Carotid artery ultrasonography and shear wave elastography in Takayasu's arteritis: a comparative analysis with diabetes mellitus

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Abstract

Objective

Takayasu's arteritis (TAK) is a chronic inflammatory large vessel vasculitis with a grim prognosis due to the excessive risk for cardiovascular (CV) diseases. Its diagnosis relies on radiographic imaging and its differentiation particularly from atherosclerosis could be challenging. Hypothesising that vascular morphology observed in TAK would be comparable to that found in type 2 diabetes mellitus (T2DM), a prototype for advanced atherosclerosis, we compared two disease groups using carotid artery B mode US and shear wave elastography (SWE).

Methods

A total of 72 patients with TAK (63F/9M; mean age: 42.7± 10.0 years) and 74 patients with T2DM (65F/9M; mean age: 50.2± 7.1 years) were studied. Intima-media thickness (IMT), outer diameter and arterial stiffness as assessed by SWE values were measured on the common carotid artery (CCA) and atherosclerotic plaques were recorded. Clinical characteristics, CV risk factors and previous history of CV diseases were determined. Framingham risk score was calculated.

Results

Patients with TAK exhibited significantly lower atherosclerotic risk but higher systolic blood pressure (BP) levels compared to those with T2DM. The mean values of CCA IMT, outer diameter, and stiffness were significantly elevated among patients with TAK compared to those with T2DM. Carotid artery plaques were evenly distributed between the study groups, but their anatomical localisation and composition differed significantly. While coronary artery disease (CAD) was more prevalent among T2DM patients, cerebrovascular diseases were more frequent among TAK patients.

Conclusion

Our study revealed distinctive vascular alterations and atherosclerotic changes when compared to advanced atherosclerosis associated with T2DM. Apart from these, higher levels of systolic BP and significantly different distribution of CV diseases between TAK and T2DM also suggest that TAK should be handled with distinct assessment strategies than that employed in conventional atherosclerotic conditions.

Key words

arterial stiffness, shear wave elastography, atherosclerosis, carotid artery, Takayasu's arteritis, diabetes mellitus, cardiovascular events

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Received on April 25, 2024; accepted in revised form on June 3, 2024.

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Competing interests: E. Seyahi has received honoraria from Novartis, UCB Pharma, Abbvie and Pfizer. The other authors have declared no competing interests.

Introduction

Takayasu's arteritis (TAK) is a large-vessel vasculitis of unknown cause characterised by chronic granulomatous inflammation and adventitial fibrosis (1-4). It is a rare disease with the highest reported prevalence rate reaching 4 per 100.000 individuals seen mostly among young women of Asian descent (1, 2).

TAK affects aorta and its first branches causing stenosis or occlusion and rarely dilatation or aneurysms. Life expectancy is decreased and cardiovascular (CV) diseases represent major causes of morbidity and mortality (5-7). The cumulative incidence of CV events at 10 years was reported to be 4.4 times higher than age and gender adjusted non-diseased control population (7). Elevated cardiovascular risk stem mainly from primary vasculitis, adventitial fibrosis, and associated inflammation, but other factors such as severe arterial hypertension, reduced elasticity of arterial walls, accelerated atherosclerosis and metabolic syndrome could also contribute (3, 8-12). Yet, evidence is scarce and the extent and causes of this CV risk have not been thoroughly assessed.

TAK has an insidious onset leading to prolonged delays in diagnosis presumably due to the several challenges in its diagnosis, presence of vague symptoms and extensive arterial collateral formation (2). Since there are no reliable clinical signs, laboratory tests, or easily accessible tissue biopsy available, its identification is based on the demonstration of homogenous and concentric arterial wall thickening on radiological imaging. However, its differential diagnosis, especially its distinction from atherosclerosis using solely radiographic data may not be always straightforward. To make things worse, TAK itself is highly susceptible to premature and accelerated atherosclerosis (8-10). Post-mortem examinations and radiological studies have uncovered clear evidence of preclinical or clinical atherosclerotic changes in young patients with TAK, even in the absence of conventional CV risk factors (12-14). We observed that a significant portion of patients with TAK exhibit diffuse aortic wall calcification (45%), coronary calcification (10%) and carotid artery plaques (up to 27%) (8-10). Moreover, we and others identified functional and morphological vascular abnormalities such as significantly increased intima-media thickening, arterial stiffness and vascular dilatation that can be attributed to the primary vasculitis, as well as to the superimposed atherosclerosis (8-10, 15-18). To note, while, these vascular changes have been evaluated in certain inflammatory disease groups or healthy individuals serving as controls, it is not known whether or how they would differ in a state of advanced atherosclerosis.

Diabetes mellitus, represents the prototype disease for its robust association with advanced atherosclerosis, surpassing the strength of any other atherosclerotic risk factors (19). Atherosclerotic CV events are the major complications and the leading cause of mortality in type 2 diabetes mellitus (T2DM), the most prevalent form of diabetes mellitus (19). Due to the excessive risk for future CV events as such, T2DM has been recognised as a coronary heart disease risk equivalent (20).

Speculating that vascular changes that we observe in our TAK cohort would be comparable to a cohort of T2DM who carry overly high atherosclerotic risk factors, we wanted to test our hypothesis in a worst-case scenario. Therefore, in this cross-sectional study our aim was to see whether carotid artery morphology and elasticity studied using ultrasonography (US) and shear wave elastography (SWE), respectively, would differ between TAK and T2DM.

Materials and methods

Participants

This cross-sectional study was conducted at Cerrahpasa Medical Faculty at Istanbul University-Cerrahpasa, Istanbul between May 2023 and August 2023. We investigated patients with TAK aged 18-55 years who were consecutively seen in the department of rheumatology. TAK patients with T2DM were excluded from the study. Similarly, consecutive outpatients with T2DM who were routinely followed up in the department of endocrinology-metabolism and diabetes, were studied.

Patients with Type 1 diabetes mellitus, those with previous auto-immune or auto-inflammatory rheumatic disease and those with renal failure (serum concentration of creatinine >1.4 mg/dl) were not included in the study. TAK and T2DM patients fulfilled the respective diagnostic criteria (21-22).

T2DM patients were gender matched with TAK patients. However, for the study purposes, we did not set an age range for T2DM patients. A total of 40% of TAK patients had a history of established CV disease such as previous history of myocardial infarction, stroke, peripheral arterial disease or heart failure or any history of cardiovascular intervention or surgery. Consequently, we intended to construct the T2DM cohort in a manner that mirrored this 40% prevalence of established CV disease among TAK patients.

