Diabetic Foot Infection, Biofilm & New Management Strategy

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Abstract

The world is facing a major epidemic of diabetes mellitus (DM) & available reports suggest that all these patients are at risk of developing diabetic foot ulcer (DFU). Approximately 50 - 60% of all DFUs can be classified as neuropathic. Signs or symptoms of vascular compromise are observed in 40 to 50% of all patients with the vast majority having neuro-ischemic ulcers, and only a minority of patients has purely ischemic ulcers. Diabetic foot infections are usually polymicrobial in nature, involving both aerobes and anaerobes, which can decay any part of the body especially the distal part of the lower leg. However, one of the hidden barriers to wound healing is the presence of biofilm in chronic DFUs. Biofilms are difficult to identify & diagnose, recalcitrant to topical antibiotics & can reoccur even after sharp debridement. More than 90% of chronic wounds are complicated with biofilms. Hence, early identification and management of diabetic foot infections becomes imperative in order to prevent complications & amputation. Debridement is considered to be the gold standard treatment approach for managing DFU manifested with necrotic tissue. However, biofilm can reform even after sharp debridement and can delay healing & recovery. Also, antibiotics & few antiseptics have limited role in managing DFUs complicated with biofilm. Until recently, Cadexomer iodine, a new generation iodine formulation with microbead technology has taken a different profile in wound care. It can effectively manage biofilm along with exudate & possesses superior desloughing action. Additionally, appropriate ways of offloading, dressings & use of newer treatment strategies like negative pressure wound therapy (NPWT), hyperbaric oxygen therapy (HBOT) and / or use of growth factors can ensure faster healing & early wound closure. Although, commendable efforts in recent years have been taken in the diagnosis and treatment of DFU, it still remains a major public health concern.

Keywords

Diabetic foot ulcer (DFU); Neuropathy; Biofilm; Cadexomer Iodine; Negative Pressure Wound Therapy (NPWT); Hyperbaric Oxygen Therapy (HBOT)

Introduction

The world is facing a major epidemic of DM. According to International Diabetes Federation, there are an estimated 425 million diabetic patients worldwide with 1 in 10 living with diabetes & 1 in 2

remaining undiagnosed [1]. Available reports suggest that all these patients are at risk of developing DFU. A DFU is any full-thickness wound below the ankle in a diabetic patient, irrespective of duration [2]. DFUs are characterized by an injury to all the layers of skin,

resulting into necrosis or gangrene as a result of neuropathy or peripheral arterial disease [3,4]. DFUs are often infected which can decay any part of the body especially the distal part of the lower leg [5-7]. This review focuses on epidemiology & pathophysiology of DFU, its complication associated with infection & biofilm along with clinical assessment, management & newer treatment strategies.

Epidemiology of diabetic foot ulcers:

Incidences of DFU continue to increase worldwide [8]. The prevalence of DFU is not accurately known and the difference in prevalence rates in each country is estimated at 4-27% of DFU sufferers worldwide [9]. The lifetime risk of foot ulcers until recently was generally believed to be 15-25%; however, recent data suggest that the figure may be as high as 34% [10]. Studies have shown that 15% of patients with DM will experience complications of DFU in the future [9].

One out of four diabetic patients have a lifetime risk of developing foot ulcer disease, which often lead to amputations, the incidence of which is quite high (one out of five patients) in India [11]. Each year there are nearly one million lower extremity amputations done for diabetic patients worldwide, that's one in

every 20 seconds. According to the Vascular Society of India, about 1 lower leg amputations occur every year due to diabetes-related problems. Australia has declared a national medical emergency as 16 legs are amputated every day. Diabetes UK reports 23 legs are being amputated daily in the NHS system [12]. The prevalence of diabetic ulcer patients in the United States is 15-20% & the risk of amputation is 15-46% more compared with non-DM patients [9].

Reported literature suggests that approximately 58% of DFU patient becomes clinically infected. Patients with DM frequently require minor or major amputations of the lower limbs and in more than 50% of cases; infection is the predominant causative factor. Major amputation is associated with significant morbidity and mortality (ranging from 13 to 40% at 1 year to 39 to 80% at 5 years) in addition to immense social, psychological, and financial consequences [2].

