Management Strategies of Diabetic Foot Ulcers with Tunneling or Undermining: A Scoping Review

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Abstract

Aim: This review summarizes the available evidence on the management of diabetic foot ulcers using tunneling or undermining and identifies potential gaps in the current research.

Methods: A scoping review was conducted according to the PRISMA-ScR guidelines. Four databases (Medline, Scopus, Google Scholar, and PubMed) were searched in May 2025 using a combination of terms related to diabetic foot ulcer, tunneling, and undermining. Two independent researchers screened the articles according to the inclusion criteria and extracted the data. The inclusion criteria were original articles/case reports, studies involving patients with diabetic foot ulcers, and studies on the management strategies of diabetic foot ulcers with tunneling or undermining.

Results: The search yielded 115 articles, of which five were included. The included studies were published between 2009 and 2024. Three studies reported that acellular dermal matrix (ADM) is effective for diabetic foot ulcers with tunneling. In contrast, another study reported that debridement of all surface areas, compression, and immobilization were effective for diabetic foot ulcers with undermining.

Conclusion: The management strategies for diabetic foot ulcers with tunneling and undermining include ADM, debridement, compression, and immobilization. While this scoping review does not aim to establish the statistical or clinical effectiveness of one intervention over another, it clearly uncovers a substantial knowledge gap and a lack of standardized protocols in the current literature. Further research is needed to develop specific recommendations based on tunnel and undermining sizes.

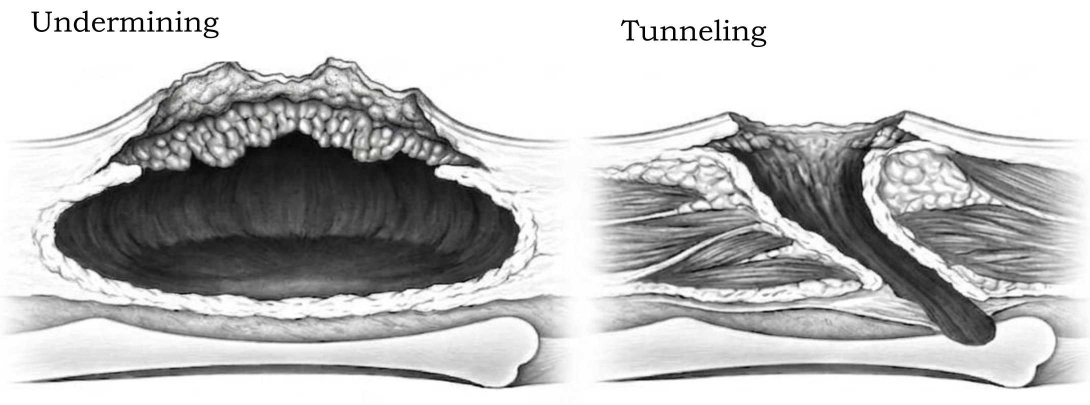
Keywords: diabetic foot, diabetes complications, wound healing.

Introduction

Diabetic foot ulcers represent one of the most serious and costly complications of diabetes mellitus, posing a major global public health challenge owing to their high prevalence, chronicity, and devastating consequences. Globally, diabetic foot ulcers affect an estimated 18.6 million individuals each year, with approximately 1.6 million cases occurring in the United States alone (Armstrong et al., 2017). The burden of this condition is further underscored by the fact that nearly 19%–34% of people living with diabetes will develop a diabetic foot ulcer at some point in their lifetime, with an annual incidence of approximately 2% (Armstrong et al., 2017). Beyond their frequency, diabetic foot ulcers are particularly concerning because of their strong association with lower limb amputations and increased mortality. Evidence indicates that diabetic foot ulcers precede nearly 80%–85% of diabetes-related, nontraumatic lower-extremity amputations, making them a critical precursor to severe disability and loss of quality of life. Even when ulcers heal, outcomes remain poor, as recurrence rates are alarmingly high, reaching up to 65% within three years after healing, highlighting the chronic and recurrent nature of the condition (Maldonado-Valer et al., 2023). Collectively, these statistics emphasize the urgent need for effective prevention, early detection, and timely management strategies to avoid delayed healing, reduce recurrence, and prevent the progression of diabetic foot ulcers into severe infections, amputations, and premature death.

