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Research paper

Clinical profile and laboratory finding of diabetic foot ulcers from tertiary hospitals in Bali

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Abstract

Introduction: Diabetic foot ulcer (DFU), as one of the chronic non-healing wounds, causes a significant financial burden on the healthcare system worldwide. Chronic wounds usually exhibit powerful pro-inflammatory stimuli, as seen in laboratory results.

Aim: For this reason, we conducted an observational study to obtain the clinical profile, hematological profile, and biochemical profile from our DFU patient laboratory examinations.

Material and methods: This study was a retrospective descriptive study conducted between March 2016 and December 2018 in Sanglah Hospital, Bali which included a total of 113 patients. The variables included in this study consisted of DFU clinical status, treatment procedures, and laboratory results. We further divided the laboratory results into two groups, haematological and blood chemistry profile. All numerical data were summarized as mean ± standard deviation, and categorical variables were summarized as frequency and percentage.

Results and discussion: The mean patient's age was 55.68 ± 10.52 years old. The most of patients were male (54.9%). Leukocytosis was observed in these patients (13.80 ± 6.48 × 10^9/L) and neutrophil dominated the white blood differential count. There were 35 patients (30.97%) with creatinine levels above 1.3 mg/dL, 73 patients (64.6%) with random blood glucose above 180 mg/dL, and 78 patients (67.3%) with HbA1c levels higher than 53 mmol/mol, even 33 patients (29.2%) with HbA1c more than 86 mmol/mol.

Conclusions: Some laboratory values have a significant meaning in diabetic foot patients, which can become instruments for the physician in diagnosing, select the most effective treatment, and predict outcome or complications in DFU patients.

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1. INTRODUCTION

Diabetes mellitus is the most common endocrine disease among adults, which affect millions of people in the entire world. In the past three decades, diabetes mellitus, primarily type 2 diabetes mellitus and its complications have reached epidemic levels, particularly in developing countries, such as Indonesia.[1] The International Diabetes Federation (IDF) Diabetes Atlas provides data in 2015, Indonesia was ranked number 7 of the country with the most significant number of diabetic people, approximately 10 million people affected. In 2040, Indonesia is expected to have 16.2 million people affected with diabetes mellitus.[2] There are several clinical importance and complications of diabetes, which involve many target organs, including vascular and neurological problems. Foot complications are among the most severe and costly complications of diabetes mellitus, which contributes to diabetic foot ulcer.[3]

Diabetic foot ulcer (DFU) poses a growing global public health challenge and becomes a significant financial burden on every healthcare system in the world.[4] The incidence of DFU is up to 25% over a patient's lifetime. Foot ulcers occur in 15%–25% of people with diabetes, which equates to slightly more than 2% annually and between 5%–75% of those patients with neuropathy and vascular complications.[5] The etiology of diabetic foot ulceration is a well-understood, but a multifactorial and complicated process. There are three main risk factors which contribute at developing foot ulcers, consist of vascular insufficiency, neuropathy, and infection.[4] If these risk factors are not treated properly, it can lead to lower extremity amputation, or worse, and death.[6]

As one of the chronic non-healing wounds, DFU consists of numerous common factors that promote adverse wound healing conditions. By definition, chronic wounds are injuries that fail to be processed through regular and timely reparations to produce anatomy, and functional integrity for 3 months. Several systemic factors, including malnutrition, ageing, tissue hypoxia, and high blood glucose, contribute significantly to the chronic wound's pathogenesis in DFU.[7] Uncontrolled blood glucose levels result in increased inflammation, reduced angiogenesis, and collagen synthesis, all of these induced chronic wound healing formation.[8] Chronic wounds typically exhibit powerful pro-inflammatory stimuli, including bacterial colonization, necrotic tissue formation, foreign bodies, and localized tissue hypoxia. Chronic wounds in DFU have high bacterial counts, which stimulates an inflammatory host response with PMNs (polymorphonuclear cells) expressing reactive oxygen species and proteases, resulting in a highly pro-oxidant environment. Disturbed oxidant balance is the crucial likely factor in the persistence of the inflammatory phase in chronic wounds.[7]

