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THE RELATIONSHIP BETWEEN ASYMMETRIC DIMETHYLARGININE AND ANKLE-BRACHIAL INDEX WITH THE SEVERITY OF DIABETIC FOOT ULCERS

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ABSTRACT

Introduction: Approximately 50% of inpatient cases for diabetic complications are diabetic foot ulcers (DFU). Peripheral artery defect is one of the mechanisms that is characterized by increased asymmetric dimethylarginine (ADMA). Severe diabetic foot ulcers are found in populations with low ankle-brachial index (ABI) values. This study aims to find the relationship between ADMA and ABI in predicting risk for DFU.

Methods: An Observational study with a cross-sectional method was conducted at Adam Malik Hospital, Medan collaboration with the Clinical Laboratory from the Faculty of Medicine, Universitas Sumatera Utara. Forty-two patients with DFU from September 2023 to April 2024 were registered with the following information: anthropometric, gender, history of drug use, comorbidities, ABI, ADMA, complete blood count, lipid profile, and fasting blood glucose.

Results: In grade II DFU, the average ADMA value was 87.6 ng/dl, grade III 231.3 ng/dl, grade IV 444.9 ng/dl, and grade V 652.3 ng/dl. ABI value using Sokoye classification shows grade II DFU has an average ABI value of 1.08 (Normal), grade III 0.74 (Mild), Grade IV 0.61 (Moderate), and grade V 0.5 (Moderate). There is a significant relationship between the severity of DFU (Wagner scale) and ADMA levels (P = 0.001) and ABI values (P = 0.001). There is a relationship between ADMA and ABI values with DFU (P = 0.001).

Conclusion: There is a significant relationship between the severity of DFU (Wagner scale) and ADMA levels (P = 0.001) and ABI values (P = 0.001). There is a relationship between ADMA and ABI values with DFU (P = 0.001).

Keywords: Diabetic foot ulcer, Asymmetric dimethylarginine, Ankle-brachial index

ABSTRAK

Pendahuluan: *Sekitar 50% kasus rawat inap untuk komplikasi diabetes adalah diabetic foot ulcers (DFU). Cacat arteri perifer adalah salah satu mekanisme yang ditandai dengan peningkatan asymmetric dimethylarginine (ADMA). Ulkus kaki diabetes parah ditemukan pada populasi dengan ankle-brachial index (ABI) values. Penelitian ini bertujuan untuk mengetahui hubungan antara ADMA dan ABI dalam memprediksi risiko untuk DFU.*

Metode: *Studi Observasional dengan metode cross-sectional dilakukan di Rumah Sakit Adam Malik Medan bekerja sama dengan Laboratorium Klinik dari Fakultas Kedokteran, Universitas Sumatera Utara. Empat puluh dua pasien DFU dari*

September 2023 hingga April 2024 terdaftar dengan informasi dari antropometri, jenis kelamin, riwayat penggunaan narkoba, komorbiditas, ABI, ADMA, hitung darah lengkap, profil lipid, dan glukosa darah puasa sebagai berikut..

Hasil: *Nilai ADMA rata-rata DFU kelas II: 87,6 ng/dl, grade III: 231,3 ng/dl, grade IV: 444,9 ng/dl, dan grade V: 652,3 ng/dl. Nilai ABI menggunakan klasifikasi Sokoye menunjukkan DFU grade II memiliki nilai ABI rata-rata 1,08 (Normal), grade III 0,74 (Mild), Grade IV 0,61 (Moderate), dan grade V 0,5 (Moderate). Terdapat hubungan antara tingkat keparahan DFU (skala Wagner) dengan kadar ADMA (P = 0,001) dan nilai ABI (P = 0,001). Ada hubungan antara nilai ADMA dan ABI dengan DFU (P = 0,001).*

Kesimpulan: *Ada hubungan antara tingkat keparahan DFU (skala Wagner) dengan kadar ADMA (P = 0,001) dan nilai ABI (P = 0,001). Ada hubungan antara nilai ADMA dan ABI dengan DFU (P = 0,001).*

