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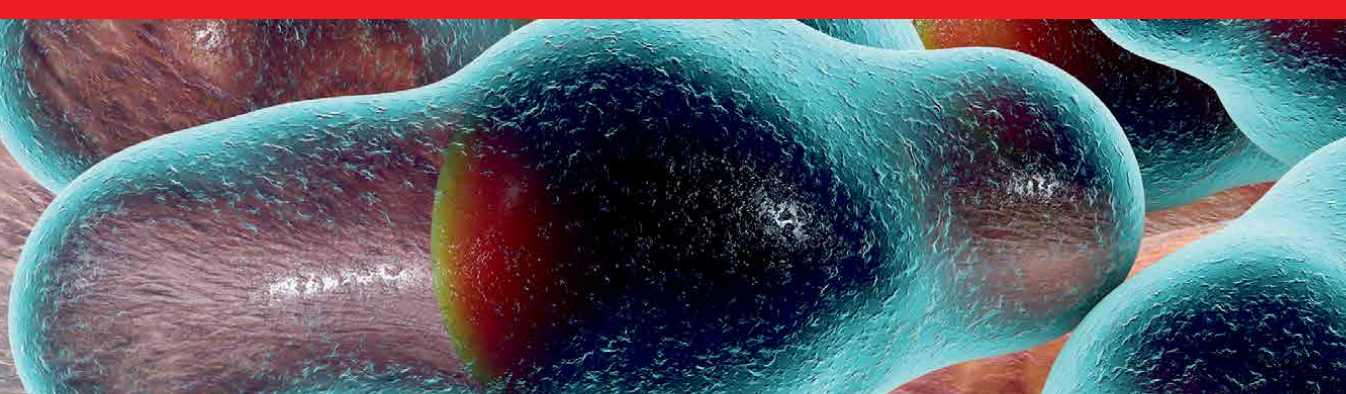
Diabetic Foot Ulcers

Pathogenesis, Innovative Treatments and AI Applications

Edited by Muhammad E. H. Chowdhury, Susu M. Zughaier, Anwarul Hasan and Rashad Alfkey



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Meet the editors

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Contents

Preface

Welcome to *Diabetic Foot Ulcers – Pathogenesis, Innovative Treatments, and AI Applications*, a comprehensive exploration of one of the most challenging complications of diabetes. This book brings together leading experts in the field to provide a thorough examination of diabetic foot ulcers (DFUs) from various perspectives, including pathophysiology, clinical management, and the integration of artificial intelligence (AI) technologies.

Diabetic foot ulcers are a significant health concern globally, affecting millions of individuals and often leading to severe complications such as infections, amputations, and impaired quality of life. Despite advancements in medical science, DFUs continue to pose a formidable challenge for patients, healthcare providers, and researchers alike. This book sheds light on the complexities of DFUs and explores innovative approaches to prevention, diagnosis, and treatment.

The book is organized into several sections, each focusing on different aspects of diabetic foot ulcer research and management. In the first section, "Understanding Diabetic Foot Ulcers", contributors delve into the epidemiology, risk factors, and pathogenesis of DFUs. Chapters in this section provide valuable insights into the underlying mechanisms that contribute to the development and progression of DFUs, laying the groundwork for subsequent discussions on innovative treatments and AI applications.

The second section, "Pathophysiology and Management of Diabetic Foot Ulcers", explores novel therapeutic strategies aimed at improving wound healing and reducing complications associated with DFUs. Contributors discuss the latest advancements in wound care, including bioengineered skin substitutes, growth factors, hyperbaric oxygen therapy, and other emerging therapies. Additionally, chapters in this section highlight the importance of multidisciplinary approaches and patient-centered care in managing DFUs effectively.

In the third section, "Advanced Approaches and Technologies in Diabetic Foot Ulcer Management", experts explore the role of AI technologies in revolutionizing the management of DFUs. Chapters in this section examine various AI-based approaches for early detection, risk stratification, and personalized treatment of DFUs. From machine learning algorithms to deep learning models and computer vision techniques, contributors showcase the potential of AI in enhancing clinical decision-making and improving patient outcomes in diabetic foot ulcer care.

Section 4, "Future Perspectives and Innovations in Diabetic Foot Ulcer Research" includes one chapter "Perspective Chapter: Diabetic Foot Pathophysiology and Prevention of Amputation through Behavioral Modification"

Throughout the book, contributors emphasize the importance of collaboration between healthcare professionals, researchers, engineers, and industry partners in

advancing the field of DFU research and management. By fostering interdisciplinary partnerships and leveraging cutting-edge technologies, we can address the complex challenges posed by DFUs and work towards improving the lives of individuals living with diabetes.

We extend our sincere gratitude to all the contributing authors for their invaluable insights and contributions to this book. Their expertise and dedication have enriched the content and ensured the quality of the chapters included herein. We also thank the editorial team and publisher for their support and guidance throughout the publication process.

It is our hope that *Diabetic Foot Ulcers – Pathogenesis, Innovative Treatments, and AI Applications* will serve as a valuable resource for researchers, clinicians, students, and healthcare professionals interested in DFU research and management. By sharing knowledge, fostering innovation, and embracing new technologies, we can make significant strides towards preventing and effectively managing DFUs, ultimately improving the health and wellbeing of individuals affected by this debilitating complication of diabetes.

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Section 1

Understanding Diabetic Foot Ulcers

Chapter 1

Diabetic Foot Ulcer: A Historical Overview

Hesham Aljohary, Musab Ahmed Murad and Rashad Alfkey

Abstract

This chapter reviews the historical discoveries and the evolution of medical practices in the management of diabetic foot ulcers (DFUs). The knowledge acquired by ancient civilizations such as Babylon, China, Egypt, and India was further developed by the Greeks and Romans, who made significant improvements in foot amputations. The Arabs preserved and expanded these records, making them accessible to scientists during the European Renaissance. It was not until the early twentieth century that a better understanding of the complex etiological factors of DFUs began to emerge. A turning moment in the history of DFUs occurred in 1921 with the discovery of insulin, which effectively divided the timeline into two distinct periods: pre-insulin and post-insulin. While the role of revascularization in treating ischemic DFUs was established in the 1950s and 1960s, the importance of offloading was recognized in the 1970s and 1980s. Recently, the focus of DFU management has shifted to prevention, and multidisciplinary care involving podiatrists, nurses, endocrinologists, surgeons, and infectious disease specialists. Through the utilization of advanced technology and innovative therapies, we are now closer than ever to a future where DFUs will no longer pose a threat to patients' health.

Keywords: history, diabetes, foot ulcer, advancement, artificial intelligence

1. Introduction

Studying the history of medicine enables us to understand the historical development of diabetic foot ulcers, to learn from the successes and failures of past medical interventions, to identify the gaps and challenges in current medical research and practice, and to anticipate the future trends and needs in medical innovation and care. Medical history, like other arts and sciences, is an ongoing and continuous journey. The knowledge and techniques we possess today did not emerge suddenly, but rather evolved over centuries through the accumulation of observations and experiments. The flourishing of medical practice throughout various historical civilizations serves as a testament to the stability they achieved.

The understanding of diabetic foot ulcers has been greatly shaped by countless discoveries throughout centuries, ranging from the prehistoric era all the way to the present day. Nevertheless, historical records pertaining to diabetic foot ulcers

are scarce, primarily due to their frequent classification as a type of gangrene or foot infection. The discovery of insulin in 1921 represents a great milestone in the history of diabetic foot as individuals with diabetes have been able to enjoy longer lives, resulting in a significant increase in the prevalence of diabetic foot ulcers. This milestone marks a clear division in the history of diabetic foot ulcers, separating it into two distinct eras: the pre-insulin and post-insulin periods.

- *The pre-insulin era*, which spans from the ancient times to the early twentieth century, when diabetes was a fatal disease and foot ulcers were often overlooked and treated with ineffective remedies or improper dressings. Medical science has evolved and progressed over time through different historical periods, including the prehistoric era before written records, as well as ancient civilizations such as Babylon, China, Egypt, and India. The first descriptions of diabetic foot ulcers date back to ancient Egypt, India, and Greece. The term "diabetes" was coined by the Greek physician Aretaeus of Cappadocia in the second century AD. The Greeks and Romans played a crucial role in establishing the foundations for the fields of dressing, debridement, and amputations. The Arabs played a pivotal role in the preservation, translation, and expansion of medical knowledge from ancient civilizations. Moreover, they made significant original contributions to various fields of medicine. Arab surgeons were responsible for inventing or enhancing numerous surgical instruments including scalpels, forceps, scissors, needles, syringes, and catheters. They recognized the importance of debridement, the removal of foreign bodies, and the utilization of sterile dressings to maintain a moist environment to enhance healing, described the use of topical medications made from natural substances, such as honey, and used sutures made of animal gut. The European Renaissance stimulated curiosity, creativity, and innovation among physicians. They sought to better understand the human body and its functions, leading to new discoveries and innovations that laid the foundations for modern medicine. During the wars of that era, surgeons gained significant expertise in the treatment of firearm-inflicted wounds.

- *The post-insulin era*, which spans from the discovery of insulin in 1921 to the present time, when diabetes became a chronic condition and foot ulcers became a major complication. The introduction of insulin therapy improved the treatment of diabetes and its complications, but also exposed the patients to long-term metabolic and vascular disorders that increased the risk of foot ulcers. The role of ischemia and peripheral neuropathic disease in diabetic foot ulcers was elucidated. The first classification systems for diabetic foot ulcers were proposed by Meggitt-Wagner in 1976 and University of Texas in 1996. From the late twentieth century to the present day, diabetes became a global epidemic and foot ulcers became a major public health problem. The role of glycemic control, offloading, debridement, wound dressings, antibiotics, revascularization, and education in diabetic foot ulcer prevention and treatment was established by various randomized controlled trials and meta-analyses. The multidisciplinary approach to diabetic foot care was pioneered by the brilliant work of Elliott Joslin in the first half of the twentieth century. This innovative approach changed the way we manage diabetes, as it focused on numerous aspects of diabetes management.

2. The prehistoric era

Amazingly, the care for wounds in prehistoric times was universal in some sense. The techniques employed in various regions of the world are remarkably similar, including the utilization of herbal medicines, the application of astringent or disinfectant-acting powders and infusions, protective bandaging, heat, and massage, as well as the use of naturally occurring styptic chemicals to control bleeding [1]. Wound care encompassed wound cleansing and dressing, provision of pain relief, and the potential application of natural substances like honey or plant-derived poultices, cloths, cobwebs, and even dung [2]. Physicians were unaware of the presence of bacteria and other germs, and the importance of keeping them away from wounds, until the emergence of germ theory in the late 1800s. However, the natural hardiness of the ancient and the absence of the extremely resistant germs encountered in the recent century could be the main causes of favorable outcomes, in addition to the clever techniques that were frequently employed.

In Paleolithic deposits found in both France and England, bone needles with eyelets were discovered. These needles were synthesized from bone splinters and were used to close wounds. Similarly, American Indian tribes utilized sinew and bone needles to create sutures. The needles were left in place while the thread was wound around them. This technique can be likened to the skewer technique, where the needle is inserted, and the thread is wrapped around it. Remarkably, this technique persisted until the late Renaissance period [3]. The Dakota Indians potentially utilized a drainage technique by inserting wicks crafted from soft tree bark to treat their wounds. Moreover, they employed a unique syringe made from a feather quill and a bladder to cleanse the wounds thoroughly [4].

Colonists discovered that natives in Australia could sew up wounds and encapsulate shattered bones in mud to heal them. Medical historians think that these abilities existed throughout prehistory. In Victoria, Australia, the locals preferred bleeding to cleanse wounds. They had developed a practice that involved promoting blood flow through suction, adjusting posture, and massaging the affected tissues. After effectively cleansing the wound using these methods, they would apply a lump of resin as a dressing. Interestingly, this tribe also acknowledged the potential danger of retained wound secretions and would reopen the wound if it closed prematurely. The Indigenous people of Australia utilized clay to treat wounds, while in Europe, tar has been a cherished and customary folk dressing. Alternatively, fresh leaves are occasionally employed as dressings, while at other times, a poultice made from herbs, or the tender bark of trees is applied to the wound.

In various parts of the world, including India, East Africa, and Brazil, termites or ants were utilized to close wounds, specifically abdominal wounds. This technique, which was one of the most astonishing practices of that era, involves pressing the edges of the wounds together, allowing the termites to bite through them. The strong jaws of these insects effectively keep the margins of the wound in close alignment, acting as metal clips. Once their task is complete, the insects' bodies are then separated from the wound [5].

The Maasai people also utilized thorns for suturing wounds. They would wrap a strip of durable vegetable fiber around the thorn in a figure-eight pattern, applying it in succession to approximate the wound. Firstly, they would cleanse the wound with a specific herbal juice, followed by the insertion of a hot metal to burn the tissues and control bleeding. While applying a poultice made of cow dung and dust to a lesion

may seem less unpleasant, it still represents a rudimentary form of wound care. This method, although less painful, was horrible. Although amputations were rarely performed by these primitive societies, the Maasai of Africa did practice it when necessary. They would tightly tie a ligature above the level of amputation and swiftly cut off the limb with a skillful swordsmanship motion [6].

Shawiya, from Algeria, employed an incredibly unique combination of ashes, rags, and dirty wool soaked in olive oil. Additionally, she incorporated green leaves, dried goat dung, and earth to create a poultice specifically designed for wound dressing [7].

While the need for amputation has likely existed since ancient times, most prehistoric communities were deeply disturbed by these invasive treatments, especially when it involved their own bodies. In Tibet, amputations were carried out for medical reasons, but tragically, the consequences were frequently deadly [4].

3. The ancient history

Thomas Sydenham, the esteemed author of the textbook "Medical Observations," remarked that just as the origins of clothing and shelter to combat harsh weather remain unknown, the beginning of Medicine is equally mysterious, comparable to the mystery surrounding the source of the Nile. The world's oldest medical manuscript was discovered on a Sumerian clay tablet dating back to approximately 2100 BC, marking a significant milestone in written historical records [8]. This ancient artifact sheds light on the "three healing gestures" that formed the foundation of wound treatment during that era: washing the wound, applying dressings or plasters, and carefully bandaging the affected area. Remarkably, these principles continue to underpin modern wound care practices. Interestingly, the Sumerians also employed beer as a prominent component in their treatments. This beverage, with its antiseptic properties, likely played a beneficial role in the healing of wounds and skin lesions. Unveiling this ancient medical manuscript not only provides us with a glimpse into the medical practices of our ancestors but also emphasizes the enduring relevance of their knowledge. The simplicity and effectiveness of the "three healing gestures" serve as a testament to the timeless wisdom of the Sumerians in the realm of wound treatment.

The ancient Egyptians, Indians, and Greeks described wounds that attracted ants and flies, which could potentially be attributed to diabetic foot ulcers. In ancient Egypt, compound fracture wounds were treated in a rather interesting manner. The Egyptians would prepare an ostrich egg, mix it with grease, and insert it into the wound. This served as a cover for the wound, allowing it to dry properly. Another fascinating method employed by the Egyptians involved the use of honey as a bandage. In the Egyptian Papyrus, honey was frequently utilized either on its own or mixed with meat and smeared over absorbent lint. This ancient practice has been revived in recent times, with numerous scientific journals publishing studies highlighting the benefits of honey as a wound dressing throughout the twentieth century [9, 10].

In ancient Babylon and Assyria, Hammurabi, an influential ruler of Babylon, established a comprehensive set of regulations. Notably, this code stipulated that "a doctor's hands should be amputated if they cause a lethal injury while operating or if they employ a knife to incise an abscess and extract an eye" [11].

The Greeks and Romans inherited and expanded upon the medical knowledge of these ancient civilizations. They emphasized the role of rationality and observation in medicine, establishing the foundations of anatomy, physiology, pathology, pharmacology, and surgery. During this period, influential figures such as Hippocrates,

Aristotle, and Galen emerged, leaving a lasting impact on the field. The earliest description of ancient Greek medical practice derives from the two epic poems attributed to Homer. His prominent works, "The Iliad" and "The Odyssey," offer precise depictions of various types of injuries [12].

During the fifth century B.C., Hippocrates, known as the Father of Medicine, had a strong belief in the healing power of nature and preferred using simple dressings in his treatments. Whether it was vinegar, wine, oil, or honey, he would combine them with lukewarm or cold water for the dressing. He understood the importance of avoiding oily dressings and favored keeping wounds dry rather than moist. Additionally, he emphasized the significance of keeping clean wound edges as close together as possible, aligning with the concept of healing through first intention. He demonstrated his unwavering faith in the body's ability to heal itself [13].

The term "diabetes "was coined by the Greek physician Aretaeus of Cappadocia in 150 A.D. to describe the sweet taste of urine. He gave a detailed description of the disease, which he considered to be a disorder of the kidneys and the bladder and described it as a condition characterized by the melting down of flesh and limbs into urine. Aretaeus wrote about the understanding and description of various diseases, including diabetes mellitus, in his work titled "On the Causes and Signs of Chronic Diseases" [14], however, he failed to mention diabetic foot as a distinct condition.

The surgeons of the Roman Empire possessed a remarkable understanding of surgical techniques, including both flap amputation and the circular method. Heliodorus, for instance, cautioned against amputating above the elbow or knee due to the significant risk posed by the size of the vessels involved. Roman medicine was an extension of Greek medicine. Most Rome's medical practitioners were Greeks and slaves, with only a few Roman physicians like Celsus. Celsus, a notable Roman physician, dealt with and described various post-wound consequences such as erysipelas and gangrene [15]. Celsus, a pioneering figure, recommended a method of tying an injured vessel in two places and then dividing it between them. Notably, Celsus was the first to describe the four cardinal signs of inflammation—heat, pain, redness, and swelling—which remain fundamental knowledge for every medical student. Galen, building upon these signs, introduced a fifth one—loss of function.

Galen advocated for a more conservative approach, favoring resection over amputation, and provided meticulous guidelines for wound treatment, emphasizing the crucial role of monitoring the patient's overall well-being [4]. Galen was the second most famous figure in ancient medicine, following Hippocrates. He acquired extensive expertise in treating wounds as a physician to gladiators before relocating to Rome, where he served as the personal physician to the Roman emperors and established the largest medical practice in the city. Galen recognized the crucial role of overall health in relation to wound healing and advocated for conservative resection rather than amputation. Galen's prominence in the field of medicine during ancient times was only surpassed by the legendary Hippocrates. Prior to his illustrious career in Rome, Galen honed his skills by tending to the wounds of gladiators, amassing invaluable experience. His reputation as a healer led him to become the trusted physician of the Roman emperors, solidifying his position as the most sought-after medical practitioner in the bustling city of Rome. One of Galen's notable contributions to the medical field was his emphasis on the significance of general health in the process of wound healing. He recognized that a person's overall well-being played a pivotal role in their ability to recover from injuries. Furthermore, Galen advocated for conservative resection as a preferred method over amputation. He believed in preserving as much of the affected area as possible, rather than resorting to drastic measures such

as limb removal. This approach showcased Galen's commitment to finding the most effective and least invasive treatments for his patients [13, 16].

The Greeks and Romans did not make many changes to traditional wound-dressing recipes. Nevertheless, they played a crucial role in establishing the foundations for the fields of dressing, debridement, and amputations, which saw remarkable advancements in skill. This period also witnessed the emergence of surgical literature, enabling individuals to compare their own experiences to those of others [4].

Amputations were often performed by barber-surgeons or other non-specialized practitioners. Techniques were crude, using saws, knives, or cautery tools. The procedure was often associated with a high risk of infection and mortality. The Greeks held a strong opposition to amputating limbs. However, Hippocrates believed in removing only the dead tissue from gangrenous limbs, rather than resorting to full amputations. Despite this, Celsus regarded amputation as a last resort, emphasizing its sorrowful nature. Interestingly, some of Hippocrates' contemporaries and immediate successors did perform amputations using techniques that were remarkably like those used in modern times. One such example is Archigenes, who carried out amputation procedures in a manner comparable to present-day practices [17].

To perform a successful amputation, Archigenes recommended a specific procedure. First, the entire area that requires amputation should be thoroughly soaked with cold water. Next, it should be carefully bandaged, ensuring cleanliness and protection. Finally, a cord should be tightly tied above the intended site of amputation to securely constrict the limb. In cases where this method is not feasible, Archigenes suggested severing and knotting the main arteries leading to the affected area. By following these guidelines, He aimed to minimize the risks associated with amputation and increase the chances of a successful outcome.

Both the flap-based and circular amputation techniques have been familiar to Roman doctors. Heliodorus suggested using a saw to cut the bone, carefully separating the muscle from the blood vessels, and tightly tying a ligature above the amputation site to minimize bleeding. He criticized surgeons who attempted to perform the operation in a single stroke [18].

4. The middle ages

The Middle Ages, often referred to as the Dark Ages, saw the downfall of the Greek and Roman scientific legacy. During this period, the number of physicians in Western Europe was extremely limited, and there were no medical colleges established. Those who pursued the study of medicine with dedication were primarily members of the Church. Their approach to healthcare centered around spiritual practices such as prayer, intercession, and the veneration of saints known for their healing abilities. While a small number of esteemed doctors catered to the needs of kings and the nobility, the responsibility of tending to wound and injuries was primarily entrusted to barbers and other individuals lacking formal education [19]. That mistreatment was about to change with the rise of the great universities of Western Europe [20].

Salerno, a city in southern Italy, became famous for its medical school, the Schola Medica Salernitana, which was founded in the ninth century and flourished in the tenth and eleventh centuries. The school was influenced by the Arabic medical writing, which had preserved and developed the ancient Greek and Roman medical knowledge. One of the most influential figures in the transmission of Arabic medical texts to Salerno was Constantine the African, a scholar who translated many Arabic works

into Latin, including those by Hippocrates, Galen, and Haly Abbas. His translations introduced the West to the Islamic world's extensive knowledge of medicine and had a lasting impact on European medical practice [21].

The notion that suppuration was a necessary step in wound healing for a long-time hindered advancement in wound care. Wounds were treated with a variety of unpleasant and dirty ointments and concoctions [22]. One of those who taught that suppuration was a hindrance to wound healing was Henri de Mondeville (1260–1320). He was a surgeon for France kings, Louis X of France, and Philip the Fair, and he also taught at Montpellier. In place of cautery, he employed ligation to control bleeding [23]. Hugh of Lucca and his son Theodoric worked for the University of Bologna. Theodoric produced a "Chyrurgia" that was distinctly original. He was the first to reject the idea that suppuration is a necessary component of normal wound healing and to strongly advocate against messy applications that impede healing. He also advised only using simple dressings to treat wounds [24]. Unlike Henri de Mondeville, Guy de Chauliac (1300–67), the author of Chirurgia Magna and the most renowned surgeon of the late Middle Ages, preferred to apply salves instead of simple dressings and to use cautery instead of ligation [25].

At the end of the medieval era, two German surgeons had special experience of war wound. One of them was Heinrich von Pfolspeundt, a Bavarian army surgeon who converted his 40 years of experience of campaigns into a book on bandaging and the treatment of wounds [26]. The other surgeon, Hans von Gersdorff wrote a book about his war experience. He explained how he used a special instrument to remove foreign bodies and dressed them with warm rather than boiling oil, as the last one was well known to be used for war wounds. He recommended to cover the stump of amputation by an animal bladder [27].

During the Dark Ages in Europe, there was a remarkable advancement in the field of medical sciences in Islamic countries. The classical Islamic medical texts contain valuable principles and practices for overall healthcare, and preventive measures, such as proper nutrition, physical activity, hygiene, and self-care. One notable figure in the field, Al-Razi (854–925 CE), also known as Rhazes [28], provided significant insights into wound management and care. In his book, Kitab al-Hawi, he emphasized the need for thorough examination and observation of wounds, considering factors like location, size, depth, and signs of infection. Al-Razi recognized the significance of debridement, the removal of necrotic tissue or foreign bodies, to facilitate healing. He also discussed various types of dressings and bandages, including materials like cotton, linen, and silk. Clean and sterile dressings were highlighted as essential for protecting wounds from further contamination and maintaining a moist environment conducive to healing. Rhazes held the esteemed position of chief physician at the prestigious hospital in Baghdad. An intriguing anecdote surrounds the selection of the hospital's location, as it is said that Rhazes hung pieces of meat at different points throughout the city, carefully observing the rate of putrefaction. Ultimately, he chose the site where decay was most significantly delayed, showcasing his meticulous approach to medical care. Additionally, Al-Razi described the use of topical medications made from natural substances, such as honey, to prevent infection, reduce inflammation, and support the healing process. One of his notable contributions was the introduction of animal guts as a material for sutures, a discovery that greatly enhanced the success of surgical procedures [29]. Albucasis (936–1013) was born near Cordova Andalusia [30], he introduced 200 surgical instruments and his writings of 30 volumes of medical encyclopedia "Kitab al-Tasrif" were invaluable. He gave a description for the treatment of abdominal wounds. He advises using big ants to stitch

the borders of the wound together for treating bowel damage. Al-Zahrawi provided detailed descriptions of various types of dressings that could be utilized to protect and promote healing in wounds. He also emphasized the importance of patient positioning and offloading pressure from affected areas to facilitate healing. Furthermore, Avicenna (960–1037), an Arab physician, accurately described the clinical features and potential complications of diabetes, such as peripheral neuropathy, gangrene, and erectile dysfunction. His influential book, Kanon, had a significant impact on the field of medicine [31].

5. The European renaissance

The European Renaissance was a remarkable era of cultural, artistic, and scientific resurgence that followed the Middle Ages. Spanning from the fourteenth to the seventeenth century, this period witnessed a profound revival of classical knowledge and wisdom. Moreover, the Renaissance was not limited to the arts and sciences alone. It permeated all aspects of society, influencing politics, religion, and education. One of the most remarkable outcomes of the Renaissance was the heightened fascination with the structure and function of the human body, which brought about a revolutionary transformation in surgical practices. During the wars of that era, surgeons acquired extensive expertise in treating wounds inflicted by firearms after the introduction of the arquebus. These wounds were particularly severe and highly prone to infection. The prevailing method involved cauterizing the wounds by injecting scalding oil. Additionally, bleeding was managed by employing hot irons or boiling oil. During the Renaissance, surgery started to gain a more prominent status compared to previous eras, where it had primarily been performed by barbers. It began to be practiced by individuals with significantly higher levels of education and training. This shift marked a significant advancement in the field of surgery during this period.

One of the most prominent Italian surgeons during that era was John of Vigo (1450–1525), who held the esteemed position of surgeon to Pope Julius II. His seminal surgical textbook, initially published in 1514, underwent over forty editions and was translated into various languages including French, Italian, Spanish, German, and English. Notably, he held the belief that gunshot wounds were contaminated, thus advocating for their treatment through cautery and the application of a plaster composed of pulverized frogs, worms, vipers, and the rust of old kettles. Tragically, even individuals with seemingly minor injuries often succumbed to their wounds.

Thomas Gale (1507–1587), a Tudor surgeon with extensive experience in wartime, vividly recounts the appalling conditions he encountered at Montreuil in 1544 during the reign of Henry VIII. In his detailed account, Gale exposes the alarming reality of unqualified individuals, such as sow-gelders, tinkers, and cobblers, assuming the role and responsibilities of surgeons. These impostors treated wounds with a repugnant concoction typically used to grease horses' feet, as well as an ointment composed of shoemakers' wax and the rust of old kettles. Shockingly, even those with seemingly minor injuries succumbed to their wounds due to the lack of proper medical care. His exceptional writings, distinguished by their practical and insightful teachings, include the notable work titled "An Excellent Treatise on Wounds made with Gunneshot" (1563) [4].

Ambroise Paré (1510–1590) changed medical practices by rejecting the conventional method of applying boiled oil to wounds and reintroducing the ligation of vessels. Instead of cauterizing the great vessels with hot irons during amputations,

Paré began tying them off. This innovative approach eventually led to the widespread adoption of ligatures in amputation procedures, becoming the new standard practice in medicine [32–34].

Fabricius Hildanus (1560–1634) is credited with introducing the tourniquet and pioneering the technique of amputating through healthy tissue in cases of gangrene. He is recognized for his innovative technique of amputation using a red-hot knife. While this method had previously been employed by Arabic surgeons, Fabricius made significant improvements by increasing the instrument's thickness. This modification enabled the knife to maintain its heat consistently throughout the operation. As a result, this method offers reduced pain, minimal bleeding, and superior muscle retraction, allowing for higher bone division. Notably, Fabricius skillfully employed this hot knife technique to amputate the leg above the knee of a severely ill patient afflicted with gangrene [35, 36].

John Woodall (1569–1643) strongly opposed indiscriminate amputation and believed that it was better to cut off a foot than a leg and even better to sacrifice a toe rather than a foot [37].

During the late seventeenth century, James Yonge, a naval surgeon from Plymouth, revolutionized the traditional circular amputation technique. In 1679, he introduced the flap operation using double flap rather than a single flap, which quickly gained popularity despite undergoing numerous modifications. Initially limited to the leg, the method expanded to include other limbs as well. However, in military practice, particularly in cases of gunshot and shattering wounds, the circular method continued to be favored [38, 39].

Thomas Willis (1621–1675) described the occurrence of gangrene and ulcers in individuals with diabetes. He was a British physician who lived in the seventeenth century, pioneered the studies of the anatomy and physiology of the brain and the nervous system, and described the circle of Willis, a ring of arteries at the base of the brain that supplies blood to the brain and surrounding structures [40].

Richard Wiseman (1622–1676) challenged the prevailing belief that gunshot wounds were venomous, instead recognizing the risk of retained foreign bodies, especially fragments of clothing. He advised extracting these foreign objects, understanding their removal as crucial for the wound's healing process. He applied fine lawn fabric soaked in oil of bitter almonds, oil of elders, egg yolks, and stramonium, among other substances. This meticulous method aimed to promote the recovery of the afflicted area [41].

In the eighteenth century, Jean Louis Petit (1674–1750), a French surgeon invented the famous screw tourniquet, a device specifically designed for amputation procedures. This ingenious invention involved the attachment of a circular bandage to a screw, which, when tightened, applied targeted pressure to a precise location. Additionally, a leather pad was incorporated into the design to enhance the effectiveness of the tourniquet [42].

Dominique Anel (1679–1730) was a French surgeon who was a pupil of J. L. Petit. He observed a common practice of sucking wounds to eliminate clots and foreign objects that hindered the healing process. However, this method was both unhygienic and perilous. In response, Anel ingeniously devised a suction syringe as a safer and more effective alternative. He is best known for his operation for aneurysms, which involved tying off the artery above and below the bulge and making an incision to drain the blood [43].

The name of François Chopart (1743–1795) is perpetuated in the amputation through the forefoot at the midtarsal joint using a long flap of the sole of the foot to cover the stump [44].

Baron Larrey (1766–1842) was a distinguished figure who played a crucial role in the Napoleonic wars. His notable contribution to medical innovation was the invention of the revolutionary "flying ambulances." Larrey's meticulous wound treatment involved excising all ragged and torn parts, as well as removing any foreign bodies or fragments of bone. Unlike many of his contemporaries, Larrey advocated against close suturing, except for facial wounds. Instead, he preferred to employ adhesive plasters and bandages to approximate the edges of wounds. This approach not only minimized scarring but also allowed for better healing [4].

The name of James Syme (1799–1870), a Professor of Surgery at the University of Edinburgh, is spread by the term "Syme's amputation," a disarticulation of the ankle joint, wherein a carefully crafted long heel flap meticulously mobilized to cover the wound [6].

Surgical anesthesia using ether and chloroform was not introduced until 1846 and 1847, respectively. Antisepsis, on the other hand, did not become common practice until after the turn of the century. The advent of anesthesia and antisepsis revolutionized the field of surgery, empowering surgeons to perform procedures that were previously deemed impossible, such as extensive amputations [45].

William Thomas Green Morton (1819–1868), an American dentist is regarded as the discoverer of surgical anesthesia, using the Ether to help the surgeon to do amputations [46].

Significant progress was made in understanding the pathophysiology and management of diabetes and its foot complications during the late nineteenth and early twentieth centuries.

Louis Pasteur (1822–1895) made important discoveries about bacteria and other microorganisms by his studies of the fermentation and putrefaction processes.

The antiseptic system was initially introduced by Lister in 1865 when he successfully treated a complex leg fracture with open wounds. Two years later, Lister published his new findings, documenting eleven cases, with nine patients fully recovering both life and limb, one requiring amputation, and one yielding astonishing result. This pivotal moment marked the widespread adoption of antisepsis, propelling it into the medical mainstream [47].

In 1928, Alexander Fleming discovered a blue mold thriving in a Petri dish. He observed that the mold had the extraordinary ability to annihilate all the bacteria surrounding it. The first article documenting the successful treatment of streptococcal meningitis with penicillin was published in 1943, marking a turning point in medical history. The advent of antibiotic medicines became paramount in the management of acute wounds and chronic lesions, as well as in the prevention of potential complications such as cellulitis, osteomyelitis, and sepsis. Antibiotics, such as penicillin, have become indispensable tools in the fight against bacterial infections [48].

Thomas Hodgkin (1798–1866) was a British physician and pathologist who is best known for describing Hodgkin's lymphoma. He recognized a connection between diabetes and foot gangrene. He suggested that diabetes could cause damage to the nerves and blood vessels of the foot, leading to ulcers and gangrene [49].

All of Lister's publications were studied by Richard von Volkmann (1830–1889), who later served as the philosopher's most ardent defender in Germany. A British surgeon who visited Volkmann's clinic in 1879 provided a detailed account of how the antiseptic ritual was carried out there. I-in-20 carbolic lotion was liberally applied to all wounds while the "donkey engine" or spray pumped antiseptic vapor into the air. When Volkmann yelled "watering can," long-spouting gardeners' watering cans filled with carbolic lotion and were emptied out by the surgeon and his assistants,

who were both wearing long rubber boots. "If dirt be unavoidable, it must be antiseptic dirt," read the clinic's catchphrase. The outbreak of the Franco-Prussian War provided a remarkable opportunity to put Lister's methods to the test. Professor von Nussbaum of Munich had a particularly striking experience. In 1872, at his hospital, eighty percent of all wounds were plagued by pyemia and gangrene, a truly terrifying rate. However, with the introduction of the antiseptic method, within a week, von Nussbaum was able to report a remarkable transformation: "Not another case of hospital gangrene appeared... Our results continue to improve, healing times shorten, and pyemia and erysipelas have completely disappeared."

Frederick Treves (1853–1923), famous for performing the first appendectomy in 1888, had established three crucial principles in the treatment of ulceration of the foot: sharp debridement, offloading pressure, and education regarding foot care and appropriate footwear. Following debridement, an antiseptic cream is applied, and plaster is subsequently utilized to alleviate pressure on the healed ulcer [49].

Jean-Martin Charcot (1825–1893) in 1883 described "Charcot foot" named after him in patients with tabes dorsalis. Charcot foot is mostly seen in diabetic neuropathy, which has replaced syphilis as a frequent cause of peripheral nerve dysfunction. Neuropathic osteoarthropathy is characterized by relatively painless swelling together with extensive damage in bones and joints, predominantly in the feet and ankles. The uncontrolled natural course of the condition leads to gross foot deformity, skin pressure ulceration, spreading infections, and sometimes amputation [50].

6. The discovery of insulin

In 1673, Johann Brunner noticed that a dog experienced excessive thirst and polyuria after the removal of its pancreas [51]. In 1884, Friedrich von Frerichs from Berlin reported that 20 percent of his diabetic patients exhibited significant changes in their pancreas. During the same year, French researchers Xavier Arnozan and Louis Vaillard found that ligation of the pancreatic ducts led to the degeneration of the acinar tissue while leaving the islets intact [52].

In 1890, Joseph von Mering and Oskar Minkowski from Strasbourg found that total removal of the pancreas in a dog resulted in diabetes. These pioneering experiments established the pancreas's involvement in diabetes and provided compelling evidence linking the pancreas to the regulation of sugar levels. Ultimately, their work laid the foundation for the study of diabetes, leading to the discovery of insulin as an effective treatment [53].

The stage was set for the collaboration between Frederick Banting and Charles Best, who made groundbreaking contributions in the field of medicine. At the time, Banting was a 29-year-old orthopedic surgeon practicing in London, Ontario. However, he was uncertain about the success of his practice. In 1921, Banting approached John Macleod, a distinguished Professor of Physiology in Toronto, seeking his approval to work in his laboratory. Macleod, recognizing Banting's potential, granted him permission to conduct his research. It was during this time that Banting enlisted the help of Charles Best, a promising medical student, to assist him in his endeavors. Their journey was not without its challenges. They faced numerous setbacks, heartbreaking trials, and disagreements along the way. With the invaluable assistance of James Collip, a talented biochemist, they successfully prepared an extract that proved effective in treating diabetic dogs and patients. Their remarkable achievement was documented in the seminal paper titled "The Internal Secretion of

the Pancreas," which was published in 1922. This remarkable work caught the attention of the scientific community, ultimately leading to Banting and Macleod being jointly awarded the prestigious Nobel Prize in Medicine and Physiology in 1923 [54].

The introduction of insulin into medical therapy reformed the treatment of diabetes, leading to better glycemic control and reduced risk of foot complications [55]. Subsequent research has greatly enhanced our comprehension of the etiology behind diabetic foot ulcers, consequently paving the way for numerous technological innovations and valuable tools. This exciting progress has altered our understanding of this condition, propelling us toward more effective treatments and improved patient outcomes.

7. Toward a better understanding

The etiology of diabetic foot ulcer is complex. It involves the interaction of various factors, such as neuropathy, ischemia, infection, inflammation, and wound healing. Many scientists have contributed to the explanation of diabetic neuropathy. One of the pioneers of research in leprosy was Paul Brand (1914–2003), an orthopedic surgeon, who taught us the principles of management of the insensitive foot, repeatedly emphasizing the need for offloading plantar neuropathic ulcers, which frequently went on to heal even in the days prior to antibiotics. He was the first surgeon in the world to use reconstructive surgery to correct the deformities of leprosy in the hands and feet. The findings from his research on leprosy were applicable to neuropathic diabetic foot care [56].

The discovery of capillary microaneurysms by Ballantyne and Loewenstein in the field of diabetic retinopathy in the 1940s brought about significant advancements [57]. However, it was the meticulous and continuous clinical observations made by Lundbaek that truly altered our understanding of diabetic microangiopathy, also known as diabetic small vessel disease. This term has now become the most comprehensive way to describe the consequences of arterioles, capillaries, and venules being affected by diabetes [58]. In the 1950s, the electron microscope emerged as a crucial tool in diabetes research, particularly in the study of the kidney. Through anatomical and biochemical investigations, it was determined that the capillary basement membrane in individuals with diabetes undergoes both thickening and chemical composition alterations. These valuable insights have significantly enhanced our comprehension of the long-term complications that manifest clinically in individuals with diabetes [59].

8. A higher standard of care

The work of Elliott Joslin (1869–1962, USA), during the first half of the twentieth century, focused on various aspects of diabetes management, including foot care. Joslin noted that mortality from diabetic coma had fallen from 60 to 5% after the introduction of insulin. As people began to live longer, they experienced complications that had not previously been seen. Deaths from diabetic gangrene of the lower extremity have risen significantly. He believed that diabetic gangrene was preventable. He introduced the team approach that included foot care, diet, exercise, prompt treatment of foot infections, and specialized surgical care. He founded the Joslin Diabetes Center in 1898. Through the efforts of Joslin and members of the

Massachusetts Chiropody Association, the first hospital foot clinic was established at the New England Deaconess Hospital (NEDH) in 1928 [60]. In 1957, the term "chiropodist" was changed to podiatrist and the National Association of Chiropodists (NAC) became the American Podiatry Association (APA). In 1984, the APA became the American Podiatric Medical Association (APMA). Leland McKittrick, MD (1893–1978) was recruited by Joslin. He suggested that amputation might be safely performed at a more distal level with a reasonable chance of success after controlling invasive infection with antibiotics. Frank C. Wheelock (1919–2006) was the first American surgeon to use an end-to-side femoral popliteal bypass graft. In 1984, the Division of Vascular Surgery at the NEDH developed the distal revascularization techniques, in particular, the dorsalis pedis bypass graft to restore pulsatile flow to the forefoot. Consequently, there was a growing recognition of the importance of foot preservation, leading to the development of distal revascularization methods aimed at restoring proper foot perfusion [60]. In 1992, Frank LoGerfo and colleagues noted that distal arterial reconstruction has greatly reduced the need for toe or transmetatarsal amputation.

Angioplasty was first described by interventional radiologist Charles Dotter in 1964 [61, 62]. In January of that year, he successfully dilated a superficial femoral artery in an 82-year-old patient. As the twentieth century progressed, the angioplasty technique underwent further development, enabling the revascularization of distal arteries all the way down to foot arteries. This breakthrough has proven to be a safe and effective method for limb salvage in patients with diabetes. Since then, revascularization has become a crucial component of the diabetic foot service.

R.D. Lawrence (1900–1987, UK) was a British physician who also faced the challenges of living with type 1 diabetes himself. His remarkable autobiography, "Young Dr. Jude" (1957), explained his personal journey and struggles with diabetes. In addition to his medical achievements, Lawrence co-founded the British Diabetic Association, now known as Diabetes UK. Through this organization, he actively worked to raise awareness about diabetes and tirelessly advocated for enhanced care and support for those affected by the condition [63].

The establishment of worldwide multidisciplinary diabetic foot teams marked a significant milestone in the field of healthcare. Recognizing the need for comprehensive care alongside targeted treatment for lower limbs disease, it became evident that patients with diabetic foot disease needed specialized attention from a diverse team of experts working not only in a dedicated diabetic foot clinic but also caring for the patient when admitted to the hospital. By assembling a diverse group of professionals, including podiatrists, endocrinologists, wound care specialists, and vascular surgeons, these teams ensure that patients receive comprehensive and specialized care [64].

The significance of diabetic foot disease on a global scale led the International Diabetes Federation (IDF) to devote the entire year of 2005 to Diabetic Foot Care. This comprehensive effort aimed to emphasize the potential for amputation prevention. Concurrently, the Lancet, a highly respected general medical journal, released an issue solely focused on diabetic foot disease, further amplifying the significance of this condition on World Diabetes Day.

9. Recent developments and future directions

The recent improvements bring forth a wave of hope and opportunities for patients suffering from DFUs. These remarkable advancements have the potential to

change the way we approach and treat these patients. With each new development, we inch closer to a future where DFUs no longer pose a significant threat to patients' well-being. The cutting-edge techniques and innovative treatments that have emerged in recent times hold immense promise in healing these stubborn wounds and restoring patients' quality of life. Thanks to these exciting developments, we are now witnessing a paradigm shift in the way we address DFUs.

Recent advances in debridement techniques include hydro surgery and ultrasound. These aim to remove nonviable (necrotic) tissue, which can hinder the healing process by obstructing the migration of cells across the wound, thereby inhibiting the natural development of the wound bed, and preventing the formation of granulation tissue.

Hydrosurgery (also known as jet lavage) uses sterile water delivered at high pressure to wash away dead tissue. Low-frequency ultrasound breaks down dead tissue. Water jet techniques have been used in industrial cutting for more than 30 years. The first medical applications were reported in the early 1980s, when the water jet was used to cut organs. These methods are painless and reduce bacterial burden. However, special training is required, and the patient will require several treatment sessions [65, 66].