Pathophysiology of Diabetic Foot Ulcers [2,9]

In DM, patients are characterized by high blood glucose levels which results in endothelial dysfunction, mitochondrial dysfunction, cellular nerve damage, microvasculature damage & also impaired myelin regeneration. DFUs result from interaction between two major risk factors: neuropathy and

peripheral vascular disease. Neuropathy leads to varying degrees of alterations in sensory, motor & autonomic functions (**Fig-1**). Approximately, 50 to 60% of all DFUs can be classified as neuropathic. In 40 to 50% of all patients, signs or symptoms of vascular compromise are observed with the vast majority having neuro-ischemic ulcers, and only a minority of patients has just ischemic ulcers.

- Autonomic neuropathy: firstly, non-myelinated autonomic nerve fibers are affected resulting in autsympathectomy with consequent medial arterial calcification, microvascular thermoregulatory dysfunction, and arteriovenous shunting. Autonomic neuropathy can cause dry skin, cracking, and fissuring which can create a portal for entry of bacteria.
- Sensory neuropathy: begins with poorly tolerated tactile allodynia and thermal hyperalgesia, progressively affecting the thicker myelinated fibers further leading to objective loss of sensation and proprioceptive dysfunction.
- Motor neuropathy: results from the axonal degeneration of the large motor myelinated fibers causing atrophy of anterior crural muscle or wasting of intrinsic muscle. Further, it results in foot deformity and consequent altered foot biomechanics with foot pressure redistribution. The foot becomes clinically

insensitive and possibly deformed as the disease progresses.

Diabetic foot infection:

In patient with DFU, deep tissues are exposed to bacterial colonization, once the protective layer of skin is broken [13]. Wound healing outcome majorly depends on qualitative and quantitative aspects of wound microbiology which are critical determinants. β -hemolytic streptococci and Staphylococcus aureus firstly colonize and acutely infect breaks in the skin. Further, chronic wounds become polymicrobial, including aerobic Gram-negative rods and anaerobes. Gram-negative bacilli, mainly Enterobacteriaceae & Pseudomonas aeruginosa, are found in many patients with chronic or previously treated infections [14]. Anaerobes often participate in mixed infection especially in cases of deep tissue infection with aerobes [15]. Such mixed infections can lead to microbial synergy, further increasing the severity of infection [13]. Diabetic foot infections (DFI) are polymicrobial in nature, involving both aerobes and anaerobes. A recent prospective study including 289 isolates obtained from 178 tissue samples of patients (n=261) with DFIs revealed that 44.3% of DFIs were monomicrobial and 55.7% DFIs were polymicrobial [16]. Etiological agents reported in DFIs are enlisted in **Fig-2** [15]. Though it is generally believed that acute infection that has not been previously treated with antibiotics is monomicrobial while the chronic ones treated with antibiotics previously are polymicrobial,

Fig-2: Etiological agents causing diabetic foot infections [15].

Involving aerobes as well as anaerobes [17], it has been demonstrated that anaerobes were the predominant pathogens seen in both, new and recurrent ulcers [18]. The co-existence of aerobes and anaerobes in a DFI helps protect the anaerobe from the harmful effects of oxygen, and hence, their survival [18].

Biofilm: the hidden barrier to healing:

A biofilm is a bacterial cluster which resides within a matrix offering protection from antimicrobials & host defenses (**Fig-3**). A single planktonic bacteria (free-floating) forms the biofilm following attachment within a protective matrix (extracellular polymeric substance [EPS]), which creates coherent clusters of cells [19]. A non-healing wound is an indicator of the presence of biofilm [20]. Biofilms cause a delay in healing by initiating an immune response leading to chronic inflammatory cycle and tissue damage due to high levels of proteases and reactive oxygen species [21,22]. Biofilms are prone to reformation and also difficult to treat because: (a) EPS matrix protects bacterial cells against topical antimicrobials; (b) Bacteria within biofilms are also metabolically dormant, resulting into antibiotic tolerance; (c) EPS components also neutralizes several antimicrobials that penetrate the matrix [23,24].