In more advanced cases, diabetic foot ulcers may progress beyond superficial tissue damage and extend into deeper anatomical structures, leading to the formation of sinus tract wounds, commonly described as tunneling wounds. These wounds are characterized by channels that extend from the primary wound bed into and through the subcutaneous tissue, fascia, or muscle, often following the path of least resistance created by tissue destruction (Vault, 2023). Tunneling wounds present a significant clinical challenge because they are frequently difficult to detect, accurately assess, and effectively manage, allowing them to persist for extended periods. The development of tunnels is multifactorial, but they are most commonly associated with underlying infections, which contribute to progressive tissue necrosis and the breakdown of normal anatomical barriers. In addition, inappropriate wound care practices, such as the use of dressings that excessively dehydrate the wound environment or improper packing techniques, including both overpacking and under packing, can further contribute to tunnel formation and impede healing. Clinically, these wounds are particularly deceptive, as the surface opening may appear relatively small or insignificant, whereas the underlying sinus tract is often deep, extensive, and irregular in shape (Ridge, 2009). When the external opening is narrow, thorough wound cleansing, adequate drainage, and effective delivery of topical therapies become more difficult than in conventional ulcers. As a result, tunneling diabetic foot ulcers are at a high risk of harboring an undetected bacterial burden, leading to deep-seated infections that may spread to adjacent tissues. This progression can significantly delay appropriate treatment, increase the likelihood of chronic infection, and ultimately cause irreversible tissue damage, substantially elevating the risk of toe, foot, and lower limb amputation.

In addition to tunneling, wound undermining is another complex and frequently encountered complication of diabetic foot ulcers that further impedes the healing process. Undermining occurs when the wound edges separate from the surrounding intact tissue, resulting in the formation of a concealed space or “pocket” beneath the wound surface. This hidden extension of tissue damage is often not immediately visible during superficial inspection, making accurate assessment and management particularly challenging for surgeons. Several mechanical and biological factors contribute to undermining, including sustained pressure, repetitive shear forces, excessive moisture, and local or systemic infection. In individuals with diabetes, these factors are often exacerbated by peripheral neuropathy, impaired microcirculation, and altered inflammatory responses, which together compromise tissue integrity and resilience. The presence of prolonged pressure or shear can cause tissue layers to slide against one another, leading to structural breakdown beneath the wound margins, while excessive moisture and infection further weaken tissue adherence and promote wound expansion (Advance Comfort Health 2024; Mendota Health 2023). As undermining progresses, the wound may increase in size and depth despite appearing relatively stable at the surface, preventing effective granulation tissue formation and delaying epithelialization. Moreover, undermined areas can serve as reservoirs for exudate and microbial growth, increasing the risk of persistent inflammation and secondary infection. Consequently, undermining significantly complicates wound management and healing outcomes, underscoring the importance of comprehensive assessment and effective therapeutic strategies to address these wound characteristics and support optimal healing of diabetic foot ulcers.



"Created by Gemini".

Figure 1. Schematic illustration of tunneling and undermining in diabetic foot ulcers.

Current international guidelines recommend the comprehensive management of diabetic foot ulcers, including debridement, infection control, perfusion assessment, offloading, local wound care, and selected adjunctive therapies (Schaper et al., 2023). However, current evidence remains fragmented, and no review has comprehensively mapped the available management strategies specifically for diabetic foot ulcers with tunneling or undermining. Existing guidelines provide general recommendations for diabetic foot ulcer care but do not distinguish treatment approaches according to the presence or severity of tunneling or undermining, resulting in considerable variations in clinical practice.

To our knowledge, this is the first scoping review to comprehensively map the available evidence on the management strategies for diabetic foot ulcers with tunneling or undermining. By identifying current interventions and evidence gaps, this review provides a foundation for future research and may support the development of more standardized management approaches for these complex wound characteristics. Accordingly, the objective of this scoping review was to summarize the available evidence on the management of diabetic foot ulcers with tunneling or undermining and to identify gaps in the existing literature. The Patient, Concept, and Context (PCC) framework, according to the Joanna Briggs Institute Manual, was defined as follows: the population comprised adults with diabetic foot ulcers, the concept was diabetic foot ulcers with tunneling or undermining, and no contextual restrictions were applied to the studies (Joanna Briggs Institute, 2020).