2. AIM

For this reason, we conducted an observational study of patients with DFU who were admitted to our hospital for treatment. This study aim is to obtain the clinical profile, hematological profile, and biochemical profile from DFU patient and discuss every aspect, which contributes delayed wound healing and associated treatment. This study can also describe real feature from DFU patients which can be seen in a developing country, particularly from tertiary hospitals in Bali, Indonesia. In the future, we hope this study can become a reference for the further improvement of diabetic foot management and other research related to diabetic foot problems.

3. MATERIAL AND METHODS

This study was a retrospective descriptive study reviewing the medical records of diabetic foot patients who were admitted to Sanglah General Hospital for surgical procedure. Sanglah General Hospital is a provincial hospital located in Denpasar, Bali, which is the central referral hospital in Bali and Nusa Tenggara islands as known as a tertiary hospital. Patients with the diverse degree of diabetic foot complications are referred to this hospital and many come from other hospitals within and around Denpasar. This study was conducted between March 2016 and December 2018, with a total of 113 patients with DFU. All DFU patients who underwent surgical procedures in Sanglah General Hospital operating theatre were included in the study. All patient medical records were provided by the Sistem Informasi Manajemen Rumah Sakit Umum Pusat Sanglah (SIMARS), our hospital information center system. A diagnosis of diabetes mellitus was defined and confirmed from International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) code E11.622 for 'Type 2 Diabetes Mellitus with other skin ulcers.' Data which we collected from SIMARS were further addressed into different aspects, which comprised of personal data, DFU severity, diabetes mellitus duration, foot ulcer duration, treatment procedures, and laboratory results. Based on our primary objective of this study, we divide the laboratory results into two groups, hematological and blood chemistry profile. The variables selected in the hematological profile were hemoglobin, hematocrit, leukocyte and differential counts, and platelet. The variables which were included in blood chemistry profile are alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin, random blood glucose, glycated hemoglobin (HbA1c), blood urea nitrogen (BUN), serum creatinine, serum sodium, and serum potassium.

The protocol of DFU management in our hospital included diagnosis and treatment of infection (local and systemic), assessment of patient's diabetic status, treatment of infection, diabetes mellitus, and wound care, and also surgical procedure, such as sharp debridement and amputations. The surgical procedures were classified into five categories, consist of debridement, finger amputation, transmetatarsal amputation, below the knee amputation, and above the knee amputation. DFU severity is classified into five different grades, based on Wagner's diabetic foot classification. In our hospital, patients with diabetic foot problems were

evaluated and treated by a team consisting of surgeons, endocrinologists, microbiologists, rehabilitation specialists, nutritionists, and nurses.

For the statistical analyses, variables were assessed using the program IBM SPSS statistics version 23.0 for Windows (IBM Corporation, New York, USA). All numerical data were summarized as mean ± standard deviation, and categorical variables were summarized as frequency and percentage. Every available data will describe the laboratory characteristics of DFU patients.

4. RESULTS

Between March 2016 and December 2018, there were 113 patients with DFU who underwent a surgical procedure in our hospital (Table 1). The most of patients were male (54.9%). The age of patients ranged from 29 to 87 years, with a mean value of 55.68 years and a median of 55 years. The average patients suffering from diabetes mellitus were more than 6 years and they had foot ulcer for more than 3 weeks. Wagner grade 4 was the most encountered from our study (50.4%). There was no patient with Wagner grade 1 and 2 recorded since surgical procedures are not necessary. The most of patients underwent debridement in operating theatre (57.5%). From 42.5% of patients who had an amputation, the majority of amputation was finger amputation (30 cases).

