Carotid artery intima-media thickness in Behcet’s disease patients without significant cardiovascular involvement

Seo Na Hong, M.D., Jong Chun Park, M.D., Nam Sik Yoon, M.D., Sang Rok Lee, M.D., Kye Hun Kim, M.D., Young Joon Hong, M.D., Hyung Wook Park, M.D., Ju Han Kim, M.D., Youngkeun Ahn, M.D., Myung Ho Jeong, M.D., Jeong Gwan Cho, M.D., and Jung Chaee Kang, M.D.

The Heart Center of Chonnam National University Hospital, Gwangju, Korea

Background/Aims : Behcet’s disease (BD) is a systemic disorder associated with a characteristic vasculitis that can involve both veins and arteries of all sizes. Endothelial activation or injury is a characteristic feature of BD. Endothelial dysfunction is widely regarded as being the initial lesion in the development of atherosclerosis. The carotid artery intima-media thickness (IMT) is a widely accepted marker of subclinical atherosclerosis. We aimed to determine the carotid IMT in BD patients using high-resolution B-mode Doppler ultrasonography.

Methods : We studied 40 patients (24 males, mean age: 39.1±8.5 years) who were diagnosed by the international diagnostic criteria of Behcet’s disease and 20 healthy controls (13 males, mean age: 40.2±5.1 years), and the two groups were matched by age and gender. No subject in either group had a history of atherosclerosis or its complications. The clinical data, including the age of onset, the duration of disease, a history of medication, the activity score and the laboratory data were analyzed.

Results: The carotid IMT in the BD group was significantly higher than that in the control group (0.71±0.22 mm vs. 0.59±0.09 mm, respectively, p<0.01). Cardiac and major vessel involvements were not identified in the BD group. However, minor vascular involvements were documented in 2 patients with deep vein thrombosis, in 4 patients with superficial thrombophlebitis and in 2 patients with pseudoaneurysms. The carotid IMT in the patients with posterior uveitis or retinal vasculitis was higher than that of the patients without these findings (0.85±0.21 mm vs. 0.64±0.10 mm, respectively, p=0.007), but there was no difference of the IMT according to minor vascular involvement.

Conclusions : Despite that there was no significant cardiovascular involvement in the BD patients, the carotid IMT was significantly higher in the BD patients as compared with the healthy controls.

Key Words : Behcet’s disease; Carotid intima-media thickness; Cardiovascular involvement

INTRODUCTION

Behcet’s disease (BD) is a chronic, relapsing, multisystemic inflammatory disease that's characterized by recurrent oral and genital ulceration and skin and ocular lesions. Cardiovascular involvement occurs in 7~31% of the BD patients. There may be different types of vascular involvement, yet the majority of the vascular involvement is in the venous system and arterial involvement is rare. In general, BD patients with major vessel involvement have a poor prognosis.

Chronic inflammation is a non-traditional risk factor in the pathogenesis of atherosclerosis, and accelerated atherogenesis
has previously been shown in inflammatory rheumatic disease such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE)\(^6,\) \(^6\). Acute systemic inflammation and chronic systemic vasculitis are associated with endothelial cell dysfunction (ECD)\(^7,\) \(^8\).

The histopathological features of BD are mainly characterized by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration.

The histopathological features of BD are mainly characterized by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pathogenic mechanism for inflammation in the perivascular regions with or without fibrin deposition is by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions with or without fibrin deposition in the vessel walls\(^9\). Although the definite pat...
RESULTS

Clinical and laboratory characteristics

The clinical characteristics are listed in Table 2. No significant differences of age, gender and the lipid profiles were observed between the groups. The mean values of the ESR, CRP and lipid profiles were within the normal limits in both groups. There were no significant differences in the laboratory findings between the groups.

The clinical findings of BD are shown Table 3. The mean age at the time of diagnosis was 32.5±11.5 years and the mean disease duration was 5.2±4.0 years. Seventeen patients (42.5%) had severe manifestations; posterior uveitis or retinal vasculitis in 10 patients, ileocecal ulcerations with bleeding or perforation in 4 patients and neuro-Behcet disease in 3 patients. However, any cardiac involvement and major vessel involvement were not detected. Twenty-four patients (60%) received immuno-suppressive therapy with one or more drugs. Ten patients took high-dose steroid, 10 took cyclosporine, 3 took cyclophosphamide and 7 took azathioprine. The disease activity score at the time of the study and during the month before the study were 0.7±0.3 and 1.3±1.3, respectively.

IMT and the clinical and laboratory variables

The carotid IMT in the BD patients was positively correlated with age (r=0.462, p=0.040), but it was not correlated with the disease duration, the cumulative steroid dose, the disease activity score, the ESR, the CRP level and the lipid profiles (Table 4).

