Soluble vascular cell adhesion molecular-1 is a potential biological indicator of hemophilic arthropathy

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Abstract
Hemophilic arthropathy is the most common chronic complication in patients with hemophilia. The pathogenesis of hemophilic arthropathy involves the inflammatory processes associated with rheumatoid arthritis (RA). Determining the severity and/or progression of joint damage is crucial when evaluating the effect of treatment modalities. Identifying reliable biomarkers in the peripheral blood of patients with hemophilic arthropathy may be beneficial in clinical practice. Circulating soluble vascular cell adhesion molecule-1 (sVCAM-1), E-selectin, and P-selectin levels are elevated in patients with RA. Our study investigated whether these soluble adhesion molecules can be used as biological indicators in the course of joint damage in patients with hemophilia A.

Patients with hemophilia A (mild, moderate, and severe) were enrolled. The plasma levels of sVCAM-1, E-selectin, and P-selectin in patients with hemophilia A and control were measured using specific enzyme-linked immunosorbent assay kits. Joint damages were evaluated using Pettersson scores.

No statistically significant differences were observed in E-selectin and P-selectin levels between patients and controls. The sVCAM-1 level was significantly higher in patients with hemophilia A than in controls. The differences remained significant in patients with severe hemophilia A but not in patients with mild or moderate hemophilia A. The degree of hemophilic arthropathy was evaluated using Pettersson scores, and a score higher than 5 indicated marked arthropathy. Patients with more than 1 joint with marked arthropathy showed significantly higher sVCAM-1 levels.

sVCAM-1 levels in patients with hemophilia A are associated with the severity of hemophilic arthropathy.

Abbreviations: CD = cluster of differentiation, CS846 = chondroitin sulfate 846, ELISA = enzyme-linked immunosorbent assay, HCV = hepatitis C virus, IL = Interleukin, MMP = matrix metalloproteinase, OA = osteoarthritis, RA = rheumatoid arthritis, RF = rheumatoid factor, sVCAM-1 = soluble intercellular adhesion molecule-1, sVCAM-1 = soluble vascular cell adhesion molecule-1, VEGF = vascular endothelial growth factor.

Keywords: E-selectin, hemophilia A, P-selectin, sVCAM-1

1. Introduction
Hemophilia is an inherited recessive, sex-linked bleeding disorder. Lack of clotting factors VIII and IX causes hemophilia A and B, respectively. According to clinical, instrumental, serological, and histological studies, hemophilia A is more severe than hemophilia B. Hemarthrosis is the most common clinical manifestation in patients with hemophilia A. Severe or repeated bleeding may lead to chronic synovitis, resulting in chronic, painful arthropathy and disability. The mechanisms of joint destruction remain unclear. The knees, ankles, elbows, hips, and shoulders are most frequently affected by hemophilic arthropathy. Prophylactic therapy (i.e., routine trickle coagulation factors) is a hemostatic management approach aimed at preventing bleeding, especially joint bleeding, in patients with hemophilia A. Depending on the time of initiation, prophylactic therapy can be classified into 3 types: primary and secondary prophylaxis (before joint disorder onset) and tertiary prophylaxis (after joint disorder onset). Although prophylactic therapy greatly suppresses the development of hemophilic arthropathy, patients with poor adherence or existing chronic arthropathy continue to experience progressive joint dysfunction. Identification of a biomarker of joint injury would be helpful in detecting hemophilic joint diseases. Studies have mostly focused on various intra-articular enzymes, cytokines, and cell types. However, synovial fluid aspiration is not conventional and may increase the risk of bleeding and infection. Therefore, identifying a reliable biomarker in the peripheral blood is crucial in clinical practice.

Hemophilic arthropathy caused by intra-articular bleeding leads to inflammation. In hemophilic arthropathy, the degenerative features of osteoarthritis (OA) and the inflammatory
characteristics of rheumatoid arthritis (RA) are both manifested. In OA and RA, many plasma constituents (e.g., enzymes, cytokines, chemokines, and growth factors) and cellular constituents (e.g., erythrocytes and leukocytes) have been detected and considered to be potentially responsible for hemophilic arthropathy. For example, immunohistologic analysis together with digital image analysis of synovial biopsy specimens from the inflamed knee joints of patients with RA have shown increased expression of macrophages marked by cluster of differentiation (CD) 68+, T cells marked by CD3+, matrix metalloproteinase (MMP)-1, MMP-3, MMP-13, Interleukin (IL)-1, IL-6, TNF-a, and vascular endothelial growth factor (VEGF).[15] In hemorrhhatic mouse model studies, increased concentrations of IL-1b, IL-6, keratinocyte-derived chemokine, and monocyte chemotactic protein-1 (MCP-1) have been reported in the bloody synovial fluid.[3,4] In addition, cytokines increase the uptake of transferrin-bound and nontransferrin-bound iron by monocytes and increase transferrin-bound iron uptake by synovial fibroblasts. This increased iron uptake facilitates the vicious cycle of synovitis bleeding. Moreover, commonly used serum and/or urinary biomarkers of cartilage and bone turnover, urinary C-terminal telopeptide of type II collagen, serum cartilage cleavage products C1, C2C, and serum chondroitin sulfate 846 (CS846) have been detected in patients with hemophilia A, and the levels of these proteins have been correlated with the overall Pettersson score and with the joint space narrowing section.[7–9]

