



Factors Related to Severity of Diabetic Foot Ulcer: A Systematic Review

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Background: Diabetic foot ulcer (DFU) is one of the diabetes complications. DFU can be the cause of a high rate of amputation, health-care costs and even death, and this condition occurs in the severity status of DFU. Severity of DFU is the cause of expensive complication incidence. Understanding the factors affecting it can help preventive functions. Adequate evidence for this problem is necessary. The aim of this systematic review is to summarize evidence on severity of diabetic foot ulcer.

Methods: A literature search was undertaken in Scopus, PubMed, Elsevier, MEDLINE, Embase, UpToDate and Google Scholar. Observational studies that assessed severity of DFU were included. The data extraction and assessment are on the basis of PRISMA.

Results: Seven studies were assessed and 25 factors that affect severity of DFU are reported in the studies. The most used score for an estimate of severity was the Wagner scale (n=5). The majority of patients were in G1 and G2 stages (67.5%; basis of Wagner) or have a superficial ulcer (62.84%) on the basis of the Texas Diabetic Wound Classification System. The main factors include high BMI, smoking, lack of diabetes control, type of diabetes treatment and older age. In addition, there were other factors that affect severity of DFU such as vascular complications, bacteria isolated, marital status, gender, high levels of cholesterol and triglycerides. Also, life location, type 2 diabetes, genotype, addiction, long-time DFU and delay to refer patients were other factors.

Conclusion: Twenty-five factors were reported. The majority of these factors related to life-style and can be prevented by self-care functions. The effect of these factors needs further study and the further studies must be better in quality.

Keywords: diabetes, diabetic foot ulcer, severity

Introduction

Diabetes mellitus (DM) is a global public health threat that has increased in the recent two decades.^{1,2} In 1985, diabetic patients numbered 30 million, which increased to 285 million in 2010, and the latest global estimate from the International Diabetes Federation in 2019 reports 463 million people with diabetes mellitus and that, in 2045, the patients will be 700 million.^{3,4} Diabetes is the leading cause of end-stage renal disease, adult-onset blindness and non-traumatic lower extremity amputations.⁵ Diabetic complications can be disabling or even life-threatening.⁶ Patients with DM are exposed to developing multiple complications, among which diabetic foot ulcers (DFUs) are very common among the diabetic population.⁷ According to the International Working Group on the Diabetic Foot (IWGDF), a diabetic foot ulcer is a full-thickness wound penetrating through the dermis (the deep vascular and collagenous inner layer of the skin) located below the ankle in a diabetic patient.⁸ The

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prevalence of DFU in hospitalized patients ranges from 4 to 10% and the risk of patients with diabetes developing a foot ulcer in their lifetime could be as high as 25%.⁹ A systematic review study reports that the prevalence of DFU is 6%.¹⁰ DFU occurs because of a lack of Hb1AC control, foot traumas, mechanical pressures, obesity and overweight, tobacco, increased diabetes duration and age.^{10–15} Also, diabetic neuropathy, vasculopathy, ischemia and neuropathy are known as causative factors.^{16,17} We know the factors that affect the incidence of diabetic foot ulcer, but it is more important to know the factors that influence the severity of foot ulcers. Diabetic foot ulcer is a marker for increased mortality rate in diabetes patients.¹⁸ Every year, 5% of patients with diabetes develop foot ulcers, and 1% require amputation.¹⁹ The healing rate is lower and amputation is higher in patients with higher severity of DFU.^{20,21} Ulcer severity is more important than the ulcer site in determining the final outcome in diabetic patients.^{22,23} In addition, DFU is the cause of emotional and physical disorders that reduce patients' quality of life.²⁴ DFU is a source of major suffering and financial costs for the patient, and also places a considerable burden on the patient's family, health-care professionals and facilities, and society, and malnutrition in general.^{25,26} Diabetic foot ulcer severity is a more significant factor of subsequent mortality than coronary artery disease, peripheral arterial disease or stroke.¹⁸ 80% of non-traumatic limb amputations are attributable to diabetes, of which 85% are due to DFU.^{9,15} Early detection and treatment, hygiene and foot care education may help to decrease the chances of amputation.⁷

As mentioned, diabetic foot ulcer, as one of the most important and most common complications in diabetic patients, has a profound effect on the patient's prognosis, amputation and even death. These problems occur during the severity of foot ulcers, so understanding the factors that influence severity of diabetic foot ulcers is very important. Understanding these factors can be helpful in estimating the severity of the disease. So far, studies have been conducted that have examined each aspect of effective factors and measured them in different populations. We intend in this study to review the results presented in various studies.

