The Correlation Between Duration of Diabetes Mellitus, Ulcer Grading, HbA1C Levels, and Peripheral Arterial Occlusion to Amputation in Patients with Diabetic Foot Ulcers at Prof. Dr. I.G.N.G Ngoerah Hospital

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ABSTRACT

Background: Diabetic foot ulcers (DFU) are a lower extremity manifestation often associated with morbidity and mortality due to diabetes mellitus. Diabetic foot ulcers arise from chronic pathological processes such as neuropathy, peripheral arterial disease (PAD), biomechanical issues, and impaired wound healing. Even with proper treatment, DFUs can eventually lead to serious complications such as infection, amputation, and even death. The risk factors that contribute to the determination of amputation in patients with diabetic foot ulcers are still debated. *Objective:* This study aims to determine which factors (duration of DM, ulcer grading, HbA1C level, and peripheral artery occlusion) have the most influence on amputation in DFU patients at Prof. Dr. I.G.N.G Ngoerah Hospital Denpasar. *Methods:* This study is an analytic observational study, with the design used being a retrospective cohort. The sample was 90 patients with diabetic foot ulcers diagnosed at Prof. Dr. I.G.N.G Ngoerah Hospital from January 2022 to December 2023. Statistical analysis was performed with SPSS ver 20.0 for univariate, bivariate, and multivariate tests. *Results:* Patient amputation in diabetic foot ulcer patients was associated with HbA1c levels, ulcer grading, and occlusion by 81.44% (p value: 0.046; OR 2.9; IK 0.99-8.59) for HbA1c >6.5, 98.6% (p value 0.001; OR 17.2; IK: 1.80-164.94) for Wagner ulcer grading 3-5, and 95.7% (p value 0.000; OR 22.3; IK: 0.56-4.17) for occlusion. Meanwhile, DM duration <10 years performed amputation for 61.4% (p value 0.088; OR 0.4; IK: 0.15-1.15). *Conclusion:* HbA1c level, ulcer grading, and occlusion were associated with amputation in diabetic foot ulcer patients, while DM duration was not associated with amputation. The adj value (OR) found that Wagner 3-5 ulcer grading had the most dominant influence compared to other variables, with an OR value of 34.4. This indicates that ulcer grading can predict amputation as much as 34.4 times.

Keywords: diabetic foot ulcer; HbA1c; ulcer grading; peripheral arterial occlusion; amputation.

INTRODUCTION

Diabetic foot ulcers (DFU) arise from chronic pathological processes such as neuropathy, peripheral arterial disease (PAD), biomechanical issues, and impaired wound healing. Although patients with diabetic foot ulcers have a high early mortality rate, patients have been shown to fear major amputation more than death. One of the most common problems in the care of diabetic patients is diabetic foot ulcers, with studies reporting an average annual incidence of 2.2%.

A European study group found that up to 5% of diabetic patients with UKD require a major amputation within 1 year (Lim, Ng, *and* Thomas, 2017).

The etiology of diabetic foot ulcers is multifactorial and includes complications of diabetic neuropathy, vasculopathy, immunopathy, and poor glycemic control. Diabetic neuropathy causes sensory, motor, and autonomic nerve dysfunction and is the most common cause of diabetic lower extremity ulcers.

Peripheral arterial disease is commonly seen in combination with neuropathy in the diabetic population and can contribute to foot complications. Approximately 50% of patients with diabetic foot disease have some degree of PAD. Endothelial damage and sclerosis of large and small blood vessels lead to decreased peripheral perfusion. This puts patients at increased risk of ulceration and leads to impaired wound healing and the ability to fight infection (Everett and Mathioudakis, 2018; Volmer-Thole *and* Lobmann, 2016).

Even with proper management, infections can be difficult to control, and patients should be counseled about the possibility of amputation. Amputation is the removal of a non-viable limb and should be considered in patients with uncontrolled infections or non-healing wounds. Studies have shown that infection is an independent risk factor for minor amputation (odds ratio: 1.56, CI 1.05-2.30), and more than 20% of moderate or severe DFIs eventually lead to amputation. Although the morbidity associated with amputation is great, certain patients can significantly improve their quality of life after amputation. In addition, amputation can provide a better chance of recovery compared to multiple salvage attempts on a sick patient (Weledji *and* Fokam, 2014).

