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Injury Precipitating Tissue Loss and Time to Referral to a Vascular Center in Patients with Chronic Limb-Threatening Ischemia

Mitsuyoshi Takahara[1], Osamu Iida[2], Norihiko Ohura[3], Yoshimitsu Soga[4], Terutoshi Yamaoka[5] and Nobuyoshi Azuma[6]

[1]Department of Diabetes Care Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
[2]Cardiovascular Center, Kansai Rosai Hospital, Hyogo, Japan
[3]Department of Plastic, Reconstructive Surgery, Kyorin University School of Medicine, Tokyo, Japan
[4]Department of Cardiology, Kokura Memorial Hospital, Fukuoka, Japan
[5]Department of Vascular Surgery, Matsuyama Red Cross Hospital, Ehime, Japan
[6]Department of Vascular Surgery, Asahikawa Medical University, Hokkaido, Japan

Aim: This study aimed to report injury precipitating tissue loss and to provide updated information on the time from tissue loss occurrence to referral to a vascular center for patients who developed chronic limb-threatening ischemia (CLTI) in Japan.

Methods: We examined 450 patients who developed CLTI with tissue loss and were registered in a multicenter prospective study between October 2017 and June 2020. They were referred to the participating vascular centers for revascularization. Information on the injury precipitating tissue loss and time to referral was collected at registration. The severity of tissue loss was evaluated using the Wound, Ischemia, and foot Infection classification.

Results: Injury precipitating tissue loss was absent in 52.0% (95% confidence interval, 47.3%–56.6%) of the patients. The absence was associated with lower albumin levels and preserved pressure sensation. Although the time to referral was significantly shorter in cases without a history of prereferral revascularization, 16.8% (12.8%–20.7%) of the patients were referred to the vascular centers more than 3 months after tissue loss occurrence. Time to referral, but not the lack of a clear precipitant for tissue loss, was significantly associated with the severity of tissue loss.

Conclusion: A clear precipitant for tissue loss was often lacking, particularly in patients with low albumin levels and preserved pressure sensation. Delayed referral to a vascular center is still common.

Key words: Chronic limb-threatening ischemia, Precipitating injury, Time to referral, Severity of tissue loss

Introduction

Chronic limb-threatening ischemia (CLTI), particularly accompanied by ischemic tissue loss, is the most advanced form of peripheral artery disease, and the prognosis is extremely poor[1, 2]. Diabetes mellitus is one of the major risk factors, and a substantial proportion of diabetic foot disease cases can be included in CLTI[1, 2]. Once CLTI develops, revascularization, either surgical or endovascular, is the first-line strategy for limb salvage[1, 2]. However, revascularization does not guarantee the salvage of all affected limbs. Primary prevention of CLTI, rather than total reliance on revascularization after CLTI development, is the ideal management strategy for patients at risk of CLTI[3].

In an ischemic foot, even minor trauma can precipitate CLTI. Therefore, clinical guidelines recommend wearing well-fitting shoes and socks and

Address for correspondence: Mitsuyoshi Takahara, Department of Diabetes Care Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan E-mail: takahara@endmet.med.osaka-u.ac.jp

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avoiding walking barefoot among patients with peripheral artery disease[3], as has long been recommended for patients at risk of diabetic foot disease[4]. However, to date, little has been reported about the initial injury leading to subsequent tissue loss in patients who develop CLTI. Such data would help develop a more practical strategy to lower the risk of local trauma that could lead to CLTI.

Apart from primary prevention of CLTI development, prompt referral to a vascular specialist after CLTI development, which will enable a timely revascularization, is important for limb salvage. In 2012 and early 2013, a substantial number of patients with CLTI faced delays in referral to a vascular center[5]. Subsequently, the management of peripheral artery disease in clinical practice appears to have improved considerably. New endovascular devices, including drug-eluting stents[6, 7], drug-coated balloons[8, 9], heparin-bonded stent-grafts[10], and interwoven stents[11], have improved the clinical outcomes of endovascular therapy, increasing its reliability[12]. Clinical guidelines on the management of peripheral artery disease, especially CLTI, have been published in rapid progression, providing systematic and practical strategies for managing CLTI[1-3, 13, 14]. Furthermore, the health insurance system in Japan has promoted the cooperation between dialysis centers and vascular specialists by reimbursing the relevant medical supervision charges since 2016 [15]. The recent substantial increase in procedural volume[16] is likely the reflection in part of an expanded domestic capacity for lower extremity revascularization and in part of the increasing familiarity with CLTI. These changes can potentially promote the prompt referral of patients with CLTI to a vascular specialist.

Aim

The aim of the present study was to report the initial mechanisms of injury leading to subsequent tissue loss and to provide updated information on the length of time from tissue loss occurrence to referral to a vascular center in patients who developed CLTI in Japan.