Review Method

Protocol and Registration

A protocol for this review was registered at Kermanshah University of Medical Sciences (GN: 97786). The focus of the review was factors affecting severity of diabetic foot ulcer.

Eligibility Criteria

Included studies were observational studies, such as cohort studies, descriptive-analysis studies and case-control studies. We included studies that assess factors in humans. We excluded case reports, letters, editorials or review studies. Studies were considered if they assess related factors in severity of diabetic foot ulcer.

Search Strategy

An unrestricted systematic search until 20 March 2020 in Scopus, PubMed, Elsevier, MEDLINE, Embase, UpToDate, Google Scholar and CINAHL was executed. We developed search strategies using keywords and MeSH terms on the diabetic foot ulcer, diabetic complications, DFU severity, complication severity and diabetic severity. In addition, the reference lists of eligible articles were screened for further relevant studies and relevant systematic reviews scanned for appropriate references.

Search Validation and Data Selection

All relevant article abstracts were discovered by using the search terms, and those that were available in the indicated databases during the period of this review were included. All articles not meeting the inclusion criteria as stated above were later discarded. Citations were downloaded into Endnote X8. Two authors (MJ and PAS) independently reviewed all titles and abstracts for irrelevant studies and eliminated duplicate articles. Articles retained were obtained in full text and examined independently. Any controversies surrounding any particular included or excluded paper were discussed by the authors (MJ and PAS), and a collective decision was taken on the article.

Data Extraction and Report

Data extraction was performed independently in tabular forms of included items. The studies were subsequently screened for reporting factors that could influence severity of diabetic foot ulcer. The characteristics of each study and the method of study are described and presented in tabular form. The country in which the study was performed is reported. Affecting factors on DFU severity are presented as reported by the authors. Where studies reported more than one factor, we included all estimates. Reports of the extracted data are based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.²⁷

Results

Study Selection

We found 46,567 studies in the initial search. After removing duplicate studies, we found 26,800 references. After screening, 126 citations were selected on the basis of their title/abstract for full-text review. Of these, 74 were considered potentially eligible for this review. Sixty-seven studies were excluded due to the lack of data on severity of diabetic foot ulcer in their full text. Finally, we included 7 studies in this

review. We adhered to reporting and conduct guidance based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (Figure 1).

Characteristics of Studies

Of these 7 studies, published between 1998 and March 2020, 2 studies were cohort and 5 were cross-sectional or descriptive-analytic (Table 1). Three of the studies were conducted on the Iranian population, with the remainder in India (n=1),