IMT of the CCAs

The carotid IMT in the BD patients was significantly higher than that in the healthy controls (0.71±0.22 mm vs. 0.59±0.11 mm, respectively, p=0.006) (Figure 1). Carotid plaque was present in 1 BD patient and in none of the controls. In the BD patient group, the BD patients with posterior uveitis or retinal vasculitis had a significantly higher carotid IMT than those without posterior uveitis or retinal vasculitis (0.85±0.21 mm vs. 0.64±0.10 mm, respectively, p=0.007) (Table 5). However, no difference of the carotid IMT in the patients with BD was observed according to the presence of vascular lesion, a history of smoking or other vascular disease.

Table 1. The disease activity score for Behcet’s disease

| Score | Clinical findings                                                                 |
|-------|----------------------------------------------------------------------------------|
| 1     | Oral ulceration                                                                  |
|       | Genital ulceration                                                               |
|       | Skin lesion: Erythema nodosum-like lesions, Pseudofolliculitis/papulopustular lesion |
|       | Monoarticular arthritis                                                           |
|       | Superficial vein thrombophlebitis                                                 |
| 2     | Arthritis involving two joints or more                                            |
|       | Gastrointestinal ulceration without complications                                |
|       | Anterior uveitis                                                                 |
|       | Small or medium-sized vessel involvement not related to vital organ               |
| 3     | Posterior/pan uveitis or retinal vasculitis                                      |
|       | Gastrointestinal ulceration with bleeding or perforation                          |
|       | Major vessel involvement                                                          |
|       | Major organ involvement such as brain, lungs or heart                              |

Table 2. Baseline clinical characteristics

|                      | BD patients (n=40) | Healthy controls (n=20) | p value |
|----------------------|--------------------|-------------------------|---------|
| Age (years)          | 39.1±8.5           | 40.2±5.1                | 0.236   |
| Male (n, %)          | 24 (60)            | 13 (65)                 | 0.783   |
| ESR (mm/hr)          | 10.7±10.4          | 10.5±9.6                | 0.997   |
| CRP (mg/dL)          | 0.51±0.52          | 0.34±0.23               | 0.151   |
| Total cholesterol (mg/dL) | 170.5±36.9     | 181.1±36.2             | 0.572   |
| Triglyceride (mg/dL) | 136.1±95.4         | 139.4±37.6             | 0.610   |
| High-density lipoprotein cholesterol (mg/dL) | 62.2±30.0  | 56.3±14.8              | 0.083   |
| Low-density lipoprotein cholesterol (mg/dL) | 103.9±27.5    | 112.1±29.6             | 0.105   |
| Lipoprotein (a) (mg/dL) | 16.2±12.7     | 14.9±14.5              | 0.632   |
| Homocysteine (umol/dL) | 10.5±5.9        | 9.0±2.9                | 0.747   |

Figure 1. Carotid intima-media thickness in the patients with Behcet’s disease and the healthy controls (p=0.006).
Table 3. Clinical findings in the patients with Behcet's disease

| Values |
|--------|
| Age at diagnosis (years) | 32.5±11.5 |
| Disease duration (years) | 5.2±4.0 |
| General manifestations (n, %) | |
| Oral ulcerations | 40 (100.0) |
| Genital ulcerations | 30 (75.0) |
| Erythema nodosum-like lesions | 26 (65.0) |
| Pseudofolliculitis/papulopustular lesions | 26 (65.0) |
| Ocular lesions | 18 (45.0) |
| Pathergy test | 10 (25.0) |
| Arthritis | 8 (20.0) |
| Ileocecal ulcerations | 12 (30.0) |
| Vascular lesion | 8 (20.0) |
| Deep vein thrombosis | 2/8 |
| Superficial thrombophlebitis | 4/8 |
| Pseudoaneurysm | 2/8 |
| Severe manifestations (n, %) | |
| Posterior uveitis or retinal vasculitis | 10 (25.0) |
| Ileocecal ulcerations with bleeding or perforation | 4 (10.0) |
| Major organ involvement (central nervous system) | 3 (7.5) |
| Major vessel involvement | 0 (0.0) |
| Disease activity score for Behcet's disease | |
| at the time of the study and | 0.7±0.3 |
| during the month before the study | 1.3±1.3 |
| Immunosuppressive therapy | |
| High dose steroid (n,%) | 10 (25.0) |
| Mean cumulative steroid dose (mg) | 6321.6±3798.1 |
| Cyclosporin (n,%) | 10 (25.0) |
| Cyclophosphamide (n,%) | 3 (7.5) |
| Azathioprine (n,%) | 7 (17.5) |
| Immunosuppressive therapy with any one drug or more (n,%) | 24 (60.0) |

