Anaemia and low body mass index are associated with increased cardiovascular disease in patients with Takayasu arteritis

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ABSTRACT

Objective. *Despite the high prevalence of cardiovascular disease (CVD) among patients with Takayasu arteritis (TA), few studies have identified its clinical correlates. The aim of this study was to analyse the prevalence of CVD and its association with traditional CV risk factors and disease-related variables in patients with TA.*

Methods. *A total of 262 consecutive patients with a diagnosis of TA between January 2009 and July 2013 were included in this study. The primary outcome was CVD, defined as the presence of a previous history of myocardial infarction, angina, coronary disease, coronary bypass surgery, coronary angioplasty, and stroke. Multivariate logistic regression analysis was used to determine the relationship of conventional CV risk factors and TA-related variables to the presence of CVD.*

Results. *CVD was present in 64 (24.4%) of patients with TA. Of the total cohort, 16 (6.1%) had a history of myocardial infarction, 31 (11.8%) had angina and 24 (9.2%) had stroke. Multivariate logistic regression analysis revealed that anaemia (OR, 2.449; 95% CI: 1.167–5.141, p=0.018), low body mass index (OR, 0.821; 95% CI: 0.723–0.932, p=0.002), advancing age (OR, 1.050; 95% CI: 1.013–1.088, p=0.007), hyperlipidaemia (OR, 3.792; 95% CI: 1.647–8.727, p=0.002), and family history of CVD (OR, 2.915; 95% CI: 1.188–7.153, p=0.019) were significantly associated with the presence of CVD.*

Conclusion. *Our study suggests that in addition to traditional CV risk factors, anaemia and low body mass index are independently associated with increased CVD in patients with TA.*

Introduction

Takayasu arteritis (TA) is a chronic inflammatory vasculitis of unknown aetiology, which primarily involves large vessels, especially the aorta and its main branches, as well as coronary and pulmonary arteries. Inflammation in arterial wall may lead to luminal stenosis, occlusion, dilation, or aneurysm formation (1, 2).

Growing evidence suggests that diseases associated with chronic inflammation result in premature atherosclerosis (3-5). In this regard, TA is associated with increased mortality, which is predominantly due to accelerated atherosclerosis (6-8). In autopsy reports, atherosclerotic changes have been found in young patients with TA (9, 10). Supporting these findings, imaging technology assessment has also confirmed early atherosclerosis in TA (11, 12). Therefore, identification of early signs of cardiovascular disease (CVD) is important so that effective CV protective strategies can be promptly implemented. The risk factors for CVD in the general population have been well characterised (13). Many of these traditional risk factors are also present among patients with TA (14, 15). However, it is unclear whether these factors are independently predictive of CVD among patients with TA. As a chronic inflammatory disease, TA-related variables may also contribute to the development and progression of these complications. Therefore, in the present study, we set out to investigate whether traditional CV risk factors, as well as TA-related disease characteristics, are associated with increased CVD in patients with TA.

Materials and methods

Patients

A total of 262 consecutive patients with TA in Fuwai Hospital from January 2009 to July 2013 were included in this study. All patients fulfilled the 1990 American College of Rheumatology criteria for TA (16): age at disease onset ≤40 years; claudication of extremities; a decreased brachial artery pressure; blood pressure difference >10 mmHg; bruits over subclavian arteries or aorta;

and abnormalities on arteriography. A patient was diagnosed with TA if at least 3 of these 6 criteria were present. The study protocol was approved by the Institutional Ethics Committee of the Fuwai Hospital, and all of the participants signed an informed consent.

Classification criteria

TA is classified into four types according to Lupi-Herrera's criteria: type I, arteritis involvement of the aortic arch and its major branches; type II, arteritis involvement of the thoracic and abdominal aorta; type III, arteritis involvement of the whole aorta; and type IV, arteritis involvement of the pulmonary artery (17).

Measured variables

The measured patient characteristics included baseline demographics (age, gender, height, weight, and body mass index [BMI, calculated as weight in kilograms divided by the square of height in metres]), past medical history (hypertension, diabetes mellitus, hyperlipidaemia, smoking, alcohol consumption, and family history of CVD), CV risk factors (systolic blood pressure, diastolic blood pressure, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol [HDL-C], triglyceride [TG], fasting glucose, serum creatinine, blood urea nitrogen, and uric acid), disease-related variables (disease duration, anaemia, albumin level, erythrocyte sedimentation rate [ESR], high-sensitivity C-reactive protein [hs-CRP], and clinical classification) and medication use (prednisone, aspirin, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, β-blockers, calcium channel blockers, diuretics, and statins).

