

## Drug Interactions in Diabetic Ulcer Patients in an Indonesian Private Hospital

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### Abstract

Diabetic ulcers can progress into tissue death, or gangrene, which create a risk for amputation. Measures for preventing other complications and accelerating wound healing in diabetic ulcers include blood sugar level control, diet adjustment, wound care, antidiabetic drug administration, and comorbid therapy. This leads to the use of various drugs that can potentially trigger drug interactions. This study aimed to identify possible drug interactions in the therapeutic management of diabetic ulcer patients treated in Husada Utama Hospital Surabaya, Indonesia, from January 2020–June 2022. This was a descriptive observational study using retrospective data from medical records. Results showed that 103 types of drugs were administered to 48 research samples with 41 of them experienced drug interactions (n=263 cases). Based on the severity of drug interactions, 31 cases were categorized as major cases (11.8%), with drug-class antibiotic-antiemetic interactions as the most frequent interactions. This study proves that it is essential for doctors and pharmacists.

**Keywords:** Diabetic ulcers, drug interaction, drug use, hospital

### Introduction

Diabetes mellitus is a metabolic disorder characterized by high blood sugar levels or hyperglycemia accompanied by disturbances in carbohydrate, lipid, and protein metabolism. Diabetes mellitus, whose blood glucose levels are poorly controlled, can cause complications, such as acute to chronic complications.<sup>1</sup> One of the complications that occur in patients with diabetes mellitus is diabetic ulcers. Ulcers occur in all layers of the skin with full depth and thickness due to peripheral neuropathy and/or peripheral arterial disease in people with diabetes mellitus.<sup>2,3</sup> Ulcers can be followed by bacterial invasion resulting in infection and decay.<sup>3</sup> These injuries can progress to gangrene or tissue death which is at risk of lower extremity amputation.<sup>4</sup>

The development of cases of diabetic ulcers has increased globally. Indonesia itself has a high prevalence of risk and incidence.<sup>3</sup> The annual incidence is 2% among all patients with diabetes mellitus, and 5–7.5% of patients with diabetes

mellitus have peripheral neuropathy.<sup>5</sup> The mortality rate due to diabetic ulcers is between 17–32% and the amputation rate is around 15–32.5%.<sup>6</sup>

Efforts that can be made to prevent the emergence of other complications and accelerate the healing of diabetic ulcers are to provide appropriate therapy.<sup>1</sup> These efforts can be made by controlling blood sugar levels, eating arrangements, wound care, and giving OAD, insulin, and antibiotics for infection treatment of comorbid patients. The large variety of drugs given can potentially occur drug interactions.

Drug interactions are modifications of drug effects caused by other drugs so that the effectiveness and toxicity of these drugs change.<sup>7</sup> Clinically, a drug interaction is considered vital if it increases toxicity and decreases the effectiveness of the interacting drug, especially if the drug has a narrow therapeutic index. The category of severity of drug interactions is classified into three, namely minor, moderate, and major. Drug interactions are minor if the effects are mild and do not require a change in therapy. Drug interactions are moderate if the effects cause changes in the patient's clinical condition and require a change in therapy. Drug interactions are significant if the effects are potentially life-threatening and require

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intervention to minimize or prevent unwanted effects.<sup>8</sup>

Therapeutic failure due to drug interactions in the world is still relatively high. Data from the WHO Global Individual Case Safety Report database, over 20 years, as many as 3,766 cases were reported related to drug interactions. In Indonesia, the exact number of drug interactions has not been obtained because the documentation has not run optimally, so a thorough study of drug interactions cannot be carried out.<sup>9</sup> The impacts caused by drug interactions are increased costs, length of treatment time, decreased effectiveness of therapy, and increased unwanted drug reactions to the risk of death.<sup>7</sup> This study was conducted to identify drug interactions in diabetic ulcer patients at Husada Utama Hospital Surabaya. The results of this study support doctors and pharmacists to monitor drug administration in the therapeutic management of diabetic ulcer patients to avoid drug interactions.