Biofilm detection and diagnosis:

Currently, no routine identification or detection

method can discriminate between biofilm- growing bacteria or planktonic organisms responsible for delayed healing. However, several surrogate markers can aid diagnosis: (a) Failure of response to appropriate antimicrobials (both antibiotics & antiseptics), since bacterial cells within biofilm matrix are inherently tolerant to both, unlike planktonic bacteria; (b) high exudate levels & recurrent inflammation/infection; (c) presence of gelatinous material on the wound that reforms quickly after its removal [24]. Infection due to presence of biofilm is very different from planktonic (acute) infection; thus, health care practitioners should understand that treatment protocols for acute infections are not effective for treating non-healing chronic wounds complicated with biofilm. Thus, treatment with an appropriate antimicrobial therapy becomes imperative which must be able to disrupt and penetrate the EPS matrix, kill the bacterial cells and provide sustained action that prevents the biofilm reformation [19,25,26].

Assessment & Clinical Diagnosis of Diabetic Foot Ulcer

Recognizing important risk factors and assessing DFI requires a consistent and thorough diagnostic approach. Such an evaluation involves careful assessment of foot, wound history; physical examination; and several complementary diagnostic procedures [27,28].

History:

Symptoms of peripheral neuropathy include hyperesthesia, paresthesia, hypoesthesia, disesthesia, radicular pain and anhidrosis. People with atherosclerotic disease in the lower extremity experience claudication, ischemic pain at rest & leg pain [29].

Physical examination:

According to Stillman, physical examination in DFU patients is divided into three parts, namely:

1. Examination of extremities and ulcers:
DFUs occur in certain areas such as heels, area of metatarsal head on the sole, fingertips; since, it often gets traumatized easily which is characterized by hypertrophic callus, brittle or broken nail, hammer toes and fissure.
2. Assessment of possible vascular insufficiency:
Physical examination shows decrease in peripheral pulse, cyanosis of toes, ischemic necrosis and ischemic necrosis and palor become pale. Noninvasive vascular examinations include transcutaneous oxygen measurements, ankle brachial index (ABI) & systolic pressure of the toes. ABI is easily performed using Doppler ultrasonography (**Fig-4**) [30-32].
3. Assessment of possible peripheral neuropathy:
Neurologic status can be examined using Semmes-Weinstein monofilament to check whether the patient has protective sensation. If the patient cannot feel the monofilament when

pressed on the foot with sufficient pressure until the monofilament is bent, this would indicate that the patient has neuropathy. Another diagnostic tool is a 128 Hz tuning fork, which can be used to examine the vibration sensation at the ankle and the first metatarsophalangeal joint. Generally, patients with DFU cannot feel the vibration of the garputala when kept for more than 10 seconds. [30,31,33].

Laboratory examination: [9]

- Blood tests: leukocytosis indicates an abscess or other foot infections.
- Metabolic profile: blood glucose, glycosylated hemoglobin (HbA_{1c}) measurement and serum creatinine helps to determine the adequacy of glucose regulation and renal function.
- Noninvasive vascular laboratory examination: pulse volume recording (PVR) or plethymography.

Radiological examination: [9]

- A plain examination of the diabetic foot may show demineralization and the Charcot joint and the presence of osteomyelitis (**Fig-5**).
- Computed tomographic (CT) scan and magnetic resonance Imaging (MRI): although an experienced examiner can diagnose an abscess with a physical examination, a CT scan or MRI may be used to help diagnose an abscess if the physical examination is unclear.

Alternatives to conventional angiography: [9]

Magnetic resonance angiography (MRA): MRA is an alternative that can be used in high-risk patients or patients who are allergic to contrast material. The contrast used was Gadolinium chelates, potentially causing side effects in patients with renal insufficiency: acute renal injury and pseudohypokalemia.

Nephrogenic systemic fibrosis and exposure to radiation are the main limitations of CT and MR angiography in patients with impaired renal function.

- Multi-detector computed tomographic angiography (MDCT) avoids arterial stabbing. By using IV contrast injection, MDCT scans (16

or 64 channels) can improve the resolution of angiographic images and at relatively high speeds. However, MDCT does use iodine-based contrast agents and, as with the use of all such contrast agents, there is a risk of contrast induced nephropathy (CIN).

- Carbon dioxide angiography is an alternative to patients with renal insufficiency, but it is not widely applicable and still requires iodine contrast material as an additional carbon dioxide gas to obtain a good image.