Definition of anaemia

Anaemia in patients with TA was defined as a haemoglobin concentration lower than 13 g/dl for male and 12 g/dl for female according to the World Health Organisation criteria (18).

Primary outcome

The primary outcome was CVD, defined as the presence of a previous history of myocardial infarction, angina, coronary disease, coronary bypass surgery, coronary angioplasty, and stroke.

Statistical analysis

Continuous data were presented as mean ± standard deviation (SD), and categorical data were expressed as total number (percentage). Kolmogorov-Smirnov test was used to evaluate the normal distribution of the numerical data. Differences between the groups were assessed using independent *t*-test or Mann-Whitney U-test for continuous data, and chi-square test or Fisher's exact test for categorical data. Multivariate logistic regression analysis was used to determine the relationship of conventional CV risk factors and TA-related variables to the presence of CVD. In all of the analyses, a two-sided significance level of 0.05 was used (SPSS 17.0; SPSS Inc., Chicago, Illinois, USA).

Results

Patient characteristics

Table I shows the clinical characteristics of 262 patients with TA. The average age of patients with TA was 39.2±13.7 years and 83.2% were female. CVD was present in 64 (24.4%) of patients with TA. Of the total cohort, 16 (6.1%) had a history of myocardial infarction, 31 (11.8%) had angina and 24 (9.2%) had stroke. The prevalence for CV risk factors was 61.5% for hypertension, 5% for diabetes, 24% for hyperlipidaemia, 10.7% for ever-smoking, 5% for alcohol consumption, and 14.1% for family history of CVD. Of the proposed disease-related factors, anaemia was found in 36.3% of patients, and the mean disease duration was 9.6±10.2 years. Elevated ESR (>20 mm/h) or hs-CRP (>3 mg/l) was found in 65 (24.8%) and 122 (46.6%) patients respectively. Based on the classification criteria, Type III (42%) was the most frequent type, followed by Type I (33.6%), Type II (17.6%), and Type IV (6.9%).

Traditional CV risk factors and the presence of CVD

The demographic and clinical characteristics of TA patients with and without CVD are presented in Table II. Advancing age (p<0.001), diabetes mellitus (p=0.001), hyperlipidaemia (p<0.001), and family history of CVD (p<0.001) were more frequent in patients with CVD than those without CVD. A similar tendency was also observed for smoking history, although the difference between groups was marginally significant (p=0.053). Fasting glucose (p=0.001), TG (p=0.023), serum creati-

Table I. Demographic and clinical characteristics of the 262 patients with TA.

Age, years	39.2 ± 13.7
Female, n (%)	218 (83.2%)
BMI, kg/m^2	22.9 ± 3.6
Disease duration, years	9.6 ± 10.2
Anaemia, n (%)	95 (36.3%)
Hypertension, n (%)	161 (61.5%)
Diabetes mellitus, n (%)	13 (5.0%)
Hyperlipidaemia, n (%)	63 (24.0%)
Smoking, n (%)	28 (10.7%)
Alcohol consumption, n (%)	13 (5.0%)
Family history of CVD, n (%)	37 (14.1%)
Systolic BP, mmHg	135.3 ± 35.0
Diastolic BP, mmHg	76.2 ± 20.5
Albumin, g/L	40.6 ± 5.1
Fasting glucose, mmol/L	4.7 ± 0.9
Serum creatinine, umol/L	67.2 ± 21.3
Blood urea nitrogen, mmol/L	5.6 ± 2.2
Uric acid, μmol/L	309.9 ± 106.0
Triglyceride, mmol/L	1.4 ± 0.7
Total cholesterol, mmol/L	4.5 ± 1.1
HDL-C, mmol/L	1.3 ± 0.4
LDL-C, mmol/L	2.6 ± 0.9
ESR, mm/h	17.1. ± 20.1
Hs-CRP, mg/L	4.9 ± 4.6
Clinical classification, n (%)	
Type I	88 (33.6%)
Type II	46 (17.6%)
Type III	110 (42.0%)
Type IV	18 (6.9%)
Medications at discharge, n (%)	
Prednisone	182 (69.5%)
Aspirin	188 (71.8%)
ACEIs	54 (20.6%)
ARBs	42 (16.0%)
β-Blockers	148 (56.5%)
Calcium channel blockers	118 (45.0%)
Diuretics	84 (32.1%)
Statins	73 (27.9%)

