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ORIGINAL ARTICLE

Metabolic syndrome is associated with increased cardiovascular risk and disease damage in patients with Takayasu arteritis

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Abstract

Objective: Metabolic syndrome (MetS) is one of the preventable risk factors for cardiovascular disease (CVD). The aim of this study was to investigate the effect of MetS on CVD and cumulative organ damage in a multi-center, large cohort of patients with Takayasu arteritis (TAK).

Methods: This is a cross-sectional study involving 192 consecutive TAK patients from seven tertiary rheumatology centers in Turkey. Clinical data of TAK patients fulfilling the 1990 American College of Rheumatology classification criteria were collected from medical records. They were evaluated for risk factors of CVD, disease activity, damage, and MetS at their last visits.

Results: A total of 192 consecutive TAK patients were included in this study. One hundred and fifty-eight (82%) were female, the mean age was 43.3 ± 13 years, and mean disease duration was 13.5 ± 9.3 years. MetS was detected in 50 (26%) of the patients and CVD was detected in 28 (14.6%). The presence of MetS was detected as an independent risk factor for CVD ($P < 0.001$). In addition, the mean vasculitis damage index of the group with MetS was significantly higher than in the other patients (4.5 ± 3.3 vs 3.2 ± 2.2, respectively, $P = 0.004$).

Conclusion: The presence of MetS in TAK is associated with increased CVD and disease damage. Awareness and management of MetS can improve disease prognosis in patients with TAK.

KEYWORDS
cardiovascular disease, metabolic syndrome, Takayasu arteritis, vasculitis

1 | INTRODUCTION

Takayasu arteritis (TAK) that affects the aorta and its large branches is a chronic vasculitis with panmural inflammation, stenosis, occlusion, and aneurysm formation.[1] Most of the clinical findings are associated with arterial ischemia, and the frequency of hypertension, cardiac valve disease, and cardiovascular disease (CVD) increases as a result.[2] These involvements, which have a distinctive negative impact on TAK prognosis, are affected by CVD risk factors as well as disease activity.[3] Hence, taking the CVD risk factors into consideration is also important in therapeutic approaches.

Metabolic syndrome (MetS) is one of the preventable CVD risk factors. The prevalence of MetS in the general population varies according to age, gender, ethnicity, and geographic origin. Weight gain, aging, and sedentary life are associated with MetS in both high-income and low- and middle-income countries. Despite its close relationship with CVD there are limited studies on the frequency of MetS in systemic rheumatological diseases. The presence of MetS is a risk factor for disease damage in systemic lupus erythematosus (SLE), suggesting that it might also affect disease course and prognosis in inflammatory disorders [4].

Only one study has been encountered so far regarding the status of MetS in TAK.[5] The aim of this study was to investigate the effect of MetS on CVD and cumulative organ damage in a multi-center, large cohort of TAK patients.

2 | MATERIALS AND METHODS

2.1 | Patients

This is a cross-sectional study involving 192 consecutive TAK patients from seven tertiary rheumatology centers in Turkey. Clinical data of TAK patients fulfilling the 1990 American College of Rheumatology classification criteria were collected from medical records.[6] They were evaluated for risk factors of CVD, disease activity, damage, and MetS at their last visits. Patients with insufficient data for the diagnosis of MetS, secondary rheumatic disease, and organ failure were excluded.

The study was approved by the Marmara University ethics committee (approval number: MAR-YÇ-2009-0230) and informed consent was obtained from all participants.

2.2 | Definitions

Radiological involvement was determined according to the Numano classification.[7] TAK disease activity and damage were evaluated by Kerr's criteria and vasculitis damage index (VDI), respectively.[8,9]

Cardiovascular disease was defined as documented coronary artery disease and/or cerebrovascular event including myocardial infarction and stroke.

MetS was defined based on the diagnostic criteria of the National Cholesterol Educational Program Adult Treatment Panel III (NCEP ATP III).[10] Three or more of the following components are defined as MetS:

- Increased waist circumference (>102 cm for men, >88 cm for women)
- Hyperglycemia, fasting blood glucose ≥110 mg/dL, or have been diagnosed with diabetes and treated.
- Elevated triglycerides ≥150 mg/dL
- Low high-density lipoprotein (<40 mg/dL in men, <50 mg/dL in women)
- Hypertension. Arterial blood pressure ≥130 mm Hg/≥85 mm Hg or currently using an antihypertensive drug.