Assessment of traditional cardiovascular risk factors

As previously described (10), CV risk factors were determined using a standardised questionnaire. Hypertension was defined as having a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg, or using antihypertensive drugs. Patients' arterial blood pressure (BP) measurements were made from both upper and lower extremities patients after a 5 min rest. Only the highest level measured was taken into consideration. However, in the TAK group arterial BP was absent on the right arm in 5 patients, on the left arm in 11, on both arms in 5, on the left leg in 2, on the right leg in 2, on either leg in five and on either four extremities in 2. In these patients, measurements were made from either available contralateral upper or lower extremity.

Blood samples were collected after overnight fasting to measure serum levels of total cholesterol, triglyceride, low density lipoprotein (LDL), high density lipoprotein (HDL), haemoglobin A1c (HbA1c), and hs-CRP. Fasting plasma glucose (FPG) was also examined. Framingham risk score which estimates 10-year risk for having any CV event was also calculated [23]. Disease duration, clinical characteristics, previous history of CV events and information related to immunosuppressive drug use were obtained from the patient's charts. The Indian Takayasu arteritis disease activity score (ITAS2010) was calculated based on the clinical and laboratory findings that were available within the last 3 months of the study entry.

Ultrasound and shear wave elastography protocol

Carotid artery B-mode US and SWE examinations were performed by a radiologist (A.K.U) as previously described in detail (10). The radiologist was blinded to the clinical identity of the patients. Aplio 500 Platinum unit (Canon Medical Systems Corporation, Tokyo, Japan) equipped with a linear transducer (14 MHz) was used.

Initially, B-mode ultrasound (US) examination was made scanning the right and left common carotid artery (CCA), carotid bulb, carotid bifurcation, and the proximal segments of the internal (ICA) and external carotid arteries (ECA) in both longitudinal and transverse planes. Then atherosclerotic plaques were documented and their localisation and composition were described. Intima-media thickness (IMT) measurements were taken from the posterior wall of both the right and left CCAs in the longitudinal plane, specifically at the level 1 cm proximal to the carotid bulb. In the presence of plaques, IMT measurements were obtained from the optimal outer margins. The cut-off for a diffuse increase in IMT was set at ≥0.9 mm, a value derived from our pioneering study's lower limit of the 95% confidence interval (8).

Furthermore, the inner and outer diameters of the CCA were measured on the side displaying the most prominent changes. Stiffness measurements using shear wave elastography (SWE) were conducted on the superficial wall of the CCA within 1–4 cm proximal to the carotid bifurcation in the axial plane, steering clear of plaques. A 1 mm-sized region of interest (ROI) was strategically placed on the carotid wall, excluding the lumen, surrounding tissues, and atherosclerotic plaques. The average of three SWE measurements was then calculated, and SWE values were expressed in kilopascals (kPa).

All data were stored in local picture archives and communication system (Extremepacs, Ankara, Turkey).

Ethical statement

The study protocol was approved by the Ethics Committee of Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty (83045809-604.01.01-692035/16/05/2023). Oral informed consent was obtained from each enrolled participant. All study procedures were carried out in accordance with the ethical standards of the Helsinki Declaration.

Statistical methods

Continuous variables were evaluated for normality distribution using the Shapiro-Wilk test, those with a more or less normal distribution were expressed as mean ± standard deviation and others as median and minimum-maximum values. Categorical variables were presented as frequencies and percentages (%). Comparisons of continuous variables were made by using Student's *t* tests and one-way ANOVA followed by *post-hoc* Bonferroni test. Continuous variables with non-normal distributions were compared by using Mann-Whitney U and Kruskal Wallis tests with Bonferroni correction for multiple pair wise comparisons. Categorical variables were compared by using Chi-square or Fisher's exact test for proportion. Univariate linear regression tests were used to compare CCA IMT, outer/inner diameters and SWE variables between the study groups. For the study purposes, no atherosclerotic risk factor adjustments were made. The distribution of atherosclerotic plaques, complete carotid occlusion and diffuse IMT thickening (≥ 0.9 mm) were evaluated by calculating binary logistic regression tests.

The link between various demographic and atherosclerotic factors and CCA IMT and stiffness was investigated through first simple then multiple linear regression analyses. Variables exhibiting p-values of <0.05 in the simple analysis were selected for the subsequent multiple regression analysis employing Enter method. To identify atherosclerotic or clinical variables linked

to the presence of plaques, univariate statistical tests such as Chi-square or t-test were employed. Variables found to be associated with plaque presence in these tests were then subjected to further evaluation using the multiple logistic regression test. These analyses were done separately for TAK and T2DM patients, as there were significant differences with regard to demographic and CV characteristics between the two groups.

Whether CCA IMT, CCA diameter and SWE values are able to discriminate TAK patients from the patients with T2DM, receiver operating characteristic (ROC) curve was plotted and area under the curve (AUC) was calculated. Then, sensitivity and specificity values were obtained for the appropriate cut-offs of these variables.

IBM SPSS Statistics for Windows, v.20.0 (IBM Corp., Armonk, NY, USA) was used in the statistical analyses. All statistical tests were two-tailed, and values of $p<0.05$ were considered statistically significant.

Table I. Demographic characteristics and atherosclerotic risk factors.