Data are presented as mean ± SD or as number (percentage).
BMI: body mass index; CVD: cardiovascular disease; BP: blood pressure; WBC: white blood cell; RBC: red blood cell; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ESR: erythrocyte sedimentation rate; Hs-CRP: high-sensitivity C-reactive protein; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.h

Table II. Demographic and clinical characteristics of the TA patients with and without CVD.

	CVD present (n=64)	CVD absent (n=198)	*p*-value
Age, years	47.6 ± 14.4	36.4 ± 12.3	<0.001
Female, n (%)	49 (76.6%)	169 (85.4%)	0.102
BMI, kg/m^2	22.5 ± 3.2	23.0 ± 3.7	0.334
Disease duration, years	14.0 ± 13.3	8.1 ± 8.6	0.002
Anaemia, n (%)	30 (46.9%)	65 (32.8%)	0.042
Hypertension, n (%)	44 (68.8%)	117 (59.1%)	0.168
Diabetes mellitus, n (%)	8 (12.5%)	5 (2.5%)	0.001
Hyperlipidaemia, n (%)	32 (50.0%)	31 (15.7%)	<0.001
Smoking, n (%)	11 (17.2%)	17 (8.6%)	0.053
Alcohol consumption, n (%)	2 (3.1%)	11 (5.6%)	0.436
Family history of CVD, n (%)	18 (28.1%)	19 (9.6%)	<0.001
Systolic BP, mmHg	133.9 ± 34.7	135.8 ± 35.1	0.712
Diastolic BP, mmHg	75.2 ± 19.4	76.5 ± 20.9	0.647
Albumin, g/L	40.3 ± 4.3	40.7 ± 5.4	0.573
Fasting glucose, mmol/L	5.1 ± 1.1	4.6 ± 0.8	0.001
Serum creatinine, umol/L	72.8 ± 23.4	65.3 ± 20.3	0.015
Blood urea nitrogen, mmol/L	6.0 ± 2.2	5.4 ± 2.1	0.066
Uric acid, μmol/L	336.1 ± 115.5	301.4 ± 101.6	0.022
Triglyceride, mmol/L	1.6 ± 0.7	1.4 ± 0.6	0.023
Total cholesterol, mmol/L	4.4 ± 1.3	4.5 ± 1.0	0.443
HDL-C, mmol/L	1.2 ± 0.4	1.3 ± 0.4	0.003
LDL-C, mmol/L	2.6 ± 1.2	2.6 ± 0.8	0.948
ESR, mm/h	18.9 ± 24.9	16.5 ± 18.3	0.801
Hs-CRP, mg/L	4.4 ± 4.4	5.0 ± 4.7	0.355
Clinical classification, n (%)			0.565
Type I	25 (39.1%)	63 (31.8%)	
Type II	8 (12.5%)	38 (19.2%)	
Type III	27 (42.2%)	83 (41.9%)	
Type IV	4 (6.3%)	14 (7.1%)	
Medications at discharge, n (%)			
Prednisone	31 (48.4%)	151 (76.3%)	<0.001
Aspirin	49 (76.6%)	139 (70.2%)	0.326
ACEIs	11 (17.2%)	43 (21.7%)	0.436
ARBs	13 (20.3%)	29 (14.6%)	0.283
β-Blockers	52 (81.3%)	96 (48.5%)	<0.001
Calcium channel blockers	34 (53.1%)	84 (42.4%)	0.135
Diuretics	20 (31.3%)	64 (32.3%)	0.873
Statins	37 (57.8%)	36 (18.2%)	<0.001

Data are presented as mean±SD or as number (percentage).
BMI: body mass index; CVD: cardiovascular disease; BP: blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ESR: erythrocyte sedimentation rate; Hs-CRP: high-sensitivity C-reactive protein; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

nine (p=0.015), and uric acid (p=0.022) were significantly higher, while HDL-C (p=0.003) was significantly lower in patients with CVD compared with those without CVD. Furthermore, more patients were prescribed β-blockers (p<0.001) and statins (p<0.001) in the CVD present group.