The cell adhesion molecules, including circulating soluble vascular cell adhesion molecule-1 (sVCAM-1), sE-selectin, and sP-selectin, have been detected in higher concentrations relative to those in controls, in the serum and other body fluids of patients with RA.[9,10] According to the American Rheumatism Association, the rheumatoid factor (RF) is the only serological index for the diagnostic classification of RA. A study indicated a significant positive correlation between the sVCAM-1 and RF levels in RA. Moreover, in patients with RA, the sVCAM-1 level initially increases and subsequently decreases after anti-inflammatory drug treatment. Therefore, sVCAM-1 levels can reflect disease severity and drug efficacy.[1,11]

A study has demonstrated that the endothelium in human RA synovium exhibits a higher expression level of sE-selectin. Moreover, a radiolabeled anti-sE-selectin antibody, a conventional tracer for bone and joint inflammation, has been used to successfully image synovitis in patients with RA.[12] sE-selectin, a leukocyte adhesion molecule expressed on the endothelium, is induced by the tumor necrosis factor and other cytokines involved in the pathogenesis of RA. The collagen-induced arthritis mouse model is widely used to study RA mechanisms and identify new treatments for RA. The endothelium in human RA synovium expresses sE-selectin. Scintigraphy using a radiolabeled anti-sE-selectin antibody has been used to successfully image synovitis in RA patients, with a 99mTc-labeled anti-sE-selectin Fab demonstrating improved specificity compared to 99mTc-oxidronate, a conventional tracer for bone and joint inflammation.[12] Activation of neoangiogenesis in the rheumatoid synovium by endothelial growth factors increases inflammatory cell migration. sVCAM-1 and sE-selectin possess angiogenic activity.[10] Therefore, cell adhesion molecules and endothelial growth factors may be involved in the infiltration of the rheumatoid synovium by mononuclear cells, causing disease initiation and progression.[13]

Our research interest is whether sVCAM-1, sE-selectin, and sP-selectin levels, all of which increase in RA, are also elevated in patients with hemophilic arthropathy. In this study, we investigated the plasma levels of the aforementioned proteins and compared these levels in patients with hemophilic arthropathy and controls.

2. Patients and methods

2.1. Clinical and laboratory analysis

Thirty-five patients with hemophilia A, aged 19 to 62 (35.66 ± 11.42) years, were enrolled in the study group, and 20 healthy individuals aged 23 to 63 (35.96 ± 10.83) years were included in the control group. In addition to the regular application of the VIII factor, Kogenate Fs (Bayer HealthCare LLC, Berkeley, CA, U.S.A), in patients with hemophilia A, the intake of antihypertensive drugs by patients with hemophilia A, and hypertension, the study participants did not consume any medication for 2 months before they donated blood for this study. Peripheral blood was sampled during regular medical visits. Evaluation of arthropathy was performed using Pettersson scores. Informed consent was obtained from all patients and controls. This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-SV-II-20150094). Clinical parameters were collected from chart records. The soluble adhesion molecules in the peripheral blood were evaluated using enzyme-linked immunosassay (ELISA).

2.2. Enzyme-linked immunoassays

The plasma levels of sVCAM-1, sE-selectin, and sP-selectin were determined using commercial ELISA kits from eBioscience Systems (San Diego, CA). The sensitivities were 0.6 ng/mL for sVCAM-1, 0.3 ng/mL for sE-selectin, and 0.2 pg/mL for sP-selectin.

2.3. Statistical analyses

Statistical analyses were performed using GraphPad Prism (Version 5, GraphPad Prism Software, Los Angeles, CA). The unpaired Student t test was used to determine the differences between the patients and controls. Linear regression was used to determine the correlation among sVCAM-1, sE-selectin, and sP-selectin. P ≤ 0.05 was considered statistically significant.

