Systematic Review on Efficacy of Collagen Dressing in Diabetic Foot Ulcer

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Abstract

Diabetic Foot Ulcer (DFU) is a severe complication of Diabetes Mellitus, leading to significant morbidity and mortality. Managing DFUs is clinically challenging, involving antibiotics, debridement, wound dressings, and surgical interventions. A systematic review analyzed data from 14 studies, revealing that 32% of DFU patients were aged 60–70 years, with a male predominance (72.4%). Approximately 50.7% had diabetes for 5–10 years, and 35% had elevated HbA1c levels (8.5–9.5%). Wound sizes ranged from 4–6 cm^2, with 58.7% having ulcer durations of 21–24 months. Infection was present in 18.8% of cases.Treatment approaches focused on collagen-based dressings, used in 67.2% of patients, while 32.7% received both collagen and antibiotics. Specific dressings included Promogran (26.9%), Integra Dermal Regeneration Template (23.9%), and antibiotic-impregnated collagen (11.9%). Collagen was found to significantly enhance wound healing. About 47% of patients experienced a 20–30% reduction in wound size, and 58% showed wound healing within 4–8 weeks, outperforming standard dressings.Collagen promotes healing by accelerating wound contraction and supporting tissue regeneration. All 14 studies supported the efficacy of collagen in reducing wound size and promoting faster healing in DFUs. However, one study noted that a gentamicin-collagen sponge did not significantly affect clinical cure or pathogen eradication.Overall, collagen dressings are considered safe and effective for DFU management, with consistent support across the literature for their role in improving healing outcomes.

Keywords: *Diabetes mellitus, Foot ulcer, Antibiotics, Collagen based dressing.*

INTRODUCTION

Diabetes Mellitus (DM), commonly referred to as "sugar," is a long-term noncommunicable disease (NCD) that has become a significant global health concern. It primarily stems from issues in insulin production or function, resulting in elevated blood glucose levels (hyperglycemia). This group of metabolic disorders is marked by persistent hyperglycemia due to defects in either insulin secretion, insulin action, or both. Over time, uncontrolled diabetes can lead to severe complications affecting various organs, including

the eyes, kidneys, nerves, heart, and blood vessels. Assessing the prevalence of type 2 DM is important for national health planners; therefore, this study is aimed at determining the prevalence of type 2 diabetes mellitus and its associated risk factors among elderly patients aged 45-80 years.(1) Type 2 diabetes mellitus, in particular, arises from a combination of insulin resistance and the pancreas's inability to secrete sufficient insulin in response.(2) Multiple mechanisms contribute to the onset of diabetes, ranging from autoimmune destruction of pancreatic β-cells, leading to insulin deficiency, to cellular resistance to insulin. The core issue in diabetic metabolism involves the inadequate action of insulin on tissues, which disrupts the normal processing of carbohydrates, fats, and proteins. Both insufficient insulin secretion and reduced tissue responsiveness to insulin can occur simultaneously, making it difficult to determine which factor primarily causes hyperglycemia. Common signs of significant hyperglycemia include frequent urination (polyuria), excessive thirst (polydipsia), unintended weight loss, increased hunger (polyphagia), and blurred vision. Chronic high blood sugar can also impair growth and increase vulnerability to infections. In severe, uncontrolled cases, diabetes may lead to life-threatening conditions such as diabetic ketoacidosis or a hyperosmolar hyperglycemic state. Diabetes is largely categorized into two main types. Type 1 diabetes results from a complete lack of insulin production, often triggered by autoimmune processes affecting the pancreatic islets. People at risk can be identified through genetic markers and autoimmune antibodies. In contrast, the more prevalent type 2 diabetes is caused by a combination of insulin resistance and insufficient compensatory insulin secretion (5) Diabetic foot ulcers are a frequent and serious complication among individuals with diabetes. These wounds are often chronic, difficult to heal, and can significantly affect a person's quality of life by limiting mobility and contributing to emotional distress. In severe cases, DFUs can result in limb amputations, leading to permanent disability and increased dependency. (5,7)

ULCER GRADING

Grade 0	No ulcer but high risk foot
Grade 1	Superficial ulcer,
Grade 2	Deep ulcer, no bony involvement or abscess ,Ulcer extends to the ligament, tendon, joint capsule
Grade 3	Abscess with bony involvement (as shown by X-ray) ,osteomyelitis or joint sepsis
Grade 4	Localized gangrene eg. toe ,heel etc
Grade 5	Extensive gangrene involving the whole foot