Methods

This study analyzed the database of the Wound-directed Angiosome RevasculaRIzation apprOach to patients with cRitical limb iSchemia (WARRIORS) study. The WARRIORS study is an ongoing prospective multicenter observational study of patients with CLTI due to atherosclerotic arterial disease, presenting with ischemic tissue loss with a skin perfusion pressure (SPP) of <40 mmHg, scheduled for infrapopliteal revascularization (either surgical or endovascular) at 29 centers in Japan. The study participants were registered at referral to the participating centers between October 2017 and June 2020. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Kansai Rosai Hospital, the principal research institution (approval date, September 26, 2017; approval number, #17C034g), and at all other centers registering patients. Informed consent was obtained from the participants or, if not possible, from their families. A total of 495 affected limbs of 450 patients registered in the WARRIORS study were included in the current analysis.

The severity of tissue loss was evaluated according to the Wound, Ischemia, and foot Infection (WIfI) classification system[14]. The WIfI wound (W) and foot infection (fI) grades were determined by an independent plastic surgeon using photographs of pedal wounds and medical records to determine the presence of systemic inflammatory response syndrome. The WIfI ischemia (I) grade was determined based on the SPP; SPPs of 30–39 and <30 mm Hg were treated as WIfI I-2 and I-3, respectively, as prespecified. Note that our SPP-based WIfI ischemia classification was in line with the latest domestic clinical guideline on peripheral artery disease[17]. As aforementioned, all study participants presented with ischemic tissue loss and an SPP <40 mmHg, therefore being categorized as ≥ WIfI W-1 and ≥ I-2. The information on the initial mechanism of injury leading to subsequent tissue loss, time to referral, and ambulatory status before CLTI onset was collected at registration and was based on medical records or interviews. Time to referral was defined as the time (months) from tissue loss occurrence to referral to the participating vascular center. The pressure sensation in the foot was assessed using a Semmes–Weinstein 5.07 monofilament at the following four podalic sites: the distal great toe and the first, third, and fifth metatarsal heads [18, 19]. Loss of pressure sensation was recorded when patients were unable to sense the pressure applied by the monofilament at any site. Prereferral revascularization denotes revascularization that was performed at another vascular center after the incidence of CLTI and before referral to the participating centers.

Statistical Analysis

Data are reported as means and standard deviations (SDs) for continuous variables or as frequencies and percentages for discrete variables, if not otherwise specified. A P value <0.05 indicated

statistical significance, and 95% confidence intervals were reported where appropriate. Since data on the time to referral were not normally distributed but skewed to the right, the distribution was crudely described as the proportions of the following categories: ≤ 1 month, 1–2 months (>1 and ≤ 2 months), 2–3 months (>2 and ≤ 3 months), 3–6 months (>3 and ≤ 6 months), and >6 months. Furthermore, in regression models, the variable was treated after logarithmic transformation. Of the 495 limbs examined in the current study, 15 (3.0% of the overall population) had missing data regarding the time to referral, whereas none had data missing on the initial mechanism of injury leading to subsequent tissue loss. Missing data were addressed using multiple imputation with the chained equations method. We generated five imputed datasets and combined the analytic results according to Rubin's rule. We also performed the sensitivity analysis in which missing data were handled using listwise deletion.

The difference in a nominal or dichotomous variable between groups with and without prereferral revascularization was tested using Pearson's chi-square test of independence for contingency tables, whereas that in an ordinal variable was tested using the chi-square test for trend in proportions. The association of clinical characteristics with the lack of a clear initial injury leading to tissue loss was investigated using the logistic regression model. We also developed a linear regression model in which the logarithmic transformation of the time to referral was the dependent variable to explore the association of clinical characteristics with time to referral. The cumulative link model with a logit link function was adopted to examine whether the lack of a clear initial injury leading to tissue loss and time to referral would be associated with the severity of tissue loss. Although our SPP-based WIfI ischemia grading (<30 mmHg as I-3 and 30–39 mmHg as I-2) was in line with the latest domestic clinical guideline[17], we additionally performed the analysis where the WIfI ischemia grade was based on another classification (an SPP of <25, 25–34, 35–44, and ≥ 45 mmHg as I-3, -2, -1, and -0, respectively)[20]. All analyses were conducted per patient; for patients with bilateral CLTI, the limb presenting with the more severe tissue loss was treated as the representative one. All statistical analyses were performed using R version 4.1.1 (R Development Core Team, Vienna, Austria).

Results

The clinical characteristics of the study population are summarized in **Table 1**. The patients were 74±9 years of age and 64.4% were men. The prevalence of diabetes mellitus and renal failure on dialysis was 72.2% and 58.4%, respectively. Prereferral revascularization was conducted in 12.7% of the population, and pressure sensation was lost in 38.5%. WIfI clinical stages 2, 3, and 4 were present in 4.8%, 29.9%, and 65.3% of the study population.

