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Original Article

Carotid sonographic features in Takayasu's arteritis: A case-control study

Maryam Haghighi-Morad (MD)[1#]
Reza Rezaei (MD) [2#]
Muhanna Kazempour (MD) [3*]
Mohammad Mehdi Emam (MD) [3]
Arezoo Ranjbar Arani (MD) [4]
Mahbobeh Taheri (MD) [5]
Parisa Delkash (MD) [6]

1. Department of Radiology, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Department of Rheumatology, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4. Department of Internal Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
5. Skull Base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
6. Department of Rheumatology, Emam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

*** Correspondence:**
Muhanna Kazempour,
Department of Rheumatology, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

E-mail:
muhannakazempour@gmail.com
Tel: +98 2155417243

 # Cofirst: contributed equally

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Abstract

Background: Takayasu arteritis (TAK) is a rare large-vessel vasculitis that affects the carotid arteries. Increased intima–media thickness (IMT) and atherosclerotic changes are detectable by ultrasonography (US). This study aimed to evaluate detailed carotid sonographic features in TAK and compare them with diabetes mellitus (DM), as well as to assess correlations between sonographic parameters and inflammatory markers.

Methods: In this case-control study, 15 patients with TAK fulfilling the 1990 American College of Rheumatology criteria (2012–2022) and 15 patients with DM were evaluated at Loghman Hakim Hospital. Cardiovascular risk factors, carotid ultrasonography, and serum inflammatory markers were assessed. Data were analyzed using univariate and multiple regression tests (SPSS V24).

Results: Atherosclerotic plaques were found in 46.7% of TAK and 53.3% of DM patients. IMT of common (CCA) and internal carotid arteries (ICA) was significantly higher in TAK ($p<0.05$). The macaroni sign (P=0.001), turbulent flow (P=0.006), and higher CCA resistivity index (RI) (P=0.047) were characteristic of TAK. ESR and CRP correlated with pre-bifurcation CCA mean IMT ($p<0.05$). Each unit increase in CRP was associated with a 0.02 mm increase in right CCA IMT (P=0.05).

Conclusion: Carotid ultrasonography is a valuable tool in evaluating TAK. Distinguishing features include the presence of the macaroni sign, turbulent flow, and higher IMT and RI. Increased IMT was associated with elevated CRP.

Keywords: Vasculitis, Takayasu's arteritis, Atherosclerosis, Ultrasonography, Diabetes mellitus.

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Takayasu arteritis (TAK) is a rare an inflammatory disease typically presenting in women before the age of 40 , that affects mostly subclavian and carotid arteries (1, 2). Stenotic or occlusive lesions occur in >90% and may be associated with limb claudication, and cerebral ischemia (2). Advanced lesions demonstrate panarteritis with intimal proliferation (3). Moreover, atherosclerosis is an inflammatory-immunological-degenerative process (4), that increases in TAK because of the intense vascular inflammation. Vascular stiffness and arterial resistance increase in TAK; also, atherosclerosis leads to similar changes (1). The carotid arteries can easily be depicted by ultrasonography (US). Generalized atherosclerosis such as atherosclerotic plaques and the measurement of intima–media thickness (IMT) can evaluate by US (5). Differential diagnoses between Takayasu and atherosclerosis in practice may be not easy for clinicians. We think that vascular changes of TAK are distinguishable from atherosclerosis when evaluated with US. In addition, we know that no specific biomarker describes these changes. ESR as an inflammatory biomarker has a low specificity and sensitivity for disease activity in TAK (6). Moreover fibrinogen, as an inflammatory marker, is correlated with subclinical CVD (7) but has not been assessed in TAK.

Also, few studies showed the association between CRP and IMT in TAK and RA (rheumatoid arthritis) (8, 9). Our study aimed to evaluate sonographic features of TAK, atherosclerosis prevalence and measurement of carotid artery IMT in TAK and patients with diabetes. Finally, we compared vascular ultrasonography parameters with the serum level of the inflammatory biomarker such as ESR, CRP and fibrinogen.