Table 1 Wagner's Classification

Globally, DFUs are a major cause of morbidity and mortality among diabetic patients. A large retrospective cohort study involving 154,664 patients and 312,744 wounds found that DFUs accounted for 19% of the case making them one of the most prevalent chronic

wounds alongside venous leg and pressure ulcers. The treatment of diabetic foot ulcers is not only medically challenging but also economically burdensome, highlighting the need for improved therapeutic strategies.(4,6) Worldwide, over 387 million people live with diabetes, including approximately 29 million in the United States. Individuals with diabetes face up to a 25% lifetime risk of developing a foot ulcer, and these wounds often heal slowly, even with adequate care. In India, which ranks highest globally in diabetes prevalence with around 42 million cases, roughly 15% of patients experience foot ulcers during their lifetime. Contributing factors include barefoot walking, lack of awareness, limited access to proper diabetic care, and socioeconomic barriers. Amputations due to diabetic foot complications profoundly affect individuals, not only by altering their physical appearance but also by reducing productivity, increasing dependency, and adding significant costs to healthcare especially when hospitalization is required.(3)

DRESSING	ADVANTAGES	DISADVANTAGES
Low adherence	Simple Hypoallergenic Inexpensive	Minimal absorbency
Hydrocolloids	Absorbent Can be left for several days Aid autolysis	Concerns about use for infected wounds May cause maceration Unpleasant odour
Hydrogels	Absorbent Aid autolysis Donate liquids	Concerns about use for infected wounds May cause maceration
Foams	Thermal insulation Good absorbency Confirm to contours	Can adhere to wound Occasional dermatitis with adhesive
Alginates	Highly absorbent Bacteriostatic	May need wetting before removal
Iodine preparations	Antiseptic	Iodine allergy

Table 2 Types of Collagen Dressings

Ulcer debridement involves removing dead tissue, bacteria, and thickened skin (hyperkeratosis) surrounding the wound to promote healing. One common method, sharp debridement with a scalpel, helps clean the wound, trim the edges, and reveal healthy granulation tissue to support epithelial regrowth. During this process, tissue samples can also be collected for culture. Selective sharp debridement followed by the application of saline-moistened gauze is a widely accepted approach for treating diabetic foot ulcers. Minor or surface-level ulcers can often be debrided in outpatient settings or at the patient's bedside, with local anesthesia if needed. In cases where peripheral neuropathy is severe, local anesthesia may not be necessary. However, more advanced ulcers that require deeper tissue removal usually necessitate surgical debridement in an operating room to ensure proper sample collection for microbiological testing. An alternative method is chemical

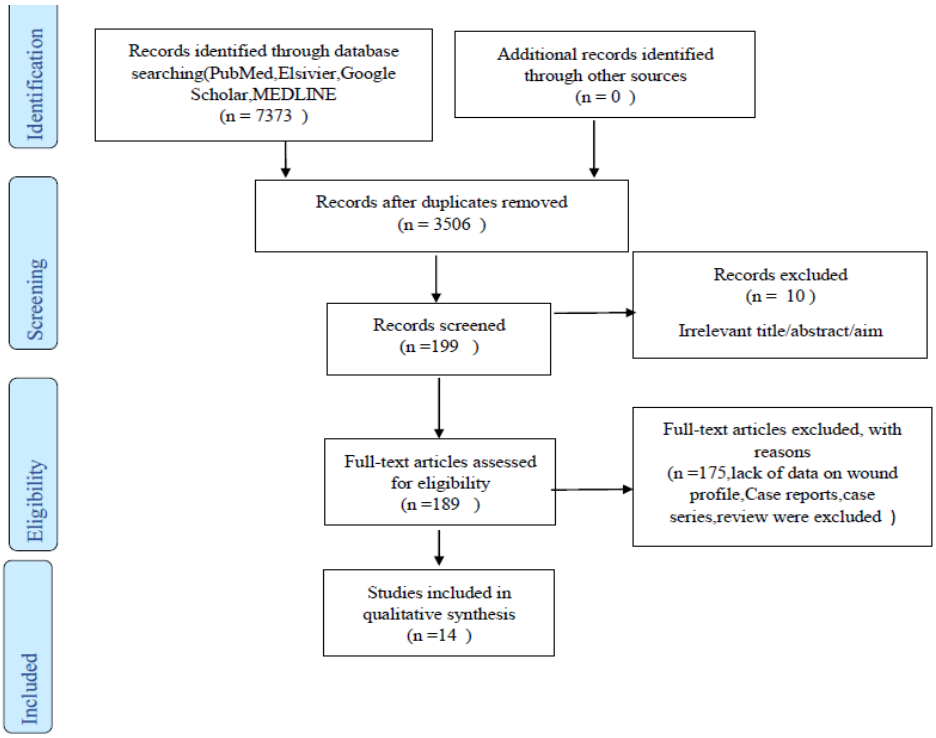
debridement, such as using clostridial collagenase ointment. Research by Tallis et al. demonstrated that this enzymatic treatment significantly reduced wound size compared to sharp debridement followed by saline gauze. Furthermore, cost analysis suggests that clostridial collagenase ointment is an economical choice across various healthcare environments. Additional debridement techniques include hydrocolloid and hydrogel dressings, which support natural tissue breakdown (autolysis) of necrotic areas, though they are unsuitable for infected wounds.