As shown in **Table 2**, 52.0% (95% confidence interval, 47.3%–56.6%) of the study participants recalled no clear initial injury leading to tissue loss. Among those with an apparent initial injury, ill-fitting shoes and mechanical injuries were the leading mechanisms of injury, accounting for 16.9% (13.4%–20.4%) and 11.9% (8.9%–14.9%) of the overall population, respectively. There was no significant difference in the initial mechanism of injury between patients with and without a history of prereferral revascularization (P=0.16). Time to referral to a vascular center ranged widely from case to case **(Table 2)**; 49.3% (44.6%–54.0%) of the overall population was referred to a vascular center within 1 month after the occurrence of tissue loss, whereas 7.3% (4.9%–9.7%) had a time to referral of more than 6 months. Time to referral was significantly shorter in cases without a history of prereferral revascularization (P< 0.001). However, a long time to referral was not rare, even for those without a history of prereferral revascularization. Time to referral exceeded 3 months for 16.8% (12.8%–20.7%) in the subgroup without the history **(Table 2)**.

Table 3 demonstrates the association between clinical characteristics and the lack of a clear initial injury leading to tissue loss. Albumin levels and loss of pressure sensation were inversely associated with the lack of a clear initial injury leading to tissue loss (adjusted odds ratio, 0.69 [0.56–0.85; P=0.001] per 1-SD increase and 0.58 [0.36–0.92; P=0.021], respectively); in other words, lower albumin levels and preserved pressure sensation were positively associated with the lack of a clear initial injury leading to tissue loss.

History of prereferral revascularization was independently associated with time to referral (P< 0.001) **(Table 4)**. Time to referral was 1.87 [1.47–2.38] times longer in patients with a history of prereferral revascularization than in those without. No other clinical characteristic was significantly associated with time to referral (all P>0.05).

The association of the lack of a clear initial injury and time to referral with the severity of tissue loss is shown in **Table 5**. Time to referral was significantly associated with the wound grade, foot infection grade, and clinical stage according to the WIfI classification. The adjusted odds ratios per two-fold increase were

Table 1. Characteristics of the study population

Patient characteristics	(n=450)	
Age (years)	74 ± 9	
Male sex	290 (64.4%)	
Non-ambulatory	102 (22.7%)	
Smoking		
Never	191 (42.4%)	
Past	222 (49.3%)	
Current	37 (8.2%)	
Body mass index (kg/m^2)	22.0 ± 4.0	
Diabetes mellitus	325 (72.2%)	
Renal failure on dialysis	263 (58.4%)	
Albumin (g/dL)	3.3 ± 0.6	(missing data, n=13 [2.9%])
Limb characteristics	(n=495)	
Prereferral revascularization	62 (12.7%)	(missing data, n=8 [1.6%])
Loss of pressure sensation	165 (38.5%)	(missing data, n=66 [13.3%])
WIfI classification: Wound		(missing data, n=34 [6.9%])
W-1	200 (43.4%)	
W-2	205 (44.5%)	
W-3	56 (12.1%)	
WIfI classification: Ischemia*		
I-2 (SPP <30 mmHg)	108 (21.8%)	
I-3 (SPP 30–39 mmHg)	387 (78.2%)	
WIfI classification: Foot infection		(missing data, n=34 [6.9%])
fI-0	82 (17.8%)	
fI-1	141 (30.6%)	
fI-2	221 (47.9%)	
fI-3	17 (3.7%)	
WIfI classification: Clinical stage*		(missing data, n=34 [6.9%])
Stage 2	22 (4.8%)	
Stage 3	138 (29.9%)	
Stage 4	301 (65.3%)	

Data are presented as mean ± standard deviation, or number (percentage). *When WIfI ischemia grade was classified according to different cutoff points (<25 mmHg as I-3, 25–34 mmHg as I-2, 35–44 mmHg as I-1, and ≥ 45 mmHg as I-0)[20], the number of patients with WIfI I-1, 2, and 3 was 47 (9.5%), 122 (24.6%), and 326 (65.9%), respectively, whereas the number of those with WIfI clinical stage 1, 2, 3, and 4 was 8 (1.7%), 33 (7.2%), 128 (27.8%), and 292 (63.3%) (missing data, n=34 [6.9%]), respectively.

1.20 (95% confidence interval, 1.03–1.39; P=0.020), 1.17 (1.00–1.37; P=0.043), and 1.24 (1.03–1.48; P=0.021), respectively. The lack of a clear initial injury leading to tissue loss was not significantly associated with WIfI severity (all P>0.05). Similar findings were observed when WIfI ischemia classification was based on other SPP cutoff points[20] **(Supplemental Table 1)**.

Supplemental Tables 2 to 5 show the sensitivity analysis in which missing data were not imputed and handled by listwise deletion. The results were similar to those based on multiple imputation **(Tables 2 to 5)**, except that the adjusted association of time to referral to a vascular center with WIfI wound grade lost statistical significance **(Supplemental Table 5)**.