In 1662, Henshaw, a British physician first utilized hyperbaric therapy, placing patients in a steel container that was pressurized with air. In 1937, Behnke and Shaw first used hyperbaric oxygen successfully for the treatment of decompression sickness. Hyperbaric oxygen therapy (HBOT) was initially used in 1885 for medical purposes, specifically to treat pneumonia. It was found to improve cellular, tissue, and organ oxygenation, exert anti-inflammatory and anti-bacterial effects, and enhance tissue repair mechanisms. It can alleviate or even heal diabetic foot ulcers (DFU) that are caused by the lack of adequate microcirculation and innervation in the extremities of diabetic patients [67].

Negative pressure wound therapy (NPWT) has been used in medicine for over 2,000 years. During the Roman era, medical personnel were attached to various armies. These individuals were believed to possess hereditary powers of healing and were assigned the task of providing direct suction to wounds by mouth. The renowned historian Suetonius documented an incident where one of these healers was instructed to apply suction to Cleopatra's wound in an attempt to revive her from the bite of an asp. In the pursuit of medical advancements, the technique of utilizing "cupping glasses" emerged. These dome-shaped glasses were employed to draw fluid out of open wounds. Placed over the wound site, they were left in position for at least an hour after being activated by applying heat to the inside of the cup. As the cup cooled, the suction effect intensified, aiding in the extraction of fluid. Advance rapidly to the eighteenth century, Dominique Anel, a French Surgeon, invented the first suction syringe. This device was primarily used to cleanse wounds from clots and foreign bodies, marking a significant milestone in medical history. In the twentieth century, Soviet Surgeon Dr. Nail Bagaoutdinov introduced a negative pressure unit with foam dressings in 1985 to treat infected wounds. This innovative approach paved the way for the development of modern Negative Pressure Wound Therapy (NPWT) systems. Drs. Louis Argenta and Michael Morykwas of Wake Forest University School of Medicine played a pivotal role in this advancement by pioneering the use of polyurethane foam and a mechanical vacuum in the 1990s [68]. It promotes wound healing in diabetic foot ulcers (DFUs) [69]. The National Institute for Health and Care Excellence (NICE, 2019) recommends the consideration of NPWT following surgical debridement for DFUs, particularly when advised by the multidisciplinary foot care service.

The complex interaction between depression and diabetes has been established in diabetics with DFUs. Earlier management of patients' depression may have implications for improved healing for those with DFUs as well [70].

Since the initial definition of the term "tissue engineering" in the late 1990s, biomaterial-based scaffolds have played a vital role in offering structural stability and creating a conducive environment for cellular regeneration, thereby mimicking the functionality of native tissue [71]. Biological scaffolds have been used to promote diabetic wound healing [72]. The use of Human Skin Equivalent (HSE) has proven to be more effective than the standard treatment of saline-moistened gauze in reducing amputation and infection rates, as well as improving the rate of ulcer healing [73]. In the realm of medical advancements, topical growth factors, with a particular focus on platelet-derived growth factors, have emerged as a highly effective intervention for promoting the healing of ulcers. In comparison to a placebo, these growth factors have consistently shown their ability to significantly enhance the rate at which ulcers heal. This is primarily due to their crucial role as immediate mediators of wound healing. When administered in the context of DFU, these growth factors work to expedite the healing process, providing a much-needed boost to patients suffering from this condition [74].

Lew Alexandrovitch Yutkin, a Russian engineer, patented the use of shock waves to break up kidney stones in 1950. He did this by employing an endoscopic electrohydraulic generator. After seeing how a lightning strike may break a log underwater, he came up with this concept and applied the same logic to the plates. The first kidney stone to disintegrate in-vitro utilizing shockwaves without making direct contact with the stone was documented by Haeusler and Kiefer in 1971. By the end of 1985, ESWL had already become a widely used operational approach [75].

Extracorporeal shockwave therapy (ESWL) has been found to expedite the healing process of soft tissue wounds in the treatment of diabetic foot ulcers (DFU). Encouraging results from clinical trials have demonstrated the superior effectiveness of ESWL over traditional methods for DFU treatment [76].

Multiple reports have demonstrated that stem cells have the ability to enhance angiogenesis in ischemic regions. Stem cell transplantation, as an innovative technology, remains a subject of controversy within the field of diabetic angiopathies when it comes to treating diabetic foot ulcers [77].

The potential advantages of using amnion/chorion membranes have been a subject of theoretical speculation for quite some time. However, recent studies have started to shed light on the practical benefits that these membranes can offer to patients. Several clinical trials have been conducted to investigate the safety and effectiveness of dehydrated amnion chorion membrane (dHACM) in the treatment of diabetic and venous lower extremity ulcers. These studies have revealed a notable improvement in the rate of wound healing among patients treated with dHACM compared to standard of care (SOC) and bilayered skin substitutes [78].

Digital applications in the daily management of DFUs have evolved rapidly in recent years to a level of remote diagnosis and monitoring of wounds in community settings. The COVID-19 pandemic has accelerated research and development of such innovative technological applications. Photographic monitoring of foot ulcers has been practiced in many centers across the world in the past few decades. The invention of digital photographic technology in 1975 further boosted DFU care because of the ease of electronic archiving of ulcer images during clinical follow-up. Photography using mobile phone cameras has become a huge leap forward in this direction in recent years empowering patients and clinicians to further improve DFU care.

AI-based digital algorithms are currently being developed rapidly through collaborative global effort between AI experts and clinical teams. Mobile camera-based digital technologic applications are under development to enhance remote diagnosis, monitoring, and follow-up care of DFUs. Prediction models of wound healing are also under development now making use of linking the ulcer characteristics of DFU images to the clinical and laboratory parameters of diabetic patients. These collaborative efforts between clinicians and computer scientists across the world should revolutionize such discoveries to empower diabetic foot patients to self-monitor and manage their DFUs to a greater extent [79].

10. Conclusion

Studying the captivating history of diabetic foot ulcers enables us to explore the fascinating evolution of diagnosis and treatment across diverse regions and populations. By doing so, we can identify the prevailing gaps and challenges, paving the way for the establishment of standardized guidelines. It is crucial to acknowledge the profound impact that diabetic foot ulcers have on the quality of life, morbidity, and mortality of patients with diabetes and their families. This knowledge ignites our enthusiasm as we embark on a journey to learn from both the triumphs and setbacks of past and present interventions. With an enthusiastic tone, we eagerly embrace the opportunity to unravel the mysteries of diabetic foot ulcers, unraveling the secrets of their historical development and unlocking the potential for innovative advancements.

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Chapter 2

Perspective Chapter: Epidemiology and Risk Factors of Diabetic Foot Ulcer

Ahmed Daniyal Nawaz, Amine Zaidi, Basant Elsayed, Khaleed Jemmieh and Mohsen Eledrisi

Abstract

Diabetes is one of the most common diseases worldwide, with steady increase in its prevalence around the globe. One of the common and most devastating complication of such disease is diabetic foot ulcer. The prevalence of diabetic foot ulcers (DFU) among adults with diabetes globally has been estimated at 6.3%, while the annual incidence has been reported to range between 9.1 to 26.1 million cases. DFU is associated with several risk factors including a longer duration of diabetes, poorly controlled diabetes, diabetic neuropathy and foot deformities such as foot callus and flat foot. It can also result in many complications, among which infections are the leading cause of morbidity and mortality. Infections are estimated to occur in 60% of all diabetic ulcers. Moreover, the mortality rate is higher by 2.5-fold in patients with diabetes with foot ulcers compared to patients with diabetes without foot ulcers. In this chapter, we discuss the epidemiology of DFU, and review its prevalence in different parts of the world, along with risk factors, complication rates and overall impact on quality of life.

Keywords: diabetes, diabetic foot ulcer, epidemiology, prevalence, incidence, recurrence, risk factors, financial cost, complications, amputation, mortality, quality of life

1. Introduction

Diabetes Mellitus is the most common metabolic disease with global prevalence of 9.3% (463 million) in 2019 and is expected to increase to 11% (700 million) by the year 2045 [1]. Patients with diabetes are prone to developing a range of complications, with the most disabling being lower extremity infections and amputations. The most common presentation of lower extremity complications is neuropathy, which is a key risk factor in developing one of the most feared and dreaded complications of diabetes, diabetic foot ulcers [2]. A trifactor of sensory, motor and autonomic neuropathy leading to loss of protective sensation, foot deformity and skin changes respectively leads to the formation of callus, which then ulcerates due to repetitive trauma and inflammation [3]. Approximately 18.6 million people with diabetes around the globe develop a foot ulcer each year [4] and 34% of all people with either type 1 or 2 diabetes will develop a foot ulcer within their lifetime [2].

Diabetic foot ulcers cause a considerable global disability burden. It is estimated that almost 20% of all diabetic foot ulcers (DFUs) eventually lead to amputations [5]. Diabetes-related lower-extremity complications account for up to 80% of all lower-extremity amputations and are a leading cause of hospitalization worldwide [6]. Furthermore, studies have shown DFU to be a cause of poorer quality of life [7] and therefore a major contributor to the global disability burden. In 2016, it was estimated that 2.1% of the global years lived with was directly caused by diabetes-related lower-extremity complications. Increased pain, poor physical function, poorer prognosis for other health conditions and lower quality of life overall are just some of the health impacts that can affect persons living with DFU [7].

The Society for Vascular Surgery in 2013 proposed a classification system, that incorporates the three most important risk factors of amputation; wound, ischemia, and foot infection [8]. The wound, ischemia, and foot infection (WIfI) classification system gives a rating that ranges from 0 to 3 for each risk factor, in which 0 represents absent, 1 mild, 2 moderate and 3 severe (**Figure 1**). The individual scores are combined and then the total number is analyzed using two tables (**Tables 1** and **2**): one table estimates the risk of amputation at 1 year and the other table estimates the need for revascularization. The limb is classified in terms of both, risk of amputation and need for revascularization, into four categories: very low, low, moderate and high [9, 10]. It is proven that this classification system is an independent predictor of wound healing in patients with DFUs [10]. WIfI scores of 1,2,3 and 4 have been associated with 1-year amputation rates of 0, 8, 11, and 38% respectively [6]. These classification tools play a vital role in determining the patient's prognosis as well as the modality of treatment offered. Currently, more research is being looked into for early and aggressive management of DFU due to its severe complications that have health impacts and financial impacts.

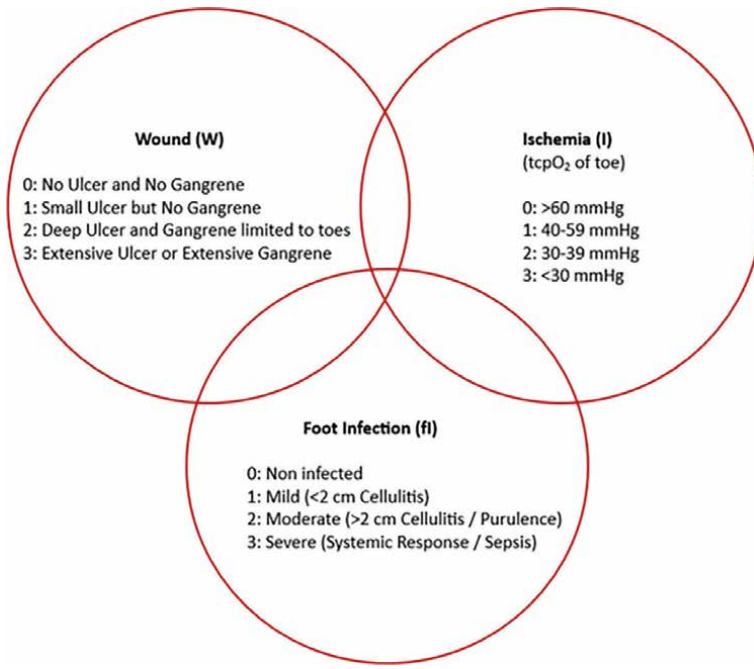

Figure 1.
The WIfI classification system. $tcpO_2$ = transcutaneous oxygen pressure.

	Ischemia 0				**Ischemia 1**				**Ischemia 2**				**Ischemia 3**			
Wound 0	**VL**	**VL**	**L**	**M**	**VL**	**L**	**M**	**H**	**L**	**L**	**M**	**H**	**L**	**M**	**M**	**H**
Wound 1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
Wound 2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
Wound 3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	fI 0	fI 1	fI 2	fI 3	fI 0	fI 1	fI 2	fI 3	fI 0	fI 1	fI 2	fI 3	fI 0	fI 1	fI 2	fI 3

VL = very low; L = low; M = moderate; H = high; fI = foot infection.

Table 1.
Estimation of risk of amputation at 1 year.

	Ischemia 0				**Ischemia 1**				**Ischemia 2**				**Ischemia 3**			
Wound 0	**VL**	**VL**	**VL**	**VL**	**VL**	**L**	**L**	**M**	**L**	**L**	**M**	**M**	**M**	**H**	**H**	**H**
Wound 1	VL	VL	VL	VL	L	M	M	M	M	H	H	H	H	H	H	H
Wound 2	VL	VL	VL	VL	M	M	H	H	H	H	H	H	H	H	H	H
Wound 3	VL	VL	VL	VL	M	M	M	H	H	H	H	H	H	H	H	H
	fI 0	fI 1	fI 2	fI 3	fI 0	fI 1	fI 2	fI 3	fI 0	fI 1	fI 2	fI 3	fI 0	fI 1	fI 2	fI 3

VL = very low; L = low; M = moderate; H = high; fI = foot infection.

Table 2.
Estimation of the need for revascularization.

2. Epidemiology and recurrence rate of diabetic foot ulcer

Diabetic foot ulcers are more common in men compared to women, and more prevalent in patients with type 2 diabetes compared to those with type 1 diabetes [11].

2.1 Global and regional prevalence rates of diabetic foot ulcer

Globally, the impact of DFU is staggering. According to the International Diabetes Foundation, between 40 to 60 million individuals are currently suffering from diabetic foot ulcers [11]. However, it is crucial to approach these prevalence figures with a discerning perspective, as they can be easily influenced through various methods, such as different surveillance approaches, and definitions of diabetic foot ulcer. In 2017, a meta-analysis carried out Zhang, P et al. reported that the global prevalence of DFU among adults with diabetes was 6.3% which translates to an estimated 33 million people [11]. The annual incidence of DFU has been reported to be between 9.1 to 26.1 million [2]. The occurrence rate of diabetic foot ulcers throughout a patient's lifetime has been reported to range between 12–25% [11]. However, it has been reported that potential lifetime risk could be even greater due to the extended life expectancy [2]. Furthermore, the overall recurrence was estimated to be 22.1% per person-year [12].

In African nations (excluding North Africa), the prevalence of DFU has been observed to range between 10 and 30% [13]. This situation is expected to further escalate as the International Diabetes Foundation is anticipating a rise in the number of patients with diabetes in Africa. In Tanzania, Abbas et al. (n.d.), have documented a 17.5% prevalence of neuro-ischemic ulcer lesions among patients with diabetes [13]. Similarly, in Ethiopia, Tolosa et al. reported an overall magnitude of foot ulcers of 12.98% in patients with diabetes [14]. A separate study further conducted in Tanzania revealed that around 15% of patients with diabetes who were admitted to inpatient services had foot ulcers, with 80% of these cases being individuals with no previous history of ulcers. A similar rate has also been reported in Mogadishu, and Somalia [15]. Moreover, in Kenya, the rate was estimated to be 9.04% [16]. The elevated prevalence of DFU can be attributed to the common practice of walking barefoot, which is practiced in rural communities in Africa. Furthermore, the limited income in these regions makes it difficult for individuals with diabetes to procure appropriate footwear, further contributing to the issue [17]. The recurrence rate of diabetic foot ulcers in African nations was found to be relatively low, reaching 16.9% [12].

In Europe, 1 in 11 adults has diabetes, mounting to – 61 million individuals [18]. This region also bears the highest number of children and adolescents with type 1 diabetes, reaching around 295,000 individuals [18]. The prevalence of DFU varies significantly, ranging from 1% in Denmark to a remarkable 17% in Belgium (**Figure 2a**). Likewise, the recurrence rate has also demonstrated wide variation as well. This is evident by the fact that it stood at 7% in Germany and Italy in 2012, but then surged to 42% in Italy by 2017. In a recent study conducted in Belgium, it was concluded that diabetic foot ulcers were more prevalent in men compared to women and were presented in a more severe form [19]. Furthermore, according to Grand View Research (n.d.), the European diabetic foot ulcer treatment market size was valued at 1.45 billion USD in 2021 and it is expected to increase at a compound annual growth rate of 5.4% between 2022 and 2030 [20].

In North America & Caribbean, approximately 1 in 7 adults have diabetes, totaling 51 million individuals [21]. This region also accounts for the highest diabetes-related

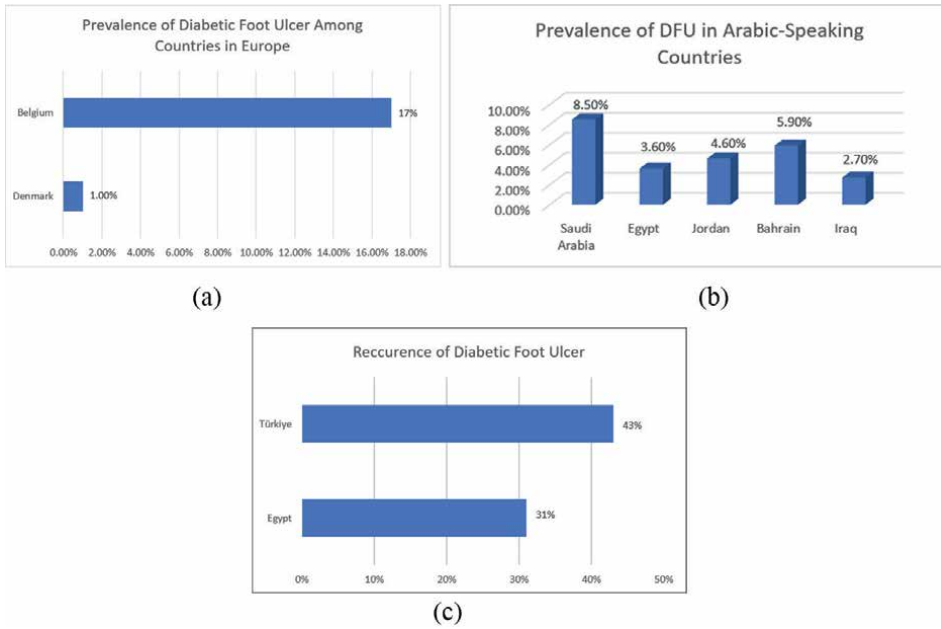

Figure 2.
a. Displays the prevalence of diabetic fot ulcer among countries in Europe. b. Displays the prevalence of DFU in countries in which Arabic is the official language. c. Displays the rate of recurrence of diabetic foot ulcer in Egypt and Türkiye.

expenditure, reaching 415 billion USD, which constitutes around 43% of global expenditure [21]. The prevalence of DFU in North America was around 13% [13]. The frequency of DFU recurrence ranged from 9% in 2013 to 52% in 2018 [22].

In South and Central America, 1 in 11 adults have diabetes, totaling 33 million individuals [23]. Carro, G et al. (2018), concluded in their transversal study the prevalence of DFU across 9 Latin American countries was 14.8% [24]. while the prevalence in Brazil was 21%.

In the Middle East and North Africa (MENA) region, 1 in 6 adults currently live with diabetes — an estimated 73 million individuals. It is predicted that the prevalence of diabetes will increase by 86%, reaching 136 million by the year 2045 [25]. The prevalence of diabetic foot ulcers in this region has been estimated to range between 5 and 20% [26]. Furthermore, in a systemic review conducted in Arabic-speaking countries, the prevalence of DFUs was found to be as follows: Saudi Arabia (8.5%), Egypt (3.6%), Jordan (4.6%), Bahrain (5.9%), and Iraq (2.7%) (**Figure 2b**) [27]. Recurrence of DFU varied widely; as an example, it was 31% in Egypt and 43% in Türkiye (**Figure 2c**) [25].

In the Southeast Asian region, approximately 1 in 11 adults are affected by diabetes, approximated to be around 90 million individuals. This number is expected to increase by 69%, reaching 152 million by the year 2045. The prevalence of DFU in this region was 15%, with a recurrence rate of less than 14% [28]. A recent meta-analysis concluded that the prevalence of diabetic foot ulcers in Pakistan was 12.16% [29].

The data shows not only the staggering prevalence of diabetes and DFU that currently exists but also points to a further increase in the future.

3. Risk factors of diabetic foot ulcers

3.1 Major risk factors of diabetic foot ulcers

A plethora of risk factors associated with DFU has been studied. The common underlying risk factors are poor glycemic control, improper foot care, underlying peripheral neuropathy and poor circulation. In addition, foot deformities such as calluses, dry poorly perfused and flat foot were considered important risk factors for DFU. A study in Sudan described the duration of diabetes for >10 years as the only statistically significant risk factor associated with diabetic foot ulcers [30]. Other factors such as hypertension, HbA1c, lipid levels, albuminuria, retinopathy, age and BMI were not associated with the development of DFU [30]. A nationwide systemic review in Ethiopia described that diabetic foot ulcers were significantly associated with the following risk factors: having callus on the foot, high BMI, poor self-care practice, type 2 diabetes and living in urban areas, while younger patients (<45 years) and those who have diabetes for <10 years were found to have decreased odds of diabetic foot ulcers [14]. Although DFUs are more common among male patients along with a tendency to progress to amputation [31], no significant association was found in this study between gender and DFU [14].

3.2 Risk factors for recurrent DFU

Demographic factors like male gender and smoking were associated with an increased incidence of DFU recurrence while age and BMI were not predictors of DFU recurrence. Also, patients having a long duration of diabetes were at a significant risk of DFU recurrence. Among different forms of DFU, patients with previous plantar ulcers were at a higher risk of DFU recurrence. No association was found between the recurrence of DFU and any of the following: age, BMI, long duration of past DFUs, hypertension, high cholesterol, nephropathy and retinopathy [32]. Patients with peripheral artery disease, diabetic neuropathy and impaired proprioception were at a significant risk of DFU recurrence [32, 33].

3.3 Financial cost of diabetic foot ulcers

The annual expenditure for any medical performance per person with diabetic foot complications was 3 times higher than that for diabetic patients without DFUs [34]. In 2017, it was estimated that the complications of diabetes in the United States carried a direct cost of $237 billion; historically approximately 33% of this cost has been accepted as attributable to DFUs [31]. Costs have been demonstrated to correlate with wound severity. The cost of individual hospitalizations for DFUs has also increased significantly independent of amputation rate and length of stay, demonstrating the importance of avoiding inpatient admissions in this patient population when possible [31].

Moreover, due to the nature of DFU, several teams are consulted for adequate management of DFU during hospitalization. This ranges from internists, endocrinologists, and surgeons to specialized services such as podiatrists and physiotherapists. Henceforth, hospital admission for patients with DFU represents one of the largest direct expenditures. Moreover, high recurrence rates for DFU, (up to 22.1% per person-year) [12], lead to recurrent hospital admissions, impaired quality of life and low productivity, which further increase the expenses.

Although the costs of DFU treatment were higher in developed and high-income countries such as the US ($10.9 billion/year), the UK ($4 billion/year) and Denmark ($150 million/year) [35], the condition has also a profound impact on the economy of middle- and low-income countries. As an example, in India, an average salary of 5.7 years will be needed to completely treat a patient with DFU [36]. Annual admission costs related to DFU were at $264 million in Brazil [37], and in Turkey, 3% of annual health expenditure was spent on DFU management alone [38].

The huge financial impact of DFUs calls for the importance of early identification and proper aggressive treatment of patients with diabetes and DFU to prevent its progression and reduce its economic burden. According to the Markov model for cost-effectiveness, targeted preventative strategies have the scope of reducing amputations and DFU incidence by almost 25%, and if these measures are applied, the likelihood of cost savings is more than 90% when dealing with DFU [39].

Studies show that although the cost is great, low cost, early implemented measures can go a great way in helping us to decrease those costs [40].

4. Complications of diabetic foot ulcers

Diabetic foot ulcers may result in several complications, some of which can be life-threatening. In this section of this chapter, we will focus on the epidemiology of these complications and their associated morbidity.

4.1 Infection

Foot infection is a leading cause of morbidity in patients with diabetes, occurring in 60% of diabetic foot ulcers [41]. Hence, such infections are a common cause of emergency department visits and hospital admissions. Foot ulcers usually precede the development of infection and infection rates are observed to be higher in patients with recurrent wounds, chronic non-healing wounds, wounds with a positive probe-to-bone test, and recent infections not related to the foot [42]. Infections associated with diabetic foot ulcers can range from superficial ones such as cellulitis to life-threatening conditions such as necrotizing fasciitis and sepsis [43]. In just more than 65% of patients with diabetic foot ulcers, infections are the leading cause of major lower extremity amputation and about 20% of moderate to severe infections lead to amputations [3, 44]. Osteomyelitis occurs in 15–20% of diabetic foot ulcers and is considered one of the most common manifestations of diabetic foot infections. It is estimated to occur in >20% of moderate infections and just more than half of severe infections [44–46]. Osteomyelitis most commonly affects the forefoot (90%), followed by the midfoot (5%) and least commonly the hindfoot (5%). Forefoot osteomyelitis appears to have the best prognosis as the risk of major amputation for such cases is less than 1% whereas that of hindfoot osteomyelitis is estimated to be at 50% [44].

4.2 Amputation

In a multicentric study based in Europe, it was found that 5% and 17% of patients with diabetic foot ulcers require major (above the ankle) and minor (below the ankle) amputation respectively, within 1 year of ulcer development [41]. Foot ulcers appear to be very prevalent in diabetic patients who require amputation as 85% of all amputations in patients with diabetes were preceded by

foot ulcers [46]. A meta-analysis involving 16 studies revealed that the prevalence of lower limb amputation in patients with diabetic foot ulcers is around 19% [47].

4.3 Mortality

Mortality rates associated with the development of a DFU are estimated to be 5% in the first 12 months. Whereas the 5-year-mortality rate is 30–42% and exceeds 70% for those with major amputations [3, 48]. The 3-year survival rate is 72% for diabetic patients with foot ulcers compared to 87% for diabetic patients without foot ulcers [49]. One study that compares death in the presence or absence of ulcers revealed that the mortality rate for people with diabetic foot ulcers is 231 deaths per 1000 person-years, compared with 182 deaths per 1000 person-years in people with diabetes without foot ulcers [3]. In a study conducted in the UK involving 20,737 patients with diabetes who newly developed foot ulcers, it was found that 5% of patients died within 1 year of their first foot ulcer visit and just more than 40% died within 5 years [50]. The study also found that death is 2.5 times more likely in diabetic patients with foot ulcers compared to those without foot ulcers. Surprisingly, the 5-year mortality rate of patients with diabetic foot ulcers seems to be comparable to that of pooled 5-year survival of all cancers and even greater in some studies [51].

4.4 Disability and low quality of life

Diabetic foot ulcers have a significant impact on the quality of life and well-being of individuals regardless of the presence of other diabetes-related complications that influence the quality of life [50]. This low quality of life is reflected by questionnaires, such as SF-36, which shows that the most significantly impacted domains are physical functioning, productivity, general health, and depressive symptoms [7]. The healing status of ulcers also seems to have an impact on welfare as patients with unhealed ulcers are more anxious and frustrated than those with healed ones [50]. Anxiety and depression seem to be fairly prevalent in patients with diabetic foot ulcers, with reported prevalence rates of 13.8 and 20%, respectively [52]. In terms of Years Lived with Disability (YLD), it is estimated that 2.5 million YLDs result from foot ulcers [46].

5. Conclusion

Diabetes is the most common metabolic disease worldwide and its prevalence and complications are on the rise. Diabetic foot ulcers are common complications of diabetes that can affect a wide range of patients around the globe, have shown increasing trends over the last decades and are associated with increased morbidity and mortality. Diabetic foot ulcers can result in significant medical, psychological, and financial consequences to patients, their families and society. Diabetic foot ulcers are a major cause of infections, lower limb amputations, disability, reduced quality of life, higher mortality and increased economic burden.

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Conflict of interest

The authors declare no conflict of interest.

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Section 2

Pathophysiology and Management of Diabetic Foot Ulcers

Chapter 3

Microbiology and Antimicrobial Resistance in Diabetic Foot Infections

Humam Rajha, Raneem Alsheikh, Amna Zar, Sara Mohsen and Susu M. Zughaier

Abstract

Diabetic foot infections (DFIs) can be caused by a wide range of microorganisms, including mainly bacteria and fungi. This class of infections poses significant medical challenges, affecting a large proportion of individuals with diabetic foot ulcers (DFUs). This chapter aims to provide a comprehensive overview of the primary microorganisms responsible for diabetic foot infections, elucidating their virulence factors, pathogenesis, and susceptibility to antimicrobial agents. It also explores the impact of antimicrobial resistance (AMR) on diabetic foot infections (DFIs), highlighting the role of biofilms in chronic diabetic foot infections and the resulting treatment difficulties, all with the goal of reducing complications. By gaining insight into the diverse spectrum of microorganisms involved in diabetic foot infections, healthcare professionals can customize treatment plans for individual patients, ultimately improving patient outcomes and quality of life.

Keywords: microbiology, diabetic foot ulcers (DFU), diabetic foot infections (DFI), antimicrobial resistance (AMR), pathogenesis, antimicrobial treatment

1. Introduction

Diabetic foot infections (DFIs) are considerable medical problems, as approximately half to six in every ten individuals with diabetic foot ulcers (DFUs) eventually contract an infection [1]. These infections can stem from a wide array of microorganisms, encompassing bacteria and fungi. Owing to the intricate nature of diabetic foot ulcers, the microbiology of these infections can exhibit diversity and present difficulties in both diagnosis and treatment. This chapter aims to offer a comprehensive overview of the major types of microorganisms responsible for diabetic foot infections, elucidating their virulence factors, pathogenesis, and susceptibility to antimicrobial agents. Additionally, it addresses the impact of antimicrobial resistance (AMR) on diabetic foot infections (DFIs), shedding light on the role of biofilms in chronic diabetic foot infections and the ensuing treatment challenges, all in a concerted effort to mitigate implications. By gaining insight into the heterogeneous spectrum of microorganisms

implicated in diabetic foot infections, healthcare providers can tailor treatment plans to individual patients, thereby enhancing patient outcomes and quality of life.

2. Epidemiology of DFU pathogens and their antimicrobial resistance

Across various countries, the microbiology of DFU exhibits notable diversity, yet specific species consistently play significant roles. *Staphylococcus aureus* (*S. aureus)*, for instance, emerges as a frequently encountered pathogen in several nations, including Pakistan, Ethiopia, Egypt, Jordan, and Lebanon, with prevalence rates of 46, 25.19, 22, 14.2, and 9% respectively (**Figure 1**) [3–7]. There is an evident tendency toward Gram-negative species in multiple countries. In Egypt, Gram-negative bacilli (rods) prevalence was reported to be 56.1% of pathogens causing DFI, where *K. pneumoniae* accounted for 26.8% of infections. Whereas Gram-positive bacteria such as coagulase-negative *Staphylococci* accounted for 22% [5]. Similarly, in Lebanon, the prevalence of Gram-negative rods is higher than Gram-positive cocci 55 vs. 39%. The most prevalent isolates in Lebanon include *Escherichia coli* (15%), followed by *Enterococcus* (14%) and *Pseudomonas aeruginosa* (11%) [7]. A similar pattern is also observed in Kuwait, where Gram-negative strains are more prevalent in ischemic ulcers, although *S. aureus* dominates in non-ischemic ulcers infections [8]. Meanwhile, in Mexico, *S. aureus* is the most commonly isolated pathogen in DFU infections, with higher prevalence of aerobic Gram-positive cocci (47%) [9]. In Pakistan, Gram-negative bacilli are predominant where the prevalence is estimated for *E. coli* (28%), *Pseudomonas aeruginosa* (6%), and *Klebsiella* (3.5%) [3]. Iranian DFU patients, especially of older age with repeated hospitalizations, were also more affected by Gram-negative bacilli [10].

Additionally, the prevalence of polymicrobial and monomicrobial DFU infections was variable among countries. In Kuwait, for instance, monomicrobial DFI was more common than polymicrobial DFI (57.3 vs. 34.8%) [8]. However, the trend is rather unclear in Lebanon, where only 38% of Lebanese patients were affected by polymicrobial DFI in 2018 [11], while between 2008 and 2017 the prevalence rate was 54% [7].

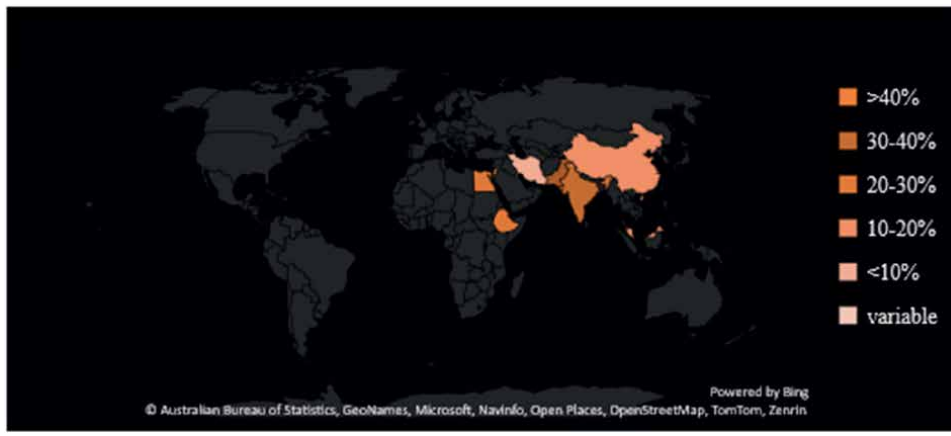

Figure 1.
Prevalence of S. aureus *among DFU infections across countries in the Middle East and Asia.* S. aureus *Emerged as a notably prevalent pathogen associated with diabetic foot ulcers (DFIs) across numerous countries. Its prevalence exhibits considerable variation, ranging from approximately 48% in Pakistan to around 8% in Iran [2]. Additional research is imperative to ascertain its prevalence in other nations.*

A variability in antibiotic sensitivity is also prominently evident across different countries. In Mexico, Penicillin and Dicloxacillin showed the lowest efficacy against Gram-positive bacteria, while Cephalothin and Penicillin were found to be least effective against Gram-negative bacteria. In contrast, Levofloxacin, Cephalothin, and Amikacin emerged as the most effective antibiotics against Gram-positive and Gram-negative bacteria, respectively [9]. Whereas in Egypt, Amikacin, Tigecycline, and Meropenem exhibited the highest activity against Gram-negative bacteria, while Linezolid and Vancomycin demonstrated effectiveness against *Staphylococci* [5]. In Lebanon, Ciprofloxacin sensitivity was observed in 72% of *Pseudomonas spp*., but for *Enterobacteriaceae*, 63.6% were sensitive to either Amoxicillin/Clavulanate or Ciprofloxacin, and 91% were susceptible to Piperacillin/Tazobactam [11]. In Pakistan, Vancomycin demonstrated sensitivity against 92% of *S. aureus*, while Clindamycin exhibited sensitivity in 67% of cases. Among *E. coli* isolates, 81% displayed sensitivity to Imipenem, 69% to aminoglycosides, and 31% to quinolones.

Multidrug resistance is a significant challenge across various nations, characterized by the diverse array of resistance mechanisms exhibited by bacterial strains [3]. The estimated prevalence of AMR among DFI pathogens in Ethiopia is 92% [4]. The presence of extended-spectrum beta-lactamase (ESBL) was identified in 52.6% of *Enterobacteriaceae* isolates, with the blaCTX-M gene being the most prevalent (90%), followed by blaTEM (65%) and blaSHV (35%) [5]. Similarly, a study conducted in Egypt showed that 78 out of the 82 isolates (95%) tested were multidrug resistant organism [5]. The prevalence of AMR among pathogens causing DFI in Iran is estimated to be 48.4%. A study reported that 37.5% of *Enterococcus spp*. were identified as Vancomycin-resistant (VRE), 48.8% of *Staphylococcus spp*. exhibited methicillin resistance (MRSA), 77.8% of isolated *E. coli* demonstrated extended-spectrum beta-lactamase (ESBL) production, and 66.7% of isolated *Pseudomonas* strains showcased multidrug resistance (MDR) [10]. In Jordan, over 75% of *E. coli* and *P. aeruginosa* isolates were resistant to Ampicillin, Cefotaxime, Ceftazidime, and Ertapenem. Among the *E. coli* and *P. aeruginosa* tested, Imipenem was effective against all strains, while Gentamicin and Sulfamethoxazole-trimethoprim were effective against 87.5% of *P. aeruginosa* and 75% of *E. coli*, respectively. As for MRSA, almost 50% of the isolates were resistant to aminoglycosides, fluoroquinolones, and macrolides, while all were susceptible to Vancomycin, Mupirocin, and Linezolid with the exception of one isolate found to be Vancomycin resistant [6].

3. Microbiology of DFU infections

Diabetic foot infection (DFI) is a common and serious complication of diabetes mellitus. It occurs when the protective skin barrier is compromised, allowing pathogens to proliferate in the soft tissues. Depending on the severity, DFIs are classified into mild, moderate, and severe cases. These infections are typically polymicrobial, involving Gram-positive cocci like *Staphylococcus aureus*, MRSA, *Enterococcus spp*, and *Streptococcus spp.*

3.1 Gram-positive bacteria

3.1.1 Staphylococcus aureus

Staphylococcus aureus is a coagulase positive cocci arranged in tetrads and clusters, resembling a bunch of grapes when viewed under a microscope. It is a facultative

anaerobic bacteria [12]. *S. aureus* is known for its aggressive nature in complicating diabetic foot wounds. It accounts for 20–25% of all isolated bacteria in patients with diabetic foot infections (DFIs), making it the most prevalent bacterial pathogen associated with DFIs in Occidental countries [13, 14].

3.1.1.1 Virulence factors of S. aureus

S. aureus produces wide range of virulence factors including various toxins and degrading enzymes as shown in **Figure 2**.

Coagulase: Clinical isolates of the human pathogen *Staphylococcus aureus* produce coagulase (*Coa*), a crucial enzyme for pathogenesis. Coagulase, existing in two forms - bound coagulase (clumping factor) and free coagulase, serves as a virulence factor by interacting with the host's blood-clotting system. Bound coagulase binds to

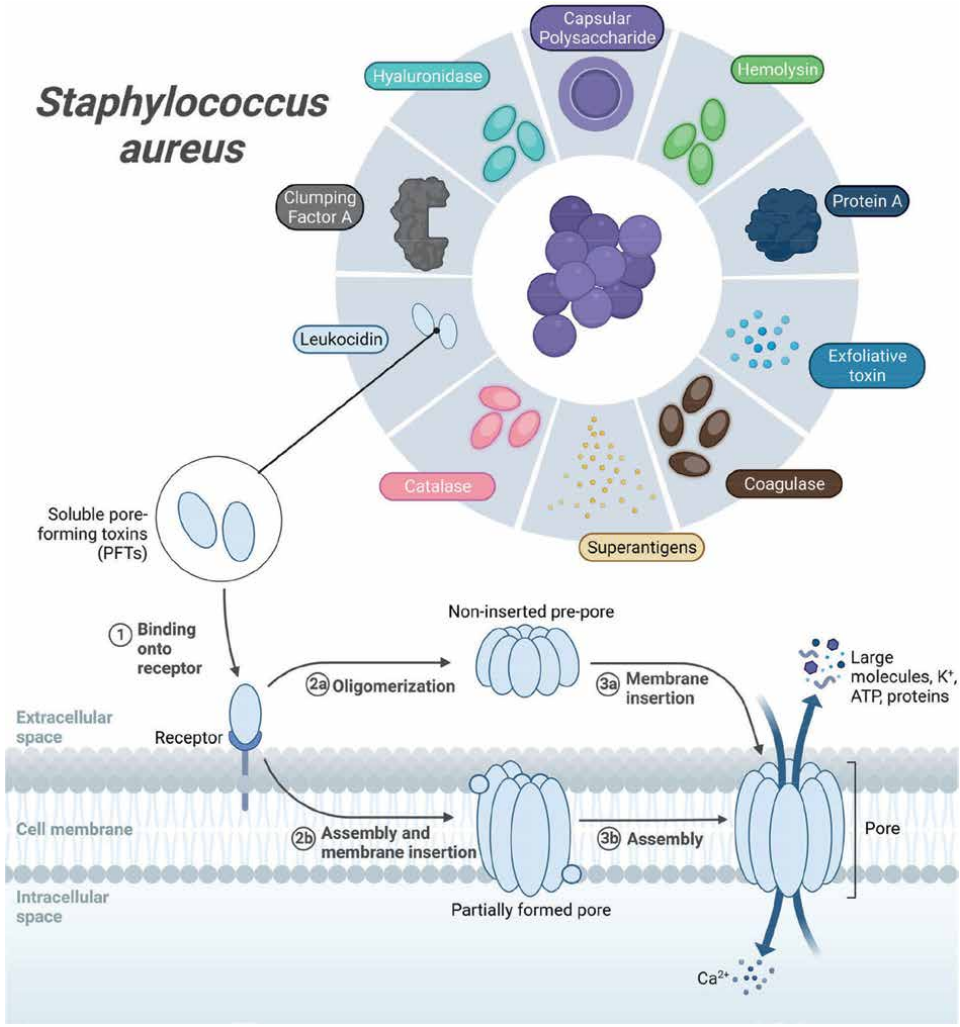

Figure 2.
Schematic depicting Staphylococcus aureus *virulence factors and mechanism of action for soluble pore-forming toxin leukocidin.*

host proteins, notably fibrinogen, leading to cell aggregation and evasion of phagocytosis by immune cells [15]. Additionally, it triggers fibrinogen conversion to fibrin, promoting blood clot formation that shields the bacterium from the host's defenses and antibiotics. Free coagulase directly activates prothrombin, further enhancing blood clot formation and aiding the bacterium in evading host defenses, facilitating localized infections [16].

Panton-Valentine leukocidin (PVL) comprises two distinct protein components, LukS-PV (slow) and LukF-PV (fast), which are chromatographically separate. These proteins collectively form a highly potent cytotoxin. The active toxin functions by creating pores in the membrane of neutrophils, leading to their lysis. Strains carrying PVL can cause chronic soft skin tissue infections (SSTI) and necrotizing pneumonia, even in healthy individuals. Studies have shown that isolates carrying the gene responsible for PVL production can exacerbate wound conditions. Nonetheless, PVL-encoding strains are relatively rare, with less than 10% of methicillin-sensitive *S. aureus* (MSSA) clinical isolates found to possess the PVL gene in the community [17].

α-toxin: Among different types of hemolysins (α-, β-, γ-, and δ-) encoded by *S. aureus*, α-hemolysin is the most extensively studied [18]. It is a pore forming toxin, produced by most *S. aureus* strains, that can cause host cell lysis. It is regulated by multiple global regulatory loci, including the accessory gene regulator, the Staphylococcal accessory gene regulator, and the Staphylococcal accessory protein effector, which control its expression in vitro [19]. It acts on a wide range of cells, but mainly on red blood cells and leukocytes [14]. Several studies have shown that *S. aureus* USA300 α-hemolysin contributes to severe infections, including pneumonia, osteomyelitis, and bacteremia [18].

Exfoliative toxins: The primary cause of Staphylococcal scalded skin syndrome (SSSS) is attributed to exfoliative toxins A (ETA) and B (ETB), which function as epidermolytic proteases. This syndrome is characterized by fever and widespread rapid skin desquamation, without affecting mucosal tissues [20]. The study conducted by Dunyach-Remy et al. (2016) mentions that exfoliative toxins A (ETA), B (ETB), and D (ETD) are linked to human infections. The distribution of these toxins varies among clinical grades of DFU infections, being more common in Grade 4 (13.8%) compared to Grade 1 (4%) or Grades 2–3 (3.5%). However, they do not follow a similar representation pattern across different grades [14].

