

World Journal of *Diabetes*

World J Diabetes 2022 December 15; 13(12): 1001-1183



REVIEW

- 1001** Non-coding RNAs: Role in diabetic foot and wound healing
Tang YB, Uwimana MMP, Zhu SQ, Zhang LX, Wu Q, Liang ZX
- 1014** Diabetic foot ulcer: Challenges and future
Yang L, Rong GC, Wu QN
- 1035** Keeping an eye on the diabetic foot: The connection between diabetic eye disease and wound healing in the lower extremity
Ramsey DJ, Kwan JT, Sharma A
- 1049** Diabetic foot ulcers: Classification, risk factors and management
Wang X, Yuan CX, Xu B, Yu Z
- 1066** Mesenchymal stem cell-derived exosomes: The dawn of diabetic wound healing
Wu J, Chen LH, Sun SY, Li Y, Ran XW

MINIREVIEWS

- 1096** Prehabilitation of overweight and obese patients with dysglycemia awaiting bariatric surgery: Predicting the success of obesity treatment
Cigrovski Berkovic M, Bilic-Curcic I, Mrzljak A, Canecki Varzic S, Cigrovski V
- 1106** Diabetic foot ulcers: A devastating complication of diabetes mellitus continues non-stop in spite of new medical treatment modalities
Akkus G, Sert M
- 1122** Hyperbaric oxygen therapy and chemokine administration - a combination with potential therapeutic value for treating diabetic wounds
Venkataseshan J, Viswanathan P
- 1131** The role of artificial intelligence technology in the care of diabetic foot ulcers: the past, the present, and the future
Pappachan JM, Cassidy B, Fernandez CJ, Chandrabalan V, Yap MH
- 1140** Single nucleotide variations in the development of diabetic foot ulcer: A narrative review
Hu YJ, Song CS, Jiang N

ORIGINAL ARTICLE

Observational Study

- 1154** Baseline moderate-range albuminuria is associated with protection against severe COVID-19 pneumonia
Bashkin A, Shehadeh M, Shbita L, Namoura K, Haiek R, Kuyantseva E, Boulos Y, Yakir O, Kruzel-Davila E

SYSTEMATIC REVIEWS

- 1168** Comparison of gliclazide *vs* linagliptin on hypoglycemia and cardiovascular events in type 2 diabetes mellitus: A systematic review

Mohan V, Wangnoo S, Das S, Dhediya R, Gaurav K

ABOUT COVER

Editorial Board Member of *World Journal of Diabetes*, Joseph M Pappachan, Professor, MBBS, MD, MRCP, FRCP, Academic Editor, Consultant Endocrinologist, Senior Researcher, Department of Endocrinology & Metabolism, Lancashire Teaching Hospitals NHS Trust, Preston PR2 9HT & Manchester Metropolitan University, Manchester, M15 6BH, United Kingdom. drpappachan@yahoo.co.in

AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

INDEXING/ABSTRACTING

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJD* as 4.560; IF without journal self cites: 4.450; 5-year IF: 5.370; Journal Citation Indicator: 0.62; Ranking: 62 among 146 journals in endocrinology and metabolism; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Xi Chen*; Production Department Director: *Xu Guo*; Editorial Office Director: *Yun-Xiaojiao Wu*.

NAME OF JOURNAL

World Journal of Diabetes

ISSN

ISSN 1948-9358 (online)

LAUNCH DATE

June 15, 2010

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Lu Cai, Md. Shahidul Islam, Jian-Bo Xiao, Michael Horowitz

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/1948-9358/editorialboard.htm>

PUBLICATION DATE

December 15, 2022

COPYRIGHT

© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Diabetic foot ulcers: Classification, risk factors and management

Xuan Wang, Chong-Xi Yuan, Bin Xu, Zhi Yu

Specialty type: Endocrinology and metabolism

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Gluvic Z, Serbia; Latiri IO, Tunisia

Received: August 27, 2022

Peer-review started: August 27, 2022

First decision: October 5, 2022

Revised: October 18, 2022

Accepted: November 18, 2022

Article in press: November 18, 2022

Published online: December 15, 2022



Xuan Wang, Chong-Xi Yuan, Bin Xu, Zhi Yu, Key Laboratory of Acupuncture and Medicine Research of Ministry of Education, Nanjing University of Chinese Medicine, Nanjing 210023, Jiangsu Province, China

Corresponding author: Zhi Yu, PhD, Lecturer, Key Laboratory of Acupuncture and Medicine Research of Ministry of Education, Nanjing University of Chinese Medicine, No. 138 Xianlin Road, Nanjing 210023, Jiangsu Province, China. yuzhi@njucm.edu.cn

Abstract

Diabetic foot ulceration is a devastating complication of diabetes that is associated with infection, amputation, and death, and is affecting increasing numbers of patients with diabetes mellitus. The pathogenesis of foot ulcers is complex, and different factors play major roles in different stages. The refractory nature of foot ulcer is reflected in that even after healing there is still a high recurrence rate and amputation rate, which means that management and nursing plans need to be considered carefully. The importance of establishment of measures for prevention and management of DFU has been emphasized. Therefore, a validated and appropriate DFU classification matching the progression is necessary for clinical diagnosis and management. In the first part of this review, we list several commonly used classification systems and describe their application conditions, scope, strengths, and limitations; in the second part, we briefly introduce the common risk factors for DFU, such as neuropathy, peripheral artery disease, foot deformities, diabetes complications, and obesity. Focusing on the relationship between the risk factors and DFU progression may facilitate prevention and timely management; in the last part, we emphasize the importance of preventive education, characterize several of the most frequently used management approaches, including glycemic control, exercise, offloading, and infection control, and call for taking into account and weighing the quality of life during the formulation of treatment plans. Multidisciplinary intervention and management of diabetic foot ulcers (DFUs) based on the effective and systematic combination of these three components will contribute to the prevention and treatment of DFUs, and improve their prognosis.

Key Words: Diabetes; Diabetes foot ulceration; Classification; Diabetes complications; Clinical management; Lower limb complications

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Diabetic foot ulcers (DFUs) are a common complication of diabetes. The high recurrence and amputation rates associated with DFUs reflect an urgent need to improve care and treatment methods, highlighting the importance of a comprehensive investigation of the important components of clinical diagnosis and treatment. This article reviews the classification and risk factors of DFUs and summarizes the common clinical management approaches.

Citation: Wang X, Yuan CX, Xu B, Yu Z. Diabetic foot ulcers: Classification, risk factors and management. *World J Diabetes* 2022; 13(12): 1049-1065

URL: <https://www.wjgnet.com/1948-9358/full/v13/i12/1049.htm>

DOI: <https://dx.doi.org/10.4239/wjd.v13.i12.1049>

INTRODUCTION

The prevalence of diabetes mellitus (DM) is rapidly spreading at an alarming rate worldwide[1]. DM is known to damage multiple organs, including the heart, kidney, eye, and nerves, leading to complications such as heart attack, stroke, blindness, kidney failure, and lower limb amputation. Diabetic foot ulcer (DFU) is a frequent complication that occurs in approximately 6.3% of patients with DM globally [2]. The high incidence of DFU and the associated mortality and morbidity are the most common reasons for hospitalization of diabetes patients. Early in the course of DM, patients experience serious foot sensitivity symptoms such as pain and tingling, while later stages of the disease course are characterized by negative symptoms such as numbness and weakness of the toes. With the progression of the disease, patients usually show mixed pain sensitivity and dullness, along with decreased limb sensation and motor function, which lead to imbalance and unsteadiness and increase the likelihood of falls[3,4]. In addition, because of the increasing morbidity, DFU is a leading cause of non-traumatic amputation and is associated with an increased risk of death[5].

The high incidence and intractability of DFU extract a substantial cost in terms of reduced productivity and increased healthcare-related expenses. Appropriate and prompt treatment of DFU requires a multifaceted approach, including timely and correct diagnosis and classification, multiple assessments of risk factors, and appropriate choice of management, all of which should be based on the patient's actual condition. This primer will present the current knowledge of the potential pathogenesis of DFU, discuss the clinical classification of DFU, highlight the corresponding approaches to diagnosis and common management techniques, and close with a call that more attention and feasible interventions are required for DFU management.

DEFINITION AND CLASSIFICATION OF DFU

Definition

The practical guidelines formulated by the International Working Group on the Diabetic Foot (IWGDF) defined DFU as a set of symptoms secondary to current or previous diabetes, including skin chapping, ulceration, infection, or destruction of foot tissue, which partly reflects the fuzzy and imprecise nature of this concept[6,7]. DFU is a complicated and multifactorial clinical problem that affects many patients with diabetes, who experience ulceration and infection, invariably with neuropathy and/or peripheral artery disease (PAD), that disrupt the foot epidermis and dermis, breach the skin envelope, expose sterile structures, and finally form full-thickness lesions[8]. In the Western world, more than 60% of non-traumatic amputations involve DFU, which leads to an increase in hospitalization rate and mortality[9] and causes reduced quality of life (QoL). Moreover, treatments based on amputation impose a heavy burden on the economic and health resources of patients with diabetes[10].

Classification

The multiple factors associated with the development of DFU, such as the complex process and complications of diabetes, may all lead to various degrees of neurological abnormalities and vascular damage (known as neuropathy and PAD)[11]. Once the ulcer is formed, the factors affecting healing may be more complex, and different factors may dominate at different stages over time. Thus, these related factors play different roles depending on the severity of disease and duration of recovery, necessitating different diagnoses and treatments for seemingly the same symptoms and causing differences in the curative effect[12]. In these circumstances, the classification and scoring criteria for describing lesions of DFU should be formatted in a manner that is clinically recognized and widely used, which will allow characterization of DFU on the basis of differences and facilitate suggestions for treatment or care programs.

Considering the different audiences and objectives of the classification and scoring systems, no universally accepted system has been published to date. Various systems are used to describe and assess the severity of DFU, and three types of key factors contributing to the scoring system have been proposed, namely, patient-related, limb-related, and ulcer-related factors, which reflect end-stage renal failure, PAD, and loss of protective sensation, along with classification of the wound grade[13]. Most systems set scoring criteria based on the size and characteristics of the wound, such as size, depth, ischemia, and infection, allowing characterization of the lesion, while risk factors such as neuropathy and peripheral arterial occlusive disease are incorporated when clinical interventions or preventive guidance are required[14,15]. In this section, we will introduce several major systems and summarize their characteristics and applications.

The Meggitt-Wagner system: This system, which was described by Meggitt in 1976 and disseminated by Wagner in 1979, was once the most widely used system[16-18]. It is a six-grade classification system mainly covering the depth of the ulcer and the degree of tissue necrosis[19] (Table 1). This system, which is essentially wound-based, is intuitive and simple to use, but since it does not consider clinical parameters such as peripheral neuropathy and PAD, it cannot distinguish between infection and ischemic lesions, which is also related to its recognized imprecision and limitations[20].

The University of Texas classification system: The classification system proposed by the University of Texas (UT) takes some common clinical signals and symptoms of DFU into consideration by using a 4 × 4 matrix assessing ulcer depth horizontally and infection and ischemia status vertically[15,21] (Table 2). Since it aims to divide patients into four categories depending on whether they are infected or ischemic on the premise of distinguishing the depth of ulcer, the UT system is more helpful to predict amputation than the Meggitt-Wagner system, which simply classifies the ulcer condition[21,22].

