

# High Prevalence of Metabolic Syndrome in Takayasu Arteritis: Increased Cardiovascular Risk and Lower Adiponectin Serum Levels

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**ABSTRACT. Objective.** The prevalence of metabolic syndrome (MetS) tends to be high among rheumatic patients, and cardiovascular disease is the leading cause of death in these conditions. We aimed to determine the prevalence of MetS in patients with Takayasu arteritis (TA) and its association with risk factors and adipokine and cytokine levels.

**Methods.** A cross-sectional study was conducted in 45 consecutive women with TA and 47 healthy controls matched by age and body mass index.

**Results.** The prevalence of MetS (International Diabetes Federation/American Heart Association criteria) was higher in TA compared to controls (33.34 vs 8.51%,  $p = 0.003$ ). Patients with TA had a higher frequency of hypertension ( $p < 0.001$ ) and dyslipidemia ( $p = 0.001$ ) and higher levels of insulin ( $p = 0.021$ ), homeostasis model assessment index ( $p = 0.024$ ), apolipoprotein E ( $p = 0.029$ ), resistin ( $p = 0.018$ ), and C-reactive protein (CRP,  $p < 0.001$ ) compared to healthy subjects, with similar levels of adiponectin and plasminogen activator inhibitor-1 (PAI-1;  $p > 0.05$ ). Further analysis of patients with TA with and without MetS revealed a higher frequency of overweight/obesity (66.66 vs 26.66%,  $p = 0.022$ ), higher Framingham score  $\geq 1$  ( $p = 0.032$ ), and lower adiponectin levels ( $20.37 \pm 21.16$  vs  $38.64 \pm 22.62$   $\mu\text{g/ml}$ ,  $p = 0.022$ ) in the patients with MetS. No differences were found regarding disease duration, activity, glucocorticoid use, resistin, and PAI-1 levels in the 2 groups of patients with TA ( $p > 0.05$ ). Patients with and without MetS showed no differences in cytokine levels [interleukin 12 (IL-12, IL-1a, IL-6) and tumor necrosis factor- $\alpha$ ]. IL-6 had a positive Pearson correlation with CRP only in TA patients with MetS ( $r = 0.57$ ;  $p = 0.050$ ).

**Conclusion.** A high prevalence of MetS was observed in patients with TA and this comorbidity seems to identify a subgroup of overweight/obese patients with high cardiovascular risk without a significant association with disease status. Further longitudinal studies are necessary to observe the effects of controlling this modifiable risk factor in the quality of life and survival of patients with TA. (First Release Sept 15 2013; J Rheumatol 2013;40:1897-904; doi:10.3899/jrheum.130162)

## Key Indexing Terms:

TAKAYASU ARTERITIS  
MORTALITY

METABOLIC SYNDROME

ADIPONECTIN  
PREVALENCE

Metabolic syndrome (MetS) is characterized by a combination of several cardiovascular risk factors (age, sex, smoking, hypertension, and dyslipidemia) that imply additional cardiovascular morbidity that is greater than the sum of the risk factors associated with each individual component<sup>1,2</sup>.

The prevalence of MetS among autoimmune disorders ranges from 14 to 62.8%, and coronary heart disease is the

leading cause of death among these patients<sup>1,3,4,5</sup>. Studies have shown that atherosclerosis is accelerated in patients with rheumatic diseases, especially in systemic vasculitis, although the causal factors have not yet been fully elucidated<sup>5,6</sup>. In fact, in Takayasu arteritis (TA), enhanced atherosclerosis has been clearly documented by ultrasonography studies showing that atherosclerotic plaques in the carotid artery were about 10 times more frequent than in age-matched, sex-matched controls<sup>6</sup>.

Adipose tissue seems to play an important role in this process, with the secretion of various hormones called adipokines<sup>7,8</sup>, which appear to contribute to the so-called "low-grade inflammatory states" that culminate in metabolic cardiovascular diseases<sup>6,7</sup> and insulin resistance<sup>8</sup>. This metabolic disturbance may be aggravated in autoimmune diseases because of the known intense inflammatory process observed in these rheumatic conditions.

TA is an inflammatory chronic vasculitis of unknown etiology, predominantly affecting the aorta and its major

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branches and pulmonary arteries, producing a variety of ischemic symptoms due to stenosis and thrombosis of large vessels<sup>9</sup>. We recently reported that TA has a proatherogenic lipid profile, predominantly characterized by low levels of high-density lipoprotein cholesterol (HDL-C) associated with disease activity<sup>10</sup>, but there are no available data regarding the prevalence of MetS in this vasculitis.