Methods

Patients and physical examination: In this case-control study, all patients with Takayasu's arteritis who had visited the Rheumatology Clinic of Loghman Hakim Hospital and Imam Hossein Hospital between 2012-2022 to perform this study were called. Fifteen patients with TAK (12 women, 3 men) aged 15 to 53 that met the criteria of the American College of Rheumatology (3) were enrolled. A diagnosis of Takayasu arteritis requires that at least 3 of the 6 criteria are met: age at disease onset less than 40 years, claudication of extremities, decreased brachial artery pulse, blood pressure difference more than 10 mm Hg, bruit over subclavian arteries or aorta, arteriogram abnormality. Patients with diabetes mellitus type 2 who were usually followed-up in the diabetes clinic were examined consecutively as a control group. We assessed risk factors for cardiovascular diseases included arterial hypertension, hypercholesterolemia, smoking, diabetes, obesity (4) and past history of stroke or myocardial infarction. The pulse difference in the upper limbs and carotid, subclavian, and kidney arteries bruit sound were investigated.

Laboratory measurement: Blood samples were collected after overnight fasting. Biochemical parameters, including CBC, ESR, CRP, Fibrinogen, FBS, cholesterol, LDL, HDL, Bun, Cr, AST, ALT, ALKP and fibrinogen levels were measured by commercial laboratory diagnostic kits.

History, physical exam, laboratory test and sonographic evaluation were done in one day.

Sonography assessments: Color Doppler US evaluation of carotid arteries was performed by an expert radiologist with 10 years' experience in neuroradiology using Toshiba Aplio300 ultrasound machine linear transducer (PLT-704SBT 4.8-11 MHz). Intima media thickness (IMT) was measured in the far wall of CCA 1-cm proximal to bulb and in ICA 1-cm distal to bifurcation in both right and left sides. An IMT < 0.7 mm considered as normal and 0.7 mm < IMT > 1.5 mm interpreted as a thickened Intima Media. Also, IMT > 1.5 mm was considered as a plaque and the ratio of stenosis was calculated by NASCET criteria (8). The presence of turbulent flow in CCA and ICA due to stenosis is defined by color Doppler map. Also, resistivity index (RI) was calculated in both CCAs in TAK patients and diabetes. Macaroni sign is defined as a long homogeneous circumferential wall thickening in both CCAs which is a pathognomonic sign for Takayasu arteritis in the US reported (9).

Statistical analysis: The numerical and categorical variables were expressed as mean ± standard deviation and frequency/percentage, respectively. The Kolmogorov-Smirnov test was used to assess variable normal distribution. Independent sample t-test was used for quantitative variables and chi-square and Fisher's exact test was used for qualitative variables. U Mann-Whitney was used for variables that did not have a normal distribution (FBS, Fibrinogen, AST, and ALT). Pearson correlation and multiple linear regression models were done for evaluation association between sonographic findings with inflammatory index (CRP, fibrinogen) and demographic information. Multiple logistic regression analysis was conducted to compare risk factors between TAK and DM patients. A p-value below 0.05 was considered statistically significant in all analyses. The analysis was performed using a statistical package for the social sciences (SPSS, Version 24).

Results

In this study, 15 patients with TAK (80% women and 20% men with a mean age of 35.20±8.85 years) and 15 patients with DM (66.7% women and 33.3% men with a mean age of 51.13±8.47 years) were enrolled. We decided to evaluate atherosclerosis, so we had not considered a matched age set for the DM group study, and, they were older than patients with TAK. Two patients with TAK had DM simultaneously. Clinical information and traditional risk factors of atherosclerosis are shown in table 1. Patients with DM had higher BMI (28.34±5.40, P=0.036) and more HTN on physical exam (5 (33.3%), P=0.042).

Pulse discrepancy and bruit of arteries (8 (53.3%), P=0.042) observed only in patients with TAK Prednisone was used by 13 patients with TAK (86.7%). Immunosuppressive drugs were used by 12 patients (80%) (Methotrexate by 2, azathioprine 5, infliximab by 4, adalimumab by 1, mycophenolate by 3). The use of statin, antiplatelet and hypertensive drugs was not significantly different in TAK and DM (p>0.05). Laboratory measurements of metabolic and inflammatory biomarkers are shown in table 2. Although the serum level of ESR, CRP

and fibrinogen was higher in patients with TAK than in DM, the difference was not statistically significant (p>0.05). WBC and platelet amounts (8.90±2.56, 325.13±118.57) were higher (P=0.039, P=0.042) and hemoglobulin was lower in the TAK group (12±1.90, P=0.043). In the DM group, a significant increase of metabolic parameters including FBS, cholesterol, LDL, triglyceride, AST, ALT, ALKP and less Cr levels showed (p<0.05) (table 2).