In relation to the laboratory results, we describe two main aspects, there were hematological profile and blood chemistry profile (Table 2). Out of 113 patient's blood tests, the hemoglobin levels ranged from 7.41 g/dL to 20.24 g/dL. Leukocytosis was observed in these patients ($13.80 \pm 6.48 \times 10^9$/L) and neutrophil dominated the white blood differential count.

We focused our attention to random blood glucose levels, HbA1c, albumin, blood urea nitrogen, and serum creatinine levels, since these blood chemistry profiles mean values were outside of normal values.[9] There were 73 patients (63.6%) with normal BUN levels and 40 patients (35.4%) with elevated BUN levels (>20 mg/dL). There were 35 patients (30.97%) with creatinine levels above 1.3 mg/dL and the highest level was 6.37 mg/dL. There were 73 patients (64.6%) with random blood glucose higher than 180 mg/dL, which considered to be uncontrolled when these patient's blood was tested. The highest blood glucose level observed in these patients was 580 mg/dL. There were only 35 patients (31.0%) with HbA1c levels below than 53 mmol/mol. There were 78 patients (67.3%) with HbA1c levels higher than 53 mmol/mol, even 33 patients (29.2%) had HbA1c levels higher than 86 mmol/mol. The highest HbA1c level recorded in these patients was 145 mmol/mol.

5. DISCUSSION

One of the most common and severe complications of diabetes mellitus is the diabetic foot. In some degree of diabetic foot ulcer, some patient will undergo lower extrem-

Table 1. Patient's (N = 113) demographic and clinical outcome.

Variables	Mean ± SD
Age, years	55.68 ± 10.52
Diabetes mellitus duration, years	6.45 ± 4.33
Foot ulcer duration, weeks	3.61 ± 2.66
Gender, %	
Male	62 (54.9)
Female	51 (45.1)
Foot Affected, %	
Right Foot	54 (47.8)
Left Foot	51 (45.1)
Bilateral	8 (7.1)
Wagner classification, %	
Grade 3	48 (42.5)
Grade 4	57 (50.4)
Grade 5	8 (7.1)
Surgical procedure, %	
Debridement	65 (57.5)
Finger amputation	30 (26.5)
Below knee amputation	10 (8.8)
Transmetatarsal amputation	7 (6.2)
Above knee amputation	1 (1)

Table 2. Patient's hematological and blood chemistry profile.

Variables	Mean ± SD
Hematology	
Hemoglobin, g/dL	10.45 ± 1.63
Hematocrit, %	32.92 ± 4.24
Leukocyte, 10^9/L	13.80 ± 6.48
Basophil	0.09 ± 0.05
Eosinophil	0.20 ± 0.20
Neutrophil	10.77 ± 6.25
Lymphocyte	1.92 ± 1.00
Monocyte	0.83 ± 0.49
Platelet, 10^9/L	379.13 ± 150.55
Blood Chemistry	
ALT, U/L	19.70 ± 19.37
AST, U/L	24.41 ± 16.67
Albumin, g/dL	2.91 ± 0.58
RBG, mg/dL	223.81 ± 89.01
HbA1c, mmol/mol	72.25 ± 6.12
BUN, mg/dL	21.28 ± 17.45
Creatinine, mg/dL	1.32 ±1.16
Sodium, mmol/L	133.24 ± 6.31
Potassium, mmol/L	3.96 ± 0.77

Comments: SD – standard deviation, ALT – alanine aminotransferase, AST – aspartate aminotransferase, RBG – random blood glucose, HbA1c – glycated hemoglobin, BUN – blood urea nitrogen.