METHODS
This study is an analytic observational study, with the design used being a retrospective cohort. The sample was 90 patients with diabetic foot ulcers diagnosed at Prof. Dr. I.G.N.G Ngoerah Hospital during January 2022 to December 2023. The inclusion criteria in this study are 1) Patients with diabetic foot ulcers at Prof. Dr. I.G.N.G Ngoerah Hospital in the period January 2022 to December 2023. 2) Patients with diabetic foot ulcers who underwent amputation at Prof. Dr. I.G.N.G Ngoerah Hospital. 3) Patients with diabetic foot ulcers who did not undergo amputation at Prof. Dr. I.G.N.G Ngoerah Hospital. 4) Patients with diabetic foot ulcers who have undergone arteriography. The exclusion criteria in this study are 1) Patients with diabetic foot ulcers at Prof. Dr. I.G.N.G Ngoerah Hospital outside the period January 2022 to December 2023. 2) Patients with diabetic foot ulcers who did not undergo arteriography at Prof. Dr. I.G.N.G Ngoerah Hospital. 3) Patients with diabetic foot ulcers who do not have data according to the independent and dependent variables. Statistical analysis was performed with SPSS ver 20.0 for univariate, bivariate, and multivariate tests.

RESULTS
Description of the Research Subjects
This study involved 40 research subjects, who were peptic ulcer patients who underwent surgery at Prof. Dr. I.G.N.G. Ngoerah Hospital. Respondent characteristics were described based on age, gender, albumin levels, creatinine levels, ASA scores, and comorbid diseases. The data are presented in Table 1.

TABLE 1: Characteristics of Peptic Ulcer Patients Undergoing Surgery Based on Amputation Outcomes.

Variable	Amputation procedure		*p*
	Amputation (n=70)	No amputation (n=20)	
Age (mean ± SD)	64,04 ± 1,04	56,30±2,60	0,002*
Gender (n, %)			
Male	34 (37,8%)	9 (10%)	0,778**
Female	36 (40%)	11 (12,2%)	
Comorbid diseases (n, %)			
Present	35 (38,9%)	10 (11,1%)	1,000**
Absent	35 (38,9%)	10 (11,1%)	
HDL cholesterol (mean ± SD)	30,34 ± 1,56	33,60±3,85	0,364*
Platelet levels (mean ± SD)	419,69± 17,44	408,40±34,47	0,764*
Hematocrit levels (mean ± SD)	29,88 ± 0,81	31,64 ± 1,08	0,155***
Albumin levels (mean ± SD)	2,7 ± 0,09	3,1 ± 0,13	0,032*
Revascularization history (n, %)			
Yes	39 (43,3%)	9 (10%)	0,397**
No	31 (34,4%)	11 (12,2%)	
Duration of DM (mean ± SD)	8,45±0,79	8,15 ± 1,02	0,726***
Ulcer grading (n, %)			
Wagner 1	0 (0%)	0 (0%)	
Wagner 2	1 (1,1%)	4 (4,4%)	
Wagner 3	11 (12,2%)	10 (11,1%)	0,000**
Wagner 4	42 (46,7%)	6 (6,7%)	
Wagner 5	16 (17,8%)	0 (0%)	
HbA1C (mean ± SD)	8,41±0,27	8,02±0,64	0,264***
Arteriography (n, %)			
Occlusion	34 (37,8%)	8 (8,9%)	
Stenosis	33 (36,7%)	6 (6,7%)	0,003**
Normal	3 (3,3%)	6 (6,7%)	

Bivariate Analysis

Bivariate analysis aims to determine the relationship between independent variables, namely DM duration, ulcer grading, HbA1C, and arteriography results, on the incidence of amputation.

TABLE 2: Bivariate Analysis of Factors Associated with Amputation in Diabetic Foot Ulcer Patients.

