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RESEARCH ARTICLE

Clinical Correlates of the Severity of Diabetic Foot Ulcers

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Abstract

Objective: Severe diabetic foot ulcer leads to amputation and is associated with higher risk of mortality. The purpose of this study is to identify clinical correlates of severe diabetic foot ulcers. Methods: The design of the study was cross-sectional survey of medical records on patients treated in Sardjito Hospital from 1 January to 31 July, 2014. Severe foot ulcer was measured as grade 4 and 5 according to Wagner classification. ABI (Ankle Brachial Index) to estimate blood flow to lower extremities and Semmes-Weinstein test using monofilament to detect neuropathy, classified as positive or negative, were done in all patients. HbA1C, serum sodium and creatinine levels were measured during the latest hospital visit. Results: The results of this study showed that 77 (36.5%) among 211 patients had severe foot ulcers (grade 4 and 5, Wagner classification). ABI and Semmes-Weinstein monofilament test failed to predict severity of diabetic foot ulcers. HbA1c increased the odds of severe ulcers while higher serum sodium level and higher diastolic blood pressure protected patients against severe ulcers. Conclusion: Better glycemic control and caution against excessive reduction of diastolic blood pressure, usually due to anti-hypertension medication, should be recommended to prevent the development of severe foot ulcer.

Keywords: *Diabetic foot ulcers, Severity, Glycemic control, Hypertension, Poor circulation, Neuropathy.*

Introduction

Diabetes is increasing in Indonesia, with 5.6% prevalence among adults aged 15 years and older in urban areas in Indonesia [1, 2], and was estimated at 10.9% in 2018 [3]. Lower-limb amputation is one of the leading diabetic complications associated with poor quality of life and mortality [4, 5]. Diabetic foot ulcers have been shown to precede lower-limb amputation in more than 75% persons with diabetes [6, 7].

Around 7-20% of diabetic patients with foot ulcers subsequently undergo amputation [8]. The underlying causes of diabetic foot ulcers include peripheral neuropathy, peripheral vascular disease, trauma, and plantar pressures [9]. Peripheral sensory neuropathy, in the context of unperceived trauma, and autonomic neuropathy, causing dry skin with cracking and fissuring, are predisposing factors of ulceration and infection [10].Several factors, such as poor glycemic control, infection, vascular supply, smoking, and plantar pressure, may compromise the healing of diabetic foot ulcers [11].

Clinical parameters, such as poor creatinine clearance [12], lower HDL cholesterol [13], presence of gram positive bacteria [14], elevated HbA1c [15] were known to increase the risk of amputations. The purpose of this study is to identify clinical factors associated with the severity of diabetic foot ulcers, known to have an independent impact on lower extremity amputation and mortality risk [16].

Materials and Methods

Design of the Study

This study is a cross-sectional, hospital-based survey of medical records, available at Dr. Sardjito Hospital, a government owned, tertiary, teaching hospital at Yogyakarta, Indonesia. The hospital is under the supervision of the Ministry of Health, but is affiliated with the Medical School of Gadjah Mada University.

Study Subjects

Subjects of the study consist of 211 diabetic patients with foot ulcers, treated at Dr. Sardjito Hospital, Yogyakarta, Indonesia from January 1 to 31 July 2014.

Data Collection

For the purpose of this study, data were extracted from medical records containing laboratory and clinical test results associated with the ulcers. The dependent variable, which is the severity of diabetic ulcers, was measured according to Wagner [17], graded from 1 (superficial skin or subcutaneous tissue), 2 (ulcers extend into tendon, bone or capsule), 3 (deep ulcer with osteomyelitis or abscess), 4 (gangrene to portion of forefoot), and 5 (extensive gangrene of foot).

For the purpose of data analyses, grade 4 and grade 5 were considered as severe ulcer. Independent variables were age (years), sex (female and male), education (junior high or below and high school or above), monthly income (below 2.5 million or 2.5 million rupiah or above). Clinical variables include onset of ulcer (weeks), systolic and diastolic blood pressure (mmHg), HbA1c (glycated hemoglobin measured in %), white blood count, serum levels of creatinine, ureum, albumin, and sodium, ABI (ankle brachial index, less than 0.9 or greater than 1.4 indicates vascular problems), and Semmes-Weinstein monofilament test result (positive or negative). ABI (ankle-brachial index) [18] and Semmes- Weinstein monofilament tests [19] indicate peripheral vascular disease and peripheral neuropathy respectively.

Data analyses

The purposes of data analyses were to estimate crude and adjusted odds ratio of developing severe diabetic ulcer (grade 4 and 5 according to Wagner). Simple and multiple logistic regressions were used to identify independent variables with statistically significant odds ratios for the development of severe foot ulcer.

Ethics statement

This study protocol was approved by Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada, Dr. Sardjito General Hospital (Reference number : KE/FK/0145/EC/2020).

Results

The prevalence of patients with severe ulcer (grade 4 and 5, Wagner classification) is 77/211 (26.5%). Demographic variables indicated that gender, age, education and monthly income were not associated with severity of foot ulcer (Table 1).

Table 1: Crude effects of demographic variables on the severity of diabetic foot ulcer

Demographic variables		Not severe	Severe	Odds Ratio	p value
Age (years)	Less than 60	80	55	1.69	0.09
	60 or above	54	22	1.00 (reference)	
Gender	Male	68	37	0.90	0.71
	Female	66	40	1.00 (reference)	
Education (level)	Junior High or below	76	42	0.92	0.76
	High School or more	58	35	1.00 (reference)	
Monthly income (rupiah)	Less than 2.5 million	74	47	1.27	0.41
	2.5 million or higher	60	30	1.00 (reference)	

To estimate the effect of each clinical independent variable on the occurrence of severe diabetic foot ulcer, a simple logistic regression was carried out for each variable (Table 2). Variables with crude odds ratio at p-value 0.1 or less were included in multiple logistic regression analyses. Onset of ulcer, diastolic pressure, HbA1c level, creatinine, white blood count and sodium level showed odds ratios with p value 0.10 or less.