The size (area, depth), sepsis, arteriopathy, denervation system: The size (area, depth), sepsis, arteriopathy, and denervation [S(AD)SAD] system was proposed in 1999 and is mainly designed for clinical audits[23]. The system was first verified in 2004, and in order to further refine the classification of ulcers for prospective research, some criteria missing from the UT system were included subsequently[24]. This system contains five elements that are scored in grades 0-3 according to severity, namely, size (area, depth), infection (sepsis), ischemia (arteriopathy), and neuropathy (denervation), and uses acronyms to facilitate memorization and feature generalization[24] (Table 3). The advantage of this system lies in its ability to allow specific recording of ulcers without requiring professional testing technology and equipment, facilitating its usage in clinics. However, because of the multiple descriptions of characteristics and irregular details of ulcers, the system is difficult to remember for operators, which may be the reason why the S(AD)SAD system is considered to be more suitable for audits while the UT system is used for clinical description and communication[25,26].

The site, ischemia, neuropathy, bacterial infection, area, depth system: A simplified and refined form of the S(AD)SAD system, the site, ischemia, neuropathy, bacterial infection, area, depth (SINBAD) system, was proposed to reduce the difficulties in clinical use caused by the inclusion of more complicating criteria while retaining the descriptions of ulcer characteristics to the maximal extent possible[12,27]. The SINBAD system still contains five elements (area, depth, infection, ischemia, and neuropathy), and grades each element as either 0 or 1 point to create an evaluation system with scores of 0-6 for description of increasing severity[27] (Table 4). The modified system is simple but sufficiently robust and allows collection of the necessary information without specialist equipment, except for routine clinical examinations[13]. It has been proven to have moderate inter-observer and excellent intra-observer reproducibility and may help accurately describe the progress of ulcers, including healing and the need for amputation, which was confirmed by the fact that IWGDF recommends the SINBAD system[28].

The Wound, Ischemia, and foot Infection system: Because of the rising prevalence of neuroischemic ulcers, the dichotomy for ischemia in the existing systems lacks effective severity grading and cannot meet clinical requirements. In 2014, the Wound, Ischemia, and foot Infection (WIFI) system was proposed by the Society for Vascular Surgery Lower Extremity Guidelines Committee, and it covered the three most important risk factors that may cause amputation of lower limbs: WIFI[29]. The three factors are assigned scores from 0 to 3, of which the wound is graded on the basis of size, depth, severity, and anticipated difficulty in achieving wound healing; ischemia is rated on the basis of ABI gradation; and foot infection is rated on the basis of the scope and depth of the wound[29] (Table 5). Clinical studies have suggested that this system primarily offers value in predicting major amputation [30]. In patients with DFU and vascular disease, the WIFI system is recommended to evaluate perfusion and vascular function and help rapidly implement revascularization and/or drainage[31]. Since the evaluation of foot perfusion indices requires specialist measurements, assessments using this system require expertise in vascular intervention, indicating that it is not ideal for use in primary and/or community care[13].

Table 1 Wagner classification system

Grade	Ulcer depth
0	Pre-ulcerative area without open lesion
1	Superficial ulcer (partial/full thickness)
2	Ulcer creep to tendon, capsule, bone
3	Stage 2 with abscess, osteomyelitis, or joint sepsis
4	Localized gangrene
5	Global foot gangrene

Table 2 University of Texas classification system[21]

	Grade 0	Grade 1	Grade 2	Grade 3
	Pre- or post-ulcerative site	Superficial wound not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Ulcer penetrating to bone of joint
Lesions without infection or ischemia				
Infected/non-ischemic lesions				
Ischemic noninfected lesions				
Ischemic infected lesions				

Table 3 Size (area, depth), sepsis, arteriopathy, denervation system

Grade	Size		Sepsis	Arteriopathy	Denervation
	Area	Depth			
0	Skin intact	Skin intact	None	Pedal pulses present	Pin pricks intact
1	< 1 cm ²	Superficial (skin and subcutaneous tissue)	Surface	Pedal pulses reduced or one missing	Pin pricks reduced
2	1-3 cm ²	Tendon, periosteum, joint capsule	Cellulitis	Absence of both pedal pulses	Pin pricks absent
3	> 3 cm ²	Bone or joint space	Osteomyelitis	Gangrene	Charcot

RISK FACTORS FOR DFU

DFU is caused by multiple interacting risk factors, of which the most common major identified factors include diabetic neuropathy (DPN), PAD, and foot deformities. These factors can be further divided into different degrees according to the severity[32-36]. In this section, the main risk factors are listed and introduced.

Neuropathy

The neuropathy induced by diabetes is a symmetric polyneuropathy that affects the sensory, motor, and autonomic components of the peripheral nerves to varying degrees[37]. Epidemiological data shows that neuropathy is responsible for 16%-66% of the cases of diabetic foot syndrome[38], and patients with neuropathy are prone to show relapse after healing, eventually leading to lower limb amputation[39]. DPN results in the loss of protective sensation, usually starting in a symmetrical and sock-like manner. Small and unmyelinated nerve fibers responsible for conducting afferent sensory perception, like C-type fibers, are the first to be damaged, resulting in tissue damage due to poor perception of trauma and/or mechanical stress. Thus, the relatively minor damage will continue to accumulate and result in a progressively worsening wound with difficulty in healing[33].

Motor neuropathy causes atrophy of foot muscles by denervation of specific muscle groups, which directly affect the function of the foot. Since the small muscles of the foot, like the extensor digitorum brevis and lumbrical and interosseous muscles, are paralyzed gradually, the anatomy of the foot arch changes, and the metatarsophalangeal joints (MTPJs) become hyperextended or over-contracted[40,41]. The joints remain movable in the initial stage, but with aggravation of the symptoms, the

Table 4 Site, ischemia, neuropathy, bacterial infection, area, depth system[13]

Category	Definition	Score
Site	Forefoot	0
	Midfoot and hindfoot	1
Ischemia	Pedal blood flow intact: At least one palpable pulse	0
	Clinical evidence of reduced pedal flow	1
Neuropathy	Protective sensation intact	0
	Protective sensation lost	1
Bacterial infection	None	0
	Present	1
Area	Ulcer < 1 cm ²	0
	Ulcer ≥ 1 cm ²	1
Depth	Ulcer confined to skin and subcutaneous tissue	0
	Ulcer reaching muscle, tendon or deeper	1
Total possible score		6

Table 5 Wound, Ischemia, and foot Infection system

Grade	Wound	Ischemia		Foot infection system	
	Clinical features	ABI (mmHg)	ASP (mmHg)	Toe pressure, TcPO ₂ (mmHg)	Clinical manifestations
0	No ulcer no gangrene	≥ 0.80	> 100	≥ 60	No symptoms or signs of infection. Infection present, as defined by the presence of at least two of the following items: (1) Local swelling or induration; (2) Erythema 0.5 cm-2 cm around the ulcer; (3) Local tenderness or pain; (4) Local warmth; and (5) Purulent discharge (thick, opaque to white, or sanguineous secretion)
1	Small, shallow ulcer(s) on the distal leg or foot; no exposed bone, unless limited to the distal phalanx	0.6-0.79	70-100	40-59	Local infection involving only the skin and the subcutaneous tissue exclude other causes of an inflammatory response of the skin (<i>e.g.</i> , trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, and venous stasis)
2	Deeper ulcer with exposed bone, joint, or tendon generally not involving the heel; shallow heel ulcer without calcaneal involvement, gangrenous changes limited to digits	0.4-0.59	50-70	30-39	Local infection with erythema > 2 cm, or involving structures deeper than skin and subcutaneous tissues (<i>e.g.</i> , abscess, osteomyelitis, septic arthritis, and fasciitis), and no systemic inflammatory response signs
3	Extensive, deep ulcers involving forefoot and/or midfoot; deep, full-thickness heel ulcers with or without calcaneal involvement, extensive gangrene involving the forefoot and/or midfoot; full-thickness heel necrosis with calcaneal involvement	≥ 0.39	< 50	< 30	Local infection with signs of SIRS, as manifested by two or more of the following: (1) Temperature > 38 °C or < 36 °C; (2) Heart rate > 90 beats/min; (3) Respiratory rate > 20 breaths/min or PaCO ₂ < 32 mmHg; and (4) White blood cell count > 12000 or < 4000 cu/mm or 10% immature bands

ABI: Ankle-brachial index; ASP: Ankle systolic pressure; TcPO₂: Transcutaneous oxygen pressure; SIRS: Systemic inflammatory response syndrome.

interphalangeal joints show flexion and malpositioning, leading to foot deformity[42,43]. Clinically, motor neuropathy often presents with sensory damage. The combination of motor and sensory neuropathy results in an unequal foot load and insecure gait with pain insensitivity, and the deformed joints and over-pressure-loaded plantar are constantly worn and develop hyperkeratosis over time, promoting the development of ulcers[32,43-45].

Autonomic system dysfunction is thought to be responsible for the pathogenesis of ulceration. Sweating dysfunction caused by autonomic neuropathy causes overheating of the skin through increased deeper blood perfusion, resulting in anhidrotic and fissural skin and a broken dermal barrier

and diminishing the effectiveness of the skin as a barrier against microbial invasion[32,46]. Moreover, the increased glycation of keratin aggravates the ulcers by causing the skin to become thick and squeezing the soft tissue that it covers[47].

PAD

PAD is a clinical term that is classically used to summarize the various diseases that affect the noncardiac and non-intracranial arteries and result in complete or partial occlusion of the peripheral arteries of the upper and/or lower limbs, leading to tissue ischemia and blood supply insufficiency[48, 49]. PAD is another equally important contributor to neuropathy in the occurrence of leg ulcers and amputation[50]. The frequency of lower limb amputations in diabetes patients with PAD is higher than that in those without PAD, which may be related to a stronger association with DM in limbs below the knee because the arteries of the lower limbs, especially distal arteries like the dorsalis pedis artery, are mostly involved in DM[51-53]. Among DM patients with PAD characterized by occlusion of the lower limb arteries, one-third will experience intermittent claudication described as pain, cramp, and/or numbness of the affected limb, which occurs when exercising and at rest[52,54]. Long-term intermittent claudication causes progressive dysfunction and disability, and in combination with an impaired vasodilatory response to plantar pressures, it can result in critical limb ischemia, thus leading to foot ischemic ulceration and amputation[55-57].

Foot deformities

Together with neuropathy and trauma, foot deformity was reconfirmed by the Task Force of the Foot Care Interest Group of the American Diabetes Association as a most common triad of causes that interact and ultimately result in ulceration[34,58]. Common structural foot deformities include interphalangeal joint deformity, MTPJ deformity, pes cavus, and pes equinus[59]. The most prevalent and common deformity in DM patients is MTPJ deformity, including hammer-and-claw toes characterized by hyperextension of interphalangeal joints, and hallux valgus characterized by outward tilting of the first MTPJ[58,60].

At present, the specific course of foot deformities in patients with DM is not clear. The widely accepted pathogeny is associated with muscle atrophy, decreased joint mobility, and uneven force on the sole as a result of motor neuropathy[58,59,61]. In DM patients, the musculoskeletal components are destroyed, which is embodied by the atrophy of intrinsic and extrinsic foot muscle and fatty infiltration [62-64]. The atrophy of small muscles like the extensor digitorum brevis and/or interosseous muscles directly affects the stability of joints and the function of the foot by destroying the structure of joints and leading to MTPJ hyperextension and interphalangeal joints hypercurvature[33,65,66]. Moreover, because of incorrect overpressure, the mobility of joints gradually decreases, further aggravating the pressure on the bony prominences, particularly the metatarsal head[67]. Persistent exposure to repetitive and excessive pressure causes deformation of the metatarsal head, and pressures exceeding the threshold may lead to prolonged ischemia, causing the skin below to weaken and break down[68-71]. Meanwhile, blood supply recovery after ischemia caused by pressure changes can lead to reperfusion injury. These ischemia-reperfusion cycles may trigger an excessive inflammatory response, further aggravating the tissue injury, which is considered to be another cause of pressure ulcers[72,73].