Variable	Amputation		OR	CI 95%	p
	Yes	**No**			
Duration of DM					
≥ 10 tahun	27 (38,6%)	12 (60%)	0,4	0,15-1,15	0,088*
< 10 tahun	43 (61,4%)	8 (40%)			
Ulcer grading					
Wagner 3-5	69 (98,6%)	16 (80%)	17,2	1,80-164,94	0,001*
Wagner 1-2	1 (1,4%)	4 (20%)			
HbA1C					
> 6,5	57 (81,4%)	12 (60%)	2,9	0,99-8,59	0,046*
≤ 6,5	13 (16,6%)	8 (38,1%)			
Arteriography					
Abnormal (stenosis/ occlusion)	67 (95,7%)	10 (50%)	22,3	5,23-95,32	0,000*
Normal	3 (4,3%)	10 (50%)			

The table shows that DM duration < 10 years was found to be amputated by 61.4% compared to ≥ 10 years (38.6%). With a p-value of 0.088 > 0.05 and OR 0.4 (IK: 0.15-1.15). This indicates that the duration of DM is not associated with amputation in diabetic ulcer patients. Ulcer grading obtained Wagner 3-5 as much as 98.6% performed amputation with a p-value of 0.001 < 0.05 and OR 17.2 (IK: 1.80-164.94), so ulcer grading is associated with amputation. The HbA1c value obtained > 6.5 was 81.44% higher than the HbA1c value ≤ 6.5, with a p-value of 0.046 and OR 2.9 (IK 0.99-8.59), meaning that there is a significant relationship between HbA1c values and amputation.

Abnormal arteriography (stenosis and occlusion) resulted in 95.7% amputations with a p-value of 0.000 <0.05 and OR 22.3 (IK: 0.56-4.17), meaning that there is a significant relationship between abnormal arteriography results and amputations in diabetic foot ulcer patients.

Multivariate Analysis

Multivariate analysis aimed to determine the effect of independent variables (DM duration, ulcer grading, HbA1C, arteriography results) when entered into the test together. The p-value <0.25 in the bivariate analysis was included together. Multivariate analysis in this study was performed with logistic regression. The omnibus test results obtained a p-value of 0.000, and the Hosmer and Lameshow test results obtained a p-value of 0.989, meaning this test model is fit for use. The classification table obtained 87.8%, which means that the test model used in predicting the variables of DM duration, ulcer grading, HbA1c, and arteriography results on the variable incidence of amputation of diabetic foot ulcer patients is 87.8%.

TABLE 3: Multivariate Logistic Regression Analysis of Factors Influencing Amputation in Diabetic Foot Ulcer Patients.

Variable	B	Adj (OR)	CI 95%	p
Age	1,39	4	0,95-17,21	0,058
Albumin	0,59	1,8	0,37-8,68	0,461
Duration of DM	-1,03	0,3	0,09-1,40	0,140
HbA1C	0,77	2,1	0,493-9,59	0,304
Ulcer grading	3,54	34,4	2,67-444,68	0,007
Arteriography	3,26	26,2	5,45-126,26	0,000

The table shows that positive B-value variables were found in age (p=0.058), albumin (p=0.461), HbA1C (p=0.304), ulcer grading (p=0.007), and arteriography (p=0.000), while DM duration (p=0.140) had a negative B-value. The results showed that ulcer grading and arteriographic examination were obtained with a p-value <0.05, meaning that these two variables had an effect on the amputation of diabetic foot ulcer patients. The adj (OR) value was found that Wagner 3-5 ulcer grading had the most dominant influence compared to other variables, with an OR value of 34.4. This indicates that ulcer grading can predict amputation as much as 34.4 times.