3. Results

3.1. Plasma sVCAM-1 level

sVCAM-1 levels were significantly higher in patients with hemophilia A than in controls (683.0 ± 392.3 vs 475.6 ± 85.75 ng/mL). Hemophilia A can be classified as mild, moderate, and severe forms according to the residual activity of clotting factor VIII. sVCAM-1 levels were 533.2 ± 161.5 ng/mL in patients with mild hemophilia A, 446.9 ± 40.34 ng/mL in those with moderate hemophilia A, and 787.3 ± 455.4 ng/mL in those with severe hemophilia A. Significantly elevated sVCAM-1 levels were noted in patients with severe hemophilia A relative to those in controls. However, no significant differences were observed in sVCAM-1 levels between patients with mild or moderate hemophilia A and controls (Fig. 1 and Table 1). Previous studies have shown that the sVCAM-1 level is associated with hypertension, late-stage ovarian cancer, colorectal cancer, microalbuminuria diabetes, and liver fibrosis.[14–19] Our study population included 3 patients with hypertension, 1 patient with hepatitis B, and 17 patients...
with hepatitis C. Most patients with hepatitis C (16/17) were cured (defined as viral RNA level less than 0.03 KIU/mL). Excluding those patients with hypertension (n = 3), hepatitis B (n = 1), and hepatitis C with viral RNA level higher than 0.03 KIU/mL (n = 1), the sVCAM-1 level remained significantly higher in all patients with hemophilia A and severe hemophilia A than in controls (Fig. 2).

3.2. Plasma sE-selectin and sP-selectin level

No significant differences were observed in sE-selectin levels between patients with hemophilia A and controls (17.15 ± 9.675 vs 14.16 ± 7.761 ng/mL). Moreover, no significant differences were observed in sP-selectin levels between patients with hemophilia A and controls (15.74 ± 4.191 vs 15.40 ± 3.084 ng/mL). No significant differences were observed in sE-selectin or sP-selectin levels between patients with mild, moderate, and severe hemophilia A and controls (Table 2 and Fig. 3). Pairwise comparisons with liner regression were conducted to analyze the correlation among sVCAM-1, sP-selectin, and sE-selectin in patients with hemophilia A. The results showed no significant correlations for each group (Table 3).

3.3. sVCAM-1 level and hemophilic arthropathy

Pettersson scores were used to evaluate joint damage in patients with hemophilia A. By referring to plain radiographs, each joint was scored 0 to 13 by radiologists specializing in hemophilic arthropathy. This study evaluated right and left joints, including the elbow, knee, ankle, shoulder, and hip, in 35 patients with hemophilia A. Group 1 comprised patients with scores of 0 to 4 for every joint, patients with scores higher than or equal to 5 for any joint comprised group 2, and those with scores higher than or equal to 5 for more than 2 joints comprised group 3. Plasma sVCAM-1 levels were significantly higher in groups 2 and 3 than in group 1 (Fig. 4).

4. Discussion

Hemarthrosis is the most common clinical symptom in patients with hemophilia A. Blood-induced joint diseases and RA share similar characteristics.[11,13] Studies have shown that sVCAM-1 levels in patients with RA are higher than those in controls.[11,13] In this study, we demonstrated that the sVCAM-1 level in the peripheral blood of patients with hemophilia A were significantly higher than those in controls. However, the sE-selectin and sP-selectin levels did not differ significantly between patients with hemophilia A and controls.

Several studies have shown that circulating concentrations of soluble adhesion molecules (CAMs), sE-selectin, and sP-selectin are higher, wherein 1 or more than 1 in coronary artery disease, myocardial infarction, atherosclerosis, or hypertension.[18,20,21] No patients in this study had coronary artery disease, myocardial infarction, or atherosclerosis. Three patients aged 38.72, 46.81, and 46.00 years had hypertension. These patients regularly used antihypertensive drugs (e.g., Amrel [TTY Biopharm Company Limited, Keelung, Taiwan], Norvasc [Pfizer Australia Pty Limited, Australia], Concor [Merck KGaA, Germany]) and had good disease control. According to their medical records, their blood pressures were within the acceptable range (i.e., diastolic blood pressure less than 90 mm Hg and systolic blood pressure less than 140 mm Hg). Although sVCAM-1 levels are most strongly associated with uncontrolled hypertensives, the sVCAM-1 level in hypertension increased irrespective of whether the hypertensives were controlled.[19] Between patients with hemophilia A with and without hypertension, the sVCAM-1 levels did not differ significantly (P = 0.7425). This result does not necessarily mean that the sVCAM-1 level is independent of hypertension, because this study only included 3 patients with hemophilia A and hypertension; in addition, the effect of the hypertension factor on the sVCAM-1 level may be suppressed by the hemophilia A disease factors. Moreover, we analyzed the sVCAM-1 level after excluding the 3 patients with hemophilia A and hypertension; the sVCAM-1 level was still higher in patients with hemophilia A than in controls (P = 0.0084, **represent P < 0.01).