The clinical question of this scoping review was, "What kinds of management strategies can be utilized for tunneling or undermining in diabetic foot ulcer patients?".

Methods

Protocol and registration

A scoping review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews ([PRISMA]) (Tricco et al., 2018). The review protocol was not published.

Eligibility criteria

We included studies involving participants of all ages with diabetic foot ulcers in any setting. Studies on the management strategies for tunneling or undermining were included, and no publication date restrictions were applied to the search strategy. This decision was made deliberately because tunneling and undermining diabetic foot ulcers are rarely isolated variables in clinical research. Omitting a timeframe filter allowed for comprehensive, maximal mapping of all available scientific evidence and clearer identification of historical and contemporary knowledge gaps. We limited our search to articles published in English. Originally published articles and case reports were included in this scoping review. Proceedings, conference abstracts, letters to the editor, editorials, guidelines, protocols, literature reviews, and meta-analyses were also excluded.

Information sources

The following bibliographic databases were searched for unlimited years: Medline, Scopus, Google Scholar, and PubMed. The search strategies were created through team discussions, and the final search results were exported to Rayyan (Qatar Computing Research Institute, Doha, Qatar).

Table 1. Search history update through May 2026

Source	Search Location	Boolean Search	Result Articles
Medline	Title/Abstract	(“diabetic foot” OR “diabetic wound” OR “diabetic ulcer” OR “diabetic foot ulcer” OR “diabetic foot problem” OR “diabetic foot lesion”) AND ("tunneling wound" OR “tunneling ulcer” OR “tunneling lesion” OR "undermining wound" OR “undermining ulcer” OR “undermining lesion”)	5
Scopus	TITLE-ABS-KEY	(“diabetic foot” OR “diabetic wound” OR “diabetic ulcer” OR “diabetic foot ulcer” OR “diabetic foot problem” OR “diabetic foot lesion”) AND ("tunneling wound" OR “tunneling ulcer” OR “tunneling lesion” OR "undermining wound" OR “undermining ulcer” OR “undermining lesion”)	12
Google scholar	All fields	(“diabetic foot” OR “diabetic wound” OR “diabetic ulcer” OR “diabetic foot ulcer” OR “diabetic foot problem” OR “diabetic foot lesion”) AND ("tunneling wound" OR “tunneling ulcer” OR “tunneling lesion” OR "undermining wound" OR “undermining ulcer” OR “undermining lesion”)	92
PubMed	Title/Abstract	("diabetic foot" OR "diabetic wound" OR "diabetic ulcer" OR "diabetic foot ulcer" OR "diabetic foot problem" OR "diabetic foot lesion") AND ("tunneling wound" OR "tunneling wounds" OR "tunneling lesions" OR "undermining ulcer" OR "undermining ulcers" OR "undermining lesion")	5

Selection of sources of evidence

The search results were imported into Rayyan (Qatar Computing Research Institute, Doha, Qatar), and duplicates were eliminated. Two independent researchers (EI and MO) read the titles and abstracts and excluded articles that did not meet the eligibility criteria. Second, the remaining full-text articles after the first screening were screened according to the inclusion criteria by four independent researchers

(EI, SK, MA, and KM). Disagreements regarding study selection were resolved through discussion.

Data charting process
A data charting form was developed by one of the authors (EI) to determine the data items to be extracted. Data were extracted by a single author (EI) and verified by the co-authors (SK, MA, MO, and KM). Discrepancies in the extracted data were resolved through discussions among the three authors (EI, MO, and KM).
Data items

The following information was extracted: (a) study authors, year of publication, and country; (b) study design/participants; (c) aim; (d) characteristics; (e) management method; and (f) outcomes.

Results
Selection of evidence sources
The initial search identified 115 studies that were screened. After removing 18 duplicates, 97 studies remained. A total of 88 studies were excluded based on title and abstract screening. Nine studies were assessed in full, with four excluded for not meeting the inclusion criteria: two had unclear results, one used a chicken tissue model, and one used a mouse model. Thus, five articles were included in this scoping review. The PRISMA flowchart is presented in Figure 2.