METHODOLOGY

This review focuses on evaluating the efficacy of collagen dressings in the treatment of diabetic foot ulcers. The eligibility criteria encompassed randomized clinical trials, observational studies, and comparative studies, specifically those conducted on human subjects. Studies were selected if they assessed the impact of collagen dressings on diabetic foot ulcers. A total of 36 articles were initially collected, and their titles, abstracts, keywords, and conclusions were reviewed to determine their relevance. Inclusion criteria required that the articles be written in English, published between 1990 and 2021, and involve clinical trials conducted on patients aged 20 years and older with diabetes. Studies were included if participants were either on oral hypoglycemic agents or insulin therapy and had a history of diabetic foot ulcers lasting more than ten years. Additional inclusion factors considered were studies focused on the effectiveness of collagen particles and various dressing methods for diabetic foot ulcers.Publications were excluded if they did not relate to diabetes or diabetic foot ulcers, focused solely on cost-effectiveness, lacked adequate information about wound characteristics, addressed the efficacy of collagen in non-diabetic chronic wounds, or were categorized as case reports, case series, review articles, or studies conducted on animals. A comprehensive literature search was conducted using multiple databases, including PubMed, Elsevier, MEDLINE, and Google Scholar. The search strategy incorporated keywords and MeSH terms related to diabetic foot ulcers, collagen dressings, and wound healing efficacy. References from eligible articles were also examined to identify additional relevant studies. Data extraction was performed independently and organized in tabular format. Each included study was assessed for its contribution to understanding the efficacy of collagen dressings in managing diabetic foot ulcers. Study characteristics were systematically presented in tables for clarity. From an initial pool of 7,373 articles, 3,506 remained after the removal of duplicates. Based on title and abstract screening, 199 citations were selected for further review, of which 189 were considered potentially relevant. Following a detailed evaluation, 175 studies were excluded due to insufficient data on wound characteristics or because they were case reports or case series. Ultimately, 14 studies met the criteria and were included in this review.

PRISMA 2009 Flow Diagram

Figure 4 PRISMA flow diagram for the literature serach and study selection-Collagen based dressing in Diabteic foot ulcer.



RESULTS

From the total of 14 literatures,all the articles are contributing to the DFU and are related to various treatment with Collagen dressings for the foot ulcer which are carried out in a total population of 1325 patients within a time period of 1990-2021.

Characteristics of studies included in review(n=14)	Study	Design	Year	Patients(n=1325)
1	Donaghue V M *et. al*	Randomized Clinical Trial	1998	75
2	Blume P *et. al*	Randomized Clinical Trial	2010	124
3	S Zwalitha *et. al*.	Comparative Study	2019	60
4	Uckay I *et. al*.	Randomized Clinical Trial	2018	88
5	Chandler L A *et. al*.	Comparative Study	2019	41

6	Veves A *et. al*.	Randomized Clinical Trial	2002	276
7	S S Shimikore *et. al*.	Randomized Clinical Trial	2018	60
8	Driver V R *et. al*.	Randomized Clinical Trial	2015	307
9	Park Y J *et. al*.	Randomized Clinical Trial	2016	30
10	Campitiello F.*et. al*	Randomized Clinical Trial	2017	47
11	Djavid G E *et. al*.	Randomized Clinical Trial	2020	61
12	Edmonds M *et. al*.	Randomized Clinical Trial	2009	72
13	Lobmann R *et. al*.	Comparative Study	2005	33
14	Kakagia D D *et.al*	Randomized Clinical Trial	2007	51