of immunosuppressive therapy or involvement of major organs (Table 5). The carotid IMT in the 20 patients who were treated with a cumulative steroid dose > 6000 mg did not significantly differ from that in the 20 patients who had not received a cumulative steroid dose ≤6000 mg (0.70±0.18 mm vs. 0.73±0.19 mm, respectively, p=0.719; the mean cumulative steroid dose, 10357.8±4818.1 mg vs. 2511.7±930.1 mg, respectively, p(0.001). On the multivariate analysis, the presence of posterior uveitis or retinal vasculitis was associated with a high carotid IMT (Table 6).

DISCUSSION

Acute systemic inflammation and chronic systemic vasculitis are known to be associated with ECD. Systemic inflammatory rheumatic diseases such as RA and SLE are associated with a significantly increased risk of cardiovascular disease, which often occurs at a younger age for these patients as compared to the normal population. Vasculitis also plays an important role in atherogenesis, as has been shown for Takayasu arteritis and Wegener's granulomatosis. BD is a chronic, systemic inflammatory disorder with a diverse spectrum of clinical manifestations, including mucocutaneous, ocular, vascular, gastrointestinal, musculoskeletal and central nervous system involvement. Vascular involvement in BD is usually recognized as an unclassified vasculitis, and it involves both the veins and arteries of all sizes. Endothelial cell injury or their pathological activation is the characteristic features of BD. An endothelial product, von Willebrand factor, was elevated in BD patients and particularly in the patients with active BD. Despite the uncertainty concerning the pathogenic mechanism of the vascular lesions in BD patients, vascular endothelial dysfunction has been recognized to occur in BD and it is thought to play an important role in the vascular lesions.

In this study, we demonstrated that the carotid IMT was significantly higher in BD patients than that in healthy controls. The previous studies demonstrated that the carotid IMT was significantly higher in BD patients than that in the healthy controls. However, the authors of those studies did not investigate the carotid IMT according to the presence of the clinical findings of BD, such as the medication history or severe
Table 4. Correlation between the carotid intima-media thickness and the clinical and laboratory variables in patients with Behcet's disease

| Variable                                | Correlation (r) | p Value |
|-----------------------------------------|-----------------|---------|
| Age                                     | 0.462           | 0.040   |
| Age at diagnosis                        | 0.297           | 0.204   |
| Disease duration                        | 0.249           | 0.291   |
| Erythrocyte sedimentation rate          | -0.327          | 0.144   |
| C-reactive protein                      | -0.184          | 0.438   |
| Total cholesterol                       | -0.236          | 0.330   |
| Triglyceride                            | 0.100           | 0.684   |
| High-density lipoprotein cholesterol    | 0.026           | 0.900   |
| Low-density lipoprotein cholesterol     | -0.339          | 0.156   |
| Lipoprotein (a)                         | -0.108          | 0.670   |
| Homocysteine                            | 0.298           | 0.230   |
| Cumulative steroid dose                 | 0.099           | 0.687   |
| Disease activity score at the time of study | 0.180     | 0.447   |

Table 5. Carotid intima-media thickness (IMT) in the patients with Behcet's disease according to the clinical findings

| Parameter                              | IMT with clinical findings (mm) | IMT without clinical findings (mm) | p value |
|----------------------------------------|---------------------------------|-----------------------------------|---------|
| Immunosuppressive therapy              | 0.71±0.15                       | 0.70±0.22                         | 0.106   |
| Cumulative steroid dose                | 0.70±0.18                       | 0.73±0.19                         | 0.719   |
| >6000 mg                               |                                 |                                   |         |
| Posterior uveitis or retinal vasculitis| 0.85±0.21                       | 0.64±0.10                         | 0.007   |
| Ileocecal ulceration with bleeding     | 0.78±0.35                       | 0.71±0.17                         | 0.724   |
| Vascular involvement                   | 0.70±0.11                       | 0.71±0.18                         | 0.933   |
| Major organ involvement                | 0.68±0.10                       | 0.71±0.18                         | 0.731   |