Other factors also contribute to ulcer formation by increasing plantar pressure. Hyperkeratosis refers to a thickening of calluses caused by sustained increasing plantar pressure, and is a crucial factor that always precedes ulcer formation[59,74]. Callus thickening has been reported frequently in the plantar area of the metatarsal heads, the heel, and the middle of the big toe[59]. Once formed, it adds gentle but sustained pressure on the underlying soft tissue, and in combination with other pressures, it leads to the formation and rupture of ulcers[58,75]. Another common factor is pathological changes in the tendon, like an increased Achilles tendon size and abnormal tendon structure[76-78]. Thickened fascia and tendon limit joint activity and weaken ankle dorsiflexion, also accelerating the formation of ulcers[62, 79].

DFU PREVENTION AND MANAGEMENT

The existing management systems for DFU have gradually expanded on the basis of the three principles established by Treves[80], namely, sharp debridement, offloading, and education. In this section, several commonly used management approaches and their applications are listed, indicating that multidisciplinary DFU care will eventually become the mainstream approach.

Preventive education

Foot care education and self-examination represent the cornerstone and the primary protective factor in DFU prevention[81]. Comprehensive foot care and intensive nursing education together with patient education are reported to be simple, feasible, and strongly effective for DFU prevention[82,83]. For physicians and/or podiatrists, periodic evaluation of arterial perfusion in patients with DM, especially those with peripheral neuropathy and/or foot deformity, which are the main predictive risk factors for

DFU, may help improve the foot condition. For medical institutions, strengthening publicity on preventive measures to improve patients' self-management is important and increasingly urgent[84]. The popularization of self-management should include multiple aspects like foot hygiene instruction, proper footwear use, skin lesion self-examination, and foot sensation self-evaluation. Guiding and encouraging patients to wash feet with water at a moderate temperature, keeping feet clean and dry, and inspecting the condition and checking the color of foot skin can help effectively avoid cracks caused by autonomic neuropathy and usual redness of the skin caused by overpressure[81]. For patients, more than improvements in self-management, regular screening for diabetes complications such as ophthalmic complications are essential and more cost-effective than no screening[82].

Debridement

Debridement can be performed by surgical and non-surgical methods, and both of them are used to remove nonviable or devitalized tissue from the wound bed to accelerate granulation tissue formation and re-epithelialization, which promote wound healing[85]. Experts have considered surgical debridement as the formation of a "new acute wound", since the nonviable tissue has to be debrided down to the bleeding tissue[33]. This mechanical separation is impossible without damaging normal tissues. The surgical removal of superficial necrotic and hyperkeratotic tissue caused by repeated pressure on the foot is essential for wound healing, and it is necessary for deep wounds with bone and soft tissue involvement. Non-surgical debridement includes autolytic debridement with hydrogels, enzymatic debridement, biosurgery, and mechanical debridement with hydrotherapy[86]. Medicinal maggots have shown the ability to remove nonviable tissue selectively and may reduce the risk of secondary superinfection[33], which may lead to a shortened period of wound-healing progression[87].

Glycemic control

The close relationship between blood glucose levels and the progression of diabetes complications has been reported extensively in the literature[88]. Intensive glycemic control in patients with DM has been reported to delay the occurrence of retinopathy, peripheral neuropathy, and nephropathy, all of which are the main risk factors for DFU, and thus show a positive correlation with wound healing. Various studies evaluated and reported the positive correlation of glycemic control and DFU outcomes[39,89,90]. Hemoglobin A1c (HbA1c) is an important clinical predictor of wound healing that shows an increase of 1% when wound healing decreases by 0.028 cm². In the Diabetes Control and Complications Trial, intensive glycemic control reduced the incidence of microvascular complications, including DPN, and a 1% decrease in the HbA1c level was accompanied by a 37% reduction in microvascular complications in the United Kingdom Prospective Diabetes Study[91].

Nevertheless, the definition of intensive beneficial glycemic control differs across trials and guidelines. The International Diabetes Federation recommended an HbA1c level lower than 6.5%[92], whereas the American Diabetes Association subdivided and specified the standards for older adults[93], children[94], and pregnant women[95], and recommended an HbA1c goal below 7% for nonpregnant adults[96]. One review of nine randomized controlled trials found that intensive glycemic control based on a target HbA1c level of 6% to 7.5% was associated with a 35% reduction in the risk of amputation in patients with diabetic foot syndrome[97,98].

However, the benefits and adverse effects of intensive glycemic control are still unclear[39]. Acute glycemic control did not show a relationship with the wound outcomes and amputation rate in DFU patients in most studies[98]. The intensity of glycemic control partly determines the incidence of hypoglycemia. In multiple types of studies, a significant adverse consequence of intensive glycemic control was the increasing incidence of hypoglycemia[39,99,100], so intensive glycemic control must also be accompanied by cautious monitoring[36]. However, the lack of clinical evidence and data supporting tight glycemic control should not deter efforts to achieve the target of optimal glycemic control, since it has been suggested to be the only significant tool to prevent complications in patients with both type 1 and type 2 diabetes[101].

Since uncontrolled hyperglycemia is one of the reasons why the readmission rate of DFU patients is as high as 30%, which is much higher than that of other patients, intensive glycemic control will help prevent such readmissions[102,103]. Besides, intensive glycemic control will help form a "glycemic memory" or "legacy effect", which implies that the benefits of earlier interventions are still evident while following the disease course[104].

Exercise

The effect of exercise on DFU is probably mediated by its effects on the risk factors. Exercise is reported to play a role in preventing or counteracting PAD in patients with type 2 DM[55], since regular physical activity may improve the claudication distance in PAD[50]. Moreover, exercise can disrupt the progression of DPN. Different types of exercise have significant effects on HbA1c reduction, and combined exercise is more effective in comparison with aerobic and resistance exercise[55]. In future studies, the exact relationship between exercise and DFU therapy should be determined to allow better integration of exercise into the treatment.

Offloading

Evidence-based guidelines have reported that reducing high foot pressure (*i.e.*, offloading) is the main objective and a significant prerequisite for promoting the healing effect and preventing ulcer[105,106]; this process involves offloading the affected area of the foot by redistributing extra pressure to other regions[107]. The majority of offloading device interventions are available for DFU and are divided into four categories: Casting, bracing, footwear, and walking aids[108]. In this section, four representative offloading devices will be introduced.

Total contact cast: The total contact cast (TCC) is often considered the gold standard device[86], and has been recommended by the guideline as the first-choice treatment option[106,109]. It protects the foot from further trauma and deformity, helps redistribution of excessive pressure[110], promotes tissue repair, and provides a protective load through below-knee-immobilization[111]. In comparison with some other approaches like removable cast walkers (RCWs) and therapeutic footwear, TCCs are reported to offer a better healing rate[108,112,113].

However, despite the substantial effectiveness of TCCs and their attractive characteristics for offloading interventions, their actual utilization rate is far from ideal. In a nationwide survey in the United States, only 1.7% of 858 centers considered a TCC as the primary offloading method in DFU treatment[114]. Moreover, 45.5% of centers nationwide reported never using the TCC as an offloading modality, and 58.1% of centers did not consider TCCs as the first choice in noninfected plantar DFU treatment[114].

The low utilization rate can be attributed to a complex interplay of multiple factors. For patients with DFU, TCC is not easy to disassemble, which ensures their fixation and stability but hampers daily wound care if new pressure ulcers occur, hinders mobility, and results in inconvenient application because of the need for skilled technicians[107]. In addition, prolonged casting can cause stiffness of the muscles and atrophy of the joints[111], potentially leading to low patient acceptance. For medical institutions and physicians, the lack of awareness or familiarity with guidelines, the unpredictable efficacy, the inertia associated with previous practices, and the lack of skilled technicians may lead to a low level of TCC use.

RCW: A RCW is a removable knee-high offloading device. It offers multiple advantages, including easy removability, convenient wound assessments and care, and comfortable movement in daily life[115]. In comparison with TCCs, the most significant advantage of RCW is the reduction in time, energy, and experience needed for proper application[116], which makes it more suitable for frequent examination and nursing in cases of new ulcer occurrence and after an operation.

RCWs provide an equal level of plantar pressure and wound healing as TCCs and have emerged as a potential alternative to TCCs[117,118]. However, the convenience of removable RCWs may be obtained at the expense of healing ability. In *in vivo* studies, RCWs showed significantly lower healing ability in comparison with non-removable knee-high offloading devices like TCCs[117]. This significant difference in healing ability may also be caused by patients' different compliance levels while wearing the device, since patients' adherence to using the devices can promote healing. Under these circumstances, while the convenient application and removal is the greatest advantage of RCW, it also reduces the patients' compliance since the TCC cannot be removed by the patients themselves, while the RCW can[114]. Patients may be unwilling to wear the device at home, so the noncompliance in using the RCW directly affects the healing process[119].

Therapeutic footwear: Proper footwear has long been considered to play an important role in DFU care [120]. Therapeutic footwear is considered an effective approach for ulcer healing and has been used as a DFU-prevention strategy for decades[86,120]. It has been generally divided into several parts like a shoe, insole, and felted foam[108,111]. Typical diabetic prescription shoes usually have a deeper, looser, rocker outsole and toe box with soft support padding and can provide better accommodation for foot deformities[121,111]. Treatment with therapeutic shoes has been reported to yield reduced relapse in comparison with non-prescription shoes[122]. Forefoot offloading shoes (FOS) are representative prescription shoes specifically designed to offload the forefoot and have been proven to be efficacious in offloading and healing diabetic plantar forefoot ulcers. FOS mainly consist of a rocker bottom outsole and a negative-heel configuration that limits active dorsiflexion of the toes and shifts weight-bearing proximally, redistributing the load of the forefoot[107]. In comparison with standard prescription shoes, FOS reduce forefoot peak pressure ranging from 15% to 20%[123] and are recommended after surgery to offload the forefoot in case of injuries and ulcers. However, the negative-heel rocker-outsole design of FOS may compromise gait symmetry and stability, potentially decreasing wearing comfort and clinical acceptance[124,125].

Insoles have been reported to show good results in reducing shear or side-to-side stresses on the foot plantar surface, which is another key factor in DFU prevention[126]. Shear-reducing insoles are similar to dynamic foot orthosis (DFO) insoles. These insoles are composed of a free-floating distal segment and anterior segment that slide over each other[127]. This special structure is designed to reduce the shear stress on both the foot and insole. Meanwhile, a reduction in the midfoot temperature increase was observed after using DFO insoles, and since a regional foot temperature increase is associated with ulcer

formation, these findings demonstrated the protective effects of DFO insoles in DFU formation.

As one of the most commonly used accommodative dressings, the combination of felted foam with other therapeutic footwear is considered a promising approach to promote ulcer healing. Zimny *et al* [128] evaluated the effect of felted foam on wound healing in comparison with classical pressure-reducing devices and confirmed its promoting effect. Nubé *et al* [129] found that felted padding applied to both skin and shoes provided similar wound-healing promoting effects for small, primarily neuropathic ulcers. Felts of different materials also influenced the healing of wounds. Pabón-Carrasco *et al* [130] reported that a combination of latex-wool felts showed great pressure-reducing ability, potentially combining wool's timely pressure capacity and latex's durability and structural stability. In comparison with wool, polyurethane, and latex, latex-wool felts offer the comprehensive advantages of hybrid materials and can serve as a great substitute for single material like wool.