TA-related variables and the presence of CVD

TA disease characteristics between patients with and without CVD are also shown in Table II. The mean disease duration was longer and anaemia was more frequently in patients with CVD compared with those without CVD (p=0.002 and 0.042 respectively). However, no significant differences regarding inflammatory markers ESR or hs-CRP were found in TA patients with and without CVD (p=0.801 and 0.355 respectively). Considering the extent of arterial involvement, there was no significant difference between the two groups (p=0.565). Fewer patients were prescribed prednisone in the CVD present group compared with CVD absent group (p<0.001). Among patients who received prednisone therapy, there was no significant difference in the mean daily dosage between the two groups (23.1±6.8 *vs*. 22.9±8.3 mg, p=0.902).

Variables independently associated with CVD in TA

The results of multivariate logistic regression analysis showed that anaemia (OR, 2.449; 95% CI: 1.167–5.141, p=0.018), low BMI (OR, 0.821; 95% CI: 0.723–0.932, p=0.002), advancing age (OR, 1.050; 95% CI: 1.013–1.088, p=0.007), hyperlipidaemia (OR, 3.792; 95% CI: 1.647–8.727, p=0.002), and family history of CVD (OR, 2.915; 95% CI: 1.188–7.153, p=0.019) were independently associated with increased CVD in patients with TA after these parameters were adjusted for sex, disease duration, smoking, alcohol consumption, hypertension, diabetes mellitus, serum creatinine and uric acid (Table III).

Discussion

To our knowledge, this is the largest study that has been conducted to date for the identification of traditional CV risk factors, as well as TA disease characteristics that contribute to the presence of CVD in patients with TA. We found that in addition to conventional CV factors, anaemia and low BMI were also independently associated with increased CVD in patients with TA.

Our analysis suggests that several traditional CV risk factors, including advancing age, hyperlipidaemia, and family history of CVD, are significant clinical correlates for CVD among patients with TA, as in the general population.

Age has been thought to be an important predictor of CVD in the general population (13). Likewise, we found 5% greater odds of having CVD for every 1-yr increase in age in the multivariable analysis. Although gender differences have been found in clinical and angiographic findings of patients with TA (19), there was no significant difference in gender distribution between patients with and without CVD in our study, which may be explained by the female preference in TA.

Table III. Multivariate logistic analysis to evaluate variables associated with CVD in TA.

Variables	OR	95% CI	*p*
Age	1.050	1.013-1.088	0.007
Sex	0.427	0.129-1.411	0.163
Body mass index	0.821	0.723-0.932	0.002
Disease duration	1.016	0.980-1.054	0.386
Anaemia	2.449	1.167-5.141	0.018
Hypertension	0.957	0.455-2.013	0.907
Diabetes mellitus	2.300	0.570-9.285	0.242
Hyperlipidaemia	3.792	1.647-8.727	0.002
Smoking	1.729	0.451-6.621	0.424
Alcohol consumption	0.370	0.053-2.603	0.318
Family history of CVD	2.915	1.188-7.153	0.019
Albumin	0.978	0.894-1.070	0.626
Serum creatinine	1.004	0.985-1.024	0.669
Uric acid	0.999	0.995-1.003	0.749

CVD: cardiovascular disease.

Our study confirms the findings of other investigators with regard to the role of hyperlipidaemia as a strong CVD correlate (13). Patients with hyperlipidaemia were 2.8 times more likely to have CVD than those without hyperlipidaemia after adjustment for other conventional risk factors and disease-related variables. With respect to the lipid profile, the levels of serum TG were significantly higher, while HDL-C was significantly lower in CVD present group compared with CVD absent group. In accordance with our results, several studies determining the cardiovascular lipid risk levels in patients with TA observed similar lipid spectrum alterations (14, 15).