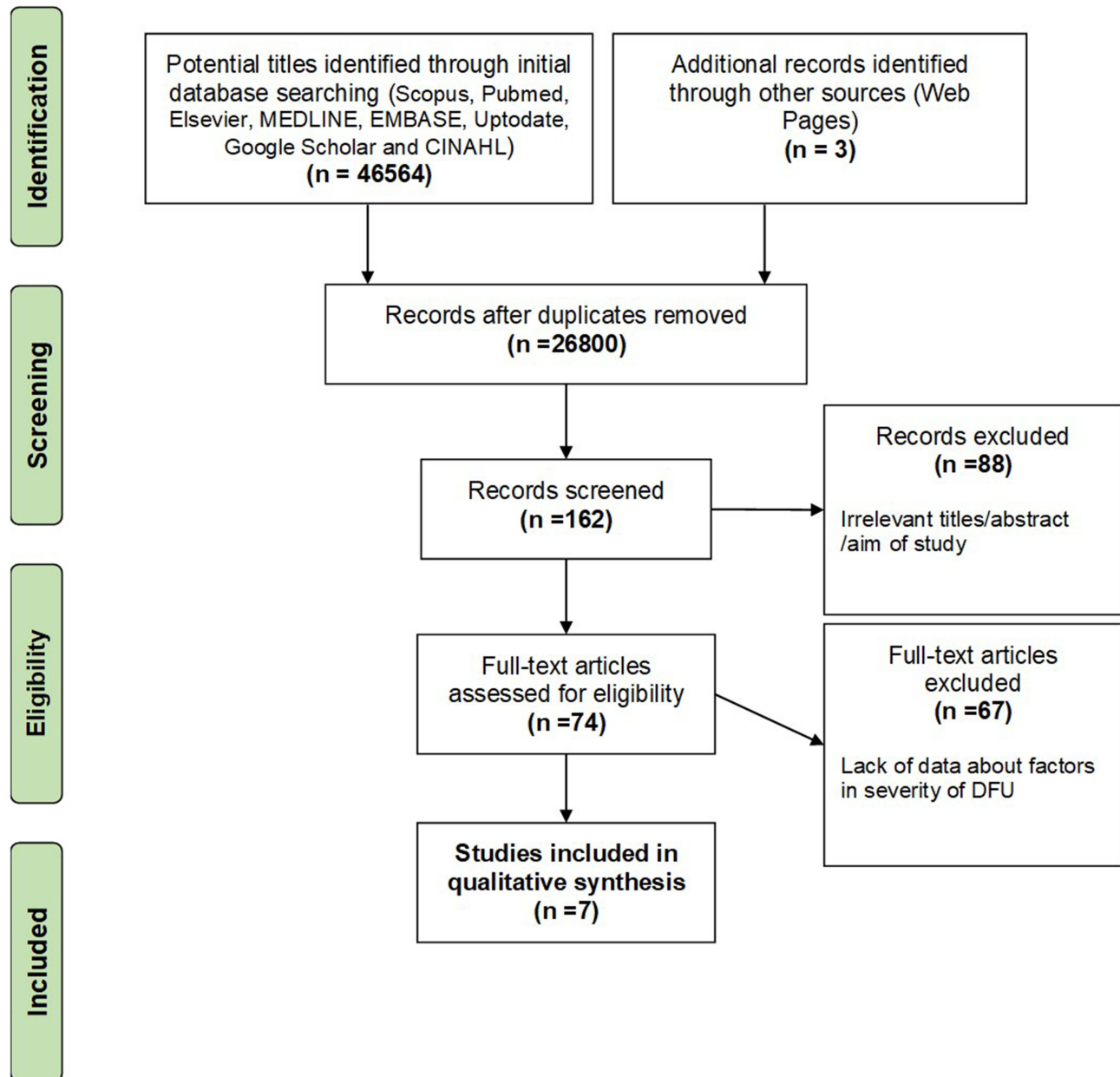


Figure 1 PRISMA flow diagram for the literature search and study selection.

Notes: Copied from Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097²⁷

Table 1 Characteristics of Included Reports (n=7)

Study	Design ^a	Patients	Type of Diabetes (%)	Country	SDFU Tool ^b	SDFU (%)
Ghobadi et al ³⁴	CS	190	1 and 2	Iran	Wagner	G1, 78 (41.1) G2, 89 (46.8) G3, 16 (8.4) G4, 7 (3.7) G5, 0
Holzer et al ³⁵	DA	3524	–	USA	Wagner	G1, 729 G2, 1500 G3, 996 G4, G5, 297
Madmoli et al ²⁹	CS, DA	4436	All	Iran	Wagner	G1, 456 G2, 2679 G3, 589 G4, 368 G5, 344
Mir et al ³⁷	DA	100	–	India	Wagner	G1, 13 G2, 22 G3, 25 G4, 31 G5, 9
Moeini et al ²⁸	DA	94	–	Iran	Wagner	G1, 3 (3.2) G2, 70 (75) G3, 17 (17.4) G4, 1 (1.1) G5, 3 (3.2)
Smith-Strøm et al ³⁶	Retro-cohort	105	T2, 83 (79.0)	Norway	TDWCS	G1, 37 (35.2) G2, 26 (24.8) G3, 42 (40)
Winkley et al ³³	Cohort	253	T1, 43 (17) and T2, 210 (83)	UK	TDWCS	Superficial, 188 (74.3) Deep, 65 (25.7)

Notes: ^aDesign; ^bSDFU Tool.

Abbreviations: CS, cross-sectional, DA, descriptive-analytic, Retro, retrospective; SDFU, severity of diabetic foot ulcer; TDWCS, Texas Diabetic Wound Classification System.

the USA (n=1), Norway (n=1) and the UK (n=1). These studies applied to all diabetic type patients. Overall, 8702 patients were assessed, with study sample sizes varying between 97²⁸ and 4436²⁹ patients.

Score for Estimates of Severity

In the 7 studies, the Wagner score (n=5) and the Texas Diabetic Wound Classification System (n=2) were used to evaluate severity of ulcers. The Wagner classification is the most commonly used for grading of diabetic foot ulcers. The Wagner ulcer scale is one of the oldest and most extensive categories in all types of ulcers. Wagner developed a classification system and a treatment

algorithm for each grade of diabetic foot ulcer. The Wagner system was developed in 1976 by Meggitt and adjusted in 1981 by Wagner.³⁰ Wagner scores classify DFU on the basis of the ulcer depth into six grades (from G0 to G5). The Texas Diabetic Wound Classification System (TDWCS) system is based in part on depth, and in part on the absence or presence of infection, ischemia or both.^{31,32} On the basis of the Wagner score (8344 patients), patients in five stages were included: G1 (15.32%), G2 (52.25%), G3 (19.69%), and G4 and G5 (12.70%). On the basis of TDWCS (358 patients), patients in two stages were included: superficial (62.84%) and Deep ulcer (37.15%).