	Takayasu's arteritis, n= 72	Diabetes mellitus, n= 74	*p* value
Female, n (%)	63 (87.5)	65 (87.8)	1.000
Age, mean ± SD, years	42.7 ± 10.0	50.2 ± 7.1	<0.001
Disease duration, mean ± SD, years	9.3 ± 7.3	8.6 ± 6.8	0.529
BMI, mean ± SD	26.6 ± 5.2	32.2 ± 5.9	<0.001
Current and past smoking history, n (%)	21 (29.6)	35 (47.3)	0.040
Familial history of cardiovascular disease, n (%)	28 (39.4)	22 (29.7)	0.228
Post-menopausal status, n (%)	26 (41.3)	41 (63.1)	0.021
Anti-hypertensive use, n (%)	49 (68.1)	37 (50.0)	0.027
Systolic BP, mean ± SD, mm Hg (upper extremities)	127.8 ± 17.5	119.2 ± 13.7	0.002
Diastolic BP, mean ± SD, mm Hg (upper extremities)	77.9 ± 11.1	75.5 ± 11.0	0.215
Systolic BP, mean ± SD, mm Hg (lower extremities)	147.3 ± 28.4	136.5 ± 14.5	0.005
Diastolic BP, mean ± SD, mm Hg (lower extremities)	82.4 ± 16.7	82.8 ± 13.3	0.862
Statin use, n (%)	30 (41.7)	46 (62.2)	0.020
Total cholesterol, mean ± SD, mg/dl	197.1 ± 50.2	190.5 ± 46.4	0.412
LDL cholesterol, mean ± SD, mg/dl	118.5 ± 37.6	113.0 ± 40.4	0.398
HDL cholesterol, mean ± SD, mg/dl	58.5 ± 17.4	49.2 ± 13.0	<0.001
Triglycerides, mean ± SD, mg/dl	119.3 ± 59.5	187.9 ± 97.3	<0.001
Fasting glucose, mean ± SD, mg/dl	88.1 ± 12.0	158.4 ± 73.6	<0.001
Hba1c, mean ± SD, mg/dl	5.6 ± 0.8	8.0 ± 2.3	<0.001
Serum urea, mean ± SD, mg/dl	27.1 ± 8.0	28.9 ± 8.8	0.207
Serum creatinine, mean ± SD, mg/dl	0.7 ± 0.1	0.7 ± 0.2	0.949
Serum uric acid, mean ± SD, mg/dl	4.1 ± 1.1	4.3 ± 1.4	0.558
Framingham risk score, median [min-max], %	3.5 [0-27]	9.0 [0-32]	<0.001
hsCRP levels, median [min-max], mg/dl	2.18 [0.0-144.0]	3.22 [0.0-33.0]	0.059
ESR, median [min-max], mm/h	14.0 [2-107]	11.0 [2-43]	0.078
Established cardiovascular disease, n (%)	29* (40.3)	29 (39.2)	NA
Coronary artery disease, n (%)	6 (8.3)	26 (35.1)	<0.001
Stroke or TIA, n (%)	16 (22.2)	4 (5.4)	0.004
Peripheral arterial disease, n (%)	2 (2.8)	1 (1.4)	0.617
Carotid-subclavian artery disease, n (%)	5 (6.9)	0	0.027
Aortic/visceral artery disease, n (%)	5 (6.9)	0	0.027

BMI: body mass index; BP: blood pressure; TIA: transient ischaemic attack; LDL: low-density lipoprotein; HDL: high-density lipoprotein; ESR: erythrocyte sedimentation rate; hsCRP: high-sensitivity C reactive protein; SD: standard deviation; NA: not applicable.
*5 patients had CV events on two different arterial anatomical areas.

Results

Demographic and clinical characteristics of the patient groups

- TAK

We studied 72 (63F/9M) patients with TAK. Their mean age was 42.7±10.0 years and mean disease duration was 9.3±7.3 years. Carotids (n=57, 79.2%) and subclavian arteries (n=52, 72.2%) followed by thoracic (n=29, 40.2%) and abdominal aorta (n=19, 26.4%) were the most commonly affected vessels. Pulmonary (n=8, 11.1%), renal (n=8, 11.1%), visceral (n=7, 9.7%) and lower extremity arteries (n=6, 8.3%) were less frequently affected. Concomitant inflammatory diseases such as ankylosing spondylitis (n=5), inflammatory bowel disease (n=5), psoriatic arthritis (n=1), and secondary amyloidosis (n=1) were observed in 12 patients (16.7%). Established CV disease was documented in 29 (25 F/4M; 40.3%) patients. Six patients (4F/2M) had history of coronary artery disease (CAD), 16 (13F/3M) were diagnosed with ischaemic cerebrovascular disease such as stroke (n=14) or transient ischaemic attack (n=2), and two females had peripheric arterial disease, involving iliac or femoral arteries. Additionally, 5 patients (4F/1M) underwent surgery or vascular intervention for aortic or visceral artery disease while another 5 (all female) underwent carotid-subclavian bypass surgery for subclavian or carotid artery stenosis or occlusion. A total of 5 patients (3F/2M) had CV events on two different arterial anatomical areas.

Apart from 2 patients who were off treatment, the remaining were using glucocorticoids (n=45, 62.5%), biological agents (n=52, 72.2%) or non-biological disease modifying anti-rheumatic drugs (DMARD's) (n=38, 52.8%). The disease was in remission in a total of 45 (62.5%) patients (ITAS2010 value: 0), while in the remaining, median ITAS2010 value was measured as 3 [min:1, max: 7].

- Type 2 diabetes mellitus

We also investigated 74 (65F/9M) patients with T2DM with a mean age of 50.2±7.1 years and a mean disease duration of 8.6±6.8 years. A total of 29 (25 F/4M; 39.2%) patients had established CV disease such as CAD (n=26), ischaemic cerebrovascular disease such as stroke (n=3) or transient ischaemic attack (n=1), and peripheral arterial disease (n=1). A total of 26 (22F/4M) described history of angina (n=18) or myocardial infarction (n=8) and 26 (22F/4M) patients underwent percutaneous coronary intervention of whom 4 (3F/1M) had also coronary by-pass grafting.