Table1. Clinical information, traditional risk factors of atherosclerosis and cardiovascular risk in TAK and DM groups

Variables	TAK (n=15)	DM (n=15)	P-value
Age	35.20±8.85	51.13±8.47	<0.001
Sex **Male** **Female**	3 (20%) 12 (80%)	5 (33.3%) 10 (66.7%)	0.682
BMI	24.41±4.36	28.34±5.40	0.036
Disease onset	7.73±5.56	7.47±5.53	0.896
CVD n (%) **Yes** **No**	5 (33.3%) 10 (66.7%)	1 (6.7%) 14 (93.3%)	0.169
IHD n (%) **Yes** **No**	2 (13.3%) 13 (86.7%)	1 (6.7%) 14 (93.3%)	>0.99
Stroke n (%) **Yes** **No**	3 (20%) 12 (80%)	0 15 (100%)	0.224
DM n (%) **Yes** **No**	2 (13.3%) 13 (86.7%)	15 (100%) 0	<0.001
Smoking n (%) **Yes** **No**	2 (13.3%) 13 (86.7%)	2 (13.3%) 13 (86.7%)	>0.99
History of HTN n (%) **Yes** **No**	4 (26.7%) 11 (73.3%)	7 (46.7%) 8 (53.3%)	0.256
Pulse discrepancy n (%) **Yes** **No**	14 (93.3%) 1 (6.7%)	0 15 (100%)	<0.001
HTN on physical exam n (%) **Yes** **No**	0 15 (100%)	5 (33.3%) 10 (66.7%)	0.042
Bruit (Totally: Carotid or Subclavian or Abdominal) n (%) **Yes** **No**	8 (53.3%) 7 (46.7%)	0 15	0.042
Carotid Bruit n (%) **Yes** **No**	5 (33.3%) 10 (66.7%)	0 15	0.042
Subclavian Bruit n (%) **Yes** **No**	7 (46.7%) 8 (53.3%)	0 14 (93.3%)	0.006
Abdominal Bruit n (%) **Yes** **No**	2 (13.3%) 13 (86.7%)	0 15	0.483

TAK: Takayasu's arteritis, DM: Diabetes mellitus, n: number, BMI: Body mass index, CVD: Cardiovascular disease, IHD: Ischemic heart disease, HTN: Hypertension.

Table 2. Laboratory measurement in TAK and DM groups

	TAK (n=15)	DM (n=15)	P-value
WBC	8.90±2.56	7.30±1.26	0.039
Hb	12±1.90	13.30±1.40	0.043
Platelet	325.13±118.57	253.20±45.79	0.042
ESR	32±31.84	22.07±13.14	0.278
CRP	15.09±20.16	7.38±8.74	0.192
FBS	120.93±79.44	197.60±82.36	0.001
Cholesterol	161.80±26.83	196.47±53.62	0.036
LDL	88.60±23.20	108.60±44.62	0.138
HDL	49.80±11.48	50.87±20.60	0.862
TG	114.53±61.31	231.47±146.00	0.010
Urea	29.87±7.00	37.67±14.15	0.066
Cr	0.85±0.11	1.01±0.21	0.012
Fibrinogen	391.60±17.16	361.40±73.70	0.707
AST	18.47±7.60	22.07±7.11	0.022
ALT	18.93±12.60	23.53±16.94	0.084
ALP	156.67±74.08	222.07±78.67	0.029

WBC, White Blood Cell, Hb, Hemoglobin; AST, Aspartate Aminotransferase; ALT, Alanine Transaminase; Cr, Creatinine; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein.

Sonographic findings of carotid of two groups are shown in table 3. Complete occlusion of CCA was seen in 3 (20%) patients, and this finding was seen only in the TAK group. Atherosclerotic plaque was seen in 7 (46.7%) patients with TAK and 8 (53.3%) patients with DM and no significant difference was detected between two groups. IMT was more in CCAs and ICAs in patients with TAK than DM.

Before bifurcation right CCA mean IMT (P=0.005), after bifurcation right ICA mean IMT (P=0.028), and before bifurcation left CCA mean IMT (P=0.015) was statistically significant higher in TAK group. Macaroni Sign (P=0.001) and turbulent flow (P=0.006) are depicted only in TAK group. Left CCA RI was higher in TAK group (P=0.047). The relationship between the atherosclerotic plaque with other sonographic findings showed a nonsignificant correlation with macaroni sign (P=0.059) and turbulent flow (P=0.054). Additional analysis showed the correlation of CRP and before bifurcation right CCA mean IMT (P= 0.051) also, correlation of ESR (P= 0.017) and CRP (P= 0.011) with before bifurcation left CCA mean IMT. Pearson correlation analysis results showed a correlation between ESR with CRP ($p<0.001$, with a coefficient correlation of 0.920 but no correlation between fibrinogen and ESR, or CRP was detected. Table 4 show associated risk factors for odds of TAK compared to DM in the multiple logistic regression model. After adjusting for potential important confounders, age and BMI were significantly associated with occurrence of TAK compared to DM. In other words, odds of developing TAK significantly decrease with age compared to DM (OR = 0.77, 95% CI = 0.62-0.94).