The age range of controls and patients in this study was wide (19–63 years). The mean ± SD of age were 35.66 ± 11.42 years in

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Table 1

Comparison of the plasma sVCAM-1 level between healthy donors and hemophilia A patients.

| Group         | Cases | sVCAM-1, ng/mL | P     |
|---------------|-------|----------------|-------|
| Healthy donors| 20    | 475.6 ± 85.75  | 0.0046* |
| HA patients   | 35    | 683.0 ± 392.3  | 0.0046* |
| Mild HA       | 9     | 533.2 ± 161.5  | 0.3373  |
| Moderate HA   | 4     | 446.9 ± 40.34  | 0.5247  |
| Severe HA     | 22    | 787.3 ± 455.4  | 0.0047* |

sVCAM-1 data presented as mean ± SD. In the table, P values are counted by GraphPad Prism 5.0. *P ≤ 0.05 means not significant. HA = Hemophilia A, sVCAM-1 = soluble vascular cell adhesion molecule-1.

* Represent P < 0.01.
controls and 35.96 ± 10.85 years in patients. Study indicated that cell surface adhesion molecules including sVCAM-1 level decreased with age range 9.5 to 15.3 years, and the value was constant with age range 18 to 65 years.\textsuperscript{22-24} Linear regression analysis of age and sVCAM-1 revealed no clear association between age and the sVCAM-1 level in patients (\( P=0.4443 \) and \( r^2=0.04238 \)) or in patients (\( P=0.0667 \) and \( r^2=0.09829 \)). Furthermore, we classified controls and patients into 2 age-based groups: 19 to 35 and 40 to 63 years; in both groups, the sVCAM-1 level was higher in patients than in controls (\( P=0.038 \) and \( P=0.036 \), respectively, \(^{*} \) represent \( P<0.05 \)), which is consistent with earlier studies that have reported that age is not a factor affecting the sVCAM-1 level in the age range 18 to 65 years.

Studies have indicated that soluble intercellular adhesion molecule-1 (sICAM-1), sE-selectin, and sP-selectin levels are complex and are regulated by ABO blood group.\textsuperscript{21,25} To clarify whether the expression of these cell surface adhesion molecules are affected by ABO blood group, the association between ABO blood group and these cell surface adhesion molecules levels was analyzed. In 27 patients with hemophilia A, whose ABO blood type were obtained through medical record review, sVCAM-1, sE-Selectin, and sP-selectin levels did not differ significantly among ABO blood groups (\( P>0.05 \)). This result suggests that elevated sVCAM-1 level in patients with hemophilia and hemophilic arthropathy are independent of blood group, but this result must be interpreted cautiously considering that our patients are not representative of the general population.

Previous studies have shown that sVCAM-1 levels are significantly elevated in hemodialysis patients. This phenomenon is considered a sign of chronic inflammation. Chronic hepatitis C virus (HCV) infection, which is highly prevalent in hemodialysis patients, can also induce chronic inflammation. sICAM-1, sVCAM-1, and sE-selectin levels are higher in the anti-HCV-positive group of hemodialysis patients.\textsuperscript{14,26,27}

HCV infection is also highly prevalent in patients with hemophilia A. However, in this study, among these patients, sVCAM-1 levels were not higher in the anti-HCV-positive group relative to the anti-HCV-negative group (\( P=0.1204 \)). In patients with liver cirrhosis, the sVCAM-1 level is associated with increasing fibrosis. Possible causes of liver cirrhosis include alcoholism, hepatitis B virus (HBV) infection, and HCV infection.

