ORIGINAL PAPER

Is there an association between upper limb claudication and handgrip strength in Takayasu arteritis?

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SUMMARY

Limb vascular claudication and hand muscle weakness are common symptoms of Takayasu arteritis (TAK). However, no studies have correlated these two symptoms. Therefore, the aim of the study was to evaluate handgrip strength and its correlation with both upper-limb vascular claudication and imaging of the vessels.

This cross-sectional study compared 36 patients with TAK who were matched by age, gender, and body mass index with 36 individuals without TAK (CTR). Hand strength (assessed with handgrip dynamometer), functional capacity (Health Assessment Questionnaire, HAQ), upper-limb vascular claudication symptoms (patients' self-reported form), and disease activity (Indian Takayasu Clinical Activity Score [ITAS] 2010; Physician Global Assessment [PGA], C-reactive protein, and erythrocyte sedimentation rate) were evaluated as well as vessel imaging (e.g., angiotomography or angioresonance) and blood pressure.

The median age of the patients was 42.0 years (35.5-51.5 years), whereas the mean disease duration was 13.1±6.8 years. No patient had active disease. Compared to the CTR, the patients with TAK showed reduced strength in the left-hand (22.9±5.9 vs 26.3±5.6 kg; p=0.014) and increased HAQ scores [0.50 (0.12-0.87) vs 0.00 (0.00-0.00); p<0.001]. Both groups had comparable blood pressure. Among patients with TAK, left-hand strength was inversely correlated with HAQ (Spearman correlation: rho=–0.584; p<0.001) and positively correlated with right-hand strength (rho=0.644; p<0.001). Moreover, neither hand's strengths in the patients were correlated with subclavian stenosis imaging, blood pressure or limb vascular claudication.

The reduction of strength in the upper left limb is inversely related to the functional capacity (HAQ score) of TAK. This reduction appears unrelated to classical vascular claudication, vessel imaging or blood pressure.

Key words: Strength, functional capacity, hand grip, limb claudication, systemic vasculitis.

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INTRODUCTION

Takayasu arteritis (TAK) is a primary systemic vasculitis that affects the large arterial vessels and their main branches (1-3). It is a rare disease that mainly affects young women (1, 2). The main characteristic of TAK is chronic vascular inflammation, leading to the presence of stenosis, occlusions, ectasias and/or aneurysms and consequently producing pulse differences between the limbs, as well as vascular claudication (3-5). The latter is a relatively common symptom in TAK patients and may even lead to discomfort and limitations to routine activities (3). Another recurrent condition in patients with TAK is decreased muscle strength and aerobic capacity (6-8). All of these factors can also limit daily activities, and impair quality of life and function. This situation may also lead to decreased handgrip, although no studies in the literature have shown this correlation yet.

In medical practice, symptom assessment lacks quantitative tools and is based primarily on physician experience, patient self-reporting and questionnaires, making it difficult to assess the true extent of symptoms or disease activity, specifically the reduction in muscle strength (9-12). In this context, the handgrip dynamometer provides a direct measure, besides being widely used in other autoimmune diseases, and may facilitate the assessment of both upper limb weakness and possible differences in

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strength resulting from long-term vascular claudication (13, 14).

Although there is no scientific evidence to date, handgrip strength may have an inverse relationship with the presence of vascular anatomical changes (arterial stenosis or occlusions) and vascular claudication, which in turn may corroborate the damage to activities of daily living and the functional capacity. Therefore, the primary objective of this study was to evaluate upper limb handgrip strength in TAK patients. The secondary objective was to evaluate possible correlations of handgrip strength, upper limb vascular claudication, blood pressure and vascular changes seen by imaging (*e.g.*, angiotomography of blood vessels) as well as possible associations between vascular symptoms and imaging findings. The final objective was to measure the symptoms' interference with these patients' functional capacity.

PATIENTS AND METHODS

This cross-sectional, single-center study was conducted between 2018 and 2019. Initially, 90 patients with TAK who met three or more of the six items of the modified 1990 American College of Rheumatology (ACR) classification criteria for TAK were evaluated (3). Instead of the arteriogram abnormality criterion, we considered abnormal angiotomography or angioresonance images of large arterial vessels and their main branches.