Kata kunci: *Ulkus kaki diabetik, Asimetris Dimetilarginin, ABI*

1. Introduction

According to the World Health Association (WHO), Diabetes Mellitus (DM) is a metabolic disease that is a major global health problem where the number is increasing, recorded based on the International Diabetes Federation (IDF) the prevalence of Type 2 Diabetes Mellitus (T2DM) with an age range of 20-79 years is 10.5% of the total population equivalent to 536,6 million people and is estimated to increase to 12.2% in 2045 [1]. Data on diabetes in Indonesia, based on *Riset Kesehatan Dasar* (Riskesdas), has a prevalence of 1.5% in 2018 or around 1 million people, which shows an increase compared to 2007 (1.1%) [2]. DM has micro-vascular and macro-vascular complications, which have significant health, economic, and social impacts [3].

The prevalence of DM will develop into diabetic foot ulcers (DFU), reaching 12% of the total DM patients, while the International Diabetes Federation (IDF) states that there are 12.9 million people who experience active DFU and around 3,5 million people with inactive DFU, this reaches 11.8% of the total cases of DM in America [4]. DFU is the main cause of hospitalization in Indonesia; around 50% of all inpatients are cases of DFU [5]. DFU is a non-traumatic lesion on the skin, part or all layers of the DM patient's feet [6]. Risk factors for DFU include the duration of DM; it is said that patients with DM for more than 10 years have a greater risk of suffering from DFU. In addition to this, other risk factors such as poor blood sugar control, age> 60 years, obesity, irregular foot care, lack of physical activity, use of inappropriate footwear, and lack of knowledge of DM sufferers [7]. Apart from the risk factors above, there are several mechanisms for the occurrence of DFU, namely peripheral neuropathy, peripheral arterial disease, foot deformities, foot trauma, and impaired resistance to infection [3].

Nitric Oxide (NO) plays an important role in vasodilation and inhibition of smooth muscle proliferation, leukocyte adhesion, and platelet breakdown. L-Arginine is the only source of NO, where asymmetric dimethylarginine (ADMA), which is a derivative of L-Arginine, is a competitor in the function of endogenous NO synthase (NOS). ADMA will, in principle, bind to Dimethylarginine dimethylaminohydrolase (DDHA), and when high ADMA levels will interfere with the formation of NO, which will cause increased blood vessel stiffness [8].

The relationship between ADMA and DM begins with the failure of blood sugar regulation due to the deactivation of the insulin signal, which is part of the polyol pathway [9]. In a study with 34 DM patients, 16 DM patients without vascular complications, and 18 patients without DM served as controls. In all of the above patients, ADMA, HbA1c, LDL, and intima thickness measurements were carried out as a screening for microvascular disorders in the study patients. In this study, a significant

difference was found in ADMA levels in DM patients and patients without DM (1.59 + 0.22 vs 0.69 + 0.04 umol/L, p < 0.01) [10].

ABI is another marker that is often measured to see if there is a disorder in peripheral blood circulation, as stated above, that disorders of blood flow will cause disorders in the flow of white blood cells, nutrients, biomarkers, and other specific proteins, which will cause the formation of diabetic foot ulcers. The ABI examination itself is the simplest and cheapest examination to diagnose PAD that can be performed at a health center [3].

From the above research on the relationship between ADMA and the development of diabetic foot ulcers, from several studies, including a cohort study from Tali Ganz et al conducted in 2016 with a sample of 105 patients using a control population showed a relationship between increased ADMA values and the incidence of complications, both microvascular and macrovascular in DM patients (OR = 4.5; 95% CI −1.4 to 14.1; P = 0.009). This is also in line with research in 2015 with a sample of 87 T2 DM patients, which showed an increase in cases of endothelial damage in patients with increased ADMA values [11].

