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Cold Atmospheric Pressure Plasma in the Treatment of Diabetic Foot Ulcers: A Systematic Review

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ABSTRACT

Cold atmospheric pressure plasma (CAPP) is an innovative energy-based therapy which has gained momentum in recent years for its wide array of therapeutic applications. This systematic review aims to evaluate the effectiveness and safety of CAPPs in treating diabetic foot ulcers. We conducted systematic literature searches on Embase, Ovid Medline, Scopus, Cochrane Central Register of Controlled Trials, The Cochrane Database of Systematic Reviews and Clinicaltrials.gov using PRISMA guidelines. We searched for randomised controlled trials (RCTs) and observational studies conducted on patients with diabetic foot ulcers in which CAPP therapy was compared with a control treatment. The risk of bias was assessed using the Cochrane Collaboration tool. Four RCTs from two countries analysing a total of 153 patients were included in the review. Three studies reported a significant reduction in ulcer area in the CAPP group, one study reported a significant decrease in inflammatory markers, and mixed results were reported regarding the reduction of bacterial load. All studies reported no adverse side effects or concerns with the safety profile of CAPP. Current evidence supports CAPP's potential as safe and effective adjunctive therapy that may accelerate wound healing, reduce wound size, promote tissue regeneration and lower infection risks. However, the limited number and size of trials, variability in treatment protocols and short follow-up periods highlight the preliminary nature of these findings. Further large-scale, well-designed studies with standardised protocols and long-term follow-up are needed to confirm CAPP's efficacy and safety, as well as to determine its cost-effectiveness in diverse healthcare settings.

1 | Introduction

Diabetic foot ulcer development is one of the most common complications of type 2 diabetes, which affects over 460 million individuals worldwide [1, 2]. In diabetes, elevated serum glucose causes vascular injury in nerves supplying the lower extremities, leading to peripheral neuropathy with symptoms of burning pain, reduced sensation, and ultimately, foot ulcers [3]. Patients with diabetes are also at increased risk for peripheral artery disease, characterised by atherosclerosis in larger blood vessels and resulting in arterial narrowing or occlusion [4]. Poor perfusion in the lower extremities not only contributes to foot ulcer formation but also significantly impedes wound healing [3–5].

An estimated 15%–25% of patients with diabetes will develop foot ulcers in their lifetime [6]. Diabetic foot ulcers lead to medical complications such as infection, tissue necrosis and osteomyelitis, which can result in limb amputation or death [2, 3, 6, 7]. Extensive

Abbreviations: CAPP, Cold atmospheric pressure plasma; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.

Summary

- Cold atmospheric pressure plasma (CAPP) is a promising therapy with expanding therapeutic applications including in diabetic foot ulcer treatment.
- This systematic review aims to evaluate the clinical efficacy and safety of CAPP therapy for diabetic foot ulcers.
- Evidence from this review indicates that CAPP may accelerate wound healing, reduce wound size, promote tissue regeneration and lower infection risks, with no significant safety concerns.
- The literature remains limited in quantity and quality, and further large-scale, well-designed studies with standardised protocols and long-term follow-up are needed.

evidence highlights the high burden of diabetic foot ulcers, including reduced quality of life, greater morbidity and significant financial costs for patients and healthcare systems [2, 3, 6, 8, 9].

Standard therapy in the treatment of diabetic wounds currently includes surgical debridement, wound dressings, wound off-loading, vascular assessment, infection control and glycemic control [2, 10]. Many foot ulcers remain chronic and non-healing despite standard therapeutic approaches [6]. Additionally, many patients with diabetic foot ulcers may either be unsuitable for surgical intervention due to comorbid conditions or may prefer non-surgical approaches to ulcer management. As a result, many adjuvant therapies have been introduced in the management of diabetic foot ulcers, with some showing more promise than others. These adjuvant therapies can be classified into different categories, including non-surgical debridement (i.e., hydrogels, clostridial collagenase ointment, maggot/larval therapy, hydrosurgery), dressings and topical ointments (i.e., honey, hydrogel), oxygen therapies (i.e., topical oxygen, hyperbaric oxygen therapy), negative pressure wound therapy, acellular bioproducts, human growth factors, skin graft and bioengineered skin, energy-based therapies (electrical stimulation, shockwave therapy, electromagnetic therapy, laser therapy, phototherapy) and systemic therapies. Despite various adjuvant therapies, many foot ulcers remain chronic, highlighting the need for alternative approaches such as cold atmospheric pressure plasma (CAPP) therapy—an emerging energy-based treatment showing promise in diabetic ulcer management [11].

CAPPs are a low-temperature, partially ionised gas formed from elements such as argon, helium or oxygen at atmospheric pressure, containing reactive species and ultraviolet radiation [11]. CAPPs exhibit properties beneficial for diabetic ulcer treatment, including pathogen elimination, accelerated blood coagulation, wound healing promotion and stimulation of skin cell regeneration [12, 13]. They have even demonstrated the ability to selectively eliminate tumour cells in vitro while sparing healthy cells [14–16]. The development of CAPPs, with demonstrated therapeutic properties, has led to the emergence of plasma medicine, opening new possibilities for diabetic wound management.