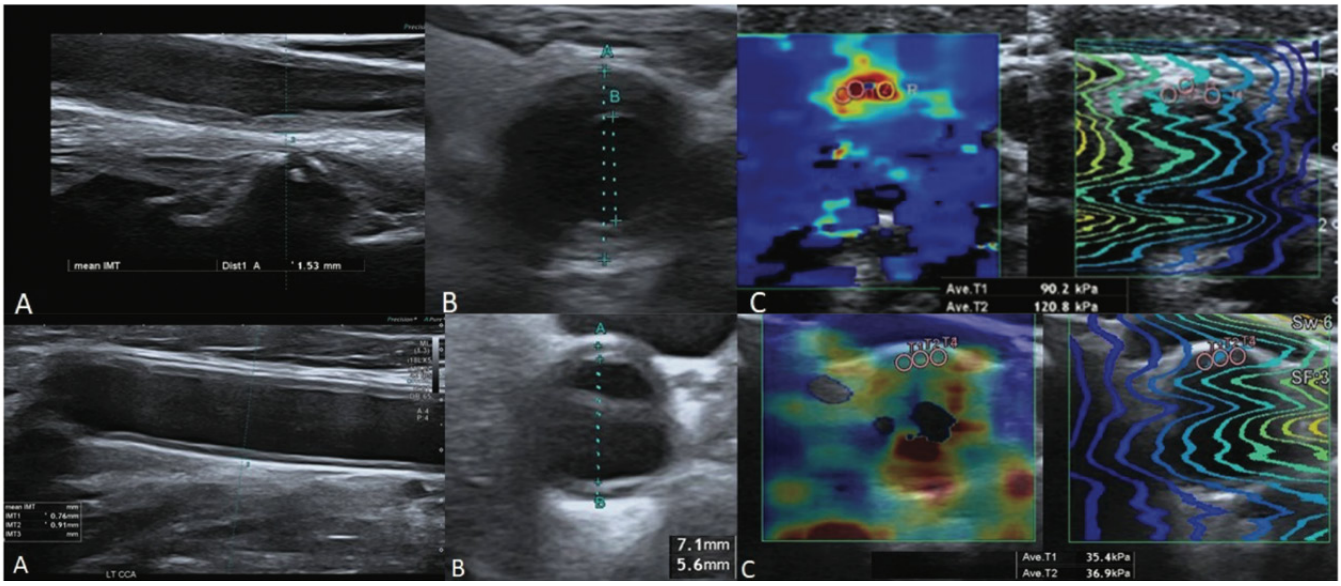

Fig. 1. Upper panel: US images of a 39-year-old female patient diagnosed with TAK.
A: B mode US image obtained from the left CCA in the longitudinal plane shows the measurement of marked thickened intima media layer.
B: The inner and outer diameters of the left CCA are measured in the transverse plane, revealing severe peripheral wall thickening and lumen narrowing.
C: SWE examination (colour and propagation map) obtained in the transverse plane shows SWE measurements in kPa using circular ROI (1 mm) at the plaque-free level from the anterior wall of the left CCA.
Lower panel: US images of a 54-year-old female patient diagnosed with T2DM.
A: B-mode US image obtained from the left CCA in the longitudinal plane shows measurement of a slightly thickened intima media layer.
B: Measurement of the inner and outer diameters of the left CCA in the transverse plane where the lumen patency appears normal.
C: SWE examination (colour and propagation map) obtained in the transverse plane shows SWE measurements in kPa using circular ROI (1 mm) at the plaque-free level from the anterior wall of the left CCA.

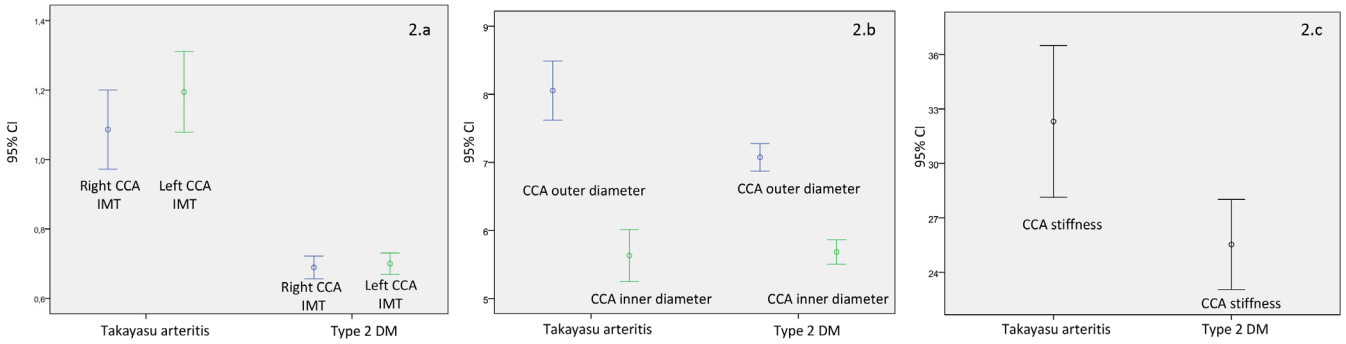

Fig. 2. Carotid artery physiological characteristics in TAK and type 2 diabetes mellitus (T2DM). 2a. The mean and 95% confidence intervals (CI) values of the right and left common carotid artery (CCA) intima media thickness (IMT). 2b. The mean and confidence intervals values of the outer and inner CCA diameters. 2c. The mean and confidence intervals values of the carotid artery stiffness measured as SWE values. CCA IMT and outer and inner diameters are expressed in mm. CCA stiffness is expressed in kPa.

A total of 25 (33.8%) patients were receiving insulin treatment with or without oral anti-diabetic agents and/or glucagon-like peptide 1 (GLP-1) agonists (n=8), while the remaining were receiving only oral anti-diabetic drugs. Oral anti-diabetic drugs that were used by the whole T2DM cohort were sodium glucose co-transporter 2 (SGLT-2) inhibitors (n=38), thiazolidinediones (n=2), biguanides (n=62), dipeptidyl peptidase-4 (DPP-4) inhibitors (n=32) and sulfonylureas (n=3). According to glycaemic control criteria, glycaemic control targets were achieved in 33 patients (20).

Atherosclerotic risk factors

Demographic and CV characteristics among patients with TAK and T2DM are shown in Table I. Patients with TAK were significantly younger ($p<0.001$) carried less atherosclerotic risk factors compared to patients with T2DM. Patients with TAK had significantly lower BMI and lower levels of FPG and Hba1c. They were less likely to be post-menopausal and less likely to smoke. Additionally, they had lower hyperlipidaemia as reflected by lower triglycerides levels and higher HDL levels and lower statin use. On the other hand, patients with TAK were significantly more hypertensive as indicated by higher systolic mean BP levels on both lower and upper extremities and more frequent antihypertensive use. The median Framingham risk score was significantly lower in the TAK group than that observed in the