In another study using a sample of 42 DM patients, where 22 patients without vascular complications and 20 patients with complications both macrovascular and microvascular and there were 22 controls, in all patients above, ADMA levels and intima thickness measurements were carried out as a benchmark for blood vessel disorders, from the results of the study it was found that there was no relationship between ADMA levels and intima thickness in DM patients [12].

The relationship between ABI and DFU can be seen from several studies, including a study from Prita Aulia et al (2018), with a sample of 41 people, which showed a relationship between a decrease in ABI values and the severity of a diabetic ulcer with the use of Wagner criteria [13]. Other studies, such as those from Ming-Chi Yang et al in 2021, showed an increase in cardiovascular events and worsening complications of diabetic foot ulcers in populations with lower ABI values [14]. Uni Gamayani et al.'s study in 2019 with 73 samples showed a relationship between low ABI values and the appearance of symptoms of Diabetic Polyneuropathy [15]. Research in 2021 also showed a relationship between low ABI values and the incidence of diabetic ulcers in a sample of 32 patients [16].

Current classification systems, such as the Meggit-Wagner and PEDIS schemes, primarily rely on clinical and morphological parameters to assess ulcer severity. However, these frameworks may benefit from the integration of molecular and functional biomarkers to enhance predictive and diagnostic accuracy. This study aims to investigate the potential utility of ADMA and ABI in stratifying the severity of diabetic foot ulcers.

2. Method

This study was conducted at the Adam Malik Hospital, Medan, with the approval of the Health Research Ethics Commission, University of North Sumatra, from September 2023 to April 2024. This study collaborates with the Clinical Laboratory from the Faculty of Medicine, Universitas Sumatra Utara. This study involved inpatients and outpatients with a total of 42 DFU patients who met the inclusion criteria. The inclusion criteria for this study are type 2 DM patients aged over 18 years. Exclusion criteria were patients who had been diagnosed or had received treatment for acute or chronic kidney failure with eGFR <23 ml/min (CKD-EPI Creatinine 2021), impaired liver function, and PAD, a history of previous amputation, or received treatment with statin, ACEi, ARB, pioglitazone, or aspirin therapy. BMI criteria classify adult weight status using numerical ranges:

under 18.5 kg/m² is Underweight, 18.5-24.9 kg/m² is Healthy Weight, 25.0-29.9 kg/m² is Overweight, and 30.0 kg/m² or higher is Obese. Data from medical records, including anthropometric data in the form of weight, height, gender, history of drug use, and comorbidities, were obtained. Assessment of DFU severity and ABI examinations are carried out, then fasting blood samples are taken from patients, which will be sent to the Clinical Laboratory from the Faculty of Medicine, Universitas Sumatra Utara, for ADMA examination, complete blood count, lipid profile, and fasting blood glucose. The data obtained is processed using a computer device in the form of a statistical application, namely SPSS version 25.

3. Result

Among 42 patients, the average age is 58 years±10.3 years, with the youngest age being 50 years and the oldest age being 81 years. In terms of gender data, 24 research samples were male, and 15 patients were female. According to BMI, there are 2 (5%) underweight populations, 27 (64%) normal, and 13 (31%) overweight or obese patients. Average of total cholesterol 130.9±35.6 mg/dl, LDL 73±34.6 mg/dl, HDL 28.6±12.6 mg/dl, and Triglyceride levels 147.3±52.6 mg/dl. ABI values with classification by Sokoye showed 4 (10%) normal results, 22 patients (52%) mild PAD, 16 (38%) moderate PAD, and no severe PAD was found in this study. Severity of DFU by Wagner classification showed 3 (7%) patients as Grade II, 17 (40%) patients Grade III, 15 (36%) patients Grade IV, and 7 (17%) patients Grade V (Table 1).

Table 1. Characteristics of DFU patients.