This study was approved by the local Ethics Committee (CAAE 89386618.0.0000.0068) and all participants signed an informed consent form. The study met all ethical criteria for conducting human studies (15). Patients who had sequelae related to cerebrovascular accidents, neurogenic claudication, fibromyalgia, overlap syndromes, or other diseases or conditions that could have affected the analyses of grip strength were excluded.

Eligible patients went through the following steps, shown in Figure 1. The following information was collected from patients' interviews. If necessary, additional patients' data were obtained from electronic medical records:

- Age, disease duration, body mass index (BMI);
- Comorbidities: diabetes mellitus was defined when the fasting plasma glucose test was ≥126 mg/dL and/or the result of the oral glucose tolerance test ≥200 mg/dL, or specific drug treatment was present (16, 17); systemic arterial hypertension was considered when blood pressure had systolic values ≥130 mmHg and/or diastolic values ≥85 mmHg, or specific drug treatment was present (18); dyslipidemia was defined when plasma total cholesterol ≥200 mg/dL, HDL-cholesterol ≤50 mg/dL, LDL-cholesterol ≥130 mg/dL, triglycerides ≥150 mg/dL, or specific drug treatment was present (19);
- Previous and current medications: glucocorticoids, immunosuppressive drugs;
- Laboratory: erythrocyte sedimentation rate (ESR) (reference value <10 mm/1st hour, by automated Westergren method) and C-reactive protein (CRP) (reference value <5.0 mg/L, by immunoturbidimetric method);
- Vessel imaging examinations (computed tomography angiography or magnetic resonance angiography) performed within four months before or after the patients' inclusion in the present study;
- Arterial stenosis was defined when there was more than 50% of vessel diameter reduction seen in computed tomography angiography or magnetic resonance angiography;
- Vascular claudication was defined as discomfort, pain, tightness, heaviness, cramping, or weakness related to arms. These symptoms subside with rest exercise;
- Questionnaires. The functional capacity through the Health Assessment Questionnaire (HAQ) (20), lower limb vascular claudication through The Edinburgh Claudication Questionnaire (ECQ) (21), and vascular claudication of the upper limbs, based patient's self-reports;
- Blood pressure assessment (TAK and CTR): To measure blood pressure, all of the evaluated patients remained seated

and rested for 5 minutes before starting the measurement. The arm to be measured remained supported and extended at the height of the sternum, and the cuff was positioned around the arm and correctly adjusted. Systolic pressure was determined by the first Korotkoff phase, and diastolic pressure by the fifth phase (22, 23);

– Disease activity was defined according to the Indian Takayasu Clinical Activity Score (ITAS) - 2010 translated and validated to the Portuguese language (11, 12). The disease was considered active when the value obtained from the questionnaire had ≥2 points. Moreover, Physician Global Assessment (PGA, classified in active, grumbling/persistent, or inactive), CRP and ESR were also analyzed;
– Handgrip assessment (TAK and CTR): Handgrip was assessed using a Crown Manual dynamometer (Industrial Technique Oswaldo Filizola, São Paulo, SP, Brazil). The patients remained in the standing position during the test, with arms extended and aligned with the trunk. They used their maximum strength one hand at a time, for 10 seconds on each hand, with a recovery period of 60 to 90 seconds between each test. This procedure was performed three times in each hand, that is, one familiarization and two valid tests. Participants were verbally motivated during each contraction. The highest value found was considered the maximum handgrip strength, respecting the coefficient of variation of 0.5%, the same day period and the evaluator (24). In addition, we calculated the ratio between the non-dominant and dominant handgrip strength of all individuals (*e.g.*, handgrip ratio = non-dominant hand/dominant hand) (25).

The control (CTR) group was composed of patients' relatives or employees from our tertiary center, who were age- and gender-matched to TAK patients. In addition, individuals with sequelae related to stroke, neurogenic claudication, fibromyalgia, systemic autoimmune diseases or other diseases or conditions that could have affected the analyses of grip strength were excluded. The following information was collected:

– Comorbidities (*e.g.*, diabetes mellitus, systemic arterial hypertension, dyslipidemia);
– Questionnaires. The functional capacity through the HAQ (20).