Although CAPP applications in wound healing are relatively new and literature remains limited, recent clinical studies have begun investigating its effectiveness in treating diabetic foot ulcers. Given CAPP's promising attributes, further research into its efficacy for diabetic ulcer treatment is crucial for advancing wound care practices. This systematic review aims to consolidate findings from recent studies and evaluate the clinical efficacy and healing potential of CAPP therapy for diabetic ulcers.

2 | Methods

2.1 | Protocol and Registration

We developed the systematic review protocol before starting the study and registered it prospectively on PROSPERO (ID: CRD42022335924). The review's design and reporting adhered to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure methodological rigour and transparency [17].

2.2 | Study Identification

A medical librarian (LHY) searched the literature for records focusing on diabetic foot and cold atmospheric plasma. The librarian developed search strategies with a mix of keywords and controlled vocabulary in Embase.com 1947-, Ovid Medline 1946-, Scopus 1823-, Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane Database of Systematic Reviews (CDSR) and Clinicaltrials.gov 1997-. All search strategies were completed on June 27, 2022, yielding 78 results without any search limits. After removing 43 duplicate records following EndNote's standard de-duplication processes [17], 35 unique citations remained in the project library. Fully reproducible search strategies for each database can be found in the Appendix A.

The searches were updated on June 20, 2024, to include studies from 2022 to 2024, resulting in 20 additional unique records after de-duplication.

2.3 | Eligibility Criteria

We included studies if they met the following criteria: (1) randomised controlled trials (RCTs) comparing CAPP with either placebo or standard wound dressing; (2) study population consisting of patients with diabetes aged 18 years or older with chronic foot ulcers; (3) English-language publications; (4) studies which reported a primary outcome of ulcer healing defined as change in ulcer area, healing time, reduction of inflammatory markers or reduction of bacterial load. We excluded studies if they met any of the following criteria: (1) non-RCTs; (2) studies in which CAPP was not compared to placebo or standard wound dressing; (3) studies which did not report ulcer healing; (4) non-English studies.

2.4 | Quality Assessment and Data Extraction

Two reviewers (AH and IA) independently screened citations for eligibility by title and abstract. We then screened the full text of the included abstracts based on the inclusion and exclusion criteria. Disagreements were resolved by discussion or, if

necessary, by consulting a third author. The reviewers extracted relevant characteristics from each study, including author, publication date, number of patients, demographic characteristics, severity of diabetic foot and reported outcome measures. Two reviewers (AH and WH) independently assessed the quality of each included study using the Cochrane Collaboration tool for evaluating domains such as selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases.

3 | Results

3.1 | Literature Search

Figure 1 shows a PRISMA diagram of the literature search and study selection process. The initial search identified 78 citations. After excluding duplicates, 32 unique citations were independently screened by title and abstract and assessed for eligibility. We excluded 16 studies for the following reasons: not an RCT ($n=4$), incorrect study population ($n=10$) or non-English language ($n=2$). We then retrieved 16 full-text articles, of which 12 were excluded due to incorrect study population ($n=10$) or lack of RCT design ($n=2$). In total, four articles met the inclusion criteria.

3.2 | Study Characteristics

Table 1 lists the characteristics of the included studies in PICO (population, intervention, comparison, outcome) format. The four RCTs included a total of 153 patients [11, 18–20]. The sample size for each study ranged from 20 to 44 patients. The intervention time ranged from 2 to 6 weeks. Three studies originated in Iran [11, 18, 19] and one study in Germany [20]. A total of 83 patients received CAPP therapy and 82 received control therapies (placebo or standard wound care). Three studies compared CAPP therapy to standard wound care [11, 18, 19] and one compared CAPP therapy to placebo [20].

3.3 | Bias Assessment

The quality of the included RCTs was assessed according to the Cochrane Reviewers' Handbook [21]. Three of the four included