Management of Diabetic Foot Ulcers

The main goal in the management of diabetic ulcers is the closure of the wound. Treatment of DFUs in DM patient depends on the presence or absence of

ischemia & severity of the ulcer. DFU therapy includes: debridement, reducing pressure/load on the injured area (offloading), managing infection with adequate antibiotics / antiseptics with appropriate dressing which might keep the wound clean and moist that would ensure faster healing [34,35].

Debridement:

Debridement should be performed on all chronic wounds to remove dead and unhealthy necrotic tissue which are difficult to recover from injury [36,37]. It also helps in eliminating the base of abnormal injury, callus (epidermal hyperkeratosis), necrotic dermal tissue, and bacterial elements which can impede

wound healing. Evidence suggests that debridement plays an important role in the granulation tissue formation that would aid wound healing.

There are five different ways debridement is carried out: surgical, mechanical, autolytic, enzymatic and biological. Surgical debridement is a sharp debridement with the help of scissors & scalpel to remove all dead tissue and bone. Mechanical debridement can be carried out physically with the help of wet-to-dry dressing, pressure irrigation, lavage and hydrotherapy. Autolytic debridement occurs naturally in healthy, moist and perfused ulcers. Enzymatic debridement involves use of proteolytic

enzymes such as collagenase, DNase, trypsin, papain/urea from papaya, streptokinase etc. Biological debridement can be carried out using proteolytic enzyme secreted by the larvae of *Lucilia sericata* fly which can dilute the necrotic tissue [36].

Limitations: Surgical debridement include adverse events from the debridement itself, for example, bleeding and possible general complications from the anesthesia. On the other hand, relative contraindication of enzymatic debridement is its use in heavily infected wounds. Furthermore, collagenase should not be used in conjunction with silver-based products or with Dakin solution. Additionally, biological debridement have several limitations and are contraindicated in abdominal wound contiguous with the intraperitoneal cavity, pyoderma gangrenosum in patients with immunosuppression therapy, and wounds in proximity to areas afflicted by septic arthritis.

Offloading:

Ulceration usually occurs in the high pressure bearing area of the foot. Offloading through several methods or tools helps to shift the weight fulcrum away from the side of the ulcer. The main objective of offloading is to facilitate wound healing by reducing pressure on the ulcer & thereby preventing any trauma to the tissue [34,37]. Thus, offloading is becoming an important component of the DFU management. Although bed rest is an ideal way to reduce pressure, it is not a feasible option in every patient population. Alternatively, total contact casting (TCC) which is made up of specially formed casts is the most effective way of offloading, to spread the patient's burden out of the ulcer area. Thus, it is useful for controlling edema that can interfere with wound healing & also allows the patient to walk during treatment. Evidence suggests that TCC can facilitate healing in 73-100% of cases with successful reduction of pressure on the wound. Additionally, several other ways by which offloading can also be achieved with variable results includes use of wheelchairs, walkers to shoes that are specially designed etc. [38,39].

Management of diabetic foot infection:

Diabetic ulcers are often infected and polymicrobial in nature. Because of the high incidence rate of infection in diabetic ulcers, a systematic approach is required for complete assessment & management which involves appropriate use of antimicrobials like antibiotics or antiseptic either topically or systemically [40].

1. Antibiotics:

Mild and moderate infections can be treated using oral antibiotics, such as cephalexin, amoxicillin-clavulanic acid, moxifloxacin or clindamycin [29,31,40]. Patients with severe infections should be hospitalized & treated with antibiotics that includes imipenem-cilastatin, B-lactam B-lactamase (ampicillin-sulbactam and piperacillin-tazobactam) and broad-spectrum cephalosporin [29].

The lists of empirical antibiotics are summarized in **Table-1**, which refers to the Infectious Disease Society of America (IDSA) and International Working Group on the Diabetic Foot (IWGDF) guidelines [41]. Despite widespread use of broad spectrum antibiotics, emergence of antimicrobial resistance has restricted their use against several clinical isolates causing wound infection.

An emerging paradigm for biofilm-based wound care takes the form of a simple step-down approach, following initial aggressive debridement, then step-up to advanced therapies if needed to enhance healing (summarized in **Fig-6**).