DISCUSSION

Characteristics of the Research Subjects

The results of the study found that the mean age of diabetic foot ulcer patients who were amputated was 64.04 years. The results of the study by Korkmaz et al (2021) found that the average age of patients was 60.69 years, and no statistically significant differences were found between groups in terms of age, gender, amputated side, duration of

DM, HbA1C, and albumin levels. Lu & Wang's (2021) study also found that the age range of patients with diabetic foot ulcers who underwent amputation ranged from 66 to 75 years. Similar research found that the average age of patients was 63.2 years (SD: 12.2) with an age range of 27 to 96 years (Moon et al., 2019). Although Orneholm et al (2015) reported that age ≥ 67 years was associated with healing without major amputation in diabetic patients with foot ulcers, and age was not a risk factor for major amputation in diabetic patients with foot ulcers (p = 0.433).

The characteristics of subjects based on gender found that more women were amputated than men, but this was not statistically significant. Different results were found in Lu & Wang's (2021) study that men with diabetic foot ulcers had more amputations, 75.5%. Men are known to have limited joint mobility and higher foot pressure. Higher average HbA1c and neuropathic peripheral insensitivity are more common in men (Cheng et al., 2006). In contrast, women may be more self-concerned and have a positive mood in being more active in wound care, whereas men may express fear, negative attitudes, and behave in a non-cooperative manner (Hjelm et al., 2002; Neto et al., 2013).

The history of comorbid diseases was found to be the same between the amputation group and the non-amputation group. Lu & Wang's research (2021) also found no effect of comorbidities on amputation (p>0.05). Nouira et al (2023) found that 58% of patients undergoing amputation suffered from hypertension. Patients with comorbid diseases can increase the risk of amputation (Rodrigues et al., 2016). Comorbid factors can worsen the condition of the diabetic foot, and hypertension is the most common comorbid factor (Irawan & Mulawardi, 2020). The most common cause of death in diabetic patients who have undergone amputation is cardiovascular disease, followed by sepsis (Yuzuguldu et al., 2023).

HDL cholesterol levels were found in the amputation group with lower mean HDL levels (30.34; SD 1.56), while the non-amputation group with a mean of 33.60 (SD: 3.85). Nouira et al (2023) found that 70% (n=12) of patients with diabetic foot ulcer amputation had low-density protein cholesterol levels above the target value. Hypercholesterolemia increases the risk of amputation by 1.7 times (Yuzuguldu et al., 2023).

Platelet levels were obtained in the amputation group with higher mean platelet levels (419.69; SD 17.44), while the non-amputation group with a mean of 408.40 (SD: 34.47). Thrombocytosis can lead to atherosclerotic plaque progression (atheroprogression) and thrombotic complications associated with plaque rupture (Lee et al., 2017). In addition, circulating platelets in diabetic patients are hyperreactive to agonist stimuli and are more likely to form aggregates with circulating leukocytes, thereby promoting inflammation (Kakouros et al., 2011; Moon et al., 2019).

Albumin levels were found in the amputation group with lower mean albumin levels (2.7 SD; 0.09) while the non-amputation group with a mean of 3.1 (SD; 0.13). Similar results were found in the study of Zhou et al (2015), albumin with a mean of 2.89, which was amputated, and 3.3, which was not amputated. Hypoalbuminemia is a major factor in wound healing (Everett et al., 2019; Sadriwala et al., 2018). Albumin levels of less than 3.5 on the first day were seen in 42 people (84%), and low albumin levels can be considered a marker of lower limb amputation (Mohan et al., 2021).

Characteristics based on revascularization history were higher in the amputation group (43.3%) compared to non-amputation, but were not statistically significantly different between the two groups (p = 0.397). The majority (70%) of people with amputation underwent endovascular revascularization procedures before amputation was performed (Rosien et al., 2023).

The duration of DM was found in the amputation group with a longer mean duration of DM (8.45 SD; 0.79) while the non-amputation group had a mean of 8.15 (SD: 1.02). The duration of DM in the study by Korkmaz et al (2021) was found to be an average of 12.49 years (SD: 6.61). Different results were also found in Lu & Wang's research (2021), which stated that the duration of diabetes was between 15.2 years and 15.53 years. According to Nouira et al (2023), the average duration of diabetes is 17 years of age older than 50 years. There are more patients with diabetes duration of more than 10 years than with shorter diabetes duration (Andhika & Ismiarto, 2020).