Table 3 Characteristics of studies included in review(n=14)

Among 14 literatures collected,it shows that 11(89.8%) were randomized clinical trial and 3(10.1%) comparative study. Out of the 14 Clinical trials,32% of patients fall under the age group of 60-70yrs,followed by 31.2% of patients under the category of 50-60 yrs,19% of patients under the range 40-50yrs.11.8% of patients were found to be between 70-80yrs and only 5.8% of patients were categorized under 20-30yrs of age. The subjects included in the trials were found to be Male, predominantly, that is,72.4% of patients who participated were males, followed by females of 27.5%.

DIABETIC SURVEY

The diabetic profile like HbA1c values, duration of diabetes are observed in patients who received collagen dressing. In this Review study, it was found that, about 35% of patients have HbA1c values ranging from 8.5-9.0% and that 34.8% of subjects have 9.5-10.0%,moreover 17.4% of patients were observed with the HbA1c values of 8.0-8.5% and 6.9% patients had HbA1c of 6.5-7.0%,about 5.7% of patients had HbA1c value ranging from 10.5-11.0%.About 50.7% of patients included in the clinical trials were found to be diabetic for 5-10yrs, 32.6% of patients were diabetic for 10-15yrs and, about 16.5% were known to be diabetic for 25-30yrs. About 40.5% of patients were suffering from diabetic foot ulcer for 21-24months followed by 34.4% of patients with history of foot ulcer over 6-9yrs and 11.9% patients have foot ulcers for about 15-18yrs and incidence of DFU for the past 9-12 yrs is about 7.2%and 5.8% patients have DFU for the past 3-6yrs. Majority of patients with DFU,58.7% had a wound of size ranging from 4-6cm² followed by 17.4% with wound size 0-2cm²,9.5% with wound size of 2-4cm² and 7.6% patients have wound

size of 12-14cm²,moreover, 4.1% patients had wound size 10-12cm²,2.4% had wound size ranging from 8-10cm².Incidence of infection in DFU patients is observed at 18.8% whereas 81.1% do not develop any associated infection. The type of treatment received by the patients were assessed and found that 67.2% of patients received Collagen based dressing,32.7% of patients received both Collagen and Antibiotics(topical,IV antibiotics) and none of the patients received Antibiotics alone.A vast variety of Collagen dressings were used in all these clinical studies.They were assessed and it was observed that 26.9% of patients received Promogran predominantly (n=173), 23.9% of patients were given with Integra Dermal Regeneration Template(IDRT)dressing(n=154) and 11.3% of patients were provided with Antibiotic impregnated Collagen dressing(n=73). Promogran-A wound dressing consisting of Collagen and Oxidized Regenerated Cellulose Integra Dermal Regeneration Template (IDRT)-Advanced, acellular, bilayer matrix specifically engineered for dermal regeneration, based on Integra's Dermal Regeneration Matrix(IRDM)Technology. Antibiotic impregnated Collagen dressing-Collagen dressing impregnated with Mupirocin 2%w/v /Metronidazole 1%w/v /Gentamicin-collagen sponge.