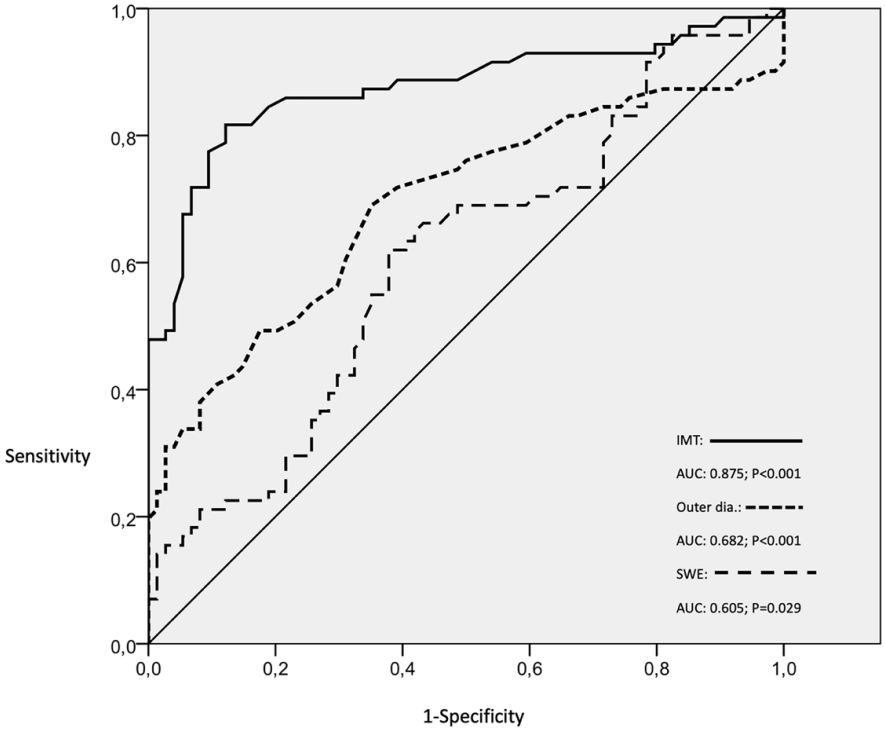

Fig. 3. Receiver operating characteristics (ROC) curves for the carotid artery intima media thickness (CCA IMT), CCA outer diameter and carotid artery stiffness as measured with shear wave elastography (SWE).

	Optimum cut-off	Area under the curve	95% confidence intervals	*p*	Sensitivity	Specificity
CCA IMT	0.783 mm	0.875	0.814-0.937	< 0.001	80.3%	87.8%
CCA outer diameter	7.25 mm	0.682	0.593-0.771	< 0.001	69.0%	64.9%
SWE value	27.0 kPa	0.605	0.513-0.697	0.029	60.6%	62.2%

Table II. Carotid artery intima media thickness, diameter, arterial stiffness and atherosclerotic plaques across study groups.

	Takayasu's arteritis, n= 72	Diabetes mellitus, n= 74	*p* value
Right CCA IMT, mean ± SD, mm	1.10 ± 0.47	0.69 ± 0.14	<0.001
Left CCA IMT, mean ± SD, mm	1.21 ± 0.47	0.70 ± 0.13	<0.001
Diffuse IMT thickness ≥0.9 mm	48 (67.6)	4 (5.4)	<0.001
Total occlusion, n (%)	8 (11.1)	0	0.003
Outer diameter, mean ± SD, mm	8.03 ± 1.84	7.07 ± 0.88	<0.001
Inner diameter, mean ± SD, mm	5.63 ± 1.62	5.69 ± 0.78	0.796
SWE value, mean ± SD, kPa	32.31 ± 17.77	25.53 ± 10.74	0.006
Atherosclerotic plaques, n (%)	23 (31.9)	31 (41.9)	0.214
Localisation			0.001
Bulb or bifurcation	3 (13.0)	15 (48.4)	
Bulb and CCA	9 (39.1)	14 (45.2)	
CCA	11 (47.9)	2 (6.4)	
Structure			0.007
Fibrofatty	8 (34.8)	21 (67.7)	
Fibrofatty and fibrocalcific	3 (13.0)	6 (19.4)	
Fibrocalcific	12 (52.2)	4 (12.9)	

CCA: common carotid artery; SWE: shear wave elastography; IMT: intima-media thickness; SD: standard deviation; kPa: kilopascal.

T2DM [3.5 (range: 0-27) *vs*. 9.0 (range: 0-32), *p*<0.001].

As planned, the overall frequency of established CV disease in both study groups was similar (TAK: 29/72: 40.3% *vs*. T2DM: 29/74: 39.2%). However, we observed that there was a statistically significant difference in their distribution. While CAD was significantly more common among T2DM patients (8.3% *vs*. 35.1%, *p*<0.0001), stroke or TIA (22.2% *vs*. 5.4%, *p*=0.004), carotid-subclavian artery disease (6.9% *vs*. 0, *p*=0.027) and aortic/visceral artery disease (6.9% *vs*. 0, *p*=0.027) were significantly more frequent among TAK patients. Peripheral arterial disease, on the other hand was rare in both study groups (2/72 *vs*. 1/74).

Carotid artery US (B-Mode and SWE findings)

Figure 1 upper and lower panels demonstrate US images of individuals with TAK and T2DM, respectively. Figure 2 depicts the mean and confidence intervals values of the right and left CCA IMT, the mean outer and inner CCA diameters, and the SWE measurements between TAK and T2DM groups, respectively. Figure 3 shows ROC curves for CCA IMT, CCA outer diameter and SWE values.

- CCA IMT

Total carotid artery occlusion was observed in 8 patients with TAK (11.1%), in contrast to none in T2DM. This occurred on the right (n=5), on the left (n=2) or on both carotids (n=1). As shown in Table II and Figure 2, both the right (β: 0.412, 95%CI: 0.298-0.527; *p*<0.001), and the left mean CCA IMT (β: 0.509, 95%CI: 0.396-0.622; *p*<0.001), were found to be significantly increased among patients with TAK compared to patients with T2DM. The optimum cut-off for CCA IMT to differentiate TAK patients from those with T2DM was calculated as 0.783 mm with AUC of 0.875 (95% CI:0.814-0.937, *p*<0.001) and fairly acceptable sensitivity (80.3%) and specificity values (87.8%). We also looked at the frequency of those with diffuse IMT thickness (≥0.9 mm) and found that it was significantly more common in the TAK group (48/72: 67.6%) as compared to T2DM (4/74: 5.4%) with an OR of 36.522 (95% CI:11.874-112.328, *p*<0.001).