Enterotoxin: Superantigens, which include Staphylococcal enterotoxins (SEs), Staphylococcal enterotoxin-like toxins (SEls), and toxic shock syndrome toxin 1 (TSST-1), can cause an excessive production of cytokines, resulting in cell apoptosis by mechanisms that are not yet fully understood. Among these superantigens, the most studied is the toxic shock syndrome toxin 1 (TSST-1), responsible for inducing toxic shock syndrome (TSS) [14]. In complicated DFUs, most *S. aureus* strains produce superantigens (Sags), particularly SEs and SEls. These toxins activate T cells, leading to the production of cytokines and causing a state of chronic inflammation, this chronic inflammation delays the wound healing process in DFIs.

3.1.1.2 Pathogenesis of S. aureus

Attachment and Adhesion: The initial event in diabetic foot infections is the attachment of *S. aureus* to surface components, including fibrinogen, fibronectin, and epidermal keratinocytes [14]. The adhesion of *S. aureus* to diabetic foot ulcer surfaces relies on the expression of microbial surface components recognizing adhesive matrix

molecules (MSCRAMMs) [14], such as clumping factor A (CIfA) and clumping factor B (CIfB) [21]. Both proteins are present on the surface of *S. aureus* and are covalently anchored to the cell wall peptidoglycan layer. They bind to fibrinogen using variants of the 'dock, lock and latch' (DLL) mechanism. For docking, the described clumping factors has two subdomains called N2 and N3. These two subdomains are positioned in a particular configuration that forms a groove between them, providing a docking site for ligands. For locking, ligand docking causes a change in the shape of the protein called DEv-IgG, specifically in the N3 subdomain. The N3 subdomain has an extension that is normally disordered, but ligand docking causes this extension to move and interact with the ligand, effectively locking it in place. For latching, the resulting change in shape facilitates the formation of an extra beta-strand referred to as the G" beta-strand within the C-terminal region of the N3 extension. This newly formed beta-strand aligns itself with the E beta-strand located in the N2 subdomain which results in a "latch" that serves to enhance the stability of the DEv-IgG-ligand complex even further [21].

Invasion: Fibronectin-binding proteins A and B (FnBPA and FnBPB) mediate *S. aureus* invasion into epithelial and endothelial cells [18]. *S. aureus* is capable of invading osteoblasts, fibroblasts, and endothelial cells, forming small-colony variants (SCVs) within the intracellular compartment. SCVs enable the bacteria to survive in a metabolically inactive state while preserving the integrity of the host cell [14]. FnBPs have high affinity fibronectin-binding repeats that at least one of them is required for internalization of the bacteria into the cells. For example, arginine–glycine–aspartate sequence is one of these sequences, when FnBPs bind to fibronectin, α5β1 integrin recognizes them, so it clusters on the host cell surface, this triggers the activating of an intracellular signaling cascade that ends up with endocytosis of bacterial cells [21].

Evasion: One of the main mechanisms by which *S. aureus* evades the host immune response is protein A mediated. *S. aureus* protein A binds to the Fc region of IgGs leads to disorientation of the IgGs coating the bacterial cell, this prevents not only neutrophil receptors recognition of the bacteria but also classical pathway activation of the complement system [21].

Other virulence factors: *S. aureus* possesses various virulence factors involved in soft tissue and bone infections. It can secrete toxins leading to tissue necrosis. It also can secrete glycocalyx, which starts after adhesion, forming a crucial component for 'biofilm' development [14].

3.1.1.3 Antimicrobial sensitivity profile

In a study conducted by Mamdoh et al. in 2023, *Staphylococci* demonstrated a significant level of resistance to amoxiclav, cefoxitin, and oxacillin. Although, most *Staphylococci spp*. exhibited susceptibility to linezolid, chloramphenicol, and rifampicin [22]. Another study conducted in 2022, Woldeteklie et al. found a high resistance in *S. aureus* to methicillin, with 81.3% (26/32) identified as MRSA, and 18.7% (6/32) were MSSA [23]. This study reported that 50% of the screened MRSA isolates were sensitive to amikacin and chloramphenicol. While previously done reports showed MSSA's susceptibility to Clindamycin, Vancomycin, and Ciprofloxacin, the findings of Woldeteklie et al.'s study remain consistent with studies conducted in Ethiopia, Egypt, and Sudan.

Methicillin-resistant *S. aureus* (MRSA) strains resist not only all β-lactam antibiotics but also a wide range of other antimicrobials, leading to a challenging management of MRSA infections Ceftaroline and Ceftobiprole are the only cephalosporins that inhibit PBP2a, making them effective against MRSA skin and skin structure infections [24].

There are two major types of MRSA infections: hospital-acquired ([HA]-MRSA) and community-acquired MRSA (CA-MRSA). Individuals with diabetes face an increased risk of contracting both variants due to their high susceptibility of developing sores and ulcerations [12]. MRSA tends to be more frequently isolated from patients with a history of hospitalization or residing in chronic care facilities, those who have recently undergone antibiotic treatment or individuals who have had a previous amputation [12, 14].

3.1.2 Enterococcus spp.

Enterococci are Gram-positive cocci that can survive in both aerobic and anaerobic environments, forming short to medium chains [25]. *Enterococci*, are typically found in the gastrointestinal tract as commensal organisms, but can cause various infections, such as urinary tract infection, bacteremia, and endocarditis [26]. DFIs with *Enterococci* were found to involve not only a polymicrobial infection but also showed positive associations with extended-spectrum β-lactamase (ESBL)-producing Gram-negative organisms and anaerobes. Conversely, DFIs with *Enterococci* were negatively associated with methicillin-susceptible or methicillin-resistant *S. aureus* and other *Streptococci* [27].

3.1.2.1 Virulence factors and pathogenesis

Aggregation substance (Agg): Formation of large aggregates has been shown to contribute to *E. feacalis* pathogenesis in an in vivo evidence. Agg that is present on the surface of the enterococcal cells is a pheromone-inducible surface glycoprotein, which means that it is produced in response to specific chemical signals. Agg is a multifunctional factor that contributes to the pathogenicity and adaptability of *E. faecalis* by multiple mechanisms. Firstly, evasion of host immune response. Agg has the ability to promote bacterial aggregation, which means that it encourages individual bacterial cells to come together and form clusters or aggregates. When these *Enterococc*i cells aggregate, it increase the hydrophobicity of their cell surfaces which leads to the localization of cholesterol to phagosomes [28]. This cholesterol localization is believed to interfere with or delay the fusion of phagosomes with lysosomes, where bacteria are typically broken down. This delay may help *E. faecalis* evade the host's immune defenses and persist within host cells, potentially leading to infections that are challenging to eliminate [28]. Secondly, Agg aids in plasmid transfer, a vital mechanism for the exchange of genetic material among bacteria. This genetic exchange can contribute to the acquisition of new traits, including antibiotic resistance, enhancing the bacterium's adaptability and survival in various environments. Thirdly, Agg assists *E. faecalis* in adhering to a wide range of eukaryotic surfaces, such as those found in host tissues. This adhesive property can promote colonization within the host, potentially leading to infections [28].

Extracellular surface protein (Esp): esp gene is believed to play a multifaceted role in bacterial pathogenicity. It contributes to adhesion, colonization, and evasion of the host immune system, while also being implicated in antibiotic resistance to Ampicillin, Ciprofloxacin and Imipenem, as demonstrated by research conducted by Foulquie Moreno et al. in 2006 [28]. Additionally, Esp plays a crucial role in the formation of enterococcal biofilms, which confer resistance to environmental stresses and facilitate adhesion to eukaryotic cells, such as those found in the urinary tract [28].

Cytolysin: It exhibits β-hemolytic properties when in contact with human red blood cells, causing them to rupture. The genes that code for cytolysin production are located on plasmids. The production of cytolysin is regulated by a quorum-sensing mechanism. This communication involves a two-component system, which consists of two proteins that work together to detect the presence of other bacteria and activate cytolysin production. The cylLs group of genes are part of the cytolysin operons, which are clusters of genes that work together to produce cytolysin. These genes are non-regulatory, which means that they do not control the production of cytolysin but are necessary for its function. Clinical isolates of *Enterococcus* species have a higher incidence of cylLs genes compared to food isolates, which suggests that these genes may be important for causing disease in humans [28].

Hyaluronidase: Hyaluronidase is an enzyme that acts on hyaluronic acid, a component of connective tissue, and it functions as a degradative enzyme. This enzyme is associated with tissue damage because it depolymerizes the mucopolysaccharide part of connective tissue. By breaking down hyaluronic acid, hyaluronidase facilitates the spread of *Enterococci* bacteria, as well as their toxins, through host tissue. This enzymatic action makes it easier for the bacteria to move within the host and potentially cause infections [28].

3.1.2.2 Antimicrobial sensitivity profile

In a multicenter study conducted in selected Hospitals in Addis Ababa, Ethiopia, all *Enterococcus* species exhibited resistance to Oxacillin, Penicillin, Cefoxitin, and Bacitracin. Moreover, a high level of resistance was observed among all *Enterococcus* isolates to Gentamycin, Doxycycline, Erythromycin, and Cotrimoxazole and it was found that all isolated *Enterococcus* strains exhibited sensitivity to Chloramphenicol (100%). However, two out of four *Enterococcus* species (50%) were resistant to Vancomycin [4]. Interestingly, no association was found between previous hospitalization within the last 6 months and antibiotic treatment within the last 3 months before admission with a higher prevalence of *Enterococcal* infection [27].

3.1.3 Streptococcus pyogenes—*group a streptococcus (GAS)*

Streptococcus pyogenes is a Gram-positive, β-hemolytic bacteria. Bacterial cells are sphericaland usually occur in chains. Complicated skin and skin structure infections (cSSSIs) encompass a range of infections, with major abscesses and diabetic foot infections (DFIs) being the predominant subtypes. *S. pyogens* and *aureus* are the primary causative agents responsible for cSSSIs [29].

3.1.3.1 Virulence and pathogenesis

Virulence factors: It possesses several virulence factors that contribute to its pathogenicity. Some of the main virulence factors of *S. pyogenes* include M Protein, which is a cell surface protein that helps the bacterium evade the host immune system by inhibiting phagocytosis. It also plays a role in adherence to host cells. *S. pyogenes* produces two types of hemolysins streptolysin O (SLO) and streptolysin S (SLS). These toxins can damage host cells and contribute to tissue destruction. Hyaluronic Acid Capsule expressed by some strains of *S. pyogenes* helps the bacterium evade the immune system by mimicking host tissues. In addition, streptokinase is an enzyme produced by the bacterium that can activate plasmin, leading to the breakdown of blood clots,

which facilitate the spread of the infection. Streptococcal Cysteine Protease (SpeB) is another virulence factors that can degrade host proteins, aiding in tissue invasion and immune evasion. Streptococcal Pyrogenic Exotoxins (SPEs) are superantigens produced by some strains of *S. pyogenes* that can cause an excessive immune response, leading to conditions such as scarlet fever and toxic shock syndrome. These virulence factors work together to help *S. pyogenes* evade the host immune system, adhere to host tissues, invade and damage host cells, and cause a range of diseases, including pharyngitis (strep throat), skin infections, and more severe conditions like necrotizing fasciitis and streptococcal toxic shock syndrome [30].

Adherence and invasion: the bacteria adhere to host epithelial cells, including those of the skin. It binds to host extracellular matrix proteins (fibronectin) mainly via fibronectin binding proteins, which is reported to be an adhesion and invasion factor [31].

Immune evasion: *S. pyogenes* evades the immune system via inactivating the human complement system by cleaving C3 and C3b, which acts as an opsonin, by several proteases it possesses. It also has been reported that a protein on the surface of *S. pyogenes*, identified as GAPDH, binds to human C5a and enhances C5a cleavage on the bacterial surface. When C5a is cleaved, its activity is hindered, thereby inhibiting its function as a chemotaxin. One more mechanism this bacterium employs to evade the immune system is by binding to C6, which contributes to inhibiting the membrane attach complex polymerization [31].

3.1.3.2 Antimicrobial sensitivity profile

In a multicenter study conducted in selected Hospitals in Addis Ababa, Ethiopia, *all S. pyogenes* and *Streptococcus viridans* species were sensitive to the majority of antimicrobial agents [4].

3.1.4 Clostridium spp.

Clostridium species are a group of Gram-positive anaerobic bacteria, marked by their rod-shaped vegetative form, particularly when reproducing. In diabetic patients, *Clostridium spp,* specifically *C. perfringens*, take an active role in the development and succession of complications associated with diabetic foot infections and ulcers [32].

3.1.4.1 Virulence factors and pathogenesis

Agr-like Quorum Sensing system: *C. perfringens* employs density-sensing quorum sensing (QS) systems as a mechanism to regulate the production of virulence factors [33]. The most crucial of these QS systems is the Agr-like system, identified for controlling the production of CPA and PFO toxins [34]. This system is vital for *C. perfringens* in causing gas gangrene [35]. Additionally, the Agr-like QS system plays a significant role in biofilm formation by *C. perfringens*, which may have implications in infections, although this is not definitively proven [33].

Biofilms: *C. perfringens* can complicate DFI through the formation of biofilms [33]. In a mouse model of type 2 diabetes, *E. coli*, *B. fragilis*, and *C. perfringens* collectively formed a polymicrobial biofilm and demonstrated a synergistic effect on each other. This synergistic interaction resulted in an increased mortality rate among the type-2 diabetic mice compared to those who received an inoculation of single bacterial strains [36].

Toxins: C. perfringens has a significant capacity to produce a wide array of toxins, leading to the development of histotoxic, enteric, and/or enterotoxemic diseases. The production of these toxins varies considerably among different strains of *C. perfringen* [37]. While not specified in the literature, it is thought that the more significant toxins in the context of DFU are *C. perfringens* Alpha Toxin (CPA) and Perfringolysin O (PFO).

C. perfringens Alpha Toxin (CPA): CPA is an enzyme capable of degrading phosphatidylcholine and sphingomyelin found in cell membranes leading to membrane disruption [33, 38]. It has the ability to hinder the movement and development of neutrophils while also triggering the arachidonic acid metabolism process. This metabolic pathway ultimately results in vasoconstriction and the aggregation of platelets. As a result, this toxin establishes a localized environment characterized by limited tissue blood flow and a compromised innate immune response [33, 38]. In addition, lethal levels of CPA can lead to significant degradation of the plasma membrane and the subsequent release of lactate dehydrogenase (LDH), which is a hallmark of necrotic cell death [37, 39]. Therefore, CPA is the critical virulence factor contributing to gas gangrene, also known as clostridial myonecrosis [37].

Perfringolysin O (PFO): also known as theta toxin, is produced by most *C. perfringens* strains except type F strains. PFO belongs to the cholesterol-dependent cytolysins family and is a pore-forming toxin (PFT) [33]. It has four domains, with the fourth domain in the C-terminal region containing three loops responsible for binding to cholesterol on target cells. This high-affinity binding to cholesterol allows PFO to concentrate on the plasma membrane, leading to toxin oligomerization and pores formation. Large pores disrupt plasma membrane integrity, leading to cell lysis through a colloid osmotic mechanism [40].

Adhesins: It has been suggested that collagen adhesion protein (CNA) and fibrinogen-binding proteins FbpA and FbpB act as adhesins in the context of various diseases mediated by *C. perfringens* [33]. While CNA plays a role in enteritis, fibronectin (Fn) is as a possible extracellular matrix glycoprotein used by *C. perfringens* for binding. In the presence of Fn, *C. perfringens* can use FbpA and FbpB to adhere to collagen, particularly types II and III. *C. perfringens* may exploit Fn to facilitate contact with host cells and enhance colonization [33].

Degradative Enzymes: *C. perfringens* secretes a wide range of extracellular enzymes with degradative properties, including proteases such as clostripain, hyaluronidase (mu toxin), collagenase, and endoglycosidases. The role of these enzymes in *C. perfringens* virulence is still investigated in research. It has been recently shown that the endo-N-acetylgalactosaminidase (EngCP), which is an enzyme that has a role in tissue degradation, is significant in gas gangrene induced by type A strains [33, 41].

3.1.4.2 Antimicrobial sensitivity profile

Resistance to Lincomycin and Clindamycin was noticed among strains of all *Clostridia* species as well as to Tetracycline and Doxycycline among strains of *C. perfringens* [42].

3.2 Gram-negative bacteria

Diabetes Miletus patients are susceptible to developing diabetic foot ulcers which can be exacerbated by vicious infections that are accompanied by peripheral neuropathy, changes in foot architecture, and trauma. In addition to these diabetic complications, pathogenic infections also dictate disease management and affect

quality of life [43, 44]. A major class of bacteria involved in DFU infections are Gram-negative bacteria classifying the infections by their causative agents is crucial for appropriate management and treatment of diabetic patients' wounds. Most common Gram-negative bacteria include *Pseudomonas aeruginosa, Escherichia coli, Klebsiella species,* and *Proteus species.* Their prevalence differs according to geographical region [45–47].

3.2.1 Pseudomonas aeruginosa

Pseudomonas aeruginosa is a Gram-negative, encapsulated, facultative-aerobic, bacilli-shaped opportunistic pathogen. *P. aeruginosa* can cause infections in patients with cystic fibrosis, burn wounds, immunodeficiency, chronic obstructive pulmonary disorder (COPD), cancer, and healthcare-acquired infections such as ventilator-associated pneumonia [48]. *P. aeruginosa* also causes diabetic foot ulcer infections [47].

3.2.1.1 Virulence factors and pathogenesis

P. aeruginosa possesses various virulence factors that enables biofilm formation and successful initiation of infection (**Figure 3**). The main virulence factors are briefly described herein.

Lipopolysaccharides (LPS): LPS is a major component of the outer membrane of *P. aeruginosa* and plays a critical role in protecting the bacterial cell from host defenses and environmental stresses. However, the lipid A component of LPS is highly endotoxic and can cause tissue damage, inflammation, and sepsis [49]. It is a potent activator of the host immune response, triggering the release of pro-inflammatory cytokines and chemokines. However, *P. aeruginosa* can modify its LPS structure to

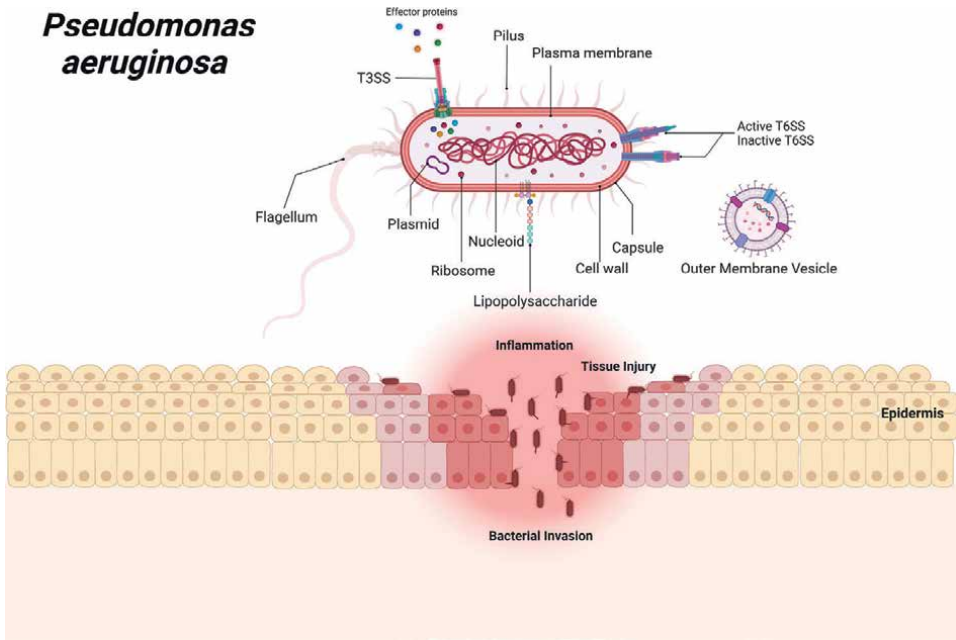

Figure 3.
Schematic depicting Pseudomonas aeruginosa *virulence factors.*

evade host immune recognition and develop antibiotic resistance [50]. For example, *P. aeruginosa* can add a positively charged amino arabinose moiety to its LPS, which reduces its negative charge and decreases it's binding to cationic antimicrobial peptides and complement proteins [51]. This modification also reduces the activation of TLR4 and the downstream immune response. LPS is also involved in bacterial adherence to host cells and biofilm formation [52].

Adherence factors: P. aeruginosa produces several adherence factors, such as pili and flagella, which enable the bacteria to attach to host cells and surfaces. Pili are hair-like structures that extend from the bacterial surface and can mediate attachment to host cells and biofilm formation. Flagella are whip-like structures that enable the bacteria to move toward nutrients and host cells. *P. aeruginosa* is characterized by a single unipolar flagellum that beats, granting the pathogen motility in pathogenesis [53].

Exotoxin A: Exotoxin A is a potent virulence factor of *P. aeruginosa* that can inhibit protein synthesis in host cells and cause tissue damage. Exotoxin A is a type of AB toxin that consists of two subunits: the enzymatic A subunit and the binding B subunit. The B subunit binds to host cell receptors, and the A subunit is internalized and cleaves elongation factor 2 (EF-2), a critical component of protein synthesis machinery. This results in inhibition of protein synthesis and cell death [54].

Deoxyribonuclease: DNase is an exoenzyme produced by *P. aeruginosa* that can degrade extracellular DNA, which can be released by host cells during tissue damage or by bacterial cells during biofilm formation. DNase can degrade extracellular DNA and promote bacterial dissemination and evasion of host immune responses. DNase can also modulate host immune responses by degrading neutrophil extracellular traps (NETs), which are web-like structures composed of DNA and antimicrobial proteins that can trap and kill bacteria. By degrading NETs, DNase can enable *P. aeruginosa* to evade host immune defenses and cause persistent infections [55].

Proteases: P. aeruginosa secretes a variety of proteases, such as elastase and alkaline protease, which can degrade host tissues and proteins and promote bacterial dissemination. Elastase is a zinc metalloprotease that can cleave elastin, collagen, and other extracellular matrix proteins. Alkaline protease is a serine protease that can degrade a wide range of host proteins, including immunoglobulins, complement factors, and cytokines [56].

Quorum sensing: Quorum sensing (QS) allows *P. aeruginosa* to coordinate the expression of virulence factors and biofilm formation in response to population density. This enables *P. aeruginosa* to form complex communities and persist in various environments, including host tissues. QS in *P. aeruginosa* is mediated by several autoinducers, such as N-acyl homoserine lactones (AHLs), which are synthesized and detected by the Las and Rhl systems [57]. Quorum sensing also regulates the production of elastase, alkaline protease, and exotoxin A, which are involved in host tissue damage and immune evasion. Inhibition of quorum sensing has been shown to reduce *P. aeruginosa* virulence and improve host survival in animal models [58, 59].

Two-component systems: Two-component systems are ubiquitous signaling regulators that play vital roles in bacterial survival, metabolism, and virulence. They allow *P. aeruginosa* to sense and respond to various environmental cues, such as pH, osmolarity, and antibiotic [60]. This enables *P. aeruginosa* to adapt to different host niches and develop antibiotic resistance. Two-component systems also regulate the expression of virulence factors including siderophores production such as pyocyanin, pyoverdine, and pyochelin, which are involved in host tissue damage and immune evasion [61]. Targeting two-component systems has been proposed as a potential strategy to control *P. aeruginosa* infections.

Secretion systems: *P. aeruginosa* has several secretion systems, such as the type III and type VI secretion systems, which can deliver effector proteins into host cells and modulate host immune responses. The type III secretion system (T3SS) is a needle-like structure that can inject effector proteins directly into host cells. The T3SS can modulate host cell signaling pathways and promote bacterial survival and dissemination. T3SS, like exoenzyme S also plays a role in the inhibition of wound repair in diabetic skin ulcers [62]. While T6SSs allow *P. aeruginosa* to deliver effector proteins into target cells, such as host cells and competing bacteria. This enables *P. aeruginosa* to manipulate host cell functions and compete for resources in various environments. T6SSs are involved in host tissue damage, immune evasion, and inter-bacterial competition [56]. The functional roles of some T6SSs are still unclear due to the limited substrates available for research.

Pyocyanin pigment and Pyoverdine siderophore: Pyocyanin and pyoverdine are two important virulence factors produced by *P. aeruginosa* and play significant roles in virulence and pathogenicity. Pyocyanin is a blue-green, water-soluble pigment that can cause oxidative damage. It generates reactive oxygen species (ROS) within host tissues, leading to tissue damage and inflammation. Pyocyanin also impairs the function of immune cells, including neutrophils and macrophages, making it more difficult for the host to mount an effective immune response against the infection. Pyocyanin also contributes to the formation and maintenance of biofilms, which are complex communities of bacteria encased in a protective matrix [63].

Pyoverdine is a siderophore, which is a molecule secreted by bacteria to scavenge iron from the host environment. It is a high-affinity iron-chelating compound with a characteristic fluorescent yellow-green color. Pyoverdine allows *P. aeruginosa* to acquire iron from the host, even in iron-restricted environments. This gives the pathogen a competitive advantage over the host in obtaining this essential nutrient [64].

Outer membrane vesicles (OMV): OMVs are small spherical structures released by *P. aeruginosa* that contain various bacterial components, including lipids, proteins, and nucleic acids. OMVs are involved in various bacterial functions, such as inter-bacterial communication, virulence, and host immune evasion [65]. OMVs are involved in *P. aeruginosa* virulence and host immune evasion by delivering virulence factors and toxins to host cells and modulating host immune responses. They can also be engineered to express specific antigens or drug molecules, which can be delivered to host cells and induce immune responses or kill bacterial pathogens [66].

3.2.1.2 Antimicrobial sensitivity profile

P. aeruginosa exhibits a high degree of resistance to a broad spectrum of antibiotics including Aminoglycosides, Piperacillin-Tazobactam, and Carbapenems [67]. Antimicrobial susceptibility of *P. aeruginosa* strains exhibited a varying degree of resistance to the antibiotics as described [68]. Multidrug resistance for about 8–11 antibiotics was observed among 55.5% of the isolates. Disk diffusion results show 100% resistance to Ampicillin, Cefoperazone, Erythromycin, Norfloxacin, and only Ceftazidime, Ciprofloxacin exhibited greater activity against *P. aeruginosa* [69]. However, some virulence factors have been linked to antibiotic resistance in specific strains. Pigment production was significantly associated with Ceftazidime susceptibility, phospholipase C production was significantly linked to sensitivity to Cefepime, and DNase production was significantly associated with intermediate resistance to Meropenem. When investigating alginate and the biofilm produced, Ambroxol showed a high anti-biofilm activity against it [70].

3.2.2 Escherichia coli

Escherichia coli (*E. coli*) is a Gram-negative, rod-shaped, facultative anaerobic bacteria. Non-pathogenic *E. coli* is considered the normal flora in the gastrointestinal tract. In diabetic foot ulcer infections, *E. coli* has been shown to be the leading cause of gram-negative diabetic foot infections in Tehran [71]. In some cases, *E. coli* may gain access to diabetic foot ulcers from urinary tract infections (UTIs), especially in patients with comorbid urinary problems.

3.2.2.1 Virulence factors and pathogenesis

Adhesins: *E. coli* can produce different types of adhesins such as type 1 fimbriae, P fimbriae, S fimbriae, and afimbrial adhesins that help in colonizing and attaching to the host cells [72, 73].

Iron-acquisition systems: *E. coli* can produce different types of iron-acquisition systems such as siderophores, hemophores, and iron-regulated outer membrane proteins that help in acquiring iron from the host cells. Siderophores are small molecules that can chelate iron and transport it into the bacterial cells. *E. coli* can produce different types of siderophores such as enterobactin, aerobactin, and yersiniabactin [74]. Hemophores are proteins that can bind to heme and transport it into the bacterial cells. *E. coli* can produce different types of hemophores such as HxuA and ChuA [75]. Iron-regulated outer membrane proteins are porins that can regulate the influx of iron into the bacterial cells. *E. coli* can produce different types of iron-regulated outer membrane proteins such as FepA and CirA [76]. Iron is an essential nutrient for bacterial growth and survival, and its acquisition can help in bacterial pathogenesis.

Capsule: *E. coli* can produce different types of capsules that help in evading the host immune system [77].

3.2.2.2 Antimicrobial sensitivity profile

E coli was found to be most susceptible to Meropenem, and least susceptible, meaning more resistant to Ciprofloxacin [46]. Other study found that the most prevalent antibiotic resistance pattern for *E. coli* was observed for ampicillin, Cotrimoxazole, and Ciprofloxacin [78].

3.2.3 Klebsiella species

Klebsiella is a Gram-negative, encapsulated, rod-shaped bacterium belongs to the *Enterobacteriaceae* family. It is an emerging pathogen in diabetic foot infections (DFIs) and has been reported to be the 3rd most prevalent Gram-negative bacteria in diabetic foot infections in Asian countries [79]. *Klebiella* has the ability to produce biofilms and its intrinsic resistance to various antibiotics contribute to its pathogenicity, which is challenging to treat [80].

3.2.3.1 Virulence factors and pathogenesis

Polysaccharide capsule: The capsule is a significant virulence factor that protects bacteria from phagocytosis and inhibits the host response. Several capsule types (K), especially K1, K2, K54, K57, K20, and K5, are commonly associated with the

pattern of community-acquired invasive pyogenic liver abscess, septicemia, and pneumonia. Moreover, K1, K2, K20, K54, and K57 are predominantly detrimental to experimental infections in mice and are frequently associated with severe infections in humans [81].

Endotoxin: Lipopolysaccharides (LPS) aka endotoxin is formed from lipid A, oligosaccharide synopsis, O antigens, and are known as endotoxins based on all Gram-negative pathogens, including *K. pneumoniae*. The outermost subunit based on LPS, O antigen, is the primary constituent faced by the innate immune system and protects bacteria against complement-mediated inflammation [82]. In particular, the O antigens bind to the complement protein C3b, which involves pore arrangement before mediating the perforation of host tissue. At present, it is not clear whether the LPS hvKP strain endotoxin activity has an individual role in hypervirulence [81].

Siderophore: Pathogenic bacteria require iron for their replication. Siderophores (iron carriers) are composites buried by microorganisms (similar to bacteria and fungi) to transport iron in the cell membranes. They bind iron with higher affinity than the host transport protein transferrin [83]. *K. pneumoniae* produces siderophores to gain iron from host iron-chelating proteins or the terrain for survival and reduplication during mammalian infection. Enterobactin, yersiniabactin, salmochelin, and aerobactin are different types of siderophores expressed by *K. pneumonia,* with the latter one enabling growth and survival of more virulent strains of the pathogen [84]. Further, *K. pneumoniae* has an iron-scavenging system that helps survival in iron-limited environments. In addition to production of siderophores production, the expression of iron-regulated outer membrane proteins (IROMPs) facilitates the uptake of iron from host proteins.

Adhesins: Adhesins are proteins that help bacteria to adhere to host cells and tissues. *K. pneumoniae* expresses several types of adhesins, including fimbriae, which are hair-like structures that help bacteria to attach to surfaces. Fimbria types 1 and 3 are crucial virulence factors contributing to biofilm formation in *K. pneumonia* [85].

3.2.3.2 Antimicrobial sensitivity profile

Klebsiella species are known for their ability to develop resistance to many antibiotics, especially in environments of chronic wound infections like diabetic foot ulcers. Yoga et al. mentioned that *Klebsiella pneumoniae* isolates were resistant to Ampicillin and Ceftazidime in 83 and 50% respectively [86].

3.2.4 Proteus species

Proteus is a Gram-negative, rod-shaped, aerobic and motile bacteria that belongs to the *Enterobacteriaceae* family. It is able to migrate across surfaces due its "swarming" characteristic [87]. In diabetic foot ulcers, *Proteus species* have been identified as one of the significant causative infective agents, particularly in polymicrobial infections [13]. *Proteus* species are well known to cause community-acquired infections, and urinary tract infections in nosocomial status.

3.2.4.1 Virulence factors and pathogenesis

Biofilms: *Proteus mirabilis* has the ability to form biofilms, which are communities of microorganisms that adhere to surfaces and are embedded in a self-produced

extracellular matrix. Biofilms protect bacteria from host defenses and antibiotics, making them difficult to eradicate [88].

Adhesion molecules: Adhesion virulence factors in *Proteus mirabilis* encompass a range of components crucial for its pathogenicity. One significant factor is the classical autotransporter, *Proteus* toxic agglutinin (pta), which functions as a serine protease and exhibits cytotoxic effects on bladder and kidney epithelial cells [89]. Additionally, fimbrial genes play a pivotal role in adhesion, with *P. mirabilis* possessing a diverse repertoire of at least 10 distinct fimbrial types that enhance its fitness during polymicrobial infections [90]. Furthermore, the flagellar cascade components contribute to *P. mirabilis*' motility, facilitating its adhesion to host tissues. In addition, cell wall features are also associated with biofilm formation, which is closely linked to adhesion in *P. mirabilis* [91].

Urease: *Proteus mirabilis* produces urease, an enzyme that hydrolyzes urea to produce ammonia and carbon dioxide. This increases the pH of the urine, leading to the formation of struvite and calcium phosphate stones, which can cause tissue damage and inflammation [92].

Proteases: *Proteus mirabilis* produces several proteases that can degrade host proteins, leading to tissue damage and inflammation [87]. One of the proteases secreted by *Proteus mirabilis* is the extracellular metalloproteinase. This metalloproteinase cleaves serum immunoglobulin A (IgA) [93], which is an important immunoglobulin for the body's defense against infections and pathogens. The cleavage of serum immunoglobulin A by the extracellular metalloproteinase produced by Proteus mirabilis can compromise the immune system's ability to neutralize and protect against invading microorganisms, contributing to tissue damage and inflammation [94].

Siderophores: *Proteus mirabilis* produces siderophores, which are small molecules that bind to iron and transport it into the bacterial cell. One of the main siderophores secreted by *Proteus mirabilis* is Proteobactin. the production of proteobactin allows the bacterium to scavenge and acquire iron from its environment, even when iron is limited. Proteobactin can bind to iron ions in the surroundings, forming a complex that the bacterium can then take up into the cell [95]. This ability to obtain iron is crucial for the bacterium's growth and survival, especially in iron-restricted conditions.

Toxins: *Proteus mirabilis* produces several toxins, including hemolysin and cytotoxic necrotizing factor, which can cause tissue damage and inflammation [87]. Hemolysin is a protein that can cause the lysis of red blood cells, leading to the release of hemoglobin and other cellular contents. This can cause tissue damage and inflammation and may contribute to the virulence of *Proteus mirabilis* [96]. Cytotoxic necrotizing factor is a protein that can cause cell death and tissue damage. It has been shown to induce apoptosis (programmed cell death) in various cell types, including epithelial cells and macrophages [97]. This can lead to tissue damage and inflammation and may contribute to the pathogenesis of *Proteus mirabilis*.

3.2.4.2 Antimicrobial sensitivity profile

Proteus isolates were found to be sensitive to Imipenem, Meropenem, and Amikacin, with some being sensitive and others being resistant to Ciprofloxacin and Gentamicin. However, tested isolated were found most resistant to Tetracycline, Ampicillin, Cefaroxin, Ceftixime, and Cefipime [98].

3.3 Non-bacterial infections (yeast/fungi)

3.3.1 Candida albicans

Candida albicans is a fungus (yeast) that is part of the human microbiota and present at different parts of human body, including the skin. This yeast can cause oral, vaginal, or dermal infections known as monilial thrush [99]. In a study conducted on a population in Delhi, *Candida spp* was identified as the most commonly isolated yeast from diabetic foot ulcers, with *Candida albicans* being reported as the most prevalent species [100].

3.3.1.1 Virulence and pathogenesis

The hallmark of *C. albicans* infections is biofilm formation [101]. This process can be summarized in the following steps:

Adherence: it begins with single fungal cells adhering to host substrate. Once the yeast cells have attached to the substrate, they start to multiply and form a layer of cells that serves as the foundation of the biofilm. This layer is called the basal yeast cell layer, and it provides a stable surface for the growth of additional layers of cells [101].

In addition, Quorum sensing, or cell-cell communication, is an important phenomenon in microbial biofilms, where cell density and secreted signaling molecules govern microbial behaviors [101]. Farnesol, a quorum-sensing molecule produced by *C. albicans* inhibits hyphal formation and promotes yeast cell formation, aiding in biofilm dispersal. At high concentrations, farnesol triggers apoptosis in *C. albicans* through oxidative stress and accumulation of reactive oxygen species [101].

3.3.1.2 Antifungal sensitivity profile

Although the highest susceptibility was observed in flucytosine and amphotericin B, *Candida* species in a study conducted at a tertiary hospital in Kenya demonstrated notable susceptibility to various antifungal agents, including voriconazole, micafungin, and fluconazole, while showing higher resistance to caspofungin. Among the *Candida* species, *C. albicans* exhibited resistance to several antifungal agents but remained susceptible to amphotericin B and flucytosine [102].

4. Polymicrobial infections

In complicated diabetes mellitus where DFU are more prevalent, polymicrobial infections are more common than mono-bacterial ones [45, 71, 103]. Polymicrobial infections can include bacterial and non-bacterial agents such as fungi or viruses, with bacteria being the most dominant infections [104]. The diverse bacteria present in these infections can synergistically enhance tissue damage, exacerbate inflammation, and impair the host immune response. Generally, DFU infections arise from skin microbiota, however the pathogenesis of these microorganisms chronically can create an environment for non-native bacterial infections [103]. It is difficult to predict the specific bacterial strains contributing to polymicrobial infection in DFU due to the variability in the bacterial composition and antimicrobial resistance patterns [103]. Chronic wound infections and ulcers often lead

to osteomyelitis. This obstacle in recognizing the causative agents and treating wounds urgently results in progression to deeper tissue ending with lower-limb amputations as a lifesaving measure [105].

5. Correlation between various pathogens and the severity of DFU

The pathogenesis of DFU as a polymicrobial disease involves various types of pathogens as previously discussed. Among the major factors contributing to the prognosis and complications of DFU, some pathogens have been shown to correlate with more severe manifestations of the disease as discussed below.

5.1 Gram-positive bacteria

Gram-positive bacteria, particularly *S. aureus*, are frequently implicated in mild and moderate infections corresponding to grades 1 and 2 on the Wagner scale measuring the severity of DFU. However, the genome of *S. aureus* found in cases of poor wound healing outcomes contained a number of genes responsible for antibiotic resistance and genes encoding staphylococcal enterotoxins leading to more severe stages of DFU [106]. An important gene is the agr type III agrABCD operon, which contains genes responsible for the AGR quorum sensing system, which produces autoinducing peptides (AIPs). This system plays a crucial role in regulating various aspects, including biofilm formation and the expression of virulence factors such as toxins and degradative exoenzymes. Clinically, a study conducted at a central Malaysian tertiary care hospital indicated that *Staphylococcus spp* infections are associated with major amputations [45]. In a similar manner, DFU patients infected with *Enterococci* exhibited a significantly higher in-hospital amputation rate (72%) compared to those with non-Enterococci infections (50%) [27]. Furthermore, DFIs caused by MRSA demonstrated a comparable level of infection severity to MSSA, with the notable exception of the α-toxin's heightened role in MSSA pathogenicity.

While various articles have presented evidence suggesting similar clinical presentations and outcomes between MRSA and other pathogens in DFIs, some authors maintain that MRSA detection in DFIs may still be associated with more severe infections [14]. In the realm of DFIs, experts continue to consider anaerobic bacteria as potential contributors to persistent and severe infections, even though their exact role in polymicrobial infections remains a subject of debate [107]. This is supported by studies indicating that anaerobic bacteria are often detected in DFIs characterized by deeper ulcers, chronicity, and associations with ischemia, necrosis, gangrene, or foul odor [108]. The presence of anaerobes may thus play a role in the severity and persistence of certain DFIs.

Additionally, *Clostridium* species presence is prominently linked to diabetic foot infection severity, indicated by severity-based grading of Wagner-Meggitt classification [109]. The presence of *Clostridium perfringens* for instance is found in mostly grade 5 diabetic foot ulcers [86]. This does not only reveal the seriousness of anaerobic infections but also highlights that their involvement is accompanied with more detrimental outcomes in DFU patients. Anaerobic infection, especially *Clostridium spp*, are present in more severe cases. As the Wagner-Meggitt classification grading advanced, there was a corresponding rise in the incidence of anaerobic pathogens.

Notably, ulcers infected with anaerobic pathogens displayed an extended healing duration compared to those infected with aerobic pathogens [110].

5.2 Gram-negative bacteria

In a study conducted at a tertiary hospital in central Malaysia, *P. aeruginosa* emerged as the primary contributor to amputations, and notably, a majority of amputee patients were male [45]. The severity of infections caused by this opportunistic pathogen was closely linked to the specific strain of *Pseudomonas* and its antibiotic sensitivity.

While *Escherichia coli* is not commonly associated with DFIs, surprisingly it was identified as the fourth most frequent Gram-negative bacterium in DFIs in central Malaysia. All *E. coli* infections resulted in major amputations, underscoring *E. coli's* aggressive capacity to infiltrate deep tissues, including bones, leading to osteomyelitis [45]. *E. coli* encompasses multiple strains, each exhibiting variations in virulence and antibiotic sensitivity. A study conducted in southern Iran reported that *E. coli* as the most prevalent infectious agent in DFIs leading to osteomyelitis [10].

Klebsiella infections are generally infrequent in DFUs. However, their occurrence often signals an immune-compromised state that allows *Klebsiella* species to invade DFU wounds. *Klebsiella* infections tend to be perilous and are typically associated with moderate to severe diabetic foot wound infections, as per the Infectious Diseases Society of America (IDSA) grading criteria [71].

Proteus species were found to be present across a spectrum of diabetic foot infections, encompassing mild, moderate, and severe cases, with varying prevalence rates. They were notably more prevalent in moderate to severe cases, corresponding to grades 3 and 4 of Wagner's DFU wound classification. Additionally, in some instances, the severity of infection was positively correlated with a higher prevalence of Proteus spp. isolates [71].

5.3 Fungi and other pathogens

A study conducted on Delhi population revealed a concerning association between chronic non-healing ulcers, which often lead to amputations, and an increasing prevalence of fungal infections [34].

6. The role of biofilms in chronic diabetic foot infection

Biofilms play an important role in developing antimicrobial resistance in diabetic foot infections. Biofilms provide a protective layer for bacteria, allowing them to survive antibiotic treatment. These complex communities produce extracellular polymeric substances (EPS) to create a symbiotic environment for bacteria to thrive in the nutrient-rich environment, triggering chronic inflammatory responses that further worsen the infection. Macrophages and neutrophils at the infection site release Reactive Oxygen Species (ROS) and proteases, which deteriorate biofilms. However, in chronic infections, neutrophils damage surrounding tissue, allowing bacteria to colonize further surrounding tissue. Various studies have shown that chronic inflammatory responses, like the over-expression of matrix metalloproteinases (MMPs) and inflammatory cytokines are associated with the chronicity of diabetic foot ulcers.

Lobmann et al. [111]. Demonstrated that MMP-1 levels were 65 times higher in chronic diabetic foot ulcers compared to normal healing ulcers. Furthermore, according to Mottola et al. [112], polymicrobial bacterial populations were found to produce larger biofilms than any individual bacteria.

