Association of Prolonged Disease Duration and TG/HDL-C Ratio in Accelerating Atherosclerosis in Patients with Takayasu’s Arteritis

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Abstract
Background and aim: Takayasu’s arteritis (TA) is a chronic inflammation that frequently involves the aorta and its major branches. It has been known that atherosclerosis can occur in some TA patients. Objectives: This study aimed to identify the risk factors associated with the development of atherosclerosis in TA. Methods: This retrospective study enrolled a total of 101 TA patients. All patients were divided into two groups according to the absence or presence of atherosclerosis. Baseline demographic features and clinical characteristics were compared between two groups. A logistic model was applied to determine the risk factors associated with the development of atherosclerosis. Results: Our data suggested that the disease duration of patients in the atherosclerosis group was significantly longer than that of patients in the non-atherosclerosis group [96(18.00, 180.00) versus 48.00(12.00, 111.00) months] (P = .015). In addition, the average age of patients with atherosclerosis was significantly older compared to patients without atherosclerosis [44.00(38.00, 48.00) versus 28.50(24.00, 37.00) years] (P < .001). Logistic regression analysis showed that the risk of developing atherosclerosis increased by 9.2% per 1 year increase in the disease duration (P = .005, OR 1.092, 95%CI: 1.027-1.162). Patients with TG/HDL-C ratio more than 0.8875 were associated with a 5.861 fold increase of risk developing atherosclerosis (P < .001, OR 5.861, 95%CI: 2.299-14.939). Conclusion: Our study indicated that prolonged disease duration and elevated TG/HDL-C ratio are associated with the development of atherosclerosis in TA patients.

Keywords
Takayasu’s arteritis, atherosclerosis, dyslipidemia, TG/HDL-C ratio

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Introduction
Takayasu’s arteritis (TA) is an autoimmune vasculitis that frequently occur in young women. Multiple previous studies have demonstrated that accelerated atherosclerotic changes were commonly found in TA patients.1-4 More specifically, data indicated that as much as 27% of all TA patients developed carotid artery plaque, while which was only 2% in the age- and sex-matched healthy individuals.1 In addition, up to 20% of TA patients developed stroke and/or transient ischemic attack (TIA), which both have been known to be associated with atherosclerotic lesions.1-3 Inflammation of the vascular wall may promotes atherosclerosis (As) in TA, which accelerates the development of As. Higher triglyceride (TG)/high-density lipoprotein cholesterol(HDL-C) ratio was

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found to be associated with presence of endothelial dysfunction and As.5

It is well studied that vessel wall inflammation plays an important role in TA associated atherosclerosis.4,5 A previous study discovered that the dyslipidemia promoted the atherosclerosis in TA, especially the reduction of HDL-C.6 However, the characteristics and risk factors associated with TA associated atherosclerosis has not been fully elucidated. This study aimed to describe the clinical manifestations, serological and imaging features of TA patients with atherosclerosis and to identify the associated risk factors.

Materials and Methods

Participants
A total of 160 patients who diagnosed with TA according to the American College of Rheumatology criteria published in 19907 at the Beijing Anzhen Hospital from January 2012 to December 2019 were screened for this study. Patients with the following conditions were excluded from the study: complicated with other autoimmune diseases, liver and kidney diseases, cancer, active infection and those with missing data. Eventually, 101 patients who were treatment naive until enrolled were enrolled in this study. Disease activity was assessed using a modified version of Kerr’s criteria8 and Indian Takayasu Activity Score (ITAS).9 Patients were divided into two groups according to the presence or absence of atherosclerosis identified by imaging (Figure 1). This retrospective study was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University (approval number: 2018016X). All patients in this study signed the informed consent.

Baseline Characteristics and Blood Sample Collection
Baseline characteristics including age, sex, disease duration, disease history, past history, and body mass index (BMI) were recorded. For each patient, venous blood was drawn in the morning after fasting for 12h. Then, routine blood tests were performed with XE2100 (SYMEX, Japan). The Hitachi 7600-120 automatic biochemical analyzer (Tokyo, Japan) was used to analyze the serum samples. Alanine aminotransferase (ALT), glutamic-pyruvic transaminase (AST), creatinine, uric acid, glucose, serum TG, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), activated partial thromboplastin time (APTT), prothrombin time (PT), D-dimer, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), immunoglobulin A(IgA), immunoglobulin G(IgG), immunoglobulin M(IgM), complement C3(C3), complement C4(C4), interleukin 6(IL-6), tumor necrosis factor-α (TNF-α), homocysteine. The LDL-C/HDL-C, TC/HDL-C, and TG/HDL-C ratios were calculated.