In conclusion, published studies recommend the use of unremovable devices like TCCs for DFU offloading. When unremovable devices are unsuitable because of social, economic, and/or patient psychological factors and acceptance, removable devices like RCW can be used to address treatment adherence since they have the same level of therapeutic effect as unremovable devices [131]. For physicians, when choosing therapeutic footwear to assist therapy, more consideration and analysis should be paid to the specific offloading location of the foot and adherence to using offloading devices clinically [132].

Surgery

Deformities that develop into DFU commonly include hammertoes, prominent metatarsal heads, and hallux limitus [133]. A fixed-location high plantar pressure caused by structural deformities can be a predisposing risk factor for DFU recurrence if it is not adequately offloaded by the abovementioned conservative non-surgical offloading approaches. In such cases, foot surgery to ameliorate the overpressure through structural reorganization or removal of the underlying bony prominences is essential [134]. For patients showing chronic deformities and ulcers, foot surgery interventions are an important component in the management of foot ulcers, and can help them get rid of wearing cumbersome braces or footwear [133].

The offloading surgeries identified in IWDGF predominantly include tendon procedures such as toe flexor tenotomy and Achilles tendon release, but other types of surgeries can also be performed to relieve plantar pressure. Foot surgery has been classified into different types on the basis of the clinical conditions. Armstrong *et al* [135] revised a foot surgery classification system based on the presence of open wounds and acuity, and the conceptual framework of the surgery definitions in their study was based on the risk of high-level amputation. This system classifies foot surgery into four classes: Class I refers to elective surgeries aimed at reconstructing a deformed foot for patients without neuropathy, class II refers to prophylactic surgery aimed at reducing the risk of recurrent ulceration for patients with neuropathy but no open wound, class III refers to curative surgery aimed at offloading the overpressure caused by bony prominences and draining the underlying abscesses for patients with open wounds, and class IV refers to emergent surgery aimed at controlling infections caused by wet gangrene, necrotizing fasciitis, *etc.* for patients with severe infections [135].

Ahluwalia *et al* [136] systematically analyzed and summarized the five discrete types of offloading surgeries usually employed in cases of recalcitrant ulcers: (1) Lesser toe tenotomies, which aim to release the tight flexor tendon and decompress a flexible hammer toe for patients with recalcitrant ulcers on the tip or the knuckle of a deformed toe; (2) Achilles tendon release and metatarsal offloading, which aim to promote ulcer healing by releasing the Achilles tendon, metatarsal head resection(s), or joint arthroplasty; (3) Hallux procedures, which aim to redistribute the forefoot pressure by resetting the first metatarsal-phalangeal or partly amputating the hallux; (4) Surgical mastectomy, which aims to offload the overload area by directly removing the bony prominences in patients with a stable, inactive Charcot deformity; and (5) Complex surgical foot reconstruction, which aims to build a stable foot structure that can help patients walk normally without pressure areas [136].

Regular postoperative care is another extremely important aspect influencing ulcer recurrence and prevention of amputation. The reported complications after exostectomy include wound non-healing, wound dehiscence, and skin and soft tissue infection, all of which will increase ulcer recurrence and amputation rates [137]. In this regard, 70% of DFU patients have been reported to show a second ulcer recurrence after discharge, directly leading to amputation [32]. Therefore, meticulous wound care, adequate nutrition, and appropriate post-care management are essential for patients presenting with DFU, especially those who have undergone foot surgery.

Infection control

The bacterial toxins in wounds can cause infection, leading to collagen degradation, stress, and malnutrition and thereby preventing wound healing, which is a known predictor of poor prognosis and amputation [138]. Thus, correct identification and appropriate control of infections is essential to improve the prognosis in patients with DFU [86]. Diabetic foot infection (DFI) is particularly difficult to manage because the absence of exact markers to measure the level of microbiological activity for a typically colonized wound forces diagnosis based on clinical judgment [139], which often depends on the characteristics of inflammation such as per ulcer redness or induration and increased purulent

drainage[140].

In the early stage, DFU usually shows monomicrobial infections, while polymicrobial infections are observed in the middle-to-late stages[141]. Polymicrobial infections and their interactions in the DFU can delay or even stop wound healing[142]. Current clinical guidelines recommend systemic antimicrobial therapy for patients with DFI[85,139], and the formulation of a specific medication regimen is important in this regard. In the guideline developed by the Infectious Diseases Society of America (IDSA), the antibiotic regimen usually depends on the degree of infection, *e.g.*, using antibiotics targeting aerobic Gram-positive cocci for patients with mild-to-moderate infections and broad-spectrum empirical antibiotic therapy for patients with severe infections[85]. The appropriate use of antibiotics plays an important role in the prognosis of DFU, and improper or excessive antibiotic usage may cause several side effects like antibiotic resistance. IDSA advised that to avoid the adverse consequences of antibiotic overuse, narrow-spectrum antibiotics should be used for clinical treatment over the shortest term possible and discontinued immediately after the symptoms have been resolved[85].

Assessment of life quality

To avoid problems with treatment acceptance and compliance, the treatment of DFU should not only be limited to objective medical evaluation but should also include consideration of the patients' subjective feelings[143]. Assessment of the health-related QoL of patients is becoming steadily more important, especially in the treatment and evaluation of chronic diseases with a high prevalence, and should be an integral part of clinical evaluations of the prognosis of diabetes and its complications. All aspects, including physical health, pain, difficulty with usual activities, social function, role emotional, *etc.*, should be considered when evaluating the prognosis of a patient[144]. In DM patients, reductions in QoL will worsen in the presence of complications[144] such as DFU since these complications can limit physical functions such as mobility and cause pain, thereby increasing the psychological burdens caused by limitations in social relationships and fear of amputation, reducing patients' compliance with treatment, and eventually decreasing the survival rate[145-147].

Different treatment measures have shown different effects on patients' QoL. The chronicity of DM causes patients to show a higher possibility of developing psychological disorders, which is more obvious in patients who have undergone a major amputation[148]. Moreover, studies have reported significantly worse stress readaptation and deterioration of glycemic control after amputation[149], which reduces patients' QoL and weakens their socio-economic status[144]. Physical activity and exercise were confirmed to effectively improve DFU-related psychological pressure. One study reported improvements in glucose control, balance, neuropathic symptoms, and QoL of patients with DPN after Tai Chi exercises[150]. In combination with other related studies, these findings showed that patients in exercise programs have better QoL in terms of physical fitness, social ability, and emotional pressure [151].

Since offloading devices are one of the commonly used treatment modalities for DFUs, the differential influence of different types of devices on QoL should be considered clinically[152]. Although offloading devices redistribute plantar pressure and improve foot health, the accompanying adverse effects on gait and mobility should not be underestimated. Therapeutic footwear, especially when used on only one side, will cause the patient to limp while walking, causing deterioration of gait speed and symmetry, stride length, and the gait cycle time of patients with DFU. To reduce the related gait disorders and improve the patients' QoL, the use of bilateral therapeutic shoes instead of unilateral shoes can be a better option[153]. Casts show a good therapeutic effect because of their sealing ability and protective effects on wounds, which may be the reason for the higher cure rate of TCC in comparison with standard treatments[154,155]. However, the low patient acceptance of TCC is because of the limitations that it imposes on daily activities, as well as the difficulties in wound care and observation[113]. In contrast, the easy disassembly of RCW makes wound care and daily activities much more convenient, making it more acceptable for patients with DFU[114].

The QoL associated with a treatment method determines the extent to which it will be accepted and used by patients and should be one of the basic considerations when choosing therapeutic options. Currently, differences in QoL associated with different therapies have not received much attention, judging from the limited research on the relevant aspects and guidelines[156]. More studies should focus on QoL assessments to help formulate more reasonable clinical treatment plans.

CONCLUSION

DFU is a common and growing problem worldwide. The treatment approach for DFU depends on a combination of various factors that have been listed and discussed in this article. The following aspects should be considered to prevent ulcer progression and promote ulcer healing: (1) Choosing a proper classification to summarize the clinical details for further management and for auditing clinical outcomes; (2) Investigating risk factors that may predict the occurrence and promote the progression of ulcers; and (3) Employing validated interdisciplinary DFU management and care pathways, and emphasizing the cultivation of patient compliance. The findings highlight the need for the development

and application of more relevant prevention and treatment measures in the clinical management of DFU.

ACKNOWLEDGEMENTS

We thank our colleagues at the Key Laboratory of Acupuncture and Medicine Research of Ministry of Education in Nanjing University of Chinese Medicine for their support in the preparation of this manuscript.

FOOTNOTES

Author contributions: All the authors contributed to the initial writing and have read and approved the final manuscript.

Supported by the National Natural Science Foundation of China, No. 81873238 and 82074532; the Open Projects of the Discipline of Chinese Medicine of Nanjing University of Chinese Medicine supported by the Subject of Academic Priority Discipline of Jiangsu Higher Education Institutions, No. ZYX03KF012; and the Postgraduate Research & Practice Innovation Program of Jiangsu Province, No. KYCX22_1963.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: China

ORCID number: Xuan Wang 0000-0002-0516-6101; Chong-Xi Yuan 0000-0001-5052-1072; Bin Xu 0000-0003-4006-3009; Zhi Yu 0000-0002-9179-2618.

S-Editor: Wang JJ

L-Editor: Wang TQ

P-Editor: Wang JJ

REFERENCES

- 1 Carracher AM, Marathe PH, Close KL. International Diabetes Federation 2017. *J Diabetes* 2018; **10**: 353-356 [PMID: 29345068 DOI: 10.1111/1753-0407.12644]
- 2 Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis [†]. *Ann Med* 2017; **49**: 106-116 [PMID: 27585063 DOI: 10.1080/07853890.2016.1231932]
- 3 Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, Sosenko JM, Ziegler D. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care* 2017; **40**: 136-154 [PMID: 27999003 DOI: 10.2337/dc16-2042]
- 4 Brown SJ, Handsaker JC, Bowling FL, Boulton AJ, Reeves ND. Diabetic peripheral neuropathy compromises balance during daily activities. *Diabetes Care* 2015; **38**: 1116-1122 [PMID: 25765355 DOI: 10.2337/dc14-1982]
- 5 Walsh JW, Hoffstad OJ, Sullivan MO, Margolis DJ. Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom. *Diabet Med* 2016; **33**: 1493-1498 [PMID: 26666583 DOI: 10.1111/dme.13054]
- 6 Bus SA, Lavery LA, Monteiro-Soares M, Rasmussen A, Raspovic A, Sacco ICN, van Netten JJ; International Working Group on the Diabetic Foot. Guidelines on the prevention of foot ulcers in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev* 2020; **36** Suppl 1: e3269 [PMID: 32176451 DOI: 10.1002/dmrr.3269]
- 7 van Netten JJ, Bus SA, Apelqvist J, Lipsky BA, Hinchliffe RJ, Game F, Rayman G, Lazzarini PA, Forsythe RO, Peters EJG, Senneville É, Vas P, Monteiro-Soares M, Schaper NC; International Working Group on the Diabetic Foot. Definitions and criteria for diabetic foot disease. *Diabetes Metab Res Rev* 2020; **36** Suppl 1: e3268 [PMID: 31943705 DOI: 10.1002/dmrr.3268]
- 8 Subrata SA, Phuphaibul R. Diabetic foot ulcer care: a concept analysis of the term integrated into nursing practice. *Scand J Caring Sci* 2019; **33**: 298-310 [PMID: 30604889 DOI: 10.1111/scs.12645]
- 9 Malone M, Erasmus A, Schwarzer S, Lau NS, Ahmad M, Dickson HG. Utilisation of the 2019 IWGDF diabetic foot infection guidelines to benchmark practice and improve the delivery of care in persons with diabetic foot infections. *J Foot Ankle Res* 2021; **14**: 10 [PMID: 33509233 DOI: 10.1186/s13047-021-00448-w]
- 10 Dalla Paola L, Faglia E. Treatment of diabetic foot ulcer: an overview strategies for clinical approach. *Curr Diabetes Rev*

