論文の内容の要旨

論文題目　　Factors associated with diabetic foot ulcers and its prognosis
（糖尿病性足潰瘍関連因子とその予後の臨床学的検討）

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[Background] The diabetic population is increasing in rapid speed worldwide, especially in the low- and middle-income countries. Diabetic foot ulcers (DFUs) are one of the most devastating complications of diabetes which not only deteriorates quality of life of individuals, but also have substantial economical impact; hence lies a considerable need for identifying the high-risk population. Factors associated with DFUs are investigated by many studies, but results vary to quite an extent. I hypothesized these discrepancies were produced due to evaluating DFUs as one entity, while they could be distinguished into ischemic, neuropathic, and in-between condition of neuro-ischemic. Furthermore, their clinical characteristics, healing process, and outcome are not well documented for each of these ulcer types. There were also a very few studies that were performed in Asian context, which arose my concern for potential differences in risk factors according to race. The purpose of this study therefore, was 1) to identify factors associated with DFUs and to develop predicting models in which we can distinguish the high-risk patients, also with regards to the low- and middle-income countries where we are now starting to diagnose many patients, 2) to understand the different factors associated with ischemic, neuro-ischemic, and neuropathic DFUs, and 3) to estimate the healing time of DFUs according to types and to evaluate other factors associated with healing.

[Methods] A total of 152 patients with type 2 diabetes were recruited from the dermatology clinic and foot care center of the National Center for Global Health and Medicine, Tokyo, Japan. The study was divided into three sections according to each study objective. In Study 1, 61 patients who complicated with DFUs were compared to those without DFUs for the demographic factors, diabetes-related factors including blood parameters and peripheral circulation measurements, comorbidities, and diabetic foot problems to elucidate on the factors associated with DFU development. In Study 2,

DFUs were grouped into three ulcer types, namely, ischemic, neuro-ischemic, and neuropathic, and were compared for their differences for the same factors studied in Study 1. Sites of the ulcers were also recorded and analyzed. In Study 3, patients were followed up until healing and were analyzed for their outcome and healing time with regards to ulcer types. In addition, healed patients were compared against non-healed patients to observe the degree of role played by ischemia and neuropathy in healing process and to reveal other potential factors in wound healing delay.

[Results] The majority of study participants were men (n=109) with an average age of 65.7 (±11.7) years. This study confirmed the important roles of neuropathy, peripheral arterial disease (PAD), family history, lower hemoglobin, poor mobility, callus formation, and no periodical follow-up at health facilities in the cause of DFUs, and intake of oral anti-diabetic medication to have a reverse role against DFUs. When variables were removed to develop a predictive model with a vision to be used by health workers in resource-scarce settings, neuropathic symptoms emerged as one of the factors in place of neuropathy and PAD. Though not significant in the multivariate analysis, body mass index (BMI) level was lower in patients with DFUs. When the patients with DFUs were taken and classified into the three groups according to ulcer types in Study 2, 32 (52.5%) were neuropathic, 11(18.0%) were neuro-ischemic, and 18 (29.5%) were ischemic. Patients in the ischemic group were significantly older and had longer duration of diabetes compared to the other two groups. BMI were significantly lower in the ischemic group compared to the neuropathic group. In addition, marital status, poor mobility, and some comorbidities differed among the three groups. Of a total of 106 sites, toe was the most common location for ulcer formation in all three groups (65.1%), while it was most common in ischemic ulcers (70.6%). Approximately, half of the ischemic ulcers presented with multiple lesions. For Study 3, patients were followed up for until complete cure or from the time of recruitment until the end of study period (30 months). As a result, complete cure was observed significantly more in neuropathic ulcers compared to ischemic ulcers (p=0.033). Only half of the patients with ischemic ulcers reached complete cure, while it was a little over than a half for neuro-ischemic ulcers. A total of 7/61(11.5%) patients underwent amputation. All these cases were associated with infection, especially osteomyelitis were examined in 6(54.5%), and 5(71.4%) had PAD as an underlying condition. The average time during

which 50% patients were free from wounds was 36 days, 113 days, and 233 days for the patients with neuropathic, neuro-ischemic, and ischemic ulcers, respectively (p=0.002). When the healed ulcers were compared against the non-healed, the analysis demonstrated skin perfusion pressure (SPP) level, multiple lesions, size, gangrene, osteomyelitis, past history of myocardial infarction, and poor mobility to be the independent factors for wound healing.

[Conclusion] Many studies exist which investigated on the risk factors for lower limb amputations in patients with DFUs. Nonetheless, once a foot ulcer develops, it requires long and intensive treatment, as also observed in this study. Therefore, it is essential to detect the high-risk patients and intervene before he/she develops ulcers. This study elucidated several new factors such as neuropathic symptoms, family history, and hemoglobin levels to be associated with DFU development. Some discrepancies were present between this study results and those of previous studies from Western countries, which implied on the possibility of population diversities in risk factors. Also, the study identified non-classifying of DFUs according to its etiology to be a possible reason for several factors, such as age and BMI, to be producing controversial results for ulcer risk between studies. On top of this, the study demonstrated patients with both neuropathy and PAD were at higher risk than either complication alone to develop foot ulcer. These findings together suggest that target groups for intervention strategies for prevention of DFUs may have to be defined separately based on their complication with PAD and neuropathy or even according to racial group if relevant. Risk assessment scale to screen high-risk patients for DFUs, which could be adopted from thoroughly reviewing these kinds of studies, would also aid in this process. Such attempts are particularly in urgent demand in the low- and middle-income countries due to their notably increasing diabetic population. In addition, there is a need to understand and develop a risk assessment scale for the patients who already developed DFUs to identify those with higher risk for wound healing delay to provide them with the most appropriate treatment and care. With view to these possible future measures, further studies should be performed, especially prospective studies, aiming at defining these high-risk groups and their risk factors.