7. Antimicrobial treatment of DFU

Empirical antibiotic treatment should be determined considering the infection's seriousness and the probability of resistant pathogens being involved. Once culture and susceptibility results are available, antibiotic therapy should be adjusted accordingly. However, it's not always essential to target every microorganism identified in cultures. Patients with non-infected ulcers should not be prescribed antibiotics. Instead, these patients typically benefit from localized wound management and

Recommended DFI Antimicrobial Regimen	
Prevention of infections	No antibiotic therapy is needed for prevention of diabetic foot infections
Mild infections	Start oral antibiotics with activity against gram-positive organisms. Prolonged antibiotic treatment (>14 days) is not recommended for mild soft tissue infections.
Moderate infections	Start antibiotics with activity against gram-positive and gram-negative organisms. Moderate infections: choose the route of administration based on the clinical situation and antibiotic choice.
Severe infections	Antibiotics with activity against gram-positive and gram-negative organisms. Begin treatment with intravenous antibiotics and then reassess based on the clinical situation.
Streptococci and *Staphylococci* (MSSA) infections	Cephalexin (500 mg every 6 hours) or Dicloxacillin (500 mg every 6 hours) or Amoxicillin-clavulanate (875/125 mg every 12 hours) or Moxifloxacin + Trimethoprim-sulfamethoxazole (2 double-strength tablets (trimethoprim 160 mg and sulfamethoxazole 800 mg per tablet) every 12 hours) or Ciprofloxacin or Levofloxacin + Clindamycin (300 to 450 mg every 6 to 8 hours)
Additional antibiotics *(in case MRSA coverage is warranted)*	Vancomycin or Linezolid (600 mg every 12 hours) or Daptomycin
Additional recommendations on dosing:	NICE recommends that patients with diabetes and osteomyelitis should be given prolonged antibiotic treatment (usually 6 weeks), taking into account local protocols IDSA recommends considering prescribing antibiotic therapy for a short duration only e.g. 2–5 days if there is no infected tissue remaining. However, prolonged antibiotics are recommended e.g. 6 weeks if there is persistent infected bone or necrosis.

Table 1.
Antimicrobial regimen for the treatment of DFU as recommended by the IDSA, NICE, and the National Guidelines in Qatar [113–115].

measures aimed at alleviating pressure at the ulceration site [113–115]. Diabetic foot infections treatment with antimicrobial usually depends on the severity of infections, whether mild, moderate, or severe, and the causative pathogens involved as detailed in **Table 1**.

Conflict of interest

The authors declare no conflict of interest.

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Chapter 4

Diabetic Foot Ulcer Neuropathy, Impaired Vasculature, and Immune Responses

Duaa Yousif, Zahra Yousif and Prakash Joseph

Abstract

Diabetic foot ulcers (DFUs) are a debilitating complication frequently observed in long-term diabetes patients. These ulcers are categorized into neuropathic, ischemic, and neuroischemic, with neuroischemia being the most prevalent. Subclinical inflammation plays a vital role in the development of diabetes complications, contributing to the severity of foot ulcers. Peripheral vascular disease and neuropathy are significant predisposing factors for DFUs. This chapter delves into the pathogenesis of DFUs, focusing on three key elements: neuropathy, impaired vasculature, and immune responses. Neuropathy in diabetes is induced by metabolic disruptions, such as hyperglycemia and advanced glycation end products (AGEs), resulting in structural and functional nerve impairments. It diminishes pain perception, increasing the risk of unnoticed injuries. Impaired vasculature, particularly atherosclerosis, plays a pivotal role in diabetic vascular complications. PKC, hyperactive metabolic pathways, and oxidative stress disrupt vascular function and contribute to atherosclerosis development, directly impacting the risk of DFUs. Immune responses within DFUs involve impaired macrophages, neutrophils, keratinocytes, and fibroblasts, which collectively hinder the healing process. Additionally, elevated glucose levels negatively affect endothelial cells, angiogenesis, and stem cells, further delaying wound repair. Understanding these intricate mechanisms is essential in developing effective interventions for preventing and treating DFUs in diabetes.

Keywords: diabetes, ulcer, neuropathy, ischemia, peripheral arterial disease, inflammation

1. Introduction

Diabetic foot ulcer is a disabling complication, and it is common in patients with long-term diabetes [1]. Etiology-wise, diabetic foot ulcers can be categorized as neuropathic, ischemic, or neuroischemic [1]. The current prevalence of each category is 35%, 15%, and 50%, respectively [1]. Therefore, the most common etiology of diabetic foot ulcers is neuroischemia. Furthermore, subclinical inflammation is a vital risk factor for the development of diabetes complications. Many studies have shown that foot ulcers and their severity are associated with a significant increase in acute-phase proteins, chemokines, and cytokines regardless of infections [2]. In addition, the presence of

peripheral vascular disease or neuropathy predispose patients with diabetes to the development of foot ulcers [3, 4]. The potential mechanisms responsible for DFUs have been the subject of growing research interest. Previous studies have specifically examined three key elements associated with DFUs: Neuropathy, impaired vasculature, and immune responses. This chapter will discuss the pathogenesis of diabetic foot ulcers in terms of neuropathy, vascular impairment, and immune responses.

2. Neuropathy

Diabetes goes beyond its well-known impact on blood sugar levels. Disturbed metabolic conditions in diabetes unleash a cascade of pathological alterations that extend their malevolent influence deep into the nervous system. This profound connection between diabetes and nerve health is a critical, yet often underappreciated aspect of this disease.

2.1 Pathological alteration in the nervous system in diabetes

Hyperglycemia and elevated levels of advanced glycation end products (AGEs) disrupt the integrity and functionality of nerve cells, leading to motor, sensory, and other functional impairments. Due to reduced pain perception, individuals with diabetes face a significantly higher risk of sustaining injuries, resulting in skin damage and ulcers that can go unnoticed for extended periods, both by the patients themselves and medical professionals [5]. AGEs, on one hand, induce alterations or loss of protein functions. On the other hand, when they bind to specific receptors known as RAGEs, they initiate changes in gene expression and facilitate intracellular signal transduction. This, in turn, leads to an increased production of inflammatory mediators and free radicals, which significantly disrupt the release and transportation of neuronal transmitters. Additionally, the excessive availability of substrates and a saturated delivery system cause the conversion of acetyl-CoA molecules into acylcarnitine. This conversion triggers a heightened stress response and mitochondrial dysfunction in Schwann cells and dorsal root ganglion (DRG) neurons, ultimately resulting in axonal degeneration. Consequently, irreversible damage is inflicted upon the nervous system of individuals with diabetes [6]. The primary signs of motor neuropathy in a clinical context include muscle wasting in the leg and foot, alongside the potential occurrence of motor weakness and a decrease in muscle reflexes. An early indicator of motor neuropathy is the impairment of the Achilles tendon reflex [7]. Autonomic neuropathy frequently leads to impaired regulation of blood vessels in the lower limbs, causing the formation of arteriovenous shunts within the cutaneous vascular network of the lower extremities [8]. Moreover, this type of neuropathy can disrupt sweat gland activity and raise blood circulation to the deeper layers of the skin, leading to elevated skin temperatures [9]. Irregularities in the sweat gland secretion within the skin can result in excessive evaporation of sweat, causing the foot skin to become dry. This further compromises the skin's natural protective ability, elevating the susceptibility to foot ulcers [10]. The simultaneous occurrence of sensory and motor peripheral neuropathies contributes to imbalanced pressure distribution on the foot and impaired walking patterns. Over a duration, the buildup of excess skin (hyperkeratosis) in pressure-prone areas can lead to the formation of a hematoma, which, due to neuropathy and increased pressure on the sole, can rupture and eventually develop into a challenging-to-heal ulcer [11].

2.2 Impact of elevated glucose levels on nervous system molecules

Research conducted on animal models indicates that elevated blood sugar levels disrupt the functioning of crucial adaptive molecules within the nervous system. This disruption extends to the way neuromodulin, β-tubulin, heat-shock protein, and poly-ADP-ribose polymerase are expressed within the dorsal root ganglia (DRG) [12, 13]. Altered functionality within the dorsal root ganglia (DRG), such as modifications in spliceosome activity, shifts in the expression of motor neuron proteins, and the heightened presence of GW-bodies (sites for mRNA processing), play crucial roles in the context of diabetic neuropathy [14].

2.3 (ROS) and other metabolic pathways

Furthermore, within individuals with diabetes, reactive oxygen species (ROS) bring about the oxidation of plasma low density lipoproteins (LDLs). These oxidized LDLs subsequently attach to receptors such as oxidized LDL receptors 1 and 4, as well as RAGE. This sequence of events triggers a cascade of signaling pathways, encompassing caspase 3 and ribonucleic acid pathways, consequently fostering further inflammatory reactions. Ultimately, this process results in the buildup of reactive oxygen free radicals, culminating in potentially irreversible harm to nerve tissues [15, 16]. Certain investigations have identified irregularities in polyol and inositol metabolic pathways in diabetic individuals. These anomalies encompass the degradation of the Na/K-adenosine triphosphate (ATP) enzyme, neurovascular abnormalities, disturbances in neurotrophic functions, issues with axonal transport, and the occurrence of nonenzymatic glycosylation affecting neurons and transport proteins within the nerves of individuals with diabetes [17, 18]. Disturbances in these pivotal pathways can result in anomalous handling of proteins, oxidative harm, and impaired functioning of mitochondria within neurons. These factors collectively contribute to the decline in peripheral nerve function [19].

3. Impaired vasculature

The most severe manifestations of diabetes are related to its vascular complications. These include diabetic retinopathy, diabetic nephropathy, and diabetic foot ulcers. One of the mechanisms of vascular impairment in diabetes is atherosclerosis.

3.1 Atherosclerosis and diabetes

Atherosclerosis leads to peripheral arterial disease, and it is the primary cause of reduced lifespan in individuals with diabetes [3]. Atherosclerosis is also associated with the development of diabetic foot ulcers [1]. Multiple microvascular mechanisms of injury induced by hyperglycemia lead to atherosclerosis and impaired vasculature and, subsequently diabetic foot ulcers. Progress in comprehending the vascular disease linked to diabetes has revealed that the development of diabetic vascular problems is influenced by an equilibrium between mechanisms causing injury at the molecular level and endogenous protective elements within the body [3]. In normal state, the protective factors prevent the development of vascular diseases. These include anti-inflammatory factors, insulin, antioxidant enzymes, platelet-derived

growth factor (PDGF), vascular endothelial growth factor (VEGF), and activated protein C. In diabetes, however, these factors are overwhelmed by the mechanisms of injury induced by hyperglycemia. Many abnormalities in cellular function have been described in diabetes, including gene expression, cell signaling, and cell biology. These abnormalities happen simultaneously during the development of vascular impairment [3]. These cellular mechanisms that lead to vascular impairment in diabetes involve protein kinase C (PKC), hyperactive metabolic pathways, and oxidative stress.

3.2 Protein kinase C (PKC)

PKC is an enzyme found throughout the body and is involved in various intracellular processes. In diabetes, its function becomes more active in vascular tissue, as seen in major arteries, the renal glomeruli, and the retina. Among the 10 PKC isoforms present in mammals, the α, β, and δ forms are the most regularly associated with vascular issues arising from diabetes. For example, in apoE null mice with PKCβ knockout, atherosclerosis was reduced significantly [3]. PKC isoforms are categorized into three groups—classic, novel, and atypical—according to their structural characteristics and methods of activation. Among these, PKCβ falls into the classic group, while PKCδ is part of the novel group. Both of these groups can be activated by diacylglycerol (DAG) [3]. In the context of diabetes, there is an elevated level of intracellular DAG present in vascular tissue. This increase can occur either by generating new DAG molecules using glyceraldehyde 3-phosphate and phosphatidic acid, or by utilizing non-esterified fatty acids. Elevated levels of glucose can also lead to increased PKC activity by triggering transcriptional upregulation. This phenomenon is demonstrated by the increased expression of PKCδ in vascular cells [20, 21].

3.3 Hyperactive metabolic pathways

When there is hyperglycemia, there is increased cellular absorption of glucose, this leads to the enhancement of the polyol pathway, alternatively named sorbitol pathway [22]. **Figure 1** illustrates that polyol pathway utilizes NADPH during the aldose reductase reaction and diminishes NAD+ in sorbitol reductase reaction.

An overactive polyol pathway can have a negative impact on cellular balance by reducing the levels of cytosolic NADPH. This NADPH is crucial for keeping the main internal antioxidant, glutathione, in its active form. Furthermore, higher glucose levels can also deplete cellular NADPH through another process: the increased glucose concentrations hinder the activity of glucose 6-phosphate dehydrogenase. This enzyme is responsible for initiating the first step in the pentose phosphate pathway, which is the main supplier of NADPH within the cell [23]. Initial investigations on blocking aldose reductase in animals displayed potential to influence vascular impairment. However, these effects have not been proven in diabetic patients [3].

Figure 1.
Polyol pathway.

Widespread elevation of aldose reductase levels in mice led to heightened atherosclerosis [24]. Interestingly, contrary outcomes were noted in mice where the aldose reductase gene was deactivated or when they were administered an inhibitor for aldose reductase; both instances resulted in increased atherosclerosis [25]. Hence, additional investigation is required to ascertain the precise role of the aldose reductase pathway in the progression of atherosclerosis in the context of diabetes.

3.4 Oxidative stress

The generation of superoxide and other reactive oxygen species (ROS) within the blood vessel lining significantly contributes to the development of vascular disorders due to vascular endothelial damage, especially within the context of diabetes [3]. A specific oxidative enzyme that favors NADH contributes significantly to the increase in the amount of superoxidase in the vascular wall [26]. This enzyme is present in the endothelial cells and smooth muscle cells [26]. The levels and function of NADH oxidase in blood vessels are heightened in rat models of both type 1 [27] and type 2 [28] diabetes. This particular enzyme could be triggered by an elevation in the ratio of NADH to NAD+, which might result from increased activity of the polyol pathway in diabetes [29].

All these mechanisms of injury favor the development of atherosclerosis in diabetic individuals. Peripheral angiopathy stands as one of the cardinal triggers for diabetic foot ulcers (DFUs), as well as the foremost contributor to both amputation and mortality [30]. Atherosclerosis constitutes the principal pathological mechanism within peripheral vascular disease. The rupture of atherosclerotic plaques, particularly in the context of diabetes, can directly result in peripheral arterial thrombosis, subsequently leading to arterial blockage and lower limb ischemia. This sequence of events ultimately culminates in the emergence of DFUs [30]. Furthermore, the impact of atherosclerosis on the lower extremities differs between diabetic and non-diabetic patients [30]. In individuals with diabetes, the inferior genicular artery (posterior tibial artery and anterior tibial artery) is predominantly affected, while there is comparatively less involvement of the femoral and popliteal artery segments (superficial femoral artery and popliteal artery). Generally, the main iliac artery remains unaffected in diabetic patients. In cases where arterial perfusion to the foot is insufficient to uphold skin integrity, the development of tibial artery occlusion or proximal artery occlusion can lead to ischemic ulcers or gangrene [30].

4. Immune responses

The healing process of diabetic foot ulcers (DFUs) is a complex interplay of diverse cellular components and unique aspects, setting it apart from the healing of normal tissue.

4.1 Components of healing in DFU

The healing process of DFUs involves various components, including immune cells, keratinocytes, fibroblasts, endothelial cells, and a range of cytokines. During the inflammatory phase, the presence of infiltrating monocytes/macrophages within the wound plays a crucial role in transitioning the wound environment from being pro-inflammatory to an anti-inflammatory state [31]. During the advanced phase of

typical wound inflammation, macrophages undergo a shift from a pro-inflammatory phenotype to an anti-inflammatory one. However, in individuals with DFUs, there is an impairment in the function and phenotypic transition of macrophages, resulting in the maintenance of a pro-inflammatory state by these cells [32].

4.2 Unique aspects of DFU healing

Clinical and experimental findings indicate that the healing process of DFUs differs from that of normal tissue [33]. Macrophages in DFU wounds have a diminished ability to effectively remove necrotic tissue, as their phagocytic function is significantly impaired. Alongside macrophage dysfunction, neutrophils contribute to an intensified inflammatory response, further impeding the healing of diabetic wounds. In diabetic wounds, the disruption of phagocytosis, neutrophil degranulation, and the anti-infective effects of reactive oxygen species (ROS) exacerbate the inflammatory condition [34]. Furthermore, elevated blood sugar levels lead to the increased expression of neutrophil protein arginine deiminase (PAD)-4. This heightened expression affects neutrophils' capacity to release NETs (neutrophil extracellular traps) upon entering the wound, causing a delay in the healing process [35]. Macrophages and neutrophils release proteases in an inactive form known as zymogen, which becomes activated outside the cells and breaks down extracellular matrix (ECM) proteins like elastin and interstitial collagen. An instance is matrix metalloproteinases (MMP), which breaks down fibronectin into fragments and additionally activates other MMPs. These fibronectin fragments lead to the infiltration of leukocytes, tissue injury, and continuous inflammation. Hence, diverse cells will contribute to the healing of diabetic wounds with distinct functions in a therapeutic capacity [36].

4.3 Re-epithelialization and dermal repair in DFU healing

In the healing phase of diabetic foot ulcers (DFUs), the regeneration of skin tissue relies heavily on re-epithelialization and dermal repair [37]. Research indicates that during the process of wound re-epithelialization, keratinocytes move to the wound site and undergo proliferation and differentiation to reconstruct the epidermis's structural and functional integrity [38]. This progression involves all of the skin layers. In the initial stages of wound healing, keratinocytes have the capability to directly combat invading pathogens by releasing cytokines, chemokines, antimicrobial peptides, and extracellular vesicles. These substances contribute to facilitating interactions between keratinocytes and circulating immune cells, promoting wound healing. However, the elevated glucose levels present in diabetic wound environments disrupt the normal functioning of keratinocytes, leading to delayed wound re-epithelialization. Dermal repair primarily depends on fibroblasts' actions, encompassing their proliferation, differentiation, and secretion of extracellular matrix (ECM) components. In the upper papillary layer, specific fibroblasts can form hair papillae and regulate hair follicle growth and regeneration. Conversely, fibroblasts in the lower reticular layer mainly maintain the structural integrity of the dermis, creating a stable environment to support activities such as angiogenesis, nerve regeneration, and immune clearance [39]. Furthermore, fibroblasts have the ability to transform into myofibroblasts. These myofibroblasts play a role in contracting wounds, releasing enzymes and MMPs to break down the inflammatory matrix, and secreting collagen and other components of the extracellular matrix to aid in the creation of

granulation tissue. Collagen III within the extracellular matrix is swapped out with collagen I, which boasts greater tensile strength. However, elevated blood sugar levels and the buildup of AGEs result in compromised fibroblast function. This translates to reduced cell growth, faster-programmed cell death, and hindered movement toward the wound site. Consequently, these factors collectively contribute to impaired skin restoration and the delayed healing observed in diabetic wounds [40].

4.4 Endothelial cells and neovascularization

The importance of wound healing is closely linked to the condition of endothelial cells and the process of neovascularization. Typically situated along the interior lining of blood vessels, endothelial cells are responsible for controlling the constriction and expansion of blood vessels by adjusting the concentrations of vasoactive substances like eNOS [41]. During the process of wound healing, endothelial cells undergoing various stages of angiogenesis are primarily under the control of VEGF. In the initial inflammatory phase, VEGF heightens the permeability of blood vessels, impacts the presence of selectin and intercellular adhesion molecules within endothelial cells, and fosters the attraction of white blood cells to the site of injury. As the proliferation stage ensues, VEGF significantly triggers both the replication and movement of endothelial cells. Subsequently, during the remodeling stage, VEGF prompts the arrangement of endothelial cells, facilitating the creation of the vascular lumen [42]. Research conducted within living organisms has demonstrated that arterial endothelial cells, when exposed to elevated glucose levels, experience a deterioration in their structural integrity. This renders them more susceptible to programmed cell death and detachment, allowing them to enter the bloodstream. Consequently, this situation disrupts the process of angiogenesis [43]. This impairment can be primarily attributed to the following five mechanisms: (a) the polyol pathway, (b) an elevation in intracellular AGEs, (c) an increase in the expression of RAGE, (d) the activation of multiple forms of protein kinase C, and (e) an excessive activation of the hexosamine pathway [44]. In diabetic conditions, reduced levels of nitric oxide synthase (NOS) due to peripheral neuropathy and peripheral arterial disease result in decreased peripheral blood flow due to blood vessel constriction. Furthermore, the absence of endothelial progenitor cells (EPCs) at the wound site hampers the creation of new blood vessels, consequently leading to a delay in the healing of wounds [45].

4.5 Stem cells and their role in DFU healing

Stem cells play a pivotal role in the recovery of diabetic foot ulcers (DFU) by overseeing the process of skin restoration after injuries and during regular maintenance. These stem cells possess distinctive attributes such as uneven replication, robust self-regeneration capabilities, and the ability to transform into various cell types [46]. Specifically, the operational condition of endothelial progenitor cells (EPCs) and epidermal stem cells (ESCs) significantly impacts the progression of wound healing. The abilities of EPCs, including migration, differentiation, adhesion, and the formation of tubes, become compromised under the hyperglycemic conditions associated with diabetes [47]. This impairment leads to persistent wound nonhealing over extended periods, especially in cases of chronic wounds like those seen in individuals with diabetes [48]. Acting as precursors to endothelial cells, endothelial progenitor cells (EPCs) move from the bone marrow into the peripheral bloodstream in response to factors like hypoxia-inducible factor-1, stromal cell-derived factor-1α, and VEGF.

These cells are subsequently directed to ischemic sites where they contribute to the formation of fresh blood vessels, utilizing processes such as adhesion, proliferation, differentiation, and the creation of tubular structures, all of which aid in wound repair [49]. Furthermore, epidermal stem cells (ESCs) also hold a vital role in the wound-healing process. Laboratory tests conducted outside the body indicate that ESCs enhance the growth and movement of diabetic fibroblasts and macrophages (Mφ), while also promoting a shift toward an alternative or M2 Mφ polarization state [50]. In the case of wounds in db/db mice, the administration of ESCs accelerates wound healing by reducing inflammation, boosting cell growth at the wound site, fostering the development of new blood vessels, and encouraging the polarization of M2 macrophages [50].

5. Conclusion

Diabetic foot ulcers (DFUs) are a significant and debilitating complication of long-term diabetes, with neuropathy, impaired vasculature, and immune responses being the key contributors to their pathogenesis. Neuropathy, driven by hyperglycemia and advanced glycation end products (AGEs), disrupts nerve cell structure and function, leading to sensory, motor, and autonomic impairments. The combination of these factors reduces pain perception, increasing the risk of unnoticed injuries and subsequent ulceration. Impaired vasculature, marked by atherosclerosis and microvascular dysfunction, leads to reduced protective factors and increased susceptibility to vascular diseases, including DFUs. Key factors in this process include PKC activation, hyperactive metabolic pathways, and oxidative stress, all of which contribute to vascular damage.

Immune responses also play a significant role in the development and progression of DFUs. Chronic inflammation driven by dysfunctional immune cells, impaired macrophage function, neutrophil dysfunction, and compromised keratinocyte, fibroblast, and endothelial cell activities hinder the normal wound healing process. Additionally, stem cell dysfunction, especially in endothelial progenitor cells (EPCs) and epidermal stem cells (ESCs), further delays wound healing in diabetic individuals.

Understanding the multifaceted pathogenesis of DFUs is crucial for developing effective prevention and treatment strategies. Addressing neuropathy through glycemic control, AGE reduction, and targeted therapies could mitigate nerve damage and reduce the risk of injury. Targeting vascular impairment with interventions focused on PKC inhibition, metabolic pathway modulation, and oxidative stress reduction could improve blood vessel integrity. Furthermore, interventions that modulate immune responses and restore normal function in immune cells, keratinocytes, fibroblasts, endothelial cells, and stem cells could enhance the healing process.

In conclusion, diabetic foot ulcers result from the intricate interplay of neuropathy, impaired vasculature, and immune responses. A comprehensive approach that targets each of these components holds promise for the effective prevention and management of diabetic foot ulcers, thereby improving the quality of life for individuals with diabetes.

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Chapter 5

Diabetic Foot Ulcer Wound Healing and Tissue Regeneration: Signaling Pathways and Mechanisms

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Abstract

This chapter digs into the complexities of diabetic foot ulcer (DFU) wound healing, encompassing cellular responses from fibroblasts, keratinocytes, and macrophages, as well as humoral responses involving the release of growth factors and cytokines. The normal wound healing process is hindered in diabetics by factors like infections, venous insufficiency, impaired oxygenation, age-related changes, immune dysfunction, and a dry environment, contributing to delayed and challenging wound healing. The discussion then focuses on the intricate interplay of signaling cascades, including PI3K/Akt, MAPK/ERK, and Wnt/β-catenin, in the pathology of DFUs. Diabetes induces disruptions in the PI3K/Akt pathway, impeding cell migration and angiogenesis due to compromised insulin signaling and increased oxidative stress. Abnormalities in the MAPK pathway, essential for inflammation and tissue remodeling, further impact wound closure in DFUs. Additionally, downregulation of the Wnt/β-catenin pathway, crucial for tissue regeneration, contributes to immune dysfunction, delaying healing in diabetic wounds. Finally, the chapter explores multifaceted factors contributing to the pathogenesis of DFUs, including epigenetic modifications, oxidative stress, advanced glycation end products (AGEs), the polyol pathway, diacylglycerol-protein kinase C (DAG-PKC) activation, and the nitric oxide (NO) pathway. Persistent hyperglycemia in diabetes hinders wound healing, causing chronic ulcers and complications. Addressing these mechanisms is crucial for revolutionizing management.

Keywords: wound healing, tissue regeneration, signaling pathways, diabetes, foot ulcer

1. Introduction

This chapter delves into the intricate world of diabetic foot ulcer wound healing and tissue regeneration. Diabetic foot ulcers pose significant challenges due to impaired healing linked to diabetes-related complications. The chapter explores the inflammatory phase of wound healing, growth factors' crucial roles, and the impact of signaling pathways like PI3K/Akt and MAPK/ERK in diabetic wound healing. It also touches on epigenetic modifications, oxidative stress, and AGEs' effects on cellular function. Emerging therapeutic approaches, including growth factor therapies and stem cells, offer hope for enhancing diabetic foot ulcer healing. Ultimately, this understanding of signaling pathways and mechanisms could revolutionize the management of this

challenging condition. We will start our chapter by talking about how the healing process of a wound happens and how it is affected in DFU.

2. Wound healing in DFU

Wound healing is a normal physiological reaction to tissue injury that usually involves cellular and humeral responses. The cellular response from fibroblasts, keratinocytes, endothelial cells, macrophages, lymphocytes, and platelets [1]. The humeral response involves the release of many growth factors and pro-inflammatory cytokines, such as transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF).

2.1 Phases of normal wound healing

The wound healing process mainly consists of four overlapping and dynamic phases, which are: hemostasis, inflammation, proliferation, and remodeling [2]. In acute wounds, the healing process goes through four phases, and they heal within a specific time as they have a specific start point and endpoint. However, the existence of some local or systemic factors can delay the acute wound-healing process and cause chronic wounds [1]. The immediate initial response after tissue injury is vasoconstriction to achieve adequate hemostasis for 5–10 minutes [1]. Simultaneously, platelets adhere to the vascular wall *via* several receptors that bind to cellular and extracellular matrix of the blood vessel wall. These interactions cause intracellular signals to be released, which activate integrins, that are involved in cell-cell and cell-matrix interactions, resulting in platelet stable adherence, activation, and aggregation. When platelets adhere to the blood vessel wall, they undergo a dramatic shape change and release their contents of granules as well as extracellular vesicles. Platelets aggregate within minutes to create the main hemostatic plug to help in stopping the bleeding [3]. Fibrin clots get more stabilized release growth factors and cytokines such as PDGF, TGF-β, IL 1, FGF, and EGF [1, 2]. The release of the growth factors and cytokines attracts the inflammatory cells to the injury site (chemotaxis) and initiates the inflammatory phase, that lasts for 1–2 days [4]. Additionally, platelets release histamine to increase vascular permeability, allowing more inflammatory cells to arrive at the injury site [5]. Neutrophils are the most prominent and the first cells to arrive after being attracted to TGF-β and IL-1 which has a role in phagocytosing the bacteria and cellular debris [5]. followed by monocyte migration, which gets selectively differentiated into macrophages with the help of TGF-β and IL-4. Macrophages start clearing the apoptotic neutrophils and foreign bodies and release more pro-inflammatory mediators such as TGF-β. TGF-β starts attracting more mast cells, which in turn release histamine, proteoglycans, and proteases that help in vasodilating the blood vessels and increasing their permeability to the released pro-inflammatory mediators. Furthermore, vasodilation and the increase in blood vessel permeability allow plasma contents to escape to the injury site, causing what is known clinically as edema. Once inflammatory cells clear almost all the debris and foreign bodies, they release again TGF-β and IL-4 inducing the resolution of the inflammation. As well, the macrophages start releasing TNF-α and IL-1 which stimulate the proliferation of fibroblasts and endothelial cells, allowing the proliferative phase to take over [1, 4]. Once fibroblast gets activated it starts releasing collagens, proteoglycans, and glycosaminoglycans. Collagens, proteoglycans, and glycosaminoglycans deposit with fibronectin to form the extracellular matrix which is

an essential and major component of the granulation tissue as illustrated in **Figure 1**. Granulation tissue starts to mature with the help of collagen crosslinking and angiogenesis. Angiogenesis is initiated by the release of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor bFGF, which are released by endothelial cells, macrophages, and keratinocytes. It was found that PDGF produced by degranulated platelets helps in increasing the structural integrity of the blood vessels which enhances the angiogenesis process. Additionally, the wound starts to contract stimulating more fibroblasts and myofibroblasts to deposit and lay down. During the formation of ECM and angiogenesis, epithelial cells start to proliferate and migrate from the wound edges and periphery to lay down on the wound and form a layer of epithelial cells (re-epithelization). Around the third week, the remodeling phase starts: excess collagen degrades, and the density of wound site capillaries returns to normal replacing the granulation tissue with normal connective tissue. Moreover, wound contraction reaches its maximal intensity by the third week, and it can last up to 12 weeks with the help of myofibroblast to give the wound site the tensile properties of normal intact skin [2, 4, 5].

2.2 Factors affecting wound healing process in diabetics

The wound healing process can be impaired and affected by various factors, as in **Figure 2**, that can be either local or systemic factors. Local factors directly affect the wound itself, while the systemic are those that are related to the diseases and overall health.

Some of the local factors that affect the wound-healing process are:

Infections: If the wound got infected, this would prolong the inflammatory phase as the clearance of the microbes would not be completed. In addition, the presence

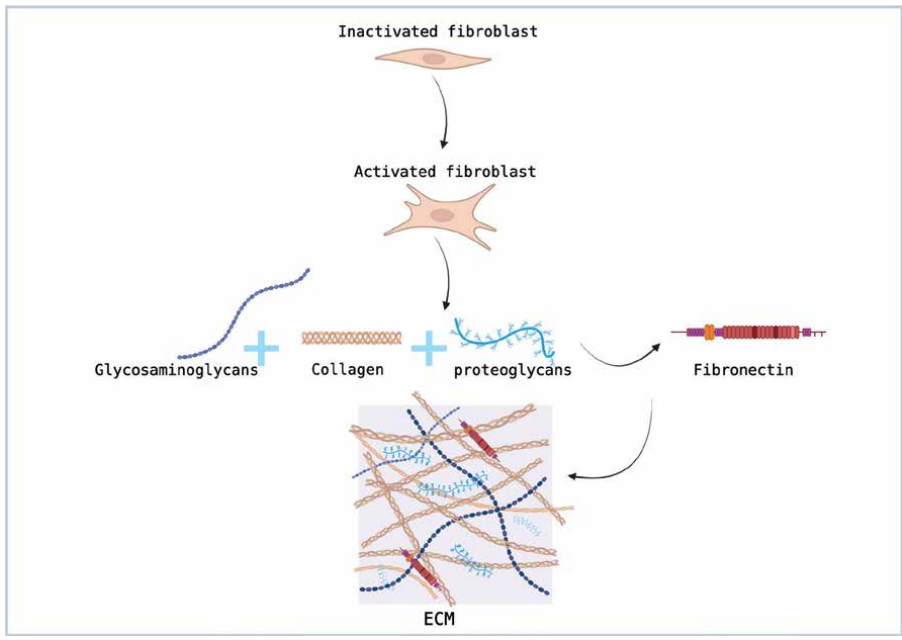

Figure 1.
Fibroblast activation as part of the proliferation phase.

of the microbes and endotoxins can lead to excessive and prolonged production of pro-inflammatory mediators such as IL-1 which in turn delay the healing process and can lead to its failure. Furthermore, some bacteria, such as *Staphylococcus aureus* (*S. aureus*), and *Pseudomonas aeruginosa* (*P. aeruginosa*), form biofilms creating a protected resistant environment to antibiotics [2].

Venous insufficiency: venous insufficiency leads to venous hypertension. The increase in hydrostatic pressure causes fibrin deposition around the blood vessels affecting oxygen transportation and permeability, which can lead to tissue hypoxia [6].

Impaired oxygenation: oxygen is an important element in inducing angiogenesis, fibroblast proliferation, collagen synthesis, and preventing infections. The early wound microenvironment is usually deprived of oxygen due to vascular disruption and increased oxygen demand by cells that are metabolically active. Systemic diseases, such as diabetes, can compromise vascular flow, laying the stage for inadequate tissue oxygenation [2, 5].

Dry environment: usually wet environment enhances the wound healing process. A hydrated and moist environment enhances the migration of epithelial cells thus improving the proliferation stage [7]. However, in the case of hyperglycemia, the body pulls fluid from its cells to make enough urine to eliminate the excess sugar. This might cause diabetic patients' skin to become dry and affect wound healing process in these patients [8].

On the other side, some of the systemic factors that affect the wound healing process are:

Age: diabetes is a common disease among elderly, as around 40% of adult diabetics are over the age of 65 [9]. Elderly people usually have delayed wound healing compared to the youth. In addition, wound healing in the elderly has some age-related changes such as, intensified platelet aggregation, increase in inflammatory mediators, delayed infiltration of macrophages and lymphocytes, decrease in growth factors production, delayed re-epithelialization, and delayed angiogenesis and collagen deposition that causes decreased wound strength [2].

Immune system dysfunction: suppression or dysfunction of the immune system causes impairment and delay of wound healing process. Diabetic patients may suffer from immune cell dysfunction in the wound healing process. One of the immune cellular dysfunctions in diabetic wound healing is the failure of macrophage transition from M1 to M2. The hyperglycemic state can increase pro-inflammatory cytokines which in turn leads to decreased phagocytosis of M1 type and block its transition to M2 phenotype. The persistence of M1 phenotype results in a sustained inflammatory phase delaying the wound healing process [10].

2.3 Wound healing in diabetic foot ulcers (DFU)

Specifically, wound healing in diabetic foot ulcers (DFU) is a serious problem that faces many diabetic patients, as around 60–80% of ulcers heal, 10–15% remain active, and 5–24% lead to amputation of the limb after the first evaluation within 6–18 months [11]. Wound healing times in diabetic people were found to be higher than in non-diabetic people, and even they differed between diabetic people, showing a direct correlation with the level of hyperglycemia. As noted, diabetic patients who experience higher levels of hyperglycemia and high HBA1c showed longer healing times for the wound compared to diabetic patients who have a lower level of HBA1c [12]. Furthermore, wound healing phases in DFU are affected by many factors. One

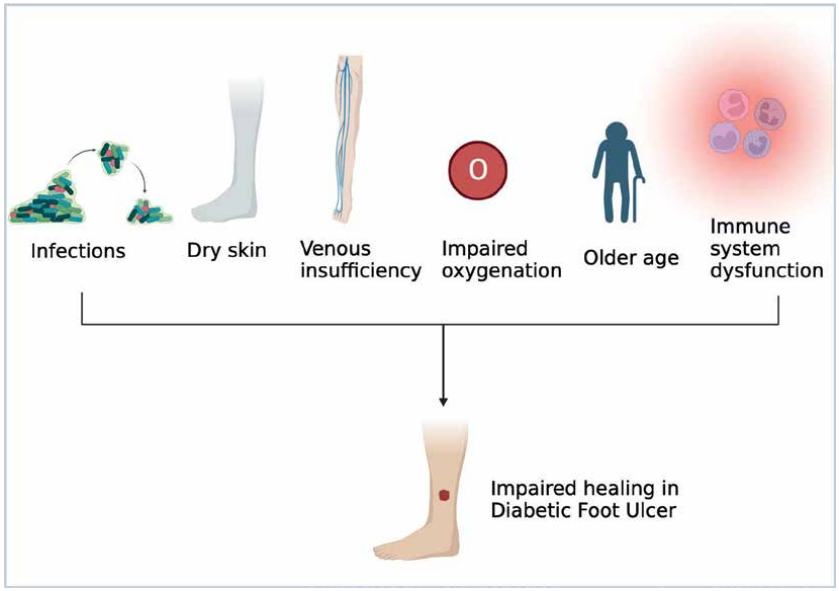

Figure 2.
Factors affecting wound healing process in DFU.

of the factors that affect wound healing in DFU is repeated trauma to the foot due to loss of sensation after ischemic neuropathy because of micro- and macrovascular diseases that compromise blood flow to the nerves. Capillary basement membrane thickening in diabetic patients delays the healing process by affecting the infiltration of cells to the wound site [13]. In addition, another study on animals showed that the total number of infiltrated leucocytes in the wound site is lower in diabetic animals compared to non-diabetic animals [14]. Capillary basement membrane thickening has been studied well especially in diabetic patients' retina. As, it was found that hyperglycemia can induce biosynthetic increase of basement membrane (BM) components like fibronectin, type IV collagen, and laminin increase. The overexpression of BM components can be explained by different mechanisms, such as increased polyol pathway flux and inflammation. Also, increased growth factor activity, protein kinase C activation, and advanced glycation end-product (AGE) accumulation are some factors that contribute to thickening of BM [15]. Prolongation of the inflammatory phase in DFU can also be attributed to excessive production of pro-inflammatory cytokines by the macrophages. Additionally, neutrophils upregulate the production of extracellular traps, which target microorganisms, causing the perpetuation of the inflammation phase [16]. Also, the phagocytic function of polymorphonuclear cells is impaired compared to non-diabetic patients due to high levels of glycosylated protein in the wound site [12]. The concentration of glycosylated wound proteins directly correlates with the activity of proteases and collagenases. The increase in the activity of proteases and collagenases inversely correlates with the amount and concentration of collagen in the wound site, affecting the proliferation phase of the ulcer healing process [17]. Insufficient angiogenesis is one of the major contributors to delayed wound healing in DFU. Deficiency in proangiogenic factors such as VEGF and upregulation of antiangiogenic factors such as Ang-1 affect maturation, regression, and stabilization of newly formed blood vessels. Angiogenesis deficiency affects oxygen transportation to the wound site, leads to impairment of leucocyte migration

into the wound, and thus increases the risk of infection [16]. Analysis of non-healing DFU in one of the studies showed high levels of inflammatory cytokines, fewer active growth factors, and higher levels of proteases. The low number of active growth factors can be attributed to the high levels of proteases, as it has been shown that the concentration of MMP is 65-fold higher in the biopsies of DFU [18]. In addition, to have a normal wound healing and remodeling phase, there should be a balance between collagenous and non-collagenous extracellular matrix components. Usually, MMP and the tissue inhibitor of metalloproteinase TIMP are responsible for the remodeling phase. In chronic wounds, as in DFU, high levels of MMP and low levels of TIMP were found and contributed to their chronicity [19]. Now after diving into how a wound is affected in a DFU patient, we can proceed to learn about the tissue repair process and what are the signaling pathways involved.

3. Signaling pathways in diabetic foot ulcers: insights into PI3K/Akt, MAPK, and Wnt/β-catenin signaling and implications for tissue repair

This section aims to provide a detailed understanding of the PI3K/Akt, MAPK, and Wnt/B-catenin signaling pathways. In addition to examining how aberrant activation or inhibition of these pathways in diabetes can disrupt wound healing and impair tissue regeneration.

3.1 PI3K/Akt signaling pathway

Starting with, the serine/threonine kinase Akt (also known as protein kinase B or PKB) which was initially identified as a proto-oncogene is an integral intracellular signaling cascade that contributes to the process of wound healing. This signaling cascade has received widespread attention due to its critical role in regulating a wide range of cellular activities, including cell cycle, apoptosis, angiogenesis, and glucose metabolism [20]. When this pathway is activated, Akt is phosphorylated and activated, which regulates several downstream targets involved in numerous cellular functions [21, 22]. The PI3K/Akt pathway is dysregulated in DFUs as a result of poor insulin signaling and increased oxidative stress [23]. Furthermore, the PI3K/Akt pathway regulates cell migration by promoting keratinocyte relocation for re-epithelialization and enhancing fibroblast proliferation and extracellular matrix formation [24]. It additionally executes an important role in angiogenesis by influencing endothelial cell activity [24]. This part provides an overview of the PI3K/Akt pathway and its relevance in wound healing, discusses the dysregulation of this pathway in diabetes, and explores its impact on cell migration, proliferation, and differentiation.

3.1.1 Overview of the PI3K/Akt pathway and its relevance in wound healing

Activation of the pathway is initiated by the binding of extracellular ligands to receptor tyrosine kinases (RTKs), leading to the recruitment and activation of phosphatidylinositol 3-kinase (PI3K), which phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3) as illustrated in **Figure 3**. Some of the components involved in the PI3K/Akt signaling pathway, such as glycogen syntheses kinase-3 (GSK-3) and mammalian target of rapamycin (mTOR) have been found to contribute to glucose metabolism and wound healing processes in diabetes mellitus [21].

3.1.2 Impact of PI3K/Akt pathway on cell migration, proliferation, and differentiation

The PI3K/Akt pathway exerts a profound influence on wound healing. Through its regulation of cytoskeletal dynamics and focal adhesion turnover, the pathway facilitates efficient cell migration into the wound bed, promoting re-epithelialization and tissue repair [24]. Akt activation stimulates the formation of lamellipodia and filopodia, facilitating cell motility and wound closure [21]. Moreover, the pathway influences cell proliferation by promoting cell cycle progression and inhibiting apoptosis, ensuring an adequate number of cells for tissue repair [24]. Additionally, the PI3K/Akt pathway regulates cell differentiation, promoting the differentiation of progenitor cells into specialized cell types such as keratinocytes, fibroblasts, and endothelial cells, required for tissue reconstruction [21].

