Introduction

Peripheral arterial occlusive disease (PAOD) refers to atherosclerosis below the bifurcation of the abdominal aorta [1]. It is a major contributor to diabetic foot (DF) in patients with diabetes mellitus (DM) [2]. The prevalence of PAOD is up to 6 times higher in the elderly with DM than in those without DM [3]. Patients with both DF and PAOD show lower limb ischemia with poor wound healing; as such, they are vulnerable to lower limb amputations [4]. Therefore, to manage foot problems in patients with DF, the risk factors associated with PAOD must be identified [2]. The general risk factors of atherosclerosis, such as systolic hypertension, smoking, dyslipidemia and old age, are closely associated with PAOD progression [5,6]. Moreover, high HbA1c, low-density lipoprotein cholesterol and smoking may also be risk factors for PAOD in patients with DM [7,8].

To date, PAOD has been recognized as an independent disease entity. Its severity is decided based on imaging studies, symptom severity, resting pain and tissue damage, as previously formulated by the Fontaine and Rutherford classification [9]. However, few studies have investigated whether the degree of peripheral arterial stenosis has significant association with the severity of DF in patients with DM.

In the present study, we explored the association between the arterial stenosis se-
verity and wound severity. Furthermore, our analysis aimed to identify factors that may affect the degree of arterial stenosis in the lower extremities, as defined using computed tomography angiography (CTA), and DF severity.

**Methods**

**Enrolled patients and setting**

We performed a retrospective review of the medical records of 71 cases with DF who were hospitalized at our medical institution between April 2014 and April 2019. The inclusion criteria were as follows: (1) diagnosis of DM; (2) diagnosis of DF; and (3) available CTA of arteries in the lower extremities. The exclusion criteria were as follows: (1) previous history of percutaneous angioplasty; and (2) previous history of drug use that could affect arterial stenosis severity, such as aspirin, clopidogrel, cilostazol and pentoxifylline [10].

We enrolled a total of 71 cases with DF who underwent CTA of the arteries in the lower extremities. We classified the blood vessels of the lower extremity into five major arteries for each DF patient and evaluated arterial stenosis using the Bollinger score, and scored DF wound severity by a self-reported wound score system. The association between the severity of arterial stenosis and DF wound severity was statistically analyzed. In addition, we analyzed statistically whether baseline characteristics were associated to DF wound severity and arterial stenosis. The study was approved by the Institutional Review Board of Konkuk University Chungju Hospital (IRB No. KUCH 2019-12-041). The need for informed consent was waived because the study was retrospective.

**CTA of arteries in the lower extremities**

To analyze the status of the vessels, the arteries of the lower extremity were classified into five major arteries or segments: femoral artery (FA), popliteal artery (PopA), anterior tibial artery (ATA), posterior tibial artery (PTA), and peroneal artery (PerA).

CTA of the arteries of the lower extremities was performed using a 320-slice CT scanner (Aquilion ONE; Toshiba Medical Systems, Tokyo, Japan), in which the patients were placed in a fixed supine position. Prior to this, they were intravenously injected with iopamidol (Iopamiro 370/150; Bracco Imaging, Seoul, Korea) via the antecubital vein using an 18-gauge intravenous catheter at a rate of 4 mL/sec to ensure that 120 mL was injected within 30 seconds [11].

**Assessment of arterial stenosis severity using CTA**

The scoring system developed by Bollinger et al. [12] was used to assess the angiographic findings. This system consists of an additive score that describes the severity and extent of arterial stenosis in each segment of the artery. The score defines four categories according to the severity of arterial stenosis: (1) complete occlusion of the lumen, (2) stenosis >50% of the luminal diameter, (3) stenosis ≤50% but >25% of the diameter, and (4) plaques impinging on ≤25% of the diameter. Each type of lesion is then further categorized based on its extent: (1) single lesion, (2) multiple lesions affecting ≤50% of the artery 5 segments, and (3) multiple lesions affecting >50% of the segment. Scores are assigned according to the severity of each category (Table 1). For example, an isolated subtotal stenosis is 4 points. If multiple plaques with stenosis of less than 25% of the lumen spread over half of the segment, 3 points are added, so the additive score is 7 (4+3).

