Contemporary Diabetes
Series Editor: Aristidis Veves

Aristidis Veves
John M. Giurini
Marc L. Schermerhorn *Editors*

The Diabetic Foot

Medical and Surgical Management

Fifth Edition

Humana Press

Contemporary Diabetes

The **Contemporary Diabetes** series focuses on the clinical aspects of obesity and diabetes and provides the practicing health provider with all the latest information regarding their management. The series also targets both basic and clinical researchers. The audience includes endocrinologists, internists, cardiologists, neurologists, nephrologists, podiatrists, ophthalmologists, family physicians, nurse practitioners, nurse educators, and physician assistants.

Aristidis Veves • John M. Giurini
Marc L. Schermerhorn
Editors

The Diabetic Foot

Medical and Surgical Management

Fifth Edition

Humana Press

Editors
Aristidis Veves
The Rongxiang Xu, MD, Center for Regenerative Therapeutics
Boston, MA, USA

John M. Giurini
Division of Podiatric Surgery
Beth Israel Deaconess Medical Center
Boston, MA, USA

Marc L. Schermerhorn
Vascular and Endovascular Surgery
Beth Israel Deaconess Medical Center
Boston, MA, USA

ISSN 2197-7836 ISSN 2197-7844 (electronic)
Contemporary Diabetes
ISBN 978-3-031-55714-9 ISBN 978-3-031-55715-6 (eBook)
https://doi.org/10.1007/978-3-031-55715-6

This Humana imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

It is with great joy that we present the fifth edition of our textbook, *The Diabetic Foot: Medical and Surgical Management*. As with previous editions, we aimed to maintain a 5-year interval between updates. While it may be argued that major breakthroughs have occurred in diabetic lower extremity problems since the last edition, nonetheless, significant advances in our understanding of their pathogenesis and management justify a new edition. We have therefore kept the structure of the book the same, dividing it into four sections that cover clinical features and diagnosis, pathophysiology, the management of diabetic foot problems, and the organization of preventive care. Each chapter has been revised to incorporate new knowledge, and additional chapters have been added, mainly in the pathophysiology section.

Although the COVID-19 pandemic has dominated news and attention in recent years, diabetes remains a serious pandemic that, unlike COVID-19, shows no signs of improvement. As a result, significant resources will continue to be necessary for its management, and every indication suggests that diabetic foot pathologies will be among the more serious problems, consuming a larger portion of the resources spent on diabetes. As with previous editions, we have taken advantage of the extensive experience accumulated at the Joslin-Beth Israel Deaconess Foot Center over the decades and described our multidisciplinary approach that combines state-of-the-art management with a focus on avoiding unnecessary waste of valuable resources.

Among the various changes in the book, the most prominent in this edition is the replacement of one of the editors. Dr. Raul Guzman has left our institution for a more prominent position as Chief of Vascular Surgery at Yale University, where we have no doubt that he will excel, as he has in all his previous positions. We are delighted that his position has been taken by Dr. Marc Schermerhorn, Chief of Vascular Surgery at our institution, the Beth Israel Deaconess Medical Center. He brings with him not only extensive experience in the clinical management of diabetic lower extremities but also an impressive research record.

The success of the previous four editions gives us confidence that the new edition will be similarly judged by the medical community as a helpful tool in improving the management of diabetic foot problems, preserving the lower extremity, and avoiding amputations. To this end, we want to acknowledge the contributions of all the authors and sincerely thank them for their outstanding work. Last but not least, we want to express our gratitude to Humana Press for their continuing support of this project.

Boston, MA, USA — Aristidis Veves
Boston, MA, USA — John M. Giurini
Boston, MA, USA — Marc L. Schermerhorn

Contents

Part IV Organization and Preventive Care

Contributors

Nathan C. Balukoff Wound Healing and Regenerative Medicine Research Program, Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Narges Maskan Bermudez Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Elizabeth A. Beverly Department of Primary Care, Ohio University Heritage College of Osteopathic Medicine, Athens, OH, USA

Ramone Brown Department of Diagnostic Sciences, School of Dental Medicine, Tufts University, Boston, MA, USA

Kevin Buczkowski Division of Podiatric Surgery, Signature Healthcare, Brockton, MA, USA

Stephanie N. Campbell Department of Orthopaedics, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

Ryan P. Cauley Division of Plastic and Reconstructive Surgery, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Juan Ceja Solorio Rio Grande Foot and Ankle Specialist, Santa Fe, NM, USA

Paschalis Chatzipantelis Medical School, Democritus University of Thrace, Alexandroupolis, Greece

Amy Chen Division of Plastic and Reconstructive Surgery, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Caitlin Connolly Nuclear Medicine, Department of Radiology, Harvard Medical School, Mount Auburn Hospital, Cambridge, MA, USA

Mauricio Contreras Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

Daniella Dennis Division of Plastic and Reconstructive Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Triantafyllos Didangelos Internal Medicine and Diabetology, Medical School, Aristotle University, "AHEPA" Hospital, Thessaloniki, Greece

Thanh Dinh Harvard Medical School, Boston, MA, USA

Division of Podiatric Surgery, Beth Israel Deaconess Medical Center, Boston, MA, USA

Arriyan S. Dowlatshahi Division of Plastic and Reconstructive Surgery, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Robert G. Frykberg College of Podiatric Medicine at Midwestern University, Glendale, AZ, USA

Jonathan A. Garlick Department of Diagnostic Sciences, School of Dental Medicine, Tufts University, Boston, MA, USA

School of Medicine, Tufts University, Boston, MA, USA

Graduate School of Biomedical Sciences, Tufts University, Boston, MA, USA

Behzad Gerami-Naini Department of Diagnostic Sciences, School of Dental Medicine, Tufts University, Boston, MA, USA

Laura Giurato Division of Endocrinology and Diabetes, CTO Andrea Alesini Hospital, Rome, Italy

Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy

John M. Giurini Division of Podiatry, Beth Israel Deaconess Medical Center, Boston, MA, USA

Department of Surgery, Harvard Medical School, Boston, MA, USA

Joslin-BI Deaconess Diabetic Foot Center, Needham, MA, USA

Bradford Greaves Department of Diagnostic Sciences, School of Dental Medicine, Tufts University, Boston, MA, USA

Allen D. Hamdan Division of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Osama Hamdy Joslin Diabetes Center, Harvard Medical School, Boston, MA, USA

Abby Hargis Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Caitlin W. Hicks Johns Hopkins University School of Medicine, Baltimore, MA, USA

Mary G. Hochman Department of Radiology, Harvard Medical School, Musculoskeletal Imaging and Intervention, Beth Israel Deaconess Medical Center, Boston, MA, USA

Ryan Imbriaco Department of Diagnostic Sciences, School of Dental Medicine, Tufts University, Boston, MA, USA

Antonios Kafanas Lincoln County Hospital, Lincoln, Lincolnshire, UK

Nikolas Kalavros Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Broad Institute of MIT and Harvard, Cambridge, MA, USA

Spatial Technologies Unit, Harvard Initiative for RNA Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

Dimitra Karagkouni Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Broad Institute of MIT and Harvard, Cambridge, MA, USA

Adolf W. Karchmer Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Olga Kashpur Department of Diagnostic Sciences, School of Dental Medicine, Tufts University, Boston, MA, USA

Xanthi-Lida Katopodi Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Broad Institute of MIT and Harvard, Cambridge, MA, USA

Natasha Khazai University of Tahran, Tehran, Iran

Robert S. Kirsner Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Mary T. LaSalvia Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Lawrence A. Lavery Department of Plastic Surgery, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Daniela Lee Division of Plastic and Reconstructive Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Jenny Li Joslin-Beth Israel Deaconess Foot Center and The Rongxiang Xu, MD, Center for Regenerative Therapeutics, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Samuel J. Lin Division of Plastic and Reconstructive Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Frank W. LoGerfo Division of Vascular and Endovascular Surgery, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA, USA

Yuling Ma Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Broad Institute of MIT and Harvard, Cambridge, MA, USA

John T. Marcoux Division of Podiatry, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

David J. Margolis Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Simon Matoori Faculté de Pharmacie, Université de Montréal, Montréal, QC, Canada

Katherine M. McDermott Johns Hopkins University School of Medicine, Baltimore, MA, USA

David J. Mooney John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge, MA, USA

Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, MA, USA

Lucas Mota Department of Surgery, Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA, USA

Thao Nguyen Division of Podiatry, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Monika A. Niewczas Section on Genetics and Epidemiology, Joslin Diabetes Center, Boston, MA, USA

Department of Medicine, Harvard Medical School, Boston, MA, USA

Irena Pastar Wound Healing and Regenerative Medicine Research Program, Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Yered H. Pita-Juarez Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Broad Institute of MIT and Harvard, Cambridge, MA, USA

Leena Pradhan-Nabzdyk Division of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Sahar Rahmani John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge, MA, USA

Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, MA, USA

Kevin Riemer Division of Podiatric Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Lee C. Rogers Department of Orthopaedics, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

Barry I. Rosenblum Harvard Medical School, Boston, MA, USA

Division of Podiatric Surgery, Beth Israel Deaconess Medical Center, Boston, MA, USA

Ruchi Roy UICentre for Drug Discovery, College of Pharmacy, University of Illinois at Chicago, Chicago, IL, USA

Andrew P. Sawaya Wound Healing and Regenerative Medicine Research Program, Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Sasha H. Shafikhani Department of Medicine, Rush University Medical Center, Chicago, IL, USA

Cancer Center, Rush University Medical Center, Chicago, IL, USA

Hetal Shah Section on Genetics and Epidemiology, Joslin Diabetes Center, Boston, MA, USA

Department of Medicine, Harvard Medical School, Boston, MA, USA

Sasha Shenk Department of Diagnostic Sciences, School of Dental Medicine, Tufts University, Boston, MA, USA

Eric Shiah Division of Plastic and Reconstructive Surgery, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Raj Singh Department of Medicine, Rush University Medical Center, Chicago, IL, USA

Arlene Smaldone Columbia University, School of Nursing, New York, NY, USA

Avi Smith Olympus Inc., Waltham, MA, USA

Lars Stangenberg Division of Vascular and Endovascular Surgery, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Mehmet A. Suludere Department of Plastic Surgery, University of Texas Southwestern Medical Center, Dallas, Texas, USA