The same was true for BMI, but the reduction in odds of TAK compared to DM with increasing BMI was borderline significant (OR = 0.71, 95% CI = 0.49-1.03). High rate of ESR was associated with TAK, with a 5% increased odds of TAK. However, it was not statistically significant. It seems that the small sample size of the study can justify these borderline findings. Other variables of CVDs and inflammatory biomarkers were not significantly different between the two groups in the multivariable model. Additionally, the relationship between sonographic findings with inflammatory markers, study groups, age, and underlying diseases was examined in multiple linear

regression models. Findings showed that, for each unit increase in CPR, the value of before bifurcation right CCA mean IMT increases by 0.02 and this increase was statistically significant after adjusting for age, CVD, and HTN (β±S.E= 0.02±0.009, p=0.05). Also, TAK patients had an average of 0.6 more before bifurcation right CCA mean IMT than DM patients (β±S.E= 0.60±0.31, P=0.07) which was borderline significant. No significant relationship was observed between other sonographic findings with inflammatory markers and demographic factors.

Table 3. Carotid sonographic findings in TAK and DM groups

	TAK (n=15)	DM (n=15)	P-Value
Complete Occlusion totally (Right and left) n (%)			0.224
Yes	3 (20%)	0	
No	12 (80%)	15	
Complete Occlusion of Rt CCA n (%)			>0.99
Yes	1 (6.7%)	0	
No	14 (93.3%)	15	
Complete Occlusion of Lt CCA n (%)			0.483
Yes	2 (13.3%)	0	
No	13 (86.7%)	15	
Before bifurcation Rt CCA IMT	1.35±0.87	0.60±0.13	0.005
After bifurcation Rt ICA IMT	0.92±0.57	0.55±0.13	0.028
Before bifurcation Lt CCA IMT	1.41±0.98	0.63±0.17	0.015
After bifurcation Lt ICA IMT	0.72±0.43	0.53±0.11	0.153
Turbulent flow Totally n (%)			0.006
Yes	7 (46.7%)	0	
No	8 (53.3%)	15	
No flow	0	0	
Turbulent flow in Rt CCA n (%)			0.017
Yes	5 (33.3%)	0	
No	9 (60%)	15	
No flow	1 (6.7%)	0	
Turbulent flow in Lt CCA n (%)			0.006
Yes	6 (40%)	0	
No	8 (53.3%)	15	
No flow	1 (6.7%)	0	
Macaroni Sign totally (Rt and Lt) n (%)			0.001
Yes	9 (60%)	0	
No	6 (40%)	15	
Macaroni Sign Rt n (%)			0.002
Yes	8 (53.3%)	0	
No	7 (46.7%)	15	
Macaroni Sign Lt n (%)			0.002
Yes	8 (53.3%)	0	
No	7 (46.7%)	15	
Atherosclerotic Plaque n (%)			0.715
Yes	7 (46.7%)	8 (53.3%)	
No	8 (53.3%)	7 (46.7%)	
Rt CCA RI	0.76±0.14	0.71±0.07	0.212
Lt CCA RI	0.79±0.17	0.68±0.06	0.047

TAK: Takayasu's arteritis, DM: Diabetes mellitus, n: number, IMT: intima–media thickness, Rt: Right, Lt: Left, CCA: Common carotid artery, ICA: Internal carotid artery, RI: Reversibility index.