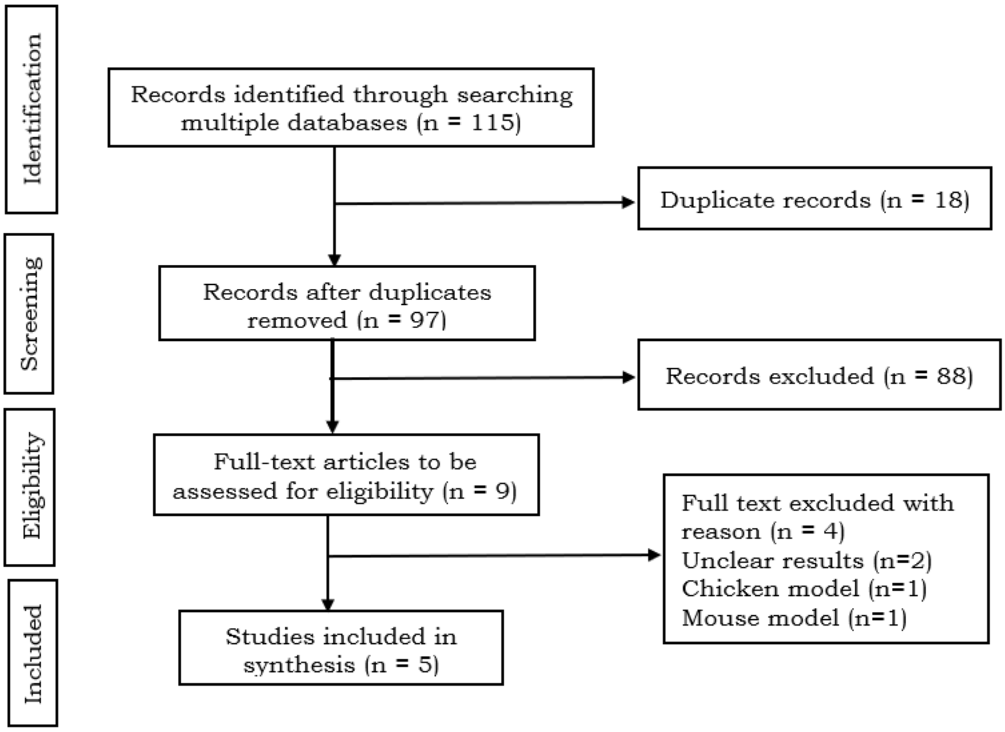


Figure 2. A PRISMA flow chart for this scoping review

Characteristics of evidence sources
Tables 2 and 3 summarize the characteristics of the included studies. Two were retrospective studies (Abdo & Couch, 2024a; Brigido et al., 2009a), one was a prospective case series (Campitiello et al., 2018), one was a randomized controlled trial (Campitiello et al., 2017a), and one was a case report (Melnycuk et al., 2023). The included studies were published between 2009 and 2024 and were conducted by research teams in Italy and the USA.

Synthesis of results

Management of diabetic foot ulcers with tunneling

Four studies have examined treatments for wound tunneling in diabetic foot ulcers, primarily using ADM as scaffolds. The first study employed a 3D acellular collagen matrix (3D-ACM) in close contact with healthy tissue (Abdo & Couch, 2024b). This matrix provides a protective microenvironment that facilitates cellular infiltration and integration, thereby promoting wound healing in tunneling wounds. In this study, 11 patients with 13 wounds were treated, and all diabetic foot ulcers healed completely after an average therapy duration of 13.1 weeks. No new infections were observed during treatment, and no adverse events were attributed to 3D-ACM (Table 2).

The second and third studies used an acellular flowable matrix that served as a scaffold for cellular and vascular ingrowth to promote wound healing (Campitiello et al., 2017b). Its composition and application method allowed it to fill tunneling wounds, thereby conforming to the lesion bed and cavity walls. The second study included two groups: one group (n=23) received a flowable matrix, while the control group (n=23) received wet dressings. Wounds were evaluated weekly for six weeks to assess epithelialization and granulation tissue formation. After 6 weeks, the overall complete healing rate among all patients was 69.5%, while complete wound healing after 6 weeks (primary endpoint) occurred in 20 (86.95%) and 12 (52.17 %) patients in the flowable matrix and control groups, respectively. The third study included 23 patients with diabetic foot ulcers of grade 3 according to the Wagner classification. After 6 weeks, a single matrix on 18 of 23 patients (78.26%) completely healed with no signs of inflammation.