Statistical analysis. Data distribution was determined by the Shapiro-Wilk test, from which normal data were expressed as mean and standard deviation. Data with asymmetric distribution were expressed as median (interquartile 25^{th}-75^{th}). Categorical data were expressed as a percentage (%) and differences were analyzed by Fisher's test. The existence of differences in quantitative variables with normal distribution was analyzed with the Student's *t* test. For quantitative variables with asymmetric distribution, the Mann - Whitney U test was used (26). The correlation between variables with symmetrical distribution was analyzed with Pearson's test and variables with asymmetric distribution with Spearman's ρ coefficient. Additionally, the point-biserial correlation (*r*pb) was used when one variable was continuous and the other dichotomous. In addition, the correlations were classified as low (<0.333), moderate (between 0.333 and 0.666) or strong (>0.666). Associations between two categorical variables were analyzed using Fisher's exact test. Differences were considered statistically significant when p values <0.05. Analyses were performed with GraphPad Prism® software version 6.01 for Windows (San Diego, California, USA).

RESULTS

Thirty-six (40.0%) of the 90 patients were included and matched for gender, age, and BMI with 36 CTR (Figure 1). All of the patients were female, with median age of 42.0 years (35.5-51.5 years), BMI of 28.1 kg/m^2 (22.4-29.7 kg/m^2) and mean disease duration of 13.1±6.8 years.

At the time of the evaluations, no patient had active disease, according to their ITAS2010 scores and PGA. In addition, pa-

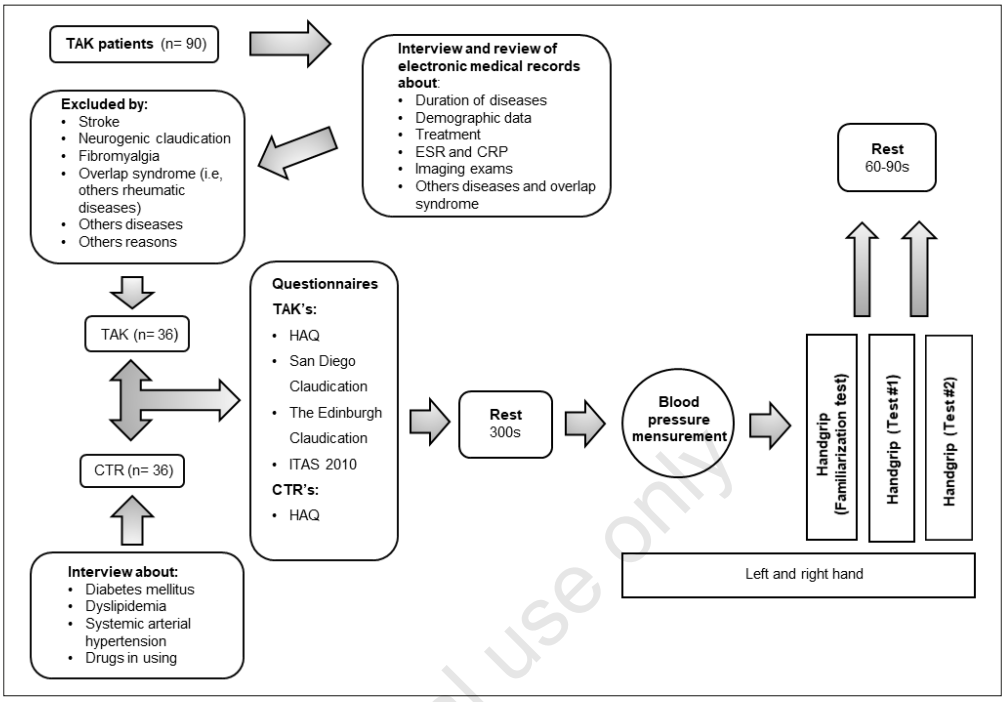

Figure 1 - Flowchart of the present study. CRP, C-reactive protein; CTR, control group; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; ITAS, Indian Takayasu Activity Index; REST, recovery; TAK, Takayasu arteritis.

tients had higher HAQ values when compared to the CTR group [0.50 (0.12-0.87) *vs*. 0.00 (0.00-0.00); p<0.001] (Table I).

