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Comparison of characteristics and healing course of diabetic foot ulcers by etiological classification: Neuropathic, ischemic, and neuro-ischemic type

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ABSTRACT

Aims: To identify differences in the characteristics of patients with diabetic foot ulcers (DFUs) according to their etiological classification and to compare their healing time.
Methods: Over a 4.5-year period, 73 patients with DFUs were recruited. DFUs were etiologically classified as being of neuropathic, ischemic, or neuro-ischemic origin. Descriptive analyses were performed to characterize study subjects, foot-related factors, and healing outcome and time. Duration of healing was assessed using the Kaplan–Meier method. Healing time among the three types was compared using the log rank test.
Results: The number of patients manifesting neuropathic, ischemic, and neuro-ischemic ulcers was 30, 20, and 14, respectively. Differences were identified for age, diabetes duration, body mass index, hypertension, and estimated glomerular filtration rate. Patients with neuro-ischemic ulcers had better ankle–brachial index, skin perfusion pressure (SPP), and transcutaneous oxygen pressure values compared to those with ischemic ulcers. The average time in which 50% of patients had healed wounds was 70, 113, and 233 days for neuropathic, neuro-ischemic, and ischemic ulcers, respectively. Main factors associated with healing were age and SPP values.
Conclusions: Based on the etiological ulcer type, DFU healing course and several patient factors differed. Failure to consider the differences in DFU etiology may have led to heterogeneity of results in previous studies on DFUs.

1. Introduction

Diabetic foot ulcers (DFUs) are one of the most serious and disabling complications of diabetes. Prevalence of DFUs among diabetic patients is reported to be between 4% and 10%, with an estimated lifetime incidence of almost 25% (Singh, Armstrong, & Lipsky, 2005). Due to delayed wound healing, DFUs may lead to lower limb amputations, which deteriorate patients' quality of life and increase morbidity (Nabuurs-Franssen, Huijberts, Nieuwenhuijzen Kruseman, Willems, & Schaper, 2005). DFUs often require prolonged hospital care, and impose a major burden not only on patients, but also on society with considerable medical cost (Prompers et al., 2008; Stockl, Vanderplas, Tafesse, & Chang, 2004). Given these various negative impacts, determination of the factors related to ulcerations and wound healing delay is of major importance.

Previous studies have reported multiple risk factors associated with DFU development (Crawford, Inkster, Kleijnen, & Fahey, 2007; Monteiro-Soares, Boyko, Ribeiro, Ribeiro, & Dinis-Ribeiro, 2012). These include, but are not limited to: age, gender, duration of diabetes, body mass index (BMI), co-morbidities including retinopathy and nephropathy, glycated hemoglobin level, macro-vascular complications, foot deformity, edema, and foot self-care habits. However, there is inconsistent evidence regarding the association between these factors and DFUs (Monteiro-Soares et al., 2012). Some studies have demonstrated that younger patients were at higher risk for DFU development than older counterparts (Armstrong et al.,

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2007), while other studies observed opposite results (Abbott et al., 2002; Monami et al., 2009). Only a few studies have shown an association between BMI and DFUs (Carrington et al., 2002; McNeely et al., 1995; Tentolouris et al., 2009), or between hypertension and DFUs (Guerrero-Romero & Rodriguez-Moran, 1998; Margolis, Hofstad, & Feldman, 2008).

To unfold the complexity of DFUs, they can be classified by their underlying etiology — by the presence of peripheral neuropathy, and/or peripheral arterial disease (PAD), *i.e.*, neuropathic, ischemic, and neuro-ischemic type (Caputo, Cavanagh, Ulbrecht, Gibbons, & Karchmer, 1994; Frykberg et al., 2000; McNeely et al., 1995). Peripheral neuropathy is one form of micro-vascular complications of diabetes, together with nephropathy and retinopathy. On the other hand, PAD is one form of macro-vascular complications and is known to be positively associated with age and other forms of macro-vascular complications, including hypertension and myocardial infarction (Savji et al., 2013). Therefore, there may be differences in patient characteristics when DFUs are grouped using this etiological classification. Previously, Zimny et al. categorized individuals with DFUs into these three ulcer types, and observed discrepancies in diabetes duration, peripheral circulation measurements, and ulcer size in relation to healing (Zimny, Schatz, & Pfohl, 2002). Thus, it is important to compare these three ulcer types and understand the differences in their characteristics and healing process. This may aid development of effective screening and management tools for DFUs. Notably, the study by Zimny et al. was limited by its small sample size and associated factors. Furthermore, to our knowledge no study has compared the healing time of these three ulcer types.

The aim of this study was to identify differences in characteristics of DFU patients according to etiological classification, namely neuropathic, ischemic, and neuro-ischemic ulcer type, and to compare the DFU healing time. The findings of this study may serve as a guide to clinical decision-making in both prevention and management of DFUs.