The fourth study utilized an injectable form of an acellular dermal regenerative tissue matrix designed to treat complex tunneling wounds in a minimally invasive manner. The sheet form of this human dermal matrix has previously been successful in aiding healing in diabetic foot ulcers. In this study, 12 patients with deep tunneling wounds were treated and followed up for 12 weeks. Complete wound healing was achieved in 10 of 12 patients, with an average time to complete healing of 8.5 weeks and an average time to depth healing of 7.8 weeks. Complete healing was defined as full epithelialization in the absence of drainage (Brigido et al., 2009b). These results suggest that this injectable dermal matrix has unique properties that facilitate the healing of complex tunneling diabetic foot ulcers.

Table 2. Management of diabetic foot ulcers with tunneling

Study authors, years/country	Study design/ participants	Aim	Characteristic	Management method	Outcomes
Abdo RJ, Couch AL, 2024, USA (Abdo & Couch, 2024b)	Retrospective case series, n=11	To examine the use of three-dimensional acellular collagen matrices (3D-ACM) in treating tunnelling, undermining, or irregularly shaped deep diabetic foot ulcers.	All patients presented with deep or tunneling diabetic ulcerations of the foot and/or ankle.	Surgical debridement was performed. • Wounds photographed and measured using a graph-based system • 3D-ACM applied to fully contact healthy tissue, including tunnel areas • Absorbent dressing or negative pressure wound therapy (NPWT) used as secondary dressing • NPWT applied in five patients • Hyperbaric oxygen therapy (HBOT) is used as an adjunctive therapy in select cases.	• 8 of 13 wounds reduced ≥50% in area within 4 weeks; 1 closed in 2 weeks • 7 of 13 wounds fully closed within 3 months: 1 closed by week 12 • All DFUs healed in an average of 13 weeks (range: 2.0 – 22.3 weeks) with no infections or 3D-ACM-related adverse events.
Campitiello et al, 2017, Italy (Campitiello et al., 2017b)	Randomized placebo-controlled clinical trial, n=46	To evaluate the efficacy of an advanced wound matrix for treating wounds with irregular geometries compared to a wet dressing in patients with diabetic foot ulcers.	Patients who had diabetic foot ulcers with grade 3 Wagner classification	Intervention group • Matrix mixed with saline and injected to fill wound; wound edges sutured Control group: • Wounds dressed in saline-moistened gauze, healing by secondary intention Both groups: • Biopsy for bacterial culture & MIC testing	• 69.56 % overall complete healing at 6 weeks • Complete wound healing after 6 weeks (primary endpoint) occurred in 20 (86.95%) and 12 (52.17 %) patients in the flowable matrix and control groups, respectively. • Intervention group showed higher healing rates and faster healing time

Study authors, years/country	Study design/ participants	Aim	Characteristic	Management method	Outcomes
				• Targeted antibiotics 7 – 10 days pre-op, continued post-op • Wound cleaning and debridement with hydro-scalpel • Compression therapy with inelastic multilayer bandage • Offloading and restricted weight-bearing for 2 weeks • Weekly exams (every 3 days in week 1) until healing • Monitored for signs of inflammation at each visit • Wound photography was performed at each step.	• Lower major amputation and rehospitalization rates were observed in the intervention group.
Campitiello et al, 2018, Italy	Prospective case series (preliminary report), n = 23	To explore the feasibility and safety of an advanced wound matrix in patients with diabetes-related cavity or tunnel lesions involving deep structures.	Patients who had diabetic foot ulcers with Wagner classification grade 3 (deep ulcer with abscess or osteomyelitis)	• Wounds were first washed with normal sterile saline solution, and then necrotic tissues were removed surgically by hydroscalpel • The matrix was prepared by mixing collagen with 3 mL of saline and injected into the debrided wound cavity using a flexible cannula.	After 6 weeks a single matrix on 18 of 23 patients (78.26%) completely healed with no sign of inflammation