Discussion

The current study reported the initial mechanism of injury leading to tissue loss and time to referral of patients with CLTI presenting with ischemic tissue loss who were referred to a vascular center for revascularization in Japan. A clear initial injury leading to tissue loss was often lacking, particularly in patients with low albumin levels and preserved pressure sensation. Delayed referral to a vascular center was still common. Time to referral, but not the lack of a clear precipitant for tissue loss, was significantly associated

Table 2. Initial mechanisms of injury leading to tissue loss and time to referral to a vascular center

	Overall population	Subgroup without prereferral revascularization	Subgroup with prereferral revascularization	*P* value
Mechanism of injury leading to tissue loss				0.16
Ill-fitting shoe	16.9% [13.4% to 20.4%]	15.9% [12.3% to 19.6%]	23.0% [12.4% to 33.6%]	
Mechanical injury	11.9% [8.9% to 14.9%]	12.0% [8.7% to 15.2%]	11.5% [3.5% to 19.5%]	
Improper nail cut or onychocryptosis	6.2% [4.0% to 8.5%]	5.1% [2.9% to 7.3%]	13.2% [4.7% to 21.7%]	
Tinea pedis	5.3% [3.3% to 7.4%]	5.9% [3.6% to 8.3%]	1.6% [0.0% to 4.8%]	
Bedsore	1.9% [0.6% to 3.2%]	1.9% [0.5% to 3.3%]	2.0% [0.0% to 5.8%]	
Thermal injury (burn)	1.8% [0.6% to 3.0%]	1.8% [0.5% to 3.1%]	1.6% [0.0% to 4.8%]	
Callus or clavus	1.6% [0.4% to 2.7%]	1.3% [0.2% to 2.4%]	3.3% [0.0% to 7.8%]	
Others	2.4% [1.0% to 3.9%]	2.5% [0.9% to 4.0%]	2.3% [0.0% to 6.6%]	
No clear injury leading to tissue loss	52.0% [47.3% to 56.6%]	53.6% [48.6% to 58.6%]	41.4% [28.8% to 54.1%]	
Time to referral to a vascular center				<0.001
≤ 1 month	49.3% [44.6% to 54.0%]	53.4% [48.4% to 58.4%]	23.0% [12.4% to 33.6%]	
>1 and ≤ 2 months	19.0% [15.3% to 22.6%]	18.9% [14.9% to 22.8%]	19.7% [9.7% to 29.8%]	
>2 and ≤ 3 months	12.0% [8.9% to 15.1%]	11.0% [7.7% to 14.3%]	18.4% [8.6% to 28.2%]	
>3 and ≤ 6 months	12.4% [9.3% to 15.6%]	10.7% [7.5% to 13.9%]	23.7% [12.8% to 34.5%]	
>6 months	7.3% [4.9% to 9.7%]	6.1% [3.6% to 8.5%]	15.1% [6.0% to 24.2%]	
Time to referral to a vascular center longer than 3 months	19.7% [15.9% to 23.6%]	16.8% [12.8% to 20.7%]	38.8% [26.5% to 51.1%]	<0.001

Data are presented as proportions [95% confidence intervals]. The analysis was performed per patient.

Table 3. Association of clinical characteristics with the lack of a clear injury that precipitated tissue loss

	Unadjusted estimates	Adjusted estimates
Age	1.07 [0.89 to 1.29] (*P*=0.46)	1.02 [0.81 to 1.27] (*P*=0.88)
Male sex	0.97 [0.66 to 1.43] (*P*=0.89)	1.05 [0.65 to 1.69] (*P*=0.84)
Non-ambulatory	1.17 [0.75 to 1.82] (*P*=0.50)	1.03 [0.64 to 1.65] (*P*=0.90)
Smoking (versus never)		
Past	0.93 [0.63 to 1.37] (*P*=0.72)	1.00 [0.63 to 1.59] (*P*=1.00)
Current	1.34 [0.66 to 2.74] (*P*=0.42)	1.55 [0.70 to 3.45] (*P*=0.28)
Body mass index	0.87 [0.72 to 1.05] (*P*=0.15)	0.95 [0.77 to 1.18] (*P*=0.66)
Diabetes mellitus	0.92 [0.61 to 1.39] (*P*=0.70)	1.05 [0.66 to 1.66] (*P*=0.85)
Renal failure on dialysis	0.93 [0.64 to 1.36] (*P*=0.72)	0.86 [0.56 to 1.31] (*P*=0.48)
Albumin	0.71 [0.58 to 0.86] (*P*=0.001)	0.69 [0.56 to 0.85] (*P*=0.001)
Loss of pressure sensation	0.61 [0.39 to 0.95] (*P*=0.030)	0.58 [0.36 to 0.92] (*P*=0.021)

Data are presented as odds ratios [95% confidence intervals] (*P* values) for the lack of a clear injury leading to tissue loss. Those of age, body mass index, and albumin are per 1-SD increase. Adjusted odds ratios were derived from the multivariate logistic regression model in which all the variables listed in the table were entered. The analysis was performed per patient.

with the severity of tissue loss.