Based on the grading of ulcers, the most Wagner 4 was 42 people (46.7%), and was significantly different between the amputation group and the non-amputation group. Lu & Wang's research (2021) also found that Wagner 4 grading was the highest at 46%. The degree of diabetic foot ≥4 (4 or 5) according to Wagner's classification was found in 24% of amputated patients (Nouira et al., 2023). Sadriwala et al (2018) reported that Wagner's degree was strongly associated with amputation.

HbA1c values were obtained by the amputation group with a higher mean HbA1c (8.41; SD 0.27) while the non-amputation group with a mean of 8.02 (SD; 0.64). Similar results were found in the study of Zhou et al (2015), which stated that the average HbA1c (%) was higher, ranging from 8.3 to 12.5 in the amputation group, while in the non-amputated group it was 7.4 to 11.3. Low levels of HbA1c are a risk factor for amputation in patients with diabetic foot ulcers (Moon et al., 2019). Different results in the study of Korkmaz et al (2021) HbA1c with a mean of 4, 93 (SD: 4.18). Characteristics based on the results of arteriography found more stenosis and occlusion results compared to normal results, statistically significantly different between the two groups (p = 0.003).

Relationship between DM duration and amputation in diabetic foot ulcer patients

The results showed that the duration of DM < 10 years performed amputation by 61.4% compared to ≥ 10 years (38.6%). DM duration is not associated with amputation in diabetic ulcer patients. Similar results were also found in the research of Yusof et al (2019), which stated that diabetic foot ulcer patients with a duration of < 10 years were found to have more amputations (55.6%), and there was no relationship between DM duration and amputation with a p-value of 0.647.

A study by Nyamu et al (2003) found a greater risk of recurrent ulcers in patients who had diabetes for three years, recorded at 35-40% and 70% had diabetes for 5 years. Long duration of diabetes was found to be a predictor for diabetes-related amputation (Davis et al., 2006; Shatnawi et al., 2018). Insulin requirements in controlling type 2 diabetes tend to increase with longer duration of diabetes, and it is an independent predictor factor for major amputation (Davis et al., 2006; Pscherer et al., 2012). Research by Rosien et al (2023) found the mean of amputated patients with DM duration was 11.6 years, and there was a significant difference between the amputated and non-amputated groups.

Relationship between ulcer grading and amputation in diabetic foot ulcer patients

The ulcer grading obtained by Wagner 3-4 as much as 98.6% performed amputation with a p-value <0.05 and OR 17.2 (IK: 1.80-164.94), so that ulcer grading is related to amputation. In line with the opinion of Nouira et al (2023) that the degree of diabetic foot ≥4 according to Wagner's classification is a predictive factor for amputation (Lin et al., 2020). Most patients with advanced Wagner classification (3-5) have poorly managed diabetes, with peripheral neuropathy and peripheral vasculopathy being significant predictors of diabetic foot ulcers (Armstrong et al, 2017).

The Wagner classification system is the most widely validated classification system for diabetic foot ulcer outcome prediction. Research conducted by Sadriwala et al (2018) reported that Wagner's degree was strongly associated with amputation compared to other risk factors on multivariate analysis (Edakkepuram et al., 2017; Sadriwala et al., 2018; Surriah et al., 2019).

Wagner grading at diagnosis is a major risk factor for amputation that allows for the prediction of prognosis. Each unit increase in Wagner grade increased the probability of amputation by 2.233 times (95% CI 1.947-2.561; p<0.001). Similar results were found in previous studies that have shown that the Wagner score is directly correlated with increased amputation risk (Oyibo et al., 2001; Teresa et al., 2016). Patients with Wagner grade 4 and 5 gangrene were 4.5 times more likely to require amputation than non-gangrenous patients. Wagner grade is an important clue to the presence of gangrene in determining amputation risk.

This finding is similar to studies in Nigeria (OR 5.953) and Ethiopia (OR 4.7) (Bekele & Chelkeba, 2020; Ugwu et al., 2019).