We studied the prevalence of MetS in patients with TA and the associated risk factors, and the levels of adipokines and cytokines.

## MATERIALS AND METHODS

**Patients.** A cross-sectional study was conducted including 45 consecutive premenopausal women with TA according to the American College of Rheumatology criteria<sup>11</sup>, who were followed at the Vasculitis Outpatient Clinic of the Rheumatology Division of Clinics Hospital, University of São Paulo, São Paulo, Brazil, from August 2009 to July 2011. Exclusion criteria were postmenopausal (based on patient history), renal dysfunction (creatinine clearance < 50 ml/min), thyroid diseases, or any other rheumatic inflammatory diseases. Forty-seven healthy female staff members of the hospital with similar age, weight, and educational level were selected as controls. Comorbidities (except hypertension, diabetes, and dyslipidemia) were exclusion criteria for healthy controls. Data were obtained by retrospective chart review (until December 1999) and from an ongoing electronic database protocol established in January 2000, which was applied to all patients at 1-month to 6-month intervals and consisted of an extensive clinical and laboratory evaluation including the relevant variables for our study: demographic data, anthropometric data [weight, height, body mass index (BMI), and waist circumference (WC)], diagnostic criteria, clinical manifestation, personal and familial risk factors of coronary disease, use of glucocorticoids, clinical and laboratory disease activity, blood pressure, prognostic factors, and treatment. The unified consensus suggests WC  $\geq$  80 cm for women as thresholds for abdominal obesity among ethnic South and Central Americans<sup>12</sup>. BMI was calculated based on the formula weight/height<sup>2</sup> (kg/m<sup>2</sup>) and patients were classified in groups: underweight (BMI < 18 kg/m<sup>2</sup>), normal weight (BMI = 18–24.9 kg/m<sup>2</sup>), overweight (BMI = 25–29.9 kg/m<sup>2</sup>), and obese (BMI  $\geq$  30 kg/m<sup>2</sup>). Current blood pressure was determined as the average of 2 measurements that were recorded 5 min apart after subjects had rested supine for 10 min, and hypertension was defined by the use of antihypertensive medication or history or current blood pressure higher than 120 mmHg (systolic) or 80 mmHg (diastolic). Family history of premature coronary artery disease (CAD) was defined as myocardial infarction or stroke before age 55 years in men or 65 years in women in a first-degree relative<sup>13</sup>. The Framingham risk score was applied to estimate the 10-year risk for CAD and expressed as a percentage<sup>13</sup>.

Clinical activity was defined based on the presence of new onset or worsening of fever or musculoskeletal problems, vascular ischemia or inflammation such as claudication, diminished or absent pulse, bruit, carotidynia, or asymmetric blood pressure<sup>14,15</sup>. Laboratory activity was characterized by a high erythrocyte sedimentation rate (ESR; > 20 mm/h) and/or C-reactive protein (CRP; > 5 mg/dl) levels in the absence of infection<sup>15</sup>.

Dyslipidemia was defined as plasma total cholesterol > 200 mg/dl, HDL-C < 40 mg/dl, low-density lipoprotein cholesterol > 130 mg/dl, triglycerides (TG) > 150 mg/dl, or drug treatment for elevated low-density lipoprotein (LDL) or TG<sup>13</sup>. A sedentary lifestyle was defined by the absence of endurance-type physical activity at least 3 h per week for at least 2 months<sup>13</sup>. The local ethics committee approved the study, and written informed consent was obtained from patients and controls.

**MetS definitions.** For the diagnosis of MetS the following criteria were used: US National Cholesterol Education Program/Adult Treatment Panel

III (NCEP/ATP III)<sup>13</sup>, the International Diabetes Federation (IDF)<sup>12</sup>, and the new criteria proposed in the IDF/American Heart Association (AHA)<sup>16</sup> partnership. To compare TA patients and healthy controls, the IDF/AHA definition was applied because of the proposal to harmonize those previous criteria.

**Laboratory examinations.** Blood samples were obtained from the participants after a 12-h overnight fast. Glucose, thyroid-stimulating hormone, free thyroxine 4, and insulin were also measured. Insulin levels were measured by immunofluorometric assay and reported as  $\mu$ U/ml.