Characteristics	n=42 (%)
Gender	
Man	24 (57)
Woman	18 (43)
BMI	
Underweight	2 (5)
Normal	27 (64)
Overweight/Obese	13 (31)
ABI	
Classification (>1.3)	0 (0)
Normal (0.91-1.31)	4 (10)
Mild PAD (0.70-0.90)	22 (52)
Moderate PAD (0.40-0.69)	16 (38)
Severe PAD (<0.40)	0 (0)
Severity of DFU (Wagner)	
Grade II	3 (7)
Grade III	17 (40)
Grade IV	15 (36)
Grade V	7 (17)

Based on Table 2, there is a significant relationship between ADMA and ABI with the severity of DFU using Wagner criteria.

Table 2. Relationship between ADMA and ABI (Wagner Classification) with the severity of DFU.

Characteristics	Severity of DFU (Wagner Classification)				
	Grade II	Grade III	Grade IV	Grade V	*P* Value
ADMA	87.6	231.3	444.9	652.3	< 0.001
ABI	1.08	0.74	0.61	0.5	< 0.001

Based on Table 3, the ABI value using the Sokoye classification associated with UFD showed that Grade II UFD has an average ABI value of 1.08 (normal), Grade III 0.74 (mild PAD), Grade IV 0.61 (moderate PAD), and Grade V 0.5 (moderate PAD).

Table 3. Relationship between ADMA levels and ABI (using Sokoye classification)

Characteristic	ABI interpretation (Sokoye)					*P* Value
	Calcification	Normal	Mild	Moderate	Severe	
ADMA (ng/dl)	-	87.6	309.6	468.7	-	< 0.001

4. **Discussion**

Research by Bogdan Stancu on 69 DM patients showed that the severity of DFU will increase with age; it is said that DFU occurs mostly in patients aged <68 years [17]. Another study by Shailesh K on 581 DM patients without DFU compared to 97 DM patients with DFU showed that the age of patients with DFU was 55.26±12.10 years, while patients without DFU tended to be younger, 47.76±8.32 years [18]. The results of this study have a presentation where the worsening of DFU is related to the work of the patient, where the patient experiences DFU while the patient is working. This is certainly contrary to previous research; this occurs due to the risk of DM patients being traumatized or injured when the patient is working [19]. Research by Munire Mutailipu on 577 patients distinguished based on Wagner criteria showed that BMI or nutrition levels decreased along with worsening on the Wagner scale, in Wagner Grade I, BMI 24.25±3.30, while in grades 4-5, BMI 24.17±3.81 [20]. Another study by Piotr Nehring on 145 DM patients showed that body weight (BMI) was related to the occurrence of DFU compared to 293 DM patients without DFU, with an average BMI of 32.36±5.35 in T2DM with DFU and 29.93±5.83 without DFU [21]. But this study did not provide information on the severity of DFU, so it cannot be used as a description of the risk factors for worsening DFU. The results of the study showed that BMI decreased in relation to the severity of DFU. This is certainly still a matter of debate, where many studies show different things. In patients with Wagner Grade V, normal BMI was found; this is related to nutritional disorders, so it is considered that the higher the Wagner grade, the more the BMI will decrease. From laboratory results, DM patients with DFU have increased glucose levels with a tendency towards anemia, while the lipid profile showed normal results, except for HDL, which had low values. This is in accordance with research from Hamdi Almaramhy with 144 patients, by comparing DM patients with Wagner grade DFU, with the results of patients with poor glycemic control with random blood glucose ≥ 220 mg/dl (57.1%) found in Grade IV and V, while in Grade II-III 51.9% had random blood glucose levels ≥ 220 mg/dl [22]. Another study by Abbott with a sample of 1,035 patients with DM monitored the occurrence of DFU; this monitoring has been running for more than 7 years. This study shows that patients with low hyperglycemia control with glucose levels > 200 mg/dl have a risk of DFU compared to lower glucose levels, with a comparison reaching 1.02 vs 2.40 [23]. The relationship between blood glucose and the severity of DFU begins with endothelial damage as a vascular complication in DM, fluctuations in blood sugar will trigger cytokine production, molecular adhesion and activation of apoptotic genes, this will cause endothelial damage to both large and small blood vessels, this can also trigger oxidative stress which will ultimately disrupt the ability of blood vessel vasoconstriction, outside of this high glucose will also trigger hyperactivation of blood clotting factors, this will cause the formation of thrombus and arteriosclerotic plaque. The results of hemoglobin (Hb) 10.2 g/dl±1.4 g/dl, this is in accordance with the research of Mitku Mammo Taderegew's study with a sample of 320 DM patients, a comparison was made with DM patients with DFU, lower Hb levels were found in the DM population with DFU with an average of 8.2 g/dl (AOR=3.06, 95% CI: 1.32–7.11) [24]. Another study from S. S. Michalak comparing DM patients