There are several rules to prevent inappropriate scoring: (1) in presence of an occlusion lesion, stenosis and plaque are not considered; if there is occlusion affecting less than 50% of the segment, the score number remains 13 even if there is plaque or stenosis in the non-occluded part. (2) When both categories of stenoses are present (>50% and ≤50%), plaques ≤25% are not considered; (3) for each occlusive pattern, only one category of extent is applied. When there are plaques ≤25% that affect more than 50% of a segment, the score number applies only to 3 and not 2 or 1. In the present study, the Bollinger scoring system was applied to two suprapopliteal level arterial segments (the superficial FA and PopA) and three infrapopliteal level ones (ATA, PTA, and PerA). Total scores were calculated as the sum of the scores for the suprapopliteal and infrapopliteal segments.

**Assessment of DF wound severity**

The criteria for assessing DF severity are as follows: the score is indicated in parentheses.

I. Depth: skin or subcutaneous tissue (1), tendon, muscle, fascia (2), bone or joint (3).
II. Size:  <1 cm² (1), 1–3 cm² (2), >3 cm² (3).
III. Infection: Inflammation (erythema, local heating) (1),
gangrene (mummification, pus) (2).
After analyzing each category, each score is added to give the
wound severity score.

Patient evaluation and criteria
The baseline characteristics of the patients included age, sex,
body mass index (BMI), wound location, wound depth,
wound size, type of infection, duration of DM, smoking status,
hypertension, laboratory measurements performed on the day
of hospitalization (C-reactive protein [CRP], erythrocyte sedimentation
rate [ESR], albumin, total protein, and white blood cell [WBC] count), and ankle-brachial index (ABI).

Statistical analysis of patient data
All data were expressed as mean±standard deviation. Statistical
analysis was performed using SPSS version 23 (IBM Corp.,
Armonk, NY, USA). Univariable regression analysis was used
to analyze the association between wound severity and mean
total Bollinger score. The Bollinger scores of each segment
were also examined for association with wound severity, using
univariable regression analysis. Multivariable regression anal-
ysis was used to additionally analyze whether the Bollinger
score of each segment was associated to wound severity. To
identify factors affecting wound severity and mean total Bol-
linger scores, a univariable regression analysis was performed.
Multivariable regression analysis was performed on the vari-
ables showing significant differences in the univariable regres-
sion analysis. All P-values <0.05 were considered statistically
significant.

Results

Baseline characteristics of the patients
Our clinical series of cases (n=71) comprised 61 unilateral cas-
es and 5 bilateral cases. From the cases, 35 cases (53.0%) were
right, 26 cases (39.4%) were left and 5 cases (7.6%) were both
right and left (bilateral). There were 49 men (69.0%) and 22
women (31.0%) with a mean age of 60.9±11.3 years. Out of the
patients, 56 cases (78.9%) had arterial stenosis and 15 (21.1%)
had no arterial stenosis. The mean wound severity score was
6.1±1.9 and the mean total Bollinger score was 19.5±17.4. The
patients’ DM had been diagnosed for an average of 16.2±9.9
years. There were 47 cases (66.2%) with a history of smoking
and 24 cases (33.8%) were nonsmokers. The 31 cases (43.7%)

had hypertension. The mean BMI was 24.3±4.0 kg/m² and the
mean ABI was 1.0±0.3. The average values of the laboratory
measurements performed on the day of hospitalization were as
follows: CRP, 9.9±8.8 mg/dL; ESR, 45.3±18.9 mm/hr; albu-
min, 3.1±0.6 g/dL; total protein, 6.7±0.8 g/dL; WBC count,
12.8±7.8 £10³/µL (Table 2).