**Lipoprotein (a).** Lipoprotein (a) was measured by immunoturbidimetric technique, using a commercial kit (DiaSorin). The instrument calibration was performed using the calibrators supplied by the kit, and cutoff for high levels was established as > 30 mg/dl.

**Lipid profile.** Total cholesterol and TG in serum samples were measured enzymatically (Boehringer Mannheim and Merck) on a Technicon RA 1000 Analyser (Technicon Instruments)<sup>17,18</sup>. HDL-C was obtained after precipitation of very LDL-C (VLDL-C) from serum and LDL-C by phosphotungstic acid and magnesium chloride<sup>19</sup>, and serum levels were determined by the colorimetric method (Roche Diagnostics). Levels of VLDL-C and LDL-C were estimated, because all samples had TG levels < 400 mg/dl<sup>19</sup>: VLDL-C levels using the TG level/5 ratio (TG/5)<sup>20</sup>, and LDL-C levels based on the following equation:

$$\text{total cholesterol} = \text{HDL} + \text{TG}/5 + \text{LDL}^{19}$$

**Inflammation markers.** CRP for all participants was determined by nephelometry, and results were expressed in mg/dl. ESR was evaluated using the modified Westergren method, and results were expressed as mm/h.

**Adipokines.** Serum adipokines [adiponectin, resistin, and plasminogen activator inhibitor-1 (PAI-1)] were determined by Luminex xMAP Technology, as described elsewhere<sup>20</sup>.

**Cytokines.** Serum levels of interleukin 12 (IL-12), IL-1a, IL-6, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were determined by Luminex xMAP Technology.

**Insulin resistance.** For evaluation of insulin resistance, the homeostasis model assessment index (HOMA-IR) was used. HOMA-IR was calculated according to the formulas in the HOMA model<sup>21</sup>. HOMA-IR > 3.4 was considered to indicate insulin resistance, as described<sup>22</sup>.

**Statistical analysis.** The results were presented as mean (SD) or percentage. The data were analyzed by t test, Mann-Whitney test, or Fisher exact test to assess differences between patients and controls. P values < 0.05 were considered statistically significant.

## RESULTS

General characteristics of patients with TA and controls are shown in Table 1. As expected, both groups had comparable age, weight, and BMI. The percentage of overweight/obese participants according to World Health Organization (WHO) classification was also similar in patients and controls. Patients with TA had a more frequent history of hypertension (p < 0.001), dyslipidemia (p = 0.001), and stroke (p = 0.010) compared to controls. Moreover, at study entry patients with TA used more antihypertensive drugs (p < 0.001) and statins (p < 0.001) than did the control group. The current systolic (129  $\pm$  20.65 vs 105.02  $\pm$  14.40 mmHg, p = 0.001) and diastolic (75.90  $\pm$  18.78 vs 68.38  $\pm$  11.17 mmHg, p = 0.021) blood pressures were more elevated in patients than controls (Table 1).

The prevalence of MetS was higher in patients than in

Table 1. Anthropometric data, clinical characteristics, and treatment in patients with Takayasu arteritis (TA) and controls.

	TA Patients, n = 45	Controls, n = 47	p
Age, yrs	33.88 ± 9.35	34.42 ± 9.95	0.789
Weight, kg	61.74 ± 9.94	61.04 ± 10.69	0.746
BMI, kg/m <sup>2</sup>	24.14 ± 3.79	24.29 ± 4.37	0.861
Underweight, n	2 (4.45)	0 (0.00)	0.832
Normal weight, n	25 (55.56)	28 (59.57)	0.462
Overweight/obesity, n	18 (40)	19 (42.23)	1.000
Waist circumference, cm	81.77 ± 9.76	78.44 ± 11.42	0.137
Current smoking, n	1 (2.22)	5 (10.64)	0.102
Hypertension, n	33 (73.34)	3 (6.38)	< 0.001
Dyslipidemia, n	21 (46.67)	7 (14.89)	0.001
Diabetes, n	3 (6.67)	2 (4.25)	0.610
Myocardial infarction, n	0 (0)	0 (0)	1.000
Stroke, n	6 (13.34)	0 (0)	0.010
Antihypertensive therapy, n	24 (53.34)	2 (4.26)	< 0.001
Statins, n	20 (44.45)	1 (2.13)	< 0.001
Metformine, n	1 (2.22)	2 (4.26)	0.583
SBP, mmHg	129 ± 20.65	105.02 ± 14.40	0.001
DBP, mmHg	75.90 ± 18.78	68.38 ± 11.17	0.021