Brandon J. Sumpio Center for Regenerative Therapeutics, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Nicholas J. Swerdlow Division of Vascular and Endovascular Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Nikolaos Tentolouris Department of Internal Medicine, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital, Athens, Greece

Solomon Tesfaye Diabetes and Endocrinology for Sheffield Teaching Hospitals and the University of Sheffield, Royal Hallamshire Hospital, Sheffield, UK

Georgios Theocharidis Joslin-Beth Israel Deaconess Foot Center and The Rongxiang Xu, MD, Center for Regenerative Therapeutics, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Marjana Tomic-Canic Wound Healing and Regenerative Medicine Research Program, Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Panagiotis V. Tsaklis Laboratory of Biomechanics and Ergonomics—@ErgoMechLab, Department of Physical Education and Sport Science, University of Thessaly, Trikala, Greece

Department of Molecular Medicine and Surgery, Growth and Metabolism, Karolinska Institute, Solna, Sweden

Luigi Uccioli Division of Endocrinology and Diabetes, CTO Andrea Alesini Hospital, Rome, Italy

Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy

Eleftheria Angeliki Valsami The Rongxiang Xu, MD, Center for Regenerative Therapeutics, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Nicole M. Vecin Wound Healing and Regenerative Medicine Research Program, Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Aristidis Veves The Rongxiang Xu, MD, Center for Regenerative Therapeutics, Joslin-Beth Israel Deaconess Foot Center, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Ioannis S. Vlachos Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Broad Institute of MIT and Harvard, Cambridge, MA, USA

Enya Wang The Rongxiang Xu, MD, Center for Regenerative Therapeutics, Beth Israel Deaconess Medical Center, Boston, MA, USA

Sophie X. Wang Division of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center, Boston, MA, USA

Mark C. Wyers Division of Vascular and Endovascular Surgery, Beth Israel Deaconess Medical Center, Boston, MA, USA

Marita Yaghi Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

Alan Z. Yang Division of Plastic and Reconstructive Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Part I

Clinical Features and Diagnosis

The Epidemiology of Diabetic Foot Ulcer and Amputation

1

David J. Margolis

Abstract

Lower extremity amputation (LEA) and foot ulcer (DFU) are important complications of diabetes. Incidence and prevalence are two epidemiologic measures that indicate new events and events that are currently present. The incidence and prevalence of LEA and DFU vary worldwide and also within countries. Of note, the incidence of LEA appeared to be decreasing in the early part of this century but now in many countries is increasing. The increase is often associated with minor amputations. Individuals who have diabetes and DFU or LEA are at increased risk of death. The costs associated with care for individuals with LEA or DFU are higher than for those with diabetes who do not have LEA or DFU.

Background and Introduction

Lower extremity complications of diabetes are an international problem [1–4]. Epidemiologic studies of these complications are difficult to conduct and can be confusing to interpret, especially if the reader does not have a good understanding of epidemiologic principles. **Epidemiology** is the study of disease in a population at large, and it includes the incidence, prevalence, distribution, cause, and natural history of the disease. The study of epidemiology is concerned with the health of populations, and it not only helps inform the natural history and treatment of disease, but it is also a basic science that is used to guide public health policy. Epidemiologic studies are often used to help guide evidence-based practice. Most epidemiologic studies are observational, which means that epidemiologists usually observe a population and how it is affected by a disease without intervening in the population. On the other hand, in experimental studies, a clinical trialist will determine how an intervention affects an individual's health by actively exposing individuals in a population to an exposure, such as a drug, of interest.

For this chapter, we will primarily focus on complications limited to the lower extremities in those with diabetes (diabetic foot ulcer (DFU) and lower extremity amputation (LEA)) and two important epidemiologic concepts: incidence and prevalence. Other important diseases of the lower extremity, like Charcot foot, will be described in other chapters. **Incidence** is the frequency of new cases of a disease or other outcomes among those who are at risk of the disease or outcomes of interest within a specified time period. For our discussion, the "at-risk population" mainly refers to individuals with diabetes who have lower extremity limbs but could include all individuals. As a result, it is important that the "at-risk" population is described. "At-risk" does not mean a person is at the highest risk but refers to anyone who can **have** an outcome of interest (e.g., if the outcome is LEA, the population at risk should have legs). Generally, a new case occurs only once. However, it could be possible to define the population as individuals who have had DFU, and the incidence estimate is for another foot ulcer. In our setting, incidence is measured by dividing the number of individuals who develop a new DFU or LEA by the number of individuals in the at-risk population (e.g., individuals with diabetes and lower extremities). The numerator and denominator can also be influenced by the method(s) used to diagnose diabetes and how the outcome is determined (e.g., minor versus major amputation, in-person examination, billing records, patient survey, etc.). The numerator can be greatly influenced by the diagnostic criteria used to determine diabetes, whether all ages were studied, whether the population studied was the full population or just those with diabetes, etc. **Prevalence** is the frequency of a disease or other outcomes of interest over a given period. In the setting of this chapter, prevalence is measured as the number of individuals with DFU or LEA divided by the number of individuals sampled (most likely with diabetes) over a specified period. Measuring prevalence

D. J. Margolis (✉)
Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
e-mail: margo@pennmedicine.upenn.edu

A. Veves et al. (eds.), *The Diabetic Foot*, Contemporary Diabetes, https://doi.org/10.1007/978-3-031-55715-6_1

is especially important and relevant for chronic diseases (i.e., diseases of longer duration resulting in prevalence rates being larger than incidence rates). Prevalence can be measured as point prevalence (i.e., Does an individual have a foot ulcer today?), yearly prevalence (i.e., Does an individual have a foot ulcer during a 12-month period?), their lifetime prevalence, or any other given period of interest. Prevalence estimates can also be greatly influenced by factors discussed above for the numerator and denominator.

While there are several other important epidemiological concepts, at a minimum, the concepts of bias and generalizability are essential when trying to interpret an epidemiological report on incidence and prevalence. Most epidemiologic studies evaluating incidence or prevalence are observational studies designed as **cohort studies**, which are often large studies for which information is documented prospectively (followed forward in time). For example, when assessing the incidence of DFUs, individuals enrolled in a cohort study did not have DFU when their observation began, and then they were followed for days, months, or years to determine if DFU occurred. **Case-control studies** enroll subjects who do (case) or do not (control) have an outcome of interest, and then important information is obtained retrospectively. As a result, the overall rate of disease (e.g., case) in the general population cannot be ascertained, but risk factors for the disease can. For example, individuals with DFU are enrolled in a study, along with individuals who do not have DFU, and then they were questioned about important historical factors in order to determine potential risk factors for DFU. **Cross-sectional studies** are the evaluation of a population at a specific point in time. While this may not be an adequate design for an incidence study, cross-sectional studies can be a good design for a point prevalence study.

When evaluating reports, it is crucial to consider potential errors in estimates of prevalence and incidence and internal (bias) and external validity (generalizability). **Selection bias** is a systematic bias in a study caused by how subjects are selected or not selected for a study. In a case-control study, selection bias can occur if the source population from which the cases are drawn is different from the control source population. In a cohort study, selection bias can result from problems with how individuals were recruited for evaluation. **Information bias** is a bias that occurs because of reporting. Reporting can vary because of the skill of the observer, the frequency of observation, the subject's memory and how their memory was prompted, how questions were asked, how information was stored and retrieved, etc. A final issue to consider is **generalizability**. Generalizability is how well the results of a study represent other populations of concern. For example, if the goal was to determine the countrywide incidence of DFU using a cohort composed of patients followed monthly in an adult-onset hospital-based diabetes clinic where routine foot examinations are a part of the clinic's standard practice, the incidence of DFU will likely be higher than for a primary care clinic in the community (poor generalizability). Fuller discussions on epidemiologic studies are best left to textbooks.

The remainder of this chapter will present incidence and prevalence estimates for DFUs and LEAs. As described above, it is important to evaluate these estimates based on the population studied and how individuals were determined to have diabetes, foot ulcers, and lower extremity amputation. Rates may vary considerably if the population evaluated is the full population, only those over a certain age, only those with diabetes, only those hospitalized, those with no previous history of amputation or foot ulcer, etc. It is important to consider the lessons learned above when interpreting these estimates.

Lower Extremity Amputation and Concerns About Available Data

The incidence of LEA is tracked by the United States (US) Centers for Disease Control and Prevention (CDC) using several publicly available datasets. CDC estimates are available at https://gis.cdc.gov/grasp/diabetes/diabetesatlas-surveillance.html. The CDC data presented here for LEA are based on hospital discharge data from the National Inpatient Sample (NIS) and the National Health Information Survey (NHIS). Data were obtained from the CDC website in February 2023. The most recently reported age-adjusted rate of LEA among hospitalized individuals with diabetes that is available from the CDC data source in the United States is 5.6 per 10,000 persons in 2019. However, using this same dataset, the rate was 5.38 in 2000, 3.07 in 2009, and 4.62 in 2015 [5]. The rate of LEA decreased over the first decade of this century but is now increasing rapidly (Fig. 1.1) [5, 6].