- 2006; **2**: 431-447 [PMID: [18220646](#) DOI: [10.2174/1573399810602040431](#)]
- 11 **Pickwell KM**, Siersma VD, Kars M, Holstein PE, Schaper NC; Eurodiale consortium. Diabetic foot disease: impact of ulcer location on ulcer healing. *Diabetes Metab Res Rev* 2013; **29**: 377-383 [PMID: [23390115](#) DOI: [10.1002/dmrr.2400](#)]
- 12 **Game F**. Classification of diabetic foot ulcers. *Diabetes Metab Res Rev* 2016; **32** Suppl 1: 186-194 [PMID: [26455509](#) DOI: [10.1002/dmrr.2746](#)]
- 13 **Monteiro-Soares M**, Russell D, Boyko EJ, Jeffcoate W, Mills JL, Morbach S, Game F; International Working Group on the Diabetic Foot (IWGDF). Guidelines on the classification of diabetic foot ulcers (IWGDF 2019). *Diabetes Metab Res Rev* 2020; **36** Suppl 1: e3273 [PMID: [32176445](#) DOI: [10.1002/dmrr.3273](#)]
- 14 **Kaufman J**, Breeding L, Rosenberg N. Anatomic location of acute diabetic foot infection. Its influence on the outcome of treatment. *Am Surg* 1987; **53**: 109-112 [PMID: [3813216](#)]
- 15 **Lavery LA**, Armstrong DG, Harkless LB. Classification of diabetic foot wounds. *J Foot Ankle Surg* 1996; **35**: 528-531 [PMID: [8986890](#) DOI: [10.1016/s1067-2516\(96\)80125-6](#)]
- 16 **Wagner FW Jr**. A classification and treatment program for diabetic, neuropathic, and dysvascular foot problems. *Instr Course Lect* 1979; **28**: 143-165
- 17 **Monteiro-Soares M**, Boyko EJ, Jeffcoate W, Mills JL, Russell D, Morbach S, Game F. Diabetic foot ulcer classifications: A critical review. *Diabetes Metab Res Rev* 2020; **36** Suppl 1: e3272 [PMID: [32176449](#) DOI: [10.1002/dmrr.3272](#)]
- 18 **Caputo WJ**. Surgical management of the diabetic foot. *Wounds* 2008; **20**: 74-83 [PMID: [25942052](#)]
- 19 **Wagner FW Jr**. The dysvascular foot: a system for diagnosis and treatment. *Foot Ankle* 1981; **2**: 64-122 [PMID: [7319435](#) DOI: [10.1177/107110078100200202](#)]
- 20 **Armstrong DG**, Peters EJ. Classification of wounds of the diabetic foot. *Curr Diab Rep* 2001; **1**: 233-238 [PMID: [12643204](#) DOI: [10.1007/s11892-001-0039-1](#)]
- 21 **Parisi MC**, Zantut-Wittmann DE, Pavin EJ, Machado H, Nery M, Jeffcoate WJ. Comparison of three systems of classification in predicting the outcome of diabetic foot ulcers in a Brazilian population. *Eur J Endocrinol* 2008; **159**: 417-422 [PMID: [18603574](#) DOI: [10.1530/EJE-07-0841](#)]
- 22 **Oyibo SO**, Jude EB, Tarawneh I, Nguyen HC, Armstrong DG, Harkless LB, Boulton AJ. The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. *Diabet Med* 2001; **18**: 133-138 [PMID: [11251677](#) DOI: [10.1046/j.1464-5491.2001.00422.x](#)]
- 23 **Macfarlane RM**, Jeffcoate WJdf. Classification of diabetic foot ulcers: The S(AD) SAD system. *Diabetic Foot J* 1999; **2**: 123
- 24 **Treece KA**, Macfarlane RM, Pound N, Game FL, Jeffcoate WJ. Validation of a system of foot ulcer classification in diabetes mellitus. *Diabet Med* 2004; **21**: 987-991 [PMID: [15317603](#) DOI: [10.1111/j.1464-5491.2004.01275.x](#)]
- 25 **Jeffcoate WJ**, Macfarlane RM, Fletcher EM. The description and classification of diabetic foot lesions. *Diabet Med* 1993; **10**: 676-679 [PMID: [8403832](#) DOI: [10.1111/j.1464-5491.1993.tb00144.x](#)]
- 26 **Abbas ZG**, Lutale JK, Game FL, Jeffcoate WJ. Comparison of four systems of classification of diabetic foot ulcers in Tanzania. *Diabet Med* 2008; **25**: 134-137 [PMID: [18215177](#) DOI: [10.1111/j.1464-5491.2007.02308.x](#)]
- 27 **Abbas ZG**, Archibald LK. Challenges for management of the diabetic foot in Africa: doing more with less. *Int Wound J* 2007; **4**: 305-313 [PMID: [17961157](#) DOI: [10.1111/j.1742-481X.2007.00376.x](#)]
- 28 **Armstrong DG**, Cohen K, Courric S, Bharara M, Marston W. Diabetic foot ulcers and vascular insufficiency: our population has changed, but our methods have not. *J Diabetes Sci Technol* 2011; **5**: 1591-1595 [PMID: [22226282](#) DOI: [10.1177/193229681100500636](#)]
- 29 **Mills JL Sr**, Conte MS, Armstrong DG, Pomposelli FB, Schanzer A, Sidawy AN, Andros G; Society for Vascular Surgery Lower Extremity Guidelines Committee. The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: risk stratification based on wound, ischemia, and foot infection (WIFI). *J Vasc Surg* 2014; **59**: 220-234.e1 [PMID: [24126108](#) DOI: [10.1016/j.jvs.2013.08.003](#)]
- 30 **Darling JD**, McCallum JC, Soden PA, Guzman RJ, Wyers MC, Hamdan AD, Verhagen HJ, Schermerhorn ML. Predictive ability of the Society for Vascular Surgery Wound, Ischemia, and foot Infection (WIFI) classification system after first-time lower extremity revascularizations. *J Vasc Surg* 2017; **65**: 695-704 [PMID: [28073665](#) DOI: [10.1016/j.jvs.2016.09.055](#)]
- 31 **Azuma N**. The Diagnostic Classification of Critical Limb Ischemia. *Ann Vasc Dis* 2018; **11**: 449-457 [PMID: [30636998](#) DOI: [10.3400/avd.ra.18-00122](#)]
- 32 **Volmer-Thole M**, Lobmann R. Neuropathy and Diabetic Foot Syndrome. *Int J Mol Sci* 2016; **17** [PMID: [27294922](#) DOI: [10.3390/ijms17060917](#)]
- 33 **Dayya D**, O'Neill OJ, Huedo-Medina TB, Habib N, Moore J, Iyer K. Debridement of Diabetic Foot Ulcers. *Adv Wound Care (New Rochelle)* 2022; **11**: 666-686 [PMID: [34376065](#) DOI: [10.1089/wound.2021.0016](#)]
- 34 **Reiber GE**, Vileikyte L, Boyko EJ, del Aguila M, Smith DG, Lavery LA, Boulton AJ. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. *Diabetes Care* 1999; **22**: 157-162 [PMID: [10333919](#) DOI: [10.2337/diacare.22.1.157](#)]
- 35 **Rahim K**, Saleha S, Zhu X, Huo L, Basit A, Franco OL. Bacterial Contribution in Chronicity of Wounds. *Microb Ecol* 2017; **73**: 710-721 [PMID: [27742997](#) DOI: [10.1007/s00248-016-0867-9](#)]
- 36 **Lim JZ**, Ng NS, Thomas C. Prevention and treatment of diabetic foot ulcers. *J R Soc Med* 2017; **110**: 104-109 [PMID: [28116957](#) DOI: [10.1177/0141076816688346](#)]
- 37 **van Dieren S**, Beulens JW, van der Schouw YT, Grobbee DE, Neal B. The global burden of diabetes and its complications: an emerging pandemic. *Eur J Cardiovasc Prev Rehabil* 2010; **17** Suppl 1: S3-S8 [PMID: [20489418](#) DOI: [10.1097/01.hjr.0000368191.86614.5a](#)]
- 38 **Reiber GE**. Epidemiology and Health Care Costs of Diabetic Foot Problems. In: Veves A, Giurini JM, LoGerfo FW. *The Diabetic Foot*. Totowa: Humana Press, 2002
- 39 **Fernando ME**, Seneviratne RM, Tan YM, Lazzarini PA, Sangla KS, Cunningham M, Buttner PG, Golledge J. Intensive versus conventional glycaemic control for treating diabetic foot ulcers. *Cochrane Database Syst Rev* 2016; CD010764