Individuals with a family history of CVD are at high risk for developing atherosclerosis and adverse CV events (20). For patients with TA, previous studies demonstrated that family history of CVD was more common in patients with carotid atherosclerotic plaques than those without plaques, although the difference was not significant (12). One major explanation for this phenomenon is that the sample size is relatively small in that study, with only 8 TA patients with plaques and 22 patients without plaques. In our study with a higher number of patients, we found that patients with family history of CVD had 1.9 times greater likelihood of having CVD than those without family history, with adjustment for other confounding factors.

Obesity has been recognised to be a risk factor for the development of CVD and is associated with increased mortality in general population (21). This is an expected observation, since obesity may potentially contribute to increased atherosclerotic burden through its adverse effects on blood pressure, lipid metabolism, and insulin resistance (22). However, in our study, we found that low BMI is associated with increased CVD in patients with TA. In consistent with our results, previous studies have revealed that low BMI is associated with a significantly increased risk of CV death among patients with rheumatoid arthritis (RA) (23, 24). The underlying mechanisms of the relationship between low BMI and the presence of CVD remain unclear. It has been reported that subjects with RA had a higher prevalence of low BMI, and the reduction in body mass was greatest for muscle mass, whereas adipose mass was well-maintained (25). Thus, low BMI in patients with TA may reflect low lean body mass, which has been found to be associated with functional impairment and physical disability in older persons (26). Patients with TA typically have impaired quality of life and reduced physical activity, which may contribute to the increased CVD in TA (27).

Disease activity assessment in TA is crucial and still remains a difficult challenge for clinicians. Recently, some novel disease specific biomarkers have been investigated for evaluation of disease activity in TA (28). However, as TA-related variables, we found no association of the presence of CVD with inflammatory markers ESR or hs-CRP, as well as clinical classification. The possible explanation is that compared with one-time measurements, serial monitoring of the changes of ESR or hs-CRP may be more valuable for the prediction of CVD in rheumatic diseases (24). There were significant differences regarding anaemia and disease duration between patients with and without CVD in the univariate analysis. However, the final multivariate model, with adjustment for other confounding factors, did not identify disease duration as a significant CVD correlate.

Anaemia has been shown to be a risk factor for mortality in patients with kidney disease and heart failure (29-31). In prospective, population-based studies, anaemia was also found to be associated with increased risk for new onset of CVD (32, 33). Furthermore, anaemia had previously been correlated to worse outcome in patients with acute coronary syndromes after percutaneous coronary intervention (34-36). In agreement with these findings, our data showed that patients with anaemia were 1.4 times more likely to have CVD than those without anaemia, with adjustment for other conventional risk factors. The exact mechanism of anaemia on the presence of CVD in TA is not fully elucidated. In part, anaemia may be a surrogate marker of a poor health status, reflecting a decreased nutritional condition or additional measures of lower socioeconomic status (37). Consistently with previous studies, the levels of albumin were significantly lower among the anemic group in our study as well (data not shown). However, results of the multivariate analysis suggested that anaemia seems to play an independent role for adverse outcome. In the presence of anaemia, maintenance of adequate tissue oxygenation may become relevant by both haemodynamic (increased preload, peripheral systemic arterial dilatation, positive inotropic and chronotropic effects) and non-haemodynamic adaptations (decreased blood viscosity and increased erythropoietin production), which is mainly mediated through an activation of the sympathetic and renin-angiotensin-aldosterone

systems (38). These changes have been found to exert a negative influence on cardiac function promoting cardiac fibrosis and left ventricular hypertrophy, which may contribute to the pathogenesis of CVD (39, 40).

Several limitations should be noted in this study. First, the cross-sectional design limits a completely evaluation of the complex relationships between many proposed factors and the presence of CVD. For example, we cannot adequately investigate the associations of disease progression or medication used and the occurrence of CVD in this study, because the temporal association between exposure and outcomes cannot be addressed. Therefore, our findings should be investigated in long-term prospective studies before any causal relationships can be established. Second, cause of anaemia are unknown, further exploration of the effect of different types of anaemia on various CVD outcomes are needed in patients with TA.

In conclusion, anaemia and low BMI confer a significantly additional risk for CVD among patients with TA, even after controlling for traditional CV risk factors. These results suggest that physicians should pay much attention to the management of CV risk factors, especially among those TA patients who have anaemia or a low BMI. Further research is needed to determine optimal approaches to reduce CV morbidity and mortality in patients with TA.

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