- CCA inner and outer diameters

While the mean outer CCA diameter (β: 0.952, 95%CI: 0.483-1.421; *p*<0.001) was significantly higher among TAK

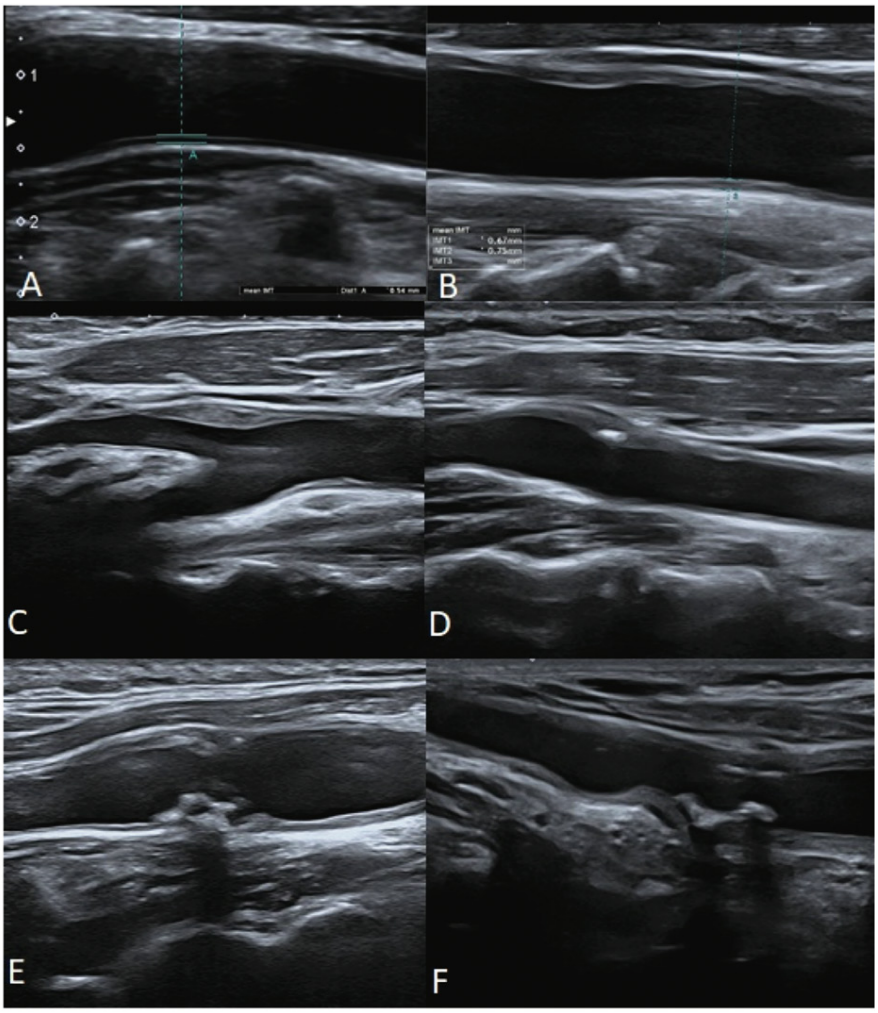

Fig. 4. CCA IMT measurement and B-mode US view of various carotid plaques in patients with T2DM (**A, B, C** and **D**) and in a patient with TAK (**E** and **F**). Measurement of CCA IMT in B-Mode longitudinal image: The two parallel lines are the lumen-intima and media-adventitia interfaces in normal common carotid artery (**A**) and IMT measurement with thickened wall in CCA (**B**). A hypoechogenic fibrofatty plaque with regular surface in posterior wall (**C**) and anterior wall of CCA (**D**). A heterogeneous plaque with a focus of calcification (**E**) and a calcified plaque with shadowing (**F**). TAK: Takayasu's arteritis; T2DM: type 2 diabetes mellitus; US: ultrasonography; CCA IMT: carotid artery intima media thickness.

patients, the mean inner CCA diameter (β: -0.054, 95%CI: -0.468-0.360; *p*=796) did not differ between the study groups (Table II and Fig. 2). ROC identified fair sensitivity (69.0%) and specificity values (64.9 %) with a threshold of 7.25 mm (Fig. 3).

- CCA stiffness

TAK patients had significantly higher carotid artery stiffness as measured with SWE (ß: 6.782, 95%CI: 1.994-11.571; *p*=0.006) (Table II and Fig. 2). A cut-off value of 27.0 kPa was found to discriminate TAK from T2DM (Fig. 3). However, sensitivity (60.6%) and specificity (62.2%) values along with AUC of 0.605 (95% CI: 0.513-0.697, *p*=0.031) were moderate.

Variables associated with CCA IMT and stiffness

- TAK

Variables associated with CCA IMT and SWE values as assessed by simple linear regression among patients with TAK are shown in Supplementary Table S1. Multiple linear regression indicated that systolic (β: 0.010, 95CI%: 0.003-0.016; *p*=0.004) and diastolic BP levels (β: -0.016, 95CI%: -0.027--0.006; *p*=0.003) and SWE values (β: 0.007, 95CI%: 0.001-0.013; *p*=0.016) were associated independently with the mean carotid IMT. On the other hand, diastolic BP levels (β: 0.698, 95CI%: 0.291- 1.105; *p*=0.001), CCA IMT (β: 10.612, 95CI%: 1.378- 19.846; *p*=0.025) and CCA outer diameter (β: 3.326, 95CI%: 1.285- 5.367; *p*=0.002) were found to be independently associated with carotid stiffness on the multiple regression analysis.

- Type 2 diabetes mellitus

There was no variable associated with CCA IMT among patients with T2DM. While both systolic and diastolic BP levels, being post-menopause and Framingham risk score were found to be associated with carotid stiffness using univariate linear analysis, on the multiple linear analysis, no parameter was found to be significant.

Atherosclerotic plaques

Patients with TAK (23, 19F/4M, 31.9%) were somewhat less likely to have atherosclerotic plaques (Fig. 4 and 5) on the carotids when compared to patients with T2DM (31, 28F/3M, 41.9%), however, this was not statistically significant (OR: 0.651, CI 95%: 0.331-1.282, *p*=0.214) (Table II). On the other hand, plaques localisation and composition differed significantly between TAK and T2DM. While plaques in TAK resided significantly more frequently in the proximal parts of the CCA, those in T2DM were mostly found in the distal parts (bulb and or bifurcation) of the CCA. Additionally, plaques in TAK were significantly more likely to be fibrocalcific, whereas those in T2DM were more likely to be fibrofatty.