2. Antiseptic:

Antiseptics are agents that hinder the growth or destroy micro-organisms on living tissue [42]. Antiseptics have broad spectrum activity when compared to antibiotics due to their multiple mechanisms of action targeting various aspects of cell biology in microbes which also reduces the likelihood of emerging resistance [42,43]. Literature supports the use of numerous antiseptics which has proven efficacy in the prevention and treatment of infection in wound care which includes iodine carriers (iodophores)

Wound assessment and biofilm identification

1. Assessment of indirect clinical signs and symptoms
2. Biopsy and biofilm lab testing, however these might not be reliable given the non-homogeneous distribution of biofilm on the surface and within the deeper layers of the wound.

Aggressive debridement

Sharp debridement is a crucial and necessary step in the wound bed preparation continuum but it is often not enough to remove all biofilm. Moreover, biofilm is known to reform rapidly following debridement.

Initiate biofilm therapies

The selection of a proven and effective anti-biofilm treatment, such as **Cadexomer iodine**, is crucial to remove residual biofilm following debridement and also ideal to address biofilm where sharp debridement is not possible.

Maintenance debridement and treatment optimization

Maintenance debridement is an important complementary step. Some dressings (such as cadexomer iodine) can also promote autolytic debridement throughout application and promote effective wound bed preparation.

Step-up to advanced therapies to kick-start healing

Once biofilm has been disrupted and removed the clinician may chose a move to standard care using a non-antimicrobial dressing or step-up to advanced therapies such as negative wound pressure therapy which can be used in conjunction with dressings that are able to prevent biofilm reformation (e.g. silver-based dressing).

Fig-6: Pathway for biofilm treatment as part of good wound bed preparation practice.

Table-1: Antibiotic recommendations for the empirical treatment of diabetic foot infections.

Severity of Infection	Additional Factors	Usual Pathogen(s)	Potential Empirical Regimens
Mild (usually treated with oral agents)	No complicating features	MSSA, <i>Streptococcus spp.</i>	1st generation cephalosporin, ampicillin/sulbactam, amoxicillin/clavulanate, clindamycin
	β -lactam allergy or intolerance	MSSA, <i>Streptococcus spp.</i>	Clindamycin, levofloxacin, moxifloxacin, doxycycline
	Recent antibiotic exposure	MSSA, <i>Streptococcus spp.</i> , <i>Gram-negative rods</i>	Levofloxacin, moxifloxacin, 2nd or 3rd generation cephalosporin
	High risk for MRSA	MRSA	Clindamycin, doxycycline, trimethoprim/sulfamethoxazole
Moderate (oral or initial parenteral) or Severe (parenteral)	No complicating features	MSSA, <i>Streptococcus spp.</i> , $\pm$ <i>Gram-negative rods</i>	2nd or 3rd generation cephalosporin $\pm$ aminoglycoside
	Recent antibiotic exposure	MSSA, <i>Streptococcus spp.</i> , $\pm$ <i>Gram-negative rods</i>	3rd generation cephalosporin $\pm$ aminoglycoside, ertapenem, piperacillin / tazobactam, cefepime
	Macerated ulcer and warm climate	Gram-negative rods, including <i>Pseudomonas</i>	Piperacillin/tazobactam, cefepime, imipenem, meropenem
	Ischemic limb/necrosis/gas forming	MSSA $\pm$ <i>Streptococcus spp.</i> $\pm$ <i>Gram-negative rods</i> $\pm$ <i>anaerobes</i>	Piperacillin/tazobactam, ertapenem, 2nd or 3rd generation cephalosporin or cefepime + clindamycin or metronidazole
	MRSA risk factors	MRSA $\pm$ <i>Streptococcus spp.</i> $\pm$ <i>Gram-negative rods</i>	Vancomycin or teicoplanin + 3rd generation cephalosporin, cefepime, piperacillin / tazobactam, ertapenem
	Risk factors for resistant Gram-negative rods	ESBL, multi-drug resistant Gram-negative	Piperacillin/tazobactam + aminoglycoside, imipenem, meropenem

with polyvinylpyrrolidone (PVP or povidone) iodine, silver, chlorhexidine, benzalkonium chloride, triclosan, octenidine, and polyhexamethylene biguanide (PHMB) [43].