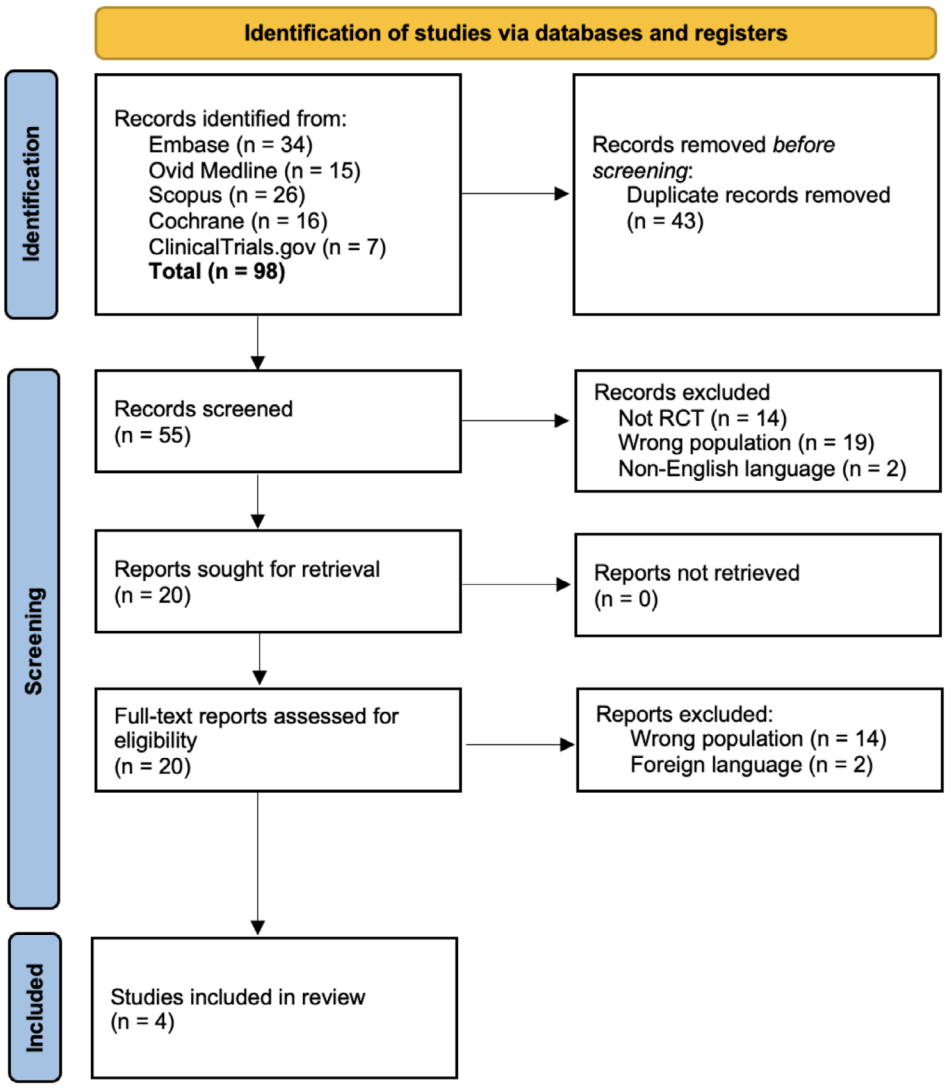

FIGURE 1 | PRISMA flow diagram outlining the selection process.

TABLE 1 | PICOs of included RCTs.

Study (country)	Population	Intervention	Comparison	Stated outcome/findings
Samsavar et al. 2021 [18] (Iran)	20 participants	Standard care + CAPP ($n=10$)	Standard care ($n=10$)	Amount of wound exudate in the intervention group was significantly reduced in the third week after complete treatment ($p=0.039$). The wound grading of the ulcers in the intervention group improved by the sixth week ($p=0.019$), and the sizes of ulcers significantly decreased in the intervention group at the end of the treatment period ($p=0.007$).
Mirpour et al. 2020 [19] (Iran)	44 participants	Standard care + CAPP ($n=22$)	Standard care ($n=22$)	CAPP treatment significantly reduced wound size ($p=0.02$). After three weeks, the wounds to reach a fraction wound size of ≤ 0.5 was significantly greater in the SC + CAP group (77.3%) compared with the SC group (36.4%) ($p=0.006$). Bacterial load was significantly decreased after each CAPP session.
Stratmann et al. 2020 [20] (Germany)	65 total wounds from 45 participants	CAPP (33 wounds from 29 patients)	Placebo (32 wounds from 28 patients)	CAPP treatment yielded a significant increase in wound healing, both in total mean area reduction and time to relevant wound reduction (>10%). Reduction of infection and microbial load was not significantly different between CAPP and placebo. No therapy-related adverse events occurred during therapy; patient's perceptions during therapy were comparable.
Amini et al. 2020 [11] (Iran)	44 participants	Standard care + CAPP ($n=22$)	Standard care ($n=22$)	At the end of the 3-week treatment, the intervention group showed significantly decreased ($p=0.001$) levels of inflammatory cytokines such as IL-1, IL-8, INF-γ and TNFα. The intervention group also showed significantly decreased bacterial loads at the end of the treatment ($p<0.0001$).

Abbreviation: CAPP, cold atmospheric pressure plasma.