Table 4. Comparison of the risk factors between TAK and DM patients in the multiple logistic regression model

Variables	TAK (n=15)	DM (n=15)	Odds Ratio (OR)	95% Confidence Interval (CI)	P-value
Age	35.20±8.85	51.13±8.47	0.77	0.62-0.94	0.01
BMI	24.41±4.36	28.34±5.40	0.71	0.49-1.03	0.07
CVD					
Yes	5 (33.3%)	1 (6.7%)	0.13	0.03-6.40	0.31
No	10 (66.7%)	14 (93.3%)	1 (Ref)	-	
History of HTN					
Yes	4 (26.7%)	7 (46.7%)	0.55	0.03-11.15	0.25
No	11 (73.3%)	8 (53.3%)	1 (Ref)	-	
CRP	15.09±20.16	7.38±8.74	0.94	0.74-1.21	0.67
ESR	32±31.84	22.07±13.14	1.06	0.91-1.24	0.40

BMI: Body mass index, CVD: cardiovascular disease, HTN: hypertension, CRP: C-reactive protein, ESR: Erythrocyte Sedimentation Rate

Discussion

Takayasu's arteritis is a rare disease that tends to present in young Asian woman (12) and considered as 6% of vasculitis cause in Iran (13). Vascular involvement is common and stroke occurs approximately 10 % in course of disease (14). In this study, the ratio of female to male was 4:1. We evaluated the carotid sonographic features in TAK when compared with DM as one of the most common cause of atherosclerosis (4). Also, we assessed the traditional risk factors of atherosclerosis, available serum level of metabolic and inflammatory biomarkers. Relation between systemic inflammation and atherosclerosis reported previously (5, 8, 11). Carotid artery plaques have been reported in one third of the patients with TAK (11). In our study, unilateral complete occlusion of carotid observed in 3 (20%) patients with TAK that they had history of stroke. (Complete occlusion of Lt CCA in 2, Rt CCA in 1,). Nevertheless, prevalence of atherosclerotic plaque was 46.7% in TAK and 53.3% in DM. It was almost similar to the results of other studies (8, 11).

Seyahi et.al reported carotid artery plaque in 27% patients with Takayasu arteritis, 18% patients with systemic lupus erythematous (SLE), and in 2% controls(5). Earliest finding of arteritis in sonography is wall thickening. First cases described by ultrasound reported the, homogeneous, circumferential vessel wall thickening in the proximal common carotid artery, had been causing a long segment of narrowing of the lumen in TAK (15-17) that is different from atherosclerosis (18). In studies, increase in intima-media thickness of carotid arteries in TAK reported (5, 10, 11, 19). We measured the IMT in multilevel such as; before bifurcation of both CCAs and after bifurcation of both ICAs, and reported with details that never reported in this format. IMT increased significantly in multi-levels of carotid arteries where our measurements performed in TAK patients compared to diabetic ones (table 3). In TAK group, the greatest IMT depicted before bifurcation of Lt CCA. (Before bifurcation Lt CCA IMT 1.41±0.98 mm in TAK, 0.63±0.17 mm in DM). We detected more increased IMT of carotid arteries in TAK, compared to other study. In the TAK group, the highest observed IMT was 1.41±0.98 mm and 1.35±0.87 mm a in the order before bifurcation Lt CCA and Rt CCA (P=0.015, P=0.005). Finally, the mean IMT of these four levels that measured was 1.1±0.71 mm.

An IMT < 0.7 mm is normal and 0.7 mm < IMT > 1.5 mm interpret as a thickened intima (10) media. In some studies, evaluation of carotid arteries has shown increased IMT in TAK, but in our study mean IMT that measured in TAK group is higher than other studies (5, 10, 11). First time, Seyahi et al. evaluated carotid arteries in TAK and systemic lupus erythematous (SLE). They reported increased of carotid arteries IMT in TAK (0.95±0.31 mm). There was no difference between IMT of SLE and healthy control (0.58±0.10 mm in SLE and 0.59±0.08 mm in controls) (5). In one study, IMT was more in DM group. IMT was reported 0.90± 0.36 mm in TAK, 0.96±0.25 in DM 0.40±0.12 mm and, 0.40±0.12 mm in healthy control by Serdal et al. that is different from our result (11).

IMT of carotid arteries in TAK compared to rheumatoid arthritis, showed , IMT of 0.91 mm±0.36 in TAK, 0.76 mm±0.15 in RA and 0.71±0.14 mm in control consecutively (8). Mean age of our patients with TAK was 35.20±8.85 with disease duration 7.73±5.56 years, that was similar to other studies in demographics however, these factors do not

seem to be the cause of the difference in IMT (5, 8). In addition to the increased IMT in sonography of TAK, the presence of macaroni sign and turbulence can be seen in affected patients that are specific for TAK. Diffuse and homogeneous intima–media thickening >1 mm, in 76 % of patients with TAK and the absence of this finding in patients with SLE or the control group by Seyahi et al. had defined as sonographic finding suggestive for involvement with Takayasu arteritis (5). Also, Serdal et al. reported macaroni sign in 78% in TAK, 2% DM and Turbulence in 14% of TAK(11). Notably, in our patient with TAK, macaroni sign was seen of 60% patients(P=0.001) and turbulent flow (P=0.006) was seen of 46% patients and, these finding did not detect in DM. Additionally, among patients with TAK, increased resistive index was detected(P=0.047). It was 0.79± 0.17 in Lt CCA that was higher when compared with measured amounts RI that reported previously (11).Thus, patients can develop this feature during course of disease.