ity amputation, which affects their quality of life. Diabetic foot risk factors consist of male sex, peripheral neuropathy, history of diabetes mellitus with more than ten years, peripheral arterial disease, history of smoking, abnormal foot structure (callus formation, thickened nails, bone abnormalities), history of the previous infection, ulcer or amputation, and poor glycemic control.[10] In our study, we found that male sex was dominant in our study population. The mean age of the total population was 55.68 ± 10.52 years, not entirely different from most studies, particularly in Asia. In a research conducted by Viswanathan et al. in India, the mean age of the total study population was 53 ± 11 years old and male sex predominate the study population with 801 patients out of 1319 (60%).[11] However, according to a study of chronic complications a chronic complication caused by diabetes mellitus conducted by Tarigan et al. in Indonesia, it was female who dominated the study population with 91 patients out of 155 (59%).[12] In another study of diabetic foot held in Indonesia by Tjokorda et al., the mean age of the total study population was 54.3 ± 8.6 years old, but male and female patients were not highly different with 96 male patients and 93 female patients.[6]

If wound closure is not possible due to wound size, necrotic tissue extent, irreversible ischemia and location of the wound, then amputation procedure may be used to optimize and reduce morbidities.[4] Some patients thought amputation would bring social stigma and were associated with a significant reduction in their qualities of life, especially major amputations. Until recently, the definition regarding minor or distal amputations and major amputations in relation to diabetic condition is still unclear. However according to Bowker, amputation of transfemoral and transtibial were considered as major amputation, and toe amputation, metatarsal amputation, ray (toe and metatarsal) amputation, or foot amputation (transmetatarsal amputation) were considered as minor amputation.[13,14] Therefore, in our study, 37 patient underwent minor amputations (77.08%) and 11 patient underwent major amputations (22.91%).

Chronic inflammation, as one of the most important risks for development of the diabetic foot, was usually studied and explored. Usually, laboratory results such as white blood count, C-reactive protein and erythrocyte sedimentation rate were noticed to denote inflammation status.[15] It has been noted that infection plays a large role in the occurrence of DFU, in addition to the inflammatory mediators that appear to play an important role, both as diagnostic markers or predictors. Due to abnormal metabolism in diabetes mellitus, there was a significant risk of developing an infection which can disturb wound healing. Neutrophil-induced monocyte adhesion and movement to the sites of trauma and inflammation and induce inflammatory process through several biochemical reactions, such as platelet aggregating factors, cytotoxic oxygen-derived free radicals and hydrolytic enzymes.[16] These theories explain why DFU shows an elevated leukocyte level, particularly neutrophil cell counts. So far, we have not found similar study regarding hematological profile in patients with DFU. However, some studies evaluated on neutrophil-lymphocyte ratio as one of the new indicators that served as a prognostic and predictor marker of inflammation status.[15–17]

From our reports, it can be assumed that the majority of patients with DFU in our study population had uncontrolled blood glucose status, with high levels of HbA1c and random blood glucose levels. This can be caused by patients not using anti-diabetic drugs correctly. It is caused by many factors, such as the absence of symptoms, unwillingness to control treatment, ignoring disease, or difficulty accessing medical services. A study by Goldman et al. stated that intensive glucose control can reduce the risk of lower extremity amputation (LEA) in patients with HbA1c levels above 7.5% or 58 mmol/mol.[18] The research by Nawaf et al. which was conducted to determine risk factors regarding major LEA in diabetes mellitus type 2 patients, showed that HbA1c levels 8% (64 mmol/mol) or above was associated with higher incidence of major amputations of lower limb. This condition of diabetes also affected albumin levels in our patients. In diabetic condition, albumin synthesis and secretion were decreased due to insulin deficiency. Bhonsle et al. stated that low plasma albumin levels had a significant association with increased plasma protein glycation and HbA1c in diabetic patients.[19] Another interesting risk factor mentioned in the previous study was chronic renal impairment, which also increased risk of LEA in diabetic patients.[20] Our study showed increased levels of creatinine serum and decreased albumin serum.