with Non DM patients, anemia was found to be more common in DM patients (median 4 (4-5) vs 3 (2–4); p <0:001) [25].

This study shows that cholesterol measurements in accordance with the results of Eren's study in 2013 which compared two groups, healthy and DFU patients, showed no difference in the two groups, both in terms of total cholesterol and LDL, but showed a difference in HDL levels, where there was a decrease in HDL in DFU patients (29.28±15.2 mg/dl) [26]. In contrast to research by Hasan with 100 samples of UFD patients and 100 samples of DM without DFU, showing a strong relationship between DFU with increased total cholesterol levels (216.52±27.3 mg/dl), LDL with an average (152.31±23.59 mg/dl), and decreased HDL (34.78±3.88 mg/dl) [27]. This is also reinforced by research by Yunes Ario with a sample of 47 DFU patients by comparing lipid profile levels in DFU with Wagner degrees, there was a relationship between increasing severity with the value of the lipid profile with LDL values in Wagner 1-2 (57% normal) and in Wagner 3-4 (41% high) with an average value of 180±35 mg/dl, while TG levels showed the same thing with an average of 237±54 mg/dl, HDL levels showed the most normal values in Wagner degrees 1-2 (90%) with an average of 29.2±12 mg/dl [28]. This is in accordance with research from Tali Ganz et al. in 2020, using a sample of 105 patients with T2DM. This study compared ADMA levels in 137 patients without diabetes with DM patients with macrovascular and microvascular complications [29]. From the results of the study it was found that there was an increase in ADMA levels in DM patients who had been monitored for 6.5 years, from the initial examination without complications, re-registration was carried out during the above period and repeat measurements were carried out, it was found that there was an increase in ADMA with a statistical value (OR 5.5; 95% CI-1.9-16; p = 0.002) in line with research from Mustafa Celik, et al. collected 50 samples of DM patients with atherosclerosis, 50 DM patients without macrovascular disease and 31 controls, from the results of measurements using outcomes in the form of macrovascular disease or not, an increase in ADMA was found in DM patients with macrovascular disease [30]. However, in another study by Zanna Fiodorenko-Dumas using a sample of 42 DM patients, where 22 patients without vascular complications and 20 patients with complications both macrovascular and microvascular and there were 22 healthy patients (without DM) as controls, in all patients above, ADMA levels and intima thickness were measured as a benchmark for blood vessel disorders, from the results of the study it was found that there was no relationship between ADMA levels and intima thickness in DM patients [31]. The relationship between ADMA and DFU can be understood by understanding the pathophysiology of DFU which consists of a complex process of Immunopathy, blood vessel disorders and neuropathy, where these three things will be disrupted by disorders in blood flow, one of the disorders that can cause this is arteriosclerosis where the ability of blood vessels is lost in the process of responding to vasodilation function, which is mediated by NO, ADMA itself is a competitive inhibitor of eNOS as a precursor of NO. In the study by Zanna Fiodorenko-Dumas, it had weaknesses in the small number of samples and non-specific measurements of the intima regarding the measurement area, where measurements were only carried out at one location of the blood vessels. The higher the severity of DFU (Wagner), the higher the degree of PAD using ABI measurements, in line with several studies, including Prita Aulia et al, a study in 2018 with a sample of 41 people showed a relationship between decreased ABI values and the severity of a diabetic ulcer using the Wagner criteria [13]. Other studies, such as from Ming-Chi Yang et al in 2021, showed an increase in cardiovascular events and worsening complications of diabetic foot ulcers in populations with lower ABI values [32]. Uni Gamayani et al, in a study in 2019 with 73 samples, showed a relationship between low ABI values and the emergence of symptoms of diabetic polyneuropathy [15]. A study in 2021 also showed a relationship between low ABI values and the incidence of diabetic ulcers in a sample of 32 patients. However, this is