Data are mean ± SD or percentages. BMI: body mass index, SBP: systolic blood pressure; DBP: diastolic blood pressure.

controls according to IDF/AHA criteria (33.34 vs 8.51%,  $p = 0.003$ ), NCEP/ATP III criteria ( $p = 0.003$ ), and IDF criteria ( $p = 0.025$ ; Table 2). Patients with TA had higher levels of insulin ( $p = 0.021$ ), HOMA-IR ( $p = 0.024$ ), apolipoprotein E ( $p = 0.029$ ), ESR ( $p < 0.001$ ), and CRP ( $p < 0.001$ ) compared to healthy subjects. Before statin use, patients with TA presented higher LDL-C levels ( $148.60 \pm 40.33$  vs  $113.14 \pm 49.59$  mg/dl,  $p = 0.001$ ). With regard to adipokines, resistin levels were higher in patients ( $22.55 \pm 12.62$  vs  $15.94 \pm 10.11$  ng/ml,  $p = 0.018$ ) compared to the control group, whereas no difference was observed for adiponectin and PAI-1 levels in these 2 groups ( $p > 0.05$ ; Table 3). In respect to cytokines, no differences were found between patients with TA and healthy controls (Table 3).

Further analysis of TA patients with and without MetS (IDF/AHA) revealed comparable age of onset, weight, and BMI. A high percentage of overweight/obesity was observed in TA patients with MetS compared to TA patients without this comorbidity (66.66 vs 26.26%,  $p = 0.022$ ). In addition, the former group had larger WC ( $90.52 \pm 7.84$  vs  $77.40 \pm 7.45$  cm,  $p < 0.001$ ). These variables were similar in TA patients with and without MetS ( $p > 0.05$ ): disease duration, disease activity, remission, months until remission, current and cumulative dose of prednisone, and current and previous use of immunosuppressive drugs. Patients with TA with MetS also presented a higher proportion of Framingham scores  $\geq 1$  than those without MetS (44.66 vs 16.66%;  $p = 0.032$ ; Table 4).

Laboratory variable evaluation disclosed higher levels of

total cholesterol, LDL-C, insulin, HOMA-IR  $> 3.4$ , and apolipoprotein B in patients with MetS compared to controls ( $p < 0.05$ ). As expected, variables included in MetS criteria (glucose, HDL-C, TG) were also higher in patients with this condition ( $p < 0.05$ ; Table 5).

Concerning adipokines, TA patients with MetS had lower adiponectin levels than those without MetS ( $20.37 \pm 21.16$  vs  $38.64 \pm 22.62$   $\mu$ g/ml,  $p = 0.022$ ) while no differences were found with respect to resistin and PAI-1 levels (Table 5). A negative Pearson correlation between adiponectin levels and WC ( $r = -0.34$ ,  $p = 0.02$ ) was observed.

Adipokines were not associated with disease duration, disease activity, remission, current and cumulative dose of prednisone, or current and previous use of immunosuppressive drugs (data not shown).

Comparing TA patients with and without MetS, we found no difference in cytokine levels (Table 5).

A positive Pearson correlation was observed between adiponectin and the following laboratory variables in TA patients with MetS: HDL-C ( $r = 0.68$ ;  $p = 0.016$ ), TG ( $r = 0.58$ ;  $p = 0.048$ ), and glucose ( $r = 0.58$ ;  $p = 0.050$ ). TA patients with MetS also showed a positive Pearson correlation between resistin levels and HDL-C ( $r = 0.78$ ;  $p = 0.003$ ).

Concerning cytokine levels, IL-6 had a positive Pearson correlation with CRP only in TA patients with MetS ( $r = 0.57$ ;  $p = 0.050$ ). TA patients without MetS presented positive correlation between IL-1a and resistin ( $r = 0.60$ ;  $p = 0.001$ ) as well as between TNF- $\alpha$  and systolic blood pressure ( $r = 0.47$ ;  $p = 0.040$ ; Table 6).

Table 2. Prevalence of metabolic syndrome (MetS) according to different criteria. Values in parentheses are percentages.