Vascular claudication was observed in 11 (30.5%) and 16 (44.4%) patients in the right and left upper limbs, respectively. In 9 patients (25.0%), vascular claudication was simultaneously present in both upper limbs. Regarding the vascular imaging findings, 13 (36.1%) and 15 (41.7%) patients presented stenosis in the right and left subclavian arteries, respectively. Nine patients (25%) had stenosis in both subclavian arteries. Patients and CTR showed similar systolic and diastolic blood pressure assessed in both upper limbs (Table I).

Six (16.6%) patients were using glucocorticoids (prednisone) <20 mg/day. In addition, 16 (44.5%) patients used one or more immunosuppressive drugs (Table I).

Higher prevalence of dyslipidemia and systemic arterial hypertension (all patients with drug treatments) was found in TAK patients when compared to the CTR group, while the distribution of diabetes mellitus was similar in both groups (Table I).

The patients and CTR were mostly right-handed. In addition, they had similar right-hand-grip strength. However, in the left hand, the patients presented reduced strength when compared to the CTR (22.9±5.9 kg *vs*. 26.3±5.6 kg, p=0.014), but with comparable values in the ratio of hand grip strength (Table II and Figure 2). Still, the difference between patients' right and left handgrip strength was greater than 10%.

The patients' HAQ presented a moderate correlation with the left-handgrip strength and the handgrip strength ratio (Figure 3). In addition, a moderate correlation between the grip strengths in both hands and between left hand strength and the hand grip strength ratio was seen (Table III). No correlations were found between handgrip strength and subclavian artery stenosis, upper limb claudication, handgrip strength ratio, or blood pressure (Table III).

Moreover, an association was found between bilateral vascular claudication and

Table I - Demographic features, disease status, drug treatment and comorbidities of patients with Takayasu arteritis. Comparison with control group.

	TAK (n = 36)	CTR (n = 36)	Valore p
Age (years)	42.0 (35.5-51.5)	41.5 (35.0-53.7)	0.883
Time of disease (years)	13.1 ± 6.8	-	-
Body mass index (kg/m^2)	28.1 (22.4-29.7)	24.2 (22.7-28.7)	0.107
Disease status			
HAQ (0.00-3.00)	0.50 (0.10-0.90)	0.00 (0.00-0.00)	< 0.001
Diseases activity (ITAS2010)	0	-	-
ESR (mm/1st hour)	18.5 (10.2-39.2)	-	-
CRP (mg/L)	3.3 (1.3-7.7)	-	-
Physician global assessment			
Active	0		
Grumbling or persistent	0		
Inactive	36 (100)		
Claudication: upper limbs			
Both limbs	9 (25.0)	-	-
Right limb	11 (30.6)	-	-
Left limb	16 (44.5)	-	-
Vessel imaging exams			
Both subclavian artery stenosis	10 (27.8)	-	-
Right subclavian artery stenosis	13 (36.1)	-	-
Left subclavian artery stenosis	15 (41.7)	-	-
Systolic blood pressure			
Right upper limb (mmHg)	121 (93-142)	113 (105-125)	0.059
Left upper limb (mmHg)	121 (107-146)	110 (103-120)	0.255
Diastolic blood pressure			
Right upper limb (mmHg)	74 (65-90)	75 (70-8)	0.870
Left upper limb (mmHg)	75 (65-86)	75 (69-81)	0.766
Treatment			
Prednisone	-	-	-
Current use (%)	6 (16.7)	-	-
Current dose (mg/day)	5; 7.5; 10; 10; 10; 20	-	-
IS or immunobiological	-	-	-
Current use of one or more	16 (44.4)	-	-
Azathioprine	4 (11.1)	-	-
Abatacept	1 (2.8)	-	-
Methotrexate	6 (16.7)	-	-
Mycophenolate mofetil	1 (2.8)	-	-
Leflunomide	5 (13.9)	-	-
Infliximab	4 (11.1)	-	-
Tocilizumab	1 (2.8)	-	-
Traditional risk factors for CVD			
Dyslipidemia	18 (50.0)	3 (8.3)	< 0.001
Systemic arterial hypertension	25 (69.4)	5 (13.9)	< 0.001
Diabetes mellitus	2 (5.6)	2 (5.6)	1

Data expressed as mean standard deviation; median (interquartile 25th-75th) or frequency (%). CRP, C-reactive protein; CTR, control group; CVD, cardiovascular diseases; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; IS, immunosuppressive; ITAS, Indian Takayasu Activity Index; TAK, Takayasu arteritis.