3.1.3 Dysregulation of PI3K/Akt pathway in diabetic foot ulcers

In diabetes, the PI3K/Akt pathway is frequently dysregulated, primarily due to impaired insulin signaling and increased oxidative stress. Insulin resistance, a hallmark of type 2 diabetes, leads to decreased activation of the pathway [25]. This disruption hinders the phosphorylation and activation of Akt, impairing its downstream signaling. Additionally, chronic hyperglycemia in diabetes induces oxidative stress, resulting in the generation of reactive oxygen species (ROS) that can directly inhibit Akt activity [26–28]. The dysregulated PI3K/Akt pathway in diabetes contributes to

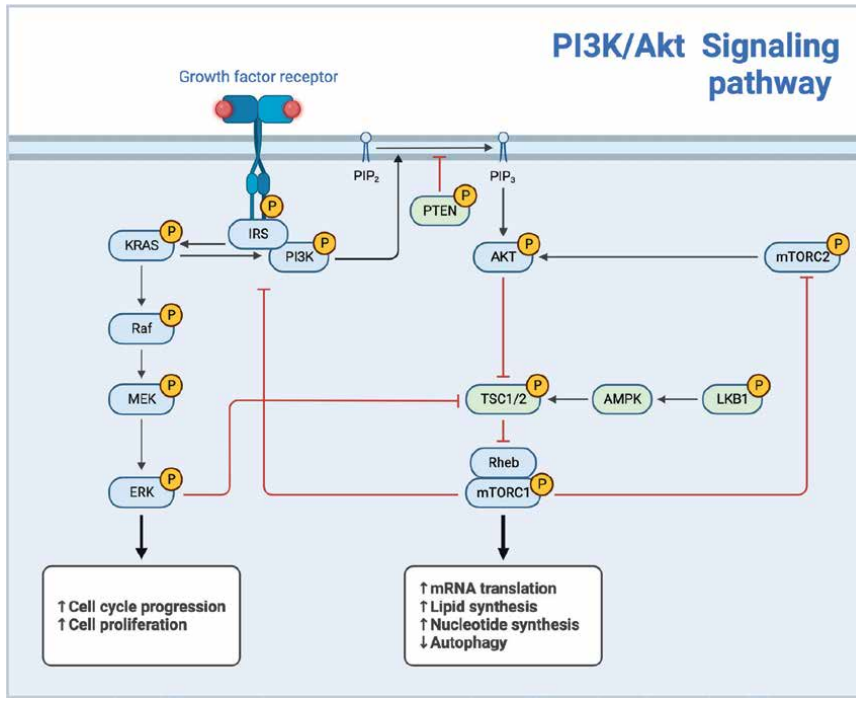

Figure 3.
PI3K/Akt signaling pathway.

impaired angiogenesis, cell survival, and proliferation, ultimately delaying wound healing, as observed in diabetic foot ulcers and other diabetes-related complications.

3.2 MAPK signaling pathway

Another key highly conserved intracellular signaling cascade involved in wound healing is the MAPK (Mitogen-Activated Protein Kinase) signaling pathway. It has been established that MAPK genes can be divided into three major subfamilies: extracellular signal-regulated kinases (ERKs), Jun N-terminal kinases (JNKs), and p38 MAPKs, which are involved in signal transduction and cellular response regulation [29, 30]. By regulating cell survival, proliferation, immune response, inflammation, and differentiation during tissue repair, the MAPK pathway plays a crucial role in wound healing [31]. A dysfunction of MAPK signaling has been observed in DFUs, resulting in impaired wound healing. Hyperglycemia-induced oxidative stress and chronic inflammation are two contributors to the dysregulation of the MAPK pathway [31]. This dysregulation negatively impacts inflammatory responses, immune cell activation, collagen synthesis, remodeling, and re-epithelialization [31]. It is of great interest to understand how the MAPK pathway influences these cellular functions to identify potential therapeutic targets for restoring normal pathway function in wound healing and enhancing wound healing outcomes.

3.2.1 Influence of the MAPK pathway on cellular functions during wound healing

The MAPK pathway exerts a significant influence on various cellular functions critical for wound healing. Activation of the ERK pathway promotes keratinocyte proliferation, migration, granulation tissue formation, and wound closure [31]. The JNK pathway regulates the production of pro-inflammatory cytokines such as TNF-α and IL-1β, chemokines, and matrix metalloproteinases, influencing the inflammatory response and immune cell recruitment [32]. Fibroblast activation, myofibroblast differentiation, and collagen synthesis, crucial for wound contraction and remodeling are regulated through a non-canonical pathway mediated by mitogen-activated protein kinase (MAPK) effectors such as MAPK kinases 6 (MKK6) and its direct downstream target kinase, p38 [33]. Collectively, the MAPK pathway ensures coordinated cellular responses during different phases of wound healing.

3.2.2 Aberrations in MAPK signaling in diabetic foot ulcers

In diabetic foot ulcers, aberrations in MAPK signaling have been observed, contributing to impaired wound healing. Chronic hyperglycemia, a hallmark of diabetes that impairs keratinocyte migration, is one of the major mechanisms contributing to diabetic wound healing delays [34]. It has been proposed that the P38/MAPK pathway affects keratinocyte migration and controls autophagy during wound healing [34]. A study discovered that the P38/MAPK pathway was down-regulated, which was accompanied by autophagy inactivation, inhibiting keratinocyte migration in high-glucose conditions. Additionally, enhanced activation of p38 MAPK and JNK pathways in response to pro-inflammatory cytokines, such as TNF-α and IL-1β has been observed, leading to excessive inflammation, and hindering the progression of the wound healing process [35]. It has been demonstrated that negative-pressure wound therapy can limit inflammation and promote wound healing in diabetic foot patients by down-regulating the MAPK/JNK signaling

pathway [35], demonstrating the importance of the MAPK pathway in diabetic wound healing. It is thought that persistent and prolonged inflammation is a significant factor that hinders the healing process of diabetic wounds. In recent times, exosomes have emerged as novel mediators of intercellular communication and play crucial roles in regulating the inflammatory immune micro-environments of diabetic wounds. According to a recent study, exosomes derived from mesenchymal stem cells (MSC-exos) possess the ability to protect β cells from apoptosis caused by hypoxia. This protective effect is attributed to their carrying of miRNA-21, which helps alleviate endoplasmic reticulum (ER) stress and inhibit P38 MAPK signaling [36]. These findings suggest that MSC-exos hold great promise in promoting the healing of diabetic wounds.

3.3 The Wnt/β-catenin signaling pathway

Finally, The Wnt/B-catenin pathway is a highly conserved signaling pathway that regulates cellular processes, including cell proliferation, differentiation, embryonic development, and adult tissue homeostasis. However, in diabetic foot ulcers, the Wnt/B-catenin pathway is often dysregulated, leading to impaired wound healing [37].

3.3.1 Wnt/β-catenin pathway and its significance

The Wnt signaling pathway is closely linked to diabetic wound healing, as it plays a crucial role in regulating processes like skin development, angiogenesis, and epithelial remodeling [38]. This pathway is a complex network comprising three branches: the canonical pathway also known as the classical Wnt signaling pathway and the noncanonical Wnt pathways are independent of B-catenin-T-cell factor/lymphoid enhancer-binding factor (TCF/LEF), such as the Wnt/planar cell polarity (PCP) pathway, and the Wnt/Ca^{2+} pathway [39]. The primary function of the canonical Wnt pathway is to regulate cell proliferation, while the noncanonical Wnt pathways control cell polarity and migration. These two main pathways work together in a network of reciprocal regulation. The classical Wnt signaling pathway is particularly relevant to diabetic wound healing. Various studies have confirmed its involvement in promoting angiogenesis, epithelial remodeling, and regulating the proliferation, and differentiation of skin cells [40]. The Wnt/B-catenin pathway consists of four segments: the extracellular signal, membrane segment, cytoplasmic segment, and nuclear segment. The signaling process is initiated by Wnt proteins, including Wnt3a, Wnt1, and Wnt5a, which serve as extracellular signals. The cell membrane segment contains specific receptors, Frizzled (a sevenfold transmembrane receptor protein), and LRP5/6. The cytoplasmic segment includes key proteins like B-catenin, DVL, GSK-3β, AXIN, APC, and CK1. In the nuclear segment, B-catenin translocates to the nucleus, where it interacts with TCF/LEF family members and regulates downstream target genes, such as MMPs and c-Myc [41]. Activation of the canonical Wnt pathway typically occurs when extracellular Wnt ligands bind to membrane receptors through autocrine/paracrine mechanisms. This leads to the stabilization of B-catenin, allowing its translocation to the nucleus, where it interacts with transcription factors to regulate gene expression involved in various cellular processes critical for wound healing [42]. In the absence of Wnts, the transmembrane receptors FZD and LRP5/6 remain separate on the plasma membrane. In the cytoplasm, a "destruction complex," comprising APC, AXIN, CK1, and GSK3 protein, captures B-catenin and initiates

its degradation. This prevents B-catenin from entering the nucleus, and target gene transcription is inhibited by the association of GROUCHOU with TCF/LEF [43]. Upon recognition of Wnts by FZD and LRP5/6, the "destruction complex" is recruited to the cell membrane through interactions with FZD, which prevents the degradation of B-catenin. Subsequently, β-catenin translocates to the nucleus and activates target gene transcription by interacting with TCF/LEF. **Figure 4** shows that the movement of B-catenin between the cytoplasm and nucleus is a crucial characteristic of Wnt/B-catenin pathway activation [44].

3.3.2 Effects of Wnt/B-catenin pathway on cell behavior, tissue repair, and wound healing

The Wnt/B-catenin pathway enhances the proliferation of progenitor cells, promoting their self-renewal and differentiation into tissue-specific cell types Through these mechanisms, the Wnt/B-catenin pathway is instrumental in orchestrating tissue regeneration processes [45]. Furthermore, during wound healing, this pathway interacts with a variety of different signaling cascades. For example, it cross-talks with growth factors such as TGF-B and VEGF, regulating angiogenesis and promoting the formation of new blood vessels necessary for nutrient supply and oxygenation during tissue repair [45]. In addition, interactions with the Notch and Hedgehog signaling pathways influence cell fate decisions during tissue repair [46]. This complex interaction between multiple pathways influences the cellular responses that eventually dictate the wound-healing outcome in DFUs.

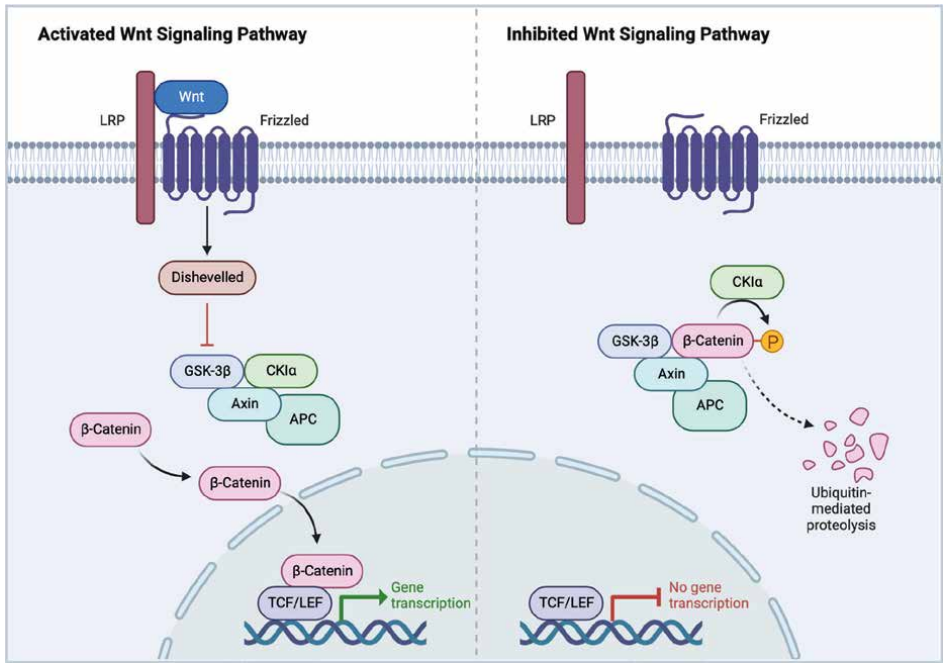

Figure 4.
Wnt signaling pathway activation and inhibition.

3.3.3 Altered Wnt/B-catenin signaling in diabetic foot ulcers

In diabetic foot ulcers, the Wnt/B-catenin signaling pathway is often downregulated, leading to the inhibition of skin cells' biological activity and reduced expression of cytokines [47]. This results in immune dysfunction in the wound, abnormal granulation tissue formation, and impaired reepithelialization, ultimately causing delays in the healing process [47]. Moreover, in diabetic wounds, pigment epithelium-derived factor inhibits Wnt/β-catenin signaling, leading to the mobilization and dysfunction of endothelial progenitor cells (EPCs). This inhibition of angiogenesis hinders the process of wound healing and causes delays in the overall healing response [48]. During the wound-healing stage of ulcers, macrophages play a significant role in the regulation of the Wnt/B-catenin pathway. Wnt5a influences the inflammatory response by modulating the phenotype of macrophages. Additionally, Wnt7b is a crucial protein that facilitates wound angiogenesis [49]. Some studies suggest that downregulation of the Wnt/B-catenin pathway might be linked to a decrease in Rspo protein caused by diabetes [50]. Multiple factors contribute to the altered signaling, including chronic hyperglycemia, oxidative stress, and inflammation associated with diabetes. Hyperglycemia has been shown to impact fibroblasts' proliferation, migration, and collagen secretion through the degradation of B-catenin [51]. In diabetic mice, impaired wound healing was associated with altered expression of WNT ligands, receptors, and downstream components, such as B-catenin and T-cell factor (TCF). These disruptions in Wnt/B-catenin signaling contribute to an imbalance in the B-catenin pool, compromising the activation of target genes involved in angiogenesis, cell proliferation, and tissue regeneration [40]. After getting to know in detail about the signaling pathways involved in the tissue repair process, it is time to comprehend how variable mechanisms play a role in the pathogenesis of a diabetic foot ulcer.

4. The role of epigenetic modifications, oxidative stress, and advanced glycation end products (AGEs) in diabetic foot ulcer pathogenesis and healing

Diabetic foot ulcers (DFUs) are a common and severe complication of diabetes mellitus [52]. Several risk factors, like arterial insufficiency, peripheral neuropathy, peripheral vascular disease, impaired resistance to infection, trauma, and foot deformities, contribute to diabetic foot ulcers [53]. It is characterized by impaired wound healing leading to chronic, non-healing ulcers. Several factors contribute to the altered gene expression, impaired cellular function, and compromised wound healing observed in diabetic individuals. Among these factors, epigenetic modifications, oxidative stress, and advanced glycation end products (AGEs) play crucial roles in the pathogenesis of DFUs.

Diabetes is characterized by a condition called stress, which is related to high levels of glucose in the blood (hyperglycemia). Among the cells affected, microvascular endothelial cells are particularly vulnerable to damage caused by hyperglycemia. These cells struggle to adjust their glucose intake when faced with high glucose levels. It is believed that this damage occurs through four pathways: (1) the polyol pathway flux, (2) increased production of advanced glycation end products (AGEs) and activation of their receptor (RAGE), (3) activation of different forms of the enzyme protein kinase C (PKC) and (4) overactivation of the hexosamine pathway. They all lead to increased

production of mitochondrial superoxide by the mitochondrial electron transport chain, which then transforms into other reactive oxygen species (ROS) leading to oxidative stress within the cell. This process also leads to the inhibition of an enzyme called glyceraldehyde 3 phosphate dehydrogenase (GAPDH). The activation of these pathways plays a role in microvascular disease and tissue damage seen in diabetic patients significantly contributing to the development of foot ulcers. Moreover, in the case of foot ulcers, there is an increase in the levels of nitric oxide (NO). This can react with superoxide to create oxygen species (ROS). At the time two reducing agents, glutathione and cysteine, were found to be downregulated. As a consequence, not only is the production of ROS increased in the diabetic foot, but the mechanisms for neutralizing them are also impaired, ultimately leading to poor wound healing outcomes [54]. This chapter provides an in-depth analysis of the influence of these factors on diabetic foot ulcer healing.

4.1 Advanced glycation end products (AGEs)

Uncontrolled hyperglycemia is the main cause of diabetic complications, as it leads to the production of advanced glycation end products (AGEs) through a complex series of reactions involving the non-enzymatic interaction of reducing sugars with proteins, lipids, and nucleic acids. Under normal physiological conditions, there is moderate AGE production, but it becomes significantly accelerated in the presence of persistent hyperglycemia due to increased glucose availability.

The pathophysiology of diabetes mellitus involves the detrimental effects of advanced glycation end products (AGEs), which can lead to insulin resistance through two primary mechanisms. AGEs can directly harm the body by trapping and cross-linking proteins, or indirectly by binding to cell surface receptors. While AGEs can interact with various receptors, the most important one is the receptor for advanced glycation end products (RAGE), a member of the immunoglobulin superfamily that was originally identified for its ability to bind AGEs.

RAGE is a multiligand receptor capable of recognizing three-dimensional structures, making it a pattern-recognition receptor. Its gene is located near the major histocompatibility complex III (MHC class III), indicating its involvement in immune responses. The full-length RAGE (fl-RAGE) is composed of extracellular domains (N-terminal V-type domain and two C-type immunoglobulin domains), a transmembrane domain, and a cytosolic domain. Recently, several naturally occurring RAGE protein isoforms have been described due to alternative splicing and proteolytic cleavage. These isoforms include truncated RAGE variants, such as soluble RAGE (sRAGE) and dominant-negative RAGE (dnRAGE), which can interfere with the signaling of fl-RAGE.

In diabetes, persistent hyperglycemia leads to elevated levels of AGEs in the bloodstream, which engage RAGE, triggering a cascade of signaling events. This includes the activation of various kinases and transcription factors, such as MAPK, p38, SAPK/JNK, ERK1/2, and JAK/STAT, ultimately leading to sustained activation of transcription factors like NF-κB, STAT3, HIF-1α, and AP-1. These signaling pathways contribute to insulin resistance through negative regulation of insulin signal transduction and altered insulin receptor signaling. Abnormal activation of the ERK1/2 pathway also influences diabetogenic factors and promotes adipogenesis.

Inflammation plays a critical role in insulin resistance as well. AGEs/RAGE signaling and increased inflammation activate additional mediators and transcription factors, including STAT3, which leads to degradation of IRS-1, exacerbating insulin resistance. The positive feedback loop of RAGE activation further upregulates RAGE receptor expression, perpetuating the process. NF-κB activation is a central player

in inflammation and insulin resistance, regulating the expression of inflammatory cytokines like IL-1β, IL-6, and TNFα.

Furthermore, RAGE/NF-κB signaling is linked to the activation of the NLRP3 inflammasome, a key component of the innate immune system that mediates the maturation and secretion of inflammatory cytokines, contributing to insulin resistance. Increased NLRP3 expression has been correlated with insulin resistance in various human studies.

In response to AGEs/RAGE signaling, increased levels of reactive oxygen species (ROS) are generated through NADPH oxidase activation, leading to oxidative stress. Mitochondrial dysfunction and ER stress also contribute to oxidative stress propagation. Mitochondrial ROS production activates kinases involved in stress responses, creating a vicious cycle of inflammation and ROS generation.

The interplay between RAGE-induced cellular dysfunction, protein kinases, inflammation, and oxidative stress attenuates insulin sensitivity in target cells. Persistent NF-κB activation positively regulates RAGE expression, further amplifying the process. Additionally, NF-κB p65 directly induces insulin resistance by repressing the transcription of the glucose transporter GLUT4 protein in skeletal muscles.

The AGEs/RAGE interaction activates several signaling cascades such as ERK/MAPK, IKK/NF-κB, PKC, and JAK/STAT and transcription factors such as STAT3, CREB, NFκB, and AP-1 which intensifies the inflammatory responses and causes oxidative stress. The AGEs/RAGE axis stimulates the infiltration of macrophages and causes an increase in the gene expression of inflammatory cytokines, extracellular matrix proteins and adhesion molecules. TGF-β, fibronectin, and collagen are overexpressed. The AGEs/RAGE axis-induced NF-B activation will result in an upregulation of RAGE expression as a positive feedback mechanism. The ongoing inflammation and oxidative stress of the signaling cascade driven by AGEs/RAGE/NFκB play are crucial in the pathogenesis of diabetic complications, such as diabetic foot ulcers [55].

4.2 Polyol pathway

In addition to advanced glycation end products (AGEs), the polyol pathway plays a role in the impaired healing of diabetic foot ulcers (DFUs). The polyol pathway is a metabolic process that converts glucose into sorbitol and fructose with the help of an enzyme called aldose reductase.

In diabetes due to increased glucose levels, the polyol pathway becomes active. This conversion of glucose to sorbitol consumes NADPH, which is a coenzyme involved in antioxidant defense mechanisms. Consequently, this decreases the cellular antioxidant capacity leading to the accumulation of oxygen species (ROS) and oxidative stress in DFUs.

The buildup of sorbitol and fructose within cells creates stress disrupting balance and hindering various essential functions required for effective wound healing. Osmotic stress causes swelling and damages cell membranes. Impairs the supply of nutrients and oxygen to the cells involved in the wound-healing process.

Moreover, converting sorbitol into fructose generates NADH that stimulates ROS production through dysfunction and activation of oxidative stress pathways. The increased production of ROS intensifies stress in DFUs causing harm to proteins, lipids, and DNA.

Activation of the polyol pathway also impacts cellular redox balance by altering the ratio between reduced glutathione (GSH) and oxidized glutathione (GSSG) affecting overall intracellular health.

The reduced GSH plays a role, as an antioxidant molecule while the oxidized GSSG serves as an indicator of stress. When there is an imbalance in the ratio of GSH to GSSG it disrupts the redox signaling system that's essential for wound healing processes as illustrated in **Figure 5**. This disruption can impair functions and compromise tissue repair.

In diabetes, the activation of the polyol pathway has been found to contribute to stress, cellular damage, and hindered wound healing. Researchers have explored targeting this pathway as an approach to enhance wound healing in diabetic foot ulcers (DFUs). Studies using models of ulcers inhibiting aldose reductase—the key enzyme, in the polyol pathway—have shown promise in reducing oxidative stress restoring cellular redox balance, and improving wound healing outcomes [56].

4.3 Diacylglycerol-protein kinase C (DAG-PKC) activation

Numerous mechanisms have been proposed to elucidate the detrimental impacts of elevated glucose levels, encompassing the polyol pathway flux, oxidative stress, non-enzymatic glycation, and the activation of diacylglycerol-protein kinase C (DAG-PKC) pathway. The DAG-PKC pathway plays a vital role in vascular function, influencing endothelial permeability, vasoconstriction, extracellular matrix (ECM) synthesis/turnover, cell growth, angiogenesis, cytokine activation, and leucocyte adhesion. Dysfunction in these systems has been associated with the diabetic state.

Studies have consistently reported heightened levels of total DAG in vascular tissues during diabetes. This increase in DAG levels can occur through multiple pathways, involving hydrolysis of phosphatidylinositides, metabolism of phosphatidylcholine by phospholipase C (PLC), or de novo synthesis from glycolytic intermediates like dihydroxyacetone phosphate and glycerol-3-phosphate. Metabolic labeling studies have demonstrated increased glucose incorporation into the glycerol backbone of DAG. The de novo synthesis of DAG involves stepwise acylation catalyzed by glycerol-3-phosphate acyltransferase and monoacylglycerol-3-phosphate acyltransferase. PKC activation is stimulated by DAG, which contains both saturated and unsaturated fatty acids, with 1-palmitoyl-2-oleoyl-sn-glycerol being significant, although 1-stearoyl-2-arachidonyl-sn-glycerol may be the most active. Moreover, the DAG-PKC pathway can be activated by hyperglycemia-induced increases in oxidants such as H_2O_2, which directly activate PKC or enhance DAG production. In hyperglycemic conditions, elevated DAG levels predominantly consist of palmitate or oleate fatty acids, supporting the notion that increased DAG levels primarily result from de novo synthesis or PLD pathways, rather than rapid formation from the actions of phospholipase C. Enhanced PKC activation has been associated with multiple diabetic

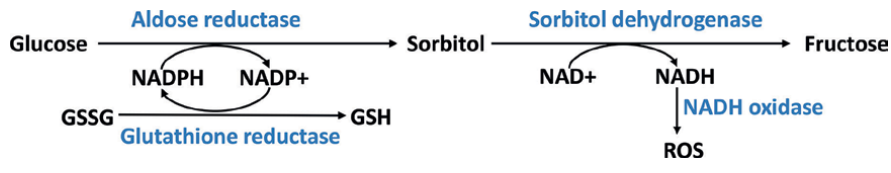

Figure 5.
This diagram illustrates how diabetes leads to the activation of the polyol pathway, converting glucose to sorbitol and fructose, which consumes NADPH and generates oxidative stress. NADPH: nicotinamide adenine dinucleotide phosphate, NADP+: oxidized Nicotinamide adenine dinucleotide phosphate, GSSG: glutathione disulfide, GSH: glutathione, NAD+: oxidized nicotinamide adenine dinucleotide, NADH: nicotinamide adenine dinucleotide, ROS: reactive oxygen species.

complications, including alterations in blood flow, basement membrane thickening, ECM expansion, vascular permeability, angiogenesis, cell growth, and changes in enzymatic activity, such as Na^+-K^+-ATPase, cPLA2, and MAP kinase [57].

4.4 The nitric oxide (NO) pathway

The nitric oxide (NO) pathway plays a crucial role in wound healing, including diabetic foot ulcers (DFUs). NO is a signaling molecule synthesized by the enzyme nitric oxide synthase (NOS) from the amino acid L-arginine. In normal physiological conditions, NO exerts beneficial effects on wound healing by promoting angiogenesis, regulating inflammation, and stimulating collagen synthesis. It has many protective roles in the treatment and prevention of diabetes complications.

However, in diabetes, the NO pathway is impaired, contributing to the delayed wound healing observed in DFUs. Several mechanisms contribute to the dysregulation of the NO pathway in diabetes:

1. Reduced NO bioavailability: diabetes is associated with decreased bioavailability of NO due to decreased NOS activity and increased oxidative stress. This imbalance disrupts the signaling cascade mediated by NO, leading to impaired vasodilation, angiogenesis, and endothelial function, which are critical for proper wound healing.

2. Advanced glycation end products (AGEs): AGEs, discussed earlier, also play a role in impairing the NO pathway. AGEs can react with NO, leading to the formation of reactive nitrogen species (RNS), such as peroxynitrite. RNS can further exacerbate oxidative stress, impair NO-mediated signaling, and induce cellular damage.

3. Diminished endothelial nitric oxide synthase (eNOS) activity: in diabetes, eNOS activity is reduced, leading to decreased NO production. This reduction is linked to alterations in intracellular signaling pathways, including decreased activation of the Akt pathway and increased protein kinase C (PKC) activity, both of which negatively impact eNOS function.

The impaired NO pathway in DFUs has detrimental effects on wound healing. Reduced NO bioavailability compromises angiogenesis, impairing the formation of new blood vessels necessary for delivering oxygen and nutrients to the wound bed. Moreover, impaired NO signaling disrupts the inflammatory response and compromises immune cell recruitment, leading to prolonged inflammation and increased susceptibility to infection.

Restoring the NO pathway represents a potential therapeutic strategy for improving wound healing in DFUs. Approaches such as the use of NO donors, NOS cofactors, and modulators of eNOS activity have been explored to enhance NO bioavailability and promote wound healing in diabetes. These interventions aim to restore proper NO signaling, improve angiogenesis, reduce inflammation, and enhance tissue repair processes.

In conclusion, the dysregulation of the NO pathway in diabetic foot ulcers contributes to impaired wound healing. Restoring NO bioavailability and improving NO-mediated signaling hold promise for developing novel therapeutic interventions to address the impaired wound healing observed in DFUs. Further research is needed

to elucidate the specific mechanisms underlying NO pathway dysfunction in diabetes and to explore targeted strategies for therapeutic intervention [58].

4.5 Epigenetic modifications

To add to what has been said, hyperglycemia was highlighted in the literature to be involved in mediating epigenetic changes that contribute to forming diabetic complications, including the cell types involved in impaired wound healing in diabetics [54].

Epigenetic modifications are heritable changes in gene expression that do not involve alterations in the DNA sequence. Various epigenetic mechanisms exist, including changes in DNA methylation, microRNA expression, and histone post-translational modifications. In the context of DFUs, epigenetic modifications have been implicated in the dysregulation of various cellular processes crucial for wound healing, such as cell proliferation, migration, angiogenesis, and inflammation.

Studies have shown that hyperglycemia-induced epigenetic changes occur in key cell types involved in wound healing, including keratinocytes, fibroblasts, and immune cells. DNA methylation, a prominent epigenetic mechanism, plays a significant role in gene silencing. Hypermethylation of specific gene promoter regions in DFUs can suppress the expression of critical genes involved in wound healing, impairing the regeneration of new tissue. Conversely, hypomethylation of genes associated with inflammation and oxidative stress exacerbates the inflammatory response and oxidative damage, further impeding the healing process.

The endothelium, which plays a critical role in maintaining vascular balance, closely interacts with various factors present in the diabetic environment. It is highly sensitive to metabolic and inflammatory signals, making it susceptible to damage and contributing to the development of atherogenesis. The harmful impact of hyperglycemia on endothelial function is widely recognized, and as a result, both activated endothelial cells and endothelial progenitor cells have become promising targets for therapeutic interventions in diabetes mellitus [59, 60].

Temporary elevation of glucose levels leads to different changes in histone lysine modifications, including the addition of a methyl group to the H3 histones at lysine 4 (H3K4m1). This modification remains present at the promoter region of the RELA gene, responsible for encoding the nuclear factor (NF)-κB-p65 subunit, for up to 6 days after vascular endothelial cells return to normal glucose levels (normoglycemia). The NF-κB-p65 subunit is a crucial proinflammatory transcription factor that plays a central role in regulating genes involved in vascular inflammation and atherosclerosis, including those responsible for adhesion molecules, cytokines, and chemokines [61].

Furthermore, there is a phenomenon, termed metabolic memory or the legacy effect, says that hyperglycemia induces vasculature damage which stays long after there is a state of normoglycemia. The mechanism is unknown yet, but it has been proposed that epigenetic changes, which happen independently of changes in the genotype, may be responsible. This is because these changes, especially histone modifications and DNA methylation, have been shown to be heritable after several rounds of cell division [54, 62].

4.6 Oxidative stress

Oxidative stress refers to an imbalance between the production of oxygen species (ROS) and the cellular defense mechanisms that protect against them. In diabetes, prolonged high blood sugar levels lead to increased ROS production through

processes, such as glucose oxidation problems with mitochondria functioning and activation of enzymes.

ROS can have effects on cellular processes that are crucial for wound healing. These effects include hindering collagen synthesis reducing the response to growth factors impeding blood vessel formation (angiogenesis) and disrupting the remodeling of the matrix. Additionally, ROS interferes with signaling pathways that are important, for cell movement, reproduction, and specialization. This disruption affects the coordinated efforts of cell types involved in repair. The persistent oxidative stress seen in foot ulcers contributes to inflammation and delays the healing process [63].

5. Conclusion

Diabetes foot ulcers (DFUs) are a common and devastating consequence of diabetes mellitus. Despite advancements in wound care, DFUs often exhibit delayed wound healing and tissue regeneration, offering substantial problems to patients and healthcare practitioners, emphasizing the need for a deeper understanding of the underlying molecular mechanisms involved in wound healing. This chapter explored the inflammatory phase of wound healing, highlighted the crucial roles of growth factors, and examined the impact of signaling pathways like PI3K/Akt and MAPK/ERK in diabetic wound healing. It also touched on epigenetic modifications, oxidative stress, and the effects of advanced glycation end products (AGEs) on cellular function. Ultimately, this understanding of signaling pathways and mechanisms has the potential to revolutionize the management.

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Chapter 6

Perspective Chapter: Clinical Features and Management of Diabetic Foot Ulcers

Reem Al-Subai, Reema M. Al-Emadi, Hesham Aljohary and Musab Murad

Abstract

This chapter aims to explore the clinical features and effective management strategies for diabetic foot ulcers (DFUs), which, if not appropriately treated, can lead to serious consequences and ultimately require amputation. It is crucial to adopt a comprehensive approach that encompasses accurate diagnosis and effective treatment plans. These ulcers have a multifactorial etiology and a wide range of clinical features that can be attributed to the ulcers themselves, the underlying causes contributing to their development, or their complications, particularly infections. However, timely and accurate diagnosis can be challenging due to a lack of sensation, making risk factor assessments and severity assessments through various classification systems necessary. Managing DFUs effectively requires a multidisciplinary approach that includes optimum glycemic control, performing wound debridement, relieving pressure from the affected area, controlling infections, and utilizing appropriate dressings.

Keywords: diabetic foot ulcers, DFU, clinical features, management, classification, neuropathy, peripheral artery disease, foot deformities

1. Introduction

The etiology of diabetic foot ulcers (DFUs) is multifactorial [1]. It often includes neuropathies, vasculopathies, immunopathies, foot deformities, biomechanical defects, suboptimal management of blood glucose as well as neglecting appropriate foot care, using inappropriate footwear, and foot skin dryness [1–4].

2. Clinical Features

2.1 Neuropathy: nerve damage in diabetic foot

Neuropathy is found in more than 80% of DFU patients [2, 3]. The sensory, motor, and autonomic nervous systems may be affected as a consequence of diabetic neuropathy [3].

Sensory neuropathy alters and reduces the perceptions of pain and pressure. The patient will normally present with altered sensations of the foot including paresthesia, hyper/hypoesthesia, and dysesthesia [1]. Due to loss of sensation, repetitive trauma and injury may occur with the patient none the wiser, preceding an ulcer; this might be due to footwear that is ill-fitted or small sprains and strains [3]. As a result, patients tend to seek care at a later, more severe stage. Since diabetic neuropathy can influence multiple body systems (autonomic neuropathy), it might also compromise the foot microcirculation, as well as result in skin changes, such as dry skin [2].

Motor neuropathy results in weakened intrinsic muscles and collapse of anatomical structures of the foot leading to deformities such as hammer toes, Charcot foot etc. [2]. These malformations can alter the distribution of pressure across the foot, deeming particular areas increasingly predisposed to injury and ulcer formation [3]. Pressure changes and loss of sensation also contribute to the formation of calluses [1].

Autonomic neuropathy will affect the integrity of the skin, since the autonomic nervous system acts on the blood vessel network as well as the physiological secretions. This will present as anhidrosis causing skin dryness, flaking, and increasing fragility. This renders the skin more vulnerable to dermal deterioration and fissure formation, increasing susceptibility to infection [3]. Changes in nail health (brittle nails) might be present [1].

2.1.1 Diabetic foot deformities

In conjunction with neuropathy and injury, foot deformity was asserted by the Task Force of the Foot Care Interest Group of the American Diabetes Association as the most prevalent trio of interconnected factors that will ultimately lead to the formation of ulcers [1, 5]. Some of the most prevalent anatomical deformities include deformities of the metatarsophalangeal joint, interphalangeal joint and prominent metatarsals. For instance, claw foot (pes cavus) manifests as flexed interphalangeal joints and hyperextended metatarsophalangeal joints while hyperextension of the metatarsophalangeal joint and distal interphalangeal joint along with flexion of the proximal interphalangeal joints indicate hammer toes [3, 6, 7]. In addition, other common deformities include pes equinus presenting with limited dorsiflexion of the foot due to tightness in the Achilles tendon and hallux valgus (bunions) characterized by the lateral deviation of the first metatarsal among others [6, 7]. These changes in the anatomical structure can limit joint movement and intensity pressure on the plantar surface [8].

The genesis of these deformities remains poorly established. A literature review conducted in 2016 discussed that there is no substantial evidence to uphold the widely held notion that foot deformities arise due to motor neuropathy leading to atrophy and imbalances of the muscles [6]. However, weak muscles and limited joint mobility were found to be linked with foot deformities and unsteady gait was linked with all the aforementioned [6].

Gait pattern can be altered in diabetic individuals [9]. A study in 2020 established gait analysis as a useful assessment for the identification of individuals at risk of ulceration [10]. They found that diabetes patients with no alteration of anatomical structures in the foot exhibited gait abnormalities like lateral shift of peak pressure when walking and elevated peak pressure at the medical heel region in those with diabetic neuropathy. Elevated peak plantar pressures and altered pressure distribution were found prior to the formation of foot deformities and deterioration of soft tissue on the underside of the foot that will lead to

ulcer formation. Dynamic plantar pressure analysis is a valuable tool for diagnosis and proactive prevention of foot deformities [10].

2.1.2 Charcot neuropathic osteoarthropathy (CNO)

CNO is a chronic inflammatory condition affecting individuals with diabetic neuropathy and those with peripheral neuropathy [11, 12]. Osseous, joint, and soft tissue damage, usually in the foot and ankle, may or may not be associated with pain and might result in chronic alterations of the foot's anatomical structure due to fractures, dislocations, and fracture-dislocations [11, 12]. Typically, clinical manifestations include a swollen and erythematous joint with a 2°C increase in temperature in comparison to the unaffected joint [13, 14]. CNO is distinguished by four stages similar to the active and inactive phases of disease including inflammation, fragmentation, coalescence, and consolidation. In the active phase, the foot becomes inflamed and often painless because of neuropathy [15]. In addition, transient osteopenia can lead to bone fragility resulting in fractures, joint destruction, and collapse of the foot's longitudinal arch [16, 17]. Meanwhile in the inactive phase, the erythema will have subsided, but some swelling of the bone marrow and soft tissues might remain. Notable joint and bone damage precedes bone overgrowth that consequently leads to prominent osteophytes (bone spurs) and palpable loose fragments within the joint [16, 17].

The most used staging system is the Eichenholtz staging system assessed via clinical manifestations and radiology [18]. In stage 0, there is little inflammation, swelling of soft tissue, and insignificant x-ray findings. However, magnetic resonance imaging (MRI) findings demonstrate microfractures, bone marrow edema, and bone contusion [19]. Recognizing and managing the disease at this stage aids in the prevention of foot deformities [20, 21]. Stage 1 (fragmentation) is marked by soft tissue swelling and inflammation becomes severe. Macro-fractures are seen on x-ray and on MRI as well, which shows bone marrow swelling, in addition to bone resorption initiated with joint dislocations [19]. Bone remodeling commences as the fracture heals and the debris is resorbed marking the end of bone resorption characterizing stage 2 (coalescence). Stage 3 (consolidation) represents the last stage of bone remodeling and reconstruction. This stage marks the transition to the chronic CNO phase in which ulcers occur frequently and substantial structural alterations are undergone by the arch of the foot [19]. The final stage of CNO is known as rocker-bottom deformity [22].

2.2 Vasculopathy

Decreased tissue perfusion can, in addition to other factors like co-existing chronic conditions and infections, hinder the wound healing process, impair the body defense system, and increase the risk of ulcerations [3]. This peripheral ischemia of large and small vessels can also increase the risk of infection and might chronically lead to the foot becoming gangrenous and thus, amputated [23]. It may be classified into macro- or microvascular disease. Macrovascular refers to peripheral arterial disease (PAD) in which the arteries of the upper or lower limbs are narrowed or occluded. Etiologies of PAD include emboli, thrombi, or vasculitis and PAD is believed to be a contributor to lower limb complications [3, 24]. However, atherosclerosis is usually the primary etiology of which diabetes is considered a risk factor as discussed by [25].

Microvascular disease refers to the damage of small blood vessels caused by diabetes mellitus. These small vessels may show capillary wall thickening, sclerotic vessel walls, endothelial proliferation, and damage [3, 26]. It can affect various organs

and tissues in the body and can impair the healing of the skin, especially in the lower extremities resulting in ulcers, infections, or gangrene.

Symptoms that are indicative of PAD include intermittent claudication, which is pain reminiscent of cramps in the leg, usually upon physical activity, and is found in 10% of individuals with PAD, while pain during inactivity might signify critical limb ischemia [27, 28]. About half of individuals with PAD will not experience any symptoms [27]. Upon examination, skin alterations related to ischemia might be present in some patients; ischemia associated trophic changes can include alopecic skin changes and glossy and lustrous skin, in addition to cool feet [3, 27]. However, note that hairless skin is clinically of little value as an indicator of ischemia [28]. Furthermore, patients with PAD can also present with postural erythema due to reduced blood flow and postural pallor upon elevation of the leg. Peripheral pulses may also be abated, especially the femoral artery, popliteal artery, posterior tibial artery, and dorsalis pedis artery [27]. It is crucial to examine regions of pressure in the foot like the plantar region, the calcaneal area, the area posterior to the malleolus, and the metatarsal heads, in addition to the interdigital area. Important to note is that the presence of blisters in a foot with ischemia foretells ulceration [28].

2.3 Infections in DFU: Clinical presentation

Diabetic foot infections can present in about 58% of individuals with an acute foot ulcer [3]. It negatively affects the quality of life as reported by individuals with diabetic foot infections [29]. The infection is initiated by the invasion of microorganisms in the ulcerated area of broken-down skin. Later, the microorganism colonizes the region and triggers an inflammatory response that will induce a breakdown of tissue [3]. Due to the abnormal mechanism of the white blood cell immune response, patients might not present with the classic manifestations of infection, such as fever, fatigue, nausea, vomiting etc. [30]. Among the most preliminary presentations of a diabetic foot infection is elevated blood glucose of unknown etiology. Patients may present with manifestations of the "diabetic flu" as well, such as nausea, vomiting, anorexia, fever, and chills; the foot must be closely inspected for infections or ulcers in this case [31].

For identification of an infection, it is most important to look for a history of chills and fever and upon the examination of the foot, the existence of pus and a minimum of two manifestations of inflammation including pain, a rise in temperature, redness, and rigidity of tissue surrounding the ulceration area [1]. A probe to bone test is conducted with a sterile, blunt metal probe on the ulcer; if the bone can be palpated by the probe, it is indicative of osteomyelitis and is especially useful for patients with diabetes [32–34]. The risk factors that exhibit higher odds of diabetic foot infections comprise palpable bone in probe to bone test, ulcers lasting for more than 30 days, reoccurring ulcers, traumatic ulcers, and having PAD, in that order [35].

Diabetic foot infections are classified into no infection where the patient does not possess any of inflammatory signs discussed above [36]. Mild infection is characterized by there being pus, any two of the signs of inflammation, and any cellulitis or redness that is localized to 2 cm or less around the ulcer and does not go deeper than superficial subcutaneous tissue. Moderate infection includes the previous but might extend above 2 cm surrounding the ulceration and can extend to the bone and might involve gangrene as well. The severe stage of infection can involve all of the above in addition to being metabolically unstable and presenting with signs of systemic toxicity such as fevers, chills, low blood pressure, confusion, elevated blood glucose, and acidosis among others [36].

2.4 Classifications

Classifications of diabetic foot ulcers are systems that help to describe the characteristics and severity of the ulcers, as well as to predict the outcomes and guide the treatment. Although there are several classifications of diabetic foot ulcers, there is no universally agreed-on standard. Some of the common classifications are discussed below.

2.4.1 Meggitt-Wagner (MW) system

The Meggitt-Wagner (MW) system was initially established by Meggitt in 1976 and further adjusted and spread by Wagner in 1981. It is considered one of the most commonly used systems for the assessment of diabetic foot ulcers [1, 37–39]. It is deemed to be a practical and simple tool for utilization in clinical settings [37, 39]. It is composed of six grades, ranging from 0 to 5 based on the ulcer depth and the extent of skin necrosis (gangrene). Most patients in clinical settings have a grade of 2 or 3 [37].

However, among the limitations affecting the precision of this classification is that it does not recognize ischemia or infection in wounds of superficial depth [37]. Ischemia is only considered in grades 4 and 5 by the presence of gangrene. In addition, infection is identified only in Meggitt-Wagner grade 3. Despite the popularity of the Meggitt-Wagner classification, it has not been validated yet [37].

2.4.2 University of Texas classification (UT) system

This classification system developed more recently in the mid 1990s by the University of Texas assesses ulcer depth, in addition to ischemia and infection as opposed to the MW classification, but does not consider wound size as discussed by [37, 38]. It is also considered to be one of the most commonly used classification systems, along with the MW system [1]. The classification is composed of a 4 by 4 matrix, where wound depth is evaluated horizontally on a 4-grade scale of 0 to 3 and the ischemia and infection vertically indicating 4 stages from A to D, with stage A indicating no ischemia or infection and D, including both [39]. Some studies suggest that the UT classification system is useful for predicting amputation whereas the MW classification can only classify wound condition, while other studies suggest that both are helpful for predicting amputation, but the UT classification system can better predict the time it will take to heal [37, 38]. This is why it is one of the most widely used systems. The UT classification system is also a validated tool [37].