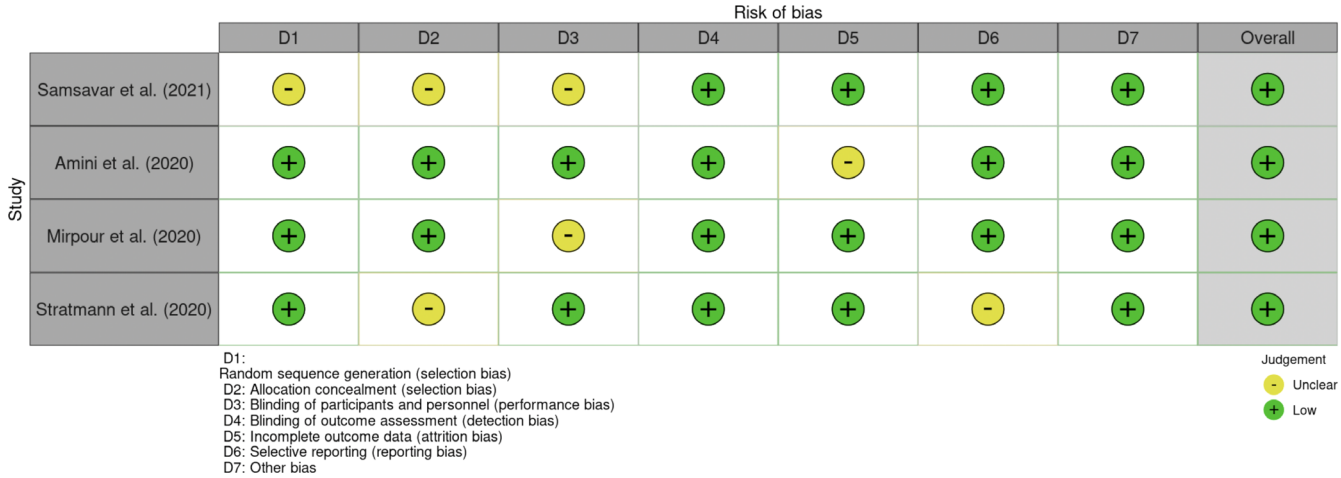

FIGURE 2 | Risk of bias of included studies.

RCTs outlined specific randomization techniques which we determined to represent a low risk of bias [11, 19, 20]. One of the studies commented that the patients were randomised into control and treatment groups, but the technique that was used for randomization was not described in the study, so the authors determined that the risk of bias in this category remains unclear [18]. Two studies reported allocation concealment methods [11, 19]. Although it is understandable that blinding of both patient and provider was challenging in the administration of CAPP therapy, two studies described efforts made by the study team to conceal the treatment as much as possible [11, 20]. Such efforts included having the patient lie down to prevent them from seeing the wound or the treatment being administered, as well as adding the sound of the CAPP device to the placebo treatment to maintain procedural blindness. All four RCTs included in this study showed comparable baseline data between the control and treatment groups. Figure 2 illustrates the risk of bias across included studies (details in Appendix A).

3.4 | Reduction in Wound Size

Three RCTs evaluated the effect of CAPP on reduction of ulcer size [18–20]. Samsavar et al. found no significant difference between the CAPP and control groups in ulcer size reduction at the third week ($p = 0.44$) but observed a significant decrease in the CAPP group by the end of the six-week treatment ($p = 0.007$) [18]. Another study found a significant reduction in ulcer size in the CAPP group compared with the control group by the end of a three-week treatment protocol ($p = 0.02$) [19]. Finally, Stratmann et al.'s study found a significant reduction in wound area in the CAPP group compared with the control group ($p = 0.03$) [20].

3.5 | Reduction in Microbial Load

Three studies evaluated the effect of CAPP on microbial load reduction in diabetic foot ulcers [11, 19, 20]. One study measured microbial load before and after each session and found that CAPP therapy significantly reduced microbial load ($p < 0.05$) [19]. However, no significant difference in microbial load was found between groups at the end of each treatment week. Another study found no significant difference in microbial load ($p = 0.59$) between the two groups at the end of the treatment protocol [20]. A third study found a significant reduction in bacterial load immediately after CAPP treatment ($p < 0.0001$), as well as a significantly lower bacterial load in the CAPP group compared with the control group by the end of the third week of treatment [11].

3.6 | Reduction in Wound Exudate and Inflammatory Markers

One study measured the effect of CAPP on wound exudate [18]. Samsavar et al. reported a significantly greater reduction in wound exudate in the CAPP group compared with the control group, at both the three- and six-week treatment points (p-values = 0.039 and 0.015, respectively) [18]. A second study measured the effect of CAPP on the following inflammatory markers: IL-1, IL-8, INFγ and TNFα [11]. Both standard wound care and CAPP therapy significantly reduced these inflammatory markers by the end of the three-week treatment. However, the levels of the inflammatory markers were significantly lower in the CAPP group compared with the control group ($p < 0.001$).

4 | Discussion

4.1 | Summary of Main Findings

To our knowledge, this is the first systematic review attempting to synthesise the available literature on CAPP—a promising technology for treating diabetic foot wounds. Limited and low-quality evidence supports CAPP's efficacy in treating diabetic foot ulcers. Specifically, data suggest that CAPP enables greater wound size reduction, shortens healing time, reduces inflammation severity, decreases wound exudate and offers antiseptic benefits.