Age (per 1-year increase) (OR=1.103; 95%CI: 1.034-1.177; *p*=0.003) and the mean carotid IMT (per 1 mm increase) (OR=7.704; 95%CI: 1.916-30.976; *p*=0.004) were found to be independently associated with atherosclerotic plaques as revealed in the multiple logistic regression analyses among patients with TAK. No parameter was found to be significantly associated with atherosclerotic plaque formation among patients with T2DM.

Discussion

We examined morphological characteristics of the carotid artery in individu-

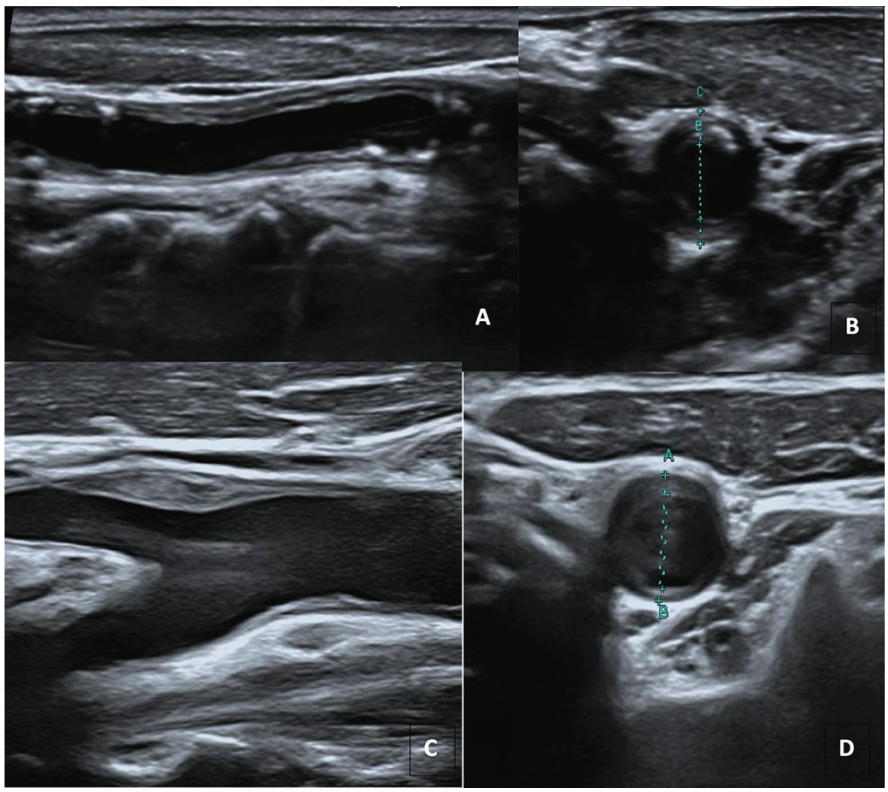

Fig. 5. CCA IMT measurement and B-mode US view of various carotid plaques in a patient with TAK (**A, B**) and in a patient with T2DM (**C** and **D**). Concentric and homogenously increased intima media thickness along with calcified plaques can be seen on the longitudinal section (**A**), as well as on the transverse section (**B**) in a patient with TAK. Fibrofatty plaque is observed in a patient with T2DM on the longitudinal (**C**) and transverse (**D**) planes.
TAK: Takayasu's arteritis; T2DM: type 2 diabetes mellitus; US: ultrasonography.

als with TAK in comparison to those with T2DM, an inflammatory disease well-recognised by its excessive risk for atherosclerotic CV events. For this purpose, we deliberately chose a cohort with T2DM exhibiting significantly elevated atherosclerotic risk factors. Despite the fact that TAK patients had significantly less atherosclerotic risk factors, with the exception of higher systolic BP levels, the mean values of carotid artery IMT, outer diameter and stiffness were found to be significantly increased and atherosclerotic plaque frequency comparable among patients with TAK compared to patients with T2DM. These findings suggest distinctive vascular alterations in individuals with TAK.

Our previous study which used the same methodology indicated that CCA IMT, outer diameter and stiffness values were significantly increased in patients with TAK (44 F/6M, mean age: 39.8±8.2 years) compared to patients with systemic lupus erythematosus (SLE) (38F/5M, mean age: 39.8±8.2) and healthy controls (HCs) (50F/7M, mean age: 39.5±7.1) (10). To note, different from our current study, age and gender were matched and apart from hypertension which was more common in TAK, atherosclerotic risk factors were evenly distributed across the study groups (10). CCA IMT, outer diameter and stiffness as measured with SWE had proven to be discriminative for TAK when compared to HCs, albeit this was less so with the outer diameter [10]. Cut-off values of 0.705 mm for CCA IMT, 6.75 mm for outer diameter and 16.05 kPa for CCA stiffness yielded good sensitivity (81.6% ,73.5% and 91.8%) and specificity values (96.5%, 75.0% and 96.5%), respectively (10). In the current study, we observed that only CCA IMT (with a cut off value of 0.783 mm) could be used to differentiate TAK from T2DM with acceptable sensitivity (80.3%) and specificity (87.8%). The remaining parameters, particularly arterial stiffness exhibited less distinctive value, most probably due to the significant atherosclerotic changes associated with T2DM. The characteristically increased IMT unique to TAK, on the other hand, is primarily due to the association of the vasculitis in the vessel wall.

We observed that the localisation and composition of the atherosclerotic plaques in TAK differed significantly when compared to T2DM, suggesting the role of local vascular factors in the generation of atherosclerosis in TAK. We have previously documented in several studies (8-10) and now confirm in the current, that atherosclerotic plaques in TAK tend to occur on the proximal parts of the CCA rather than bulbus or bifurcation. This is in contrast to 'systemic atherosclerosis' associated with T2DM. Our observation of a significant increase in the development of fibrocalcific plaques, as opposed to fibrofatty plaques, in TAK is a novel finding. While this phenomenon could be due to the increased calcification tendency in TAK (9), it may also have important prognostic implications as such, fibrocalcific plaques are regarded as stable atheromatous changes (24).