Ill-fitting shoes and mechanical injuries as the leading apparent initial mechanisms would support the importance of teaching patients about healthy foot behaviors, including wearing well-fitting shoes and socks and avoiding walking barefoot, which are emphasized in clinical guidelines[3]. However, an apparent initial injury was lacking in about half of the study population, suggesting tissue necrosis and microtrauma as major triggers of ischemic tissue loss. Furthermore, the severity of tissue loss precipitated by a latent episode was as severe as that precipitated by an apparent episode. Tissue necroses and nonhealing microtraumas can develop in the foot with decreased perfusion that causes ischemia, hypoxia, inflammation, endothelial dysfunction, and inappropriate platelet aggregation, which lead to microthrombosis, tissue edema, and cellular

Table 4. Association of clinical characteristics with time to referral to a vascular center

	Unadjusted estimates	Adjusted estimates
Age	0.95 [0.87 to 1.03] (P=0.24)	0.96 [0.87 to 1.06] (P=0.39)
Male sex	0.90 [0.76 to 1.07] (P=0.25)	0.92 [0.76 to 1.12] (P=0.42)
Non-ambulatory	0.98 [0.81 to 1.20] (P=0.87)	1.01 [0.83 to 1.23] (P=0.93)
Smoking (versus never)		
Past	0.86 [0.73 to 1.02] (P=0.087)	0.84 [0.69 to 1.02] (P=0.073)
Current	0.97 [0.71 to 1.33] (P=0.86)	0.97 [0.70 to 1.34] (P=0.84)
Body mass index	1.02 [0.94 to 1.11] (P=0.59)	1.01 [0.93 to 1.11] (P=0.76)
Diabetes mellitus	0.97 [0.81 to 1.17] (P=0.75)	0.95 [0.78 to 1.16] (P=0.65)
Renal failure on dialysis	1.00 [0.84 to 1.18] (P=0.97)	1.03 [0.86 to 1.23] (P=0.77)
Albumin	1.02 [0.94 to 1.10] (P=0.67)	1.03 [0.95 to 1.12] (P=0.42)
Prereferral revascularization	1.84 [1.45 to 2.33] (P<0.001)	1.87 [1.47 to 2.38] (P<0.001)
Loss of pressure sensation	1.15 [0.95 to 1.39] (P=0.15)	1.14 [0.94 to 1.38] (P=0.17)

Data are presented as the exponential of regression coefficients [95% confidence intervals] (P values) for the log-transformed duration of tissue loss, i.e., indicating the fold change of the duration that corresponds to the respective explanatory variables. Those of age, body mass index, and albumin are per 1-SD increase. Adjusted values were derived from the multivariate linear regression model in which all the variables listed in the table were entered. The analysis was performed per patient.

Table 5. Association of the lack of a clear precipitating injury leading to tissue loss and time to referral with the severity of tissue loss

	Unadjusted odds ratio	Adjusted odds ratio
WIfI classification: Wound (W grade)		
Lack of a clear injury precipitating tissue loss	0.87 [0.61 to 1.25] (P=0.45)	0.77 [0.52 to 1.14] (P=0.19)
Time to referral to a vascular center (per 2-fold increase)	1.21 [1.05 to 1.40] (P=0.007)	1.20 [1.03 to 1.39] (P=0.020)
WIfI classification: Ischemia (I grade)		
Lack of a clear injury precipitating tissue loss	1.17 [0.75 to 1.83] (P=0.49)	1.10 [0.69 to 1.75] (P=0.69)
Time to referral to a vascular center (per 2-fold increase)	1.01 [0.84 to 1.21] (P=0.94)	1.04 [0.87 to 1.25] (P=0.68)
WIfI classification: Foot infection (fI grade)		
Lack of a clear injury precipitating tissue loss	0.77 [0.54 to 1.10] (P=0.15)	0.70 [0.48 to 1.03] (P=0.068)
Time to referral to a vascular center (per 2-fold increase)	1.20 [1.03 to 1.40] (P=0.018)	1.17 [1.00 to 1.37] (P=0.043)
WIfI classification: Clinical stage		
Lack of a clear precipitating injury leading to tissue loss	0.91 [0.61 to 1.35] (P=0.62)	0.88 [0.57 to 1.37] (P=0.57)
Time to referral to a vascular center (per 2-fold increase)	1.24 [1.05 to 1.47] (P=0.013)	1.24 [1.03 to 1.48] (P=0.021

Data are presented as odds ratios [95% confidence intervals] (P values) for the severity of tissue loss. Adjusted odds ratios were obtained from the multivariate model applied to lack of a clear injury precipitating tissue loss, time to referral to a vascular center, age, sex, ambulatory status, smoking, body mass index, diabetes mellitus, renal failure on dialysis, albumin levels, and loss of pressure sensation. The analysis was performed per patient.