contrary to the study of Dimitri Aerden et al., which was published in 2011, where 187 DFU patients underwent intra-arterial angiography (IAA) and ABI examinations. In patients, IAA examinations were carried out using the Joint Vascular Societies reporting standard classification, which is divided into 4 classes depending on the severity of AR in patients [33]. Janssen A, et al. studied 106 samples with IAA evidence showing 71% sensitivity and 30% specificity, this is the same as the study of Potier L, et al. with a sample of 83 patients showing lower values with the same sample criteria as evidenced by Doppler USG, the values of 50% sensitivity and 79% specificity are the results obtained, from the above procedures that are in accordance with good equipment with trained examiners can affect the results of ABI measurements [34]. The study also conducted an analysis of the relationship between ABI and ADMA, where the Normal ABI found the average ADMA value was 87.6 ng/dl, in mild PAD the average ADMA value was 309.6 ng/dl and moderate PAD had an average ADMA value of 468.7 ng/dl, while in the interpretation of calcification and severe PAD there were no samples, with a value of P <0.05 considered significant, this is in accordance with the research conducted by Andrew M., et al. with 1050 samples with PAD, ABI, and ADMA examinations were carried out, from this study it was found that the average age was 72 years with the results of multivariate regression and Independent correlates showing a relationship between ADMA and ABI ($p = 0.008$) [35]. The relationship between the two is not related to cholesterol levels and DM from this study; it was found that the relationship between ADMA and ABI is the presence of blood vessel disorders and blockages, but it was said that the involvement of ADMA from the NO metabolic pathway in causing PAD is not yet well known. While other studies from Stanton K., et al., examine the relationship between ADMA and the presence of AR in blood vessels [36]. In this study with a sample of 510 patients referred for cardiac catheterization, ADMA and ABI measurements were carried out, the sample was patients with CAD with stenosis > 60%, a relationship was found between ADMA with BMI ($p < 0.001$), Mean arterial pressure ($p = 0.03$) and DM T2 ($p = 0.04$), univariate analysis showed an increase in ADMA levels in patients with PAD (ABI < 0.9) (mean = 0.51±0.2) compared to the population without PAD, a relationship was found between the severity of PAD and ADMA levels (r2 linear = 0.029, $p = 0.0001$) in univariate and p value = 0.0003 in multivariate analysis. It is among the first to directly examine the relationship between ADMA and ABI within the context of diabetic foot ulcer patients, a linkage that, based on extensive searches of major journal databases, has not yet been explored in a single integrated study. This positions the research as a potential starting point for further development of ADMA as a biomarker beyond its conventional role in vascular health. Another advantage lies in the comprehensive inclusion of ulcer severity, ranging from Wagner grade 1 to grade 4, which allows for meaningful comparisons across different levels of clinical severity. If you'd like, I can help you expand this into a full discussion section or align it with your study's objectives and implications. Want to keep building?

4. Conclusion

From 42 DFU patients in this study, the average age is 58 years±10.3 years, where most of the samples were male, still working, with normal body weight, blood glucose, total cholesterol, LDL, and triglyceride, with other measurement results indicating anemia, perfusion restriction disorders with low-risk ADMA levels, and Grade III DFU disorders. There is a significant relationship between the severity of DFU on the Wagner scale and ADMA levels, with $P = 0.001$. There is a relationship between the severity of DFU on the Wagner scale and the interpretation of ABI values, with $P = 0.001$. There is a significant relationship between ADMA and the interpretation of ABI values in the population with DFU ($P = 0.001$).

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Conflict of Interest

All the authors declare that there are no conflicts of interest.

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