Waist circumference was measured at the end of a normal expiration, in a horizontal plane around the abdomen at the level of the iliac crest, parallel to the floor. Blood pressure was measured twice in rested patients.

2.3 | Statistical analysis

Statistical analyses were performed using SPSS 21.0 (SPSS Statistics for Windows; IBM, Armonk, NY, USA). CVD and VDI between TAK patients with MetS (MetS + TAK) and without MetS (MetS – TAK) were analyzed. Kolmogorov-Smirnov test was used to check whether a continuous variable follows a normal distribution. Differences between continuous variables and categorical data were tested using the Student's *t* test or Mann-Whitney *U* test and χ^2 test. Those factors associated with MetS on univariate analyses at significance level $P < 0.2$ were tested with multivariate analysis using logistic regression. All analyses used a 5% two-sided significance level and results were expressed as odds ratio and 95% confidence interval.

3 | RESULTS

Ninety-five of the 287 registered patients were excluded from the study because of insufficient data for MetS. In all, 192 consecutive TAK patients were included in this study. One hundred and fifty-eight (82%) patients were female, the mean age was 43.3 ± 13 years, and mean disease duration was 13.5 ± 9.3 years. The most common radiological subtype was type V (49%). Immunosuppressive drug usage distribution of the patients was 141 (77%) for methotrexate, 87 (47%) for azathioprine, 49 (27%) for leflunomide, and 14 (8%) for cyclophosphamide. Forty-one (26%) of the patients used at least one biological disease-modifying drug. Tumor necrosis factor inhibitors were used by 40 patients, and 17 used tocilizumab. All of the patients were receiving corticosteroids, and immunosuppressive drugs were not used in only 6 (3%) of the patients.

MetS was detected in 50 (26%) of the patients and CVD was detected in 28 (14.6%). The most frequent criterion of MetS in TAK patients was hypertension (47%); abdominal obesity was second with presence in almost half of the patients (41%) (Table 1). Clinical characteristics of the patients according to their MetS and CVD status are shown in Table 2. The mean age and smoking rates of the TAK patients with MetS were higher than of those without MetS (50.3 ± 12.0 vs 40.8 ± 12.4 years, $P = 0.000$ and 41% vs 20%, respectively, $P = 0.007$). The mean VDI of the group with MetS was also significantly higher (4.5 ± 3.3 vs 3.2 ± 2.2, $P = 0.004$). As expected, the mean VDI was higher in the group with CVD (5.8 ± 2.7 vs 3.1 ± 2.3, $P = .000$).

Patients with TAK who had CVD were similar to the non-CVD group in terms of age, gender, disease duration, radiological type, and other clinical features. The smoking rate was also significantly higher in the TAK group with CVD (44% vs 22%, $P = 0.043$). The rate of active disease was found to be high in the group with MetS at the last visit (23% vs 10%, $P = 0.018$). There was no significant difference between the groups in terms of presenting symptoms and median number of relapses.

In the multivariable analysis shown in Table 3, the presence of MetS was detected as an independent risk factor for CVD ($P = 0.007$). In addition to MetS, cumulative prednisolone was also found to be an independent risk factor for CVD ($P = 0.037$).

4 | DISCUSSION

Although the rate of MetS in our TAK cohort (26%) was lower than the prevalence of MetS in the general population of Turkey, which was reported as 33% (38% in women, 27% in men),[11] we showed that MetS was associated with CVD. In addition, the VDI of TAK patients with MetS was found to be high.

At first glance, a lower rate of MetS in TAK patients compared with the general population may be surprising, because of glucocorticoid (GC) treatment in TAK, which may cause weight gain, hypertension, and hyperglycemia. However, control of disease activity by GC treatment, which may allow successful exercise and weight loss, as well as physician-patient awareness (diet, salt restriction, and use of statins), may be responsible for the low rates of MetS in our TAK cohort. Finally, the tendency for using lower doses of GC, supported by more frequent use of other conventional immunosuppressives, in Turkey might have affected our results. Indeed, only a few of our patients did not use immunosuppressive therapy. In the only study that can be compared with our data, the prevalence of MetS was found to be higher in Brazilian TAK patients compared with the general population. However, this finding was the result of an unbelievable low rate of MetS in the Brazilian general population (33.3% vs 8.5%).[5]

TABLE 1 Subsets of metabolic syndrome (MetS) in Takayasu arteritis (TAK) patients

Subset	n (%)
Hypertension	91 (47%)
Abdominal obesity	79 (41%)
Increased TG level	57 (30%)
Hyperglycemia	24 (12%)
Decrease HDL level	16 (8%)

Abbreviations: HDL, high-density lipoprotein; TG, triglyceride.