| Variable                  | Value          |
|---------------------------|----------------|
| Age (yr)                  | 60.9±11.3      |
| Sex                       |                |
| Men                       | 49 (69.0)      |
| Women                     | 22 (31.0)      |
| Laterality                |                |
| Right                     | 35 (53.0)      |
| Left                      | 26 (39.4)      |
| Both                      | 5 (7.6)        |
| Arterial stenosis         |                |
| Positive                  | 56 (78.9)      |
| Negative                  | 15 (21.1)      |
| Wound score               | 6.1±1.9        |
| Bollinger score           |                |
| Femoral artery            | 3.9±3.9        |
| Popliteal artery          | 2.6±3.3        |
| Anterior tibial artery    | 4.8±5.4        |
| Posterior tibial artery   | 4.5±5.2        |
| Peroneal artery           | 3.6±4.3        |
| Mean total Bollinger score| 19.5±17.4      |
| DM period (yr)            | 16.2±9.9       |
| Smoking status            |                |
| Smoking                   | 47 (66.2)      |
| Non-smoking               | 24 (33.8)      |
| Hypertension              | 31 (43.7)      |
| Body mass index (kg/m²)   | 24.3±4.0       |
| Laboratory measurements   |                |
| CRP (mg/dL)               | 9.9±8.8        |
| ESR (mm/hr)               | 45.3±18.9      |
| Albumin (g/dL)            | 3.1±0.6        |
| Protein (g/dL)            | 6.7±0.8        |
| WBC (10³/µL)              | 12.8±7.8       |
| ABI                       | 1.0±0.3        |

Values are presented as mean±SD or number (%).
DM, diabetes mellitus; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell count; ABI, ankle-brachial index.
Association between the severity of arterial stenosis and DF wound severity

Univariable regression analysis showed that Bollinger score of FA showed significant association with wound severity. However, there was no significant association between wound severity and mean total Bollinger score. In multivariable regression analysis, Bollinger score of FA showed a significant association with wound severity (Table 3). A scatter plot was used to show the relationship between the Bollinger score and wound severity (Fig. 1).

Factors affecting wound severity and Bollinger score

Univariable regression analysis showed that albumin and protein showed significant association with wound severity. In multivariable regression analysis, only albumin had a significant association with wound severity (Table 4). Univariable regression analysis showed that age and ABI had a significant association with mean total Bollinger score. In multivariable regression analysis of mean total Bollinger score, both age and ABI showed significant association (Table 5). Duration of DM, smoking status, BMI, ESR, CRP and WBC count were not associated with wound severity and mean total Bollinger score. Hypertension was not associated with wound severity or mean total Bollinger score.

Pattern of arterial occlusion by segment

The normal ratio of the FA was the lowest among all the arterial segments (29.6%), while the ratio of ≤50% stenosis plus ≤25% plaque was the highest (47.9%). However, the proportion of occlusion plus >50% stenosis was the lowest (22.5%) in the FA. Of the arterial segments, both the ATA and PTA were found to have the highest degree of occlusion (18.3%). The normal ratio of the PopA was the highest (46.5%). With regards to the total value according to occlusive pattern, occlusion and >50% stenosis accounted for 25.3%, stenosis ≤50%, plaque ≤25% and normal accounted for 74.6% (Table 5). Mild obstruction (≤50% of lumen) occupied a large portion (Table 6).

Discussion

Patients with DM show metabolic derangement and alterations in arterial structure and function [13]. Such alterations may occur even prior to the clinical diagnosis of DM [14]. Several hypotheses have been proposed to explain the pathogenesis of DF. According to the hemodynamic hypothesis, the onset of hyperglycemia in the early stages of DM leads to derangements in blood flow, resulting in increases in flow, capillary filtration capacity, and microvascular pressure. This likely results in structural alterations in diabetic microangiopathy, such as a thickened basement membrane with microvascular sclerosis. The resulting decrease in microvascular vessel elasticity disturbs vasodilatation and may be coupled with impaired secretory functions in the endothelium. It may then also lower the hyperemic response in patients with DM [3]. Additionally, sympathetic innervation of the microvasculature is disturbed by autonomic neuropathy and thereby causes a loss of vasoconstriction in patients with DM, which may eventually lead to changes in blood flow through the capillaries and arteriovenous anastomoses [3].