However, in vitro studies have demonstrated that antiseptics can inhibit collagen synthesis & microcirculation, toxic to fibroblasts, keratinocytes, leukocytes and impair epithelial cell migration [42,44]. Clinicians today have innumerable options of antiseptics; yet, the debate was born in the shadow of the several in vitro evidences on cytotoxicity.

Use of iodine in wound care dates back to 1919 when Alexander Fleming studied the effect of antiseptics in septic wounds. The study found that wounds treated with 2% iodine compared to carbolic acid showed lower incidence of gas gangrene in hospitalized patients during World War I [45]. However, use of antiseptics declined when Fleming discovered penicillin in 1929 and during the late 1980s the routine use of antiseptics was questioned [46]. With the emergence of multi-resistant strains of organisms and a better understanding of the dynamics of wound healing, the use of topical

iodine in wound care has taken a different profile [42].

Dressing:

Dressing is a material used topically on the wound to protect the wound and help wound healing. Dressing will experience direct contact with the wound and is distinguished by plaster as a dressing barrier. There are several types of dressings: Hydrogel dressing, film, composite film is well used for cuts with a small amount of exudate, whereas for wound with high exudate levels hydrocolloid, alginate, foam and other absorptive dressings are used widely. Injuries with large necrotic tissue should be done debridement before dressing [47,48]. (Fig-7)

Newer Management Strategy

Formerly, it was believed that simply saline dressings & conventional therapeutic interventions might be sufficient to heal the wound. However, very recently newer concepts have been introduced, that have completely revolutionized the wound management strategy.

Cadexomer Iodine:

Cadexomer iodine is a new generation iodine formulation manufactured using smart microbead

Fig-7: Management of diabetic foot infections (DFIs) [2].

technology for managing infected chronic exudative wounds. It consists of three dimensional lattices of micro spherical, polysaccharide beads of cadexomer iodine with 0.9% elemental iodine loaded into it. The sterile antimicrobial dressing of cadexomer iodine is a water-soluble preparation which provides controlled release of iodine at the wound site [49,50]. Cadexomer iodine is different from povidone iodine since it is made up of micro beads of modified biodegradable starch which has a considerable affinity for wound exudate. As the starch becomes wet, it allows slow and sustained release of iodine into the wound bed and maintains a concentration gradient between the ulcer surface and the cadexomer beads. Iodide is normally inactivated in a few minutes by protein. However, this form allows slow release of this ion, thus conferring a prolonged antiseptic action. In addition, the cadexomer starch forms a gel on contact with exudate, and this gel supports autolytic debridement and desloughing of the wound bed. Conversely, in povidone iodine, iodine is loosely combined with PVP which allows only for gradual release of free iodine, suggesting that iodine is rapidly consumed by protein component and its antiseptic effect is attenuated promptly [51].

In highly exuding, infected and chronic wounds, cadexomer effectively decreases the critical infection

colonization, preparing the wound due to its unique pharmacological 4 in 1 actions which are presented in the **fig-8** [52]. Clinical evidences for managing infection & biofilm complicated diabetic foot ulcers are summarized in the **Table-2**.

Growth factors:

Currently, new generation of modern wound dressing is gaining importance; these more advanced dressings can release therapeutic agents and healing enhancers such as growth factors (GFs), stem cells, peptides and other bioactive substances. Importance of extracellular matrix for wound healing has influenced researchers to generate more advanced wound dressings including collagen and other ECM proteins, also called biological dressings, such as collagen, hyaluronic acid, chitosan, elastin and fibrin [57,58]. Such dressings could reduce inflammation and wound proteases & increase GFs in the wound environment. For patients with recalcitrant foot ulcers, advanced biological therapies including recombinant growth factors (r-GF), platelet-rich plasma, bioengineered cell-based therapies may benefit the patients with optimum healing and improving their quality of life. Among r-GFs, the only FDA-approved GF for DFUs is platelet derived growth factor (PDGF) which is most widely investigated & shows promising results [59]. Moreover, a novel

Figure 8: Unique pharmacological actions of cadexomer iodine [52]

Fig-8: Unique pharmacological actions of cadexomer iodine [52]