	TA Patients, n = 45	Controls, n = 47	p
IDF/AHA, n	15 (33.34)	4 (8.51)	0.003
NCEP/ATP III, n	12 (26.67)	2 (4.25)	0.003
IDF, n	13 (28.89)	5 (10.64)	0.025
IDF/AHA criteria			
Hypertension, n	39 (86.67)	5 (10.64)	< 0.001
Waist circumference $\geq$ 80 cm, n	25 (55.56)	22 (46.80)	0.414
HDL-C < 50 mg/dl, n	19 (42.22)	18 (38.29)	0.832
Triglycerides $\geq$ 150 mg/dl, n	11 (24.44)	4 (8.51)	0.049
Glucose $\geq$ 100 mg/dl, n	3 (6.67)	3 (6.38)	1.000
IDF/AHA criteria for MetS, n			
0	2 (4.44)	19 (40.42)	
1	14 (31.12)	13 (27.66)	
2	12 (26.67)	9 (19.15)	
3	10 (22.22)	4 (8.51)	
4	6 (13.34)	1 (2.13)	
5	1 (2.22)	1 (2.13)	

TA: Takayasu arteritis; IDF/AHA: International Diabetes Federation/American Heart Association; NCEP/ATP: US National Cholesterol Education Program/Adult Treatment Panel III; HDL-C: high-density lipoprotein cholesterol.

Table 3. Laboratory tests, adipokines, and cytokines in patients with Takayasu arteritis (TA) and controls.

	TA Patients, n = 45	Controls, n = 47	p
Glucose, mg/dl	86.84 $\pm$ 23.99	80.98 $\pm$ 28.92	0.294
Total cholesterol, mg/dl	189.06 $\pm$ 44.89	194.00 $\pm$ 41.14	0.583
LDL-C, mg/dl	113.14 $\pm$ 40.59	117.93 $\pm$ 30.53	0.523
HDL-C, mg/dl	55.04 $\pm$ 15.71	57.27 $\pm$ 18.66	0.538
TG, mg/dl	105.74 $\pm$ 63.43	93.02 $\pm$ 44.23	0.266
Insulin, mU/ml	11.02 $\pm$ 11.68	6.74 $\pm$ 4.24	0.021
HOMA-IR	2.41 $\pm$ 2.65	1.43 $\pm$ 1.21	0.024
HOMA-IR > 3.4, n	9 (20)	4 (8.51)	0.114
apoA1, mg/dl	146.02 $\pm$ 28.87	153.21 $\pm$ 40.22	0.329
apoA2, mg/dl	34.28 $\pm$ 18.12	36.32 $\pm$ 11.25	0.516
apoB, mg/dl	84.95 $\pm$ 32.67	85.86 $\pm$ 21.74	0.875
apoE, mg/dl	4.56 $\pm$ 1.38	3.95 $\pm$ 1.26	0.029
Lipoprotein A, mg/dl	52.93 $\pm$ 70.04	39.70 $\pm$ 40.84	0.313
CRP, mg/dl	9.88 $\pm$ 11.71	2.77 $\pm$ 2.17	< 0.001
ESR, mm	18.34 $\pm$ 20.10	5.82 $\pm$ 3.41	< 0.001
Creatinine, mg/dl	0.77 $\pm$ 0.16	0.72 $\pm$ 0.12	0.092
Adiponectin, $\mu$ g/ml	33.16 $\pm$ 23.21	40.54 $\pm$ 50.98	0.417
Resistin, ng/ml	22.55 $\pm$ 12.62	15.94 $\pm$ 10.11	0.018
PAI-1, ng/ml	51.71 $\pm$ 23.80	42.38 $\pm$ 17.83	0.128
IL-12, pg/ml	4.11 $\pm$ 8.89	3.33 $\pm$ 32.90	0.781
IL-1a, pg/ml	7.43 $\pm$ 11.03	9.66 $\pm$ 29.87	0.448
IL-6, pg/ml	9.32 $\pm$ 3.70	1.47 $\pm$ 4.94	0.108
TNF- $\alpha$ , pg/ml	4.71 $\pm$ 7.07	19.19 $\pm$ 4.03	0.581

Data are mean  $\pm$  SD or percentage. LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; HOMA-IR: homeostatic model assessment of insulin resistance; apo: apolipoprotein; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PAI-1: plasminogen activator inhibitor-1; IL: interleukin; TNF- $\alpha$ : tumor necrosis factor- $\alpha$ ; TG: triglycerides.

## DISCUSSION

To our knowledge, this is the first reported study of high frequency of MetS in patients with TA.

An advantage of the present study was the inclusion of

only premenopausal women matched for age and BMI variables with healthy controls, because these variables are risk factors for MetS<sup>23</sup>.