## Methods

Descriptive retrospective analysis of 48 research subjects received from medical records of diabetic ulcer patients for the period January 2020 - June 2022 at Husada Utama Hospital Surabaya with inclusion criteria, namely: 1) Diabetic ulcer patients with or without comorbidities, 2) Patients with ICD code -10 E11.5 Type 2 diabetes with complications of peripheral vascular circulation, 3) Patients older than 18 years, and 4) Patients treated during the study period at Husada Utama Hospital Surabaya and the exclusion criteria were: 1) The patient died, and 2) The patient is referred to another hospital or forced to go home. The method of taking the subject is done using total sampling. The analysis was carried out descriptively by screening using the online drug interaction checker medscape.com. Drug interaction data are grouped by severity level into three categories: minor, moderate, and major. Interaction if the effects are mild and do not require a change in therapy. Moderate interaction if the effect causes a change in the patient's clinical condition and requires a change in therapy. A major interaction is when the effect is potentially life-threatening and requires intervention to minimize or prevent the undesired effect. The study was conducted after obtaining a research permit from Husada Utama Hospital Surabaya and ethical clearance from the University of Surabaya Health Research

Ethics Committee with No. 96/KE/VI/2022.

## Results

Characteristics of the subjects showed 68 patients with a diagnosis of diabetic ulcer. After being grouped, 48 subjects met the inclusion and exclusion criteria. Table 1 shows the demographics of the subjects. Based on age, the age range is 41–81 years, with the dominance of subjects being male. Length of Stay (LOS) subjects were divided into three groups ranging from 3–21 days. Based on the medical treatment obtained, subjects who received debridement and amputation also received wound care. There were 21 comorbidities in diabetic ulcers. The most common comorbidities were anemia and hypertension. Drug use data shows 47 patients received more than five drugs during hospitalization.

Table 2 describes the drug use profile with acquiring 35 drug classes. The total types of drugs used in the research subjects were 103 drugs. The highest frequency of drug classes were antibiotics (100.97%), antidiabetic (84.47%), non-opioid analgesics (55.34%), and fluids and electrolytes (55.34%). The profile of drug use by research subjects can be observed in Table 2.

Table 3 and Table 4 shows that of the 48 research subjects who experienced diabetic ulcers at Husada Utama Hospital Surabaya, 41 subjects (85.42%) experienced drug interactions with a drug interaction case rate that occurred in as many as 263 cases. Cases of drug interactions that occur are divided into three categories, namely major (11.79%), moderate (67.30%), and minor (20.91%). Most interactions occur in the Antibiotic-antiemetic drug class, followed by the NSAID-non-opioid analgesic, anti-ulcer, and antiplatelet.

## Discussion

Table 1 shows the characteristics of the subjects. Most cases of diabetic ulcers occurred in the category of the early elderly 46–55 years (33.33%). Age is one of the risk factors for diabetes mellitus and diabetic ulcers.<sup>10</sup> In older people, there are many changes in the body's physiological decline, including a decrease in the hormone insulin.<sup>5</sup> Another factor that can occur is insulin resistance due to a lack of physical activity that is not balanced with food intake.<sup>5</sup> The aging process can also reduce skin cells'

**Table 1 Characteristics of Subjects**

Variables	Amount (n=48)	Percentage (%)
Age (years)		
36-45	5	10
46-55	16	33
56-65	12	25
>65	15	31
Sex		
Male	26	54
Female	22	46
LOS (days)		
3-7	35	73
8-14	12	25
15-21	1	2
Medical treatment		
Wound care	48	100
Debridement	17	35
Amputation	17	35
Comorbid		
Anemia unspecified	10	21
Hypertension	9	19
Sepsis unspecified	8	17
Observation febrile	6	12
Chronic kidney disease	4	8
Hyponatremia	3	6
Cyst of kidney	2	4
Hypoglycemia	2	4
Diabetic nephropathy	2	4
Acute renal failure	1	2
Metabolic acidosis	1	2
Hypernatremia	1	2
Hypoalbuminemia	1	2
Hypokalemia post hyperkalemia	1	2
Hypothermia	1	2
Dyspnea	1	2
Osteomyelitis	1	2
Other and unspecified atrioventricular block	1	2
Parkinson	1	2
Pneumonia unspecified	1	2
Urinary tract infection	1	2
Drug use in patients		
≤5 drugs	1	2
>5 drugs	47	98

elasticity and decrease vascularized fluid in the skin and fat glands.<sup>11</sup> Decreased skin elasticity will reduce cell regeneration ability when an injury occurs, and wound healing becomes slower.<sup>11</sup>

This study shows that the highest gender is male, with as many as 26 subjects (54%). Based on a study, male patients tend to be less worried

about their illness, so they rarely make hospital visits, check themselves, and perform wound care compared to female patients.<sup>12</sup> According to the Global Adult Tobacco Survey, the highest prevalence of active smokers mostly occurs in men in Indonesia. The nicotine content in cigarettes can damage the endothelium, which causes the attachment and aggregation of