Overview of Factors Influencing Severity of DFU

Twenty-five factors that can influence severity of diabetic foot ulcer have been reported in studies (Table 2). These factors were obtained during cohort, descriptive-analytical and cross-sectional studies. By eliminating the duplicate factors reported in the studies, 19 factors affecting severity of diabetic foot ulcer have been introduced. Repeated factors in various studies include smoking, high BMI, blood sugar, type of diabetes treatment, other complications in patients and high age.^{28,29,33} A significant relation between severity of DFU with other complications of diabetes is considered. Although it is not known precisely which complication of diabetes has more effect, it appears that the effect of microvascular complications is more than others in the severity of DFU.^{33,34} Inadequate vascular status was

another factor in DFU severity.³⁵ High BS, FBS and BS 2 hours after breakfast have been reported as other effective factors ($P<0.05$, $P=0.026$, $P=0.016$).^{28,29} In addition, the results of Madmoli et al's study have shown that the type of bacteria from ulcer infection also affects severity of the DFU; this means that the ulcer containing coagulase-negative *Staphylococcus* bacteria has severity.²⁹ There was also a significant relationship between medication use and severity of DFU. In Winkley et al's study, patients treated with insulin had more severe DFU (hazard ratio=1; 95% CI), and Madmoli et al's study reported a relation between both oral medication and insulin injections with severity of DFU ($P=0.035$).^{29,33} The correlation between marital status and gender was reported only in one study ($P=0.004$).²⁸ This relation consists of the effects of single marriage status and male gender in severity of diabetic foot ulcer. Also, high cholesterol levels and triglycerides have been reported in one study ($P<0.05$).²⁹ There are other factors that include: the relationship between the depth of the ulcer and severity of DFU measured with the Wagner score ($P=0.036$), duration of the DFU ($P=0.031$) and the delay-time between the incidence of DFU and referral ($P=0.042$).^{28,36} One study reported a relationship between type 2 diabetes mellitus and wound severity (hazard ratio=1.84; 95% CI), and a relationship between wound location (plantar ulcer) and wound severity was also reported (hazard ratio=1; 95% CI).³³ In Mir et al's study on 100 patients in India, a significant association was found between the HSPA1B genotype (AG genotype) and severity of DFU in diabetic patients ($P=0.008$).³⁷ Also, another factor that affects severity of DFU is drug use (addiction) ($P=0.006$).²⁹

Table 2 Factors Affecting Severity of DFU

Study	Factors
Ghobadi et al ³⁴	Other complications in diabetic patients with DFU
Holzer et al ³⁵	Inadequate vascular status
Madmoli et al ²⁹	Smoking BMI Blood glucose level Type of bacteria in ulcer Drug use (addiction) Diabetes treatment (oral hypoglycemic tablets and insulin therapy) Triglyceride and cholesterol
Mir et al ³⁷	HSPA1B genotyping (the AG genotype)
Moeini et al ²⁸	Smoking BMI FBS BS 2 hours after breakfast Depth of ulcer Age Duration of DFU Gender (man) Marriage (single)
Smith-Strøm et al ³⁶	Duration time from ulcer onset until referral
Winkley et al ³³	Age Type of diabetes (type 2) Diabetes treatment (insulin) Microvascular complications Location of ulcer

Abbreviations: BMI, body mass index; BS, blood sugar; FBS, fast blood sugar.

Discussion

DFU is one of the most common, severe and expensive complications of diabetes and the major cause of hospitalization in the world.³⁸ The total cost of treating the DFU is close to \$11 billion in the US and \$456 million in the UK.^{39,40} The prevalence of diabetic foot ulcer in a varied population is 3–18%.^{10,41–43} DFU causes a high rate of amputation, and emotional disorders, socioeconomic problems, low quality of life-style and even death^{24,44–47}, and if it occurs in younger patients can exclude the community's workforce. Today, we know the factors that affect the incidence of DFU. Because the duration of diabetes is one of the contributing factors in the occurrence of foot ulcer, diabetic patients are likely to get it throughout their lives and it is more effective to identify the factors that affect the severity or reduction of foot ulcers. Understanding the exacerbating factors of diabetic foot