This rate fluctuation could represent changes in care over time but could also potentially be affected by the epidemiologic concepts discussed above. The definition of diabetes changed between 1997 and 2010 [5–7]. As compared to pre-1997, the changes in the definition of diabetes were related to the criteria used to diagnose diabetes, which included diagnosing diabetes in patients using a lower value of fasting blood sugar, the use of a decreased magnitude in glycemic index from a glucose tolerance test, and the acceptance of hemoglobin A1c as a diagnostic test [5–7]. These changes could result in diagnosing diabetes earlier in the course of the disease, thereby diagnosing diabetes in individuals who are less likely at the time of diagnosis to develop DFU or have LEA [2, 5–7]. As would be expected, these changes resulted in an increase in newly diagnosed (incidence of) diabetes in the late 1990s and early 2000s. Community

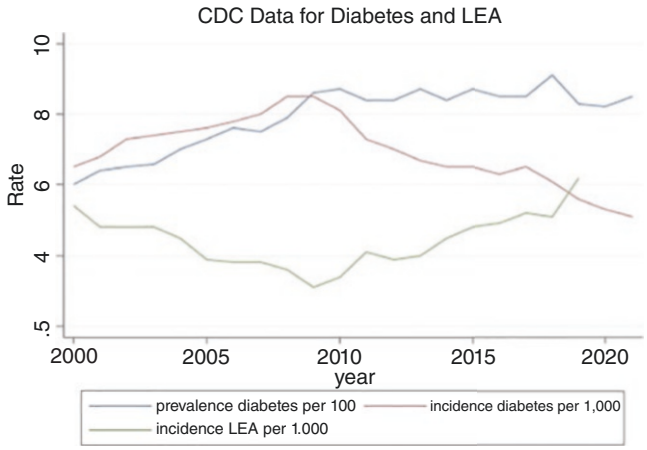

Fig. 1.1 US incidence (per 1000) and prevalence of diabetes (per 100) and incidence of hospital-reported lower extremity amputation (per 1000 with diabetes) from 2000 to 2021 (if data were available). Data were obtained from the Centers for Disease Control and Prevention (https://gis.cdc.gov/grasp/diabetes/diabetesatlas-surveillance.html) in March 2023

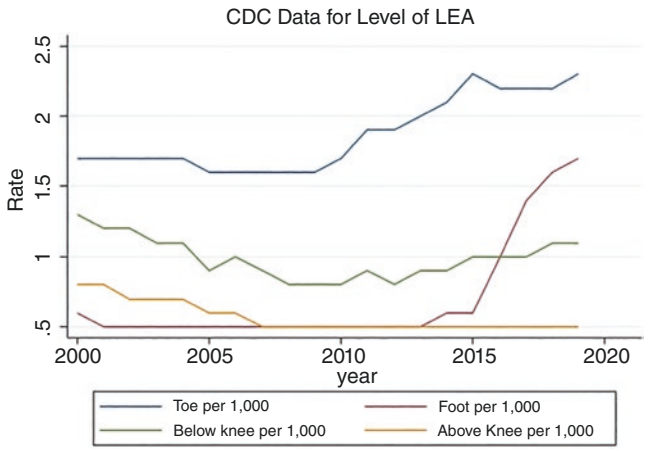

Fig. 1.2 US incidence of hospital-reported lower extremity amputation by highest level: toe, foot, below the knee, and above the knee (per 1000 with diabetes) from 2000 to 2019. Data were obtained from the Centers for Disease Control and Prevention (https://gis.cdc.gov/grasp/diabetes/diabetesatlas-surveillance.html) in March 2023

screening for diabetes also improved. Overall, the incidence of diabetes per age-adjusted 1000 people in the United States first increased and then decreased from 2000 to 2021 in the United States from about 6.5 per 1000 to about 5.1 per 1000 and the prevalence of diabetes stabilized ranging from 6 per 100 in 2000 to 8.5 per 100 in 2021 (Fig. 1.1). Initially, as the incidence and prevalence of diabetes increased, there was a marked decrease in the rate of LEA. Whereas many attributed this change to improved care, an explanation for this sharp decrease in the rate of LEA could have been related to the fact that the actual number of LEA remained stable (e.g., a numerator with a minimal change), while at the same time, the number of patients with diabetes rapidly increased (e.g., an enlarging denominator, including individuals earlier in the diabetes disease course) [5]. Since LEA and DFU are a later complication of diabetes, as patients with earlier forms of diabetes matured with their disease, the potential for DFU and LEA increased. Over the past several years, the rate of LEA is now increasing toward rates noted at the end of the last century. Figure 1.1 is a graphical presentation of this phenomenon using data from the United States Diabetes Surveillance System obtained in February 2023 (US CDC; https://gis.cdc.gov/grasp/diabetes/DiabetesAtlas.html#).

In addition, a second important epidemiologic issue with respect to the prevalence and incidence of LEA is related to the appropriateness of the outcome. Based on data from the CDC, the increasing rate of LEA is primarily associated with an increased incidence of minor amputations (toes and foot) (Fig. 1.2). The rate of major amputations has been stable over many years. Many clinicians have argued that minor amputations could represent a successful outcome that maximizes limb salvage (i.e., a minor amputation should be viewed as a treatment success) [8]. However, about 25–34% of individuals who had LEA will have a second amputation within 6–12 months on the same limb, and some minor amputations will become major amputations [9–11]. CDC data also show that unlike LEA rates, the rates of other diabetes-associated comorbidities, such as ischemic heart disease or end-stage renovascular disease, did not appreciably change with a change in the diagnosis of diabetes and ischemic heart disease decreased over time. As a result, it is important to be very careful when interpreting changes in LEA rates over time.

Lower Extremity Amputation

Worldwide reviews and meta-analyses show marked variation in the rates of LEA from country to country, between regions within countries, and between continents. A review from 2013 noted concerns about variations in the diagnosis of diabetes and the importance of differentiating the level of amputation and highlighted the variations both between countries and within countries [12]. The lowest incidence of LEA noted in that report was in Ireland, with a rate of 1.76 per 1000 diabetics, and the highest was 5.0 per 1000 diabetics, which was reported in the United States [12–14]. In other studies, as large as an eightfold variation in the incidence of LEA was noted independently within regions in the United States and the United Kingdom [14–16]. While the variation was comparable within the two countries, the rate of LEA was greater in the United States than in the United Kingdom [16, 17]. A global review and meta-analysis from 2023 examined 23 studies, noting that the worldwide incidence of minor LEA was 1.40 per

Table 1.1 Examples of incidence estimates for individuals with lower extremity amputation

Year (citation)	Cohort	Incidence estimate
2000–2019	US Hospitalized (CDC)	4.3–5.6 per 1000 hospitalized with diabetes
2006–2009 [14]	US Medicare	4.0–5.0 per 1000 with diabetes
2008–2018 [19]	US Veteran's	1.3–1.8 per 1000 veterans
2012 [16]	UK General Practice	2.51 per 1000 with diabetes

1000 individuals with diabetes and 0.95 per 1000 for major amputations [4]. Overall, LEA rates varied from a low of 0.22 per 1000 in Italy to a high of 6.11 per 1000 individuals with diabetes in the United States [4]. These authors also noted a variation based on the type of diabetes and that the rates over time increased or were stable in all countries worldwide [4]. These rates are summarized in Table 1.1.

Specifically, for the United States, per the CDC, from 2010 to 2019, the rate of hospitalization for LEA among hospitalized diabetics in the country varied from 4.2 to 5.6 per age-adjusted 1000 persons (Fig. 1.1). More specifically, the rates for toe amputation were 1.7–2.3, foot amputation 0.5–1.7, and below-knee amputation 0.8–1.1 per age-adjusted 1000 persons in hospitals. In a study of 100% of the US Medicare population with diabetes between 2006 and 2008, the prevalence of LEA associated with diabetes was 1.8 per 100 enrolled in Medicare, and the incidence was about 0.5 per 100 [14, 18]. Rates varied widely by state and between Dartmouth Health Referral Regions (HRR) [14–15, 17–18]. A recent analysis of the Veterans Health Administrative Services (VA) in the United States revealed that between 2008 and 2018, the rate of LEA increased from 12.89 per 10,000 persons treated in the VA system (in- or outpatients) to 18.12 per 10,000, representing a net increase of 5.23% [19]. The largest increase was for toe amputations (3.24%), which accounted for 62% of the overall increase, and transmetatarsal amputations (1.54%), with below the knee increasing only 0.81% during this time frame [19]. These estimates include individuals with and without diabetes. The majority of the LEA did occur in those with diabetes, and there was minimal increase over time in the rate of LEA among those without diabetes [19].

Risk factors for LEA consistently include lower extremity arterial flow; demographics; age; gender; race; smoking status; cardiovascular status; obesity; glycemic control; hypertension; peripheral arterial disease; cerebrovascular disease; renal function, including the severity of chronic renal disease; and previous history of amputation and/or foot ulcer, as well as characteristics of the foot ulcer. The magnitude of the risk factor does vary from study to study, and these factors will be reviewed in other chapters [1, 3, 13–14, 17, 19–21].

One of the most worrisome associations with LEA is the increased risk of mortality. A recent review and meta-analysis revealed that pooled mortality rates 1, 2, 3, 5, and 10 years after a major nontraumatic LEA were 33.7%, 51.5%, 53%, 64.4%, and 80%, respectively [22]. For those with diabetes and a major LEA, the 1- and 5-year mortality rates were 27.3% and 63.2% [22]. A study from the Netherlands revealed a 1-year mortality rate of 34% among those with poor vascular flow with or without diabetes after LEA [10]. The 1-year mortality rate for older individuals (>75 years of age) with a major LEA was nearly 50% [10]. In a UK-based study, those with diabetes and any LEA had a 3.02 risk of death as compared to individuals with diabetes who did not have LEA, and the overall 5-year mortality rate was 27.2% [23]. The risk of death was not altered by a statistical adjustment of the many factors that might be associated with LEA and death, such as renal disease, glycemic control, history of cerebrovascular disease, peripheral vascular disease, and myocardial ischemia, indicating that the risk of LEA was separate from the risks associated with these illnesses, thereby indicating that LEA by itself is a risk factor for death [23].

Diabetic Foot Ulcer

One of the best-studied chronic wounds is the DFU [1]. DFUs have an important impact on public health because of their association with LEA, as well as death [21, 23]. About 17% of individuals with a healed DFU will experience a recurrence in the same location, and 48% will recur on the contralateral foot [24]. Those with diabetes and DFU are more than ten times more likely to have LEA than those with diabetes and no DFU [25]. About 85% of individuals with diabetes who have LEA had a preceding DFU [26].

A recent meta-analysis estimated that the global prevalence of DFU was 6.3% [27]. The prevalence varied by region [27]. For example, the highest prevalence was in North America at 13.0%, and the lowest was estimated for Oceania at 3.0% [27]. By country, the highest prevalence was Belgium (16.6%) and the lowest was Australia (1.5%) [27]. Variations were also noted by sex (higher males), the type of diabetes (higher type 2), and whether the sample was from a hospital (higher) or community [27]. Although not specifically stated, the assumption is that these estimates were from populations with diabetes. As noted above, prevalence differs from incidence in that an incident ulcer occurred during the period of observation and a prevalent wound is present. The duration of the wound can link incidence with prevalence.