Table 6. Multiple regression analysis for the co-factors that affect the carotid intima-media thickness

| Parameters                          | Odds Ratio | 95% CI       | p Value |
|-------------------------------------|------------|--------------|---------|
| Posterior uveitis or retinal vasculitis | 5.262      | 1.234-18.808 | 0.034   |
| Cumulative steroid dose             | 1.023      | 0.078-13.388 | 0.986   |
| Immunosuppressive therapy           | 0.603      | 0.043-8.443  | 0.707   |

disease manifestations, Alan et al. reported that the carotid IMT was significantly higher and the arterial distensibility was significantly lower in patients with BD as compared to the controls. The IMT values were even higher in BD patients with vascular involvement compared to those without vascular involvement. However, BD patients with major vascular involvement were included in that study, and no information was given regarding the use of steroid, the smoking status and the conventional risk factors of atherosclerosis. Rhee et al. reported on the IMT and arterial stiffness of the carotid artery in Korean patients with BD and they demonstrated that BD patients had significantly increased arterial stiffness in all the regional arterial segments. In that study, there were significant differences in the carotid arterial stiffness parameters between the BD patients and the control subjects; however, the carotid IMT of the patients with BD was not different from that of the control group. They did not evaluate the influence of the serologic markers and the clinical manifestation of BD on the carotid IMT. In our study, the carotid IMT was significantly higher in the BD patients with posterior uveitis or retinal vasculitis than that in those BD patients without posterior uveitis or retinal vasculitis. There were no significant differences of the IMT in the subgroups of BD with regard to the presence of vascular involvement and other severe manifestations such as major organ involvement and a history of immunosuppressive therapy. Major vascular involvements were not detected in our study group. Posterior uveitis or retinal vasculitis was the most frequent severe manifestation of BD and this recurred frequently in our study group. Also, carotid plaque was detected in the patient with recurrent posterior uveitis.

CRP is a powerful predictor of cardiovascular disease and this was independent of the serum lipid levels. An elevated CRP level is a very accurate marker of ECD. Our data failed to show a significant correlation between the IMT and the ESR and the
CRP level. The absence of a significant association between the carotid IMT and the CRP level might be explained by our use a conventional CRP assay, rather than using a high-sensitivity CRP (hsCRP) assay. If we had used a hsCRP assay, we might have found a positive correlation. Alternatively, the serum CRP level as determined by conventional assay fluctuates in BD patients and the median of the serial measurements may be more reliable than a single measurement.

In this study, the carotid IMT in the BD patients was positively correlated with age, but it was not correlated with the disease duration and cumulative steroid dose. Additionally, we could not demonstrate any correlation between the disease activity score and the carotid IMT in the BD patient group. BD is characterized by remissions and exacerbations, and it is a multisystemic inflammatory disorder. Each of the BD patients had different and various clinical manifestations. Most patients were in the inactive period and their CRP and ESR values were within the normal limits at the time of the study. Severe disease manifestations appeared less frequently and so the disease activity score at the time of study and during the month before the study started was low in our study group. Further studies on patients with higher disease activity will clarify whether the disease severity increases the risk of subclinical atherosclerosis in patients with BD.

In conclusion, the BD patients without significant cardiovascular involvement demonstrated a higher carotid IMT compared with the healthy control subjects. The increased arterial wall thickness was independently associated with the disease duration and the disease activity score. Our data did not show a significant association between the carotid IMT and immunosuppressive therapy, including high dose steroid therapy for BD. These results suggest that BD itself may lead to an increased carotid IMT, and this is possibly due to an increase in the atherosclerotic changes.