Study authors, years/country	Study design/ participants	Aim	Characteristic	Management method	Outcomes
				• Patients avoided walking for 2 weeks, followed by limited ambulation with a removable offloading device. • During the first week, follow-up visits were conducted every 3 days. • Outpatient postoperative follow-ups were scheduled weekly until complete healing was achieved.	
Brigido et al, 2009, USA (Brigido et al., 2009)	Retrospective observational study, n = 12	To assess the safety and performance of a human injectable dermal scaffold in the treatment of diabetic sinus tract wounds.	Patients with diabetic foot ulcers who had a full-thickness sinus tract wound were treated with the flowable scaffold. Sinus tract wounds have a depth greater than both the width and length	• Wounds measured weekly for 12 weeks using tracings • Full-thickness debridement performed to bleeding base • A human injectable dermal scaffold (2 cc) applied, filling ⅓ – ⅔ of sinus tract volume • Total contact cast used for pressure offloading • Weekly follow-ups; nonadherent dressings until healing • Offloading continued for two weeks post-healing.	• Most wounds fully healed by 12 weeks • All patients showed ≥ 50% depth reduction within 14 days • The complete depth reduction in the healed wounds averaged 7.8 ± 2.2 weeks.

Management of diabetic foot ulcers with undermining

One case study used the "Soap Scrap" approach to treat wounds with undermining in diabetic foot ulcers. This approach involves a three-step method for wound closure in areas with undermining: debridement of all surface areas, compression, and immobilization. The technique follows an old, thrifty practice of reusing leftover soap bars: first, the soap bars are softened (performing debridement), then compressed together (applying NPWT, compression wrapping, or both), and finally, they are left undisturbed for some time (immobilization) until they fuse. The results of the study showed that wounds healed on average within 9.1 weeks, with all wounds healing between 3 and 15 weeks (Melnycuk & Juriga, 2023)(Table 3).

Table 3. Management of diabetic foot ulcers with undermining

Study authors, years/country	Study design / participants	Aim	Characteristic	Management method	Outcome
Melynchuk I, Juriga J, 2023, USA (Melnycuk & Juriga, n.d.)	Case reports, n=3	To evaluate the efficacy of the "Soap Scrap" approach to treating wounds with undermining or pockets.	• 83-year-old: diabetic foot ulcers with 1.5×1.7×0.4 cm malleolar ulcer, 0.4 cm undermining at 9 – 1 o'clock • 71-year-old: 10×28×0.5 cm shin laceration, 0.7 cm undermining at 12 o'clock • 67-year-old: 10.7×27×1 cm foot abscess, 1.3 cm undermining at 6 – 11 o'clock	• Surgical debridement • Immobilizing tissue in areas where tissues move and shear • Using multilayered compression alone • Modified NPWT • Multilayered compression and modified NPWT.	• Wound healed on average in 9.1 weeks • All wounds healed between 3 and 15 weeks after treatment.

Discussion

This is the first review to attempt to map the treatment of diabetic foot ulcers with tunneling or undermining techniques. The results showed that ADM is effective for diabetic foot ulcers with tunneling, whereas debridement of all surface areas, compression, and immobilization are effective for diabetic foot ulcers with undermining. However, the number of studies examining these treatments was limited to four and focused only on ADM and Soap Scrap. It is essential to incorporate diverse treatment perspectives and comparative control approaches employed in the management of diabetic foot ulcers.

This review found that acellular dermal matrix (ADM) was the most frequently reported intervention for diabetic foot ulcers with tunneling deformity. This finding is consistent with previous studies showing that ADM promotes granulation tissue formation, neovascularization, and wound closure in diabetic foot ulcers (Byeon et al., 2023; A. Reyzelman et al., 2009). However, previous studies have primarily evaluated ADM in general diabetic foot ulcers rather than wounds with tunneling, which limits direct comparisons. This present review extends the current evidence by highlighting that injectable ADM may be particularly suitable for tunneling wounds because it conforms better to irregular wound cavities. Nevertheless, the available evidence is limited to a small number of observational studies, emphasizing the need for well-designed randomized controlled trials to confirm these findings.

