbidity was higher in RA patients compared to patients with other rheumatic conditions such as polymyalgia rheumatica, psoriasis, and giant cell arteritis (GCA). In addition, an increased risk of AA was found primarily in males, in patients over the age of 65 years and in patients with RA lasting more than 5 years from diagnosis [18].

Several isolated case reports have demonstrated an association between AA, aortic dissection, and RA [8, 18–20].

AA may be a manifestation of systemic rheumatic disorders of them vasculitis is the leading reported cause. It seems in vasculitis that the inflammatory condition also enhances atherosclerosis contributing to the formation of AA. For example, it was found that aneurysms of the ascending thoracic aorta were 17-fold more common in patients with GCA than in a control group and abdominal AA was 2.5-fold more frequent [21]. Although stenosis is the hallmark of Takayasu's disease, AA with a variable distribution along the aorta is a widespread finding [22]. In addition, AA formation secondary to aortitis has been reported in patients suffering from Cogan's syndrome, relapsing polychondritis and long-standing ankylosing spondylitis [23–25].

AA and aortic dissection may appear rarely as a late complication of systemic lupus erythematosus (SLE) [13, 26, 27]. Along with the improvement in the prognosis of SLE patients, the incidence of these manifestations rises. Recently, the results of a large study including 5018 patients with SLE and 25,090 age- and sex-matched controls demonstrated a higher proportion of AA in SLE patients in comparison with matched controls [13]. A multivariate analysis revealed that SLE was highly associated with AA (OR of 4.5), and this fact reflects the contribution of SLE itself the formation of AA. A similar

trend was observed in a previous study that demonstrated a threefold increase in the incidence of AA and aortic dissection in SLE patients compared to healthy subjects [27]. In both studies, risk factors for AA and aortic dissection in SLE patients were older age and gender (males had higher risk than females) [13, 27]. It has been established that the increased risk of AA was attributable to hypertension and the duration of SLE (greater than 3 years) [27].

A meta-analysis of 35 publications on AA in patients with SLE revealed two different pathways for aneurysm development. One of them has been attributed to aortic circulatory disturbances resulting generally from vasculitis and cystic medial degeneration. These disturbances are presumed to play a crucial role in the pathogenesis of fatal non-atherosclerotic thoracic aneurysms. The second pathway described was atherosclerotic abdominal aneurysm formation associated with long-term steroid treatment, and the prognosis for this type of AA was more favorable [26].

The precise pathogenesis of AA formation in RA patients remains undetermined. Similar to SLE, the possible underlying mechanisms include accelerated atherosclerosis, degenerative changes in the aortic wall, and vasculitis.

Multiple factors may be involved in the development of accelerated atherosclerosis in RA patients, including the clustering of traditional CV risk factors and inflammatory-mediated factors. The presence of traditional risk factors for vascular disease such as smoking, hypertension, diabetes, and hyperlipidemia are extremely important in RA patients, but RA itself is also directly ascribed to the higher risk of CV disorders in these patients [1, 2].

Accelerated atherosclerosis and aneurysm development may be influenced by RA-related systemic inflammation and immune dysregulation through several mechanisms. These mechanisms include endothelial dysfunction, activation of immune cells by raised CRP levels, and alteration of inflammatory-related markers including lipoproteins, ox-LDLs, nitric oxide (NO), TNF-α, RANKL, CD40L, IL-18, MMP-9, and MCP-1 [28–35].

Another potential mechanism of AA development in RA patients is progressive elastic fiber degeneration in the aortic wall that results in decreased elasticity of the aorta and increased aortic stiffness. In this regard, it has been reported that RA is associated with increased aortic stiffness in both genders [36]. Also, aortic stiffness in RA patients was associated with prolonged disease duration and higher extra-articular disease severity and CRP levels, reflecting that ongoing inflammation may be responsible for the arterial stiffening in addition to older age, smoking, visceral obesity, and high triglycerides [36].

Several reports have shown that arterial wall inflammation is an integral part of the systemic inflammatory process of RA. In an interesting study, Vizzardi et al. [37] measured aortic elastic properties by echocardiographic-derived thoracic aortic diameters; they observed that anti-TNF-α treatment after 12 months significantly modified the elastic properties of the aorta. Increased arterial stiffness as assessed by aortic pulse-wave velocity has been reported in RA patients with active disease whereas anti-TNF-α therapy was shown to reduce this stiffness to levels comparable with those measured in healthy individuals [38]. These findings have been also been corroborated by observed increased aortic (18)F-fluorodeoxyglucose uptake in patients with RA who have stable cardiovascular disease; similarly anti-TNF-α therapy reduced the extent of inflammation, a parameter that was found to be in concordance with the aortic stiffness [39].

Therefore, it is plausible that AA formation may occur secondary to rheumatoid vasculitis, but this is considered to be uncommon. Usually, rheumatoid vasculitis involves small- and medium-sized vessels and occurs in 1–5 % of RA patients, especially in those with severe deforming RA and high titers of rheumatoid factor [40].

The present study has several limitations. We had no data on the severity and the duration of RA as well as information regarding the treatment of RA patients. Due to the large number of samples and the structure of the CHS database, it was impossible to validate each case. Patients with several congenital diseases predisposing for AA and aortic dissection such as Turner syndrome, aortic coarctation, bicuspid aortic valve, Marfan syndrome, and Ehler-Danlos syndrome were not excluded from the study but they were present in both the study group and the control group.

In summary, our study has demonstrated the existence of increased prevalence of AA in patients with RA in comparison with the general population. Future large randomized studies are important to address and define the prevalence of AA in patients with RA and the relationship between RA and cardiovascular- and disease-related risk factors.

Compliance with ethical standards

Disclosures None.

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