Other studies have estimated that the prevalence of DFU varies from 1.2% to 20% for patients with diabetes in the hospital and from 0.02% to 10% for patients with diabetes in the community [1, 20, 28]. In the US Medicare population, the yearly prevalence of DFU among Medicare beneficiaries over 65 years of age was 8.0 and 8.1 per 100 individuals between 2006 and 2008 [18]. In a recent meta-analysis, DFU prevalence varied by age, the presence of other complications of and diseases associated with diabetes, and region [1, 14, 17, 18, 25]. In a study of all US Medicare beneficiaries, DFU varied by age from a low of 6.1% for those with diabetes between 65 and 74 years of age to a high of 15.0% for those over 95 [18]. It also varied in the United States by region (HRR) [18].

From a review in 2014, among those with diabetes, the worldwide incidence of DFUs has been reported to vary from 5 per 100 person-years to 8 per 100 person-years [1, 28]. The incidence of DFU in 2006–2008 in the US Medicare population was about 6% between 2006 and 2009 [14]. A variation in DFU incidence was noted by age with an overall rate of 6 per hundred person-years, with a low of 4.6 for those aged between 65 and 74 and a high of 11.5 per hundred person-years for those over 95 [14]. All rates varied three- to five-fold by US HRR [14, 17–18]. A study in the UK of first DFUs occurring in 2007–2017 revealed yearly incidence estimates of 1.4–3.6 per 1000 person-years of type 2 diabetes [29]. DFUs were more common in those with type 2 diabetes [29]. A regional variation has also been noted in the UK [16]. These rates are summarized in Table 1.2.

Those with DFU, like those with LEA, are also at an increased risk of death. The increased risk of death among those with diabetes and DFU is about two times the risk of death for those with diabetes who do not have a foot ulcer [21, 23]. As reported for those with LEA, the reason for this association is not fully explained by the same factors reported above [21]. In the UK, *1-year mortality* for those with type 2 diabetes and DFU the mortality 1 year after the diagnosis of DFU is 11.7% and 33.1% at 5 years [29]. In another UK study, after the diagnosis of DFU, the 5-year mortality was 42.2% for those diabetics who had DFU, and they were more than twice as likely to die than those with diabetes and no history of DFU [21]. A recent meta-analysis evaluated the global mortality of DFU [26]. The meta-estimate for survival rates were 86.9% at 1 year, 66.9% at 3 years, 50.9% at 5 years, and 23.1% at 10 years [26]. The study noted that cardiovascular disease and infection were the leading causes of death among those with DFU, but these illnesses did not explain the full increased risk of death [26].

Table 1.2 Examples of incidence estimates for individuals with diabetic foot ulcers

Year (citation)	Cohort	Incidence estimate
2006–2009 [18]	US Medicare	6.0 per 100 with diabetes
2007–2017 [29]	UK General Practice	1.4–3.6 per 100 with type 2 diabetes

Burden of Diabetic Foot Ulcer and Lower Extremity Amputation

The burden of DFU and LEA is related to factors such as mortality and economics. Mortality is described above and is a key driver with respect to the burden of an illness. As noted, both DFU and LEA are associated with an increased risk of death as compared to those with diabetes who did not have LEA or DFU [1, 3, 10, 21–22, 29]. A recent report equated the LEA-associated 5-year mortality to the risk of death from cancer [30]. The risk of death associated with DFU and LEA at 5 years was greater than the risk of death from breast cancer [30]. The risk of death after a major amputation was greater than the combined risk from all cancers and only about 25% less than from lung cancer [30].

Estimating the cost of care can be difficult because not all countries accrue health costs in a similar way. As a result, determining direct economic costs for care is difficult, and comparing between countries is problematic. In the United States, medical care is mostly fee-for-service, and many studies (US and others) try to determine costs based on US expenditure models. For example, a recent study from Singapore evaluated costs accrued between 2013 and 2017 based on in- and outpatient care among individuals with DFU [31]. The average cost for those with DFU was USD 3368 per patient-year; for minor amputation, it was USD 10,468 per patient-year, and major amputation was USD 30,131 per patient-year [31].

In a study evaluating 100% of Medicare beneficiaries from 2006 to 2008, the annual cost per beneficiary for those with DFU was between US$31,600 and US$35,000, and US$1800 to US$1900 were for services thought to be directly related to DFU [32]. Individuals with DFU were, on average, seen by healthcare providers 14 times per year and were hospitalized 1.5 times per year [32]. For LEA, the costs were between US$49,300 and US$54,000 for all medical services and US$7600 and US$8000 for select services directly related to LEA [32]. These costs varied by state and HRR. In 2014, using a 5% random sample of Medicare and data from a private insurer, it was estimated that the treatment of DFU cost an additional US$2021 than other Medicare beneficiaries, and the overall medical costs for DFU patient was between US$11,170 and US$16,883 for the 12-month period following their DFU [33].

A review from 2018 found somewhat similar costs in European countries [34]. Overall, the European costs for patients with DFU were estimated to be approximately USD 13,561 per year [34, 35]. More specifically, monthly costs in

France were about USD 1265 for DFU patients; in the UK, the yearly costs were about USD 7539 per DFU patient, and in Belgium, the yearly costs were about USD 10,572 per DFU patient [34, 36, 37]. More specifically, for the National Health Service (NHS) in the UK, in 2014–2015 the overall cost of care (hospital, outpatient, community and primary care) for a DFU or LEA was estimated to be between £837 million and £962 million, respectively [36]. The overall cost to the NHS was greater for DFU than for LEA because in absolute terms, there are more patients with DFU than LEA.

Conclusion

DFU and LEA are worldwide important complications of diabetes. When evaluating published rates of DFU and LEA, it is important to determine if the reported rate is incidence or prevalence. It is important to evaluate the study design and consider inherent biases in the estimates as well as the generalizability of the estimates. The rate may also vary widely based on the at-risk population under consideration. The burden of these complications includes the increased rate of death and economic costs. DFU and LEA are significant and burdensome complications of diabetes worldwide.

References

1. Margolis DJ, Jeffcoate WJ. Epidemiology of foot ulceration and amputation-can global variation be explained? Med Clin North Am. 2013;2013(97):791–805.
2. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016;387(10027):1513–30.
3. McDermott K, Fang M, Boulton AJM, Selvin E, Hicks CW. Etiology, epidemiology, and disparities in the burden of diabetic foot ulcers. Diabetes Care. 2023;46(1):209–21.
4. Ezzatvar Y, García-Hermoso A. Global estimates of diabetes-related amputations incidence in 2010-2020: a systematic review and meta-analysis. Diabetes Res Clin Pract. 2023;195:110194.
5. Geiss LS, Li Y, Hora I, Albright A, Rolka D, Gregg EW. Resurgence of diabetes-related nontraumatic lower-extremity amputation in the Young and middle-aged adult U.S. Population. Diabetes Care. 2019;42(1):50–4.
6. Li Y, Burrows NR, Gregg EW, Albright A, Geiss LS. Declining rates of hospitalization for nontraumatic lower-extremity amputation in the diabetic population aged 40 years or older: U.S., 1988-2008. Diabetes Care. Feb 2012;35(2):273–7.
7. Shaw JE, de Courten M, Boyko EJ, Zimmet PZ. Impact of new diagnostic criteria for diabetes on different populations. Diabetes Care. 1999;22(5):762–6.
8. Brown BJ, Crone CG, Attinger CE. Amputation in the diabetic to maximize function. Semin Vasc Surg. 2012;25(2):115–21.
9. Malay D, Margolis DJ, Hofstad O, Bellamy S. The incidence and risks of failure to heal following lower extremity amputation for the treatment of diabetic neuropathic foot ulcer. J Foot Ankle Surg. 2006;2006(45):366–75.
10. Fard B, Dijkstra PU, Voesten H, Geertzen JHB. Mortality, reamputation, and preoperative comorbidities in patients undergoing dysvascular lower limb amputation. Ann Vasc Surg. 2020;64:228–38.
11. Littman AJ, Tseng CL, Timmons A, et al. Risk of ipsilateral reamputation following an incident toe amputation among U.S. military veterans with diabetes, 2005-2016. Diabetes Care. 2020;43(5):1033–40.
12. Margolis DJ, Jeffcoate W. Epidemiology of foot ulceration and amputation: can global variation be explained? Med Clin North Am. 2013;97(5):791–805.
13. Buckley CM, O'Farrell A, Canavan RJ, et al. Trends in the incidence of lower extremity amputations in people with and without diabetes over a five-year period in the Republic of Ireland. PLoS One. 2012;7(7):e41492.
14. Margolis D, Malay DS, Hoffstad OJ, et al. Incidence of diabetic foot ulcer and lower extremity amputation among Medicare beneficiaries, 2006 to 2008. Rockville, MD: Agency for Healthcare Research and Quality; 2010.
15. Wrobel JS, Mayfield JA, Reiber GE. Geographic variation of lower-extremity major amputation in individuals with and without diabetes in the Medicare population. Diabetes Care. 2001;24(5):860–4.
16. Holman N, Young RJ, W.J. J. Variation in the recorded incidence of amputation of the lower limb in England. Diabetologia. 2012;55(7):1919–25.
17. Margolis DJ, Hoffstad O, Nafash J, et al. Location, location, location: geographic clustering of lower-extremity amputation among medicare beneficiaries with diabetes. Diabetes Care. 2011;34(11):2363–7.
18. Margolis D, Malay DS, Hoffstad OJ, et al. Prevalence of diabetes, diabetic foot ulcer, and lower extremity amputation among Medicare beneficiaries, 2006 to 2008. Rockville, MD: Agency for Healthcare Research and Quality; 2010.
19. Cai M, Xie Y, Bowe B, et al. Temporal trends in incidence rates of lower extremity amputation and associated risk factors among patients using veterans health administration services from 2008 to 2018. JAMA Netw Open. 2021;4(1):e2033953.
20. Heyer K, Herberger K, Protz K, Glaeske G, Augustin M. Epidemiology of chronic wounds in Germany: analysis of statutory health insurance data. Wound Repair Regen. 2016;24(2):434–42.
21. 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(11):1493–8.
22. Meshkin DH, Zolper EG, Chang K, et al. Long-term mortality after nontraumatic major lower extremity amputation: a systematic review and meta-analysis. J Foot Ankle Surg. 2021;60(3):567–76.
23. Hoffstad O, Mitra N, Walsh J, Margolis DJ. Diabetes, lower-extremity amputation, and death. Diabetes Care. 2015;38(10):1852–7.
24. Petersen BJ, Rothenberg GM, Lakhani PJ, et al. Ulcer metastasis? Anatomical locations of recurrence for patients in diabetic foot remission. J Foot Ankle Res. 2020;13:1.
25. Margolis DJ, Hofstad O, Feldman HI. Association between renal failure and foot ulcer or lower-extremity amputation in patients with diabetes. Diabetes Care. 2008;31(7):1331–6.
26. Chen L, Sun S, Gao Y, Ran X. Global mortality of diabetic foot ulcer: a systematic review and meta-analysis of observational studies. Diabetes Obes Metab. 2023;25(1):36–45.
27. 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(2):106–16.
28. Graves N, Zheng H. The prevalence and Incidence of chronic wounds: a literature review. Wound Pract Res. 2014;22:4–16.
29. Røikjer J, Werkman NCC, Ejskjaer N, et al. Incidence, hospitalization and mortality and their changes over time in people with a first ever diabetic foot ulcer. Diabet Med. 2022;39(4):e14725.