MetS frequency data also vary in other systemic inflammatory rheumatological diseases. In the meta-analysis of Zhang et al, MetS was reported more frequently in rheumatoid arthritis patients than in the normal population with increased mortality due to CVD.[12] In an antiphospholipid syndrome cohort, the prevalence of MetS (34.5%) was found to be similar to the general population,[13] whereas in antineutrophil cytoplasmic antibody-associated vasculitis an increased prevalence was present, which was associated with relapses.[14] The use of GC can be considered as a risk factor for MetS, affecting factors such as weight gain, hypertension, and hyperglycemia. However, disease activity, which may prevent weight gain or physician-patient awareness (higher exercise, use of statins etc), may be responsible for the low rates of MetS in our TAK population. Similarly, in another study from Turkey, Demir et al reported the prevalence of MetS in SLE patients as 19%, which, like our results, was also lower than in the general population.[4] Lower doses of GC are preferred in Turkey with high use of other conventional immunosuppressives.

Whether the use of biological agents apart from GC has an effect on MetS is another factor that needs to be clarified. It has been reported that the frequency of MetS in patients with ankylosing spondylitis who use biological drugs is higher than the group without the use of biologicals.[15] In our study, use of biological drugs was not found to be associated with MetS. However, the use of fewer biological drugs in TAK patients may be a confounding factor.

Although in previous studies MetS was shown to be an independent risk factor for CVD in patients with ankylosing spondylitis, SLE, and rheumatoid arthritis, to our knowledge, this is the first study reporting a similar finding in TAK.[4,12,15] CVD has an increased frequency in TAK and causes mortality.[3] In inflammatory rheumatic diseases, direct atherogenic effects of proinflammatory cytokines predispose the patients to CVD. Although GC show disturbance effects on metabolic pathways, they also reduce systemic inflammation and control disease activity, thereby having a dual effect on CVD.[16] In our study, high cumulative GC is also seen as a risk factor for CVD. Effective control of the disease using the lowest possible dose of GC reduces the risk of CVD. However, it is understood that the effect of MetS on CVD cannot be eliminated by controlling the use of GC. The management of MetS, as one of the general risk factors for CVD, is also important for reducing mortality and morbidity in TAK patients.

Apart from CVD, another factor that may be associated with mortality and morbidity is vascular disease damage. We have previously shown that higher damage scores were associated with higher cumulative GC doses in patients with TAK.[17,18] Our results in the present study showed that MetS was another factor affecting the vascular damage score in TAK. Similar to our results, Demir

TABLE 2 Clinical characteristics of Takayasu arteritis patients according to their metabolic syndrome and cardiovascular disease status

