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Portraying Diabetic Foot Ulcers: Comparative Evaluation of Diabetic Foot Infections versus Diabetic Foot Ulcers

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Abstract

Background: Confusion often arises in caring for diabetic foot infections and ulcers, especially with antimicrobials; we aim to shed light on this entity and alert healthcare workers to its stewardship. **Methods:** Records were reviewed between February 2016 and September 2023. Data for patients diagnosed with diabetes and foot ulcers, infected or not, were examined following ICD 9 search terms. Records for patients were included if they were prediabetic/diabetic adults with foot ulcers, more than 18 years old, and on antidiabetic treatment. Patients were excluded if they insulin resistant, with normal HgbA1c levels, wheel-chair dependent, bed-bound, non-diabetic patients, diabetic patients who had vascular lower limb surgery earlier to ulcers, diabetic patients who had aortocoronary bypass, deep venous thrombosis within six months, malignancy, and severe clinical depression. A modified IWGDF/IDSA guidelines definitions for DFI and DFU was considered. Statistical analysis was done using R programming. Statistical methods were employed as appropriate, and a significant P-value was considered for $P < 0.05$. **Results:** Most characteristics were well balanced between DFI and DFU, on

imaging osteomyelitis and tissue swelling were significantly more in DFI. Endovascular radiological procedures showed angiograms to be considerably more in DFI, while angioplasty was more in DFU, in addition to smoking. Bacteremia was uncommon, and swab cultures were mostly polymicrobial in both ulcers; no clear association with blood bacteria was detected with the polymicrobial growth, though few were concordant. Antimicrobials prescribed for both ulcers were not statistically different except for carbapenems, which were more in DFI ($P < 0.0001$). **Conclusion:** Attention should be paid to best practices while caring for diabetic ulcers. These include swab culture interpretations, the use of antimicrobials, and plan management according to DFI or DFU to utilize either local care or combination with antimicrobials.

Keywords

Diabetic Foot Ulcers, Diabetic Limb Amputation, Antimicrobials Stewardship, Broad-Spectrum Antimicrobials in Diabetic Foot Ulcers

1. Introduction

Diabetic foot ulcers affect about 5% of the world's diabetic patients, and their lifetime prevalence is about 15%. A cross-sectional study in Jordan found similar rates at 5.3% in individuals attending diabetes clinics [1] [2]. DFI is a severe condition that largely contributes to the loss of toes, feet, and legs; it starts as such or as a complication of DFU. Foot deformities and, or trivial injury may lead to DFU and DFI, as they may turn out to be the herald of a complicating chronic condition requiring close attention. Appropriate DFI management may halt the progression to a more severe condition and reduce patient suffering and surgical interventions and amputations [3]. Duration of diabetes, poor glycemic control, smoking, neurological impairment, peripheral vascular disease, and microalbuminuria [4], various foot deformities like Hallux valgus, claw\hammer toe, prominent metatarsal head, limited joint mobility, pes cavus, and Charcot's foot, were detected in about 1.7% - 17.4% of diabetic patients are factors that tempt DFI [5] [6].

Making an accurate DFI diagnosis, having local care experience, starting an appropriate antimicrobial, and avoiding inappropriate and unnecessary antimicrobial (UAU) use is imperative. A significant concern is wisely using antimicrobials to provide adequate care while mitigating bacterial resistance in the causative bacteria of DFI, considering the escalating resistant bacteria at alarming rates in the last decades [7] [8].

P. aeruginosa has initially dominated the treatment regimens, but its importance has changed remarkably with the SIDESTEP study; when ertapenem was compared to piperacillin-tazobactam and was found non-inferior, despite the isolation of *P. aeruginosa* in both study arms and the lack of anti-pseudomonal activity in ertapenem [9]. Inappropriate bacteria sampling misses the overall

management should a non-existent infection and an inappropriate antibiotic be prescribed. Hitherto, the prescription of broad-spectrum antimicrobials has not added value over the narrow-spectrum antimicrobial in treating DFI due to the persistently high reinfection rates and comparable amputation rates [10].

This study describes complications in diabetic foot ulcers (DFI and DFU) up to ninety days: the rates of amputations of the toes, feet, and legs and the frequency of ulcer-significant debridement [11].