30. Armstrong DG, Swerdlow MA, Armstrong AA, Conte MS, Padula WV, Bus SA. Five year mortality and direct costs of care for people with diabetic foot complications are comparable to cancer. J Foot Ankle Res. 2020;13(1):16.
31. Lo ZJ, Surendra NK, Saxena A, Car J. Clinical and economic burden of diabetic foot ulcers: a 5-year longitudinal multi-ethnic cohort study from the tropics. Int Wound J. 2021;18(3):375–86.
32. Margolis D, Malay DS, Hoffstad OJ, et al. Economic burden of diabetic foot ulcers and amputations among Medicare beneficiaries, 2006 to 2008. Rockville, MD: Agency for Healthcare Research and Quality; 2010.
33. Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons NB. Burden of diabetic foot ulcers for medicare and private insurers. Diabetes Care. 2014;37(3):651–8.
34. Raghav A, Khan ZA, Labala RK, Ahmad J, Noor S, Mishra BK. Financial burden of diabetic foot ulcers to world: a progressive topic to discuss always. Ther Adv Endocrinol Metab. 2018;9(1):29–31.
35. Prompers L, Huijberts M, Schaper N, et al. Resource utilisation and costs associated with the treatment of diabetic foot ulcers. Prospective data from the Eurodiale study. Diabetologia. 2008;51(10):1826–34.
36. Kerr M, Barron E, Chadwick P, et al. The cost of diabetic foot ulcers and amputations to the National Health Service in England. Diabet Med. 2019;36(8):995–1002.
37. Van Acker K, Oleen-Burkey M, De Decker L, et al. Cost and resource utilization for prevention and treatment of foot lesions in a diabetic foot clinic in Belgium. Diabetes Res Clin Pract. 2000;50(2):87–95.

Clinical Examination and Risk Classification of the Diabetic Foot

2

Lawrence A. Lavery and Mehmet A. Suludere

Abstract

A consistent, thoughtful assessment of the diabetic foot is pivotal to identifying patients at risk for ulceration. In this chapter, we discuss the key risk factors to screen patients for foot complications, a history of lower extremity disease, the presence of peripheral neuropathy, and foot deformities. We discuss the practical approach and background of these key risk factors and, subsequently, the two most commonly used classification systems for diabetic foot ulcers. Many of the risk factors for ulceration may be identified using simple, inexpensive techniques in a primary care setting. Appropriate classification of the wound becomes paramount in our efforts to document and communicate the level of risk and facilitate amputation prevention.

Foot ulceration is one of the most common precursors to lower extremity amputations among persons with diabetes [1, 2]. Ulcerations are pivotal events in limb loss for two important reasons. First, they allow an avenue for infection, and second, they can cause progressive tissue necrosis and poor wound healing in the presence of critical ischemia. Infections involving the foot rarely develop in the absence of a wound in adults with diabetes, and ulcers are the most common type of wound in this population [3]. Foot ulcers therefore play a vital role in the causal pathway to lower extremity amputation.

The etiology of ulcerations in persons with diabetes is commonly associated with the presence of peripheral neuropathy and repetitive trauma due to normal walking activities to areas of the foot exposed to moderate or high pressure and shear forces [4]. Foot deformities, limited joint mobility, partial foot amputations, and other structural deformities often predispose diabetic patients with peripheral neuropathy to abnormal weight-bearing, areas of concentrated pressure, and abnormal shear forces that significantly increase their risk for ulceration [5, 6]. Brand theorized that when these types of forces were applied to a discrete area over an extended period, they would cause a local inflammatory response, focal tissue ischemia, tissue destruction, and ulceration [7]. The identification of persons at risk for ulceration is of vital importance in any plan for amputation prevention and diabetes care.

Diabetic Foot Risk Classification

Preventing foot complications begins with identifying patients at risk for developing a foot ulcer. Diabetic foot screening programs are inexpensive and can be performed by technicians or nurses with basic training. In patients with signs or symptoms of loss of protective sensation caused by peripheral neuropathy, examinations should include obtaining a detailed history of ulceration and amputation of the lower extremities and screening for the presence of peripheral artery disease and foot deformities. On top of that, other patient-related factors, like inappropriate footwear, foot hygiene, and preulcerative signs on the foot should be identified. In the updated consensus document of the International Working Group on the Diabetic Foot (IWGDF), a screening interval is added to the widely used classification system of the key risk factors [8–10].

Lavery et al. reported that a patient with neuropathy but no deformity or history of ulcer or amputation has a 1.7 times greater risk for ulceration compared with a patient without neuropathy [11]. Neuropathy with concomitant

L. A. Lavery (✉) · M. A. Suludere
Department of Plastic Surgery, University of Texas Southwestern Medical Center, Dallas, Texas, USA
e-mail: Larry.Lavery@utsouthwestern.edu

A. Veves et al. (eds.), *The Diabetic Foot*, Contemporary Diabetes, https://doi.org/10.1007/978-3-031-55715-6_2

Table 2.1 The IWGDF 2019 Risk Classification System for prevention screening frequency

Category	Characteristics	Frequency
0	No peripheral neuropathy	Once a year
1	Peripheral neuropathy or peripheral arterial disease	Once every 6–12 months
2	Peripheral neuropathy and peripheral arterial disease **or** Foot deformity with peripheral neuropathy or peripheral arterial disease	Once every 3–6 months
3	Peripheral neuropathy or peripheral arterial disease with – A history of foot ulcers **or** – Lower extremity amputation **or** – End-stage renal disease	Once every 1–3 months

deformity or limited joint mobility yields a 12.1 times greater risk. Lastly, a patient with a history of previous ulceration or amputation has a 36.4 times greater risk of presenting with another ulcer. These risk factors are compared to the categories in the classification system promoted by the International Working Group on the Diabetic Foot [8, 11–13] (Table 2.1) and similar classification systems described by Rith-Najarian [14] and Armstrong [15]. A comparison was made between this system and four other classification tools in a systematic review in 2011 [16]. The core values of the stratification systems were very similar, but the risk groups and number of variables that were included varied.

History of Foot Pathology

A history of foot disease is the strongest predictor of ulceration and amputation and the least expensive screening measure [17–19]. It is the easiest risk group to identify and the group most in need of frequent foot assessment, intensive education, therapeutic shoes, padded stockings, and rigorous blood glucose control. A current ulcer or a history of previous ulceration or amputation heighten the risk for further ulceration, infection, and subsequent amputation [8, 16, 20, 21]. Patients in this risk group (Risk Category 3) are about 50 times more likely to have an ulcer in the next year and 36 times more likely to have an amputation compared to patients with no neuropathy or peripheral arterial disease (PAD) [22]. The presence of preulcerative lesions, such as abundant callus, hemorrhage, or a blister, is a strong determinant of ulcer recurrence, especially in patients with recurrence caused by unrecognized repetitive trauma [23].

There are several potential explanations for the increased risk. Diabetic patients with a history of ulceration or amputation have all the risk factors to reulcerate. Ulceration and amputation damage the integument and alter the biomechanics of the foot. After healing by secondary intention, the skin and soft tissue are scarred, and they may be less resilient and less pliable, so they are more prone to injury. In addition, persons with a partial foot amputation often develop local foot deformities secondary to biomechanical imbalances that may cause further foci of pressure and shear [24, 25]. Structural deformities increase pressures on the sole of the foot and are associated with ulceration. A classic example is clawing of the lesser toes and subluxation and dislocation of the metatarsophalangeal joints. As the toes hammer and the metatarsophalangeal joint subluxes/dislocates, the fat pad under the ball of the foot is anteriorly displaced. The fat pad ends up under the sulcus of the toes. The metatarsal head is often driven through the bottom of the foot (Fig. 2.1).

Peripheral Neuropathy

Neuropathy is a major component of nearly all diabetic ulcerations [18, 26, 27]. Consensus statements about neuropathy have used the following definition of diabetic neuropathy: "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes" [28]. To help identify people with diabetes at risk of foot complications, the term diabetic neuropathy with a loss of protective sensation (LOPS) has been used based on screening tools associated with ulceration. LOPS describes a level of sensory loss that allows patients to injure themselves without recognizing the injury. These patients are vulnerable to physical and thermal traumas, which increases the risk of foot ulceration twofold [29]. Patients with neuropathy often wear a hole in their foot, much as a sensate patient might wear a hole in their stocking or shoe. One of the misconceptions about neuropathy for patients and healthcare providers is that it is an all-or-none proposition. Sensory neuropathy runs on a continuum. Often people will have no symptoms of neuropathy, yet they have enough sensory loss to have a painless foot ulceration.