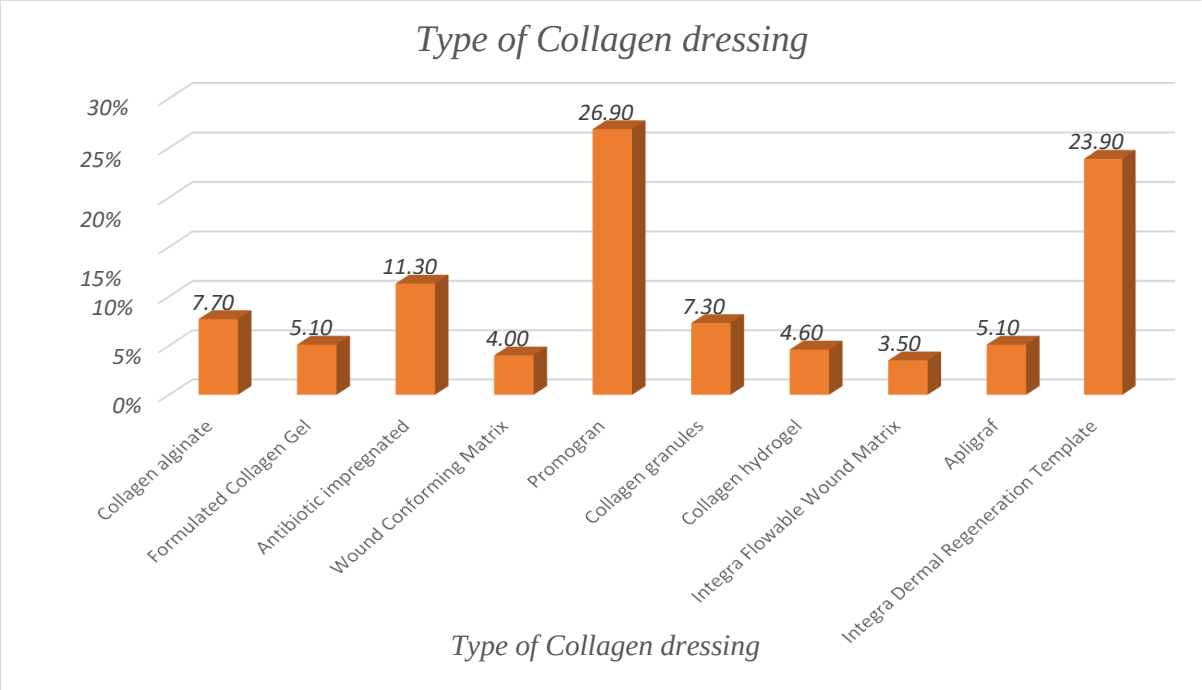


Figure 1: Type of Collagen dressing

OUTCOME MEASURES

A significant reduction in size of wound is found in the participants who received Collagen dressing. It was found that there is a significant reduction in wound size in DFU patients who received Collagen based dressings.About,47% of patients showed 20-30% reduction in wound size and about 17.2% of patients had wound reduction of about 80-90%,8.5% patients had wound reduction of about 30-40% ,moreover,7.7% of patients showed 50-

60% wound size reduction and 7.7% patients showed 70-80%,in addition to this,60-70% wound reduction was found with 6.7% of patients and only 4.6% of patients had wound reduction of 10-20%.