Relationship between HbA1c Level and Amputation in Diabetic Foot Ulcer Patients

The results showed that the HbA1C value was obtained> 6.5 as much as 81.44% with a p-value of 0.046 and OR 2.9 (IK 0.99-8.59), meaning that there is a significant relationship between the HbA1C value and amputation. In line with research by Moon et al (2019) found that serum HbA1c levels are a risk factor for amputation with OR 0.570 and p = 0.008. Likewise, research by Kusuma et al (2018) states that HbA1C> 6.5 is a risk factor for amputation in diabetic foot ulcer patients.

HbA1c is an important serum marker for monitoring the level of glucose control in diabetic patients. Total (Zhou et al., 2015). HbA1c can be used as a parameter of DM because it has a strong correlation with blood glucose. Dwikayana et al in 2017 concluded that diabetes control based on HbA1c picture tends to lead to poor diabetes control.

Low HbA1c levels are associated with amputation in diabetic foot ulcer patients. This is counterintuitive as chronic hyperglycemia is known to impair wound healing in diabetic patients. One possible reason may be that the unknown hypoglycemia may cause a stress response that impairs wound healing through immune dysregulation (Godbout & Glaser, 2006; Moon et al., 2019).

The results of Lu & Wang (2021) showed that HbA1c was associated with amputation risk with OR: 1.23 and p value = 0.03), the average HbA1c was 8.80 in major amputation and 8.10 in minor amputation, and there was no difference in DM duration. Regarding the influence of HbA1c level, previous studies reported conflicting results. Yesil et al. found diabetes duration and HbA1c were not risk factors predicting overall amputation in patients with diabetic foot ulcers (Yesil et al., 2009). However, HbA1c was a risk factor for major amputation (Moon et al., 2019).

Relationship between occlusion and amputation in diabetic foot ulcer patients

The results showed that abnormal arteriography results (stenosis and occlusion) resulted in 95.7% amputation with a p-value of 0.000 <0.05 and OR 22.3 (IK: 0.56-4.17), meaning that there is a significant relationship between abnormal arteriography results and amputation in diabetic foot ulcer patients. Multivariate results also showed that arteriography was the dominant factor for amputation. Intra-arterial angiography as the gold standard for arterial imaging due to its high spatial resolution. It allows endovascular therapy during the same procedure and is highly accurate for small vessels in the ankle and foot (Akkus & Sert, 2022).

Angiographic evaluation can also provide prognosis information. By assigning a score that considers the stenosis found through angiography in terms of

extent of (percentage reduction of the vessel lumen) and diffusion (involving the vessel segment), it is possible to obtain a numerical index. Arteriography has become the gold standard for investigation, but it is an invasive, relatively expensive examination with little morbidity and mortality. However, arteriography also carries certain risks, such as intense reactions to contrast material, decreased renal function, and local complications (dissection, atheroembolism, or access site-related problems such as bleeding, pseudoaneurysms, or arteriovenous fistulas) (Serrano Hernando & Conejero, 2007).

Multivariate analysis showed that the arteriography result was the independent variable associated with amputation. Evaluation of the extent of stenosis in the popliteal and infrapopliteal arteries is very important when there is total occlusion of >2 of each artery, the probability of amputation is very high (Faglia et al., 1998). Effective revascularization in patients with peripheral arterial disease is more than just a procedure. The approach to patients with symptom-limiting intermittent claudication or limb-threatening ischemia begins with an understanding of the population at risk and variations in clinical presentation. The urgency of revascularization varies greatly based on symptoms from patients with intermittent claudication who should undergo structured exercise rehabilitation prior to revascularization (if required) to those with acute limb ischemia, medical emergencies requiring revascularization within hours (Beckman et al., 2021).

CONCLUSIONS

HbA1c level, ulcer grading, and occlusion were associated with amputation in diabetic foot ulcer patients, while DM duration was not associated with amputation. The adj value (OR) found that Wagner 3-5 ulcer grading had the most dominant influence compared to other variables, with an OR value of 34.4. This indicates that ulcer grading can predict amputation as much as 34.4 times.

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