2. Materials and Methods

2.1. Study Design and Settings

In a multicenter cross-sectional study, records were reviewed for February 2016 - September 2023 in three private hospitals in Amman, Jordan. The hospitals encompassed around 700 beds. Strengthening the Reporting of Observational Studies in Epidemiology (STROPE) was followed in preparing the cross-sectional design [12]. Data for patients diagnosed with diabetes and foot ulcers, infected or not, were reviewed following the search terms as in ICD 9: diabetic foot infection, diabetes with a foot infection, diabetic foot, diabetic foot ulcer, diabetic gangrene toes, diabetes, peripheral vascular disease, below knee amputation, and above knee amputations. The characteristics, features, and comorbidities of patients (sex, age, duration of diabetes, types of diabetes, antidiabetic treatment, duration of DFU or DFI, location of the ulcer, duration of ulcer, DFI evidence, hgbA1c level, weight, height, the distribution of isolated bacteria from blood culture and swab culture, foot clinical/imaging findings, PEDIS score, frequency of debridement, location of amputation, antimicrobials, mobile CVA, smoking, nephropathy, microalbuminuria, neuropathy, retinopathy, ischemic heart disease, hypertension, dyslipidemia. Patients were followed up to ninety days through readmissions or through phone calls if discharged home. Due to the nature of the study, it did not have treatment modification during the medical record review, but the standard of care does not raise any concern about the safety of patients. IRB approval was obtained for the three participating hospitals: The Specialty (5/1/T/112974), Al Khalidi (KHMC/22/R/104), and Jordan (Issue no.: JH/IRB/2023/03).

2.2. Inclusion and Exclusion Criteria

Records for patients were included if they were prediabetic and diabetic adults with foot ulcers, more than 18 years old, on oral agents, Insulin, or both. Patients were excluded if they were patients described as Insulin resistant, with normal HgbA1C levels, wheel-chair dependent, bed-bound for any reason, non-diabetic patients who had vascular lower limb surgery, patients whose veins were harvested for aortocoronary artery bypass graft surgery, deep venous thrombosis within six months, malignancy, and severe clinical depression.

2.3. Definitions

DFI: An infection that results in or is associated with a foot ulcer in a patient who carries the diagnosis of prediabetes and diabetes mellitus; a DFI is an infra-malleolar soft tissue or bone infection; it is clinically diagnosed based on at least two classic findings of inflammation or purulence. This definition was a modified version of the IWGDF/IDSA guidelines: when there is redness >= 2 cm around the edges, purulence, or the presence of both signs simultaneously [11] [13].

DFU: A full-thickness wound through the dermis, below the ankle, on a weight-bearing or exposed surface in an individual with diabetes. DFU is defined as ulcers with purely neuropathic, purely Ischemic, or mixed neuro-ischemic, and do not have the criteria for infection as above [11] [14].

Acute ulcer: an ulcer that remains less than 12 weeks; otherwise, it is a chronic ulcer that remains 12 or more weeks [15].

2.4. Statistical Analysis

Descriptive patient analysis for the characteristics and features. Outcomes were analyzed based on the comparison between DFI and DFU. Data were analyzed using Pearson's Chi-squared test with Yates continuity correction and Fisher's exact test. Where significant global chi-square measured P-value was found < 0.05 in some categories, Bonferroni adjusted p-values were calculated for subcategories to reveal the location of substantial difference. An independent t-test tested the difference in the means of a few variables. Statistical analysis was made through data science R- program *R* (*R version* 4.2.1, 2022-06-23 *ucrt*) *and R Studio* (*RStudio Team* (2020). *RStudio*: *Integrated Development for R. RStudio*, *PBC*, *Boston*, *MA URL* (http://www.rstudio.com/). Significant P-value considered for < 0.05.