Evaluation of Atherosclerosis
Atherosclerosis (As) is a pathological change in arterial vessels. It is characterized by vascular endothelial injury, followed by lipid deposition, macrophage phagocytosis and foam cell formation, as well as the formation of lipid core under the action of pro-inflammatory factors, accompanied by the formation of fiber cap. The chemicals released by inflammatory cells promote the proliferation of smooth muscle cells and stromal cells, leading to the thickening of inner and middle membranes. However, in order to facilitate the study, we grouped Takayasu arteritis with or without atherosclerosis using the typical imaging changes. According to the 2018 EULAR LVV management recommendation,10 the thoracic aorta and its branches were evaluated by magnetic resonance angiography (MRA) or computed tomography angiography (CTA). Atherosclerosis does not show any contrast enhancement, and wall thickening is eccentric and focal.11 Conversely, vasculitis shows perivascular contrast enhancement and wall thickening can be characterized as concentric and in a long vessel segment in MRA images. Atheroma plaques may cause mild local inflammation, and CTA may detect slight and irregular, nonconcentric wall thickening surrounding the plaque. CTA abnormalities observed in large-vessel vasculitis are more prominent and characteristic and consist of concentric aortic wall thickening, frequently greater than 3 mm.12 Each potential lesion was evaluated by two specialists consulted all lesions and identified the atherosclerosis or non-atherosclerosis. The abdominal aorta and the peripheral arteries were observed by doppler ultrasound. Plaque is a typical feature of atherosclerosis indoppler ultrasound.

Angiographic Classification
The location of TA lesions were classified according to the angiographic classification of the International TA Conference published in 199413 as introduced below: type I (branches of the aortic arch); type IIa (ascending aorta, aortic arch and its branches); type Ib (ascending aorta, aortic arch and its branches, and thoracic descending aorta); type III (thoracic descending aorta, abdominal aorta, and/or renal arteries); type IV (abdominal aorta and/or renal arteries), and type V (combined features of types Ib and IV).

Pathological Staining of Aortic Tissue
One TA patient underwent Bentall operation due to severe aortic insufficiency and ascending aortic dilatation. The tissue of aortic root was obtained after operation. Specimens were fixed in 4% neutral formalin for 24 h, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Verhoef-van Gieson was applied to demonstrate areas of degeneration, elastic fiber disorder and fragmentation.

Statistical Analysis
According to the normality of the data, variables were described as means ± SE or medians (Q1, Q3). Differences between measured parameters between groups were assessed using the unpaired t test. If data were not normally distributed, the Mann-Whitney test was used. The χ² test was used to compare qualitative parameters. The Pearson approach was used to quantify the correlation between variables. The cutoff
values of LDL-C/HDL-C ratio and TC/HDL-C ratio and TG/HDL-C ratio was calculated by using ROC curve. To identify the relevant risk factors of atherosclerosis, following variables were included in the logistic regression model: disease duration, hypertension history and TG/HDL-C ratio \((\geq 0.8875 = 1, <0.8875 = 0)\). \(P\) value \(<0.05\) was considered statistically significant. All statistical analyses were performed using the SPSS program (version 26.0, SPSS Inc., Chicago, Illinois, USA).

**Results**

**Baseline Characteristics of TA Patients with and Without Atherosclerosis**

Atherosclerosis was observed in 43 TA patients (42.57%). The average age of patients with atherosclerosis was significantly older than that without atherosclerosis \([44.00(38.00, 48.00)\) versus \(28.50(24.00, 37.00)\) years \(P<.001\)]. Similarly, the disease duration was significantly longer in patients with atherosclerosis compared to non-atherosclerosis patients \([96.00(18.00, 180.00)\) versus \(48.00 (12.00, 111.00)\) months, \(P=.015\)]. In addition, our data indicated that significantly more patients developed atherosclerosis with the prolongation of disease duration, the proportion of TA with atherosclerosis was increased. There was significant difference in the proportion of atherosclerosis when their disease duration was longer than or equal to 20 years \((P=.016)\). Next, we compared the prevalence of conventional risk factors of atherosclerosis between two groups and discovered that histories of hypertension \((32.56\% \) vs \(13.79\%, P = .024\) was more common among patients with atherosclerosis compared to patients without atherosclerosis. Although the BMI was significantly higher in patients with atherosclerosis, the index was within the normal range \((23.08 \pm 3.18\) vs \(21.56 \pm 3.48, P=.026\) (Table 1). Meanwhile, no significant difference of clinical manifestations such as dizziness, carotidynia, chest tightness, unequal blood pressures in the upper extremities, chest pain, claudication, pulseless, malaise, fever, and weight loss \((P>.05)\).