Although severe arterial stenosis has a significant effect on wound healing, major amputation, and mortality in patients with DF [15], few studies have investigated the association between DF wound severity and arterial stenosis severity. In the present study, only the Bollinger score of the FA showed a sig-
Fig. 1. Scatter plot of Bollinger score and wound severity. (A) Scatter plot of mean total Bollinger score and wound severity. (B) Scatter plot of Bollinger score of femoral artery and wound severity. There was a significant association in regression analysis. (C) Scatter plot of Bollinger score of popliteal artery and wound severity. (D) Scatter plot of Bollinger score of anterior tibial artery and wound severity. (E) Scatter plot of Bollinger score of posterior tibial artery and wound severity. (F) Scatter plot of Bollinger score of peroneal artery and wound severity.

significant association with wound severity. There was no significant association between mean total Bollinger score and wound severity. Therefore, even though the prevalence of arterial stenosis increases in patients with DM, the severity of arterial stenosis is not associated with DF wound severity. The authors’ opinion is that Bollinger scores of more distal arterial segments would have less significant association with wound severity because of more active compensatory mechanisms.
such as collateral circulation development. However, the FA is a proximal main vessel with less compensatory mechanisms, which may explain why it particularly can affect DF severity. Of the 71 cases, 15 (21.1%) had no arterial stenosis lesions in their CTA, even though their DF required hospitalization.

### Table 4. Factors affecting wound severity

| Variable                  | Wound severity |          |          |          |
|---------------------------|----------------|----------|----------|----------|
|                           | Univariable regression analysis | Multivariable regression analysis |          |          |
|                           | B (95% confidence interval) | P-value | B (95% confidence interval) | P-value |
| Sex                       | –0.458 (–1.399 to 0.483) | 0.335    |          |          |
| Smoking status            | 0.793 (–0.114 to 1.699) | 0.086    |          |          |
| Hypertension              | –0.457 (–1.334 to 0.419) | 0.302    |          |          |
| Age (yr)                  | –0.022 (–0.061 to 0.016) | 0.253    |          |          |
| DM period (yr)            | –0.022 (–0.066 to 0.022) | 0.316    |          |          |
| Body mass index (kg/m²)   | –0.015 (–0.124 to 0.094) | 0.791    |          |          |
| Laboratory measurements   |          |          |          |          |
| CRP (mg/dL)               | 0.039 (–0.011 to 0.088) | 0.123    |          |          |
| ESR (mm/hr)               | 0.011 (–0.015 to 0.037) | 0.391    |          |          |
| Albumin (g/dL)            | –1.216 (–1.897 to –0.535) | 0.001a   | –1.162 (–1.989 to –0.334) | 0.007b |
| Protein (g/dL)            | –0.552 (–1.076 to –0.290) | 0.039a   | –0.144 (–0.721 to 0.433) | 0.619  |
| WBC (10³/µL)              | 0.036 (–0.020 to 0.092) | 0.209    |          |          |
| ABI                       | –1.212 (–2.615 to 0.191) | 0.089    |          |          |

DM, diabetes mellitus; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cells; ABI, ankle-brachial index.