**Table 2 Profile of the Drug Use of Research Subjects**

Drug Group	Frequency of Drug Use (n=103)	Percentage (%)
Antibiotics	104	100.97
Antidiabetic	87	84.5
Non-opioid Analgesics	57	55.3
Fluids and electrolytes	57	55.3
Antihypertensive	34	33.0
Anti-ulcer	33	32.0
Nausea and vertigo	26	25.2
Diuretics	21	20.4
Vitamins and supplements	18	17.4
Antiemetic	9	8.7
Opioid analgesics	7	6.8
Mucolytic	7	6.8
Antiepileptic	6	5.8
Gout and hyperuricemia	4	3.9
Statins	4	3.9
Hypnosis and anxiety	3	2.9
Corticosteroids	3	2.9
Anemia and other blood disorders	2	1.9
Antianginal	2	1.9
Antiarrhythmic	2	1.9
Anti-asthma and bronchodilator	2	1.9
Antiplatelet	2	1.9
Antithrombotic	2	1.9
Acute diarrhoea	2	1.9
Hormones	2	1.9
Minerals	2	1.9
Antifibrinolytic	1	0.9
Anti-inflammatory	1	0.9
Antifungal	1	0.9
Antiparkinsonian	1	0.9
Beta-blockers	1	0.9
Co-enzyme	1	0.9
Dementia	1	0.9
SSRI	1	0.9

SSRI= Selective Serotonin Reuptake Inhibitors

**Table 3 Drug Interactions on Subject by Case**

Interaction Incident	Patients (n=48)	Percentage (%)
There was interaction	41	85
No interaction	7	14

**Table 4 Category of Drug Interaction Based on Severity Level**

Category	Number of Cases (n=263)	Percentage (%)
Major	31	11.8
Moderate	177	67.3
Minor	55	20.9

platelets to leak and lipoprotein lipase, slowing down blood lipids and facilitating the onset of atherosclerosis. The presence of atherosclerosis results in decreased blood flow to the arteries.<sup>13</sup>

Research results based on LOS showed the highest length of stay was 3–7 days with 35 subjects (73%), 8–14 days with 12 subjects (25%), and 15–21 days with one subject (2%). The average length of stay is 6.35 days with an interval of 3–21 days. The length of hospitalization for diabetic ulcers depends on the type of ulcer, the infection’s severity, and the treatment given.<sup>10</sup>

All study subjects received wound care or dressings, meaning that wound care was also given to subjects who underwent debridement and amputation. Wound care is one of the essential therapies in diabetic ulcers to keep the wound closed and clean or provide a moist healing environment to facilitate cell migration and prevent dry wounds. The choice of dressing depends on the amount and type of exudate present in the wound. Wound dressings that can be used, such as conventional dressings, are sterile gauze moistened with 0.9% NaCl or modern dressings available today, such as hydrocolloids, hydrogels, calcium alginate, etc.<sup>3,14</sup> The wound care used in this study were sterile gauze, hydrogel (Duoderm Gel), tensocrepe, cutimed sorbate, 0.9% NaCl, and antiseptic.

Another medical action given to research subjects is debridement. Debridement is done to remove dead tissue that can make wounds difficult to heal is debridement.<sup>3</sup> In this study, debridement was carried out on 17 subjects (35%). After debridement, irrigation should be

performed on the wound with normal saline or 0.9% NaCl followed by wound care or dressings to keep the wound in good moisture and protect it from bacterial contamination.

Amputation was performed on 17 subjects (35%). In another study, the incidence of amputation was found to be 37.5% and 39.5%.<sup>12,15</sup> Amputation in diabetic ulcers often occurs due to a history of diabetes of 10 years or more, history of previous amputation, inadequate glycemic control, history of hypertension, hyperlipidemia, peripheral arterial disease, history of peripheral neuropathy, history of osteomyelitis, and severity of the wound. Other factors contributing to the aggravation of having to be amputated include increasing age, smoking history, anemia, increased white blood cell count, hypoalbuminemia, and other microvascular and macrovascular complications.<sup>15,16</sup> Based on Wagner's classification, amputation occurs mainly in class 4 diabetic ulcers, namely gangrene in some leg tissue, and class 5, namely gangrene in the entire leg.<sup>15</sup>