3. Results

Characteristics of patients (**Table 1**) that did not significantly differ when analyzed as DFI versus DFU (P = NS) included sex, age, duration of the foot ulcer, PEDIS score, level of academic achievement, duration of diabetes, antidiabetic treatment, type of diabetes, BMI, imaging findings and interventional radiological and endovascular procedures, and medical comorbidities including peripheral vascular disease, a patient had a cerebrovascular accident but ambulatory, neuropathy, retinopathy, ischemic heart disease, hypertension, dyslipidemia, antiplatelets, statins, urine microalbuminuria, immunosuppression, and nephropathy. A few characteristics and confounders significantly differ between DFI and DFU; the level of academic achievement was statistically significantly higher in DFI among the higher education and school subcategory (P < 0.05, global P = 0.01); meanwhile, no significant difference in the diplomas was found. Also, Imaging findings were statistically significant in three subcategories: osteomyelitis, soft tissue swelling, and no abnormalities (P < 0.05, global P-value < 0.0001),

but no significant difference between the two arms for Charcot. Interventional radiological and endovascular procedures were significant for balloon angioplasty (P value < 0.05, global P value = 0.02) but not specifically vascular stenting (P = NS).

Table 1. Characteristics and epidemiological factors for **432** patients with diabetic foot Infection and diabetic foot ulcer.

Characteristic	Diabetic Foot Disorder		P-value[2]
	DFI N (%) = 250 (58)[1]	DFU N (%) = 182 (42)[1]	
Sex			
Female	60 (13.9)	51 (11.8)	
Male	190 (44.0)	131 (30.3)	0.40
Age (range)	62.2 (25 - 89)	63.2 (30 - 91)	0.40
Duration of the ulcer (months)			
Acute	170 (42.4)	114 (28.4)	
Chronic	71 (17.7)	46 (11.5)	0.967
PEDIS score	6.45	6.11	0.080
level of academic achievement (P^2 = 0.01)			
Diploma	29 (10.0)	22 (7.6)	0.34
Higher education	74 (25.7)	29 (10.0)	<0.05*
School	71 (24.7)	63 (21.9)	<0.05*
Duration of diabetes (years)			
0 - 10	72 (18.9)	4211.0)	
11 - 20	104 (27.4)	63 (16.6)	0.30
21 - 30	37 (9.7)	36 (9.5)	
> 31	17 (4.5)	9 (2.4)	
Antidiabetic treatment			
Insulin	109 (25.2)	82 (19.0)	
Insulin and oral agents	74 (17.1)	43 (10)	0.34
Oral agents	67 (15.5)	57 (13.2)	
Diabetes mellitus			
Type 1	8	7	0.04
Type 2			
Prediabetes	24 (5.9)	18 (4.4)	0.97
Diabetes	215 (52.7)	151 (37.0)	
BMI (body mass index)			
Underweight	6 (1.9)	5 (0.71)	
Healthy	50 (11.6)	53 (12.3)	
Overweight	103 (23.8)	76 (17.6)	0.11
Obesity Class 1	62(14.4)	30(6.9)	
Obesity Class 2	26 (6.0)	14 (3.2)	
Obesity Class 3	3 (0.69)	4 (0.92)	

Continued

Imaging ($P^2 < 0.0001$)			
Charcot	13 (3.0)	6 (1.4)	NS
Osteomyelitis	37 (8.6)	14 (3.2)	<0.05*
Soft tissue swelling	115 (26.6)	58 (13.4)	<0.05*
No abnormality	85 (19.0)	104 (23.1)	<0.05*
Imaging vascular intervention ($P^2 = 0.02$)			
Angiogram	54 (26.7)	30 (14.9)	<0.05*
Angioplasty	29 (14.4)	40 (19.8)	<0.05*
Stenting	25 (12.4)	24 (11.9)	NS
Peripheral vascular disease	157 (36.3%)	113 (26.2)	0.96
Ambulatory CVA	21 (4.7)	25 (5.8)	0.11
Neuropathy	162 (37.5)	102 (23.6)	0.08
Retinopathy	109 (31.6)	66 (9.3)	0.91
Ischemic heart disease	123 (28.5)	88 (20.4)	0.93
Hypertension	196 (45.4)	144 (33.3)	0.95
Dyslipidemia	145 (33.6)	91 (21.1)	0.12
Antiplatelet	179 (41.4)	138 (31.9)	0.38
Statins	151 (34.9)	104 (24.1)	0.56
Urine microalbuminuria	107 (24.8)	62 (14.4)	0.08
Smoking	124 (28.7)	63 (14.6)	0.003*
Immunosuppression	16 (3.7)	13 (3.0)	0.91
Nephropathy	87 (25.8)	58 (17.2)	0.77