2.4.3 The size (area, depth), sepsis, arteriopathy, denervation [S(AD)SAD] system

The S(AD) SAD system is mainly used for clinical audit rather than in clinics as explained by [37, 39, 40]. This system evaluates five features that differentiate the lesions from each other and are given a score of 0, 1, 2, or 3 based on severity; the five features include the size (area and depth), sepsis if infected, arteriopathy if ischemic and denervation if neuropathic, with the latter two being assessed at each depth within the matrix [37, 40]. The S(AD)SAD system was validated prospectively in which four of the five clinical features correlated significantly and independently with wound healing and it has also been validated by looking at associations with outcome in internal and external settings as discussed in [37, 40].

2.4.4 The site, ischemia, neuropathy, bacterial infection, area, depth (SINBAD) system

The SINBAD system is a simple version of the S(AD)SAD classification, and it has gained validation in three separate continents for the reliable prediction of healing time [41]. It is also utilized by the UK National Diabetes Foot Care Audit [40]. It shares the same five characteristics of the S(AD)SAD system, with the additional factor of site distinguishing between the forefoot and hindfoot. The grades are calculated based on if a factor is found (1) or not (0); a maximum grade of 6 can be obtained [39, 40].

2.4.5 The perfusion (ischemia), extent (area), depth, infection, sensation (neuropathy) (PEDIS) system

The PEDIS system was first constructed by the International Working Group of Diabetic Foot (IWGDF) for utilization and classification in clinical research as stated by [37, 40, 42]. It consists of five features: perfusion (peripheral artery disease), extent (area), depth, infection, and sensation (neuropathy); the criteria are considered to be a bit complex with specific definitions and so the system is challenging to apply to all situations, as it was constructed mainly for research purposes [42].

2.4.6 The wound, ischemia, and foot infection (WIfI) system

The Society for Vascular Surgery Lower Extremity Guidelines Committee developed the wound, ischemia, and foot infection system to serve the increasing prevalence of ulcers with both neuropathy and ischemia. This system includes the three main features that are most likely to predict amputation risk at 1 year that will act as a guide to determine prognosis and select the most appropriate therapy and treatment options as discussed by [39, 42]. The components were graded on a scale of 0 to 3, including wound depth, extent of the ischemia, and if the foot is infected or not [42].

The ulcer region is appraised qualitatively. The ischemia is evaluated on the foundation of ankle brachial pressure index (ABPI), transcutaneous oxygen tension, and toe systolic pressure. Furthermore, the grading for infection was assessed via the Infectious Diseases Society of America (IDSA)/International Working Group on Diabetic Foot (IWGDF) criteria [42]. The evaluation for ischemia requires a level of aptitude and specific equipment that might not be accessible or obtainable in certain regions, countries, or institutions. However, it is important to note that the primary aim of this classification system was to be able to objectively determine the requirement for revascularization therapy [42].

2.5 Vascular and neurological assessment and imaging studies

2.5.1 Vascular assessment

The peripheral pulses including the femoral, popliteal, posterior tibial, and dorsalis pedis pulses are palpated and a comparison is made between the two sides [28]. Note the presence (+), diminished/weak (+/−), or absence (−) of peripheral pulses. Record the existence of any thrills; however, thrills give limited indication as to the location and extent of the disease [28]. The chance of having PAD is 4.9 times more likely if the peripheral pulses are absent, but PAD cannot be excluded if peripheral pulses are present [43].

Patients will usually present with diabetic retinopathy, nephropathy, or neuropathy in case the small arteries are affected. However, in other cases where larger vessels like the deep femoral artery are affected, abnormal non-invasive vascular testing

evaluating blood flow, velocity, and waveforms (triphasic, biphasic, or monophasic) is suggestive of macrovascular disease [3, 43].

A Doppler assessment should be carried out and the ankle brachial index (ABI) measured [44]. To measure the ABI, the systolic blood pressure is calculated at the ankles (dorsalis pedis artery or posterior tibial artery) and at the arm (brachial systolic pressure) via a manual sphygmomanometer with the aid of a Doppler probe [28, 45]. The higher of the ankle pulses is considered and divided by the highest brachial pressure of the two arms giving the ABI, measured for both limbs. The characteristic of the Doppler signal must be noted (waveform) [28].

In addition, usage of the ABI, toe-brachial index (TBI), and absolute toe pressures is considered the most common [43, 46]. An ABI >0.9 is considered normal, <0.9 is abnormal and may indicate claudication, <0.4 is often linked with tissue death and ischemia-related pain during rest, and > 1.2 might be suggestive of calcification in the arteries in patients with diabetes [28, 45].

PAD is indicated by a low ABI and TBI of below 0.91 and 0.7, respectively [43, 46]. The TBI supports the ABI. In cases of calcinosis, the arteries become less compliant and as a result, ABI might appear to be higher than expected with regard to PAD. As such, TBI is used as a supporting measure for the diagnosis of PAD, since the distal arteries (blood vessels of the digits) are not as influenced by calcifications than those proximal [43]. Transcutaneous oxygen pressures (TcPO2) can also shed light on alterations in the microvascular circulation and the capacity for wounds to heal [3].

2.5.2 Neurological assessments

The neurological tests are used to look for loss of protective sensation in patients with diabetes mellitus, in lieu of early neuropathy detection [45]. It is usually assessed via the Semmes-Weinstein 5.07 (10 g) monofilament, paired with one of the following: vibration testing, pinprick sensation, and ankle reflexes [2].

Semmes-Weinstein 10 g monofilaments evaluate cutaneous pressure in twelve different regions on the foot [2]. The monofilament is first tested on the proximal brachial area for patient demonstration. The patient is instructed to keep their eyes closed and indicate verbally ("yes" or "no") whether they are able to sense the monofilament's presence and the location in which the pressure was applied. Pressure perception must not be tested on callused areas [45]. When the ability to sense the pressure in any of the 12 regions is not present, this foretells an increased risk for ulcer formation [2]. It is also advised to perform this test on four anatomical regions of both feet, including the first, third, and fifth metatarsal heads and plantar surface of the distal hallux [45]. Failure to detect the nylon monofilament sensations in more than one of the plantar foot regions is suggestive of diminished large fiber nerve function [45].

Likewise, when a patient fails in the detection of pinprick sensations, it is linked with an increased risk of ulcer formation [47]. Failure to sense the pinprick just below the dorsal surface of the big toe on either foot is not normal [45].

Usually, vibration testing is carried out with a 128-Hz tuning fork placed on the bony prominence at the same location described above. The patient is asked to verbalize the initiation and cessation of vibration [2]. Loss of vibratory sensation is when the patient can no longer feel the vibration from the tuning fork, but the examiner still can [47, 48]. A biothesiometer, on the other hand, can quantitatively assess vibratory sensation by identifying the vibration-perception threshold (VPT), which is the minimum voltage required for sensing vibration on the pulp of the hallux [2]. A VPT greater than 25 is a strong predictor of sequential ulcer formation [49, 50].

The ankle jerk reflex is assessed over the Achilles tendon. If not present at first, the ankle reflex is reevaluated with reinforcement by locking the fingers together and pulling [45]. Abnormal reflexes are diminished with or without reinforcement and are linked with a high risk of ulcer formation [45, 47].

Another quick and simple technique is the Ipswich touch test, in which the clinical examiner gently and quickly touches their index finger to the patient's first, third, and fifth toe in either foot [2]. A patient's sensation is considered impaired when two or more areas (out of six in the 2 feet) lack sensation [2].

2.5.3 Imaging studies

Sometimes, it is difficult to evaluate the extent of the ulceration especially in the presence of exudates and slough [51]. So, medical imaging usually involves plain x-rays to detect potential undetectable osteomyelitis, there being air in subcutaneous tissue and any foreign bodies and any indications of concealed fractures [1]. Plain x-ray can also detect loss of bone density, CNO, and ulcer depth [51, 52]. In cases of CNO, x-rays may reveal eroded bones, fractures, manifestations of bone sclerosis,

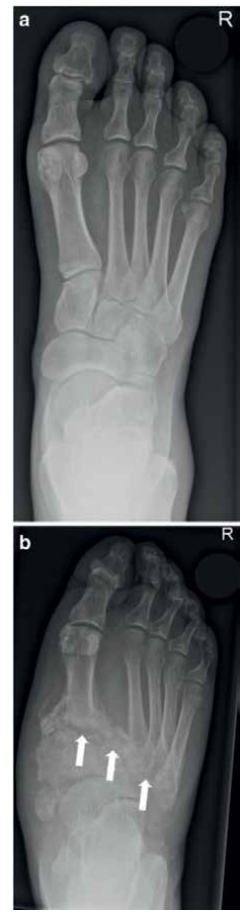

Figure 1.
Ref. [22]: Weight bearing x-ray in dorsal plantar projection. Fractures, subchondral cysts, erosions and luxation of Lisfranc's joint (white arrows) developed 5 months post baseline (b). Baseline (a).

fractures, and subluxations or dislocations of more than one joint, especially of the Lis Franc joint that, though common, frequently go unnoticed by experienced radiologists unless a CNO is kept in mind (**Figures 1** and **2**) [14, 53].

MRI is considered a favorable test especially for detecting osteomyelitis and CNO (**Figures 2** and **3**) [1, 51]. It is utilized for the assessment of the magnitude of ulcer infection by evaluating its depth, the presence of edema, as well as localized edema in the soft tissues, joints, and tendon sheaths [51]. In addition, positron emission tomography is highly specific for osteomyelitis [54]. Computed tomography (CT) scans and MRIs are useful for diagnosing abscesses if physical examination is inconclusive; however experienced examiners would be able to detect abscesses without radiological means [52].

Bone scans with technetium can be utilized for the diagnosis of underlying osteomyelitis, as well [1]. However, its utility is considered questionable as it often produces false negative and positive results [52].

Conventional angiography is used to evaluate the progression of vascular (atherosclerosis) disease and is important to carry out before vascular and endovascular surgery [52]. If patients are at increased risk or allergic to the injected substance, multidetector computed tomographic angiography (MRA) can be utilized instead. However, the MRA utilizes Gadolinium chelates as a contrast that can manifest three adverse events in those with renal insufficiency including pseudo hypokalemia, systemic nephrogenic fibrosis, and acute renal injury. Other options include multidetector computed tomographic angiography (MDCT), which evades arterial punctures

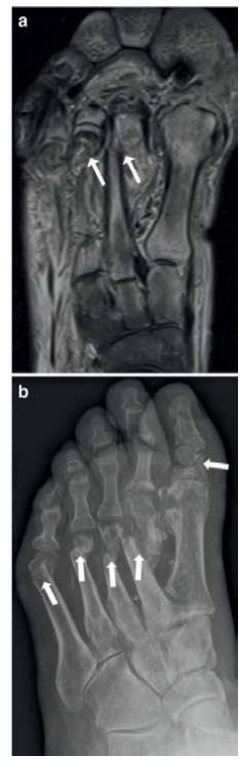

Figure 2.
Ref. [22]: Eichenholtz stage 1 (fragmentation) of CNO showing gross cortical fractures of the second to fifth metatarsals (white arrows) on MRI (a) and x-ray (b).

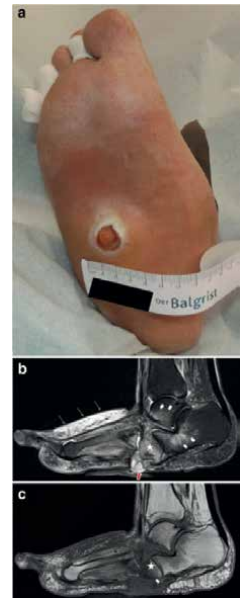

Figure 3.
Ref. [22]: (a) rocker-bottom deformity complicated by an ulcer on the plantar region of the foot, under the cuboid bone. (b) Shows spreading of infection to form a sinus tract to cuboid bone (asterisk) and bone marrow swelling as a result of active CNO (white arrows). (c) Shows osteomyelitis within the cuboid bone on a sagittal T1-weighted sequence.

and presents with the same adverse events as MRA. Those with renal impairment can opt for carbon dioxide angiography, but it requires iodine contrast material as well and so, is not that commonly used [52].

3. Management

The management of diabetic foot ulcers is a complex and multidisciplinary process that aims to prevent complications, promote healing, and improve quality of life. Clinical evaluation includes patient and wound assessments. Patient assessment encompasses assessing the parameters that affect the prognosis of DFU, including glycemic control, CBC testing, and other comorbid conditions like renal disease and heart failure that would worsen the prognosis. This requires a thorough history and physical examination, as well as laboratory tests, imaging studies, and vascular studies.

Wound assessment begins with debridement cleaning, and applying appropriate dressings, moisturizers, and topical agents. The wound care should be tailored to the characteristics of the ulcer, such as its size, depth, exudate, and infection. The ulcer should be classified according to its depth, infection, and ischemia. Antibiotic therapy is required for nearly all infected diabetic lesions; the use of antibiotics should be deferred for wounds that are not clinically infected. It depends on the classification of wound infections to mild-moderate and severe infections. The initial antibiotic medication must usually be decided empirically; it could be adjusted subsequently based on the availability of additional clinical and microbiological results. Antibiotics may be prescribed, either orally or intravenously, depending on the type and extent of the

infection. Microbial analysis is crucial to identify the specific pathogens behind the infection; it includes obtaining pus discharge sample from the wound and processing it. The infection should be monitored regularly, and the antibiotic therapy adjusted accordingly.

Offloading is necessary to reduce the pressure and friction on the ulcer, which can impair healing and worsen the wound. This can be achieved by using various devices, such as casts, braces, crutches, wheelchairs, or special shoes.

Revascularization should be considered to improve the blood supply to the ulcer and the affected limb, enhance healing, and reduce pain especially if there is evidence of peripheral artery disease or critical limb ischemia. This can be done by using medical, endovascular, or surgical interventions, depending on the severity and location of the vascular lesions.

3.1 Debridement

Debridement is a word borrowed from the French word "débrider," which means "to unbridle, unharness." It is the removal of non-viable or dead tissue from the site of the wound in order to promote the development of granulation tissue and re-epithelialization, two processes that aid in the healing process [38]. Eradication of the local infection will minimize the bacterial load and lower the risk of antibiotic treatment resistance. Debridement can be divided into mechanical and non-mechanical. Mechanical includes surgery, wet-to dry dressings, ultrasound debridement, biosurgery, and hydro-surgery. Non-mechanical includes enzymatic agents and autolytic debridement [55].

Mechanical debridement is relatively quicker than non-mechanical debridement; however, depending on which method is utilized, it might be selective or nonselective. It is also associated with more discomfort and pain relative to non-mechanical debridement, and more expensive. On the contrary, non-mechanical debridement tends to be more specific for non-viable tissue, simpler application with minor discomfort but it tends to be a slower process [56].

3.1.1 Surgical debridement

Surgical debridement is considered the most widely used method; it involves cutting away necrotic tissue with sharp instruments such as a scalpel or scissors [55]. It could be performed in inpatient or outpatient settings. The decision on where to carry out the debridement is determined by the patient's level of comfort, the level of anesthetic necessary, and the extent of the debridement process required [56].

It is the most appropriate choice for removing large areas of necrotic tissue and is indicated in cases of sepsis. 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. Potential adverse effects from this type of treatment include bleeding from the debridement itself, and anesthesia complications [57].

Conservative surgery for DFUs in patients with chronic forefoot OM is a safe and effective approach that improves recovery and minimizes the risk of limb loss and mortality when compared to radical amputation operations. The aim of the surgeon is to avoid amputation and keep it as a last but necessary action. The indications for limb amputation are life-threatening sepsis, wet gangrene, extensive muscle necrosis, and bed-ridden patients with impossible revascularization. This decision was taken

by vascular surgeons. DM-related lower limb amputation can be classified into minor and major amputations; minor involves minimal removal of tissue, typically at the level of the ankle or below including digits amputation, and partial foot amputation. Major amputation involves below and above the knee amputation and is indicated after a minor amputation if the wound is unlikely to recover, or if the necrosis has progressed to the legs [58].

3.1.2 Wet-to-dry debridement

Wet-to-dry debridement is a form of mechanical debridement that involves removing necrotic tissue from the wound. During this procedure, saline wound gauze is placed in the wound and allowed to dry completely, then it is removed from the wound bed without moistening it first, so it removes the dead tissue [59]. As saline evaporates, it becomes hypertonic, and fluid from the wound is sucked into the dressing, causing tissue desiccation [58].

This form of debridement is one of the most used dressing methods. However, in the literature, some would argue against it concluding that it does not constitute advanced wound care [58]. It increases the likelihood of external contamination compared to other debridement techniques and requires multiple dressing changes. As well as being often a painful experience for the patient, and in addition to removing dead tissue, it often removes viable tissue as well [57].

3.1.3 Ultrasound debridement

Ultrasound debridement is a technique that uses sound energy to mechanically debride wounds by contact or noncontact use of low-frequency ultrasound energy. The procedure employs a cavitation approach to generate sound energy from a handheld tool, which mechanically destroys devitalized tissue [56]. This method of debridement removes dead tissue, stimulating necrotic tissue, lessening bacterial colonies formation [60].

3.1.4 Bio-surgery (maggot-larvae)

Maggots are the larvae of the fly *Lucilia sericata* that are placed on necrotic wounds to consume dead and necrotic tissue. They are placed on the wound as their secretions have antibacterial features that have a bacteriostatic impact, as well as proteolytic enzymes including collagenase that break down collagen matrix [61]. It possesses features of debridement, antimicrobial, and healing stimulation. It is a selective process, which makes it advantageous.

3.1.5 Hydro-surgery

Hydro-surgery is a high-pressure process that can be performed using a syringe or a saline jet stream. It is used for disposing of foreign bodies and debris from the wound; it is a nonselective method of debridement that can remove granulation tissue and may endanger the health care practitioner. The mist produced by high-pressure watering may contaminate the provider. It does not take much time and it is suitable for large wounds [56].

The ability to integrate this technology with antiseptic remedies is an intriguing part of it. This has the potential to increase antibacterial activity, which is an important aspect of debridement operation [61].

3.1.6 Enzymatic debridement

Enzymatic debridement is applying proteolytic enzymatic substances to the wound. Many agents are used, for example, collagenase, bromelain, and papain. The most used enzyme is collagenase—sourced from strain of *Clostridium histolyticum*—which breaks down the collagen in the necrotic tissue to debride Clostridium bacteria. It's advantageous since it is highly selective for collagen, and it is pain-free [62].

However, a study discussed the possibility of collagenase acting as a stimulant to keratinocyte and endothelial cell migration, increasing epithelization rather than acting as a stringent debridement agent [62]. It remains a good option in patients who require debridement but are not surgical candidates.

3.1.7 Autolytic debridement

The most conservative debridement method, phagocytic cells and proteolytic enzymes break down the necrotic tissue during this natural debridement process. Only necrotic tissue will be impacted by the debridement, making it a very selective process. It is indicated for non-infected wounds. Infected wounds may potentially benefit from its usage as an additional treatment. When treating infected wounds, it could be used with other debridement methods, such as mechanical debridement [63]. Below is a table summarizing the types of debridement mentioned in this chapter (**Table 1**).

3.2 Infection control

The likelihood of delayed wound healing and amputation is known to increase with wound infection. To improve outcomes, it is crucial to diagnose an infection in a diabetic foot infection and treat it with antibiotics [64]. Following the proper management of debridement of necrotic tissue, infection, and ischemia, there are a variety of adjuvant treatments that may be useful to accelerate wound healing.

Antibiotics are not indicated for diabetic ulcers unless there are signs of infection. Patients with mild infections are treated with oral antibiotics that target gram-positive cocci like streptococci and *Staphylococcus aureus* and can be treated in outpatient settings. Effective options include medications like cephalexin, dicloxacillin, amoxicillin-clavulanate, or clindamycin [65].

Patients must be admitted for parenteral antibiotic treatment when they have moderate-to-severe infections. Gram-positive cocci, obligate anaerobes, and aggressive gram-negative aerobes should all be included in the empiric options. Vancomycin, linezolid, or daptomycin is effective against MRSA [65].

Mechanical debridement	Non-mechanical debridement
Surgery	Enzymatic agents (collagenase)
Wet-to-dry (saline wound gauze)	Autolytic (proteolytic enzymes)
Ultrasound (sound energy)	
Bio-surgery (maggot larvae)	
Hydro-surgery (syringe/saline jet stream)	

Table 1.
Types of debridement.

3.3 Topical antimicrobial therapy

3.3.1 Iodine-based

Cadexomer iodine (e.g., Iodosorb) is an antibacterial that promotes healing by maintaining a moist wound environment. Cadexomer iodine kills all gram-positive and gram-negative microorganisms. There is some indication that cadexomer iodine produces greater healing rates than normal treatment in topical formulations, although it should most likely only be considered for short-term use [57].

3.3.2 Silver-based

Silver dressings can be utilized as the primary or secondary dressings to treat mild, moderate, or heavy discharge in both acute and chronic wounds such as DFU, pressure ulcers, and ulcers of the legs.

The findings of a meta-analysis revealed that silver dressings improve DFU healing rate, decrease time required for full healing, reduce in-hospital length, and increase the infection clearance rate, while having no significant impact on ulcer area reduction [66].

3.3.3 Honey-based

Honey has broad-spectrum antibacterial activity due to its high osmolarity and hydrogen peroxide content. According to a meta-analysis, honey dressing effectively promoted wound healing and bacterial clearance time within the first 1 to 2 weeks of application.

According to the findings of systematic reviews evaluating honey's ability to aid healing in a variety of wounds, there are insufficient data to make recommendations for the routine use of honey for all wound types; specific wound types, such as burns, may benefit, while others, such as chronic venous ulcers, may not [57].

3.4 Wound dressings

3.4.1 Alginate

Alginate dressings are made of natural polysaccharides derived from several types of algae. They're available in a variety of forms, including beads, and pads. These dressings form a gel that is characteristically highly absorbent, which makes it better suited for wounds that are moderately to extensively exudative, while keeping the skin moist [64].

3.4.2 Vacuum-assisted closure

Negative pressure wound therapy (NPWT), also known as vacuum-assisted closure, is an adjuvant therapy that is utilized in the treatment of open wounds that imparts sub atmospheric pressure to the wound surface. The wound care system comprises an open-cell foam dressing, a semi occlusive adhesive cover, a fluid collection device, and a suction pump. NPWT promotes wound healing [67].

3.5 Oxygen therapy

3.5.1 Hyperbaric oxygen therapy

Hyperbaric oxygen therapy entails inhaling 100% pure oxygen in a hyperbaric chamber. Many individuals with DFUs have poor oxygenation to injured areas, especially if they have vascular disease. It promotes angiogenesis by increasing local tissue oxygen perfusion of the wound. HBOT may be particularly effective in people with diabetes who have undergone wound care for more than 4 weeks and have had a poor or no response to wound care treatment [56].

3.5.2 Topical oxygen

Topical oxygen therapy entails providing oxygen over the site of the ulcer rather than through the circulatory system as in hyperbaric oxygen therapy. Patients who are not eligible for HBOT may find this approach more appealing. The impact of topical oxygen therapy on the healing process is difficult to notably explain, but it provides an option with some marginal potential advantages and relatively minor risks [56].

This is administered by a high-flow oxygen concentrator machine and applied through a bag or container enclosed around the wound. Sustained topical oxygen therapy is administrated directly to the wound and uses pure (>99%) humidified oxygen supplied by a tiny, electrochemical oxygen generator [68].

Another way of administering topical oxygen is by applying hemoglobin containing spray to the wound. It functions by binding oxygen from the atmosphere and diffusing it into a wound to speed up the wound-healing process [69]. After adequate debridement, the spray is applied for 1–2 seconds, and the wound is covered with a dressing. In a 2018 study that observed the healing effect of various wound types, it concluded significant improvements that were detected very early following the introduction of hemoglobin spray, with statistically significant benefits identified within 1 week of the first application across wound types [70].

3.6 Offloading techniques

According to evidence-based guidelines, offloading is an essential step in aiding recovery and limiting foot ulcers and is a key aspect of DFU treatment. Mechanical offloading proves helpful for ulcers that undergo prolonged or frequent pressure and stress or recurrent mild pressure. To reduce the incidence of foot ulcers and infection, they disperse pressure on plantar surfaces, decreasing pressure on the ulcers [71]. For healing to be maintained, the offloading system must reach a threshold peak pressure of 200 KPa. The patient needs shoes for indoor and outdoor use, which the orthopedic specialist must provide [72]. Offloading devices include total contact casts, cast walkers, shoe modifications, and other devices to assist in ambulation [57].

3.6.1 Total contact cast

Total contact casting is considered the gold standard treatment for offloading DFU [71]. A total contact cast is a non-removable semi-rigid molded cast wrapped around and in contact with the foot and a portion of the leg using the TCC technique. To have complete access to the foot's sole, the cast is frequently placed on a patient

who is lying on his or her back with the knee flexed and the ankles in a neutral posture. Indications of this type of cast include plantar non-infected neuropathic ulcers of forefoot and midfoot (Meggitt-Wagner grade I and II) and early stages of Charcot arthropathy. The principle behind it is raising the weight-bearing surface area and distributing pressure over a broader region, reducing pressure. It is important to note that fracture stabilization in Charcot arthropathy -main goal rather than unloading- results in less localized tissue inflammation and swelling. The duration of the TTC is until the swelling subsides and stage III consolidation of Charcot arthropathy is achieved and until the ulcer heals.

3.6.2 Cast walkers

Cast walkers relieve pressure on the forefoot. Removable cast walkers keep the ankle at a 90-degree angle, reducing pressure on the forefoot. They can be removed by the patient, allowing for frequent ulcer inspection and dressing changes. For this reason, they can be used for infected ulcers [57].

3.6.3 Therapeutic shoes

Following ulcer healing, therapeutic shoes with orthotic insoles are recommended as a safeguard against recurrent ulcers.

A study demonstrated findings show the use of offloading therapeutic footwear minimizes the occurrence of DFU significantly. However, the positive impact may gradually subside with time [73].

Wedge shoes are a type of therapeutic footwear to offload the forefoot and heel. These shoes could be beneficial in some conditions. Plantar heel ulcers, for example, tend to be more challenging to heal due to an inability to effectively offload this area of the foot, but the heel wedge shoe may be helpful in achieving this goal. The downside of wedge shoes is that most individuals, particularly older adults, or those with proprioception disorders, may find it difficult, if not impossible, to keep their balance while wearing them [57].

3.7 Multidisciplinary approach to diabetic foot care

The MDT approach requires an integrated and shared effort among health care experts from several disciplines. According to a meta-analysis [70], lower extremity amputations (LEAs) and diabetic foot ulcerations (DFUs) have been demonstrated to decrease with the use of MDTs.

MDT includes medical professions, including Endocrinology, General Medicine, Infectious Disease, and Physical Medicine & Rehabilitation. Surgical disciplines like General Surgery, Orthopedics, Vascular, Surgery, Plastic Surgery, and Podiatry, in addition to nurses. It has been proposed that podiatrists serve as "gatekeepers" for the management and prevention of DFUs [74]. Physicians are required to assure optimal metabolic regulation and to assess long-term consequences such as infections, renal insufficiency, and nutrition. Surgeons can execute urgent debridement or limb amputation for control of infection. Vascular surgeons assess the extent of ischemia associated with wounds, develop a treatment plan, perform open or endovascular surgery, and manage peripheral arterial disease. Rehabilitation staff will screen and categorize risk, select footwear and orthotics, educate the patient, and provide psychological support.

3.8 Preventive strategies and patient education

Prevention of DFU requires lifestyle adjustment, lipid control, blood pressure management, and glucose regulation [75]. Once a year, complete foot exams should be performed on all diabetic patients. The purpose of this evaluation is to identify the risk factors that could lead to a foot ulcer and, ultimately, limb amputation. The physical examination includes vascular and neurologic assessment [75].

Patient education is crucial to avoid developing DFU and detect them early on. Some of the important recommendations for foot care include [2] avoiding activities that can cause foot injury, like walking barefoot. Both feet should be checked regularly for any deformities, blisters, or swelling and be careful while trimming the nails to prevent them from digging into the skin causing irritation. Smoking can aggravate heart and circulation issues, as well as limit blood flow to the feet, and should be stopped.

3.9 Emerging technologies

Various mobile phone applications are being developed with the aim of providing an easy means of monitoring DFU. Cassidy [76] created the first smartphone app capable of accurate DFU detection. This system was evaluated in a 6-month clinical trial at two NHS hospital sites in the UK (Lancashire Teaching Hospitals and Salford Royal Hospital) and is now being improved in terms of functionality and accuracy [58]. Additional app features include automated DFU wound pathology classification.

Medical conditions like renal diseases, and immunocompromised states as well as variables such as anemia and hyperglycemia may influence DFU development and healing. The incorporation of these parameters into machine learning algorithms should aid in the advancement of AI-based prediction models [77].

4. Conclusion

DFUs have a multifactorial etiology that most commonly includes neuropathies, vasculopathies, foot deformities, and inappropriate footwear. Patients may exhibit a variety of clinical manifestations including erythema, edema, painfulness or painlessness, loss of sensation, foot deformities, and skin changes among others. If DFUs are not managed properly, infections can arise. This is why appropriate physical examination, imaging, vascular and neurological studies completed as indicated, and classification of ulcers are important for guiding the clinician towards the best management plan for each individual patient. Management of DFU is very broad; the ones included in this chapter include debridement (mechanical and non-mechanical), infection control depending on the severity and type of wounds, topical therapy, wound dressings, oxygen therapy, and offloading techniques. To put it simply, DFU has complex etiology and diverse presentations and is optimally managed by a multidisciplinary team.

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Section 3

Advanced Approaches and Technologies in Diabetic Foot Ulcer Management

Chapter 7

Low-Frequency Contact Ultrasonic Debridement in Diabetic Foot Ulcer

Sebastián Flores-Escobar, Francisco Javier Álvaro-Afonso, Yolanda García-Álvarez, Mateo López-Moral, Marta García-Madrid and José Luis Lázaro-Martínez

Abstract

Diabetic foot ulcers (DFUs) are important causes of morbidity and mortality in people with diabetes mellitus (DM). Between 19 and 34% of patients with DM will develop a DFU in their lifetime. If not treated correctly, these wounds can result in complications such as infection, amputation, and the death of the patient. A fundamental part of local wound care is debridement, which consists of removing non-viable tissue from the wound bed in order to obtain healthy tissue to promote healing. An alternative to traditional debridement techniques (sharp, enzymatic, autolytic, and biological debridement) is low-frequency ultrasonic debridement (LFUD). The effectiveness of LFUD is based on the non-thermal effects of cavitation and microstreaming, which generate a series of clinical effects on the wound bed: debridement effect, wound healing stimulant effect, and bactericidal effect. Several recent studies have demonstrated a positive effect of LFUD with higher healing rates, shorter healing times, greater percentages of wound area reduction, and a significant reduction in bacterial load in DFUs. This chapter aims to give an overview of this type of recent mechanical debridement in the treatment of patients with DFUs.

Keywords: diabetic foot ulcer, local wound care, debridement, low-frequency ultrasonic debridement, wound healing

1. Introduction

The International Working Group on the Diabetic Foot (IWGDF) defines diabetic foot ulcers (DFUs) as a break of the skin of the foot that involves a minimum of the epidermis and part of the dermis in a person with current or previously diagnosed diabetes mellitus (DM) and is usually accompanied by peripheral neuropathy and/or peripheral artery disease (PAD) in the lower extremity [1]. DFUs are important causes of morbidity and mortality in people with DM, associated with impaired physical function, reduced quality of life, and increased use of healthcare services [2, 3].

The global prevalence of DFUs is 6.3%, being higher in men (4.5%) than in women (3.5%) and affecting a higher proportion of patients with type 2 DM (6.4%) than patients with type 1 DM (5.5%) [4].

Approximately 19–34% of patients with DM will develop a DFU in their lifetime [5], which can lead to a number of complications such as infection, lower limb amputation, and, in some cases, death of the patient [6].

About 50% of DFUs progress to infection, and 15–20% of moderate-severe diabetic foot infections eventually lead to lower limb amputation [3, 6]. In addition, patients with DFUs have a 5-year mortality rate of 30%, which increases to 70% if they have undergone a major lower limb amputation [7, 8]. Thus, patients with a history of DFUs are 2.5 times more likely to die compared to patients without a history of DFUs [9].

Therefore, knowledge of the pathophysiology of the diabetic foot and early treatment of DFUs and their complications may delay and prevent the development of adverse events [2]. The standard of care (SoC) in patients with DFUs is based on local wound care, use of pressure off-loading devices, infection control, PAD management, metabolic control of diabetes, and treatment of co-morbidities [10].

However, local wound care involves wound bed preparation, based on four components that are summarized in the acronym TIME (non-viable tissue management, inflammation/infection control, moisture imbalance, and epithelial edge advancement) that aim to promote natural wound healing and correct the alterations that lead to impaired healing [11]. The TIME framework describes various wound bed aspects to be systematically addressed to promote wound healing [12].

In cases where the wound evolution is not satisfactory and the wound size is not reduced by 50% after 4 weeks of SoC, advanced therapies are recommended [13], such as negative pressure wound therapy [14], hyperbaric oxygen therapy [15], autologous stem cells [16], as well as low-frequency ultrasonic therapy [17].

2. Debridement

A fundamental part of local wound care is debridement, which aims to remove non-viable or contaminated tissue and foreign material from the wound bed and wound edge in order to obtain healthy, viable tissue, such as granulation tissue, to promote healing [18]. Since non-viable tissue can represent a risk of colonization and infection due to the fact that it promotes biofilm formation, its removal through debridement is essential to encourage the local effectiveness of antibiotic therapy and minimize antibiotic resistance, as well as to allow the clinician to determine the true wound size, facilitate wound drainage, or take a microbiological culture if necessary [8, 19, 20].

In summary, debridement is considered an effective intervention to accelerate DFU healing and reduce the risk of serious complications [19].

2.1 Methods of debridement

Among traditional debridement methods, we can find on the one hand mechanical debridement, which includes sharp debridement and wet-to-dry debridement, and on the other hand non-mechanical debridement, which refers to autolytic, enzymatic, osmotic, and biological debridement [12, 19–21].

- Mechanical debridement
    - *Sharp debridement*: the European Wound Management Association (EWMA) and IWGDF consider sharp debridement to be the standard debridement

method in wound care [18, 22]. Sharp debridement is the quickest and least expensive method of preparing the wound bed; it is a non-selective procedure that can cause damage to healthy tissue [23]. It is carried out using dissecting instruments such as scalpels, scissors, forceps, or curettes to remove devitalized tissue and can be performed in an operating room or in a clinic setting, with the only difference being the use of anesthesia [24].

- *Wet-to-dry debridement*: it is generated after applying a gauze saturated in saline to the wound bed. Once dry, the gauze adheres to the wound, and when it is removed, both devitalized tissue and healthy tissue are eliminated in a non-selective manner [22, 23].

- Non-mechanical debridement

  - *Autolytic debridement*: the aim is to obtain a moist wound environment in order to facilitate the endogenous enzymes produced by the wound itself to digest the non-viable tissue and preserve the healthy tissue [19, 25].

  - *Enzymatic debridement*: it involves the use of exogenous enzymes such as collagenase, which degrades fibrin and denatures the collagen and elastin that are part of the devitalized tissue while maintaining the integrity of the viable tissue [19, 20].

  - *Osmotic debridement*: it requires the creation of a moist environment to generate autolytic debridement due to the application of honey to the wound bed [20]. In addition, honey has an antibacterial effect as it reduces the pH of the wound, making it an acidic environment unfriendly to bacteria and other pathogens [26].

  - *Biological debridement*: it is also known as larval or maggot debridement and is mainly performed by a specimen of the green bottle fly (*Lucilia sericata*) that is reared under sterile laboratory conditions [27]. It is a selective debridement method in which the larvae destroy dead tissue, leaving healthy tissue intact [28].

Although sharp debridement is considered the gold standard form of debridement, there is no evidence to support the choice of one method of debridement over another [29]. The selection of the optimal method of debridement will depend mainly on the practitioner's competence and will be based on a variety of factors, such as etiology, location or wound appearance, patient preference, and cost of the procedure [30].

At present, it is calculated that around 50% of patients with diabetes have PAD, and 65% of DFUs are estimated to have an ischemic component; therefore, an effective alternative to traditional debridement techniques is low-frequency contact ultrasonic debridement, which is useful when sharp debridement is contraindicated, such as in patients with a poor vascular status [31, 32].

3. Low-frequency ultrasonic debridement

Ultrasound is defined as acoustic energy transmitted in the form of sound waves at a frequency above the range of human hearing (>20 KHz) [33]. According to the frequency, ultrasounds can be of two types: high-frequency and low-frequency.

High-frequency ultrasound can be used as a diagnostic imaging modality when frequencies are around 5–12 MHz or for therapeutic purposes, taking advantage of its thermal effects in the treatment of different musculoskeletal disorders, when the devices operate in a range of 1–3 MHz. However, low-frequency ultrasound uses frequencies ranging from 20 to 60 KHz to generate non-thermal effects known as cavitation and micro-streaming, which will lead to a variety of clinical effects on the wound bed [34, 35].

3.1 Mechanism of action

The low-frequency ultrasound device consists of a generator, a handpiece known as a sonotrode, and irrigation equipment. In the sonotrode, electrical energy produced from the generator is converted into sound energy, which is transmitted in the form of ultrasound through a fluid medium to the wound surface, where cavitation and micro-streaming effects are produced [36].

Cavitation refers to the formation of oscillating gas microbubbles in a fluid medium; when cavitation occurs, the microbubbles expand, contract, and implode, which in turn generates an interstitial fluid flow induced as a result of the vibration generated, commonly referred to as micro-streaming (**Figure 1**) [37–39].

3.2 Clinical effect of low-frequency ultrasonic debridement

Non-thermal effects (cavitation and micro-streaming) will cause on the wound a debridement effect, a bactericidal effect, and a stimulating effect on wound healing (**Table 1**):

- *Debridement effect*: ultrasonic debridement uses acoustic energy to mechanically remove non-viable tissue from the wound bed [41]. When the gas microbubbles generated during cavitation collapse, selective tissue debridement is achieved. Selectivity will depend on the tensile strength and elasticity of the tissue, which will be determined by the amount, type, and organization of the collagen fibers. Therefore, healthy tissue, being more resistant and elastic, remains intact, while devitalized tissue is removed [36, 42, 43].

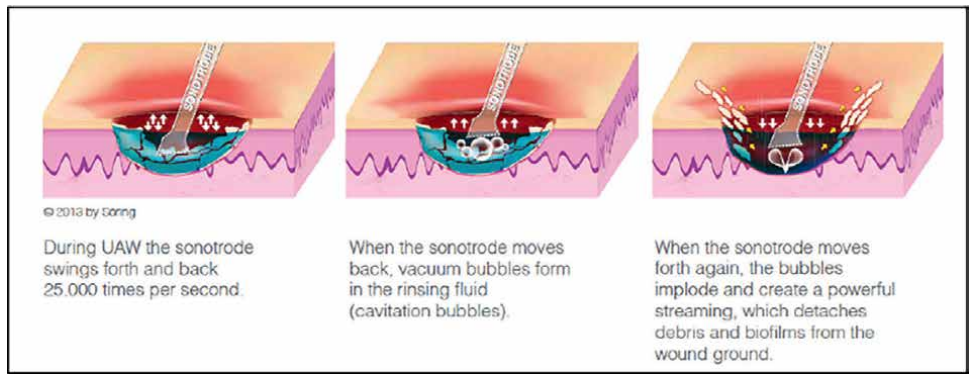

Figure 1.
Mode of operation of low-frequency ultrasound [36].

- Stimulation of angiogenesis-related cytokines:
  - Interlukin-8 (IL-8)
  - Tumor necrosis factor-α (TNF-α)
  - Basic fibroblast growth factor (bFGF)
  - Vascular endothelial growth factor (VEGF)
- Immune response to induce tissue repair:
  - Leukocyte adhesion
  - Grown factor production
  - Fibroblast proliferation
  - Protein synthesis
  - Collagen deposition
  - Increased fibrinolysis
  - Promotes granulation tissue formation
- Reduce bacterial bioburden
  - Increased nitrous oxide
  - Increased macrophage responsiveness
- Prevent biofilm formation
- Remove non-viable tissue

Adaptation of Rastogi et al. [40].

Table 1.
Clinical effects of low-frequency ultrasonic.

- *Wound healing stimulant effect*: the interstitial fluid flow produced by ultrasound stimulates signal transduction pathways involved in wound healing, thereby altering the permeability of the cell membrane and second messenger activity, resulting in increased protein synthesis such as collagen, mast cell degranulation, leukocyte adhesion, and increased growth factor production, which ultimately leads to enhanced immune response through neo-angiogenesis and fibroblast stimulation at the wound site to induce tissue repair [33, 42, 44].

- *Bactericidal effect*: the destruction of the bacteria and the interruption of the biofilm are produced by the effect that the ultrasonic waves cause, favoring the generation of highly reactive radicals and molecular products such as nitrous oxide or hydrogen peroxide that alter the cell membrane of the bacteria. Subsequently, due to cavitation and microstreaming, a cutting and washing effect is generated in which the bacteria are dislodged and washed away by the saline [36, 45, 46].

3.3 Modalities of low-frequency ultrasonic debridement

Low-frequency ultrasonic debridement can be conducted with contact or non-contact devices. A non-contact ultrasonic device delivers acoustic energy in the form of ultrasound to the wound bed through a fine mist of sterile saline applied at a distance between 5 and 15 mm from the wound [34, 44].

Both modalities have similar clinical effects on wounds; the only difference between them is how the ultrasound is applied. Although the debridement effect and bactericidal effect are less effective in the non-contact modality due to being farther away from the wound, there is a dissemination of the ultrasonic waves [45, 47].

In the contact ultrasound modality, the handpiece or sonotrode is in direct contact with the wound bed to mechanically remove non-viable tissue. The sonotrode can be of three types, and its choice will depend mainly on the location and depth of the wound. The double ball handpiece is used for cavity wounds, the hoof is used for undulated flat-surfaced wounds with sloped edges, and the spatula is used for large, flat-surfaced wounds (**Figure 2**) [36, 43].

In addition to the type of sonotrode, there are different techniques for performing ultrasound debridement, such as slicing, sliding, sliding with rotation and milling, and the non-contact option of moistening. Undermining is produced using the double-ball sonotrode for cavities. The most damaging techniques are slicing or sliding with rotation and milling, as the sonotrode is used to contact the wound and uses the technique and instrument to mechanically remove devitalized tissue (**Figure 3**) [48].

Another factor to consider is the ultrasonic device settings: ultrasound intensity (amplitude) and saline flow rate (irrigation), which are manually set by the clinician according to wound features and patient tolerance. Improper setting of the ultrasonic device could have a detrimental effect on the wound bed [48, 49].

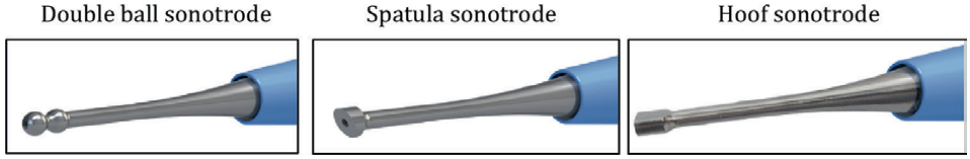

Figure 2.
Different types of handpieces or sonotrodes [43].