Although evidence indicates that bacterial load decreases significantly immediately after CAPP therapy, these antiseptic effects may be transient, explaining why two studies did not find a significant decrease in bacterial load from baseline at the end of the treatment protocol [19, 20]. All studies assessing wound size found that CAPP significantly reduced wound size compared

with the control group [18–20], suggesting CAPP therapy is effective for wound healing. Regarding CAPP's safety, most ultraviolet radiation from the treatment is in the 300–400 nm range, which is not typically associated with DNA damage [22]. A 2018 pilot study by Peters et al. found that CAPP therapy is safe and well-tolerated [23], and none of the reviewed articles reported adverse effects. Overall, the results of the included studies suggest CAPP is a safe and effective tool for accelerating healing and potentially reducing infection risk in diabetic foot wounds.

4.2 | Limitations

A major limitation of this study is the limited number of available RCTs from two countries exploring CAPP's effectiveness in diabetic foot wound healing. The inconsistent outcome reporting among studies prevented meta-analysis, limiting data synthesis. As more research emerges on this technology's role in diabetic foot wound treatment, a future meta-analysis could combine results and allow important statistical analyses.

The quality of the included studies also presents certain limitations, as some lacked methodological rigour, such as appropriate blinding, consistent or robust randomisation procedures and adequate sample sizes. These limitations in study design may reduce the reliability of findings and introduce bias into the results. Furthermore, this review may be subject to publication bias, given that studies with favourable results are more likely to be published than those with null or negative outcomes, potentially overestimating the perceived efficacy of CAPP therapy.

Geographically, three of the four included studies were conducted in Iran, which may limit the generalisability of findings due to potential cultural, genetic and healthcare system differences. Additionally, variation in the application protocols for CAPP, such as differences in treatment duration, frequency and device parameters, further complicates the comparability of results and underscores the need for standardised protocols to guide clinical practice.

Another limitation is the short follow-up periods in the included studies, which leave the long-term sustainability of CAPP's therapeutic effects, such as wound healing durability and infection control, uncertain. The limited analysis of adverse events also presents a concern. Although no adverse effects were reported, the relatively small sample sizes and short follow-up periods might not be sufficient to fully evaluate the safety profile of CAPP therapy. Larger studies with extended follow-up durations are needed to confirm the absence of potential risks.

Finally, none of the studies included a cost-effectiveness analysis of CAPP therapy, an important factor for its practical implementation in diverse healthcare settings, particularly those with limited resources.

4.3 | Implications for Clinical Practice and Future Research

Integrating CAPP into clinical practice for diabetic foot ulcer treatment has broad implications. CAPP's anti-inflammatory and wound-healing properties position it as a promising adjunctive therapy, especially for diabetic foot ulcers resistant to conventional treatments. Future studies should evaluate the durability of CAPP-induced healing and monitor patients over longer follow-up periods. Additionally, researchers could also consider stratifying outcomes by ulcer type and stage to determine whether CAPP is particularly effective for specific subsets of ulcers. Additionally, further investigation into CAPP's antimicrobial effects is needed, as infection and sepsis are common, serious complications of diabetic foot wounds. CAPP may offer a new approach to reducing these risks.

As research advances, developing standardised protocols and guidelines will be essential to ensure the safest, most effective CAPP delivery methods. Future studies should focus on refining optimal CAPP parameters (treatment duration, frequency and intensity) to maximise therapeutic efficacy while minimising side effects. Collaboration between clinicians, biomedical engineers and plasma physicists will be crucial for advancing this research and improving diabetic foot ulcer management.

5 | Conclusion

This systematic review on CAPP therapy provides preliminary insights into its potential as a valuable adjunct to standard care for diabetic foot wounds. Evidence from this review indicates that CAPP may accelerate wound healing, reduce wound size, promote tissue regeneration and lower infection risks, with no significant safety concerns reported thus far. These findings are particularly encouraging given the significant challenges in managing diabetic foot wounds.

However, the limited number of high-quality RCTs, inconsistent protocols and short follow-up durations in the current evidence base underscore the preliminary nature of these findings. Further research is essential to validate these promising results, establish optimal CAPP treatment parameters and clarify the therapy's mechanisms of action. Long-term outcome evaluations and rigorous cost-effectiveness assessments are also necessary to fully determine CAPP therapy's clinical and economic viability.

While this study highlights the potential role of CAPP as a complementary intervention for diabetic foot wounds, larger, well-designed trials with standardised protocols are needed to confirm its benefits. By addressing delayed healing and infection risks commonly faced by diabetic patients, CAPP therapy may ultimately improve patient outcomes and quality of life. Clinicians and researchers should continue to explore and refine CAPP applications in diabetic wound care to maximise its potential as a valuable tool in managing this challenging clinical condition.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this article.

References

1. M. A. B. Khan, M. J. Hashim, J. K. King, R. D. Govender, H. Mustafa, and J. Al Kaabi, "Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends," *Journal of Epidemiology & Community Health* 10, no. 1 (2020): 107–111, https://doi.org/10.2991/jegh.k.191028.001.