Table II - Dominant hand, handgrip strengths and ratio in patients with Takayasu arteritis and control group.

	TAK (n = 36)	CTR (n = 36)	Valore p
Dominant hand right (%)	35 (97.2)	34 (94.4)	>0.999
Grip strength in right hand (kg)	26.2±6.2	27.7±5.2	0.254
Grip strength in left hand (kg)	22.9±5.9	26.3±5.6	0.014
Grip strength ratio	0.88 (0.79-0.95)	0.95 (0.88-1.00)	0.006

CTR, control group; Grip strength ratio, ratio between non-dominant hand and dominant hand; TAK, Takayasu arteritis.

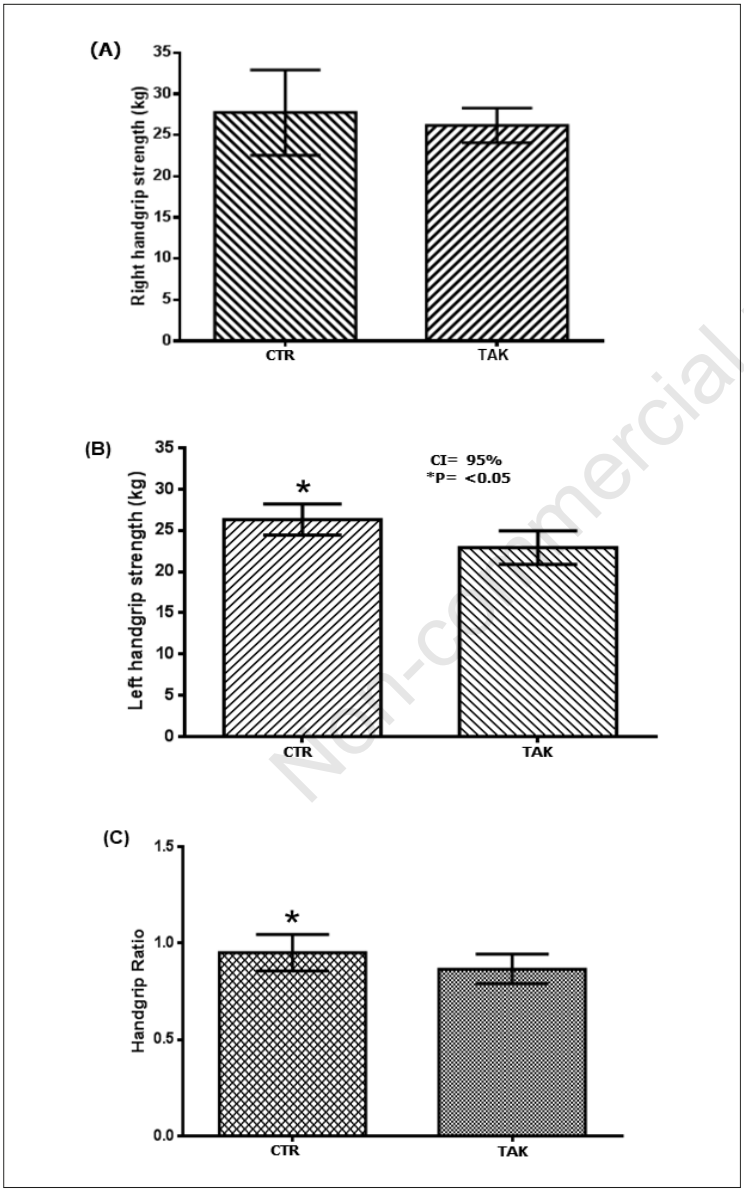

Figure 2 - Handgrip strength in patients with Takayasu arteritis and control group. CI, confidence interval; CTR, control group; Handgrip ratio, ratio between non-dominant hand strength and dominant hand strength; TAK, Takayasu arteritis.