### Table 5. Factors affecting mean total Bollinger scores

| Variable                  | Mean total Bollinger score |          |          |          |
|---------------------------|---------------------------|----------|----------|----------|
|                           | Univariable regression analysis | Multivariable regression analysis |          |          |
|                           | B (95% confidence interval) | P-value | B (95% confidence interval) | P-value |
| Sex                       | –3.526 (–12.443 to 5.391) | 0.433    |          |          |
| Smoking status            | 2.172 (–6.569 to 10.913) | 0.622    |          |          |
| Hypertension              | 6.193 (–2.025 to 14.411) | 0.137    |          |          |
| Age (yr)                  | 0.800 (0.486 to 1.114) | 0.000a   | 0.507 (0.113 to 0.902) | 0.013a |
| DM period (yr)            | 0.182 (–0.235 to 0.599) | 0.387    |          |          |
| Body mass index (kg/m²)   | –0.044 (–1.075 to 0.987) | 0.933    |          |          |
| Laboratory measurements   |          |          |          |          |
| CRP (mg/dL)               | –0.365 (–0.831 to 0.101) | 0.122    |          |          |
| ESR (mm/hr)               | –0.001 (–0.244 to 0.242) | 0.994    |          |          |
| Albumin (g/dL)            | 3.262 (–3.696 to 10.219) | 0.353    |          |          |
| Protein (g/dL)            | –1.212 (–6.320 to 3.896) | 0.637    |          |          |
| WBC (10³/µL)              | –0.217 (–0.751 to 0.317) | 0.421    |          |          |
| ABI                       | –28.165 (–41.313 to –15.016) | 0.000a | –20.926 (–34.662 to –7.190) | 0.003a |

DM, diabetes mellitus; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cells; ABI, ankle-brachial index.

aStatistical significance at P<0.05.
74.6%. The rate of obstruction ≤50% of the vessel lumen was much higher. Therefore, DF wound severity could not be predicted by circulation alone. The aforementioned functional and structural changes of the microvasculature, neuropathy, foot trauma, foot deformity, foot edema, and callus formation seem to be more important factors in DF than arterial stenosis severity.

Many scoring systems have been proposed and used for the evaluation of DF wound and critical limb ischemia. The Wound, Ischemia, and foot Infection (WIfI) score system made by modifying many of these score systems is currently being widely used. The system conducts the assessment using three major factors (wound, ischemia, foot infection) that influence amputation risk and clinical management [16]. Among the factors, ischemia is evaluated using toe pressure or transcutaneous oximetry or ABI. In the present study, we wanted to analyze the relationship between the angiographic finding and the severity of the DF wound itself. Therefore, the WIfI score system, which includes ischemia evaluation, could not be used in our study.

Previous studies have reported that the pattern of atherosclerotic lesions is more severe in distal segments and more diffuse in patients with DM than in those without DM [17]. According to Graziani et al. [18], lesions in the infrapopliteal arteries, especially the ATA and PTA, show more occlusion than those in proximal segments. In the current study, the mean Bollinger score and the proportion of arterial occlusions were higher in the ATA and PTA than in other arterial segments. In the FA proximal segment, the rate of obstruction of >50% of the lumen was 22.5%, which was lower than that in the infrapopliteal segments. In addition, the rate of obstruction ≤50% of the lumen was 47.9% in the FA, which was higher than that in the infrapopliteal segments. It is unknown why arterial stenosis is diffuse and more severe in the distal segment in patients with DM. According to van der Feen et al. [17], DM may interfere with the compensatory enlargement of vessel circumference that preserves vessel lumen diameter even with atherosclerotic plaques. As a result, it may lead to a pattern of diffusely narrowed arteries. Furthermore, remodeling leading to paradoxical shrinkage, with subsequent diffuse narrowing and occlusion of distal vessels, may cause different patterns in the DM. It is estimated that these events are more likely to occur in distal vessels, and our results support this.

The PopA segment had the lowest mean Bollinger score; 46.5% of segments had no atherosclerotic lesion, and the proportion of stenosis >50% was the lowest (11.3%). Among all segments, the PopA showed the lowest arterial stenosis severity. We propose that the chance of atherosclerotic lesions is relatively low in the PopA because it is the shortest segment and the popliteal region is a joint, with a large range of motion, and fast, uncongested blood flow. Additionally, 29.6% of FA segments were normal. This was the lowest proportion among the segments and may have occurred because the FA is the longest of the segments; therefore, the chance of atherosclerotic lesions may be higher.