2. W. Jeffcoate, E. J. Boyko, F. Game, P. Cowled, E. Senneville, and R. Fitridge, "Causes, Prevention, and Management of Diabetes-Related Foot Ulcers," *Lancet Diabetes and Endocrinology* 12, no. 7 (2024): 472–482, https://doi.org/10.1016/S2213-8587(24)00110-4.

3. D. G. Armstrong, T. W. Tan, A. J. M. Boulton, and S. A. Bus, "Diabetic Foot Ulcers: A Review," *JAMA* 330, no. 1 (2023): 62–75, https://doi.org/10.1001/jama.2023.10578.

4. R. J. Hinchliffe, R. O. Forsythe, J. Apelqvist, et al., "Guidelines on Diagnosis, Prognosis, and Management of Peripheral Artery Disease in Patients With Foot Ulcers and Diabetes (IWGDF 2019 Update)," *Diabetes/Metabolism Research and Reviews* 36, no. Suppl 1 (2020): e3276, https://doi.org/10.1002/dmrr.3276.

5. F. M. Davis, A. Kimball, A. Boniakowski, and K. Gallagher, "Dysfunctional Wound Healing in Diabetic Foot Ulcers: New Crossroads," *Current Diabetes Reports* 18, no. 1 (2018): 2 2018 Jan 23., https://doi.org/10.1007/s11892-018-0970-z.

6. D. G. Armstrong, A. J. M. Boulton, and S. A. Bus, "Diabetic Foot Ulcers and Their Recurrence," *New England Journal of Medicine* 376, no. 24 (2017): 2367–2375, https://doi.org/10.1056/NEJMra1615439.

7. L. Giurato, M. Meloni, V. Izzo, and L. Uccioli, "Osteomyelitis in Diabetic Foot: A Comprehensive Overview," *World Journal of Diabetes* 8, no. 4 (2017): 135–142, https://doi.org/10.4239/wjd.v8.i4.135.

8. G. H. Skrepnek, J. L. Mills, Sr., L. A. Lavery, and D. G. Armstrong, "Health Care Service and Outcomes Among an Estimated 6.7 Million Ambulatory Care Diabetic Foot Cases in the U.S," *Diabetes Care* 40, no. 7 (2017): 936–942, https://doi.org/10.2337/dc16-2189.

9. F. D. Alosaimi, R. Labani, N. Almasoud, N. Alhelali, L. Althawadi, and D. M. AlJahani, "Associations of Foot Ulceration With Quality of Life and Psychosocial Determinants Among Patients With Diabetes; a Case-Control Study," *Journal of Foot and Ankle Research* 12 (2019): 57 2019 Dec 10, https://doi.org/10.1186/s13047-019-0367-5.

10. N. C. Schaper, J. J. van Netten, J. Apelqvist, et al., "Practical Guidelines on the Prevention and Management of Diabetes-Related Foot Disease (IWGDF 2023 Update)," *Diabetes/Metabolism Research and Reviews* 40, no. 3 (2024): e3657, https://doi.org/10.1002/dmrr.3657.

11. M. R. Amini, M. Sheikh Hosseini, S. Fatollah, et al., "Beneficial Effects of Cold Atmospheric Plasma on Inflammatory Phase of Diabetic Foot Ulcers; a Randomized Clinical Trial," *Journal of Diabetes and Metabolic Disorders* 19, no. 2 (2020): 895–905, https://doi.org/10.1007/s40200-020-00577-2.

12. J. Gao, L. Wang, C. Xia, et al., "Cold Atmospheric Plasma Promotes Different Types of Superficial Skin Erosion Wounds Healing," *International Wound Journal* 16, no. 5 (2019): 1103–1111, https://doi.org/10.1111/iwj.13161.

13. B. Haertel, T. von Woedtke, K. D. Weltmann, and U. Lindequist, "Non-Thermal Atmospheric-Pressure Plasma Possible Application in Wound Healing," *Biomolecules & Therapeutics* 22, no. 6 (2014): 477–490, https://doi.org/10.4062/biomolther.2014.105.

14. G. Bauer, "Targeting Protective Catalase of Tumor Cells With Cold Atmospheric Plasma- Activated Medium (PAM)," *Anti-Cancer Agents in Medicinal Chemistry* 18, no. 6 (2018): 784–804, https://doi.org/10.2174/1871520617666170801103708.

15. J. Xia, W. Zeng, Y. Xia, et al., "Cold Atmospheric Plasma Induces Apoptosis of Melanoma Cells via Sestrin2-Mediated Nitric Oxide Synthase Signaling," *Journal of Biophotonics* 12, no. 1 (2019): e201800046, https://doi.org/10.1002/jbio.201800046.

16. C. Schneider, S. Arndt, J. L. Zimmermann, Y. Li, S. Karrer, and A. K. Bosserhoff, "Cold Atmospheric Plasma Treatment Inhibits Growth in Colorectal Cancer Cells," *Biological Chemistry* 400, no. 1 (2018): 111–122, https://doi.org/10.1515/hsz-2018-0193.