From this study, we can conclude that some laboratory values have a significant meaning in diabetic foot patients. These hematological and blood chemistry profiles can become a tool for the physician in diagnosing, predicting outcome and complications, and picking the most effective treatment for diabetic foot patients. Some studies have used these laboratory values in predicting outcomes, such as infections,[21] major or minor amputations[3] in diabetic foot patients. Other studies concentrate on using these values to signify severity degrees or as a marker in diabetic foot wound healing.[22,23] Nevertheless, these laboratory results can be useful for diabetic patients and physicians. Physicians must be reminded when facing a patient with diabetic foot problems, laboratory results alone cannot be enough for comprehensive management. History takings, physical examination, wound characteristics, and other diagnostic tools can aid physicians to achieve the best plan for treatment. We are now planning to further study the relationship between these laboratory findings and their usage in determining future complications and their application in treatment

Limitations

There were some limitations to this study, similar to any descriptive studies using only a medical record and hospital system database. Further studies regarding this topic are needed. First, there are several laboratory values which are not included in our study. These variables including erythrocyte sedimentation rate, C-reactive protein, and

lipid profile, which were not routinely checked in patients with DFU. Lipid profiles are usually associated with atherosclerosis process, while C-reactive protein and erythrocyte sedimentation rate are inflammatory markers, and also good markers for osteomyelitis in diabetic foot patients.

Second, this study was done in the referral hospital. All diabetic patients who seek our medical attention usually were already in a complicated stage, which was the reason there were no diabetic foot lesions with Wagner grade I and II. There was also lack of clinical information, which could not be obtained from our information sources, such as vascular and neurologic status because the data was taken retrospectively. We could only present patient's Wagner status to describe their clinical severity.

6. CONCLUSION

Hematological and biochemical profile in DFU can be used to achieve a comprehensive approach in diabetic foot patients. Some laboratory values, such as leukocyte, neutrophil, HbA1c, random blood glucose levels, and renal markers, have a particular amount, which can be used for future studies regarding diabetic foot. Some studies also used this value to predict outcome and complications, setting a better treatment plan, and determining prognosis.

Conflict of interest

All the authors have no conflicts of interest.

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None.

Ethics

The study is registered at ClinicalTrials.gov, identifier: NCT03939000.

References

1 Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol*. 2018;14(2):88–98. https://doi.org/10.1038/nrendo.2017.151.

2 Zimmet PZ, Alberti KG. Epidemiology of Diabetes-Status of a Pandemic and Issues Around Metabolic Surgery. *Diabetes Care*. 2016;39(6):878–883. https://doi.org/10.2337/dc16-0273.

3 Balducci S, Sacchetti M, Haxhi J, et al. Physical exercise as therapy for type II diabetes. *Diabetes Metab Res Rev*. 2014;30(Suppl 1):13–23. https://doi.org/10.1002/dmrr.2514

4 Kayssi A, Rogers LC, Neville RF. General Considerations in Diabetic Foot Ulcers. In: Sidawy AN, Perler BA, eds. *Rutherford's Vascular Surgery and Endovascular Therapy*. 9th Ed. Philadelphia: Elsevier Inc. 2019;1514–1526.

5 International Diabetes Federation. *IDF Clinical Practice Recommendations on the Diabetic Foot – 2017: A Guide for Healthcare Professionals*. Brussels: International Diabetes Federation; 2017. https://www.idf.org/component/attachments/?task=download&id=1152. Accessed: 03.08.2020.

6 Pemayun TGD, Naibaho RM. Diabetes Management Diabetic Foot Ulcer Registry at a Tertiary Care Hospital in Semarang, Indonesia: an Overview of its Clinical Profile and Management Outcome. *J Clin Diabetes Pract*. 2016;6(4):82–89.

7 Leong M, Murphy KD, Phillips LG. Wound healing. In: Townsend Jr CM, Beauchamp RD, Evers BM, Mattox KL, eds. *Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice*. 20th Ed. Philadelphia: Elsevier. 2017;130–162.

8 Barbul A, Efron DT, Kavalukas SL. Wound healing. In: Brunicardi FC, Andersen DK, Billiar TR, et al., eds. *Schwartz Principles of Surgery*. 10th Ed. New York: McGraw Hill Education. 2015;241–271.