- [PMID: 26758576 DOI: 10.1002/14651858.CD010764.pub2]
- 40 **Bus SA**, Yang QX, Wang JH, Smith MB, Wunderlich R, Cavanagh PR. Intrinsic muscle atrophy and toe deformity in the diabetic neuropathic foot: a magnetic resonance imaging study. *Diabetes Care* 2002; **25**: 1444-1450 [PMID: 12145248 DOI: 10.2337/diacare.25.8.1444]
 - 41 **Bernstein RK**. Physical signs of the intrinsic minus foot. *Diabetes Care* 2003; **26**: 1945-1946 [PMID: 12766145 DOI: 10.2337/diacare.26.6.1945]
 - 42 **Murray HJ**, Young MJ, Hollis S, Boulton AJ. The association between callus formation, high pressures and neuropathy in diabetic foot ulceration. *Diabet Med* 1996; **13**: 979-982 [PMID: 8946157 DOI: 10.1002/(SICI)1096-9136(199611)13:11<979::AID-DIA267>3.0.CO;2-A]
 - 43 **Dumville JC**, Deshpande S, O'Meara S, Speak K. Hydrocolloid dressings for healing diabetic foot ulcers. *Cochrane Database Syst Rev* 2013; CD009099 [PMID: 23922167 DOI: 10.1002/14651858.CD009099.pub3]
 - 44 **Andersen H**. Motor dysfunction in diabetes. *Diabetes Metab Res Rev* 2012; **28** Suppl 1: 89-92 [PMID: 22271730 DOI: 10.1002/dmrr.2257]
 - 45 **Said G**. Diabetic neuropathy. *Handb Clin Neurol* 2013; **115**: 579-589 [PMID: 23931803 DOI: 10.1016/B978-0-444-52902-2.00033-3]
 - 46 **Tesfaye S**, Stevens LK, Stephenson JM, Fuller JH, Plater M, Ionescu-Tirgoviste C, Nuber A, Pozza G, Ward JD. Prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors: the EURODIAB IDDM Complications Study. *Diabetologia* 1996; **39**: 1377-1384 [PMID: 8933008 DOI: 10.1007/s001250050586]
 - 47 **Chambers N**. Wound Management. In: Hogston R, Simpson PM, editors. *Foundations of Nursing Practice*. London: Macmillan Education UK, 1999: 240-266
 - 48 **Ikem R**, Ikem I, Adebayo O, Soyoye D. An assessment of peripheral vascular disease in patients with diabetic foot ulcer. *Foot (Edinb)* 2010; **20**: 114-117 [PMID: 20951569 DOI: 10.1016/j.foot.2010.09.002]
 - 49 **Morley RL**, Sharma A, Horsch AD, Hinchliffe RJ. Peripheral artery disease. *BMJ* 2018; **360**: j5842 [PMID: 29419394 DOI: 10.1136/bmj.j5842]
 - 50 **Soyoye DO**, Abiodun OO, Ikem RT, Kolawole BA, Akintomide AO. Diabetes and peripheral artery disease: A review. *World J Diabetes* 2021; **12**: 827-838 [PMID: 34168731 DOI: 10.4239/wjd.v12.i6.827]
 - 51 **Jude EB**, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. *Diabetes Care* 2001; **24**: 1433-1437 [PMID: 11473082 DOI: 10.2337/diacare.24.8.1433]
 - 52 **Marso SP**, Hiatt WR. Peripheral arterial disease in patients with diabetes. *J Am Coll Cardiol* 2006; **47**: 921-929 [PMID: 16516072 DOI: 10.1016/j.jacc.2005.09.065]
 - 53 **American Diabetes Association**. Peripheral arterial disease in people with diabetes. *Diabetes Care* 2003; **26**: 3333-3341 [PMID: 14633825 DOI: 10.2337/diacare.26.12.3333]
 - 54 **Schainfeld RM**. Management of peripheral arterial disease and intermittent claudication. *J Am Board Fam Pract* 2001; **14**: 443-450 [PMID: 11757887]
 - 55 **Liao F**, An R, Pu F, Burns S, Shen S, Jan YK. Effect of Exercise on Risk Factors of Diabetic Foot Ulcers: A Systematic Review and Meta-Analysis. *Am J Phys Med Rehabil* 2019; **98**: 103-116 [PMID: 30020090 DOI: 10.1097/PHM.0000000000001002]
 - 56 **Wang N**, Yang BH, Wang G, Gao Y, Cao X, Zhang XF, Yan CC, Lian XT, Liu BH, Ju S. A meta-analysis of the relationship between foot local characteristics and major lower extremity amputation in diabetic foot patients. *J Cell Biochem* 2019; **120**: 9091-9096 [PMID: 30784095 DOI: 10.1002/jcb.28183]
 - 57 **Hiatt WR**. Preventing atherothrombotic events in peripheral arterial disease: the use of antiplatelet therapy. *J Intern Med* 2002; **251**: 193-206 [PMID: 11886478 DOI: 10.1046/j.1365-2796.2002.00947.x]
 - 58 **Cheuy VA**, Hastings MK, Mueller MJ. Metatarsophalangeal Hyperextension Movement Pattern Related to Diabetic Forefoot Deformity. *Phys Ther* 2016; **96**: 1143-1151 [PMID: 26916930 DOI: 10.2522/ptj.20150361]
 - 59 **Allan J**, Munro W, Figgins E. Foot deformities within the diabetic foot and their influence on biomechanics: A review of the literature. *Prosthet Orthot Int* 2016; **40**: 182-192 [PMID: 26209425 DOI: 10.1177/0309364615592705]
 - 60 **van Schie CH**, Vermigli C, Carrington AL, Boulton A. Muscle weakness and foot deformities in diabetes: relationship to neuropathy and foot ulceration in caucasian diabetic men. *Diabetes Care* 2004; **27**: 1668-1673 [PMID: 15220244 DOI: 10.2337/diacare.27.7.1668]
 - 61 **Molines-Barroso RJ**, Lázaro-Martínez JL, Aragón-Sánchez FJ, Álvaro-Afonso FJ, García-Morales E, García-Álvarez Y. Forefoot ulcer risk is associated with foot type in patients with diabetes and neuropathy. *Diabetes Res Clin Pract* 2016; **114**: 93-98 [PMID: 26810268 DOI: 10.1016/j.diabres.2016.01.008]
 - 62 **Hastings MK**, Commean PK, Chen L, Zellers JA, Sinacore DR, Baker JC. Qualitative study of musculoskeletal tissues and their radiographic correlates in diabetic neuropathic foot deformity. *Foot (Edinb)* 2021; **47**: 101777 [PMID: 33957525 DOI: 10.1016/j.foot.2021.101777]
 - 63 **Hastings MK**, Mueller MJ, Woodburn J, Strube MJ, Commean P, Johnson JE, Cheuy V, Sinacore DR. Acquired midfoot deformity and function in individuals with diabetes and peripheral neuropathy. *Clin Biomech (Bristol, Avon)* 2016; **32**: 261-267 [PMID: 26588885 DOI: 10.1016/j.clinbiomech.2015.11.001]
 - 64 **Bittel DC**, Bittel AJ, Tuttle LJ, Hastings MK, Commean PK, Mueller MJ, Cade WT, Sinacore DR. Adipose tissue content, muscle performance and physical function in obese adults with type 2 diabetes mellitus and peripheral neuropathy. *J Diabetes Complications* 2015; **29**: 250-257 [PMID: 25547717 DOI: 10.1016/j.jdiacomp.2014.11.003]
 - 65 **Faris IB**. Management of the diabetic foot. Edinburgh: Churchill Livingstone, 1991
 - 66 **Cheuy VA**, Hastings MK, Commean PK, Mueller MJ. Muscle and Joint Factors Associated With Forefoot Deformity in the Diabetic Neuropathic Foot. *Foot Ankle Int* 2016; **37**: 514-521 [PMID: 26666675 DOI: 10.1177/1071100715621544]
 - 67 **Sinacore DR**, Gutekunst DJ, Hastings MK, Strube MJ, Bohnert KL, Prior FW, Johnson JE. Neuropathic midfoot deformity: associations with ankle and subtalar joint motion. *J Foot Ankle Res* 2013; **6**: 11 [PMID: 23531372 DOI: 10.1186/1757-1146-6-11]

- 68 **Boulton AJ**, Meneses P, Ennis WJ. Diabetic foot ulcers: A framework for prevention and care. *Wound Repair Regen* 1999; **7**: 7-16 [PMID: [10231501](#) DOI: [10.1046/j.1524-475x.1999.00007.x](#)]
- 69 **Mervis JS**, Phillips TJ. Pressure ulcers: Pathophysiology, epidemiology, risk factors, and presentation. *J Am Acad Dermatol* 2019; **81**: 881-890 [PMID: [30664905](#) DOI: [10.1016/j.jaad.2018.12.069](#)]
- 70 **Malhotra S**, Bello E, Kominsky S. Diabetic foot ulcerations: biomechanics, charcot foot, and total contact cast. *Semin Vasc Surg* 2012; **25**: 66-69 [PMID: [22817854](#) DOI: [10.1053/j.semvascsurg.2012.05.001](#)]
- 71 **Bus SA**, Maas M, de Lange A, Michels RP, Levi M. Elevated plantar pressures in neuropathic diabetic patients with claw/hammer toe deformity. *J Biomech* 2005; **38**: 1918-1925 [PMID: [16023481](#) DOI: [10.1016/j.jbiomech.2004.07.034](#)]
- 72 **Cui FF**, Pan YY, Xie HH, Wang XH, Shi HX, Xiao J, Zhang HY, Chang HT, Jiang LP. Pressure Combined with Ischemia/Reperfusion Injury Induces Deep Tissue Injury via Endoplasmic Reticulum Stress in a Rat Pressure Ulcer Model. *Int J Mol Sci* 2016; **17**: 284 [PMID: [26927073](#) DOI: [10.3390/ijms17030284](#)]
- 73 **Peirce SM**, Skalak TC, Rodeheaver GT. Ischemia-reperfusion injury in chronic pressure ulcer formation: a skin model in the rat. *Wound Repair Regen* 2000; **8**: 68-76 [PMID: [10760216](#) DOI: [10.1046/j.1524-475x.2000.00068.x](#)]
- 74 **Arosi I**, Hiner G, Rajbhandari S. Pathogenesis and Treatment of Callus in the Diabetic Foot. *Curr Diabetes Rev* 2016; **12**: 179-183 [PMID: [26054651](#) DOI: [10.2174/1573399811666150609160219](#)]
- 75 **Cheuy VA**, Hastings MK, Commeyan PK, Ward SR, Mueller MJ. Intrinsic foot muscle deterioration is associated with metatarsophalangeal joint angle in people with diabetes and neuropathy. *Clin Biomech (Bristol, Avon)* 2013; **28**: 1055-1060 [PMID: [24176198](#) DOI: [10.1016/j.clinbiomech.2013.10.006](#)]
- 76 **Batista F**, Nery C, Pinzur M, Monteiro AC, de Souza EF, Felipe FH, Alcântara MC, Campos RS. Achilles tendinopathy in diabetes mellitus. *Foot Ankle Int* 2008; **29**: 498-501 [PMID: [18510903](#) DOI: [10.3113/FAI.2008.0498](#)]
- 77 **Abate M**, Schiavone C, Di Carlo L, Salini V. Achilles tendon and plantar fascia in recently diagnosed type II diabetes: role of body mass index. *Clin Rheumatol* 2012; **31**: 1109-1113 [PMID: [22349878](#) DOI: [10.1007/s10067-012-1955-y](#)]
- 78 **Giacomozzi C**, D'Ambrogio E, Uccioli L, Macellari V. Does the thickening of Achilles tendon and plantar fascia contribute to the alteration of diabetic foot loading? *Clin Biomech (Bristol, Avon)* 2005; **20**: 532-539 [PMID: [15836941](#) DOI: [10.1016/j.clinbiomech.2005.01.011](#)]
- 79 **Gelber JR**, Sinacore DR, Strube MJ, Mueller MJ, Johnson JE, Prior FW, Hastings MK. Windlass Mechanism in Individuals With Diabetes Mellitus, Peripheral Neuropathy, and Low Medial Longitudinal Arch Height. *Foot Ankle Int* 2014; **35**: 816-824 [PMID: [24917647](#) DOI: [10.1177/1071100714538416](#)]
- 80 **Treves F**. Treatment of perforating ulcer of the foot. *The Lancet* 1884; **124**: 949-51 [DOI: [10.1016/S0140-6736\(02\)28929-1](#)]
- 81 **Ren M**, Yang C, Lin DZ, Xiao HS, Mai LF, Guo YC, Yan L. Effect of intensive nursing education on the prevention of diabetic foot ulceration among patients with high-risk diabetic foot: a follow-up analysis. *Diabetes Technol Ther* 2014; **16**: 576-581 [PMID: [25004241](#) DOI: [10.1089/dia.2014.0004](#)]
- 82 **Siegel KR**, Ali MK, Zhou X, Ng BP, Jawanda S, Proia K, Zhang X, Gregg EW, Albright AL, Zhang P. Cost-effectiveness of Interventions to Manage Diabetes: Has the Evidence Changed Since 2008? *Diabetes Care* 2020; **43**: 1557-1592 [PMID: [33534729](#) DOI: [10.2337/dci20-0017](#)]
- 83 **American Diabetes Association**. *Standards of Medical Care in Diabetes-2020* Abridged for Primary Care Providers. *Clin Diabetes* 2020; **38**: 10-38 [PMID: [31975748](#) DOI: [10.2337/cd20-as01](#)]
- 84 **Yang W**, Lu J, Weng J, Jia W, Ji L, Xiao J, Shan Z, Liu J, Tian H, Ji Q, Zhu D, Ge J, Lin L, Chen L, Guo X, Zhao Z, Li Q, Zhou Z, Shan G, He J; China National Diabetes and Metabolic Disorders Study Group. Prevalence of diabetes among men and women in China. *N Engl J Med* 2010; **362**: 1090-1101 [PMID: [20335585](#) DOI: [10.1056/NEJMoa0908292](#)]
- 85 **Lipsky BA**, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, Deery HG, Embil JM, Joseph WS, Karchmer AW, Pinzur MS, Senneville E. 2012 infectious diseases society of america clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *J Am Podiatr Med Assoc* 2013; **103**: 2-7 [PMID: [23328846](#) DOI: [10.7547/1030002](#)]
- 86 **Everett E**, Mathioudakis N. Update on management of diabetic foot ulcers. *Ann N Y Acad Sci* 2018; **1411**: 153-165 [PMID: [29377202](#) DOI: [10.1111/nyas.13569](#)]
- 87 **Game FL**, Apelqvist J, Attinger C, Hartemann A, Hinchliffe RJ, Löndahl M, Price PE, Jeffcoate WJ; International Working Group on the Diabetic Foot. Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review. *Diabetes Metab Res Rev* 2016; **32** Suppl 1: 154-168 [PMID: [26344936](#) DOI: [10.1002/dmrr.2707](#)]
- 88 **Ajjan RA**. How Can We Realize the Clinical Benefits of Continuous Glucose Monitoring? *Diabetes Technol Ther* 2017; **19**: S27-S36 [PMID: [28541132](#) DOI: [10.1089/dia.2017.0021](#)]
- 89 **Markuson M**, Hanson D, Anderson J, Langemo D, Hunter S, Thompson P, Paulson R, Rustvang D. The relationship between hemoglobin A(1c) values and healing time for lower extremity ulcers in individuals with diabetes. *Adv Skin Wound Care* 2009; **22**: 365-372 [PMID: [19638800](#) DOI: [10.1097/01.ASW.0000358639.45784.cd](#)]
- 90 **Hemmingsen B**, Lund SS, Gluud C, Vaag A, Almdal TP, Hemmingsen C, Wetterslev J. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2013; **CD008143** [PMID: [24214280](#) DOI: [10.1002/14651858.CD008143.pub3](#)]
- 91 Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; **352**: 837-853 [PMID: [9742976](#)]
- 92 **IDF Clinical Guidelines Task Force**. Global Guideline for Type 2 Diabetes: recommendations for standard, comprehensive, and minimal care. *Diabet Med* 2006; **23**: 579-593 [PMID: [16759299](#) DOI: [10.1111/j.1464-5491.2006.01918.x](#)]
- 93 **American Diabetes Association**. 12. Older Adults: *Standards of Medical Care in Diabetes-2021*. *Diabetes Care* 2021; **44**: S168-S179 [PMID: [33298423](#) DOI: [10.2337/dc21-S012](#)]
- 94 **American Diabetes Association**. 13. Children and Adolescents: *Standards of Medical Care in Diabetes-2021*. *Diabetes Care* 2021; **44**: S180-S199 [PMID: [33298424](#) DOI: [10.2337/dc21-S013](#)]