**Comparison of Laboratory Parameters and Disease Activity Between Two Groups**

We compared laboratory parameters from age - and sex-matched healthy controls. The results showed that the serum level of TG \((1.08 \pm 0.70\) vs \(0.80 \pm 0.30\) mmol/L, \(P<.001\)) was significantly higher than that of the healthy control group, while the serum level of HDL-C was significantly lower than that of the healthy control group \((1.25 \pm 0.39\) vs \(1.45 \pm 0.21\) mmol/L, \(P<.001\)) (Supplementary Table). In addition, our data indicated that the serum levels of LDL-C/HDL-C ratio and TG/HDL-C ratio were
significantly increased in patients with atherosclerosis compared to patients without atherosclerosis \[2.34 \pm 1.04 \text{ versus } 1.98 \pm 0.72, \ P = .048\] and \[0.95(0.57, 1.19) \text{ versus } 0.69(0.41, 0.93), \ P = .018, \ \text{respectively}\]. No significant difference of serum levels of TC, HDL-C, LDL-C and TC/HDL-C ratio were discovered between two groups (Table 2).

Interestingly, we discovered that the ITASA score was significantly decreased in patients with atherosclerosis compared to those without atherosclerosis group \[7.02 \pm 4.37 \text{ vs } 8.93 \pm 4.71, \ P = .041\], while no significant difference was discovered in Kerr’s and ITAS2010 scores between two groups\(P>.05\). No significant difference of APTT, PT, D-dimer, ESR, CRP, immunoglobulin G (IgG), immunoglobulin M (IgM), immunoglobulin A (IgA), complement C3 (C3), complement C4 (C4), TNF and IL-6 were discovered between two groups \(P>.05\) (Table 2).

**Angiographic Manifestation of Affected Arteries**

In our study, a total of 133 plaques were identified in 43 TA patients. The most common involvement was right subclavian artery \[13.53\% (18/133)\], followed by abdominal aorta \[12.78\% (17/133)\] (Table 3).

As shown in Figure 3A, ring thickening of the vascular wall was identified in the left carotid artery, eccentric thickening of the vascular wall and arc change of the arterial intima was observed in the left subclavian artery. Representable images of eccentric thickening of the vascular wall and punctate calcification of the arterial intima of abdominal aorta were shown in Figure 3B.

**Identification of Risk Factors Associated with the Development of Atherosclerosis**

The area under the ROC curve of TG/HDL-C was 0.641, which was statistically significant \(P = .018\). The cut-off point of TG/HDL-C was 0.8875 (sensitivity 64.3%, specificity 72.7%).

Parameters that differently expressed between two groups including disease duration, hypertension history and TG/HDL-C ratio were entered into the regression analysis. The result suggested that the risk of developing atherosclerosis increased by 9.2% per 1 year increase in the disease duration \(P = .005, \ \text{OR } 1.092, \ 95\%\text{CI: } 1.027-1.162\). In addition, patients with TG/HDL-C ratio more than 0.8875 were associated with a 5.861-fold increase of risk developing atherosclerosis \(P < .001, \ \text{OR } 5.861 \ 95\%\text{CI: } 2.299-14.939\) (Table 4).

**Histopathological Atherosclerosis Features of Involved Aortic Wall**

The specimen was obtained from a 44-year-old female patient with a history of TA for 25 years who had no CVD risk factors. Bentall procedure was performed due to severe aortic insufficiency and ascending aorta dilatation. Hematoxylin and eosin staining showed proliferated intima, chronic inflammation of the aortic wall, a large number lymphocytes and macrophages infiltration and formation of foam cells (Figure 3C). Van Gieson staining showed extensive elastic fiber disorder, and the wall of nutrient arteries was significantly thickened (Figure 3D).