9 Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Normal reference laboratory values. *N Engl J Med*. 2004;351(15):1548–1563. https://doi.org/10.1056/NEJMcpc049016

10 Powers AC. Diabetes mellitus. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th Ed. New York: McGraw Hill Education. 2011;2968–2970.

11 Viswanathan V, Thomas N, Tandon N, et al. Profile of diabetic foot complications and its associated complications - A multicentric study from India. *J Assoc Physicians India*. 2005;53:933–936.

12 Tarigan TJE, Yunir E, Subekti I, Pramono LA, Martina D. Profile and analysis of diabetes chronic complications in Outpatient Diabetes Clinic of Cipto Mangunkusumo Hospital, Jakarta. *Med J Indones*. 2015;24(3):156–162. https://doi.org/10.13181/mji.v24i3.1249.

13 Pemayun TGD, Naibaho RM, Novitasari D, Amin N, Minuljo TT. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: A hospital-based case-control study. *Diabet Foot Ankle*. 2015;6. https://dx.doi.org/10.3402%2Fdfa.v6.29629.

14 Bowker JH. Minor and major lower-limb amputations and disarticulations in patients with diabetes mellitus. In: Bowker JH, Pfeifer MA. *Levin and O'Neal's the Diabetic Foot*. 7th Ed. Philadelphia: Elsevier Inc. 2008;403–428.

15 Demirdal T, Sen P. The significance of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and lymphocyte-monocyte ratio in predicting peripheral arterial disease, peripheral neuropathy, osteomyelitis and amputation in diabetic foot infection. *Diabetes Res Clin Pract*. 2018;144:118–125. https://doi.org/10.1016/j.diabres.2018.08.009.

16 Metineren H, Dülgeroğlu TC. Comparison of the Neutrophil/Lymphocyte Ratio and C-Reactive Protein Levels in Patients With Amputation for Diabetic Foot Ulcers. *Int J Low Extrem Wounds*. 2017;16(1):23–28. https://doi.org/10.1177/1534734617696729.

17 Balta S, Celik T, Mikhailidis DP, et al. The relation between atherosclerosis and the Neutrophil-Lymphocyte ratio. *Clin Appl Thromb Hemost*. 2016;22(5):405–411. https://doi.org/10.1177/1076029615569568.

18 Goldman MP, Clark CJ, Craven TE, et al. Effect of intensive glycemic control on risk of lower extremity amputation. *J Am Coll Surg*. 2018;227(6):596–604. https://doi.org/10.1016/j.jamcollsurg.2018.09.021.

[19] Bhonsle HS, Korwar AM, Kote SS, et al. Low plasma albumin levels are associated with increased plasma protein glycation and HbA1c in dDiabetes. *J Proteome Res*. 2012;11(2):1391–1396. https://doi.org/10.1021/pr201030m.

[20] Shatnawi NJ, Al-Zoubi NA, Hawamdeh HM, Khader YS, Garaibeh K, Heis HA. Predictors of major lower limb amputation in type 2 diabetic patients referred for hospital care with diabetic foot syndrome. *Diabetes Metab Syndr Obes*. 2018;11:313–319. https://dx.doi.org/10.2147%2FDMSO.S165967.

[21] Kahraman C, Yümün G, Kahraman NK, Namdar ND, Cosgun S. Neutrophil-to-lymphocyte ratio in diabetes mellitus patients with and without diabetic foot ulcer. *Eur J Med Sci*. 2014;1(1):8–13.

[22] Vatankhah N, Jahangiri Y, Landry GJ, et al. Predictive value of neutrophil-to-lymphocyte ratio in diabetic wound healing. *J Vasc Surg*. 2016;65(2):478–483. https://doi.org/10.1016/j.jvs.2016.08.108.

[23] Semadi IN, Irawan H. Blood glucose and lipid profile in patients with diabetic foot ulcer that underwent hyperbaric oxygen therapy. *Bali Med J*. 2017;6(2):405–408. https://doi.org/10.15562/bmj.v6i2.606.