- 95 **American Diabetes Association.** 14. Management of Diabetes in Pregnancy: *Standards of Medical Care in Diabetes-2021. Diabetes Care* 2021; **44**: S200-S210 [PMID: [33298425](#) DOI: [10.2337/dc21-S014](#)]
- 96 **American Diabetes Association.** 6. Glycemic Targets: *Standards of Medical Care in Diabetes-2021. Diabetes Care* 2021; **44**: S73-S84 [PMID: [33298417](#) DOI: [10.2337/dc21-S006](#)]
- 97 **Jones NJ, Harding K.** 2015 International Working Group on the Diabetic Foot Guidance on the prevention and management of foot problems in diabetes. *Int Wound J* 2015; **12**: 373-374 [PMID: [26138717](#) DOI: [10.1111/iwj.12475](#)]
- 98 **Peled S, Pollack R, Elishoov O, Haze A, Cahn A.** Association of Inpatient Glucose Measurements With Amputations in Patients Hospitalized With Acute Diabetic Foot. *J Clin Endocrinol Metab* 2019; **104**: 5445-5452 [PMID: [31246256](#) DOI: [10.1210/je.2019-00774](#)]
- 99 **Ma J, Yang W, Fang N, Zhu W, Wei M.** The association between intensive glycemic control and vascular complications in type 2 diabetes mellitus: a meta-analysis. *Nutr Metab Cardiovasc Dis* 2009; **19**: 596-603 [PMID: [19819121](#) DOI: [10.1016/j.numecd.2009.07.004](#)]
- 100 **Mattila TK, de Boer A.** Influence of intensive versus conventional glucose control on microvascular and macrovascular complications in type 1 and 2 diabetes mellitus. *Drugs* 2010; **70**: 2229-2245 [PMID: [21080740](#) DOI: [10.2165/11585220-000000000-00000](#)]
- 101 **Ang L, Jaiswal M, Martin C, Pop-Busui R.** Glucose control and diabetic neuropathy: lessons from recent large clinical trials. *Curr Diab Rep* 2014; **14**: 528 [PMID: [25139473](#) DOI: [10.1007/s11892-014-0528-7](#)]
- 102 **Remington AC, Hernandez-Boussard T, Warstadt NM, Finnegan MA, Shaffer R, Kwong JZ, Curtin C.** Analyzing treatment aggressiveness and identifying high-risk patients in diabetic foot ulcer return to care. *Wound Repair Regen* 2016; **24**: 731-736 [PMID: [27144893](#) DOI: [10.1111/wrr.12439](#)]
- 103 **Chin YF, Huang TT, Yu HY, Yang HM, Hsu BR.** Factors related to hospital-to-home transitional self-monitoring blood glucose behaviour among patients with diabetes-related foot ulcer. *Int J Nurs Pract* 2021; **27**: e12950 [PMID: [33915598](#) DOI: [10.1111/ijn.12950](#)]
- 104 **Giacco F, Brownlee M.** Oxidative stress and diabetic complications. *Circ Res* 2010; **107**: 1058-1070 [PMID: [21030723](#) DOI: [10.1161/CIRCRESAHA.110.223545](#)]
- 105 **Robinson C, Major MJ, Kuffel C, Hines K, Cole P.** Orthotic management of the neuropathic foot: an interdisciplinary care perspective. *Prosthet Orthot Int* 2015; **39**: 73-81 [PMID: [25614503](#) DOI: [10.1177/0309364614545422](#)]
- 106 **Bus SA.** Priorities in offloading the diabetic foot. *Diabetes Metab Res Rev* 2012; **28** Suppl 1: 54-59 [PMID: [22271724](#) DOI: [10.1002/dmrr.2240](#)]
- 107 **Bus SA, van Deursen RW, Kanade RV, Wissink M, Manning EA, van Baal JG, Harding KG.** Plantar pressure relief in the diabetic foot using forefoot offloading shoes. *Gait Posture* 2009; **29**: 618-622 [PMID: [19217785](#) DOI: [10.1016/j.gaitpost.2009.01.003](#)]
- 108 **Lung CW, Wu FL, Liao F, Pu F, Fan Y, Jan YK.** Emerging technologies for the prevention and management of diabetic foot ulcers. *J Tissue Viability* 2020; **29**: 61-68 [PMID: [32197948](#) DOI: [10.1016/j.jtv.2020.03.003](#)]
- 109 **Armstrong DG, Nguyen HC, Lavery LA, van Schie CH, Boulton AJ, Harkless LB.** Off-loading the diabetic foot wound: a randomized clinical trial. *Diabetes Care* 2001; **24**: 1019-1022 [PMID: [11375363](#) DOI: [10.2337/diacare.24.6.1019](#)]
- 110 **Lavery LA, Vela SA, Lavery DC, Quebedeaux TL.** Reducing dynamic foot pressures in high-risk diabetic subjects with foot ulcerations. A comparison of treatments. *Diabetes Care* 1996; **19**: 818-821 [PMID: [8842597](#) DOI: [10.2337/diacare.19.8.818](#)]
- 111 **Sahu B, Prusty A, Tudu B.** Total contact casting versus traditional dressing in diabetic foot ulcers. *J Orthop Surg (Hong Kong)* 2018; **26**: 2309499018802486 [PMID: [30295168](#) DOI: [10.1177/2309499018802486](#)]
- 112 **Lavery LA, Higgins KR, La Fontaine J, Zamorano RG, Constantinides GP, Kim PJ.** Randomised clinical trial to compare total contact casts, healing sandals and a shear-reducing removable boot to heal diabetic foot ulcers. *Int Wound J* 2015; **12**: 710-715 [PMID: [24618113](#) DOI: [10.1111/iwj.12213](#)]
- 113 **Fife CE, Carter MJ, Walker D, Thomson B, Eckert KA.** Diabetic foot ulcer off-loading: The gap between evidence and practice. Data from the US Wound Registry. *Adv Skin Wound Care* 2014; **27**: 310-316 [PMID: [24932951](#) DOI: [10.1097/01.ASW.0000450831.65667.89](#)]
- 114 **Wu SC, Jensen JL, Weber AK, Robinson DE, Armstrong DG.** Use of pressure offloading devices in diabetic foot ulcers: do we practice what we preach? *Diabetes Care* 2008; **31**: 2118-2119 [PMID: [18694976](#) DOI: [10.2337/dc08-0771](#)]
- 115 **Ababneh A, Finlayson K, Edwards H, Lazzarini PA.** Factors associated with adherence to using removable cast walker treatment among patients with diabetes-related foot ulcers. *BMJ Open Diabetes Res Care* 2022; **10** [PMID: [35144940](#) DOI: [10.1136/bmjdr-2021-002640](#)]
- 116 **Miller J, Armstrong DG.** Offloading the diabetic and ischemic foot: solutions for the vascular specialist. *Semin Vasc Surg* 2014; **27**: 68-74 [PMID: [25812760](#) DOI: [10.1053/j.semvascsurg.2014.10.002](#)]
- 117 **Lazzarini PA, Jarl G, Gooday C, Viswanathan V, Caravaggi CF, Armstrong DG, Bus SA.** Effectiveness of offloading interventions to heal foot ulcers in persons with diabetes: a systematic review. *Diabetes Metab Res Rev* 2020; **36** Suppl 1: e3275 [PMID: [32176438](#) DOI: [10.1002/dmrr.3275](#)]
- 118 **Faglia E, Caravaggi C, Clerici G, Sganzeroli A, Curci V, Vailati W, Simonetti D, Sommalvico F.** Effectiveness of removable walker cast versus nonremovable fiberglass off-bearing cast in the healing of diabetic plantar foot ulcer: a randomized controlled trial. *Diabetes Care* 2010; **33**: 1419-1423 [PMID: [20357377](#) DOI: [10.2337/dc09-1708](#)]
- 119 **Crews RT, Shen BJ, Campbell L, Lamont PJ, Boulton AJ, Peyrot M, Kirsner RS, Vileikyte L.** Role and Determinants of Adherence to Off-loading in Diabetic Foot Ulcer Healing: A Prospective Investigation. *Diabetes Care* 2016; **39**: 1371-1377 [PMID: [27271185](#) DOI: [10.2337/dc15-2373](#)]
- 120 **Maciejewski ML, Reiber GE, Smith DG, Wallace C, Hayes S, Boyko EJ.** Effectiveness of diabetic therapeutic footwear in preventing reulceration. *Diabetes Care* 2004; **27**: 1774-1782 [PMID: [15220265](#) DOI: [10.2337/diacare.27.7.1774](#)]
- 121 **Tyrrell W.** Orthotic intervention in patients with diabetic foot ulceration. *J Wound Care* 1999; **8**: 530-532 [PMID: [10827660](#) DOI: [10.12968/jowc.1999.8.10.26212](#)]
- 122 **Elraiyyah T, Prutsky G, Domecq JP, Tsapas A, Nabhan M, Frykberg RG, Firwana B, Hasan R, Prokop LJ, Murad MH.** A systematic review and meta-analysis of off-loading methods for diabetic foot ulcers. *J Vasc Surg* 2016; **63**: 59S-68S.e1