Data available on general prevalence of MetS in the

Table 4. General characteristics of Takayasu arteritis (TA) in patients with and without metabolic syndrome (MetS) according to International Diabetes Federation/American Heart Association criteria.

Characteristics	TA Patients with MetS, n = 15	TA Patients without MetS, n = 30	p
Age at onset, yrs	24.89 ± 9.96	23.84 ± 6.90	0.653
Weight, kg	52.00 ± 16.46	60.00 ± 6.30	0.247
BMI, kg/m <sup>2</sup>	34.10 ± 24.60	37.30 ± 24.00	0.730
Underweight, n	0 (0.00)	2 (6.66)	0.439
Normal weight, n	5 (33.34)	20 (66.66)	0.028
Overweight/obesity, n	10 (66.66)	8 (26.66)	0.022
Waist circumference, cm	90.52 ± 7.84	77.40 ± 7.45	< 0.001
SBP, mmHg	144.16 ± 21.93	119.91 ± 30.39	0.009
DBP, mmHg	84.58 ± 19.00	74.75 ± 20.68	0.285
Hypertension, n	14 (87.5)	21 (61.76)	0.049
Duration of disease, mo	104.71 ± 54.21	111.16 ± 82.63	0.786
Disease activity, n	6 (40.00)	15 (50.00)	0.526
Months until remission	60.80 ± 13.08	62.78 ± 52.54	0.887
Current prednisone use, n	8 (53.34)	10 (33.34)	0.197
Current prednisone dose, mg	6.00 ± 7.12	7.41 ± 13.47	0.707
Cumulative prednisone dose, g	9.05 ± 13.76	10.34 ± 9.31	0.711
Current use of immunosuppressive drugs, n	9 (60.00)	19 (63.34)	0.828
Previous use of immunosuppressive drugs, n	5 (33.34)	8 (26.67)	0.642
Framingham score ≥ 1, n	7 (46.66)	5 (16.66)	0.032

Data are mean ± SD or percentage. BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 5. Laboratory tests, adipokines, and cytokines in Takayasu arteritis (TA) patients with and without metabolic syndrome (MetS) according to International Diabetes Federation/American Heart Association criteria.

	TA Patients with MetS, n = 15	TA Patients without MetS, n = 30	p
Glucose, mg/dl	97.94 ± 38.13	81.30 ± 8.52	0.026
Total cholesterol, mg/dl	207.93 ± 48.90	179.94 ± 40.55	0.041
LDL-C, mg/dl	131.93 ± 45.12	103.74 ± 36.26	0.028
HDL-C, mg/dl	43.94 ± 10.06	60.60 ± 15.17	< 0.001
TG, mg/dl	162.47 ± 64.78	77.37 ± 39.76	< 0.001
Insulin, mU/ml	16.26 ± 0.51	7.40 ± 4.89	< 0.001
HOMA-IR	4.28 ± 3.76	1.48 ± 1.04	0.568
HOMA-IR > 3.4, n	7 (46.67)	2 (6.67)	0.002
apoA1, mg/dl	140.62 ± 25.95	148.72 ± 30.28	0.381
apoA2, mg/dl	32.89 ± 4.89	34.97 ± 20.03	0.839
apoB, mg/dl	104.93 ± 37.12	74.96 ± 25.38	0.003
apoE, mg/dl	5.06 ± 1.82	4.32 ± 1.04	0.089
Lipoprotein A, mg/dl	58.80 ± 76.12	50.00 ± 67.97	0.697
CRP, mg/dl	10.94 ± 12.74	9.34 ± 11.34	0.671
ESR, mm	16.14 ± 9.15	19.27 ± 18.37	0.537
Creatinine, mg/dl	0.75 ± 0.15	0.78 ± 0.17	0.565
Adiponectin, μg/ml	20.37 ± 21.16	38.64 ± 22.62	0.022
Resistin, ng/ml	18.98 ± 9.11	24.08 ± 13.72	0.246
PAI-1, ng/ml	56.48 ± 20.19	49.68 ± 25.25	0.415
IL-12, pg/ml	2.27 ± 1.85	5.08 ± 11.03	0.892
IL-1α, pg/ml	6.23 ± 7.87	8.38 ± 12.56	0.847
IL-6, pg/ml	1.38 ± 2.01	3.25 ± 5.88	0.834
TNF-α, pg/ml	5.62 ± 2.65	7.23 ± 4.89	0.264

Data are mean ± SD or percentages. LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; HOMA-IR: homeostatic model assessment of insulin resistance; apo: apolipoprotein; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PAI-1: plasminogen activator inhibitor-1; IL: interleukin; TNF-α: tumor necrosis factor-α; TG: triglycerides.