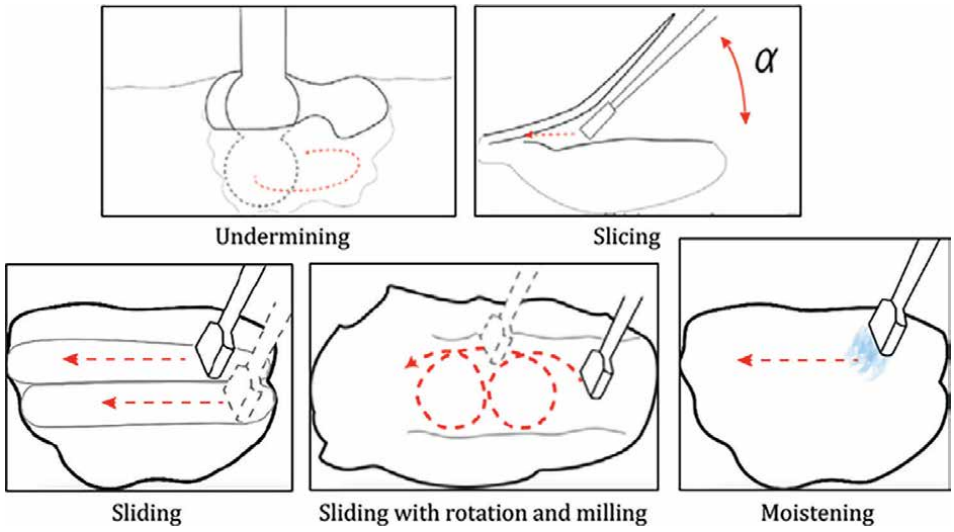

Figure 3.
Contact ultrasonic debridement techniques [48].

Personal protective equipment consisting of a disposable long-sleeved gown, a surgical mask, a face shield with a plastic visor, and sterile gloves is indispensable during ultrasonic debridement to protect the patient and clinician from contamination that may occur due to the dispersion of solution and microbes (aerosolization) from the wound bed into the clinical environment [50].

In order for ultrasonic wound debridement to be effective, a certain degree of training and clinical experience is required [34].

3.4 Clinical effectiveness in DFUs

Low-frequency ultrasonic debridement is a novel technique that has shown great potential for wound bed preparation, with sufficient evidence to indicate that it is a safe and effective method [37, 40].

Several investigations have studied the clinical effect of ultrasonic debridement on DFUs compared to sharp debridement, placebo, or other debridement methods. Ennis et al. [17] in their randomized, double-blinded, controlled, multicenter study compared ultrasonic debridement with placebo (sham device), observing a higher healing rate (40.7% vs. 14.3%, $p = 0.03$) and shorter healing time of DFUs in the ultrasonic debridement group (9.12 ± 0.58 vs. 11.74 ± 0.22 weeks, $p < 0.01$).

In a clinical trial comparing the effect of ultrasonic debridement applied three times or once a week versus SoC, a reduction in pro-inflammatory cytokines (IL-6, IL-8, IL-1β, TNF-α, and GM-CSF), matrix metalloproteinase-9 (MMP-9), vascular endothelial growth factor (VEGF), and macrophages was found, indicating an improvement in tissue regeneration that translates into a percentage of DFUs area reduction of 86% versus 39% ($p < 0.05$) when ultrasonic debridement was applied three times a week [51].

Bactericidal and clinical effects of ultrasonic debridement on neuroischaemic DFUs were assessed over 6 weeks in a single-center, non-comparative study, where it was observed that ultrasonic debridement disrupts biofilms and reduces bacterial load independent of bacterial species. Bacterial load reduction was associated with an improvement in the condition of the wound bed with a higher percentage of granulation tissue and a significant reduction in wound size (4.45 cm^2 at week 0 and 2.75 cm^2 at week 6, $p = 0.04$) [52].

An open-label, randomized, controlled, and parallel clinical trial comparing ultrasonic debridement versus surgical debridement in patients with DFUs demonstrated a significant improvement in cellular proliferation, with an increase in endothelial cells (neo-angiogenesis) and an enhancement in collagen deposition and fibroblast proliferation. Furthermore, this study showed a reduced bacterial load and shorter healing time in patients in the ultrasonic debridement group (9.7 ± 3.8 vs. 14.8 ± 12.3 weeks, $p = 0.04$), but healing rates of DFUs were similar between both groups [53].

Recent systematic reviews and meta-analyses have shown a positive effect of low-frequency ultrasonic debridement with higher healing rates, shorter healing times, greater percentages of wound area reduction, and a significant reduction in bacterial load in DFUs [54–56]. However, IWGDF guidelines recommend not using any form of ultrasonic debridement over standard of care (sharp debridement) due to the studies performed having a high risk of bias, low certainty of evidence of benefit, and lack of cost-effectiveness data [57].

4. Conclusion

Although the quality of the evidence is generally low due to the high risk of bias and the absence of blinding in the studies, low-frequency ultrasonic has been demonstrated to have a debridement effect, wound healing stimulant effect, and bactericidal effect on wound beds. These effects are reflected in higher healing rates, a greater percentage of wound area reduction, shorter healing times, and a significant reduction in bacterial load, but greater quality evidence is needed to confirm these findings. Likewise, low-frequency ultrasonic debridement could be an effective alternative when traditional debridement methods are not available or are contraindicated for use on patients with DFUs.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 8

AI-Driven Personalised Offloading Device Prescriptions: A Cutting-Edge Approach to Preventing Diabetes-Related Plantar Forefoot Ulcers and Complications

Sayed Ahmed, Muhammad Ashad Kabir, Muhammad E.H. Chowdhury and Susan Nancarrow

Abstract

Diabetes-related foot ulcers and complications are a significant concern for individuals with diabetes, leading to severe health implications such as lower-limb amputation and reduced quality of life. This chapter discusses applying AI-driven personalised offloading device prescriptions as an advanced solution for preventing such conditions. By harnessing the capabilities of artificial intelligence, this cutting-edge approach enables the prescription of offloading devices tailored to each patient's specific requirements. This includes the patient's preferences on offloading devices such as footwear and foot orthotics and their adaptations that suit the patient's intention of use and lifestyle. Through a series of studies, real-world data analysis and machine learning algorithms, high-risk areas can be identified, facilitating the recommendation of precise offloading strategies, including custom orthotic insoles, shoe adaptations, or specialised footwear. By including patient-specific factors to promote adherence, proactively addressing pressure points and promoting optimal foot mechanics, these personalised offloading devices have the potential to minimise the occurrence of foot ulcers and associated complications. This chapter proposes an AI-powered Clinical Decision Support System (CDSS) to recommend personalised prescriptions of offloading devices (footwear and insoles) for patients with diabetes who are at risk of foot complications. This innovative approach signifies a transformative leap in diabetic foot care, offering promising opportunities for preventive healthcare interventions.

Keywords: diabetes, neuropathy, forefoot ulceration, plantar pressure offloading, footwear, insole, artificial intelligence (AI), decision tree, random forest

1. Introduction

Diabetes-related foot ulcers are a significant complication that can lead to serious consequences, including lower extremity amputation and even mortality [1]. Diabetic foot ulcers have become a major burden on the healthcare industry, with limited treatment options and a high risk of progressions [2]. Furthermore, diabetic foot ulcers not only reduce the quality of life for patients but also impose a substantial financial burden on individuals and society as a whole [3]. Treatment of diabetic foot ulcers is protracted and intensive, requiring extensive wound care, infection control, and management of underlying vascular disease [4]. This necessitates the need for innovative approaches to prevent and manage diabetic foot ulcers effectively.

One promising approach is the use of AI-driven personalised offloading device prescriptions. AI-driven personalised offloading device prescriptions have the potential to revolutionise the prevention and management of diabetic foot ulcers.

By leveraging artificial intelligence, healthcare providers can analyse large amounts of patient data, including medical history, foot morphology, and gait analysis, to develop personalised offloading device prescriptions. This cutting-edge approach allows for the customisation of offloading devices, such as orthotic inserts or specialised footwear, to match the specific needs of each individual patient. This personalised approach is crucial because not all offloading devices are suitable for every patient. The importance of offloading devices in the management of diabetic foot ulcers has been recognised by national and international guidelines [5]. However, the current utilisation of offloading devices in clinical practice is suboptimal. Research conducted in the UK found that only 5% of patients with diabetic ulcers received a pressure-offloading device [5]. This low utilisation of offloading devices could be attributed to various factors, including a lack of awareness among healthcare providers, inadequate training, and challenges in accessing orthotic services [3]. To address these barriers and improve the utilisation of offloading devices, AI-driven personalised offloading device prescriptions offer several key advantages [6]. Firstly, AI-driven personalised offloading device prescriptions can enhance the accuracy and effectiveness of offloading interventions [7].

By taking into account a patient's individual characteristics and needs, AI algorithms can recommend offloading devices that will effectively redistribute pressure and relieve the abnormal load on the plantar foot surface. This personalised approach increases the likelihood of successful ulcer healing and reduces the risk of complications associated with diabetic foot ulcers.

Furthermore, AI-driven personalised offloading device prescriptions can also address barriers to adherence and compliance with offloading devices [8]. For example, one of the barriers to adherence is postural instability caused by wearing offloading devices, which can lead to falls and accidents while performing daily activities [2]. However, by utilising AI algorithms to analyse gait patterns and biomechanical data, personalised offloading devices can be designed to minimise gait disturbances and improve stability, thereby reducing the risk of falls.

The use of AI-driven personalised offloading device prescriptions can also help overcome the challenges in accessing pedorthic services. Due to the shortage of pedorthic professionals and the limited availability of pedorthotic clinics, many patients face difficulties in accessing offloading devices [9].

AI algorithms can bridge this gap by remotely analysing patient data and prescribing personalised offloading devices that can be manufactured using 3D printing or other advanced fabrication.

2. Study background

This study is deduced from four earlier series of individual studies, and they are presented in the below diagram with further brief description of the individual studies to provide the contexts (**Figure 1**).

2.1 Study 1: systematic literature review

Twenty-five studies were reviewed systematically. The included articles used repeated measure (n = 12), case-control (n = 3), prospective cohort (n = 2), randomised crossover (n = 1), and randomised controlled trial (RCT) (n = 7) designs. This involved a total of 2063 participants. Eleven studies investigated footwear, and 14 studies investigated insoles as an intervention. Six studies investigated ulcer recurrence; no study investigated the first occurrence of ulceration. The most commonly examined outcome measures were peak plantar pressure (PPP), pressure-time integral (PTI) and total contact area. Methodological quality varied.

Strong evidence existed for rocker soles to reduce peak plantar pressure. Moderate evidence existed for custom insoles to offload forefoot plantar pressure. There was weak evidence that the insole contact area influenced plantar pressure. Footwear and insoles are complex interventions, and the outcome measure is still limited to PPP reduction and ulcer recurrence. Rocker soles, custom-made insoles with metatarsal additions and a high degree of contact between the insole and foot reduce plantar pressures in a manner that may reduce ulcer occurrence.

Most studies rely on reduction in PPP measures as an outcome as a proxy for the occurrence of ulceration. There is limited evidence to inform footwear and insole interventions and prescriptions in this population. Further high-quality studies in this

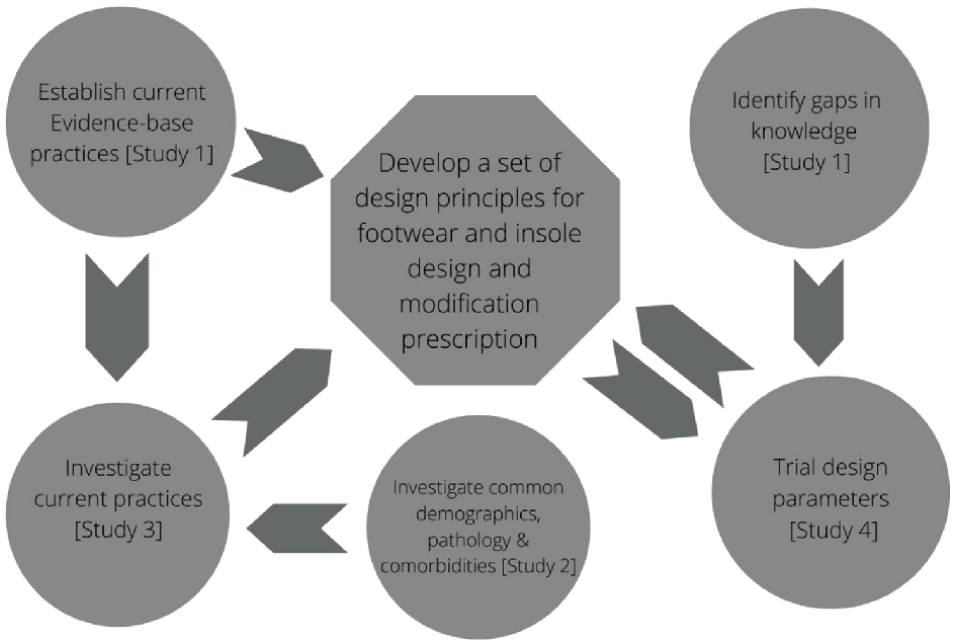

Figure 1.
Schematic of research approach and connections among background studies.

field are required. Approaches to measuring patient adherence are lacking but play a vital role in the overall outcome of the treatment.

2.2 Study 2: retrospective clinical audit

A retrospective clinical audit of a cohort of 70 patients at a suburban pedorthics clinic was undertaken to understand the pedorthists' patient profile, including sociodemographic, pathological, comorbidity-related, and other individual characteristics.

The mean age of participants was 64.69 (SD 11.78) years, ranging from 27 to 90 years old. They were more likely to be male (n = 43 males (61.4%)). All participants were overweight to obese, with a mean weight (kg) of 91.37 (SD 14.73). The average BMI was 30.96 (SD 4.15).

Most (97.2%) participants had Type-2 diabetes mellitus (T2DM), and only a few (2.8%) had type-1 DM (T1DM). Australia was the birthplace of the highest number of participants (n = 28) and majority of the participants (n = 42) were born outside of Australia. About 5.7% (n = 4) were of Aboriginal or Torres Strait Islander origin.

The mean duration of diabetes among the participants was 14.09 years (SD 6.58). The mean duration of neuropathy was 8.56 (SD 4.16) years.

Approximately 47% (n = 33) of participants had HAV; 39% (n = 27) participants had hammertoe and cavus foot conditions, and 33% (n = 23) of participants had clawed toes. Common foot pathologies among the participants were: bony prominence at 71% (n = 50), rigid flat foot, and limited joint mobility (LJM) (53%, n = 37). Hyperkeratosis was the most common condition in the participant group; everyone (n = 70) had this condition. Of previous foot pathology, about half (47%) of the participants had a history of forefoot ulceration. Around one-third, 34% (n = 24) of participants, had forefoot amputation, and around 34% (n = 24) had undergone a digital amputation.

The most common comorbidities in this group were rheumatoid arthritis (RA) 36%, Peripheral vascular disease (PVD) 41%, lymphodema 20%, and posterior tibialis tendon dysfunction (PTTD) 26%.

The main funding providers for footwear in this populations group, comprising 78% (n = 55), was Enable NSW, followed by privately (self) funded at 10% (n = 7), Closing the Gap at 4.3% (n = 3), private health insurance 2.9% (n = 2), and aged care package 1.4% (n = 1).

This shows the complexity of patients, highlights the variations in social issues, funding models, cultural needs, and personal preferences, and how this might impact the outcome of patient care through appropriate footwear and insoles for their conditions. This guides the variations in the case studies to represent a "typical" male or female patient seen at the pedorthics clinic, particularly the sociodemographic, foot pathology, and comorbidity characteristics.

2.2.1 Clinical case studies

The audit results were used to create four 'typical patient' case studies based on the categories of age, gender, country of birth, duration of diabetes and neuropathy, foot pathology, comorbidity, and health fund access provision for representing patients who come to pedorthic clinics for the provision of appropriate footwear and insoles. The cases were verified by an expert panel and incorporated into Study 3 which was used to help understand Pedorthic prescribing practices.

2.3 Study 3: Australian pedorthist's survey

The purpose of this study was to examine the current prescription habits of Australian pedorthists when designing and altering footwear and insoles with the goal of offloading for neuropathic plantar forefoot ulcer prevention and improved patient adherence for the four case studies developed in Study 2.

The survey questionnaires explored pedorthist's practice in terms of:

1. Footwear design and modification parameters and.

2. Insole design and modification parameters, including adherence-related challenges for footwear and insoles and their overcoming strategies.

Multiple-choice and open-ended questions were used to explore pedorthist's prescribing behaviour in terms of the case studies. The criteria explored in Sections 2 and 3 were adopted from Study 1 [9] and Diabetes Feet Australia (DFA) guidelines [10].

Nineteen pedorthists completed the survey (45% of pedorthists).

There was some level of consensus among pedorthists around the treatment of patients for the four case studies. The area of highest consistency was the recommendation to use custom-made footwear for case 3, which was a particularly complex case study. The domains that achieved the greatest consensus for treatment among pedorthsists in footwear and insole design were upper height and rocker sole design profiles, insole type, and design characteristics. The areas with the least consensus were the prescription of prefabricated medical grade footwear recommendations with or without modifications (cases 1, 2, and 4) and the heel height, toe spring, footwear materials, insole materials, casting methods, and evaluating the pressure offloading efficacy of the devices.

Most of the recommendations by the pedorthists fall within existing accepted practice guidelines, and variations were likely to be due to the different pedorthist training and the scope of practice [11]; available options of footwear type supply in their practices and variation in material supply for manufacture and modifying insoles; health fund availability; patient's preferences; and intended activity.

The findings from this study were also limited by the relatively small sample. This, in part, reflects the small size of the profession, so the overall possible numbers of responses were limited, but a large variation is likely with a small sample size.

This study highlights the complexity of footwear as an intervention for people with diabetes-related foot disease and the high level of variation possible because of the multiple components associated with shoes. Given that the primary goals of footwear as an intervention are to prevent injury (largely by accommodating existing foot deformities) and reduce plantar pressure, it is clear that there are a number of different routes to achieving this goal, which will be impacted heavily by patient preference and adherence. Therefore, a less clinically prescriptive approach may be necessary that takes into account a range of social and more subjective factors, such as patient preference and goals, activity levels, funding source, and availability, and the availability of different materials and footwear – this then leads into the n = 1 study that varied a number of attributes of footwear with a goal of achieving the greatest reduction in plantar pressure while optimising patient adherence.

The results present a lot of variation in clinical recommendations for the same patient; however, they appear largely based on valid considerations and assumptions.

The variations in recommendations were in footwear type, upper height, heel height, toe spring, rocker sole design profile, insole casting method, insole materials, and insole design parameters. This also highlights the need for an evidence-based guideline to guide practice and help reduce variations in clinical practice or provide guidance that can increase the consistency of prescribing patterns. Evidently, there is no 'one size fits all' – and there is probably no 'rule' to dictate that. The results of this study, together with the results from Study 1 [9], have been used to form the knowledge base for footwear and insole design and modifications and to test those parameters in Study 4 towards recommending a set of design principles for footwear and insole design and modification prescriptions.

2.4 Study 4: a series of N-of-1 trials

Building on the learning from the previous studies, which demonstrate, first, the diversity and complexity of patient needs and preferences, and second, the wide range of treatment options to achieve the common goals of optimal protection of the foot and a reduction in plantar pressure, this study used a patient-centred intervention approach and study design, the N-of-1 trial (a series of). This study allowed the application of a range of variables in footwear and insole design tailored to the individual patient's needs, with a view to achieving optimal pressure reduction and adherence.

The series of N-of-1 trials included 12 patients that formed 12 individual N-of-1 studies. Two footwear prototypes, and three insole prototypes, each with some level of customisation for the patients, were applied and modified over no more than three iterations.

The interventions were fully custom-made footwear (Shoe A) and prefabricated medical-grade footwear (Shoe B) with modifications. There were three different types of custom-made insoles; Insole A (to follow custom shoe last plantar profile through heat moulding method), Insole B (3D printed insole base from TPU filament combined with Poron and EVA/Plastazote top cover (for Shoe B), Insole C through conventional heat moulded manufacturing method to (fit into shoe B). All the footwear and insoles underwent a series of modifications guided by in-shoe pressure mapping and patient feedback on balance and suitability for purpose. Individual treatment goals (target PPP) were met for each case, and the exploration for variations in enhancing adherence continued.

Barefoot static and dynamic pressure analysis and in-shoe pressure analysis on the baseline footwear were done at the initial appointment (T0). The intervention footwear and insole design were decided at T0. Intervention footwear and insole were fitted at the 2nd appointment (T1). A maximum of three rounds of modifications were carried out on the footwear and insoles until an acceptable plantar pressure offloading threshold was achieved. Patient satisfaction and adherence-related information were captured at each appointment (T1–T4). The results show that with tailored responses to individual patient needs, PPP can be reduced substantially, and there is a strong need to consider multiple, complex patient issues to enhance adherence.

It is already proven that there is no panacea for footwear and insole prescription; instead, there are a series of principles based on, first, patient needs and preferences, and second, patient pathology. Those are the guiding factors for the treatment plan and options. These complex factors around patients' pathology, comorbidity, and personal and social perspectives need to be put in the bigger picture, and the design

principles proposed in the study have considered all these factors for improved clinical and patient adherence outcomes.

3. Design principles

Here, the design principles for footwear prescription for people with diabetes-related foot disease and at risk of neuropathic plantar forefoot ulceration that arose from the above studies are outlined. These principles underpinning footwear and insole design aim to guide pedorthists involved in prescribing footwear for people with diabetes-related foot disease to prescribe and produce footwear based on the best evidence for plantar pressure offloading and strategies to improve patient satisfaction and adherence. The outcomes of Studies 1 [9] and 3 (Australian pedorthists survey) provided the knowledge base of various footwear and insole design and modification parameters in the literature and in real practices by the pedorthists. The common agreements and the variations were both noted, and patient adherence-related challenges and overcoming strategies were also noted [Study 3]. Then these parameters were tested further and explored the outcome on individual patients through a series of N-of-1 trials [12] to establish more specific design and modification parameters for specific forefoot pathologies in people with diabetes and neuropathy and their adherence-related factors to improve the outcomes were also established.

These parameters were then presented in a patient-centric Clinical Decision Support Database (CDSD) for footwear and insole prescribing to ensure the prescription is made based on the most suitable option for the individual. These are presented in **Table 1**. This CDSD theme aims to ensure the maximum possible adherence by the person when all possible factors are considered for the individual associated with their therapy and treatment goals. Then the information or output from this CDSD is taken into the framework of a set of design principles for the technical prescription to ensure optimum clinical outcomes such as plantar pressure offloading and walking comfort, ease of use of the patient and such. This information is aligned with the workflow presented in **Figure 2**. The core information for this set of design principles is based on our systematic literature review [9], DFA guideline [10], Australian pedorthists' survey [Study 3], the series of N-of-trials [Study 4] and [13]. The main framework of the CDSD is based on the results of Study 4 and the other studies [9, 10], including Study 3 results that have been used to complement the database. **Table 2** presents how the CDSD model functions can be used for clinical decision making for the pedorthists.

The treatment goals underpinning this set of design principles are to:

1. Optimise patient satisfaction and adherence to therapy (by improving walking comfort, ease of use and aesthetics and also considering the personal circumstances of the patients).

2. Protect the foot from injury and cause no further injury to the foot.

3. Reduce peak plantar pressure.

4. Optimise balance and mobility.

To achieve this treatment goal requires that the patient will wear the footwear >80% of the time [14]; therefore, a further treatment principle is that the footwear

CDSD parameters	Descriptions
Person's preferences and intended activity (PPIA)	Low-cut casual shoes for outdoors and walking (PPIA1), A low-cut dress shoe (PPIA2), A low-cut indoor shoe with a soft fabric upper (PPIA3), High-cut casual shoes for outdoor and walking (PPIA4), A high-cut dress shoe (PPIA5), Low-cut summer sandal or shoe (PPIA6), High-cut summer sandal or shoe (PPIA7), Extra high-cut casual shoes for outdoor and walking (PPIA8), An extra high-cut dress shoe (PPIA9), Extra high cut summer shoe or sandal (PPIA10), Extra high cut reinforced upper for drop foot (PPIA11), Separate AFO for drop foot (PPIA12)
Foot structure and shape (FSS)	Normal (FSS1), Wide (FSS2), Very Wide (FSS3), Narrow heel, wide forefoot (FSS4), Swollen rearfoot, narrow forefoot (FSS5), Mismatch foot shape (FSS6)
Main foot pathology (MFP)	Limited joint mobility of the ankle (MFP1), Pes cavus and claw toes (MFP2), Claw and hammer toes (MFP3), Flexible pes planus with hallux valgus (MFP4), Rigid pes planus with hallux valgus (MFP5), Hallux Rigidus (MFP6), Hallux Limitus (MFP7), Pes equines (MFP8), Hallux or toe amputation (MFP9), Forefoot amputation (MFP10)
Co-morbidity (CM)	PAD/PVD (CM1), Drop foot (CM2), Lower limb oedema (CM3), Higher BMI (CM4), Poor vision (CM5), Renal disease, needing dialysis (CM6), History or at risk of falls (CM7), Leg length discrepancy (CM8)
Person's body weight (PBW)	60–75 Kg (PBW1), 76–90 Kg (PBW2), 91–110 Kg (PBW3), 111–130 Kg (PBW4), 131+ Kg (PBW5)
Person's mobility status (PMS)	Active at home and indoors (PMS1), Active in the community (PMS2), Mostly staying at home (PMS3), Active outdoors and a regular bushwalker (PMS4), Limited mobility, uses 4WW for balance (PMS5), Limited mobility, uses single walking aid for balance (PMS6), Can reach to the toes easily (PMS7), Both hands and fingers are full functioning (PMS8), Single hand and fingers are full functioning (PMS9)
Family/partner/carer/peer preferences and advocacy (FCPA)	Family/partner/carer/peer agrees to person's choice (FCPA1), Family/partner/carer/peer does not agree to person's choice being impractical or contradicting and advocates towards practitioner's recommendations (FCPA2), Family/friend/carer agrees to person's choice, but peer does not agree due to impractical or contradicting choices (FCPA3), A common agreement was made following further discussion, motivation and advocacy with all parties on the appropriate footwear choices that person is well accepting (FCPA4)
Fund options (FO)	Self-fund with the flexibility of pursuing the best recommendations (FO1), Self-fund with limitations or restrictions in pursuing the best recommendations (FO2), Health fund support with a co-payment by the person (FO3), Health fund support without a co-payment by the person (FO4), Non-government organisation (NGO) or donor's support for funding (FO5)
Fund options influence footwear type selection (FOIS)	Fund options influence the footwear type selection (FOIS1), Fund options do not influence the footwear type selection (FOIS2), Fund options partially influence the footwear type selection (FOIS3)
Footwear type (FWT)	Fully custom-made (Orthopaedic medical-grade footwear) (FWT1), Prefabricated medical-grade footwear (pedorthic footwear) without any further modification (FWT2), Prefabricated medical-grade footwear (pedorthic footwear) with further modification (FWT3)
Footwear style (FWS)	Casual shoe (FWS1), A dress shoe (FWS2), Indoor shoe (FWS3), Walking shoe (FWS4), Leisure shoes e.g. Golf, lawn bowling (FWS5)
Footwear upper height (FWUP)	Low cut (FWUP1), High cut (FWUP2), Extra high cut (FWUP3), Slide (FWUP4)
Footwear lining material (FWL)	Soft Leather lining (FWL1), Micro-fabric with a padded back (FWL2), Mesh with a padded back (FWL3)

CDSD parameters	Descriptions
Footwear fastening system (FFS)	Lace (FFS1), Velcro (FFS2), BOA lacing (FFS3), Lace or velcro with a medial zipper for easy foot entry (FFS4), Lace or Velcro with lateral zipper for easy foot entry (FFS5), Lace or Velcro with medial and lateral zippers for easy foot entry (FFS6), Hook & Dow Stick with Velcro (FFS7), Hook & Dow Stick with zippers and larger ring with the runner (FFS8)
Pressure offloading evaluation method (POEM)	In-shoe pressure analysis (POEM1), Clinical experience and observations (POEM2), Ulcer recurrence (POEM3)
Footwear upper flexibility (FWUFL)	Suppled (FWUFL1), Rigid (FWUFL2), Stiffened/Reinforced (FWUFL3)
Footwear upper stiffened location (FWUSL)	Medial (FWUSL1), Lateral (FWUSL2), Medial + Lateral (FWUSL3), Not required (FWUSL4)
Footwear tongue flexibility (FWTFL)	Suppled (FWTFL1), Stiffened/Reinforced (FWTFL2), Standard as comes with footwear (FWTFL3)
Footwear heel counter (FWHC)	Standard (FWHC1), Medial extended and reinforced (FWHC2), Lateral extended and reinforced (FWHC3), Medial + Lateral extended and reinforced (FWHC4),
Footwear heel height (FWHH)	Standard (FWHH1), Lowered (FWHH2), Increased (FWHH3)
Footwear heel modification (FWHM)	Heel rounded (FWHM1), Heel flared (FWHM2), Not required (FWHM3)
Footwear outsole (FWOS)	Suppled (FWOS1), Semi-rigid (FWOS2), Stiffened/Reinforced (FWOS3)
Footwear rocker profile (FWRP)	No additional rocker is to be added (FWRP1), Additional rocker profile is to be added (FWRP2)
Footwear rocker apex position (FWRAP)	Rocker apex position standard/just behind the metatarsal heads (FWRAP1), Rocker apex position early/posterior to metatarsal heads (FWRAP2), Rocker apex position delayed/anterior to metatarsal heads (FWRAP3)
Footwear rocker apex angle (FWRAA)	Standard (FWRAA1), Medial direction (FWRAA2), Lateral direction (FWRAA3)
Footwear rocker angle (FWRANG)	Standard/12–15° (FWRANG1), Moderate/≥20° (FWRANG2), Severe /≥30° (FWRANG3)
Insole type (INST)	Prefabricated/Standard insole that comes with the footwear (INST1), Custom-made insole (INST2)
Custom-made insole shape (CMINS)	Regular shape (CMINS1), Medial wall extended (CMINS2), Lateral wall extended (CMINS3), Medial + Lateral wall extended (CMINS4), Toe modelling for partial (toe/s) amputation (CMINS5), Forefoot modelling for forefoot amputation (CMINS6)
Insole base layer material (INSBLM)	Hard/firm (INSBLM1), Medium hard (INSBLM2), Soft (INSBLM3)
Insole mid-layer material (INSMLM)	Medium soft (INSMLM1), Soft (INSMLM2)
Insole top layer material (INSTLM)	Soft (INSTLM1), Medium soft (INSTLM2), Very soft (INSTLM3)
Insole heel cup (INSHC)	Regular (INSHC1), Lowered (INSHC2), Increased (INSHC3)

CDSD parameters	Descriptions
Insole heel wedge (INSHW)	Medial (INSHW1), Lateral (INSHW2)
Insole MLA height (INSMLAH)	As per cast/scan (INSMLAH1), increased (INSMLAH2)
Insole metatarsal addition (INSMA)	No metatarsal addition (INSMA1), Metatarsal bar (INSMA2), Metatarsal pad (INSMA3), Metatarsal dome (INSMA4), Morton's extension (INSMA5), Reverse Morton's extension (INSMA6)
Insole metatarsal addition position (INSMAP)	Standard/just behind the metatarsal heads (INSMAP1), Early/posterior to metatarsal heads (INSMAP2), Standard position for Morton's extension (INSMAP3), Standard position for Reverse Morton's extension (INSMAP4)
Insole metatarsal addition thickness (INSMATH)	Standard/just supporting the metatarsal heads (INSMATH1), Increased/correcting the metatarsal heads alignment (INSMATH2)
Insole metatarsal addition material type (INSMAMAT)	Hard/firm (INSMAMAT1), Medium soft (INSMAMAT2), Soft (INSMAMAT3)
Insole modification (INSMOD)	Removal of hard materials (INSMOD1), Local cushioning (INSMOD2), Replacement of top cover (INSMOD3), No further modification required (INSMOD4)

Table 1.
Person-centric CDSD for footwear and insole prescription for people with diabetes and at risk of neuropathic plantar forefoot ulceration.

needs to meet the aesthetic and/or social requirements of the patient and/or their main decision maker (e.g., spouse or partner).

The footwear needs to be affordable for the patient [15, 16], and the guidance towards available funding is as important as educating the patient on foot self-care [17]. The inability to afford the cost of therapy and having no access to health funds can limit treatment options in this population group [17].

The footwear needs to be fit for its purpose [18]. To increase adherence by achieving the patient's goals and aesthetic requirements, additional individual factors need to be considered as appropriate such as appropriateness for the climate and cultural and religious beliefs.

A summary of the design principles for footwear and insole design and modifications in the form of an infographic to demonstrate the workflow and relevant measures in each step has been presented in **Figure 2**.

3.1 Multidisciplinary and person-centric team approach

The person to be treated needs to be engaged in the process at the very beginning and needs to be at the centre of the overall activities. All relevant health professionals need to be engaged and provide input into the care plan. Engaging a friend or family or a career as appropriate is very important for better treatment and adherence-related outcomes. Studies 3 and 4 have demonstrated the evidence of these approaches for a positive outcome.

The CDSD model (**Table 1**) has described the various evidence-based parameters around this step under *"Person's preferences and intended activity", "Person's mobility status", "Family/partner/carer/peer preferences and advocacy"* and the parameters are

Figure 2.
Workflow and infographic for the design principles for footwear ad insoles.

extracted from our systematic literature review [9], DFA guideline [10], (Australian pedorthists' survey [Study 3], the series of N-of-trials [Study 4] and Zwaferink et al.'s algorithm [13].

		CDSD parameters description	Participant 1	Participant 2	Participant 3
Decision input	Person-centric data	Person's preferences and intended activity (PPIA)	PPIA10	PPIA5	PPIA4
		Foot structure and shape (FSS)	FSS2	FSS4	FSS3
		Person's mobility status (PMS)	PMS6	PMS2	PMS2
		Family/partner/carer/ peer preferences and advocacy (FCPA)	FCPA4	FCPA4	FCPA1
	Diagnosis related data	Main foot pathology (MFP)	MFP5	MFP1	MFP6
		Co-morbidity (CM)	CM1	CM7	CM4
		Person's body weight (PBW)	PBW4	PBW2	PBW5
	Fund data	Fund options (FO)	FO3	FO3	FO2
		Fund options influence footwear type selection (FOIS)	FOIS1	FOIS1	FOIS3
Decision output	Footwear design and modification features	Footwear type (FWT)	FWT 3	FWT3	FWT3
		Footwear style (FWS)	FWS1	FWS2	FWS2
		Footwear upper height (FWUP)	FWUP3	FWUP2	FWUP2
		Footwear lining material (FWL)	FWL2	FWL3	FWL3
		Footwear fastening system (FFS)	FFS4	FFS1	FFS1
		Footwear upper flexibility (FWUFL)	FWUFL1	FWUPFL1	FWUPFL1
		Footwear upper stiffened location (FWUSL)	FWUSL4	FWUSL2	FWUSL1
		Footwear tongue flexibility (FWTFL)	FWTFL3	FWTFL3	FWTFL3
		Footwear heel counter (FWHC)	FWHC2	FWHC1	FWHC1
		Footwear heel height (FWHH)	FWHH2	FWHH1	FWHH2
		Footwear heel modification (FWHM)	FWHM3	FWHM2	FWHM2
		Footwear outsole (FWOS)	FWOS3	FWOS3	FWOS3
		Footwear rocker profile (FWRP)	FWRP2	FWRP2	FWRP2
		Footwear rocker apex position (FWRAP)	FWRAP2	FWRAP2	FWRAP3
		Footwear rocker apex angle (FWRAA)	FWRAA1	FWRAA2	FWRAA3
		Footwear rocker angle (FWRANG)	FWRANG1	FWRANG2	FWRANG2

		CDSD parameters description	Participant 1	Participant 2	Participant 3
Decision input	Person-centric data	Person's preferences and intended activity (PPIA)	PPIA10	PPIA5	PPIA4
		Foot structure and shape (FSS)	FSS2	FSS4	FSS3
		Person's mobility status (PMS)	PMS6	PMS2	PMS2
		Family/partner/carer/peer preferences and advocacy (FCPA)	FCPA4	FCPA4	FCPA1
	Diagnosis related data	Main foot pathology (MFP)	MFP5	MFP1	MFP6
		Co-morbidity (CM)	CM1	CM7	CM4
		Person's body weight (PBW)	PBW4	PBW2	PBW5
	Fund data	Fund options (FO)	FO3	FO3	FO2
		Fund options influence footwear type selection (FOIS)	FOIS1	FOIS1	FOIS3
Decision output	Insole design and modification features	Insole type (INST)	INST2	INST2	INST2
		Custom-made insole shape (CMINS)	CMINS2	CMINS1	CMINS1
		Insole base layer material (INSBLM)	INSBLM1	INSBLM1	INSBLM1
		Insole mi-layer material (INSMLM)	INSMLM1	INSMLM2	INSMLM1
		Insole top-layer material (INSTLM)	INSTLM1	INSTLM1	INSTLM2
		Insole Heel cup (INSHC)	INSHC1	INSHC1	INSHC1
		Insole Heel Wedge (INSHW)	INSHW1	INSHW2	INSHW1
		Insole MLA Height (INSMLAH)	INSMLAH1	INSMLAH2	INSMLAH2
		Insole Metatarsal addition (INSMA)	INSMA3	INSMA3	INSMA5
		Insole metatarsal addition position (INSMHAP)	INSMAP2	INSMAP1	INSMAP3
		Insole Metatarsal addition thickness (INSMATH)	INSMATH1	INSMATH2	INSMATH2
		Insole metatarsal addition material type (INSMAMAT)	INSMAT3	INSMAT3	INSMAT2
		Insole modification (INSMOD)	INSMOD2	INSMOD1, INSMOD3	INSMOD1, INSMOD2
	Pressure Offloading Evaluation	Pressure offloading evaluation method (POEM)	POEM1	POEM1	POEM1

Table 2.
Workflow and output of the CDSD model with a real-case scenario.

3.2 Comprehensive assessment of the lower limb

A comprehensive assessment of the person's foot condition and foot structure, current mobility status and mobility goals are the second steps in the process. Some of the information is also available in the referral and medical notes. The person's goals recorded in the referral form need to be checked against during the assessment for currency and a clear understanding by all parties involved in the process.

Other assessment aspects involve assessing the extent of peripheral neuropathy, foot deformities, areas of high pressure (ROIs), and any previous or existing foot ulcers or wounds. Attention should be paid to the person reporting any pain or discomfort at any part of the foot or lower limb or during any specific activities or mobility phases.

The CDSD model (**Table 1**) has described the various evidence-based parameters around this step under *"Main foot pathology", Comorbidity" "Body weight."* and the parameters are extracted from **Table 3**, our systematic literature review [9], DFA guideline [10] clinical audit [Study 2], Australian pedorthists' survey [Study 3], the series of N-of-trials [Study 4] and Zwaferink et al.'s algorithm [13].

3.3 Understanding the person's needs and setting treatment goals

Gathering information on the person's lifestyle, daily activities including social and religious rituals is critical for a comprehensive treatment plan and device design workflow. Understanding the person's needs relating to occupation, exercise routines, and specific foot and mobility-related challenges are integral parts of the workflow. Assessing the mobility of the upper limb is important to identify the person's ability that influences donning and doffing. A person's affordability to the therapy and access to funds are also important factors to consider when designing the treatment plan. Studies 3 and 4 report on the importance of fund access for these populations. From this step, tailored primary design features to suit the person's goals can be drawn. Studies 3 and 4 have demonstrated evidence of these workflows.

The CDSD model (**Table 1**) has described the various evidence-based parameters around this step under *"Person's preferences and intended activity", "Person's mobility status", "Family/partner/carer/peer preferences and advocacy"* and the parameters are extracted from **Table 3**, our systematic literature review [9], DFA guideline [10], clinical audit [Study 2], Australian pedorthists' survey [Study 3], the series of N-of-trials [Study 4] and Zwaferink et al.'s algorithm [13].

3.4 Assess footwear history and footwear-wearing period

It is important to encourage the person to bring any current and old footwear to evaluate the footwear choices and gait patterns in real life. A thorough assessment to identify any issues or discomfort associated with their existing footwear, such as poor fit, excessive pressure points, or lack of cushioning and support needs to be conducted. An in-depth exploration in identify the current wearing period of footwear indoor and outdoor, events of going barefoot or in socks are critical for appropriate device design principles and setting education goals. Studies 3 and 4 have demonstrated evidence of these workflows that influence the treatment plan and device design specifications.

This information complements the CDSD parameters under *"Person's preferences and intended activity".*

Foot pathology	Description
Neuropathy	"The neuropathic foot is described as a loss of peripheral nerve function, which can be sensory, motor, autonomic or usually, a mixture. This loss of function leads to structural changes and function of the foot towards ulceration and subsequent amputation."
Hyperkeratosis	"It is commonly called calluses, and the formation of calluses is due to repeated excessive pressure on the skin. In patients with neuropathy, the presence of callus increases peak plantar pressure and increases the risk of ulceration in that area. Calluses are commonly seen in diabetic feet, even in the absence of neuropathy."
Bony prominences at metatarsal heads	"Claw and hammer toes are associated with plantar fat pad displacement and metatarsal head prolapse on the plantar surface. Any ulcers in the metatarsal heads need to be treated with urgency, especially in the hallux base, due to the increased risk of amputation."
Hallux Abducto Valgus (HAV)	"Due to the structural deformity caused by HAV and the abnormal foot shape, the normal push-off becomes difficult and results in increased friction on the medial aspect of the 1st MTP Joint."
Flexible flat gait foot	"Flexible flatfoot results in reducing the shock-absorbing capacity of the foot and increases pressure on the medial border."
Rigid flat foot	"The rigidity of this condition results in excessive pressure on the medial border of the foot. Ankle-high shoes with shock absorber heels, stronger medial heel counter and rockers with apex position posterior to metatarsal heads are ideal features to protect the foot from worsening in positioning."
Forefoot amputation	"There are many similarities in the effect of forefoot amputation with Hallux amputation, with the additional risk of the foot taking an equines structure and increased pressure at the lateral border of the foot [19]. The shock absorption capacity decreased due to the stiffness of the foot structure."
Hallux amputation	"Amputation of the Hallux results in altered pressure distribution, and the pattern is significantly influenced by this [20]. During the push-off phase, the force is transferred through the 1st metatarsal bone and results in increased shear force. This mechanism frequently results in a wrinkle on the shoe's upper and pressure ulcers on the dorsal aspect of the foot."
Neuropathy	"The neuropathic foot is described as a loss of peripheral nerve function, which can be sensory, motor, autonomic or, usually, a mixture. This loss of function leads to structural changes and function of the foot towards ulceration and subsequent amputation."
Hammer & clawed toes	"A typical neuropathic foot with stiff structure and minimal shock absorbing and contact area due to the dorsiflexed position of the Metatarso Phalangeal Joints (MTPJ's)."
Limited joint mobility	"Limited joint mobility in the diabetic foot has been described by the limited range of motion (ROM) at the ankle joints and 1st Metatarso Phalangeal Joints (MPJ) [21–25]. Ankle joint limited ROM or equinovarus foot structure increases the pressure at the forefoot area, specifically at the metatarsal zone, which accelerates the risk of ulceration in that area. In addition, Hallux limitus or rigidus can generate foot ulcers in the medial and dorsal aspects of the 1st Hallux [26]. As the foot is stiff in nature [27], the force is transferred through the heel during heel strike yielding less shock absorption within the foot at the gait cycle. As the forefoot has limited dorsiflexion, that results in friction between the forefoot and shoe at the push-off phase."