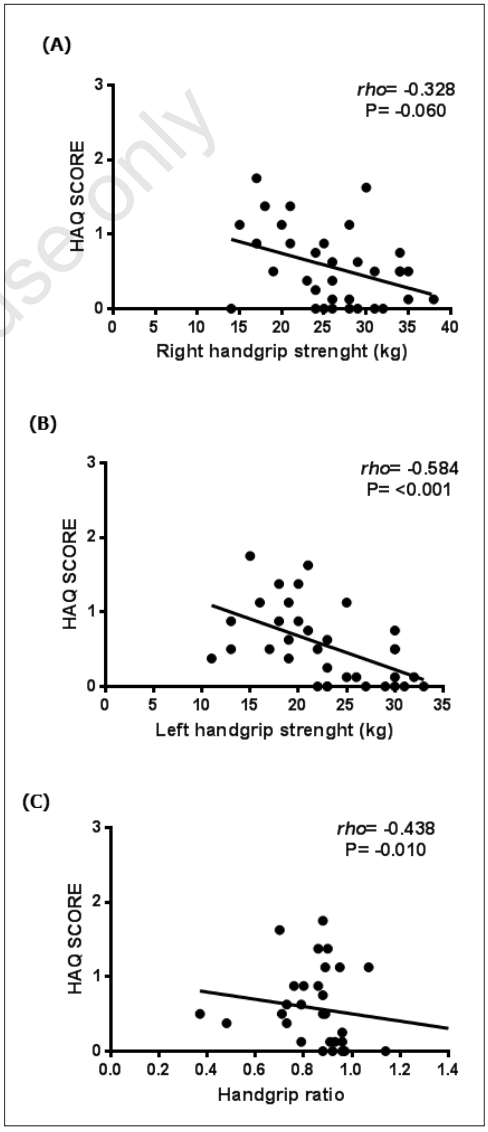

Figure 3 - Correlation between Health Assessment Questionnaire score and hand grip strength in patients with Takayasu arteritis. Handgrip ratio, ratio between non-dominant hand and dominant hand; HAQ, Health Assessment Questionnaire; TAK, Takayasu arteritis.

left subclavian artery stenosis, but without any other unilateral or contralateral association (Table IV).

DISCUSSION AND CONCLUSIONS

The present study shows that patients with TAK have lower handgrip strength in the left upper limb and a lower ratio between their dominant and non-dominant hand. Moreover, reduction of strength was inversely correlated with functional capacity and was not correlated with limb claudication, arterial pressure or subclavian artery stenosis. Additionally, we found an association between simultaneous vascular claudication (*e.g.*, both sides) and stenosis in the left subclavian, with no further associations between the imaging examinations and vascular symptoms.

Although TAK is considered a rare systemic vasculitis, we included an expressive sample of TAK patients who were also matched by gender, age and BMI with the control group. Furthermore, we provided detailed information about disease status and drug use.

Our patients with TAK showed a significant reduction in strength in the left hand.

Table III - Correlation among handgrip strength, HAQ, claudication in upper limbs, stenosis in upper limbs and blood pressure in patients with Takayasu arteritis.

Variables	Right handgrip		Left handgrip		Handgrip ratio	
	rho/r_{pb}	p	rho/r_{pb}	p	rho/r_{pb}	p
HAQ	–0.328	0.060	–0.584	<0.001	–0.438	0.010
Claudication in upper right limb	–0.092	0.601	–0.174	0.317	–0.058	0.714
Claudication in upper left limb	0.051	0.770	–0.333	0.050	0.490	0.003
Stenosis in right subclavian	–0.085	0.627	0.181	0.298	0.209	0.228
Stenosis in left subclavian	–0.179	0.304	0.053	0.761	0.057	0.747
Right handgrip	-	-	0.586	<0.001	–0.168	0.334
Left handgrip	0.586	<0.001	-	-	0.505	0.002
Systolic blood pressure (mmHg)						
Right upper limb	–0.133	0.453	0.024	0.892	0.063	0.723
Left upper limb	0.096	0.621	0.108	0.578	0.093	0.633
Diastolic blood pressure (mmHg)						
Right upper limb	–0.095	0.594	0.030	0.867	–0.089	0.618
Left upper limb	0.216	0.260	0.022	0.910	–0.320	0.091

HAQ, Health Assessment Questionnaire; rpb, the point biserial correlation coefficient; rho, Spearman correlation. Point-biserial correlation was used when one variable was continuous and the other dichotomy (e.g., yes or no, presence or absence).