Table 6. Correlation between cytokines, anthropometrical data, and laboratory tests in Takayasu arteritis (TA) patients with and without metabolic syndrome (MetS) according to International Diabetes Federation/American Heart Association criteria.

	IL-12				IL-1a				IL-6				TNF-α			
	TA Patients with MetS		TA Patients without MetS		TA Patients with MetS		TA Patients without MetS		TA Patients with MetS		TA Patients without MetS		TA Patients with MetS		TA Patients without MetS	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Age	0.01	0.982	0.07	0.702	-0.08	0.799	-0.14	0.477	0.14	0.660	-0.16	0.407	0.25	0.418	0.12	0.516
BMI	0.01	0.995	-0.14	0.487	0.03	0.920	-0.27	0.176	-0.49	0.104	-0.25	0.203	-0.43	0.160	-0.16	0.408
WC	-0.29	0.355	-0.19	0.367	0.38	0.219	-0.06	0.747	-0.4	0.190	-0.29	0.146	-0.51	0.090	-0.03	0.883
SBP	-0.01	0.993	0.32	0.186	-0.04	0.914	0.36	0.133	0.03	0.928	-0.09	0.716	0.15	0.713	0.47	0.040
DBP	-0.54	0.160	0.06	0.796	-0.36	0.378	0.01	0.981	0.01	0.979	-0.13	0.586	0.07	0.865	0.01	0.985
TC	-0.22	0.490	0.05	0.800	-0.01	0.963	-0.31	0.110	-0.12	0.697	-0.24	0.220	0.30	0.337	-0.05	0.771
HDL	-0.24	0.445	0.05	0.771	-0.01	0.972	-0.01	0.939	-0.02	0.943	-0.06	0.738	0.26	0.399	-0.25	0.206
LDL	-0.27	0.394	0.07	0.746	-0.03	0.935	-0.30	0.136	-0.22	0.498	-0.18	0.379	-0.43	0.159	0.09	0.678
TG	0.29	0.350	-0.15	0.451	-0.01	0.964	-0.16	0.426	0.14	0.656	-0.22	0.275	0.13	0.665	-0.14	0.490
Glucose	-0.18	0.570	0.05	0.793	-0.21	0.500	-0.34	0.080	-0.23	0.461	-0.21	0.295	0.09	0.766	-0.14	0.468
Insulin	0.32	0.307	-0.13	0.498	0.47	0.116	-0.13	0.590	-0.12	0.710	0.01	0.948	-0.28	0.367	-0.26	0.186
HOMA-IR	0.22	0.488	-0.11	0.579	0.39	0.206	-0.15	0.439	-0.21	0.492	-0.02	0.897	-0.26	0.413	-0.21	0.283
Adiponectin	0.09	0.802	0.16	0.444	-0.16	0.636	0.07	0.742	-0.07	0.833	-0.05	0.794	0.37	0.266	-0.29	0.151
Resistin	0.12	0.728	0.04	0.845	-0.17	0.614	0.60	0.001	-0.10	0.771	0.09	0.646	0.49	0.126	-0.08	0.700
ESR	-0.03	0.927	-0.18	0.386	-0.15	0.640	0.02	0.912	0.40	0.202	0.25	0.229	-0.02	0.956	0.02	0.939
CRP	-0.22	0.501	-0.15	0.470	-0.11	0.733	0.00	0.997	0.57	0.050	0.04	0.845	0.08	0.803	0.13	0.551

Data expressed as correlation coefficients (r) calculated using Pearson's correlation test. BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HOMA-IR: homeostatic model assessment of insulin resistance; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; IL-12: interleukin 12; TNF-α: tumor necrosis factor-α; TG: triglycerides.

Brazilian female population show higher frequency of this condition than data found in healthy controls in the present study<sup>24,25</sup>. This may be explained by the fact that our healthy control group had a high level of education (> 9 yrs), were younger, and presented lower BMI compared to other surveys<sup>24,25</sup>.