Table 3.
List of forefoot pathology based on the literature review.

3.5 Determine foot measurements, shape, and footwear type

Measuring the person's feet by using any suitable methods to determine the correct size and shape is critical for footwear selection. The width, length, arch type, and any foot abnormalities or deformities are the guiding factors for the correct size, width, and type of footwear to be recommended. The measuring process involves acquiring three-dimensional data of the foot, ankle, and leg to obtain precise measurements to make the shoe last or to determine the shoe size and width. This helps determine ideal footwear type such as custom-made or prefabricated footwear with or without modifications and the type of insoles required. The ratio of rearfoot volume and forefoot volume is critical to determine the appropriate footwear type to optimally offload the forefoot PPP. For example, a Cavus foot with narrow rearfoot and wide forefoot should be recommended a fully custom-made footwear and insole for a better fit and reduce shear that a prefabricated medical grade footwear in unable to deliver. Very often the prefabricated medical-grade footwear is too loose at the back when an adequate forefoot width is chosen for this type of foot. Some participants in Study 4 have demonstrated evidence of such needs.

This information helps develop and select the CDSD parameters under *"Foot structure and shape", "Footwear type"* and the parameters are extracted from **Table 3**, our systematic literature review [9], DFA guideline [10], clinical audit [Study 2], Australian pedorthists' survey [Study 3], the series of N-of-trials [Study 4] and Zwaferink et al.'s algorithm [13].

3.6 Prescribing appropriate footwear features

Proper fit of the footwear is the most critical factor in offloading and adherence to the therapy and the benefits multiply when they are equipped with appropriate design features such as soft and seamless interior. Other critical design features for the footwear are cushioning and shock absorption, breathability, adjustable closures and sturdy and supportive soles. Strong evidence is present for rocker sole design features for optimum plantar pressure offloading and maintaining stability as reported in Studies 1 [9], 3 and 4.

This information helps develop the CDSD parameters under *"Footwear style", "Footwear upper height", "Footwear lining material", "Footwear fastening system", "Footwear upper flexibility", "Footwear tongue flexibility", "Footwear heel counter", "Footwear heel height", "Footwear heel modification", "Footwear outsole", "Footwear rocker sole profile", "Footwear apex position", "Footwear apex angle", "Footwear rocker angle".* The above-mentioned parameters are extracted from our systematic literature review [9], DFA guideline [10], clinical audit [Study 2], Australian pedorthists' survey [Study 3], the series of N-of-trials [Study 4] and Zwaferink et al.'s algorithm [13].

3.7 Prescribing appropriate insole features

The selection of an appropriate casting method and cast modifications are influential factors in outcomes when designing an insole that is optimal for PPP reduction and increasing contacts.

The selection of appropriate materials for various layers can achieve the above goals.

Other strategies for enhancing offloading are through increased MLA heights, adding metatarsal bar, dome or pad and ideal positioning of them, material hardness and height of them. Studies 1 [9], 3 and 4 have confirmed the features and benefits of such strategies.

This information helps develop the CDSD parameters under *"Insole type", "Custom-made insole shape", "Insole base layer material", "Insole mid-layer material", "Insole top layer material", "Insole heel cup", "Insole heel wedge", "Insole MLA height", "Insole metatarsal addition", "Insole metatarsal addition position", "Insole metatarsal addition thickness", "Insole metatarsal addition material type", "Insole modification".* The above-mentioned parameters are extracted from our systematic literature review [9], DFA guideline [10], clinical audit [Study 2], Australian pedorthists' survey [Study 3], the series of N-of-trials [Study 4] and Zwaferink et al.'s algorithm [13].

3.8 Evaluate offloading and ensure pressure redistribution

It is very important to evaluate the efficacy of PPP offloading and redistribution of the designed devices through in-shoe pressure mapping at the fitting of current footwear and insole and during any subsequent post modifications. Various strategies are successful in increasing offloading capacity of the footwear and rocker design parameters for PP offloading and balance are the most popular ones. Its efficacy and design features have been reported in Studies 1 [9], 3 and 4.

Among other popular strategies to increase PP offloading are the insole modifications that include removal of hard materials and adding local cushioning, replacing top covers. Studies 1 [9], 3 and 4 have reported the features and benefits of such strategies.

This information helps develop the CDSD parameters under *"Pressure offloading evaluation method"* and the parameters are extracted from our systematic literature review [9], Australian pedorthists' survey [Study 3] and the series of N-of-trials [Study 4].

3.9 Provide education and regular follow-up

The success of the treatment plan and the footwear and insoles are largely dependent on education on wearing footwear and insoles, regular reviews, repair, maintenance, and timely replacement. It is also important to refer to a podiatrist or other relevant health professional when necessary.

A person's satisfaction and adherence to the devices can vary depending on various factors, and it is critical to keep monitoring a person's satisfaction and adherence to footwear and insoles. If there are any concerns or issues reported by the person or observed during the appointments, it is critical to attend to any issues that arise.

3.9.1 Foot pathologies associated with neuropathic plantar forefoot ulcers

The table below describes the common pathology seen in people with diabetes and neuropathy and associated with plantar forefoot ulceration. This is a general guide for the pedorthists for what pathology this algorithm is suitable for. This information is collated from the systematic literature review [9].

4. Design considerations

4.1 Upper design

For footwear upper height, the following classification is used:

a. Low cut = below the malleolus.

b. High cut = at the level of the malleolus.

c. Extra high cut = above the malleolus and up to the knee.

The purpose of the adequate upper height of footwear is to influence forefoot plantar pressure reduction and accommodation of the feet [9].

4.1.1 Principles to prevent or reduce injury

Current evidence: Some common principles need to be considered when prescribing footwear for people with diabetes and neuropathy [13]. Each shoe must have sufficient interior space in length and width, with a minimum of 1 cm space in length between the longest toe and the inner of the shoe. The toe box must be sufficiently high to accommodate a non-correctable claw, hammer toes, or a hyperextended hallux. The inner lining should not have any seams. Shoes should have laces or velcros depending on hand functions, and BOA lacing and zippers can be considered for further support to aid foot entry.

4.1.2 Management of oedema

Current evidence: With the presence of oedema or vulnerable skin in the lower leg, a low-cut shoe is preferred to avoid pressure from the shoe upper or the top line on the sensitive area. If a high-cut shoe is indicated, the inner should be padded, and the top edge of the shoe should be above the vulnerable area. A 1.5 mm-thick flat layer of material (single or multiple layers as needed) below the insole creates the opportunity to moderate interior volume with changing oedema [13].

4.2 Footwear upper flexibility

Treatment goal: The treatment goals related to upper flexibility are the accommodation of the feet, supporting feet structure and ensuring walking comfort and ease of use. Patient's stability increase, reduced risk of falls and improved balance are some of the key focuses for footwear upper design.

Current evidence: If the lower limb pathology has a combination of muscle weakness of the tibialis anterior or peroneus longus muscles, an extra high cut upper with reinforcement between the upper and lining should be considered [9, 13]. This is to support the dorsiflexion of the ankle.

Another alternative approach is to add an external orthosis or bracing in the form of an ankle-foot orthosis (AFO) when a foot drop is present.

4.3 Rocker sole profile

Treatment rationale: The purpose of a rocker sole is to reduce peak pressure under the forefoot [9] by redistributing the plantar pressure.

- With fully custom-made shoes, the rocker is applied in the insole, with the outsole following this insole rocker configuration one-on-one.
- With prefabricated medical-grade footwear, the rocker is in the outsole.

Current evidence for rocker apex position: The rocker apex is the central point on the rocker axis and should be at 60–65% of the shoe length or 10–15 mm behind the metatarsal heads (MTHs) [9]. The % of the length is measured from the rear of the shoe to provide optimal balance for pressure relief under the different metatarsal heads. This relates to a rocker axis that is ~1.3 cm proximal to MTH 1 and ~2.6 cm proximal to MTH 2 for shoe size US9.5 [13]. Barefoot pressure mapping or a pedograph or in-shoe pressure mapping, or both should be considered for the further precision design of the rocker profile.

4.3.1 Considerations for severe neuropathy or poor balance

The rocker apex position must be set carefully for people with severe neuropathy and poor balance. A distal apex location may help support them during the stance phase.

Current evidence for rocker angle: The rocker angle is the angle between the ground and the bottom surface of the shoe from the rocker apex forward and should be 15–20° in each shoe, independent of shoe size [13]. This should be guided by pressure mapping or a pedograph and checking the person's balance. The thickness of the rocker sole also needs to be considered with the aim of fall risk assessment and aesthetics of the footwear. This should determine the precise rocker angle for the prescribed footwear.

Current evidence for apex angle: The apex angle is the angle between the rocker axis and the longitudinal axis of the shoe and should be 95° [9, 28]. This means that the rocker axis is medially more distal than laterally. With an exhortation position of the foot, the rocker axis must be corrected to give an apex angle of 95° in the direction of walking [13]. This angle may change where the metatarsal head orientations are unique and the ROI for offloading is unique.

4.4 The outsole profile

Treatment rationale: The purpose of the outsole is to protect the midsole that contains the rocker profile and support the rocker profile structurally. This is the interface between the walking surface and the other parts of the footwear that accommodate the foot. It is also one of the most visible and visual factors affecting patient satisfaction and adherence.

A number of different outsole options are possible. There is not sufficient evidence to be prescriptive about the outsole except the shape of them based on practical requirements, such as with a separate heel or in a wedge shape. A separate heel is considered for the patient's aesthetic preference or occupational needs, and the wedge shape is considered when the base of ground contact needs to be more, and the stability and balance of the patient are the priorities.

The footwear outsole should provide cushioning and can be made supple or toughened or can be reinforced with a carbon, fibreglass or metal layer over the partial or entire length of the footwear to create a rigid outsole profile that cannot be bent. The shoe outsole should have adequate shock absorption characteristics while providing sufficient durability for active users and be as lightweight as practically possible. With clearly reduced proprioception, opt for a semi-rigid outsole for improved balance. It is important to consider slip-resistant outer soles for people with moderate to severe peripheral neuropathy.

4.5 Tongue

The footwear tongue can be made supple or reinforced, and it is always padded. A rigid tongue with thermoplastic material reinforcement is used mainly with forefoot amputation.

4.6 The heel height of the footwear

Treatment rationale: The heel of the footwear can have several configurations and this aid with ankle ROM and stability. Changes in heel height influence forefoot PP and stability of the person.

Current evidence: Normal heel height for men is 1.5–2 cm, and for women, 2.5–3 cm in regular prefabricated footwear [13]. Our findings from Study 4 are to have a heel height between 1 cm and 1.5 cm for improved offloading at the forefoot. An increased heel lift or height is provided in fully custom-made shoes via heel lift in the shoe and in prefabricated shoes via heel lift in the insole (maximum 1 cm) [13]. This can be limited if the footwear is a low-cut version. The increased heel lift in pes equines is dependent on the available ankle range of motion.

4.7 The insole design, material and modification features

Treatment rationale: Insole can provide base or surface of foot contact, support the medial and transverse arches and accommodate any bony prominences through an appropriate deflection and combination of multiple cushion materials. They also provide cushion to the overall foot, reduce shock during weight-bearing, help stabilise the foot and reduce shear when objectively designed.

The casting method for capturing the plantar foot profile is recommended to be a non-weight-bearing or semi-weight-bearing cast and 3D scan with the aim of further correction of the cast digitally, where possible, for an improved outcome. This concept is verified by our Study 3. The other casting method that can sometimes be recommended is a full-weight-bearing cast when indicated and can be filled with plaster or 3D scanned to make the mould for insole production as practical for the facilities. For a plaster cast mould, generally, a conventional heat moulding of multi-layered and multidensity materials is used. For the 3D scanned and designed process, the output can be either by CNC milling of multidensity and multilayered block or 3D printing method out of soft filament or powder with specific geometric pattern or lattice design.

Current evidence: The base of the insole in fully custom-made footwear should be with good structural strength capable of shape retention during manufacturing and providing support during everyday use by the patient. This layer also provides the base layer for the mid-layers and top cover to form the complete insole. The hardness of the base layer can be from 55° Shore A onwards, such as a 5-mm-thick micro cork. The base layer can be of dual density with multilayers, and the upper of the base layer materials hardness can be 35–40° Shore A, such as a 5-mm-thick Ethylene Vinyl Acetate (EVA). This layer provides shock absorption properties during weight-bearing. With prefabricated pedorthic footwear, the base may consist of 6-mm-thick EVA (35–40° Shore A) [13]. Any other suitable materials with similar compressibility and durability can also be considered [29]. A 3D printed

three-quarter or full-length base with thermoplastic polyurethane (TPU) filament of 45–55° Shore A or a filament with similar functionality can also be used when a 3D print insole is considered.

The insole mid-layer primarily provides shock absorption during weight-bearing and contouring to the plantar foot profile for increasing base of contact and may be made of a 3–6 mm thick Poron or PPT. The hardness of the mid-layer can be between 30 and 35^0 Shore A. The thickness is dependent on whether custom-made footwear or prefabricated footwear is considered and the level of cushioning required for optimum pressure offloading of the specific foot.

The top layer of the insole is recommended to provide cushion and sometimes specifically to reduce shear. This layer can be made out of Plastazote or similar characteristic material, and the thickness can be 3–5 mm and is also dependent on footwear type and offloading requirements. A Plastazote is more effective in pressure offloading than the leather insole top cover [30]. Other patient-specific factors may be considered when choosing an appropriate type of top cover materials from the range of commercially available materials.

4.8 The metatarsal additions (metatarsal bar, pad or dome)

Treatment rationale: Metatarsal additions can help reduce plantar pressure at the metatarsal area significantly [9].

Current evidence:

- A transmetatarsal bar is recommended to offload all metatarsal heads [31]. A metatarsal bar or dome is recommended if only one metatarsal head is the ROI to offload the plantar pressure [13].

- The material of the metatarsal additions should be 5–11 mm thick [9], made out of PPT or PORON, TPU (or similar 3D printable filament) with 30–35^0 Shore A hardness. These configurations are proven to be effective and more comfortable for the persons, as found in our study four. The addition is covered by the insole top cover.

- The location of the addition should be 6–11 mm proximal to the metatarsal head in a static position [9, 32]. Consider the top cover thickness, as this will change the effective position of the addition, moving it more distally.

4.9 The medial arch support

Treatment rationale: A medial foot arch support is proven to reduce a greater amount of peak plantar pressure at the forefoot [9].

Current evidence: Addition of 3-5 mm height to the existing foot medial arch support obtained from the total contact through a semi-weight-bearing cast or scan [30, 33]. Full-length medial arch support, in combination with a full-length varus wedge, can improve plantar pressure offloading under the Hallux [34].

When a plantar fascia is tightly tensioned or nodules in the fascia (e.g., in patients with Morbus Ledderhose [plantar fibromatosis]), customisation of the medial arch support should be considered. Support at the sustentaculum tali could be an alternative approach [13].

4.10 The insole modification

Current evidence: The cut-out should be circular or slightly oval in shape in the walking direction and be minimally larger than the ROI. The cut-out should be 5 mm deep and padded with a 3 mm durable material up to 30^0 Shore A [13]. The top cover of the insole should be checked regularly and replaced as needed. The replacement frequency of the top cover could be between three to 6 months, depending on the use and requirements of positioning or adding the metatarsal additions [9, 30].

The above information in **Table 1** has the potential to put through a decision tree through an artificial intelligence (AI) powered database to use for machine learning and to develop an AI-powered clinical decision support system (CDSS) on specific footwear and insole type selection for each person based on their main pathology, comorbidity, preferences, and mobility status (treatment goals), How this CDSD works:

Result of the case scenario (participant 1): A low-cut sandal design was the patient's initial desire, but the clinical requirements suggest extra high-cut sandal design shoes (due to lower limb oedema). The family was involved, and a common agreement was made following further discussion, motivation, and advocacy with all parties on the appropriate footwear choices that person was well accepting. The patient had wide foot structure, limited mobility, and used single hand walking aid for maintaining balance. Patient had rigid pes planus and hallux valgus on the right foot and hallux limitus on the left foot. The patient also had PAD/PVD, lower limb oedema and higher BMI (body weight 120 kg). Patient's affordability was dependent on health fund availability and had access to health funds. A prefabricated medical-grade casual design extra high-cut upper design footwear with further sole modification was planned. Microfabric upper lining suitable for PVD/PAD and oedema and Velcro fastening systems with medial zipper was selected. The footwear needed to add a rigid forefoot rocker and higher density rigid outsole to withstand the higher body weight. The overall thickness of the sole needed to be lower to reduce weight and improve balance which was achieved by adding standard rocker angle and positioning the apex posterior to the metatarsal heads and in medial rocker direction. The insole was custom-made insole with regular shape, medial extended wall with lowered heel cup and adding medial heel wedge due to oedema and pes planus feet. A Bilateral Morton's extensions were added with standard thickness with firm material where the insoles had hard base, medium soft mid-layer and soft top cover. No additional modifications to the insoles were required. An in-shoe plantar pressure measurement system was used to evaluate the PP reduction efficacy of the footwear and insoles.

5. Towards AI-powered clinical decision support system

In recent years, the integration of machine learning techniques into healthcare has shown great promise in enhancing clinical decision support systems (CDSS) [35]. This section explores the potential of machine learning techniques in developing CDSS for diabetic foot care. We consider a patient scenario, followed by a detailed analysis and the deduction of two exemplary rules that highlight the capabilities of these advanced systems.

Machine learning, a subset of artificial intelligence, can offer a transformative approach to diabetic foot care [36, 37]. It can empower CDSS to analyse vast datasets, identify intricate patterns, and make data-driven recommendations tailored to each

patient's unique needs. Decision tree [38, 39] and random forest [37] algorithms are particularly well-suited for this task, as they excel in decision-making and classification tasks. Decision tree algorithms construct hierarchical trees of decisions based on input features, partitioning data into subsets until a prediction or recommendation is reached. Random forest, an ensemble method, leverages multiple decision trees to enhance accuracy and robustness. These techniques can be applied to various aspects of diabetic foot care, including patient-specific factors, clinical diagnoses, and funding considerations.

Consider a patient scenario that exemplifies the power of machine learning-based CDSS in diabetic foot care:

"A low-cut sandal design was the patient's initial desire, but the clinical requirements suggest an extra high-cut sandal design shoes (due to lower limb oedema). The family was involved, and a common agreement was made following further discussion, motivation, and advocacy with all parties on the appropriate footwear choices that person was well accepting. The patient had a wide foot structure, limited mobility and used a single-hand walking aid for maintaining balance. The patient had rigid pes planus and hallux valgus on the right foot and hallux limitus on the left foot. The patient also had PAD/PVD, lower limb oedema and a higher BMI (body weight 120 kg). Patient's affordability was dependent on health fund availability and access to health funds. A prefabricated medical-grade casual design extra high-cut upper design footwear with further sole modification was planned. Microfabric upper lining suitable for PVD/PAD and oedema and Velcro fastening systems with medial zipper was selected. The footwear needed to add a rigid forefoot rocker and higher density rigid outsole to withstand the higher body weight. The overall thickness of the sole needed to be lower to reduce weight and improve balance which was achieved by adding standard rocker angle and positioning the apex posterior to the metatarsal heads and in a medial rocker direction. The insole was custom-made insole with regular shape, medial extended wall with lowered heel cup and adding medial heel wedge due to oedema and pes planus feet. Bilateral Morton's extensions were added with standard thickness with firm material where the insoles had hard base, medium soft mid-layer, and soft top cover. No additional modifications to the insoles were required. An in-shoe plantar pressure measurement system was used to evaluate the plantar pressure reduction efficacy of the footwear and insoles.

This patient scenario vividly demonstrates the complexity of diabetic foot care and the need for a comprehensive CDSS. The patient's initial preference for low-cut sandals clashed with clinical requirements, highlighting the importance of data-driven decision-making. Family involvement and advocacy further emphasised the need for a holistic approach, integrating both clinical expertise and patient preferences. The patient's unique clinical profile, including wide foot structure, limited mobility, and various foot pathologies, underscored the necessity for personalised recommendations. Machine learning algorithms can analyse such profiles, considering factors like patient mobility, body weight, and comorbidities, to tailor offloading device prescriptions.

Table 2 presents the representation of scenarios of these three patients (including the one described above as participant 1) in the clinical decision support database. Below two exemplary rules can be deduced from the table:

Rule 1: Family Matters in Footwear Choices.

If (FCPA equals FCPA4 or FCPA3) and (FOIS equals FOIS3 or (FO equals FO2 or FO3)), then FWT should be FWT3.

Rule 1 emphasises the importance of family involvement when deciding on the right shoes for diabetic foot care. If the patient's family or loved ones are actively engaged in the decision-making process and there are certain financial limitations or restrictions, then the CDSS recommends choosing a specific type of footwear that's adaptable to the patient's needs (FWT3). This rule highlights that involving the patient's family and working together to make the best choice for the patient's health is crucial, especially when there are budget constraints or differences in opinion.

Rule 2: Customising Insoles for Complex Foot Conditions.

If (MFP equals MFP3 or MFP4 or MFP5 and FCPA equals FCPA1 or FCPA4 and FOIS equals FOIS1 or FOIS3), then INST should be INST2.

Rule 2 focuses on creating personalised insoles for patients with complex foot conditions. If a patient has specific foot problems like rigid arches, bunions, or limited movement in the big toe and their family supports their choices, then the CDSS suggests using custom-made insoles (INST2). These insoles are designed to fit the patient's unique foot shape and conditions. This rule underscores the importance of tailoring foot support to the individual's foot issues, especially when their family agrees with their decisions.

These exemplary rules exemplify how machine learning algorithms can deduce recommendations based on a patient's clinical and personal factors, family involvement, and funding options. By analysing historical data and considering the interplay of these variables, the CDSS can provide informed, data-driven guidance for diabetic foot care, optimising patient outcomes and reducing the risk of complications.

Table 2 highlights the complexity of the clinical decision support database for diabetic foot care, which includes 9 input features and 21 output features, with each feature capable of having between 2 and 10 different possible values. Developing a CDSS utilising machine learning to handle such a wide range of input features and decision output attributes poses significant challenges. These encompass managing high-dimensional data, ensuring data accuracy and reliability, addressing feature selection and dimensionality reduction, dealing with model complexity and potential overfitting, handling imbalanced data classes, modelling intricate feature interactions, providing explainable predictions, adhering to strict data privacy and ethical standards, integrating the CDSS into clinical workflows, accommodating continuous learning and updates in medical knowledge, and maintaining real-world usability and trust among healthcare professionals. Meeting these challenges necessitates a multidisciplinary approach, close collaboration between machine learning experts and healthcare practitioners, and ongoing monitoring and validation in clinical settings.

6. Limitations of the study

Pedorthics is a small profession, but it plays a vital role in managing long-term plantar pressure offloading for patients with high-risk feet. Various National guidelines and standards [9, 10, 15, 16] have recognised the importance of engaging pedorthists in the multidisciplinary team to bridge the gap and enhance patient care. However, the relatively small numbers of registered and certified pedorthists mean that only small sample sizes were available to understand the maximum variations in prescription and practice habits.

Footwear is a complex intervention that needs to meet clinical and patient personal goals and aesthetics. There are some additional variations that may play roles in

the decision-making, such as family or spouse's preferences, health fund availability, climate, and cultural influences. The methods used, and the set of design principles derived from this chapter have set the cornerstone for future studies for various patient groups to explore future findings towards evidence-based guidelines.

The studies in the chapters were conducted during the COVID-19 pandemic, which impacted each study, particularly the number of study participants and the timeliness of this research.

The set of design principles for footwear and insole design and modifications derived from this chapter was set out to try to determine the 'science' of orthopaedic footwear manufacture for people with diabetes, but it is not a sole science; it is heavily contextually dependent on social issues and patient preferences. Future research based on this set of design principles can increase the scope of practice for various populations.

7. Conclusion

The most recent guideline on footwear and insole design and modification for people with diabetes and neuropathy by Zwaferink et al. [13] is aimed at recommending for up to 80% of the population seen in the clinical environment. This guideline [13] is for fully custom-made footwear only and is only feasible for people in developed countries who have different health education and healthcare systems with a variety of fund options. This is a foot pathology-driven guideline and does not include comorbidity, participant mobility concerns and preferences on footwear choices [13]. However, there is a 20% gap that those people are likely to have more complex conditions and requirements without a proper personalised guideline [9]. Moreover, all the current guidelines are developed based on the environment of the developed countries with better healthcare systems [10, 13]. A set of design principles that are universally applicable that include the provision for people from different climates and developing countries are nonexistent [9]. Hence, our set of design principles is universal and bridges the gap in practice to help the practitioners enable practical decision-making to design personalised footwear and insole for people at moderate to high risk of plantar forefoot ulceration. This set of design principles also includes design and modification features for fully custom-made and prefabricated medical-grade footwear (Pedorthic footwear) provision with further modification to match the affordability, intended activities and increased adherence.

The set of design principles and knowledge gained from this thesis would benefit future researchers exploring personalised medical device design for other healthcare domains. Further research is encouraged for improved clinical and adherence-related outcomes.

It is already proven that there is no panacea for footwear and insole prescription; instead, there are a series of principles based on, first, patient needs and preferences, and second, patient pathology. Those are the guiding factors for the treatment plan and options. These complex factors around patients' pathology, comorbidity, and personal and social perspectives need to be put in the bigger picture, and the design principles proposed in the study have considered all these factors for improved clinical and patient adherence outcomes.

The proposed AI-driven prescription parameters can bridge the gap in current practice and offer more comprehensive design principles leading to improved prescription for personalised device design for the specific patient group.

Definition

Pedorthist: A person who provides medical-grade footwear and/or orthotic appliances and appropriate advice to a patient after assessment and analysis of the patient's problem(s). This includes the provision of prefabricated footwear, modification of prefabricated footwear, custom-designed and manufactured footwear and/or orthotic appliances and advice on the need and application of medical-grade footwear, orthotic appliances and other footwear.

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Section 4

Future Perspectives and Innovations in Diabetic Foot Ulcer Research

Chapter 9

Perspective Chapter: Diabetic Foot Pathophysiology and Prevention of Amputation through Behavioral Modification

Jun Hyeok Kim

Abstract

Diabetic foot complications are the result of a complex interplay involving various physiological factors, including macrovascular and microvascular alterations, neuropathy, inflammation, immune responses, hyperglycemia, oxidative stress, and susceptibility to infection. Macrovascular elements, such as atherosclerosis, give rise to tissue ischemia, while microvascular dysfunction exacerbates impairments in perfusion. Neuropathy plays a pivotal role in the development of these complications, manifesting as sensory loss, motor impairments, and autonomic dysfunction. These neurological deficits lead to the occurrence of unnoticed injuries, muscle atrophy, deformities, and dry skin, thereby increasing the vulnerability to nonhealing wounds and infections. Inflammation and immune responses intricately augment tissue damage while concurrently impeding the healing process. The persistent elevation of blood glucose levels in diabetes leads to the formation of advanced glycation end products, which contribute to tissue stiffening. Additionally, oxidative stress exacerbates the extent of damage. Mitochondrial dysfunction further exacerbates these challenges by compromising cellular energy production, thereby exacerbating the difficulties in tissue repair. These multifaceted factors collectively form a significant contributory framework for the onset and progression of diabetic foot complications. Moreover, with regard to modifiable factors, an examination of the influence of behaviors such as smoking, excessive alcohol consumption, and physical activity on the likelihood of lower extremity amputation (LEA) among individuals with diabetes becomes evident. Comprehensive data analysis discerns an elevated risk of LEA associated with smoking and heavy alcohol consumption, while regular exercise is associated with a decreased risk. The cumulative effect of these behaviors underscores the paramount importance of behavior modification in the prevention of LEA and the enhancement of the overall well-being of diabetic patients. Profound comprehension of these mechanisms is imperative for the formulation of efficacious preventive measures, diagnostic protocols, and therapeutic interventions, thereby addressing the considerable impact of diabetic foot complications on both individuals and healthcare systems.

Keywords: diabetic foot, pathophysiology, amputation, surgical, risk reduction behavior

1. Introduction

The diabetic foot represents a multifaceted complication associated with diabetes, characterized by concurrent peripheral neuropathy and vasculopathy driven by intricate metabolic pathways, as indicated in prior research [1–3]. The escalating prevalence of this condition is intricately connected to the growing incidence of diabetes and the extension of life expectancy [2]. Foot ulcers affect 15–25% of diabetic patients [4, 5], significantly impacting their lives and mortality rates [6, 7]. Remarkably, 28% of these ulcers lead to lower limb amputations [8], with a 5-year mortality rate ranging from 42 to 79% [9, 10]. In the Korean population, the prevalence of diabetes stands at approximately 14.4%, with a notable concentration among the elderly demographic. This condition imposes substantial healthcare expenditures, accounting for an estimated 12 billion dollars and representing approximately 7.7% of the total health insurance costs.

This study undertakes an in-depth examination of the pathophysiological mechanisms underpinning diabetic foot complications and investigates the potential for amputation prevention through behavioral interventions. Leveraging a comprehensive review of existing literature, our objective is to elucidate the intricate facets of this condition and proffer pragmatic strategies for its mitigation and prevention.

2. Pathophysiology of diabetic foot

Diabetic foot complications arise from complex interplay between macrovascular and microvascular alterations, neuropathic changes, inflammatory processes, immune responses, persistent hyperglycemia, oxidative stress, and an increased susceptibility to infections

2.1 Macrovascular changes

Macrovascular alterations in the context of diabetic foot complications are principally characterized by atherosclerosis, a persistent malady afflicting larger blood vessels [11]. This intricate process commences with hyperglycemia, a defining feature of diabetes, initiating a sequence of events culminating in endothelial dysfunction [12]. Elevated levels of blood glucose precipitate harm to the fragile endothelial cells that line the arterial walls, providing a foundation for ensuing inflammation and the deposition of lipid-laden plaques within the arterial walls [13, 14]. Over time, these plaques accumulate and undergo rigidification, constricting the arteries and diminishing blood flow to the lower extremities.

The repercussions of macrovascular modifications are of significant consequence. The diminished blood flow to the feet can lead to chronic ischemia, resulting in the deprivation of tissues from the requisite oxygen and nutrients for proper function [15]. This compromised circulation contributes to tissue damage and amplifies the susceptibility to complications, such as ulcers and infections. Furthermore, macrovascular changes can also incite arterial thrombosis, compounding the issue by obstructing blood flow.

2.2 Microvascular changes

Microvascular alterations within the diabetic foot are, if not more so, of equal importance when compared to macrovascular changes. These modifications

predominantly affect the small blood vessels, encompassing arterioles, capillaries, and venules [12]. A distinctive hallmark of these microvascular changes is diabetic microangiopathy, with chronic hyperglycemia serving as a pivotal initiator and perpetuator of these alterations.

Within the realm of diabetic microangiopathy, there is observed thickening of the basement membranes of small blood vessels coupled with an escalation in capillary permeability [16]. This culminates in an impairment of normal vascular regulation and functionality. Consequently, the delivery of oxygen and nutrients to the tissues becomes compromised, while the removal of waste products is hindered [17]. The end result is tissue hypoxia, which can lead to cellular dysfunction and eventual demise.

The ramifications of these microvascular changes are substantial. The reduced blood supply to the foot tissues heightens susceptibility to injury and impedes the body's natural wound healing processes [18]. This diminished perfusion contributes to tissue deterioration, the formation of ulcers, and delayed wound healing. Furthermore, it impairs the regular functionality of sweat glands and the skin, rendering the skin more prone to dryness and fissures.

2.3 Neuropathy

Neuropathy represents another pivotal facet of diabetic foot pathophysiology, profoundly influencing both the somatic and autonomic nervous systems [19]. Sensory neuropathy, arguably the most recognized variant of neuropathy in the context of diabetes, results in the loss of protective sensation, rendering patients less attuned to injuries or trauma to their feet [20]. Patients may inadvertently step on sharp objects, develop blisters, or sustain minor injuries without perceptible awareness [21]. This absence of pain perception underscores the propensity for the development of neuropathic ulcers, a characteristic hallmark of diabetic foot complications.

Conversely, motor neuropathy can lead to muscle weakness and the emergence of foot deformities [22]. Muscles may undergo atrophy, and patients may exhibit altered gait patterns that accentuate pressure on specific regions of the foot [23]. This aberrant mechanical stress further heightens the diabetic foot's predisposition to injury and ulceration.

Autonomic neuropathy exerts its impact on the autonomic nervous system, regulating functions such as blood pressure, heart rate, and sweat production [20]. Within the diabetic foot, autonomic neuropathy may result in fluctuations in skin blood vessel tone, giving rise to erratic changes in blood flow. These fluctuations can induce episodes of hyperemia or ischemia, both of which significantly contribute to the risk of foot-related complications [21].

2.4 Hyperglycemia

Hyperglycemia stands as the cardinal hallmark of diabetes, serving as the foundational factor underpinning a multitude of the pathophysiological alterations evident in the diabetic foot [24]. Elevated blood glucose levels facilitate the onset of oxidative stress and inflammation, disrupt vital metabolic pathways, and compromise cellular function.

One of the central mechanisms through which hyperglycemia imparts its deleterious impact is *via* the generation of advanced glycation end-products (AGEs) [25]. AGEs result from nonenzymatic reactions between glucose and proteins or lipids and accumulate within tissues, thereby contributing to processes of inflammation,

oxidative stress, and tissue damage. Within the diabetic foot, there is a notable increase in AGEs, which, in turn, can catalyze the development of ulcers while impeding the physiological course of wound healing [26].

2.5 Inflammation

Inflammation is a hallmark of diabetic foot pathophysiology. Elevated glucose levels in diabetes activate proinflammatory pathways, leading to the release of cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [27]. These cytokines promote inflammation and immune cell recruitment in the affected tissues.

The chronic inflammatory state observed in the diabetic foot has several detrimental consequences. It compromises the immune system's ability to mount an effective defense against pathogens. Immune cells may become less responsive, impairing the body's ability to control infections [28]. Additionally, chronic inflammation contributes to tissue damage and the development of fibrosis, further hindering tissue repair and regeneration.

2.6 Immune responses

In diabetes, immune responses are often compromised due to the chronic inflammatory state and impaired immune cell function. Hyperglycemia impairs the function of immune cells, such as neutrophils and macrophages, making them less effective at combating infections [29].

Neutrophils, which play a crucial role in fighting bacterial infections, exhibit reduced chemotaxis and impaired phagocytosis in the presence of high blood sugar levels. This impaired neutrophil function increases susceptibility to bacterial infections, which are common in diabetic foot ulcers [30].

Macrophages, important in wound healing and infection control, also experience dysfunction in the hyperglycemic environment [31]. They may exhibit delayed or impaired wound healing responses, contributing to the chronic nature of diabetic foot ulcers.

2.7 Oxidative stress

Hyperglycemia in diabetes leads to oxidative stress, a condition where there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify them [32]. ROS are highly reactive molecules that can damage cellular components, including proteins, lipids, and DNA [33].

Oxidative stress plays a multifaceted role in the pathophysiology of the diabetic foot. It contributes to endothelial dysfunction, impairing the function of blood vessels and reducing blood flow [34]. Additionally, oxidative stress can damage peripheral nerves, exacerbating neuropathy [35]. It also damages tissue repair processes, hindering wound healing.

2.8 Infection susceptibility

One of the most concerning aspects of the diabetic foot is its heightened susceptibility to infections. The combination of neuropathy, impaired circulation, hyperglycemia, inflammation, and immune dysfunction creates an environment conducive to microbial invasion [36].

The impaired sensation resulting from sensory neuropathy means that patients may not notice small injuries or infections until they have progressed significantly [37]. Even minor cuts or blisters can become entry points for bacteria. Furthermore, the compromised immune responses and reduced blood flow make it difficult for the body to control and resolve infections [38].

Chronic hyperglycemia also provides a favorable environment for microbial growth. Elevated glucose levels can serve as a source of nutrients for pathogens, further promoting infection.

3. Modifiable behavioral factors to prevent lower extremity amputations in diabetic patients

A thorough investigation carried out within a Korean population unveiled compelling evidence that among individuals with diabetes the probability of lower extremity amputations (LEA) exhibited a pronounced increase in the presence of active tobacco use and substantial alcohol consumption. In contrast, the consistent engagement in physical activity appeared to serve as a mitigating factor in this risk [39]. Interventions encompassing the modification of current smoking habits, the reduction of heavy alcohol consumption, and the incorporation of regular exercise regimens present themselves as prospective strategies for averting LEA among diabetic patients.

Furthermore, it is essential to acknowledge that the risk of LEA exhibits a synergistic escalation in the presence of unhealthy behaviors. This phenomenon is most strikingly manifested in individuals who are concurrently devoid of exercise, engage in current smoking, and indulge in heavy alcohol consumption as they exhibit the highest risk profile for LEA.

This result originated from the NHIS database, encompassing nearly 97% of the Korean populace who undergo biennial medical examinations subsidized by the Korean government [40]. Out of the entire cohort of 2,644,440 diabetic patients, 0.33% (n = 8778) individuals underwent LEA. A multivariate analysis revealed that the risk of LEA was found to be higher among current cigarette smokers and heavy alcohol consumers (hazard ratio [HR], 1.503 and 1.187), while it was reduced among individuals engaged in regular exercise (HR, 0.865). The scoring system, based on lifestyle choices, assigned zero points for healthy habits (smoking cessation, no alcohol consumption, and regular exercise), one point for each worsening lifestyle choice, and three points for the combination of current smoking, heavy drinking, and lack of exercise. After adjusting for the mentioned variables, an increase in LEA risk was observed with each one-point increment (Score 1: HR, 1.366; Score 2: HR, 1.752; and Score 3: HR, 2.448) [39].

A comprehensive meta-analysis incorporating five cohort studies and three case-control studies highlighted the significant association between cigarette smoking and increased risk of LEA in diabetic patients without publication bias [41]. The pathophysiology of smoking-induced damage lies in the reduced oxygen-carrying capacity of the blood due to harmful cigarette by-products, resulting in tissue hypoxia and arteriospasm [42]. This, in turn, leads to compensatory erythrocytosis, increasing blood viscosity while decreasing tissue perfusion, ultimately inhibiting diabetic ulcer healing, and elevating the risk of LEA [43].

Additionally, chronic and even moderate alcohol consumption among individuals with diabetes can lead to hyperglycemia and peripheral neuropathy, contributing to

diabetic ulcer, and increasing the risk of LEA [44]. This highlights the adverse effect of heavy alcohol consumption on LEA risk. Chronic alcohol intake with diabetes often correlates with poor compliance regarding diet and medication, which further hampers glycemic control [45].

On a positive note, evidence from six controlled clinical trials suggests that regular physical activity and exercise can significantly improve diabetic foot outcomes and help prevent complications, including diabetic ulcers, infections, and LEA [46]. Exercise in diabetic patients has shown benefits in terms of improved glycemic control, enhanced nerve velocity conduction, and better gait function [47, 48]. Furthermore, it delays the onset of diabetic peripheral neuropathy, a pivotal risk factor for diabetic ulcers, by enhancing sensory and motor nerve velocity conduction in the lower limbs [49, 50]. Regular exercise also improves balance, foot rollover, dynamic plantar loading, and overall quality of life in diabetic patients [47, 50]. Remarkably, weight-bearing from physical activity does not pose an increased risk of diabetic foot re-ulceration [51].

4. Conclusion

The pathophysiology of diabetic foot complications represents an intricate and multifaceted process, underpinned by a confluence of macrovascular and microvascular alterations, neuropathy, inflammation, immune responses, hyperglycemia, oxidative stress, and an augmented susceptibility to infections. These elements intricately intertwine and mutually potentiate one another, culminating in an inhospitable milieu within the foot tissues. Gaining a profound comprehension of this intricate interplay among these pathophysiological mechanisms is of paramount importance for healthcare professionals to proficiently engage in the prevention, diagnosis, and management of diabetic foot complications. This, in turn, enhances the overall quality of life for individuals grappling with diabetes.

Furthermore, the modification of behaviors encompassing the cessation of current smoking, the reduction of heavy alcohol consumption, and the incorporation of regular exercise regimens represent a fundamental approach in preventing lower extremity amputation, concurrently enhancing the physical, emotional, and social dimensions of life for individuals afflicted with diabetes.

Conflicts of interest

The authors declare no conflicts of interest.

Competing interests

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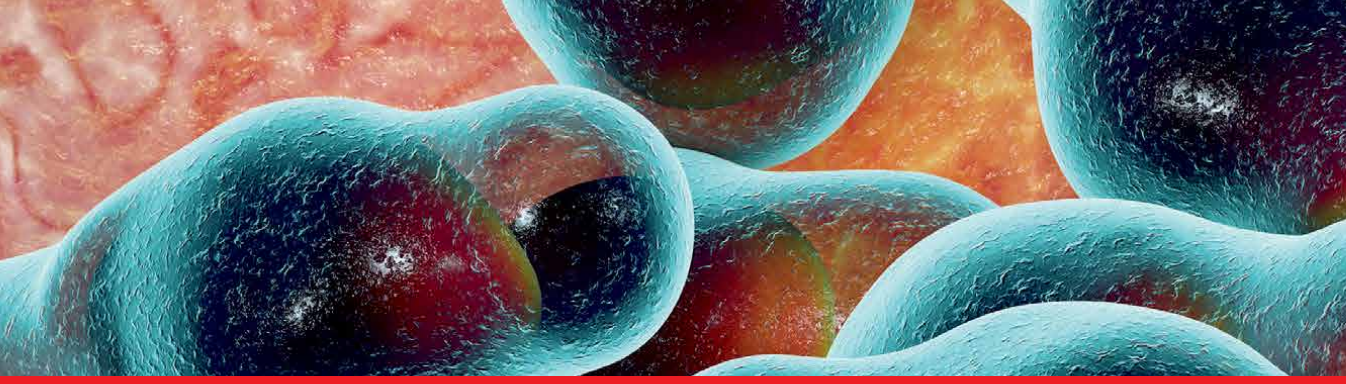

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Diabetic Foot Ulcers - Pathogenesis, Innovative Treatments, and AI Applications is a groundbreaking compilation that offers a comprehensive examination of diabetic foot ulcers (DFUs) from multiple perspectives. With contributions from leading experts in the field, this book explores the epidemiology, risk factors, and underlying pathophysiology of DFUs, providing valuable insights into the complexities of this debilitating complication of diabetes. Innovative treatments for DFUs are explored in depth, including the latest advancements in wound care, bioengineered skin substitutes, growth factors, and hyperbaric oxygen therapy. Contributors also discuss the importance of multidisciplinary approaches and patient-centered care in effectively managing DFUs and reducing complications. A highlight of this volume is the exploration of artificial intelligence (AI) applications in DFU management. From machine learning algorithms to deep learning models and computer vision techniques, experts showcase the potential of AI in early detection, risk stratification, and personalized treatment of DFUs, paving the way for more efficient and effective clinical decision-making. With its interdisciplinary approach and cutting-edge insights, *Diabetic Foot Ulcers - Pathogenesis, Innovative Treatments, and AI Applications* is a valuable resource for researchers, clinicians, students, and healthcare professionals interested in DFU research and management. By sharing knowledge, fostering innovation, and embracing new technologies, this book aims to make significant strides towards preventing and effectively managing DFUs, ultimately improving the health and well-being of individuals affected by this challenging complication of diabetes. *Diabetic Foot Ulcers - Pathogenesis, Innovative Treatments, and AI Applications* is available now, providing essential reading for anyone seeking to deepen their understanding of DFUs and explore the latest advancements in treatment and care.

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