dysregulation[21]. In the development of CLTI, these latent episodes are as important triggers of tissue loss as local trauma. In this context, ischemic ulceration contrasts with neuropathic ulceration, which is attributed chiefly to apparent triggers including tissue loss resulting from minor trauma (e.g., from ill-fitting shoes or an acute mechanical or thermal injury) and abnormal biomechanical loading due to foot deformities, limited joint mobility, and callus formation[4]. The inverse association between loss of pressure sensation and the lack of an apparent mechanism of initial injury would support the idea that an ischemic foot without neuropathy is more likely to develop CLTI from latent episodes than one complicated by neuropathy. The lack of apparent episodes was also associated with hypoalbuminemia. Hypoalbuminemia is a marker of malnutrition as well as a common cause of edema. Nutrient deficiency and tissue edema increase the probability of CLTI by accelerating the disruption of tissue homeostasis, potentially resulting in tissue necrosis and interfering with the healing of microtrauma. Our findings suggest that daily attempts to avoid precipitating injuries do not entirely prevent the development of CLTI. Promoting the prompt referral to a vascular specialist after development of CLTI is all the more crucial for limb salvage.

This study showed that a substantial number of

patients still face delays in referral to a vascular center. In our previous study of patients with CLTI between January 2012 and March 2013, the time to referral exceeded 3 months for 15.9% (95% confidence interval, 12.4%–19.4%) of the population without a history of prereferral revascularization[5]. The corresponding proportion in the present study, in which patients who were registered between October 2017 and June 2020 were surveyed, was 16.8% (12.8%–20.7%), indicating that delayed referral did not decrease during recent years. Despite the apparent drastic improvements in the management of CLTI in recent years[1-3, 6-11, 13-16], cooperation between home doctors and vascular specialists has still plenty of room for improvement.

The time to referral was longer in patients with a history of prereferral revascularization than in those without. These patients' first touch with a vascular specialist was earlier than the index referral, and therefore, one can interpret in a favorable light that their net time to referral was shorter. However, prereferral revascularization also poses the question of whether the initial revascularization had been the optimal treatment choice. The current study did not collect detailed data on prereferral treatment, and it remains unknown whether the initial plan for revascularization was appropriately drawn up at the referring vascular center.

Although the causality between time to referral and WIfI wound grade, foot infection grade, and clinical grade remains unproven, it can be surmised that tissue loss progresses over time. A number of clinical studies have identified the severity of tissue loss at revascularization as an independent risk factor for poor prognosis after revascularization[22-28]. Severity is also associated with increased resource utilization and costs[29-31]. A prompt referral would enable timely revascularization with minimal tissue loss, potentially improving clinical outcomes and reducing the health care burden.

Prereferral revascularization as the only predictor of prolonged time to referral indicates that delayed referral is observed in every healthcare setting. Although the obstacles to prompt referral remain unknown, delayed referral might be due to poor awareness of the disease among both patients and general practitioners[32-34]. Improving the public and healthcare workers' awareness of the disease could shorten the referral time to a vascular specialist after CLTI onset.

This study has some limitations. First, although the data on the preceding injury and the time of tissue loss occurrence were prospectively obtained from medical records and interviews in this study, they were often based on self-report and could therefore be inaccurate. Second, data on the treatment before the index referral, primary foot care, and patient education were unavailable in this study. The treatment before the referral could influence the time to referral and the deterioration of ischemic wounds. Reasons for delayed referral also remain unknown. Third, the current study included patients with CLTI for whom infrapopliteal revascularization was scheduled. Although most patients with CLTI undergo infrapopliteal revascularization, patients with CLTI not requiring infrapopliteal revascularization were excluded from our study. Furthermore, patients with an SPP of 40 mmHg or higher were not included. It remains unknown whether the current findings are true for patients with CLTI undergoing revascularization of other vascular territories or with SPP of 40 mmHg or higher. Fourth, our study did not control who assessed the pressure sensation, neither did we collect data on who assessed the pressure sensation. Fifth, the WARRIORS study is an ongoing cohort, and the prognostic impact of the initial mechanisms of injury leading to tissue loss and time to referral to a vascular center currently remains unknown. Patients with peripheral artery disease are at very high risk of major adverse cardiovascular and limb events[1-3, 35-40]. A future study is warranted to determine the association of initial mechanisms of injury and time to referral with prognoses.

Conclusion

The current study reported on the initial mechanisms of injury leading to tissue loss and provided updated information on the time to referral to a vascular center for revascularization of patients with CLTI presenting with ischemic tissue loss in Japan. Although ill-fitting shoes and mechanical injuries were the leading mechanisms of injury, a clear preceding injury was often absent, particularly in patients with low albumin levels and preserved pressure sensation. Delayed referral was still common, even in cases without a history of prereferral revascularization. Time to referral, but not the lack of a clear preceding injury, was significantly associated with the severity of tissue loss. Greater efforts to promote foot care and prompt referral to a vascular specialist in daily clinical practice are warranted.

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The authors declare that there is no conflict of interest.