In our patients, although 17 patients had HCV infection and 1 patient had HBV infection, none of them had liver cirrhosis. Under our advocacy, nearly all patients with HBV and HCV infection received treatment and have become asymptomatic. These observations may explain why the sVCAM-1 level was not higher in anti-HCV-positive patients relative to the anti-HCV-negative patients with hemophilia A. Studies have reported that the sVCAM-1 level does not differ significantly between healthy volunteers and asymptomatic chronic hepatitis C carriers with minimal inflammatory grade.\textsuperscript{26,28} The sVCAM-1 level increased only in the advanced fibrosis stage of HCV infection. Although patients with hemophilia A in this study did not exhibit symptoms of liver fibrosis, we nevertheless attempted to rule out the suspicion of chronic hepatitis C interference in sVCAM-1 levels. We excluded all patients with hepatitis B and HCV infection from the analysis and found that sVCAM-1 levels continued to be higher in patients with hemophilia A than in controls (\( P=0.046 \), \(^{*} \) represent \( P<0.05 \)). Thus, that the chronic joint inflammation in patients with hemophilia A is the major factor affecting sVCAM-1 levels is a reasonable conclusion. According to the aforementioned indications that the elevation in sVCAM-1 levels is a multifactorial effect, hemophilia A is still a crucial factor inducing sVCAM-1 expression in the peripheral blood.

| Table 2 |

Comparison of the plasma sE-selectin and sP-selectin level between healthy donors and hemophilia A patients.

| Group         | Cases | sE-selectin, ng/mL | P   | sP-selectin, ng/mL | P   |
|---------------|-------|--------------------|-----|--------------------|-----|
| Healthy donors| 9     | 14.16 ± 7.761      | 0.4068 | 15.40 ± 3.084      | 0.8241 |
| HA patients   | 28    | 17.15 ± 9.675      | 0.4209 | 15.74 ± 4.191      | 0.3757 |
| Mild HA       | 8     | 17.53 ± 9.364      | 0.7384 | 14.03 ± 3.097      | 0.3480 |
| Moderate HA   | 4     | 15.76 ± 7.673      | 0.4500 | 17.22 ± 3.093      | 0.8293 |
| Severe HA     | 16    | 17.3 ± 10.73       | 0.4068 | 15.75 ± 4.36       | 0.3757 |

sE-selectin and sP-selectin data presented as mean ± SD. In the table, P values are counted by GraphPad Prism 5.0. \( P \geq 0.05 \) means not significant. HA = Hemophilia A.
Some studies have shown that sE-selectin levels are significantly elevated in patients with RA, but others have reported that sE-selectin levels do not differ between patients with RA and controls. The latter group of studies that failed to find associations between patients with RA and controls all employed a cross-sectional study design and had examined patients with chronic RA. In this study, the sE-selectin level was not significantly elevated in patients with hemophilia A. This might be because in our analyses, we did not stratify patients on the basis of the severity of hemophilic arthropathy (i.e., acute and chronic inflammation).

Hemarthrosis cause cartilage and bone degradation, inflammation, and angiogenesis. The association of soluble biomarkers, including C-terminal telopeptides of type I collagen, cartilage oligomeric matrix protein, TIMP-1, MMP-3, MMP-9, VEGF, and CS846, with these symptoms in hemophilia A have been investigated, but no obvious associations between these soluble biomarkers and MRI joint scores have been reported, except for the positive association of CS846 with MRI joint scores in Oldenburg study. The joint arthropathy in hemophilia A is not a systemic disease, so the analysis of biomarkers of joint arthropathy may be more complex than in RA and OA.

### Table 3
Correlation among sVCAM-1, sE-selectin, and sP-selectin.

| Group                | \( r^2 \) | \( P \)  |
|----------------------|--------|--------|
| sVCAM-1 & sE-selectin| 0.8309 | 0.001787 |
| sVCAM-1 & sP-selectin| 0.2696 | 0.04666 |
| sE-selectin & sP-selectin| 0.2571 | 0.04910 |

A linear regression analysis among plasma levels of sVCAM-1, sE-selectin, and sP-selectin. In the table, \( P \) value and \( r^2 \) values are counted by GraphPad Prism 5.0. \( P \geq 0.05 \) means not significant. sVCAM-1 = soluble vascular cell adhesion molecule-1.

Multiple biomarkers can perhaps more effectively and accurately detect the severity of joint arthropathy. Furthermore, whether soluble CS846 and sVCAM-1 levels increase at the same time points or at different time points in hemophilic arthropathy is worth investigating.

Except for sE-selectin, sP-selectin, and sVCAM-1, various other markers such as ICAM-1, ICAM-3, and L-selectin are also increased in RA patients relative to controls. Whether these markers are increased in hemophilia A patients is worth examining. Acharya et al. reported that angiogenic factors, such as VEGF A, stromal cell–derived factor, and MMP-9, were upregulated in the plasma of patients with hemophilic arthropathy.
hemophilic arthropathy, which has a potential to be a modality of joint bleeding and whether it can be detected in the early stages of hemophilic arthropathy, which has a potential to be a modality for long-term follow-up of hemophilia arthropathy.

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