Screening for neuropathy is noninvasive, fast, and inexpensive. Several consensus documents recommend that all patients with diabetes should be screened annually for sensory neuropathy [8, 10]. There are several techniques to screen for neuropathy. The absence of protective sensation may be determined using a tuning fork, a Semmes-Weinstein 10 g monofilament (MF) nylon wire, or a calibrated vibration perception threshold (VPT) meter or by Ipswich touch test or a comprehensive physical examination.

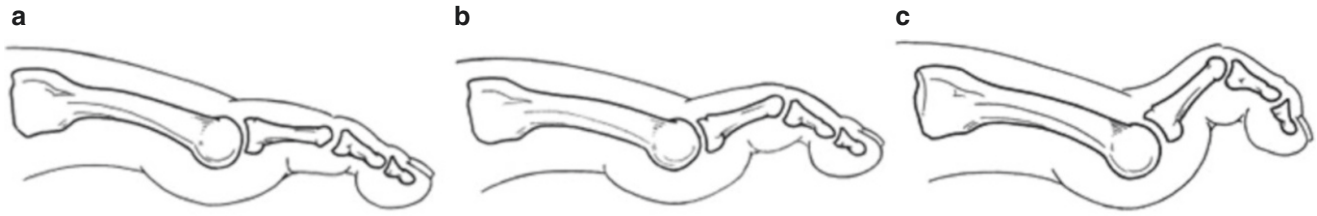

Fig. 2.1 Illustration of the normal toe (**a**), hammer toe (**b**), and subluxated MTPJ (**c**)

History and Symptoms

Patients will often tell the healthcare provider they have sensory neuropathy if you ask them. Patients will often say their feet are numb or feel like they are wearing a thick stocking when they are barefoot. Patients complain their feet feel cold but they are warm to the touch and are otherwise well perfused. People complain of burning, electrical and shooting pains, and a sensation that feels like insects are crawling on their skin. There are several scoring systems to diagnose diabetic sensory neuropathy [30]. Armstrong found that a history of numbness, burning, formication, and tingling was effective in identifying people with LOPS [31]. This was an abbreviated version of the neuropathy symptom score (NSS).

Clinical assessment can be used to score peripheral neuropathy's severity to identify high-risk patients. The modified neuropathy disability score (NDS) is a clinical assessment scoring scheme that uses standard clinical tools. These include deep tendon reflexes of the Achilles tendons, vibration sensation with a 128 Hz tuning fork, pinprick, and hot and cold rods. The use of these instruments, combined into a disability score, has proven to be predictive of future diabetic foot complications [19, 30]. In a population-based prospective study, Abbot evaluated 9710 patients with diabetes from six health districts in the United Kingdom. During the 2-year follow-up period, there were 291 ulcers. Only 1.1% of patients with an NDS less than six developed a foot ulcer, and 6.3% of patients with an NDS greater than six developed an ulcer [19].

Inspection

Inspection of the feet may provide valuable clues as to the presence and severity of sensory neuropathy. Atrophy of the intrinsic muscles of the hands and feet is often a late-stage condition that is very frequently associated with polyneuropathy. When this occurs, the extrinsic muscles of the foot are unopposed, thus causing the hammering of the toes and retrograde buckling of the metatarsal heads. Thus, both the toes (dorsally) and the metatarsal heads (plantarly) are more prominent and therefore more prone to neuropathic ulceration. In the presence of sensory loss, this has been associated with an increased risk for neuropathic ulceration. Similarly, bleeding into a callus is a preulcerous condition that is associated with neuropathy. Patients with autonomic neuropathy may present with dry skin that is poorly hydrated, resulting in cracks and fissures and potential portals of entry for bacteria.

Tuning Fork

The conventional 128 Hz tuning fork is an easy and inexpensive tool to assess vibratory sensation. The test is considered positive when the patient loses vibratory sensation while the examiner still perceives it [32]. The tuning fork is struck until it clangs, and the tip of the tuning fork is held against a bony prominence, such as the distal tip of the great toe. The patient is asked if they can feel the vibration. If they feel pressure but no vibration, they have a loss of vibration sensation. In addition, the patient should be able to feel the vibration for about 20 s. If they cannot feel the vibration for 20 s, they have an abnormal vibration sensation.

Semmes Weinstein Monofilament

The Semmes Weinstein monofilament is one of the most frequently utilized screening tools for identifying the loss of protective sensation in the United States [33, 34]. The inability to perceive the 10 g Semmes Weinstein monofilament has been associated with large-fiber neuropathy [35, 36]. In three prospective studies, the 5.07- or 10 g Semmes Weinstein monofilament identified persons at increased risk of foot ulceration with a sensitivity of 65% to 91%, a specificity of 36% to 86%, and a positive predictive value of 18% to 39% and a negative predictive value of 90% to 95% [18, 35, 36]. The Semmes Weinstein monofilament consists of a plastic handle supporting a nylon filament. It is portable, inexpensive, and easy to use and provides excellent negative predictive ability for the risk of ulceration and amputation [37].

There are a number of important concerns regarding the Semmes Weinstein monofilament. There is wide variability in the accuracy and durability of monofilaments sold in the United States. Certain brands of monofilaments are more accurate than others [38]. Instruments made in the United Kingdom seem to have better initial accuracy and calibration [37]. Semmes Weinstein monofilaments experience material failure of the nylon monofilament and become less accurate with repeated measurements. Therefore, it is important to purchase calibrated instruments and replace them on a regular basis. In a clinical setting, it is best for the evaluator to have more than one monofilament available as after numerous uses without a chance to "recover," the monofilament may buckle at a reduced amount of pressure, thus making it oversensitive and therefore less accurate [38]. Longevity and recovery testing results from an independent study suggest that each monofilament, regardless of the brand, will survive usage on approximately ten patients before needing a recovery time of 24 h before further use [38, 39]. Furthermore, differences in materials used in the manufacturing process and environmental factors may also change the characteristics of the monofilament [38, 40].

Testing with the Semmes Weinstein monofilament is best performed with the patient sitting or supine in the examination chair with both feet level (Figs. 2.2 and 2.3). The monofilament is applied perpendicular to the skin until it bends or buckles from the pressure. It should be left in place for approximately 1 s and then released [26]. The monofilament should be demonstrated on the patient's hand so they can understand the level of pressure provided during testing. The patient should close their eyes for the foot examination. They should be instructed to say "yes" each time that they feel the monofilament and then to identify the site where they felt the monofilament. The number of sites that should be tested with monofilaments is unclear. However, because testing is noninvasive and inexpensive, the number of sites should not be a limiting factor in testing protocols. Some authorities recommend that measurements be taken at each of the ten sites on the foot [41]. These include the first, third and fifth digits, plantarly, the first, third, and fifth metatarsal heads plantarly, the plantar midfoot medially and laterally, the plantar heel, and the distal first interspace, dorsally (Fig. 2.3). However, testing just four plantar sites on the forefoot (the great toe and the base of the first, third, and fifth metatarsals) identifies 90% of patients with a loss of protective sensation [42].

Vibration Perception Threshold (VPT) Testing

A VPT meter is a semi-quantitative tool to assess large fiber neuropathy. The VPT meter (also known as the biothesiometer or neurothesiometer) is a handheld device that vibrates at 100 Hz. An electrical cord to a base unit connects the handheld unit. This unit contains a linear scale that displays the applied voltage, ranging from 0 to 100 volts (converted from microns [43, 44]. The device is held with the tactor balanced vertically on the pulp of the toe. The voltage amplitude is then increased on the base unit until the patient can perceive a vibration. A mean of three readings (measured in volts) is generally used to determine the vibration perception threshold for each foot. The "loss of protective sensation" with VPT has commonly been considered to be about 25 volts. The level of vibration perception threshold testing can help pre-

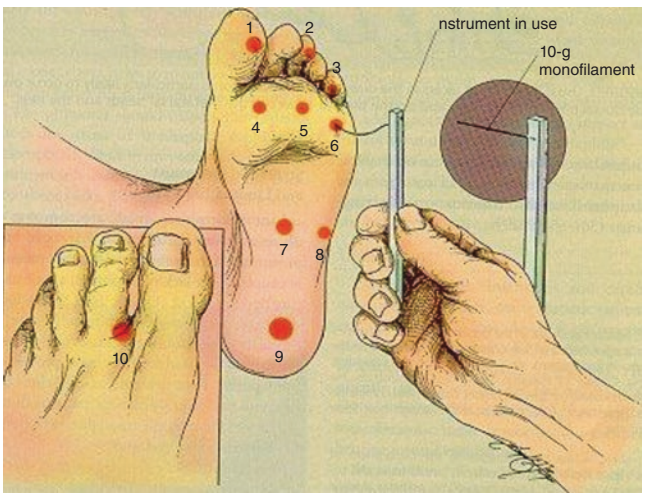

Fig. 2.3 Ten sites of the foot to use the 10 g monofilament

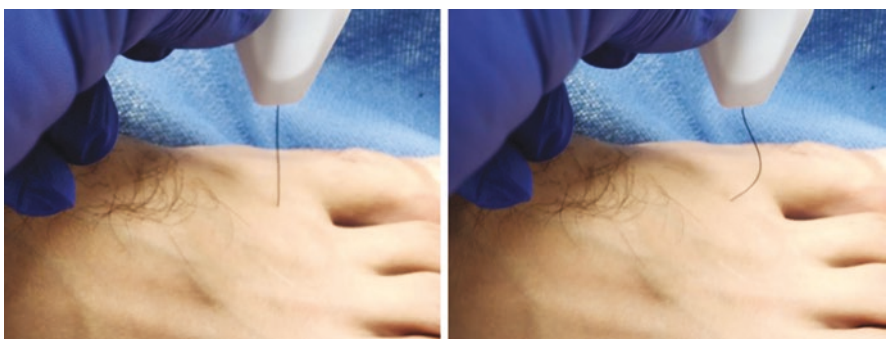

Fig. 2.2 Use of the 10 g monofilament

dict ulceration [45]. In a prospective cohort study, Abbott and colleagues evaluated 1035 patients with diabetes, no history of a foot ulcer, and a VPT greater than 25. During the follow-up period, the yearly ulcer incidence was 7.2%. For every 1-volt increase in VPT, there was a 5.6% increase in the risk of foot ulceration [46]. VPT testing has been shown to have very good sensitivity and specificity.