[1]number (%). [2]Pearson's Chi-squared test, Wilcoxon rank sum test, Fisher's exact test, and t. test. *The exact location of statistically significant difference within a tested category, by the Bonferroni test. [$]Other foot deformities (Imaging): limited joint mobility, hallux valgus, prominent metatarsal head. DFI: diabetic foot infection. DFU: diabetic foot ulcer. CVA: cerebrovascular accident.

The microbiological characteristics of patients (Table 2) with systemic sepsis were significantly higher among DFI = 13.4% than DFU = 5.0% (P = 0.004). The bacterial species isolated from blood on either arm did not statistically differ (P = 0.63). Cultures processed from ulcer swabs demonstrated remarkably significant differences among the different isolated bacteria: Enterobacteriaceae, Proteobacteria, *S. aureus*, Enterococci, and unspecified bacteria (<0.004). The bacterial growth of MDR Enterobacteriaceae, *P. aeruginosa,* and Acinetobacter species was not significantly different between DFI and DFU (P = NS).

The distribution rates of antimicrobial classes prescribed for DFI or DFU (Table 3) were not statistically different for all antimicrobials, except for carbapenems, which were significantly used more in patients with DFI (P < 0.0001). Patients with DFU had systemic antimicrobial administration 225 times in 182 patients, and dual parenteral therapy was prescribed 43 times.

Table 2. Clinical/Microbiological characteristics of patients with diabetic foot infection and diabetic foot ulcer.

Characteristic	Bacterial growth based on the type of diabetic disorder		P-value[2]
	DFI N = 250 (58)[1]	DFU N = 182 (42)[1]	
Sepsis	58 (13.4)	22 (5.0)	0.004
Bacteremia			
Enterobacteriaceae	3 (0.70)	1 (0.23)	
MRSA	6 (1.34)	3 (0.7)	
P. aeruginosa	3 (0.70)	0 (0.0)	0.63
Streptococcus spp.	3 (0.70)	3 (70)	
No growth	235 (54.4)	175 (40.51)	
Total bacteremic episodes	15 (6)	7 (4)	0.80
Swab Bacterial growth			
Enterobacteriaceae	59 (68.6)	27 (31.4)	0.0006
MDR Enterobacteriaceae	35 (61.4)	22 (38.6)	0.09
P. aeruginosa	25 (56.8)	19 (43.2)	0.37
Acinetobacter	11 (52.4)	10 (47.6)	0.83
S. aureus	55 (56.7)	42 (43.3)	< 0.0001
Proteobacteria	39 (78)	11 (22)	< 0.001
Enterococci	43 (68.3)	20 (31.7)	< 0.004
Others	63 (65.6)	33 (34.4)	< 0.002

[1]number (%). [2]Pearson's Chi-squared test; Fisher's exact test; T.test. DFI: diabetic foot infection. DFU: diabetic foot ulcer. CVA: cerebrovascular accident.

Table 3. Antimicrobials used for the treatment of diabetic foot infection, and prescribed for diabetic foot ulcer without evidence of infection.

Antimicrobials	N	Antimicrobial distribution for each agent on the type of foot disorder		P-value[2]
		DFI N = 250 (58)[1]	DFU N = 182 (42)[1]	
Cephalosporines	55	30 (50)	25 (50)	0.5
B-lactams B-lactamases inhibitors	54	33 (60)	22 (40)	0.38
Carbapenems	162	144 (70)	51 (30)	<0.0001
Glycopeptides	105	57 (50)	48 (50)	0.38
Fluoroquinolones	101	52 (70)	51 (30)	0.91
Tigecycline	51	33 (60)	19(40)	0.052
Clindamycin	25	16 (60)	9 (40)	0.16

[1]number (%). [2]P value by Chi-square test. DFI: diabetic foot infection. DFU: diabetic foot ulcer. CVA: cerebrovascular accident.