17. M. J. Page, J. E. McKenzie, P. M. Bossuyt, et al., "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews," *International Journal of Surgery* 88 (2021): 105906, https://doi.org/10.1016/j.ijsu.2021.105906.

18. S. Samsavar, H. Mahmoudi, R. Shakouri, et al., "The Evaluation of Efficacy of Atmospheric Pressure Plasma in Diabetic Ulcers Healing: A Randomized Clinical Trial," *Dermatologic Therapy* 34, no. 6 (2021): e15169, https://doi.org/10.1111/dth.15169.

19. S. Mirpour, S. Fathollah, P. Mansouri, et al., "Cold Atmospheric Plasma as an Effective Method to Treat Diabetic Foot Ulcers: A Randomized Clinical Trial," *Scientific Reports* 10, no. 1 (2020): 10440 2020 Jun 26, https://doi.org/10.1038/s41598-020-67232-x.

20. B. Stratmann, T. C. Costea, C. Nolte, et al., "Effect of Cold Atmospheric Plasma Therapy vs Standard Therapy Placebo on Wound Healing in Patients With Diabetic Foot Ulcers: A Randomized Clinical Trial," *JAMA Network Open* 3, no. 7 (2020): e2010411, https://doi.org/10.1001/jamanetworkopen.2020.10411.

21. J. P. Higgins and S. Green, *Cochrane Handbook for Systematic Reviews of Interventions 5.1.0* (Cochrane Collaboration, 2011).

22. M. Laroussi and F. Leipold, "Evaluation of the Roles of Reactive Species, Heat, and UV Radiation in the Inactivation of Bacterial Cells by Air Plasmas at Atmospheric Pressure," *International Journal of Mass Spectrometry* 233, no. 1–3 (2004): 81–86, https://doi.org/10.1016/j.ijms.2003.11.016.

23. E. J. Peters, R. Lagrand, P. Smits, et al., "Cold Atmospheric Pressure Plasma as a Novel Treatment Modality in Diabetic Foot Ulcers: A Pilot Study," *Diabetes* 67 (2018): 44-LB, https://doi.org/10.2337/db18-44-LB.

Appendix A

Full Search Strategies

Embase

Date Searched: 6/27/2022

Applied Database Supplied Limits: none

Number of Results: 26

Updated: 6/20/2024.

Date limited: 2022–2024

Results: 8

Full Search Strategy:

('diabetic foot'/exp OR 'diabetic foot infection'/exp OR (diabetic NEAR/2 (foot OR feet)):ti,ab,kw) AND ('atmospheric pressure plasma'/exp OR 'atmospheric pressure plasma jet'/exp OR 'cold atmospheric plasma'/exp OR 'cold atmospheric plasma therapy'/exp OR 'cold atmospheric plasma treatment'/exp OR 'plasma gas'/exp OR ((argon OR 'ionized helium' OR helium OR plasma) NEAR/2 (gas OR gases)):ti,ab,kw OR ('atmospheric pressure plasma' OR 'cold atmospheric plasma' OR 'cold plasma jet*' OR 'non thermal plasma' OR 'thermal plasma' OR 'plasma irradiation'):ti,ab,kw OR (CAP NEAR/2 (exposure OR therap* OR treatment*)):ti,ab,kw)

Ovid Medline

Date Searched: 6/27/2022

Applied Database Supplied Limits: none

Number of Results: 12

Updated: 6/20/2024

Date limited: 2022–2024

Results: 5

Full Search Strategy:

(exp Diabetic Foot/OR (diabetic ADJ2 (foot OR feet)).ti,ab,kf.) AND (exp Plasma Gases/OR ((argon OR ionized helium OR helium OR plasma) ADJ2 (gas OR gases)).ti,ab,kf. OR (atmospheric pressure plasma OR cold atmospheric plasma OR cold plasma jet* OR non thermal plasma OR thermal plasma OR plasma irradiation).ti,ab,kf. OR (CAP ADJ2 (exposure OR therap* OR treatment*)).ti,ab,kf.)

Scopus

Date Searched: 6/27/2022

Applied Database Supplied Limits: none

Number of Results: 22

Updated: 6/20/2024

Date limited: 2022–2024

Results: 12

Full Search Strategy:

(TITLE-ABS-KEY(diabetic W/2 (foot OR feet))) AND ((TITLE-ABS-KEY((argon OR "ionized helium" OR helium OR plasma) W/2 (gas OR gases))) OR (TITLE-ABS-KEY("atmospheric pressure plasma" OR "cold atmospheric plasma" OR "cold plasma jet*" OR "non thermal plasma" OR "thermal plasma" OR "plasma irradiation")) OR (TITLE-ABS-KEY(CAP W/2 (exposure OR therap* OR treatment*))))

The Cochrane Library

Date Searched: 6/27/2022

Applied Database Supplied Limits: none

Number of Results

CENTRAL: 16

CDSR: 0.