- [PMID: 26804369 DOI: 10.1016/j.jvs.2015.10.006]
- 123 **Giacalone VF**, Armstrong DG, Ashry HR, Lavery DC, Harkless LB, Lavery LA. A quantitative assessment of healing sandals and postoperative shoes in offloading the neuropathic diabetic foot. *J Foot Ankle Surg* 1997; **36**: 28-30 [PMID: 9031024 DOI: 10.1016/s1067-2516(97)80007-5]
 - 124 **Paton JS**, Thomason K, Trimble K, Metcalfe JE, Marsden J. Effect of a forefoot off-loading postoperative shoe on muscle activity, posture, and static balance. *J Am Podiatr Med Assoc* 2013; **103**: 36-42 [PMID: 23328851 DOI: 10.7547/1030036]
 - 125 **Bus SA**, Maas JC, Otterman NM. Lower-extremity dynamics of walking in neuropathic diabetic patients who wear a forefoot-offloading shoe. *Clin Biomech (Bristol, Avon)* 2017; **50**: 21-26 [PMID: 28985487 DOI: 10.1016/j.clinbiomech.2017.10.003]
 - 126 **Lavery LA**, LaFontaine J, Higgins KR, Lancot DR, Constantinides G. Shear-reducing insoles to prevent foot ulceration in high-risk diabetic patients. *Adv Skin Wound Care* 2012; **25**: 519-24; quiz 525 [PMID: 23080240 DOI: 10.1097/01.ASW.0000422625.17407.93]
 - 127 **Wrobel JS**, Ammanath P, Le T, Luring C, Wensman J, Grewal GS, Najafi B, Pop-Busui R. A novel shear reduction insole effect on the thermal response to walking stress, balance, and gait. *J Diabetes Sci Technol* 2014; **8**: 1151-1156 [PMID: 25107709 DOI: 10.1177/1932296814546528]
 - 128 **Zimny S**, Schatz H, Pfohl U. The effects of applied felted foam on wound healing and healing times in the therapy of neuropathic diabetic foot ulcers. *Diabet Med* 2003; **20**: 622-625 [PMID: 12873288 DOI: 10.1046/j.1464-5491.2003.01011.x]
 - 129 **Nubé VL**, Molyneaux L, Bolton T, Cligan T, Palmer E, Yue DK. The use of felt deflective padding in the management of plantar hallux and forefoot ulcers in patients with diabetes. *Foot* 2006; **16**: 38-43 [DOI: 10.1016/j.foot.2005.11.005]
 - 130 **Pabón-Carrasco M**, Juárez-Jiménez JM, Reina-Bueno M, Coheña-Jiménez M. Behavior of provisional pressure-reducing materials in diabetic foot. *J Tissue Viability* 2016; **25**: 143-149 [PMID: 26922270 DOI: 10.1016/j.jtv.2016.02.003]
 - 131 **Racaru S**, Bolton Saghdaoui L, Roy Choudhury J, Wells M, Davies AH. Offloading treatment in people with diabetic foot disease: A systematic scoping review on adherence to foot offloading. *Diabetes Metab Syndr* 2022; **16**: 102493 [PMID: 35468484 DOI: 10.1016/j.dsx.2022.102493]
 - 132 **Bus SA**, Armstrong DG, Gooday C, Jarl G, Caravaggi C, Viswanathan V, Lazzarini PA; International Working Group on the Diabetic Foot (IWGDF). Guidelines on offloading foot ulcers in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev* 2020; **36** Suppl 1: e3274 [PMID: 32176441 DOI: 10.1002/dmrr.3274]
 - 133 **Frykberg RG**, Bevilacqua NJ, Habershaw G. Surgical off-loading of the diabetic foot. *J Am Podiatr Med Assoc* 2010; **100**: 369-384 [PMID: 20847351 DOI: 10.7547/1000369]
 - 134 **Frykberg RG**, Wukich DK, Kavarthapu V, Zgonis T, Dalla Paola L; Board of the Association of Diabetic Foot Surgeons. Surgery for the diabetic foot: A key component of care. *Diabetes Metab Res Rev* 2020; **36** Suppl 1: e3251 [PMID: 31820543 DOI: 10.1002/dmrr.3251]
 - 135 **Armstrong DG**, Frykberg RG. Classifying diabetic foot surgery: toward a rational definition. *Diabet Med* 2003; **20**: 329-331 [PMID: 12675649 DOI: 10.1046/j.1464-5491.2003.00933.x]
 - 136 **Ahluwalia R**, Maffulli N, Lázaro-Martínez JL, Kirketerp-Møller K, Reichert I. Diabetic foot off loading and ulcer remission: Exploring surgical off-loading. *Surgeon* 2021; **19**: e526-e535 [PMID: 33642205 DOI: 10.1016/j.surge.2021.01.005]
 - 137 **Brodsky JW**, Rouse AM. Exostectomy for symptomatic bony prominences in diabetic charcot feet. *Clin Orthop Relat Res* 1993; **21**: 21-26 [PMID: 8222428]
 - 138 **Kurup R**, Ansari AA. A study to identify bacteriological profile and other risk factors among diabetic and non-diabetic foot ulcer patients in a Guyanese hospital setting. *Diabetes Metab Syndr* 2019; **13**: 1871-1876 [PMID: 31235108 DOI: 10.1016/j.dsx.2019.04.024]
 - 139 **Lipsky BA**, Aragón-Sánchez J, Diggle M, Embil J, Kono S, Lavery L, Senneville É, Urbančič-Rovan V, Van Asten S; International Working Group on the Diabetic Foot, Peters EJ. IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. *Diabetes Metab Res Rev* 2016; **32** Suppl 1: 45-74 [PMID: 26386266 DOI: 10.1002/dmrr.2699]
 - 140 **Hurlow JJ**, Humphreys GJ, Bowling FL, McBain AJ. Diabetic foot infection: A critical complication. *Int Wound J* 2018; **15**: 814-821 [PMID: 29808598 DOI: 10.1111/iwj.12932]
 - 141 **Citron DM**, Goldstein EJ, Merriam CV, Lipsky BA, Abramson MA. Bacteriology of moderate-to-severe diabetic foot infections and in vitro activity of antimicrobial agents. *J Clin Microbiol* 2007; **45**: 2819-2828 [PMID: 17609322 DOI: 10.1128/JCM.00551-07]
 - 142 **Du F**, Ma J, Gong H, Bista R, Zha P, Ren Y, Gao Y, Chen D, Ran X, Wang C. Microbial Infection and Antibiotic Susceptibility of Diabetic Foot Ulcer in China: Literature Review. *Front Endocrinol (Lausanne)* 2022; **13**: 881659 [PMID: 35663325 DOI: 10.3389/fendo.2022.881659]
 - 143 **Anand SC**, Dean C, Nettleton R, Praburaj DV. Health-related quality of life tools for venous-ulcerated patients. *Br J Nurs* 2003; **12**: 48-59 [PMID: 12574726 DOI: 10.12968/bjon.2003.12.1.11000]
 - 144 **Goodridge D**, Trepman E, Embil JM. Health-related quality of life in diabetic patients with foot ulcers: literature review. *J Wound Ostomy Continence Nurs* 2005; **32**: 368-377 [PMID: 16301902 DOI: 10.1097/00152192-200511000-00007]
 - 145 **Al Hayek AA**, Robert AA, Al Saeed A, Alzaid AA, Al Sabaan FS. Factors Associated with Health-Related Quality of Life among Saudi Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Survey. *Diabetes Metab J* 2014; **38**: 220-229 [PMID: 25003076 DOI: 10.4093/dmj.2014.38.3.220]
 - 146 **Wilson KA**, Dowling AJ, Abdolell M, Tannock IF. Perception of quality of life by patients, partners and treating physicians. *Qual Life Res* 2000; **9**: 1041-1052 [PMID: 11332225 DOI: 10.1023/a:1016647407161]
 - 147 **Vileikyte L**, Rubin RR, Leventhal H. Psychological aspects of diabetic neuropathic foot complications: an overview. *Diabetes Metab Res Rev* 2004; **20** Suppl 1: S13-S18 [PMID: 15150807 DOI: 10.1002/dmrr.437]
 - 148 **Adili F**, Larijani B, Haghighatpanah M. Diabetic patients: Psychological aspects. *Ann N Y Acad Sci* 2006; **1084**: 329-349 [PMID: 17151313 DOI: 10.1196/annals.1372.016]
 - 149 **Fejfarová V**, Jirkovská A, Dragomirecká E, Game F, Bém R, Dubský M, Wosková V, Křížová M, Skibová J, Wu S. Does

- the diabetic foot have a significant impact on selected psychological or social characteristics of patients with diabetes mellitus? *J Diabetes Res* 2014; **2014**: 371938 [PMID: [24791012](#) DOI: [10.1155/2014/371938](#)]
- 150 **Ahn S**, Song R. Effects of Tai Chi Exercise on glucose control, neuropathy scores, balance, and quality of life in patients with type 2 diabetes and neuropathy. *J Altern Complement Med* 2012; **18**: 1172-1178 [PMID: [22985218](#) DOI: [10.1089/acm.2011.0690](#)]
 - 151 **Matos M**, Mendes R, Silva AB, Sousa N. Physical activity and exercise on diabetic foot related outcomes: A systematic review. *Diabetes Res Clin Pract* 2018; **139**: 81-90 [PMID: [29477503](#) DOI: [10.1016/j.diabres.2018.02.020](#)]
 - 152 **Pollo FE**, Gowling TL, Jackson RW. Walking boot design: a gait analysis study. *Orthopedics* 1999; **22**: 503-507 [PMID: [10348111](#)]
 - 153 **Ling E**, Lepow B, Zhou H, Enriquez A, Mullen A, Najafi B. The impact of diabetic foot ulcers and unilateral offloading footwear on gait in people with diabetes. *Clin Biomech (Bristol, Avon)* 2020; **73**: 157-161 [PMID: [31986461](#) DOI: [10.1016/j.clinbiomech.2020.01.014](#)]
 - 154 **Yazdanpanah L**, Nasiri M, Adarvishi S. Literature review on the management of diabetic foot ulcer. *World J Diabetes* 2015; **6**: 37-53 [PMID: [25685277](#) DOI: [10.4239/wjd.v6.i1.37](#)]
 - 155 **Mueller MJ**, Diamond JE, Sinacore DR, Delitto A, Blair VP 3rd, Drury DA, Rose SJ. Total contact casting in treatment of diabetic plantar ulcers. Controlled clinical trial. *Diabetes Care* 1989; **12**: 384-388 [PMID: [2659299](#) DOI: [10.2337/diacare.12.6.384](#)]
 - 156 **Cohen J**. Statistical power analysis for the behavioral sciences. 2nd ed. British: Routledge, 1988



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