REFERENCES

1) Sakane T, Takeno M, Suzuki N, Inaba G. Behçet’s disease, N Engl J Med 341:1289-1291, 1999
2) Roguin A, Edoute Y, Milo S, Shtiwi S, Markiewicz W, Reisner SA. A fatal case of Behçet’s disease associated with multiple cardiovascular lesions, Int J Cardiol 59:267-273, 1997
3) Han SW, Kang YM, Kim YW, Lee JT, Cardiovascular involvement in Behçet's disease, Korean J Med 64:542-551, 2003
4) Danesh J, Whincup P, Walker M, Lunnom L, Thomson A, Appleby P, Gallimore JR, Peto RB, Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses, BMJ 321:199-204, 2000
5) Bacon PA, Stevens RJ, Carruthers DM, Young SP, Kitas GD, Accelerated atherogenesis in autoimmune rheumatic disease, Autoimmun Rev 1:338-347, 2002
6) Manzi S, Selzer F, Sutton-Tyrrell K, Fitzgerald SG, Rairie JE, Tracy RP, Kuller LH, Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus, Arthritis Rheum 42:51-60, 1999
7) Hingorani AD, Cross J, Kharbanda RK, Mullan MJ, Bhagat K, Taylor M, Donald AE, Palacios M, Griffin GE, Deanfield JE, MacAllister RJ, Vallance P. Acute systemic inflammation impairs endothelium-dependent dilation in humans, Circulation 102:994-999, 2000
8) Raza K, Thambirajah J, Townsend N, Eley AR, Hertas C, Fler A, Carruthers DM, Bacon PA, Suppression of inflammation in primary systemic vasculitis restores vascular endothelial function: lessons for atherosclerotic disease? Circulation 102:1470-1472, 2000
9) Jorizzo JL, Abemethy JL, White WL, Mangelendorf HC, Zouboulis CC, Sarica R, Gaffney K, Mat C, Yazici H, al ilaa T, Mucocutaneous criteria for the diagnosis of Behçet’s disease: an analysis of clinicopathologic data from multiple international centers, J Am Acad Dermatol 32:968-978, 1995
10) Chambers JC, Haskard DO, Kooner JS, Vascular endothelial function and oxidative stress mechanisms in patients with Behçet’s syndrome, J Am Coll Cardiol 37:517-520, 2001
11) Ross R. Atherosclerosis:an inflammatory disease, N Engl J Med 340:1125-126, 1999
12) Juonala M, Viikari JS, Laitinen T, Marniemi J, Helenius H, Ronnemaa T, Raitakari OT, Interrelations between brachial endothelial function and carotid intima-media thickness in young adults: the cardiovascular risk in young Finns study, Circulation 110:2918-2923, 2004
13) International Study Group for Behçet’s Disease, Criteria for diagnosis of Behçet’s disease, Lancet 335:1078-1080, 1990
14) Krause I, Molad Y, Mirani M, Weinberger A, Pathergy reaction in Behçet’s disease: lack of correlation with mucocutaneous manifestations and systemic disease expression, Clin Exp Rheumatol 18:71-74, 2000
15) Lee SS, Yoon HJ, Chang HK, Park KS, Fibromyalgia in Behçet’s disease is associated with anxiety and depression, and not with disease activity, Clin Exp Rheumatol 23(4 Suppl 38):S15-S19, 2005
16) Pignoli P, Tremolli E, Poli A, Oreste P, Paoletti R, Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging, Circulation 74:1399-1406, 1986
17) Keser G, Aksoy K, Tansel S, Ozmen M, Kitapcicoglu G, Kabaroglu C, Killi R, Bayindir O, Doganavargi E, Increased thickness of the carotid artery intima-media assessed by ultrasonography in Behçet’s disease, Clin Exp Rheumatol 23(4 Suppl 38):S71-S76, 2005
18) Numano F, Vasa vasorum, vasculitis and atherosclerosis, Int J Cardiol 75(Suppl 1):S1-S8, 2000
19) Seyahi E, Ugurlu S, Cumali R, Balci H, Seyahi N, Yurdakul S, Yazici H, Atherosclerosis in Takayasu arteritis, Ann Rheum Dis 65:1202-1207, 2006
20) de Leeuw K, Sanders JS, Stegeman C, Smit A, Kallenber CG, Blij M, Accelerated atherosclerosis in patients with Wegener’s granulomatosis, Ann rheum Dis 64:753-759, 2005
21) Ehrlich GE, Vasculitis in Behçet’s disease, Int Rev Immunol 14:81-88, 1997
22) Kosar F, Sahin I, Gullu H, Cehreli S, Acute myocardial infarction with normal coronary arteries in a young man with the Behçet’s disease,
Int J Cardiol 99:355-357, 2005

23) Persson J, Formgren J, Israelsson B, Berglund G. Ultrasound-determined intima-media thickness and atherosclerosis: direct and indirect validation. Arterioscler Thromb 14:261-264, 1994

24) Alan S, Ulgen MS, Akdeniz S, Alan B, Toprak N. Intima-media thickness and arterial distensibility in Behcet’s disease. Angiology 55:413-419, 2004

25) Öztürk MA, Oktar SO, Ünverdi S, Çreten K, Güker B, Haznedaroğlu S, Sungur G, Reis KA, Orat AM. Morphologic evidence of subclinical atherosclerosis obtained by carotid ultrasonography in patients with Behcet’s disease. Rheumatol Int 26:867-872, 2006

26) Rhee MY, Chang HK, Kim SK, Intima-media thickness and arterial stiffness of carotid artery in Korean patients with Behcet’s disease. J Korean Med Sci 22:387-392, 2007

27) Rhee MY, Na SH, Kim YK, Lee MM, Kim SK, Kim W. Increased arterial stiffness in Behcet’s disease patients. Korean Circ J 36:676-682, 2006

28) Fichtlscherer S, Rosenberger G, Walter DH, Breuer S, Dimmel S, Zeiher AM. Elevated C-reactive protein levels and impaired endothelial vasoreactivity in patients with coronary artery disease. Circulation 102:1000-1006, 2000