The Ipswich Touch Test

Several studies have validated the Ipswich Touch Test (ITT) against the other commonly used screening tests [47, 48]. Ipswich Touch Test (ITT) involves lightly touching/resting the tip of the index finger for 1–2 s on the tips of the first, third, and fifth toes and the dorsum of the hallux [49]. A direct comparison of the ITT and monofilament testing showed an almost perfect agreement, with positive predictive values indicating at-risk feet of ITT 89% and MF 91% and negative predictive values of ITT 77% and MF 81%. The ITT has also been evaluated to detect reduced foot sensation in the setting of the patient's home [50]. Having a simple method to detect a loss of sensation at home might improve awareness of foot disease in patients with diabetes and empower them to seek appropriate care [51].

Peripheral Arterial Disease (PAD)

PAD is a central component of diabetic foot ulcers and a risk factor for poor healing and proximal limb amputation [52]. Assessing PAD is an essential component of classifying risks. A history of previous vascular intervention, ulcers/amputation healing, and palpation of arterial pulses is an important component of history and physical examination. Several guidelines have suggested that advanced vascular testing (ankle systolic pressures, ankle-brachial indices, toe systolic pressures, waveforms, skin perfusion pressure, and transcutaneous oxygen) should be performed in people with foot ulcerations because clinical examination does not exclude PAD [9, 53].

Limited Joint Mobility and Structural Deformity

Neuropathy and foot deformity, when combined with repetitive or constant stress, can lead to ulceration. Characteristically, the highest plantar pressure is associated with the site of ulceration [54–57]. In one study of patients with peripheral neuropathy, 28% with high plantar pressure developed a foot ulcer during a 2.5-year follow-up compared with none with normal pressure [58].

Clinicians should examine the feet for structural abnormalities, including hammer or claw toes, flat feet, bunions and calluses, and reduced joint mobility to help identify pressure points that are susceptible to future ulceration. Structural deformity is frequently accompanied by limited joint mobility. Nonenzymatic glycosylation of periarticular soft tissues or tendons may contribute to limited joint motion in a person with diabetes. Neuropathy can lead to atrophy of the intrinsic muscles of the hands and feet, which can cause instability at the metatarsophalangeal joint and digits [59]. Limitation of motion reduces the foot's ability to accommodate ground-reactive force and, therefore, increases plantar pressures [60–62]. Limitation of motion of the first metatarsophalangeal joint has been defined as less than 50 degrees of passive dorsiflexion of the hallux (Fig. 2.4). Additionally, glycosylation may deleteriously affect the resiliency of the Achilles tendon, thereby pulling the foot into the equinus

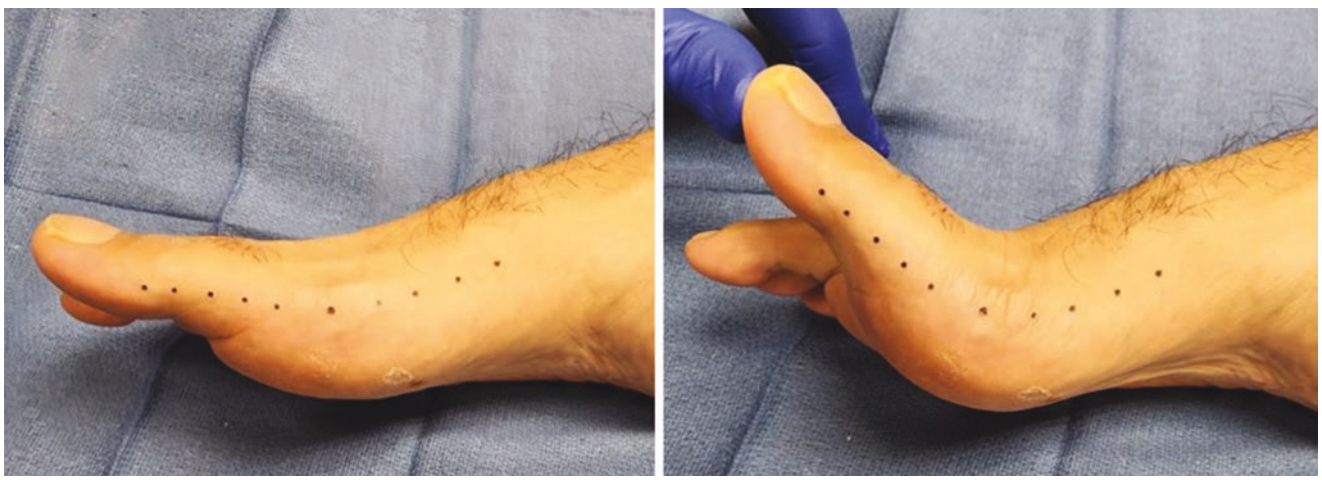

Fig. 2.4 First metatarsophalangeal joint dorsiflexion evaluation

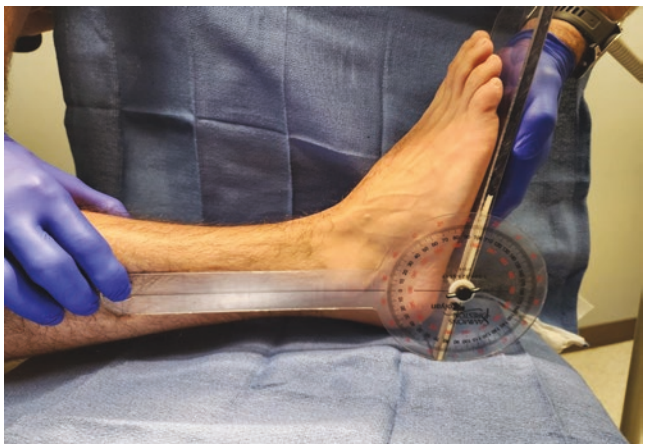

Fig. 2.5 Ankle joint dorsiflexion evaluation

and further increasing the risk for both ulceration and Charcot arthropathy [63] (Fig. 2.5). In a case-control study, plantar and dorsal flexion of the feet of 87 patients with diabetes was measured, and the incidence of foot ulcers was reported over a follow-up period of 8 years. Diabetes specifically reduced the plantar flexion in the feet, and patients with a history of foot ulceration had significantly lower ankle joint mobility [64].

Diabetic Foot Ulcer Classification

Foot ulcers in patients with diabetes are one of the most common precursors to lower extremity amputation. Appropriate care for diabetic foot ulceration requires a clear, descriptive classification system that can be used to direct therapy, communicate risk, and possibly predict outcomes. Speaking a "common language" when communicating risks in the diabetic foot is therefore essential. A classification system, if it is to be clinically useful, should be easy to use, reproducible, and effective to accurately communicate the status of wounds in persons with diabetes mellitus. Several variables could be included in such a system, such as faulty wound healing, compliance issues, quality of wound granulation tissue, host immunity, nutritional status, and comorbidities. However, most of these variables are difficult to measure or categorize and can complicate a system. In contrast, three relatively quantifiable factors associated with poor wound healing and amputation include the depth of the wound, the presence of infection, and the presence of ischemia.

Five Essential Questions to Ask when Assessing a Diabetic Foot Wound

A classification system has little value if the clinician employing it does not approach each wound in a stepwise consistent, logical fashion. The questions are directly related to how ulcer classification systems are scored. Ulcers should be debrided before they are scored unless there is critical limb ischemia (see Figs. 2.6 and 2.7). Ulcers are often surrounded by callus, dry skin, and remnants of dressing materials. Likewise, the ulcer bed can be covered by slough and devitalized tissue.

1. Is there peripheral arterial disease?

   The identification of peripheral arterial disease (PAD) is of utmost importance when evaluating a diabetic foot ulcer. Ischemic wounds take longer to heal and are more likely to result in a proximal amputation compared to neuropathic wounds without PAD [52]. Noninvasive vascular studies (systolic ankle pressures and ankle-biracial indices, toe pressures and toe brachial indices, waveforms, skin perfusion pressure, and transcutaneous oxygen measurements) should be obtained in diabetic patients with foot wounds because simply palpating peripheral arterial pulses is not reliable in identifying PAD [9, 53].
2. Where is the ulcer located?

   The location of a wound, its etiology, and treatments go hand in hand. Generally, wounds on the medial aspect of the foot are caused by constant low pressure (e.g., tight shoes), whereas wounds on the plantar aspect of the foot are caused by repetitive moderate pressure (e.g., repetitive stress on prominent metatarsal heads during ambulation). The need for more aggressive off-loading is dictated by ulcer location.
3. How large is the ulcer?

   The size of the wound plays a key role in determining the duration of wound healing. Time to heal has been best associated with ulcer duration, depth, and wound area [65]. Simply measuring the length, width, and depth of the ulcer is the easiest and fastest approach. However, ulcers are often irregular, and the longest measure for the length and widest measure for the width are not reflective of wound area changes. Many wound measurement programs are Health Insurance Portability and Accountability Act (HIPPA) compliant and can be used on your cell phone or on a tablet. Often these programs measure both wound area and volume.
4. How deep is the ulceration? Are there underlying structures involved?

   These two questions are so closely related that they are combined into one. There is a possible contribution of depth to ulcer healing times. Wounds that penetrate the bone are at higher risk of having osteomyelitis [66, 67]. Additionally, we have observed that morbid outcomes are intimately associated with progressive wound depth. The probe-to-bone test (PTB) has been advocated to evaluate the involvement of underlying structures (such as capsules, tendons, muscles, and bones). The probe-to-bone test is performed by inserting a sterile blunt metallic probe into the wound.