4. Outcomes

We assessed two points as outcomes (Table 4): the frequency of surgical debridement and the ninety days of any extent lower limb amputation. For debridement, there was no statistical difference between DFI and DFU for the

Table 4. Ninety-days associated outcomes of diabetic foot ulcer (DFU) and diabetic foot infection (DFI).

Characteristic	N = 432	Type of diabetic ulcer		P-value[2]
		DFI N = 250 (58)[1]	DFU N = 182 (42)[1]	
Surgical debridement				
None		107 (25.48)	28 (6.67)	0.66
Once		129 (30.71)	39 (9.28)	
Twice		47 (11.19)	10 (2.38)	
Three or more		50 (14)	10 (14)	
Ninety days outcome				
Cured		76 (18.1)	20 (8.4)	0.44
Some remaining ulcer		76 (23)	24 (27)	
Toes amputation		58 (18)	8 (7.9)	
Foot amputation (TMA)		12 (2.9)	3 (0.7)	
Below knee		29 (6.9)	5 (1.2)	
Above knee amputation		4 (1.0)	2 (0.5)	
Death		20 (4.8)	4 (1.0)	
Lost to follow		58 (13.8)	21 (5.0)	

[1]number (%). [2]Pearson's Chi-squared test. TMA: trans-metatarsal amputation. DFI: diabetic foot infection. DFU: diabetic foot ulcer. CVA: cerebrovascular accident.

procedure frequency (P = 0.66). The ninety-day rates for the levels of amputations; toes, feet (trans metatarsal), below-the-knee, and above-the-knee amputations, a remaining ulcer, cure, and death, all outcomes were not statistically different between both diabetic ulcers (P = 0.44).

5. Discussion

It is imperative to diagnose and classify diabetic ulcers early with the initial patients' approach and to abide by guidelines-based definitions for those ulcers, *i.e.*, DFI or DFU. This would help in recommending the best management course, and a decision would be made whether proper local care alone or combined with an appropriate antimicrobial should be initiated in an attempt to avoid grave complications, as 80 % of lower extremities amputations were preceded by diabetic ulcers [16].

In our study, there were 432 patients, 250 (57.8%) patients with guidelines-driven evidence as DFI, and the rest were classified as DFU, comprising 182 (42.2%) patients. Inappropriately, systemic parenteral antimicrobials were prescribed in all 182 DFU patients, 43 in combination. This inappropriateness was due to the misinterpretations of the swab culture polymicrobial isolates and the worry about treating with combination antimicrobials from such DFU swabs. The available data was drafted as guidelines recommending not using antibiotics on DFU, neither systemic nor local, and stressing proper local care [11].

Obesity as a risk factor was earlier evaluated with conflicting results; our study assessed the difference between DFI and DFU for different BMI categories and demonstrated no statistically significant difference (P = 0.11); others were looking at different BMI categories and the incidence of diabetic ulcers, and showed no difference [17]. Paradoxically, other studies showed that being overweight and obese is a protective factor for diabetic foot ulcers and measured the favorable relation with increased body weight for every 5 kilograms/meter^2 increase in body surface; even wound healing was reported to be better in severely obese patients due to the increase in endothelial progenitor cell levels that function as a protective vascular factor against atherosclerosis [18] [19] [20].

We tried to assess the education achievements as a factor that may affect the prevalence of diabetic ulcers; no significant difference was found between either ulcer in the diploma education achievement levels (P = 0.34). However, patients with background school education or higher degrees significantly had higher DFI rates (P < 0.05, global P = 0.01); this disparity was against our expectations; however, a study showed the relationship between educational attainment and self-care health behaviors was modest in strength for different education achievement levels, with no preponderance in a unique level [21], this suggests that self-care is not related to the academic achievement in patients with diabetic ulcers.

The duration of diabetes was categorized into four durations in patients, at ten-year intervals starting with less than ten years, 11 - 20, 21 - 30, and then thirty-one years or more; none of the durations have impacted the prevalence of either ulcer [22]. To evaluate if the type of treatment may affect diabetic ulcer distribution (P = NS) or the distribution rates for the outcomes between the two ulcers (P = NS), no difference was found here. Metformin may influence the activity of keratinocytes and fibroblasts in human skin cells on a cellular level; this was not translated into a clinical effect in our patients, though nested analysis was not looked for [23].