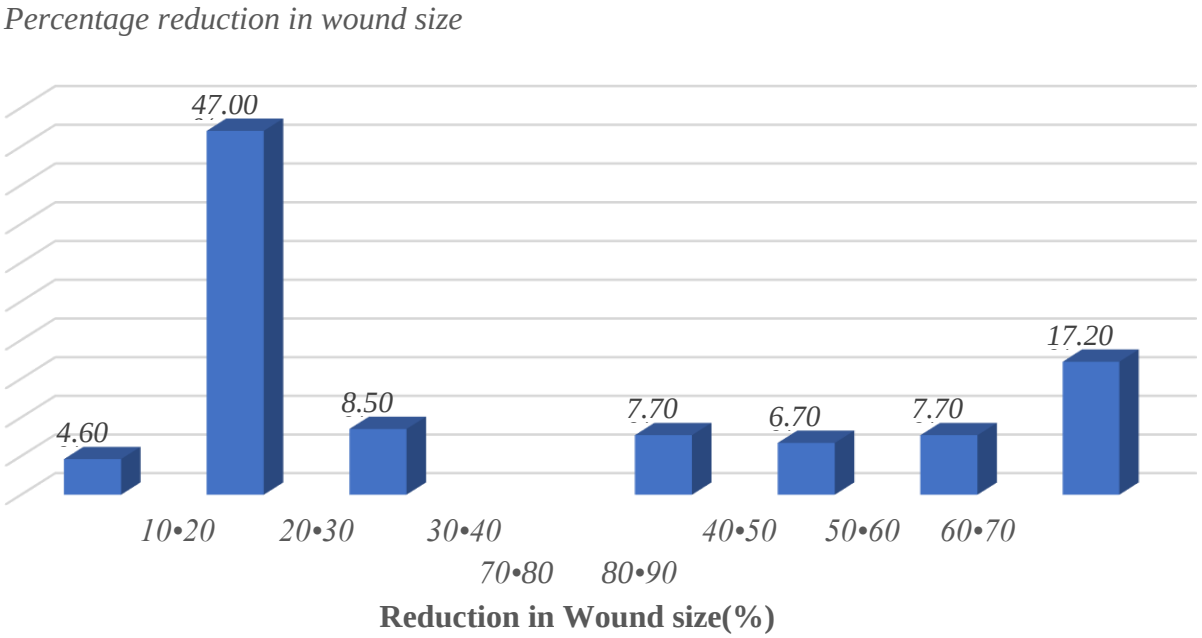


Figure 2: Percentage reduction in wound size

An insufficiency was observed in data regarding the reduction in infection in patients who received Collagen based dressing and about 13.3% of patients exhibited a reduction in infection whereas,no data on infection reduction was obtained for about 86.6% patients. The duration of wound healing in 58% patients who received Collagen dressing is found to be about 4-8weeks,31.7% of patients had complete wound healing by 1-4weeks followed by 10.4% of patient with complete wound healing by 8-12 weeks. 18 literature compared the efficacy of Normal Saline dressing with that of other dressing in wound healing in DFU and it was observed that 81.8% received Normal saline dressing for DFU. 4 literature compared the efficacy of Povidone iodine dressing with that of other dressings in Diabetic foot and that 18.1% received Povidone Iodine dressing over the non healing wound. No literature compared the efficacy of Magnesium sulphate with that of other dressings in DFU.

DISCUSSION

Diabetes attribute to the non healing chronic ulcers and the Diabetic Foot Ulcers are the major cause of hospitalization worldwide which on progression requires Amputation. In this Systematic review,it was observed that about 32% of patients fall under the age group of 60-70 yrs, predominantly Males(72.4%).It was found that 50.7% of patients have diabetes for over 5-10yrs[7].The diabetic profile like HbA1C is known to be 8.5-9.5% among 35% of patients[6][13]. A variable size of wounds ranging from 4-6cm² [8][11]with

the duration of 21-24 months[12] was noted in 58.7% of patients.The incidence of infection was found in 18.8% of patients whereas 81.1% do not develop any infection.

About 67.2% of patients received only the Collagen based dressings, 32.7% of patients received both Collagen and Antibiotics(topical,IV antibiotics)and none of the patients received Antibiotics alone[4] Various types of collagen dressing were given to the patient.About,26.9% of patients received Promogran dressing over their wounds.23.9%of patients were given with Integra Dermal Regeneration Template.About,11.9% received Antibiotic impregnated Collagen.[18][19] Treatment with Collagen showed better efficacy in wound healing process.47% of patients showed remarkable reduction in wound size about 20-30%[8][11]. The data on reduction in infection was found to be inadequate, with the data available, it was found that the reduction in infection was about 13.3%.The data on reduction in infection was not available in 86.6%.

The patients who received Collagen dressing had a faster wound healing. Wound healing was observed in 58% of patients within 4-8 weeks than compared with Normal Dressings. The median time taken for complete closure of wound was 43 days[8].The healing time was significantly shorter(29.73days)in first group compared to the control group[10].

Collagen dressing is found to be effective and safe in treatment of wound healing in Diabetic Foot Ulcers. However, all the 14 literatures support the study in terms of collagen that helps in reduction in wound size and faster wound healing. Moreover, one of the study concluded that (Gene Activated Matrix)GAM501,a proprietary product along with the Formulated Collagen Gel improves the wound healing rate[17]One of the study describing Mupirocin Metronidazole impregnated collagen granules doesn’t offer better results compared with conventional dressings in terms of completeness of healing but may decrease the duration of Oral/Systemic Antibiotic therapy to attain culture negative.[18]Another literature studied that the Gentamicin-collagen sponge in diabetic foot did not influence overall clinical cure or the eradication of wound pathogens[19].Pomogran,a combination of collagen and oxidized regenerated cellulose, was found to be equally effective in promoting complete wound healing[6].The more relevant ratio of MMP-9/TIMP-2 was deceased in the treatment group(Promogran treated)[13].A greater reduction in all dimensions of ulcers were found in Group C(combination of autologous growth factors and Promogran) than the reduction observed in each of Group A and Group B[14].

CONCLUSION

Diabetic foot ulcers represent a significant complication associated with diabetes. Collagen has been shown to play a beneficial role in wound healing by accelerating wound contraction and promoting tissue regeneration. All 14 studies reviewed consistently supported the effectiveness of collagen in treating diabetic foot ulcers. Based on these findings, it can be concluded that collagen contributes to a noticeable reduction in wound

size and the severity of associated complications, offering a more efficient treatment option within a shorter healing period.

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