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Supplemental Table 1. Association of the lack of a clear precipitating injury leading to tissue loss and time to referral with the severity of tissue loss based on another SPP grading system

	Unadjusted odds ratio	Adjusted odds ratio
WIfI classification: Wound (W grade)		
Lack of a clear injury precipitating tissue loss	0.87 [0.61 to 1.25] (*P*=0.45)	0.77 [0.52 to 1.14] (*P*=0.19)
Time to referral to a vascular center (per 2-fold increase)	1.21 [1.05 to 1.40] (*P*=0.007)	1.20 [1.03 to 1.39] (*P*=0.020)
WIfI classification: Ischemia (I grade)		
Lack of a clear injury precipitating tissue loss	1.46 [1.00 to 2.16] (*P*=0.053)	1.45 [0.97 to 2.18] (*P*=0.068)
Time to referral to a vascular center (per 2-fold increase)	1.02 [0.87 to 1.20] (*P*=0.78)	1.06 [0.90 to 1.25] (*P*=0.46)
WIfI classification: Foot infection (fI grade)		
Lack of a clear injury precipitating tissue loss	0.77 [0.54 to 1.10] (*P*=0.15)	0.70 [0.48 to 1.03] (*P*=0.068)
Time to referral to a vascular center (per 2-fold increase)	1.20 [1.03 to 1.40] (*P*=0.018)	1.17 [1.00 to 1.37] (*P*=0.043)
WIfI classification: Clinical stage		
Lack of a clear precipitating injury leading to tissue loss	0.90 [0.61 to 1.33] (*P*=0.60)	0.90 [0.59 to 1.38] (*P*=0.64)
Time to referral to a vascular center (per 2-fold increase)	1.22 [1.04 to 1.44] (*P*=0.017)	1.21 [1.02 to 1.44] (*P*=0.027)

Data are presented as odds ratios [95% confidence intervals] (*P* values) for the severity of tissue loss. WIfI ischemia classification was based on other SPP cutoff points (25 mmHg as I-3, 25–34 mmHg as I-2, 35–44 mmHg as I-1, and ≥ 45 mmHg as I-0). Adjusted odds ratios were obtained from the multivariate model applied to lack of a clear injury precipitating tissue loss, time to referral to a vascular center, age, sex, ambulatory status, smoking, body mass index, diabetes mellitus, renal failure on dialysis, albumin levels, and loss of pressure sensation.

Supplemental Table 2. Initial mechanisms of injury leading to tissue loss and time to referral to a vascular center (analysis without imputation)

	Overall population	Subgroup without prereferral revascularization	Subgroup with prereferral revascularization	*P* value
Mechanism of injury leading to tissue loss				0.10
Ill-fitting shoe	76 (16.9%)	60 (15.6%)	14 (24.1%)	
Mechanical injury	55 (12.2%)	48 (12.5%)	7 (12.1%)	
Improper nail cut or onychocryptosis	28 (6.2%)	20 (5.2%)	8 (13.8%)	
Tinea pedis	24 (5.3%)	23 (6.0%)	1 (1.7%)	
Bedsore	9 (2.0%)	7 (1.8%)	1 (1.7%)	
Thermal injury (burn)	8 (1.8%)	6 (1.6%)	1 (1.7%)	
Callus or clavus	7 (1.6%)	5 (1.3%)	2 (3.4%)	
Others	11 (2.4%)	9 (2.3%)	1 (1.7%)	
No clear injury leading to tissue loss	232 (51.6%)	207 (53.8%)	23 (39.7%)	
Time to referral to a vascular center*				<0.001
≤ 1 month	214 (49.0%)	200 (53.8%)	13 (22.4%)	
>1 and ≤ 2 months	84 (19.2%)	72 (19.4%)	12 (20.7%)	
>2 and ≤ 3 months	52 (11.9%)	39 (10.5%)	11 (19.0%)	
>3 and ≤ 6 months	54 (12.4%)	39 (10.5%)	14 (24.1%)	
>6 months	33 (7.6%)	22 (5.9%)	8 (13.8%)	
Time to referral to a vascular center longer than 3 months*	87 (19.9%)	61 (16.4%)	22 (37.9%)	<0.001

Data are presented as counts (proportions). *Data on time to referral to a vascualr center were missing in 13 patients, all of whom belonged to teh subgroup without prereferral revascularization.

Supplemental Table 3. Association of clinical characteristics with the lack of a clear injury that precipitated tissue loss (analysis without imputation)

	Unadjusted estimates	Adjusted estimates
Age	1.06 [0.88 to 1.28] (P=0.52)	1.02 [0.80 to 1.31] (P=0.86)
Male sex	0.98 [0.67 to 1.44] (P=0.92)	0.99 [0.59 to 1.65] (P=0.96)
Non-ambulatory	1.13 [0.73 to 1.76] (P=0.59)	0.94 [0.56 to 1.57] (P=0.81)
Smoking (versus never)		
Past	0.97 [0.66 to 1.42] (P=0.86)	1.08 [0.65 to 1.80] (P=0.78)
Current	1.39 [0.69 to 2.89] (P=0.36)	1.55 [0.63 to 3.85] (P=0.34)
Body mass index	0.88 [0.73 to 1.06] (P=0.18)	0.94 [0.74 to 1.19] (P=0.60)
Diabetes mellitus	0.93 [0.62 to 1.41] (P=0.74)	1.12 [0.68 to 1.84] (P=0.65)
Renal failure on dialysis	0.91 [0.62 to 1.32] (P=0.62)	0.68 [0.43 to 1.08] (P=0.11)
Albumin	0.70 [0.57 to 0.85] (P<0.001)	0.65 [0.52 to 0.82] (P<0.001)
Loss of pressure sensation	0.58 [0.38 to 0.88] (P=0.011)	0.61 [0.39 to 0.94] (P=0.027)