Table IV - Fisher's exact test between vascular claudication and stenosis in upper limbs pressure in patients with Takayasu arteritis.

Variables	p value	
	Right subclavian arterial stenosis	Left subclavian arterial stenosis
Vascular claudication		
Both upper limbs	0.118	0.039
Upper right limb	0.304	0.126
Upper left limb	>0.999	0.622

As a hypothesis, this may be related to limb disuse associated with reduced functional capacity. Furthermore, patients at disease onset can suffer from novel limb claudication, pain, immobilization, or fatigue. Consequently, these negative experiences can be reflected in chronic reduction in strength and muscle mass, or in other mechanisms (27-29). However, further studies with large samples are needed to confirm our hypothesis.

Drug treatment, such as the use of glucocorticoids, may also interfere with strength and muscle mass (30). However, this possibility is remote since most of our patients used low-dose glucocorticoids.

Despite the higher prevalence of systemic arterial hypertension and dyslipidemia found in our series, when compared to the control group, and despite the use of statins that can produce muscle pain and calf cramps, mimicking the vascular claudication of the lower limbs (31-34), we evaluated the strength in the upper limb, reducing the interference of this confounding factor. Moreover, one study (32) shows that statins were not capable of promoting reduction in strength, muscle quality and volume.

Among the general population, reduced muscle strength may be a risk factor for negative long-term outcome; regardless of the individuals' level of physical activity or amount of lean mass, muscle quality (e.g., the ratio of strength to muscle area) is relevant for mortality (35).

Corroborating Metter et al. (35), Artero et al. (36) demonstrated that increased strength is related to reduced risk of cardiovascular disease, regardless of other factors such as body composition and aerobic capacity. In addition, reduced handgrip strength was correlated with increased risk of chronic diseases and mortality, and reduced long-term functional capacity (35, 37, 38). In patients with systemic autoimmune diseases, impaired strength in this test is also related to reduced functional capacity or activities of daily living, thus corroborating our study's findings (14, 39).

To our knowledge, the study by Oliveira et al. (6) has been the only one to evaluate handgrip strength in TAK patients: these authors also found a reduced strength. However, the study did not analyze the differences in strength between limbs, their ratios, or correlations between handgrip, systemic blood pressure, vessel stenosis and vascular claudication. In our study, the difference in strength was evident in the left hand. Additionally, the difference between the hands was greater than 10%, a value recognized as a limit of normality in the literature, suggesting to be a difference not caused by the right arm's dominance (40, 41). The reduction in strength in the left hand and the ratio between the hands found in our study also corroborate the results found for rheumatoid arthritis (25).

Our data showed a higher rate of vascular claudication when compared to stenotic lesions in the same limb, and these parameters did not correlate. In our hypothesis, the greater presence of "pseudo-claudication" (clinical but not pathologic changes) may be a consequence of the central nervous system dysfunction (42, 43) trigged by chronic limb pain, similar to that found in low back pain, osteoarthritis, fibromyalgia, headache, among others (42-45). All these diseases may also lead to low functional capacity. Additionally, studies show that pain can cause sensitization in the contralateral patients' limb (46, 47). Based on this assumption, the presence of claudication in one limb in our TAK patients could also cause "pseudo-claudication" in the contra-lateral patient's limb.

As the main limitation of the present study, we can cite the participant selection by convenience, providing increased selection bias. In addition, we included only patients with inactive disease and long disease duration.

The patients with TAK presented reduced left handgrip strength, as well as a reduction in the ratio between the non-dominant side over the dominant side. Grip strength was inversely related to the HAQ score of patients with TAK. This ultimately represented a reduction in the ability to perform activities of daily living. However, this reduction was not related to stenosis or blood pressure, and vascular claudication seemed not to be associated with subclavian artery

stenosis in our sample. Further studies with large samples are needed to confirm our data.

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Conflict of interests
All authors declare no conflict of interests.

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