Many serum inflammatory markers are used to determine whether a wound infection has occurred. Procalcitonin, ESR, and CRP show reasonable accuracy for predicting DF wound severity, and the elevation of these values predicts the occurrence of osteomyelitis and arterial stenosis with good accuracy and acceptable sensitivity [19]. Serum WBC count is also a significant marker for distinguishing infection, although its sensitivity and specificity are lower than those of ESR and CRP [20]. In the present study, WBC count, CRP and ESR did not show any significant association with wound severity and mean total Bollinger score.

In chronic diseases such as DM, poor nutritional status affects prognosis. Serum albumin is widely used as a nutritional

### Table 6. Distribution of cases according to occlusive pattern

| Case               | Occlusions | Stenosis >50% | Stenosis ≤50% | Plaque ≤25% | Normal |
|--------------------|------------|---------------|---------------|-------------|--------|
| Femoral artery     | 5 (7.0)    | 11 (15.5)     | 18 (25.4)     | 16 (22.5)   | 21 (29.6)     |
| Popliteal artery   | 2 (2.8)    | 6 (8.5)       | 17 (23.9)     | 13 (18.3)   | 33 (46.5)     |
| Anterior tibial artery | 13 (18.3) | 13 (18.3)     | 6 (8.5)       | 10 (14.1)   | 29 (40.8)     |
| Posterior tibial artery | 13 (18.3) | 9 (12.7)      | 10 (14.1)     | 10 (14.1)   | 29 (40.8)     |
| Peroneal artery    | 5 (7.0)    | 13 (18.3)     | 9 (12.7)      | 16 (22.5)   | 28 (39.4)     |
| Total              | 38 (10.7)  | 52 (14.6)     | 60 (16.9)     | 65 (18.3)   | 140 (39.4)    |

Values are presented as number (%).
indicator [21,22]. Lower serum albumin levels affect non-healing ulcers and prognosis in DF. Serum albumin and protein level were significantly associated with wound severity in the present study. Therefore, while the treatment of the wound itself is important, the overall improvement of the nutritional condition is also likely to be important.

The prevalence of arterial stenosis increases with age [4]. In the present results, there was a positive association between age and mean total Bollinger score, but age had no significant association with wound severity. Therefore, as age increases, arterial stenosis tends to get worse, but this is not associated with increased DF severity. ABI, which is widely used as a simple method for evaluating arterial stenosis, showed negative association with mean total Bollinger score and no significant association with wound severity. The negative association between ABI and mean total Bollinger score verifies that ABI indeed can be used as an indirect index of arterial stenosis.

As per popular perception, smoking status was estimated to affect wound severity and arterial stenosis, but there was no significant association in the present study [15]. Nevertheless, smoking interferes with wound healing via various mechanisms and reduces tissue blood flow and oxygen supply. It also causes microvascular alterations, such as impaired vasodilation, sympathetic stimulation by nicotine, atherosclerosis of the lower extremities and cellular oxygen metabolism disturbances due to carbon monoxide. Chronic hypoxia reduces fibroblast activity and interferes with collagen synthesis and angiogenesis [23]. Cigarette smoking increases the risk of DF-related amputation and smoking has been associated with serious postoperative complications. Smoking cessation for more than three weeks prior to surgery reduced the incidence of impaired wound healing and reduced postoperative morbidity [23].

As shown in the current study, diverse factors, such as albumin, protein, age and ABI, had a significant association with arterial stenosis and DF severity. However, the degree of arterial stenosis was not significantly associated with wound severity, and patients with normal blood vessels were also hospitalized with DF and had to undergo surgery. Therefore, rather than evaluating patients with DF based on the severity of blood vessel obstruction, clinicians should consider a multitude of factors to plan the diagnosis and treatment of DF.

If research methods used in the study could quantitatively measure the degree of vascular obstruction or peripheral blood flow in the arteries, more objective data could have been obtained. Future studies should involve a larger number of cases and focus on a wider variety of factors, as well as on the location of arterial stenosis in blood vessels. Such research may inform more specific treatment for diabetic arteriosclerosis.

**Conflict of interest**

No potential conflict of interest relevant to this article was reported.

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