Metabolic syndrome in 14 to 62.8% of patients with autoimmune disorders had been observed. Also, atherosclerosis in patients with rheumatic diseases, reported(4). Some studies, however, have suggested an association between atherosclerosis and traditional atherosclerotic risk factors in TAK (12) but in our study patients with DM showed more CVD risk factors including HTN on physical exam (P= 0.042), higher BMI (P=0036) and greater level of FBS, cholesterol, LDL, triglyceride, AST, ALT, ALKP and less Cr levels (p<0.05), despite equivalent atherosclerosis rate and lower IMT compared with TAK. On the other side, CVD was higher in TAK group. ESR, CRP were higher in TAK however analysis cannot declare this fact, perhaps due to the small size of a sample because of the rarity of TAK. That seems the inflammation has a core stone of CVD in TAK. We interpret that whatever is important increasing IMT in Tak is not traditional CVD risk factor. To our knowledge, no reliable serological marker for TAK course has been described. However, ESR and CRP are commonly used to monitor disease activity in TAK but cannot distinct TAK progression always (20).

ESR has a sensitivity of 72% and specificity of 56% for active TAK, while CRP has a sensitivity of 71.4% and specificity up to 100% (6, 21). However, TAK can persist in the normal ESR and CRP (21). Also, fibrinogen is an acute-phase protein, a well-known marker of inflammation (7) that we assessed in this study, is higher in people with cardiovascular system diseases(22, 23) and never evaluated before in TAK. Although the serum level of ESR, CRP and fibrinogen was higher in patients with TAK than in DM, the difference was not statistically significant (p>0.05). On the other side, CBC seem to be simple and clear to show inflammation is better than ESR, CRP when compared in two group. WBC and platelet amounts were higher (P=0.039, P=0.042) and hemoglobulin (P=0.043) was lower in the TAK group. We detected the correlation of CRP and before bifurcation right CCA IMT (P= 0.051) also, correlation of ESR (P= 0.017) and CRP (P= 0.011) with before bifurcation left CCA IMT. A study on RA and TAK reported that CRP > 12 mg is strongly associated with accelerated atherosclerosis development (13).

As well another study evaluation of carotid IMT in patients with RA showed that CRP is correlated with the degree of preclinical atherosclerosis (9).Additionally, we showed the correlation between ESR with CRP (p-<0.001), with a coefficient correlation of 0.920 but no correlation between fibrinogen and ESR, or CRP detected. Interestingly, our findings showed that, for each unit increase in CPR, the value of before bifurcation right CCA mean IMT increases by 0.02 and this increase was statistically significant after adjusting for age, CVD, and HTN (P=0.05) that was never reported previously. Also, TAK patients had an average of 0.6 more before bifurcation right CCA mean IMT than DM patients (P=0.07) which was borderline significant. In other words, according to other studies (8, 9), we showed that what is related to the increase in the thickness of the intima-media is a higher CRP.

Our study like other studies of Takayasu arthritis has limited sample sizes due to the rarity of the disease, and heterogenous disease with varying clinical presentation making it difficult to achieve statistically significant results. So, a meta-analysis by combining data from multiple studies can increase the statistical power of analysis and provide a more reliable and precise estimate of the effect of sonography in Takayasu arthritis studies. Carotid sonography can be valuable in the management of Takayasu arteritis. Our study showed the parameters that can differentiate TAK from other causes of atherosclerosis including; the presence of macaroni sign, turbulence, and higher IMT and resistivity index and interestingly what is associated with increased intima–media thickness is higher CRP.

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Authors' contribution: Maryam Haghighi-Morad and Reza Rezaei: contributed equally; Resources, Validation. Muhanna Kazempour: Conceptualization, Methodology, Validation, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Project administration, funding acquisition. Mohammad Mehdi Emam: Resources, Validation. Arezoo Ranjbar Arani: Resources, Validation. Mahbobeh Taheri: Formal analysis. Parisa Delkash: Resources, Validation.

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