In this review, debridement was identified as a key component in the management of diabetic foot ulcers with undermining. This is consistent with previous evidence demonstrating that debridement removes devitalized tissue, reduces the bacterial burden, and promotes granulation tissue formation (Dayya et al., 2022; Holmes et al., 2019; Yamamoto et al., 2015). Although hydro-surgical debridement has shown additional benefits for complex wounds (Sharma et al., 2024), none of the included studies directly compared different debridement techniques for undermining wounds. Therefore, current evidence does not support recommending one debridement method over another, specifically for diabetic foot ulcers with undermining.

These findings showed that NPWT was used as an adjunctive therapy to manage undermining wounds. Previous studies have reported that NPWT promotes wound contraction, reduces exudate, and stimulates granulation tissue formation in complex diabetic foot ulcers (Hasan et al., 2015; Laila et al., 2020; Noble-Bell & Forbes, 2008). However, evidence specifically evaluating NPWT for undermining wounds remains scarce because most studies include mixed wound types. Therefore, the role of NPWT in undermining foot ulcers requires further investigation through comparative clinical studies.

NPWT, compression therapy, and offloading were identified as adjunctive therapies rather than primary interventions for diabetic foot ulcers with tunneling or undermining. This is consistent with previous studies demonstrating that NPWT promotes wound contraction, removes excess exudate, and enhances granulation tissue formation in complex foot ulcers (Hasan et al., 2015; Noble-Bell & Forbes, 2008). Compression therapy has been shown to reduce edema and improve the wound healing environment (Castonguay, 2008a), while offloading remains a cornerstone of diabetic foot ulcer management, reducing plantar pressure and mechanical stress (Ababneh et al., 2022; Fife et al., 2014).

However, the evidence identified in this review differs from that in the broader literature because these interventions were not specifically evaluated for tunneling or undermining wounds. Instead, they were incorporated as part of multimodal treatment protocols alongside debridement and acellular dermal matrix. Consequently, the independent contributions of NPWT, compression therapy, or offloading to the healing of tunneling or undermining wounds cannot be determined from the available evidence.

The available evidence suggests that NPWT, compression therapy, and offloading have supportive roles in wound management, but their effectiveness for diabetic foot ulcers with tunneling or undermining has not been fully established. Future comparative studies should evaluate these interventions individually and in combination to determine their effectiveness based on wound characteristics, including the extent and severity of tunneling or undermining.

Limitations
The number of available studies specifically addressing tunneling and undermining in diabetic foot ulcers is limited. Heterogeneity in wound characteristics, treatment approaches, and outcome measures across studies also makes direct comparisons difficult. In addition, the lack of standardized definitions and assessment tools for tunneling and undermining limits the strength of our conclusions. Further large-scale, well-designed randomized controlled trials are required to establish clear, evidence-based management recommendations.

Contribution to global nursing practice
This scoping review provides a comprehensive synthesis of the available evidence on the management of diabetic foot ulcers with tunneling or undermining, two complex wound characteristics rarely addressed in current clinical guidelines. The findings highlight evidence-based management strategies, including debridement, acellular dermal matrix, negative pressure wound therapy, compression, and offloading, which may support nurses in clinical decision-making and comprehensive assessments of wounds. This review also identifies important evidence gaps, emphasizing the need for standardized assessment methods, management protocols, and comparative studies. These findings may contribute to strengthening nursing practice, supporting multidisciplinary diabetic foot care, informing future clinical guideline development, and improving wound care outcomes for patients with diabetic foot ulcers.

Conclusion
This scoping review confirmed that ADM is effective for diabetic foot ulcers with tunneling, whereas debridement of all surface areas, compression, and immobilization are effective for diabetic foot ulcers with undermining. Although several interventions have demonstrated potential benefits, the lack of standardized, severity-based guidelines for managing tunneling and undermining remains a major gap in current practice. These findings underscore the need for early recognition, thorough assessment, and multidisciplinary management to optimize healing outcomes. Future research with robust study designs is essential to establish clear, evidence-based recommendations that can guide clinical decision-making and improve outcomes for patients with diabetic foot ulcers with tunneling and undermining defects.

Author contribution
All authors accept responsibility for the entire content of this manuscript. EI took responsibility for the analysis, investigation, and writing of the original draft; SK and MK performed the investigation, writing, review, and editing; KM performed supervision, writing, review, and editing; MO performed supervision, writing, review, and editing, and funding acquisition. The authors have read and approved the final manuscript.

Conflict of interest
The authors declare no conflicts of interest.

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