Updated: 6/20/2024.

Date limited: 2022–2024

Results

CENTRAL: 2

CDSR: 0

Full Search Strategy:

([mh “diabetic foot”] OR [mh “diabetic foot infection”] OR (diabetic NEAR/2 (foot OR feet)):ti,ab,kw) AND ([mh “atmospheric pressure plasma”] OR [mh “atmospheric pressure plasma jet”] OR [mh “cold atmospheric plasma”] OR [mh “cold atmospheric plasma therapy”] OR [mh “cold atmospheric plasma treatment”] OR [mh “plasma gas”] OR ((argon OR “ionized helium” OR helium OR plasma) NEAR/2 (gas OR gases)):ti,ab,kw OR (“atmospheric pressure plasma” OR “cold atmospheric plasma” OR “cold plasma jet*” OR “non thermal plasma” OR “thermal plasma” OR “plasma irradiation”):ti,ab,kw OR (CAP NEAR/2 (exposure OR therap* OR treatment*)):ti,ab,kw)

ClinicalTrials.gov

Date Searched: 6/27/2022

Number of Results: 2

Updated: 6/20/2024

Date limited: 2022–2024

Results: 4.

Full Search Strategy:

(“diabetic foot”) AND (“atmospheric pressure plasma” OR “cold atmospheric plasma” OR “cold plasma jet*” OR “non thermal plasma” OR “thermal plasma” OR “plasma irradiation”)

Risk of Bias in the included Studies.

Samsavar 2021.

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Unclear risk	‘Patients were randomised to receive standard wound care (control group) or plasma treatment in addition to standard care twice a week for 6 weeks (treatment group)’. The study authors do not comment on the technique that was used to randomise the patients, and for this reason the risk of bias in this category is unclear.
Allocation concealment (selection bias)	Unclear risk	The study authors did not comment on concealment of groups following randomization.
Blinding of participants and personnel (performance bias)	Unclear risk	The study authors did not comment on blinding of the participants or physicians.
Blinding of outcome assessment (detection bias)	Low risk	The investigators analysing the wound dimensions in this study were blinded.
Incomplete outcome data (attrition bias)	Low risk	No evidence of incomplete outcome data.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No evidence of other bias.

Amini 2020

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low risk	‘Patients divided into two groups based on block randomization table, one group receive standard care (SC) of diabetic foot and the other one receive SC plus CAP’.
Allocation concealment (selection bias)	Low risk	‘In the randomization process and treatment assignment, a trained physician and nurse, who were blinded to this process, collected the data’.
Blinding of participants and personnel (performance bias)	Low risk	‘Patients were told to lie down and not to see the wound position when the plasma was irradiated or not irradiated’.
Blinding of outcome assessment (detection bias)	Low risk	‘The data also was analysed by a blinded investigator to the study groups’.
Incomplete outcome data (attrition bias)	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No evidence of other bias.

Mirpour 2020

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low risk	'Patients were randomly, double-blind, assigned to an SC group or SC + CAP using block randomization with mixing block sizes of 4'.
Allocation concealment (selection bias)	Low risk	'The size of blocks was not disclosed for minimising the chance of cracking the code'. 'An investigator with no clinical involvement in the trial prepared a computer random number list for block randomization. A trained physician and nurse who were blinded to the randomization method and treatment assignment collected the data'.
Blinding of participants and personnel (performance bias)	Unclear risk	It is understandable that when receiving cold atmospheric plasma therapy, it is not possible to blind the patient. However, this study makes no mention on the efforts made to conceal the treatment from the patient/personnel.
Blinding of outcome assessment (detection bias)	Low risk	'The data also were analysed by a blinded investigator to the study groups'.
Incomplete outcome data (attrition bias)	Low risk	No evidence of incomplete outcome data.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No evidence of other bias.

Stratmann 2020

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low risk	'Wounds of the participants were equally randomised to receive either CAP (kINPen Med; neoplas tools GmbH) or placebo intervention by stratified randomization using Research Randomizer software, version 14.0 (Social Psychology Network)'.
Allocation concealment (selection bias)	Unclear risk	The study authors did not comment on concealment of groups following randomization.
Blinding of participants and personnel (performance bias)	Low risk	'Patients receiving placebo were treated in a patient-blinded format with the device with the electric field switched off on the device. To maintain procedural blindness for the patient, the sound of the device was added to placebo treatment'.
Blinding of outcome assessment (detection bias)	Low risk	'At each visit, wound size was determined by the physician, and photographs with rulers were taken for blinded evaluation by a third person'. 'The microbial experts were Blinded'.
Incomplete outcome data (attrition bias)	Low risk	'There were 2 cases in which patients dropped out, were lost to follow up, or withdrew'.
Selective reporting (reporting bias)	Unclear risk	Not reported.
Other bias	Low risk	No evidence of other bias.