**Discussion**

This study examined and identified risk factors associated with the development of atherosclerosis in TA patients. We discovered that long disease duration and elevated TG/HDL-C ratio were associated with the development of atherosclerosis in TA patients. Furthermore, the atherosclerosis plaques most frequently occurred in the right subclavian artery and abdominal aorta.
It has been known that women older than 45-55 years starts to become more vulnerable to suffer from atherosclerosis diseases. A number of previous studies have demonstrated accelerated vascular stiffening with menopause and suggested a 6- to 10-year transition period to achieve an unfavorable postmenopausal vessel status. Atherosclerosis is more common in men than in women before the age of 58, and women after the age of 58 are the inflection point of the aggravation and development of atherosclerosis. However, different gender groups have different effects on atherosclerosis. In women, atherosclerosis is mainly aimed at optimizing heart rate control, while in men, it should be aimed at the control of risk factors such as hypertension, diabetes, obesity, blood lipid level and nonalcoholic liver disease. The median age of TA patients with atherosclerosis in our study was 44 years old. These results demonstrated that the atherosclerosis changes observed in TA patients at least partially due to the disease itself, rather than the age. Therefore, the treatment of Takayasu arteritis and early discovery of atherosclerosis are particularly important.

We also found the disease duration in the TA atherosclerosis group was significantly longer than that of the non-atherosclerosis group. Our results showed that the risk of developing atherosclerosis increased by 9.2% per 1 year increase in the disease duration. Interestingly, the prolonged disease duration associated with atherosclerosis TA patients did not translate into higher disease activity, if not lower. We proposed that the long duration disease, extensive vascular involvement...
The reduction in HDL-C showed the clinical characteristics of controls, which was consistent with the results of the present study. Serum HDL-C level was lower in TA patients than in healthy controls, suggesting in TA. Another study showed that disorders of lipid metabolism that chronic systemic inflammation and increased the risk of developing atherosclerosis.21,22 A study suggested that autoimmune diseases may cause changes in blood lipid profile. The 2009 EULAR recommendations promoted the use of TC/HDL-C ratio as a better CVD risk predictor in RA compared to individual lipid components.26–28 Atherogenic index (LDL-C/HDL-C) and coronary risk index (TC/HDL-C) are significantly associated with the risk of developing atherosclerosis.29 A previous study reported that higher TG/HDL-C ratio was associated with the presence of endothelial dysfunction and atherosclerosis.30 Another study demonstrated that the TG/DL-C ratio was a powerful independent predictor of cardiovascular events and all-cause mortality.31 Another study found that the high TG/HDL-C ratio (TG/HDL-C > 0.8853) group had higher morbidity of cardiovascular events.32 Similar with these results, our study found that patients with elevated TG/HDL-C ratio was associated with 5.861-fold increase risk of suffering from atherosclerosis.

As shown in the representable image obtained from a 44-year-old female patient with 25 years of TA without prominent CVD risk factors, it suggested that vasculitis and atherosclerosis could be identified simultaneously (Figure 3A–D) and might provide evidence of the close association between inflammation and atherosclerosis. The vascular endothelial dysfunction, dyslipidemia, glucocorticoid treatment, and other traditional risk factors collectively accelerated the process of atherosclerosis in primary systemic vasculitis.33

In our study, 43 TA patients (42.57%) had atherosclerosis. A total of 133 artery plaque formations were identified. The most common site of plaque formation was right subclavian artery, followed by abdominal aorta. Generally speaking, atherosclerotic patches are easily formed at branches, bifurcations, or bending parts of arteries because of increasing blood turbulence and decreasing shear stress. However, our study found that the plaques were more common to located arteries with signs of inflammation, which was consistent with previous studies.4 The local inflammation may induce stenotic or dilated of arteries and result in disturbed local blood flow and increase exposure areas of the arterial wall to oscillatory shear stress therefore make these arteries more vulnerable.34

This study has some limitations. Firstly, this study was a retrospective study conducted in a single center and we hope to cooperate with multi-centers to expand the sample size to get more persuasive conclusions. Secondly, the prognosis of TA patients with atherosclerosis was not evaluated and neither the efficacy of conventional anti-atherosclerosis treatment. In the future, we can give statins to these patients for lipid-lowering and anti-atherosclerosis treatment and design atherosclerotic vascular events to analyze the prognosis of patients with Takayasu arteritis combined with atherosclerosis.