All examined comorbidities did not show a significant difference between DFI and DFU (P = NS), except for smoking (P = 0.003), which was significantly higher in DFI patients. Expectedly, in imaging, there was a clear statistically significant finding for osteomyelitis and soft tissue swelling (P < 0.05, global P < 0.0001) in DFI, but not for Charcot (P = NS) because Charcot is diabetes dependent phenomenon. This was followed by a significantly more angiogram in DFI and angioplasty in DFU (P < 0.05, global P = 0.02), which may point to the chronicity of DFU and its association with the neurovascular diabetic compromise. Still, both ulcers did not differ in stenting (P = NS) (**Table 1**).

The uncommon (7%) bacteremic episodes patients had in either ulcer (**Table 2**) and grown from blood were MRSA, Enterobacteriaceae, *Pseudomonas aeruginosa*, and various Streptococci, with no statistically significant difference between both ulcers (P = 0.63). Despite patients with the diagnosis of sepsis syndrome, there were significantly more patients with DFI than in DFU (13.4% vs 5.0% respectively, P = 0.004). We found that bacteremia in DFI patients is not

common; in 250 DFI patients, there were 15 (6%) bacteremic patients and 7 (4%) patients among the 182 DFU patients (P = 0.80), reflecting the mostly colonization nature of the wounds, possibly due to healthcare system exposure. Few strains may express invasiveness irrespective of whether they cause a local infection [24].

Broad-spectrum and presumably ought-to-be-restricted antimicrobials, including carbapenems, were freely and frequently prescribed for DFI and DFU. No antimicrobial restriction policies are being implemented in the country. There was a significantly increased rate for the use of carbapenems in the treatment of DFI (P < 0.0001). Other antimicrobials were prescribed almost with the same rates for both ulcers (P = NS). Published guidelines encourage the use of narrow-spectrum antibiotics in DFI, avoid dual and broad-spectrum antibiotics for they show similar effectiveness, and avoid prescribing antibiotics for DFU. Inappropriately, narrow-spectrum antimicrobials like clindamycin and second, and third-generation cephalosporins were utilized less (**Table 3**). Over the past few decades, due to overprescribing antimicrobials and broad-spectrum antimicrobials, trends in bacterial resistance have increased remarkably in our region, although a glimpse of opportunities for using appropriate antimicrobials, de-escalating, and avoiding unnecessary antimicrobials (UAU) may be practiced without untoward effects [25]. In the assessment of the outcomes, surgical debridement did not significantly differ in the frequency for both ulcers (P = 0.66), denoting that diabetic ulcers need to receive adequate debridement in an attempt to help ulcer base granulation, allowing proper drainage and removal of necrotic infected tissues as well as wound edge refreshment, and not to focus on antimicrobial prescription as a savior. The ninety-day outcome demonstrated no statistically significant difference between DFI and DFU for toes, trans-metatarsal, below-the-knee, or above-the-knee amputation. Furthermore, the rates of ulcer cure, a remaining ulcer on day ninety, and death were all statistically not different for both ulcers(P = 0.44).

6. In Conclusion

A precise diagnosis should be exercised for a proper approach to diabetic ulcers to recommend the best management plan; local care or local care and systemic antimicrobials in the pursuit to avoid UAU, broad-spectrum antimicrobials where narrow-spectrum antimicrobials do well and to avoid unwise interpretations of the isolated bacteria from ulcers, especially those that grow from DFU. No swab cultures are needed in DFI and mainly in the acute presentation, which may suggest the virulent bacteria in a polymicrobial culture result. Amputation rates, death, cure, and residual ulcers on day ninety were almost similar, denoting that diabetic ulcers share the seriousness and the need for utmost care and not only the infection factor that decides the limb and patient outcomes, and teams caring for diabetic ulcers must abide by the recommended guidelines in addition to the antimicrobials stewardship helping to maximize outcomes, avoid unnecessary side effects, reduce costs, and mitigate bacterial resistance.

Conflicts of Interest

None for all contributors.

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