ulcers can help preventive functions to improve the quality of life and reduce complications of foot ulcers. Twenty-five factors were reported in 7 studies that affect severity of DFU. The most repeated factors were smoking, high BMI, blood sugar, type of diabetes treatment, other complications in patients and high age.^{28,29,33} Factors such as smoking and high BMI, which affect the severity of a foot ulcer, can be influenced by the patient's life-style. Also, the effect of lack of diabetes control shown by abnormal Hb1AC and the delay-time between³⁶ the incidence of DFU and referral can reflect inadequate life-style, awareness and self-care. The improvement of knowledge and awareness of patients can be useful. In addition, diabetes has other complications such as cardiovascular disease, retinopathy and renal failure.^{48,49} Multiple complications can occur in diabetes patients and can affect them. It is not known exactly which complication of diabetes has more effect on severity of DFU, but Winkley et al's study reported that the effects of microvascular complications are more than others in severity of DFU.³³ Also, in Ghobadi et al's study, cardiovascular complications showed more in DFU patients.³⁴ Brennan et al stated that ulcer severity is a more significant predictor of subsequent mortality than other complications.¹⁸ Coagulase-negative *Staphylococcus* bacteria isolated from DFU were correlated with severity of DFU. In other studies, *Staphylococcus aureus* was the bacterium most isolated from DFU and other bacteria were Enterobacteriaceae and *Pseudomonas aeruginosa*.⁵⁰ Also, a significant relation between diabetes treatment and severity of DFU is reported.^{29,33} Although there is no clear reason for this relation, consider that insulin injection is more related to severity of DFU and can be due to the inflammation reaction in the body. Similar, in the effect of high cholesterol levels and triglycerides in severity of DFU,²⁹ this effect can be due to inflammation.⁵¹ Preventing and reducing the effect of this factor can be easily controlled through the creation of a regular, personalized diet plan. The relation between depth and severity of DFU in Moeini et al's study²⁸ is clearly because one of the contexts of the Wanger score is on the basis of ulcer depth.³⁰ Similarly, the effect of duration of DFU on severity of foot ulcers²⁸ can be due to the cumulative effect of foot ulcers, and prolonged duration of DFU can be a sign of severity of DFU and the ineffectiveness of treatments. Only one study reported the effect of diabetes type and ulcer location on DFU severity³³ and this result should be of more interest to researchers for future studies in order to be more precisely confirmed or rejected. The effect of ulcer location on the severity of foot ulcers may be due to the effect

of mechanical pressure on the wound that needs to be controlled. Also, a higher severity of wounds has been reported in addicted patients,²⁹ which may be due to a lack of personal hygiene. Although the relation between genotype and DFU severity is reported,³⁷ the effect of genotyping on the severity of foot ulcer needs further studies because other genetic factors are likely to be involved, as well as the differences between races. Inadequate vascular status was another factor.³⁵ In contrast, Hao et al reported that there is no significant relation between peripheral artery disease and DFU severity.⁵²

There are many heterogeneities between studies, but based on the findings we can improve the patient's status with hygiene education and improvement of awareness and function in self-care. In addition, the quality of studies is considered poor to fair and future studies with better quality must be done.

Limitations

In this study, we employed a comprehensive search strategy for key review tasks that contains all of the studies that assessed factors affecting severity of diabetic foot ulcer. However, it is possible that we missed unpublished data because we did not search the gray literature, and due to the novelty of the subject, few studies have been conducted on this. But the importance of the problem of DFU severity needs further study. This study will not be the final review of studies in this regard.

Implications and Recommendations

This study has implications for further research and for clinical practice.

For further studies, the methodological flaws and inadequate reporting should be improved. More complete reports of the factors affecting DFU severity should be provided. Also, the study method should be adjusted according to the guidelines provided to improve the quality of studies. Findings that are reported must be considered for the treatment of patients.

Conclusion

DFU is a severe complication of diabetes. Twenty-five factors were reported in studies that can affect severity of DFU. Many of these factors related to life-style and self-care, and health system programs may be effective in preventing severe foot ulcer. Further studies must be done for additional information about it. For this purpose, we present the following recommendations:

1. Proper hygiene and foot-care teaching and training for patients to reduce the risk factors.
2. Providing teaching and training for care-providers of patients due to knowing factors and reducing them.
3. Do other studies with better quality to increase the information about DFU.

Abbreviations

DFU, diabetic foot ulcer; BS, blood sugar; FBS, fast blood sugar; BMI, body mass index.

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Author Contributions

MJ, PAS and SO contributed to designing the study. MJ, PAS and SO contributed to the initial search and data extraction. The final report and manuscript were written by MJ, PAS and SO. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no conflicts of interest in this work.

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