At the beginning of the study, we had predefined both study groups to incorporate a 40% prevalence of established CV disease, since both diseases were prone to have excessive risk for CV. However, the distribution of the CV events differed significantly between the study groups. While CAD was significantly more prominent among T2DM patients, ischaemic cerebrovascular diseases were the dominant vascular disease among patients with TAK. Additionally, 10 (13.9%) patients with TAK had subclavian, aortic or visceral/renal artery disease that required vascular intervention or surgery in contrast to none in T2DM. In this context, it is noteworthy that total carotid occlusion occurred in eight patients with TAK, whereas individuals with T2DM did not exhibit such severe carotid disease. Our findings are in line with previous reports suggesting that coronary arteries are relatively less affected (25-26), while there is a notable frequency of cerebrovascular events in TAK (27-29). Similarly, in a study using multi-detec-

tor computed tomography, we have observed that aortic calcifications (45%) were more common than coronary calcifications (11%) in TAK, while these were in similar frequency in SLE (23% and 21%, respectively) and HCs (both were 2.9%) (9). Our results also highlight the selectivity of cardiovascular events in both TAK and T2DM, despite being similarly excessive in both diseases. While advanced atherosclerosis linked to T2DM rarely leads to severe vascular issues in arteries beyond the coronaries, the opposite appears to be true for TAK.

As revealed in the current study and reported previously by a number of researches (7-10, 30), systemic hypertension is a major complication and an important contributor to arterial wall thickening and stiffness in TAK. Our findings suggest that systolic BP levels rather than diastolic are distinctively elevated among patients with TAK compared to T2DM, though the reasons remain unclear. On the other hand, this holds particular significance, since, as a T2DM cohort, despite having elevated atherosclerotic risk factors and a substantial portion with a history of CV events, might not parallel TAK in terms of severe systolic hypertension. The strong association of diastolic BP with carotid arterial stiffness is intriguing and deserves further exploration.

In line with our previous surveys and others (8-10), we again observed an elevated frequency of familial history of CV disease among patients with TAK compared to those with T2DM (39.4% *vs*. 29.7%). While the difference between the study groups did not achieve a statistical significance in the current study, this phenomenon seems to be consistently linked to TAK, with the underlying cause remaining unknown.

Wall *et al*. assessed coronary arterial inflammation in TAK by employing a methodology similar to ours to evaluate atherosclerosis (31). They examined peri-coronary adipose tissue (PCAT) and peri-aortic adipose tissue (PAAT) density on coronary computed tomography angiography (CCTA) among patients with TAK with (32F/4M; median age:53 years) and without CAD (16 F/2M; median age: 42 years) (31). As controls, they studied older patients with atherosclerotic CAD (6F/26M; median age: 65) and also apparently healthy individuals without TAK or CAD (12F/10M; median age: 52) (31). The findings revealed that PCAT and PAAT density on CCTA were higher in TAK patients compared to those with atherosclerotic CAD or the control group, indicating that younger, predominately female TAK patients without traditional CV risk factors were more prone for atherosclerosis than their much older counterparts with established CV diseases. Wall's study (31) supports our findings as well.

Carotid IMT and arterial stiffness are regarded as early indicators for atherosclerosis and are well recognised in T2DM and even in prediabetic states and metabolic syndrome (32-39). Both are associated with CV risk factors and serve as predictive markers for CV diseases. According to a comprehensive meta-analysis involving 23 studies, the observed mean difference of 0.13 mm in carotid IMT between individuals with T2DM and their age-matched HCs implies that T2DM patients exhibit an aging effect equivalent to a decade compared to the healthy group (34). The mean difference in IMT is also correlated with a rise in relative risks of 38% for myocardial infarction and 37% for stroke, respectively. Nevertheless, the meta-analysis also indicated that there was a great heterogeneity between IMT measurements across diabetic cohorts, due to the variances in sample size, demographic characteristics and the preferred US method (predefined versus thickest segment measurement) (34). Arterial stiffness, on the other hand, has been evaluated using various methods in T2DM with pulse wave velocity being the most prevalent (35-38). In general, the data suggest that diabetic arteries appear to age at an accelerated rate at an earlier age compared to arteries in non-diabetic peers (39). To our knowledge, our study seems to be the first to explore arterial elasticity loss in a diabetic cohort using SWE. Although Zhang *et al*. used real-time US elastography, they calculated the strain ratio (SR) described as the blood strain divided by that of the carotid arterial wall (35). They found a higher SR among diabetic patients with microalbuminuria than those without.

Our study has several limitations. Importantly, as we discussed earlier, there were obvious differences regarding demographic and atherosclerotic risk factors between the study groups. We chose not to adjust them, because: a. our goal was to specifically compare the authentic populations of TAK and T2DM, each with its own inherent characteristics and b. propensity matching or another method could weaken the generalisability of our results (31, 40). We did not include HCs as a control group for the same reason as well. Because type 1 DM has a different pathogenesis than T2DM, we did not include patients with T1DM, either. We could choose a much younger cohort with TAK, but this would be smaller and not quite representative. In the current study we did not assess inter-observer and intra-observer variability, because, our previous study (9) using the same US technique demonstrated that our method was quite reliable.

Our study revealed important findings:

- Takayasu arteritis demonstrates a unique carotid artery morphology when compared to advanced atherosclerosis associated with T2DM. Carotid artery wall thickness is characteristically increased, parallel to the increase in thickness, arterial wall elasticity is decreased and carotids are enlarged. While similar changes can be observed in T2DM, they are less prominent, particularly with less pronounced IMT.
- Additionally, there is strong association with atherosclerosis which appears to differ from what is observed in T2DM, tending to be localised rather than systemic and linked with calcification. Moreover, the so-called atheromatous lesions of the TAK are highly localised and lie directly across from pre-existing inflammatory lesions, particularly in the supra-aortic trunk.
- Beyond carotid morphology, additional characteristic features associated with TAK distinct from T2DM were identified, including significantly higher levels of systolic BP

levels, higher frequency of cerebrovascular diseases along with a lower frequency of CAD.

All these findings could suggest whether so-called atherosclerotic plaques in the arterial wall in TAK could be indeed repair of granulomatous inflammatory lesions in the form of fibro-calcifications (Saadoun, personnel communications).

In conclusion, as we suggested previously (8-10), current study confirms that TAK has unique vascular characteristics and its associated atherosclerotic changes seem to be quite distinct from what is observed in the general population. Traditional tools such as Framingham risk scoring seem unable to capture its excessive CV risk. We propose that patients with TAK require distinct risk assessment strategies. Additionally, further research is needed to investigate whether early and intensive immunosuppressive treatment can potentially reverse the atherosclerotic burden in this particular disease.

Acknowledgements

The authors wish to thank Professors Gokhan Keser and David Saadoun for their valuable comments.

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