	MetS + TAK (n = 50)	MetS − TAK (n = 142)	*P*	CVD + TAK (n = 28)	CVD − TAK (n = 164)	*P*
Age (y), mean ± SD	50.3 ± 12.0	40.8 ± 12.4	**.000**	46.9 ± 12.3	42.7 ± 13	.103
Gender (female), n (%)	40 (80)	118 (83)	.668	21 (75)	137 (83)	.288
Smoking, n (%)	18 (41)	22 (20)	**.007**	11 (44)	29 (22)	**.024**
Disease duration (y), mean ± SD	13.4 ± 8.6	13.6 ± 9.6	.885	16.3 ± 10.9	13 ± 9	.147
Presenting symptoms, n (%)						
Fever	7 (15)	29 (22)	.407	3 (12)	33 (21)	.367
Weight loss	17 (36)	49 (37)	.513	8 (32)	58 (37)	.371
Extremity claudication	30 (62)	85 (63)	.464	15 (57)	99 (63)	.391
Pulseless	24 (62)	58 (56)	.106	14 (66)	68 (56)	.245 .094
Murmur	34 (72)	94 (71)	.493	21 (84)	107 (70)	
Smoking	18 (45)	22 (19)	**.008**	11 (44)	29 (22)	**.043**
Radiological type, n (%)						
I	12 (24)	39 (29)	.634	8 (30)	43 (27)	.709
II	9 (18)	2 (1.4)		3 (11)	31 (19)	
III	0	1 (0.7)		1 (4)	1 (0.6)	
IV	4 (0.8)	5 (0.3)		2 (7)	7 (4)	
V	24 (49)	66 (49)		13 (48)	77 (48	
Active disease in last visit n, (%)	11 (23)	13 (10)	**.018**	6 (24)	18 (11)	.084
Number of relapses, median (min-max)	0 (0-4)	0 (0-5)	.559	0 (0-5)	1 (0-4)	.489
CVaD, n (%)	7 (14)	25 (18)	.565	6 (22)	26 (16)	.643
Cumulative PRD (g), mean ± SD	9.5 ± 7.0	9.7 ± 8.7	.903	12.8 ± 11.2	9.2 ± 7.7	.202
Methotrexate, n (%)	37 (79)	104 (76)	.430	20 (77)	121 (77)	.596
Leflunomide, n (%)	13 (28)	36 (26)	.497	11 (42)	38 (24)	**.047**
Azathioprine, n (%)	21 (45)	66 (48)	.404	13 (50)	74 (47)	.464
Cyclophosphamide, n (%)	2 (4)	12 (8)	.255	1 (4)	13 (8)	.382
Biologic drug, n (%)	8 (19)	33 (28)	.307	7 (26)	34 (25)	.521
VDI, mean ± SD	4.5 ± 3.3	3.2 ± 2.2	**.004**	5.8 ± 2.7	3.1 ± 2.3	**.000**
VDI items, n (%)						
Musculoskeletal	17 (34)	26 (18)	.243	8 (29)	35 (21)	.290
Skin/mucous membranes	10 (20)	7 (5)	.108	4 (14)	13 (79)	.428
Ocular	13 (26)	33 (23)	.496	7 (25)	39 (24)	.579
ENT	1 (2)	0	.253	1 (4)	0	.176
Pulmonary	13 (26)	20 (14)	.375	7 (25)	26 (16)	.297
Cardiovascular	49 (98)	83 (58)	**.006**	23 (82)	109 (66)	.200
Peripheral vascular	50 (100)	118 (83)	.437	26 (93)	142 (87)	.384
Gastrointestinal	2 (4)	1 (7)	.444	1 (4)	2 (1)	.322
Renal	4 (8)	2 (1)	.156	2 (9)	4 (2)	.444 **.000**
Neuropsychiatric	7 (14)	16 (11)	.645	14 (50)	9 (5)	
Other	12 (38)	13 (9)	.068	1 (4)	24 (15)	.066

Abbreviations: CvaD, cardiac valve disease; CVD, cardiovascular disease; ENT, ear; nose, throat; MetS, metabolic syndrome; PRD, prednisolone; SD, standard deviation; TAK, Takayasu arteritis; VDI, Vasculitis Damage Index.

TABLE 3 Multivariable analysis for cardiovascular disease in Takayasu arteritis patients

	P	OR	95% CI
Smoking	.054	3.3	0.9-11.2
Metabolic syndrome	**.007**	4.9	1.5-15.6
Cumulative prednisolone	**.037**	1.1	1.0-1.1

Abbreviations: CI, confidence interval; OR, odds ratio.

et al found that presence of MetS was associated with higher SLE disease damage scores.[4] On the other hand, high VDI in TAK patients with CVD is an expected finding, because cardiovascular and neuropsychiatric items in the VDI overlap with CVD items. As a result, it is not possible to make further comments for these data in our study.

The main limitation of our study is its cross-sectional design with lack of baseline data of VDI and MetS. However, we think long disease duration in a sizeable patient cohort increases the validity of our results.

In conclusion, the frequency of MetS in patients with TAK was observed to be lower than the reported series for the general population of Turkey. However, the presence of MetS in TAK is associated with increased CVD and disease damage. When managing comorbidities such as hypertension, hyperlipidemia, and hyperglycemia during the follow up of TAK patients, improvement of waist circumference and high-density lipoprotein levels among other MetS components should be taken into consideration. Whether management of MetS positively affects the prognosis and the existence of links between MetS, CVD, and long-term damage require further studies in TAK patients.

CONFLICT OF INTEREST

Haner Direskeneli is an Editorial Board member of the journal and co-author of this article. He was excluded from the peer-review process and all editorial decisions related to the acceptance and publication of this article. Peer-review was handled independently by members of the Editorial Board to minimize bias. All other authors have no conflicts of interest to declare.

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