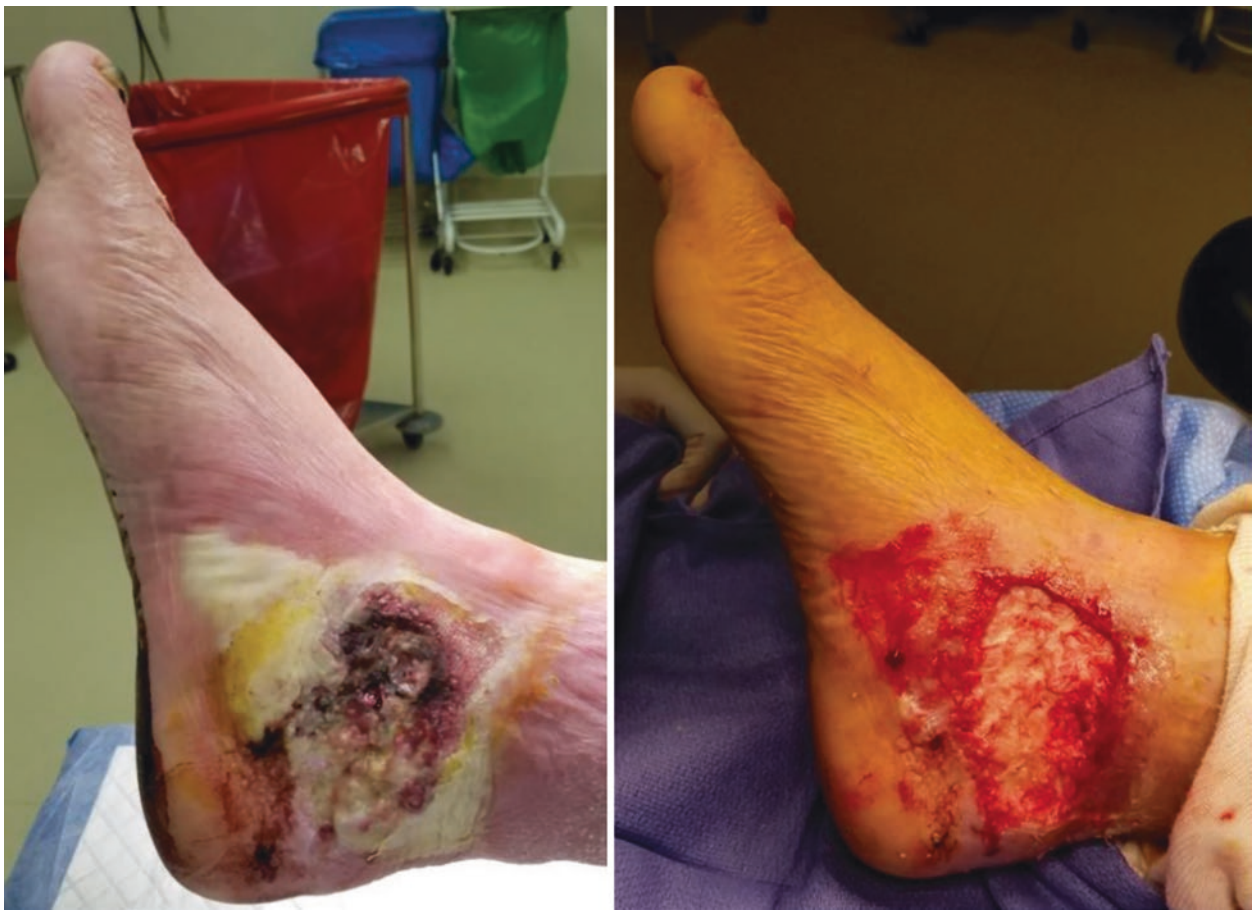

Fig. 2.6 Pre- and postdebridement of a medial ankle wound

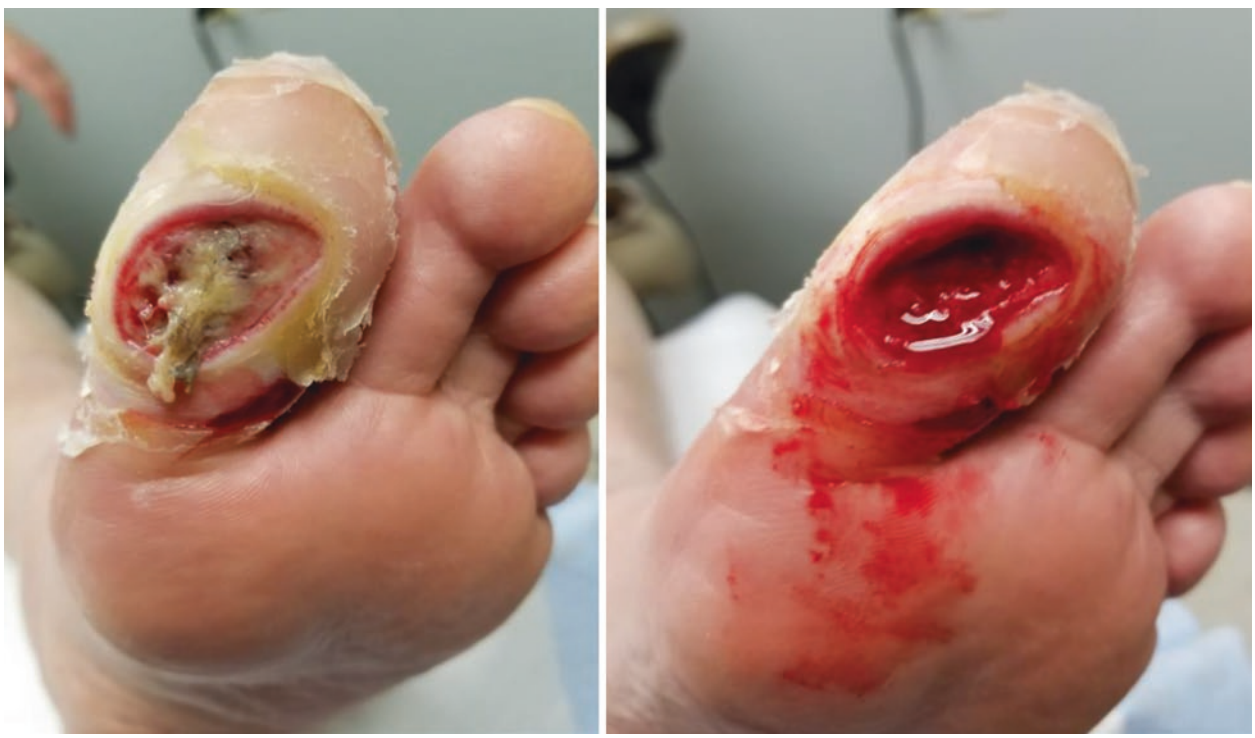

Fig. 2.7 Pre- and postdebridement of an ulcer

The identification of the specific structures that can be determined by evaluating a wound with a sterile probe is not precise. The agreement between investigators is poor [68]. It is difficult for the examiner to determine if they feel a bone, joint capsule, or scar. Combining PTB with radiographic changes may improve the diagnostic accuracy of these tests [69].

5. Is there infection?

The definition of bone and soft tissue infection is not an easy one. The diagnosis of infection should be based on clinical findings (redness, local warms, swelling, pain, purulence) and not based on wound cultures of ulcers with no clinical signs of infections [70, 71]. In contrast, the gold standard to diagnose osteomyelitis is bone culture and histology. Infection is one of the most important risk factors for foot amputation. Therefore, in an effort to facilitate communication and affect consistent results, the foot care team should agree on criteria for this very important risk factor.

Ulcer Classifications

Many authors, including Forrest and Gamborg-Nelson [72], Pecoraro and Reiber [20], Arlt and Protze [73], and Knighton [74], have proposed their own wound classifications; however, these systems have not gained universal acceptance. More recent classification systems that have been proposed include the University of Texas (UT) classification modification [75]; the perfusion, extent, depth, infection, and sensation (PEDIS) system by the IWGDF [76]; the S(AD) SAD system proposed by Macfarlane [77]; and the wound, ischemia, foot infection (WIfI) classification system. The National Pressure Injury Advisory Panel's (NPIAP's) pressure injury/ulcer classification system has recently been updated. It is important to use consistent language to communicate with other healthcare providers. As our population ages, pressure injuries and ulcers become more common.

The Society for Vascular Surgery Lower Extremity Guidelines developed the WIfI (wound, ischemia, foot infection) ulcer classification. The WIfI system expanded on the criteria described in the UT classification for infection and PAD into specific categories [78]. The system has been validated by several groups [78–80]. The challenge is to balance the number of criteria that are included in an ulcer classification and how the next level of data affects the outcomes. Complex ulcer classifications like WIfI are difficult to use in clinical practice because of their complexity.

Pressure Ulcer Classification

With the aging of the population around the world, there has been an increase in pressure injuries and pressure ulcers of the feet in people with diabetes. It is tempting to use the classification that has been developed for diabetic foot ulcers that are not specifically related to pressure injuries. However, using the terminology that has been established by pressure injury experts improves communication and treatments. The National Pressure Injury Advisory Panel (NPIAP) published guidelines on the classification and treatment of pressure injuries/pressure ulcers. In 2016, the classification was changed [81].

The National Pressure Ulcer Advisory Panel (NPUAP) decided to replace the term ulceration with injury because ulceration did not accurately describe Stage 1 injuries or deep tissue injuries. Roman numerals were also changed to Arabic numerals for each stage, so Stage IV injuries will now be identified as Stage 4 injuries. The classification remains a four-level system. The stages of the classification are described in Table 2.2. This system is designed so the ulcer classification does not change as the ulcer improves. It seems counterintuitive because one of the goals of ulcer documentation is to record the progression of the ulcer (Fig. 2.8). This system does not include any designation for infection or ischemia.

Table 2.2 Pressure injury staging system

Stage	Description
1	The skin is still intact; the ulcer affects the upper layer of the skin. The area affected by pressure is characterized by nonblanchable erythema that does not turn white when pressed. Changes in sensation (temperature, pain, itching) or hardness of the skin may occur
2	The skin is partially damaged, the epidermis is affected, and the dermis may be affected. It presents as an open wound or as a blister filled with fluid. The wound bed is red or pink, and the deeper tissues are not visible
3	The entire thickness of the skin is damaged. Due to the depth of the injury, the adipose tissue is visible, but there are no deeper structures to be seen. The wound bed may be fibrinous or necrotic. Infection can be present
4	The entire thickness of the skin and the underlying tissue are damaged. The injury involves deep structures; muscle, bone, fascia, tendon, or cartilage may be visible. Fibrinous or necrotic tissue may be present
Unstageable	The entire thickness of the skin is damaged; the depth of the injury cannot be determined due to obstruction of the view, which may be caused by the fibrinous or necrotic tissue