2. Subjects and method

2.1. Patients

Between October 2009 and March 2013, we prospectively recruited a total of 84 type 2 diabetic patients with DFUs, aged between 35 and 87 years (average age 65.2 ± 12.1 years), who were treated in a tertiary hospital in Japan. All patients received standardized treatment. The end-points of follow-up were healing, lower limb amputation, or death, or the end of the study period. We defined DFUs as ulcers located below the ankle that needed more than 14 days to heal, and we defined healing as complete epithelialization without amputation and without recurrence for more than 6 months (Apelqvist & Agardh, 1992). We excluded patients with secondary diabetes, autoimmune disease, or malignancies (n = 11), which left 73 patients for our analyses. The study protocol was approved by the Ethical Committee of the National Center for Global Health and Medicine, Japan.

2.2. Peripheral neuropathy

We evaluated peripheral neuropathy using Semmes-Weinstein 5.07/10 g monofilament, 128-Hz tuning fork, Achilles tendon reflexes, and coefficient of variation for the R–R intervals (CVRR). Sixty patients underwent nerve conduction velocity (NCV) exams. The remaining 13 patients were unable to undergo NCV exams due to pain and other medical conditions. We recorded neuropathic symptoms such as pain, paresthesia, tingling, discomfort, and numbness. Assessments of peripheral neuropathy were performed based on these findings, as previously described (Tesfaye et al., 2010).

2.3. Peripheral arterial disease

To assess the severity of PAD, we performed ankle–brachial index (ABI) (BP-203RPEIII, OMRON Corporation, Kyoto, Japan), skin perfusion pressure (SPP) (SensiLase™ PAD3000, Vasamed Inc., Minnesota, USA), and transcutaneous oxygen pressure ($tcpO_2$) (TCM400, Radiometer Medical, Bronshoj, Denmark) on all patients. We obtained multiple measurements from two sites on each foot. The lowest values we obtained were recorded in the data set for these examinations. For patients whose measurements were difficult to obtain due to condition of the lesion(s), we took measurements from the opposite foot. Patients who were suspected with PAD due to these measurements (either one of the three: ABI below 0.9 or above 1.4; SPP below 40 mmHg; $tcpO_2$ below 40 mmHg Norgren et al., 2000) underwent enhanced computed tomography (CT) scan for diagnostic confirmation (n = 37). For those who met the criteria but also had severe nephropathy as a complication, we assessed measurements of ABI, SPP, and $tcpO_2$ comprehensively for diagnosis of PAD (n = 8). We excluded ABI values above 1.4, with suspected mediasclerosis, from our analyses (n = 2).

2.4. Other clinical parameters

We measured basic demographic data for these patients, including age, sex, duration of diabetes, body mass index (BMI), family history of diabetes, marital status, mobility, previous periodical follow-up of diabetes, smoking history, and alcohol intake, using an interview-administered questionnaire and electronic medical records. We recorded family history of diabetes (*i.e.*, having a first-degree relative (parent, sibling, or child) with diabetes) to determine whether there are any possible hereditary or habitual associations to DFU development in patients with a positive family history (Potisat, Krairittichai, Jongsareejit, Sattaputh, & Arunratanachote, 2013; Scollan-Koliopoulos, Walker, & Bleich, 2010). We defined smoking as current smoking of at least one cigarette per week or past smoking within three years prior to recruitment (Ghanassia et al., 2008). Alcohol intake was defined as drinking more than 23 g ethanol per day within the last three years (Nakanishi, Suzuki, & Tatara, 2003). We measured glycated hemoglobin (HbA1c), fasting glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride, hemoglobin, and serum albumin at recruitment. We calculated estimated glomerular filtration rate (eGFR) with the formula: eGFR ($ml/min/1.73\ m^2$) = $194 \times \text{serum creatinine}^{-0.094} \times \text{age}^{-0.287} \times 0.739$ (if female) (Matsuo et al., 2009). Dyslipidemia, retinopathy (both non-proliferative and proliferative diabetic retinopathy), renal dialysis, hypertension, history of myocardial infarction, and history of amputation were recorded.

2.5. Foot characteristics

We recorded diagnosis of plantar callus, tinea pedis, onychomycosis, edema, and deep fissure (defined as fissures that penetrate into the dermis). Foot deformity was noted when patients presented with claw toe, hammer toe, crowed toes, hallux valgus (bunion), digitus quintus varus (bunionette), prominent metatarsal heads, high arch, flat feet, and Charcot neuroarthropathy.

In addition, we characterized DFUs by the number of lesion(s) (single or multiple), size, site, presence of gangrene, infection, and osteomyelitis. Size was measured by the longest diameter multiplied by the intersecting diameter at 90° (cm^2). We defined infection as the presence of warm skin, redness, swelling surrounding the wound, elevated values in white blood cells (>8000/μL) and C-reactive protein (>0.3 mg/dL). We diagnosed osteomyelitis with images of bone destruction from X-ray exam and/or decreased signal on T1 weighted images and increased signal on T2 weighted images of MRI. When both exam results were negative or not available but the ulcer depth reached the