The observed prevalence is also higher than that reported for patients with systemic lupus erythematosus (SLE)<sup>26,27,28</sup> and is similar to that found in rheumatoid arthritis (RA)<sup>29</sup>, Sjögren syndrome<sup>30</sup>, and primary antiphospholipid syndrome<sup>31</sup>. Regarding antineutrophil cytoplasmic antibody-associated vasculitis (AAV), the prevalence of MetS was higher than in patients with TA<sup>32</sup>. Because patients with TA evaluated herein were younger compared to the patients described in these rheumatic diseases, other factors besides age are possibly involved in the prevalence of this metabolic condition, such as other known associated comorbidities including systemic arterial hypertension.

It is interesting that patients with TA and healthy controls had comparable WC and HDL-C. This observation could be explained by several factors: first, the matched BMI between patients and controls may explain the similar WC; second, the statin use in almost half of patients with TA could explain similar levels of cholesterol between patients with TA and controls. Moreover, the literature regarding MetS and other forms of vasculitis also revealed that fewer criteria were fulfilled for the diagnosis of MetS comparing patients and controls, suggesting that some conditions are

more relevant for the diagnosis of this comorbidity in vasculitis<sup>32</sup>.

Concerning adiponectin, a protein almost exclusively synthesized by adipocytes with an established systemic antiinflammatory effect<sup>33</sup>, we did not observe any difference between patients and controls, and this finding is almost certainly related to the fact that patients and controls had similar BMI, weight, and percentage of WHO BMI classification. Although insulin, HOMA-IR, and apolipoprotein E levels were higher in patients with TA than controls, the prevalence of diabetes, another risk factor that has been associated with elevated adiponectin concentration, was similar in both groups<sup>8</sup>.

By contrast, resistin — an adipokine induced by several proinflammatory cytokines<sup>34</sup> — was higher in patients with TA than in healthy controls. In fact, studies conducted in other forms of vasculitis, such as Kawasaki disease<sup>35</sup> and Behçet disease<sup>36</sup>, showed higher resistin levels than healthy controls but no differences in adiponectin levels. Further, increased levels of resistin serum were also found in patients with other rheumatic disease such as SLE<sup>37</sup> and RA, and in the latter disease this adipokine was correlated with CRP and disease activity<sup>38</sup>. Accordingly, CRP levels observed herein were higher in patients with TA than in controls.

Further evaluation of TA patients with and without MetS revealed lower adiponectin levels in the former group. This finding is probably due to a higher proportion of overweight/obesity and insulin resistance found in patients

with MetS. In fact, this adipokine has an insulin-sensitizing effect related to an increased fatty acid oxidation on skeletal muscles and inhibition of gluconeogenesis in liver and other tissues reducing glucose synthesis<sup>8,39,40</sup>. Sanjari, *et al* also identified that a lower level of adiponectin was a good predictor for MetS in women<sup>41</sup>. Further, serum levels of adiponectin were inversely correlated with HOMA-IR in patients with SLE<sup>20</sup>.

TA patients with and without MetS showed similar resistin levels, probably because inflammatory markers and frequency of disease activity had not presented differences in these subgroups.

Surprisingly, we observed no association between steroids and MetS, and this finding is in agreement with most studies in other rheumatic diseases, including SLE<sup>27,42,43</sup>, RA<sup>44,45</sup>, and AAV<sup>32</sup>. Further, these findings may be related to low current and cumulative doses of glucocorticoids in patients with TA, suggesting that most patients had mild to moderate disease in our study. This may, however, give clues to how inflammation and metabolic factors interact in patients with TA and is a subject worthy of further study. We observed that the disease and its treatment did not seem to be a major trigger for this condition in patients with TA.

In fact, overweight/obesity was identified as the main component of this syndrome in TA, reinforced by the finding of a negative correlation between WC and adiponectin levels observed in our patients with TA and also in women with MetS<sup>39</sup>. In addition, these patients also had a higher frequency of Framingham scores, emphasizing the relevance of evaluating this underrecognized disturbance in TA.

No differences regarding cytokines and presence or absence of MetS were found. However, we found a positive correlation between CRP and IL-6 levels only in TA patients with MetS. As many authors have shown, IL-6 is an important marker for disease activity<sup>46,47</sup>, these data may denote an indirect association between disease activity in TA and the presence of MetS.

A high prevalence of MetS was observed in patients with TA, and this comorbidity seems to identify a subgroup of overweight/obese patients with high cardiovascular risk without a significant association with disease status. Further longitudinal studies are necessary to observe the effect of controlling this modifiable risk factor on the quality of life and survival of patients with TA.

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