### Table 3. Location of Plaque in TA Patients.

| Location          | Number | (%)   |
|-------------------|--------|-------|
| Carotid artery    |        |       |
| Left              | 14     | 10.52 |
| Right             | 13     | 9.77  |
| Vertebral artery  |        |       |
| Left              | 0      | 0.00  |
| Right             | 1      | 0.75  |
| Subclavian artery |        |       |
| Left              | 9      | 6.77  |
| Right             | 18     | 13.53 |
| Innominate artery | 1      | 0.75  |
| Abdominal aorta   | 17     | 12.78 |
| Renal artery      |        |       |
| Left              | 0      | 0.00  |
| Right             | 1      | 0.75  |
| Iliac artery      |        |       |
| Left              | 6      | 4.51  |
| Right             | 7      | 5.26  |
| Lower limb artery |        |       |
| Left              | 7      | 5.26  |
| Right             | 9      | 6.77  |
| Aorta             |        |       |
| Ascending aorta   | 7      | 5.26  |
| Aortic arch       | 7      | 5.26  |
| Descending aorta  | 8      | 6.02  |
| Coronary artery   | 8      | 6.02  |
|                   | 133    |       |

and chronic inflammation in TA patients may collectively accelerate the formation of plaque and development of atherosclerosis, which eventually lead to serious ischemic manifestations of important organs.

We compared the conventional CVD risk factors between TA patients with and without atherosclerosis. The results showed that hypertension history was more frequently observed in TA patients with atherosclerosis. The hypertension may induce vascular damage and contribute to the development of atherosclerosis that may involve the renal artery or aorta which can further increase the blood pressure. The patients enrolled in this study were new diagnosed and did not receive any previous treatment that might induce hypertension such as glucocorticoids. We concluded that hypertension was an important cause of atherosclerosis in TA patients.

Previous studies showed that various autoimmune diseases can lead to dyslipidemia and atherosclerosis, and advanced atherosclerosis may increase the morbidity and mortality of cardiovascular diseases in autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and vasculitis. A study suggested that chronic systemic inflammation and vasculitis might lead to endothelial dysfunction and increased the risk of developing atherosclerosis in TA. Another study showed that disorders of lipid metabolism are related to the disease activity in TA. Guleria et al found that serum HDL-C level was lower in TA patients than in healthy controls, which was consistent with the results of the present study. The reduction in HDL-C showed the clinical characteristics of atherosclerosis caused by dyslipidemia in TA patients. Our results showed that the development of atherosclerosis was accelerated with the prolonged disease duration of Takayasu arteritis and dyslipidemia.

The average LDL-C/HDL-C and TG/HDL-C ratios were significantly increased in patients with atherosclerosis. However, no significant difference of serum LDL-C, TC and HDL was discovered. Recent studies have suggested that autoimmune diseases may cause changes in blood lipid profile. The 2009 EULAR recommendations promoted the use of TC/HDL-C ratio as a better CVD risk predictor in RA compared to individual lipid components. Atherogenic index (LDL-C/HDL-C) and coronary risk index (TC/HDL-C) are significantly associated with the risk of developing atherosclerosis. A previous study reported that higher TG/HDL-C ratio was associated with the presence of endothelial dysfunction and atherosclerosis. Another study demonstrated that the TG/DL-C ratio was a powerful independent predictor of cardiovascular events and all-cause mortality. Another study found that the high TG/HDL-C ratio (TG/HDL-C > 0.8853) group had higher morbidity of cardiovascular events. Similar with these results, our study found that patients with elevated TG/HDL-C ratio was associated with 5.861-fold increase risk of suffering from atherosclerosis.

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Conclusion

Our study indicated that prolonged disease duration and elevated TG/HDL-C ratio were closely associated with the development of atherosclerosis in TA patients.

Authors' Contributions

JD conceived the study, performed the statistical analysis, and drafted the manuscript. YR, TL, YZ, SY, TK, SN and XG collected data and revised the manuscript. JL and XG performed the imaging evaluation. WL and LP guided the design of this study and modified the paper. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Table 4. Analysis of Risk Factors for Atherosclerosis by the Model of Logistic Regression.

| Variables     | OR (95%CI)          | P-value |
|---------------|---------------------|---------|
| Disease duration | 1.092 (1.027-1.162) | .005    |
| TG/HDL-C      | 5.861 (2.299-14.939)| <.001   |

Abbreviations: TG, triglyceride; HDL-C, high-density lipoprotein cholesterol.
Supplemental Material

Supplemental material for this article is available online.

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