Multiple logistic regressions (Table 3) indicate that sodium level in the serum and higher diastolic blood pressure protect against severe foot ulcer, while the level of glycosylated hemoglobin (%) increases the risk for severe foot ulcer. Reduced sodium level may be attributed to hyperglycemia, which produces osmotic diuresis and causes a dilutional effect on electrolyte concentration [20]. There is inverse relationship between blood glucose and serum sodium levels [21].

Decreased diastolic pressure is associated with lower perfusion to diabetic ulcer [22], therefore potentially hinders the healing of the ulcer. Diastolic blood pressure lower than 70 mmHg increases cardiovascular risk [23].Intensive blood glucose control is recommended despite the lack of strong evidence of its effectiveness in the healing of diabetic foot ulcers [24]. Poor glycemic control, represented as higher HbA1c level, is associated with severe foot ulcer in this study. Good glycemic control is essential to prevent amputation [25].

Table 2: Crude odds ratio of clinical variables on the severity of diabetic foot ulcer*

Independent Variables	Mean for Non Severe	Mean for Severe	Odds Ratio	p-value
Duration of diabetes (years)	8.7	8.8	1.00	0.88
Body Mass Index	23.1	22.8	0.98	0.61
Blood pressure				
Systolic (mmHg)	138.6	134.1	0.99	0.12
Diastolic (mmHg)	83.0	81.1	0.96	0.02
Pulse Pressure (mmHg)	55.0	53.1	0.99	0.39
Glycemic control				
HbA1c (%)	7.8	8.4	1.12	0.07
Renal impairment				
Creatinine (mg/dl)	2	1.6	0.87	0.10
Ureum (mg/dl)	33	28.6	0.99	0.31
Albumin (g/dl)	2.5	2.4	0.84	0.36
Blood count				
White Blood Count (1000 / □l)	15.7	18.4	1.04	0.03
Peripheral vascular disease				
ABI	13.1	9.9	0.99	0.69
Serum electrolyte				
Sodium (mmol / liter)	133.8	131.1	0.93	0.003

*Proportion of positive Semmel-Weinstein test for neuropathy for those with non-severe diabetic foot ulcer is 0.90, and for those with severe diabetic ulcer is 0.88. Odds ratio for severity of diabetic foot ulcer is 1.13 (p value = 0.78)

Table 3: Adjusted effects odds ratios (OR) of clinical variables on the severity of diabetic foot ulcer

Independent Variables	Logistic Regression			
	Model 1 OR (p value)	Model 2 OR (p value)	Model 3 OR (p value)	Model 4 OR (p value)
Sodium (mmol / liter)	0.94 (0.025)	0.94 (0.025)	0.93 (0.003)	0.93 (0.004)
Diastolic pressure (mmHg)	0.96 (0.020)	0.96 (0.019)	0.96 (0.025)	0.96 (0.029)
Creatinine (mg/dl)	0.79 (0.057)	0.79 (0.054)	0.82 (0.085)	-
White Blood Count (1000/ml)	1.04 (0.060)	1.04 (0.078)	-	-
HbA1c (%)	1.13 (0.063)	-	-	-

Discussion

The findings in this study support the role of sodium as protective factor against severe foot ulcer. Hyponatremia has been implicated as the most common electrolyte abnormality among people with diabetes, and the condition is responsible for an increased diabetic morbidity and mortality [26]. Significant decrease of sodium and magnesium was found among people with diabetes compared to those with normal regulation of glucose [27]. There is inverse association between serum sodium level and blood glucose in people with diabetes, due to

Na^+ correction factor to achieve osmotic equilibrium [28]. Hyponatremia could potentially reflect uncontrolled hyperglycemias, which predict all-cause mortality in stable patients undergoing hemodyalisis [29]. In this study the level of HbA1c was significantly associated with the severity of foot ulcer, although only marginally significant ($p = 0.07$).Elevated serum creatinine level was not associated with severe foot ulcer ($p = 0.1$) in this study.

The findings did not support those found in Iran [30], where elevated serum creatinine was strongly associated with increased risk of lower extremity amputation. Reduced creatinine clearance hindered wound healing of diabetic foot ulcer [31]. Diastolic blood pressure was significantly lower among diabetics with foot ulcer compared to those without foot ulcer in this study, similar to the findings in China [32].

The findings in this study did not support the significant effect of pulse pressure on the severity of foot ulcer, as other studies identified pulse pressure as a risk factor for the incidence of foot ulcer [33]. Two important determinants of severe foot ulcer are glucose control and blood perfusion to the lower limb. Blood glucose level is represented by the HbA1c proportion (%) and blood natrium level. Low diastolic pressure indicates inadequate blood perfusion to the feet and ankles.

Conclusion

Severe diabetic foot ulcer is more likely when glycemic control is poor, and sodium level in the serum is lower. It is not known whether the effect of sodium level on the healing of ulcer is concomitant or independent to the glycemic level. The diastolic pressure is a significant determinant of severe diabetic foot ulcer, as poor tissue perfusion may prevent healing of the ulcer. The results of this study were consistent with the recommendation to control blood sugar level effectively and to exercise caution against too tight lowering of blood pressure with excessive diastolic pressure reduction.

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