Data are presented as odds ratios [95% confidence intervals] (P values) for the lack of a clear injury leading to tissue loss. Those of age, body mass index, and albumin are per 1-SD increase. Adjusted odds ratios were derived from the multivariate logistic regression model in which all the variables listed in the table were entered.

Supplemental Table 4. Association of clinical characteristics with time to referral to a vascular center (analysis without imputation)

	Unadjusted estimates	Adjusted estimates
Age	0.96 [0.88 to 1.04] (P=0.33)	0.98 [0.88 to 1.09] (P=0.73)
Male sex	0.90 [0.76 to 1.07] (P=0.23)	0.92 [0.74 to 1.15] (P=0.47)
Non-ambulatory	0.99 [0.82 to 1.21] (P=0.94)	1.10 [0.88 to 1.37] (P=0.42)
Smoking (versus never)		
Past	0.87 [0.73 to 1.04] (P=0.12)	0.89 [0.72 to 1.11] (P=0.30)
Current	0.97 [0.71 to 1.33] (P=0.86)	0.96 [0.66 to 1.40] (P=0.83)
Body mass index	1.02 [0.94 to 1.11] (P=0.66)	1.04 [0.94 to 1.15] (P=0.42)
Diabetes mellitus	0.96 [0.80 to 1.16] (P=0.67)	0.96 [0.78 to 1.19] (P=0.73)
Renal failure on dialysis	0.98 [0.83 to 1.16] (P=0.85)	1.05 [0.86 to 1.28] (P=0.64)
Albumin	1.02 [0.94 to 1.11] (P=0.68)	1.04 [0.95 to 1.14] (P=0.38)
Prereferral revascularization	1.79 [1.41 to 2.26] (P<0.001)	1.98 [1.52 to 2.58] (P<0.001)
Loss of pressure sensation	1.22 [1.01 to 1.47] (P=0.042)	1.14 [0.95 to 1.38] (P=0.17)

Data are presented as the exponential of regression coefficients [95% confidence intervals] (P values) for the log-transformed duration of tissue loss, i.e., indicating the fold change of the duration that corresponds to the respective explanatory variables. Those of age, body mass index, and albumin are per 1-SD increase. Adjusted values were derived from the multivariate linear regression model in which all the variables listed in the table were entered.

Supplemental Table 5. Association of the lack of a clear precipitating injury leading to tissue loss and time to referral with the severity of tissue loss (analysis without imputation)

	Unadjusted odds ratio	Adjusted odds ratio
WIfI classification: Wound (W grade)		
Lack of a clear injury precipitating tissue loss	0.81 [0.57 to 1.16] (P=0.25)	0.69 [0.44 to 1.07] (P=0.099)
Time to referral to a vascular center (per 2-fold increase)	1.19 [1.03 to 1.37] (P=0.020)	1.15 [0.98 to 1.36] (P=0.090)
WIfI classification: Ischemia (I grade)		
Lack of a clear injury precipitating tissue loss	1.14 [0.73 to 1.78] (P=0.56)	1.15 [0.68 to 1.95] (P=0.59)
Time to referral to a vascular center (per 2-fold increase)	1.01 [0.85 to 1.21] (P=0.92)	1.00 [0.82 to 1.21] (P=0.99)
WIfI classification: Foot infection (fI grade)		
Lack of a clear injury precipitating tissue loss	0.71 [0.50 to 1.01] (P=0.060)	0.71 [0.50 to 1.01] (P=0.060)
Time to referral to a vascular center (per 2-fold increase)	1.20 [1.04 to 1.40] (P=0.013)	1.19 [1.01 to 1.41] (P=0.034)
WIfI classification: Clinical stage		
Lack of a clear injury precipitating tissue loss	0.81 [0.55 to 1.20] (P=0.30)	0.94 [0.57 to 1.53] (P=0.80)
Time to referral to a vascular center (per 2-fold increase)	1.24 [1.05 to 1.46] (P=0.013)	1.23 [1.02 to 1.50] (P=0.036)

Data are presented as odds ratios [95% confidence intervals] (P values) for the severity of tissue loss. Adjusted odds ratios were obtained from the multivariate model applied to lack of a clear injury precipitating tissue loss, time to referral to a vascular center, age, sex, ambulatory status, smoking, body mass index, diabetes mellitus, renal failure on dialysis, albumin levels, and loss of pressure sensation.