Anemia and hypertension are the most common comorbidities in diabetic ulcer patients. Anemia was found in 10 of 48 subjects (21%). The results of this study are supported by a meta-analysis involving 15 studies with 2,895 diabetic ulcer patients, showing the prevalence rate of anemia in the severity of mild, moderate, and severe diabetic ulcers, respectively, was 69.7%, 49.5%, and 73%. One study in this meta-analysis reported that ulcers that did not heal occurred in 127 of 236 (53.8%) diabetic ulcer patients with anemia compared with 34 of 117 (29.1%) diabetic ulcer patients without anemia.<sup>17</sup> Chronic inflammation, diabetic nephropathy, and malnutrition are factors thought to cause anemia in diabetic ulcer patients. Of these factors, inflammation or chronic inflammation is most often associated with anemia in patients with diabetic ulcers. Several studies have shown that pro-inflammatory cytokines can suppress hematopoietic function and reduce serum iron levels, causing a shortage of hematopoietic raw materials.<sup>18</sup> Anemia is also associated with the degree of wound healing, the incidence of amputation, and increased mortality. Good healing of diabetic ulcers requires adequate blood flow to provide oxygen and other essential nutrients to damaged tissues. Increased deformability of red blood cells in diabetic ulcer patients can cause decreased blood flow and delay wound healing. Decreased oxygenation due to anemia can also exacerbate ulcer conditions.<sup>19</sup> The incidence of hypertension as a comorbid

in this study reached a relatively high number, 9 out of 48 subjects (18%). These results follow a study that showed that 296 of 602 DM patients (49.17%) had comorbid hypertension.<sup>20</sup> In another research article, as many as 8 subjects (26.7%) had comorbid hypertension.<sup>21</sup> Hypertension in DM occurs because high blood viscosity decreases blood flow so vascular deficiency can occur. Hypertension with blood pressure >130/80 mmHg can cause damage to blood vessel lesions. Endothelial damage will affect macroangiopathy through platelet adhesion and aggregation, leading to vascular deficiency so that hypoxia can occur in tissues, which can increase the risk of ulcers.<sup>22</sup>

Table 2 shows that as many as 35 classes of drugs were used in 48 research subjects with the most frequently administered drugs being Antibiotics (100.97%), Antidiabetic (84.5%), Non-Opioid Analgesics (55.3%), and Fluids and electrolytes (55.3%). Antibiotics are one of the most widely used because of the high incidence of infection in diabetic ulcers. Antibiotics are the most effective drugs to fight infections, especially infections caused by bacteria. Antidiabetics such as insulin and oral antidiabetics are recommended therapies for controlling blood glucose during infection or controlling and eliminating the infection itself.<sup>23</sup> Non-opioid analgesics in diabetic ulcer patients are used as pain relievers. Non-opioid analgesics work well for pain when damage or injury to body tissues occurs.<sup>24</sup> Fluid and Electrolyte Groups are given as the main fluid choice to balance fluids and electrolytes in the body.

Table 3 shows that of the 48 study subjects who experienced drug interactions, 41 subjects (85%) and 7 subjects did not experience drug interactions (15%). Table 4 shows that drug interactions are grouped into three categories based on severity: major, moderate, and minor. Drug interactions that occurred in 41 study subjects found 263 cases based on the severity of the interaction, consisting of 31 major interactions (11.8%), 177 moderate interactions (67.3%), and 55 minor interactions (20.9%).

Drug interactions are essential things to be considered by doctors and pharmacists in monitoring drugs for patients, especially patients with drug use of more than five drugs. This effort is one way to minimize the risk of drug interactions. Collaboration between doctors and pharmacists needs to be carried out in considering the risks and benefits that will be received to minimize the incidence of drug interactions.<sup>8</sup>

Major interactions are interactions that cause permanent disability to be life-threatening.<sup>9</sup> If a significant interaction occurs, the patient needs intervention to minimize or prevent unwanted effects. Handling major interactions can also be done by avoiding using drugs that cause simultaneous interactions. In this study, there were 31 major interactions (11.8%), one of which was the interaction between Levofloxacin and Ondansetron. When combined with ondansetron, Levofloxacin can increase the risk of QT interval. The causative mechanism in this interaction is the additive elongation effect on the QT interval.<sup>25</sup> These two drugs should be avoided or replaced with other drug alternatives.<sup>26</sup>

There are limitations in this study, where it is necessary to conduct similar studies related to drug research in diabetic ulcer patients in other hospitals to obtain different data. In addition, conducting a similar study with a prospective data collection direction is necessary to obtain more complete data.

This study demonstrates that the large number of drugs used to treat diabetic ulcers triggers drug interactions. It has been shown that the use of 103 types of drugs in 48 study samples obtained 41 patients experiencing drug interactions with a total of 263 cases. The data from this study prove that it is important for doctors and pharmacists to monitor drugs for patients with polypharmacy to avoid or minimize the incidence of drug interactions.

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