Table-2: Clinical evidences for managing infection & biofilm complicated diabetic foot ulcers					
Author	Study Type	Study Patients	Treatment Duration	Study Results	Study Conclusion
Schwartz JA <i>et al</i> [53]	Prospective, Longitudinal Cohort	Fifteen diabetic foot ulcer patients displaying clinical signs of infection or critical bacterial colonization were enrolled in the study	6 weeks	i) Cadexomer iodine significantly reduces DFU bioburden by 46% following 3 weeks treatment & 89% following 6 weeks.	Cadexomer iodine decreases wound bioburden and heals difficult to treat diabetic foot ulcers.
				ii) Overall patients showed 53.6% reduction in ulcer surface area and 50% decrease in ulcer depth from baseline.	
Apelqvist J [54]	Open, randomized comparative trial	Forty-one patients with diabetes were randomized to treatment with cadexomer iodine (CI) (n=22) and standard dressings (n=19; gentamicin solution, streptokinase, dry saline gauze).	12 weeks	i) Percentage patients showing complete healing was higher with CI (29%) compared to standard treatment (11%).	Cadexomer iodine ointment is a cost-effective and useful addition in the treatment of exudating cavity ulcers in diabetic patients compared with standard treatment, including topical antibiotics.
				ii) Fewer weekly dressing changes were required for CI (4.7) compared to standard treatment (9.9).	
Malone M <i>et al</i> [55]	Clinical, in vivo	17 patients with chronic diabetic foot ulcer (DFU) due to suspected biofilm involvement were enrolled.	1 week (total three applications)	i) The median value of DFU biofilm architecture reduced between pre- and post-treatment with cadexomer iodine; pretreatment median was 4 (large microcolonies 100 cells and a continuous film/matrix) and the post-treatment median was 3 (large microcolonies 100 cells).	Cadexomer iodine effectively reduces microbial load in chronic non-healing diabetic foot ulcers complicated by biofilm.
				ii) 64.7% patients showed significant reduction in mean microbial load post-treatment with Cadexomer iodine.	

Raju R et al [56]	Open-label, randomized, prospective, multi-centre, comparative	A total of 81 patients with chronic exuding wounds (like diabetic foot ulcer, pressure ulcer & venous ulcer) were enrolled and randomized to receive cadexomer iodine (n=41) & standard saline dressing (n=40)	12 weeks	<p>i) Percentage reduction in wound area from baseline to 12 weeks was found to be 94.3% with cadexomer iodine and 67.8% with standard dressing (p=0.0001).</p> <p>ii) Mean reduction in exudate following treatment with Cadexomer iodine vs. baseline was found to be 80.8% by end of 4th week & 84.6% at the end of 10th week treatment.</p>	Cadexomer iodine, when tested in Indian patients with chronic exuding wounds was found to be effective significantly as compared to standard saline dressings.
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therapy involving the use of intralesional injection of recombinant human epidermal growth factor can prevent amputations in selected complicated DFUs, non-responsive to standard care [60]. Further clinical trials are required to evaluate the clinical efficacy and safety of such therapies, although these products are the benchmarks of biological therapies [57].

Negative pressure wound therapy (NPWT):

NPWT or wound closure with a vacuum using a sponge on the wound, covered with an airtight dressing can be used for wounds with large lymphatic leaks and fistulas. Several studies have suggested that this novel system presents potential advantages, which includes removal of infectious organism and non-viable material [9]. The main mechanism of NPWT is also to eliminate edema that removes the fluid of the lymph or the lymph in interstitial, thus improving oxygen diffusion into the cell [57]. It also eliminates collagenase and matrix metalloproteinase (MMP) enzymes that are increased in chronic wounds which hinder wound healing and is one of the most effective current strategies in reducing the risk of amputation and improving healing rates in patients with DFUs [9]. A more recent meta-analysis of 11 RCTs further supported the use of NPWT in the management of patients with DFUs [61].

Hyperbaric oxygen therapy (HBOT):

In recent years, hyperbaric oxygen therapy (HBOT) has shown increased attention as an adjuvant treatment for managing DFUs [57]. Chronic wounds are usually hypoxic, which means for adequate wound healing, it requires an increase in oxygen supply. HBOT is a technique by virtue of which oxygen is delivered at pressures greater than normal atmospheric (sea level) pressure or more pressure than one atmosphere absolute (ata). In HBOT, the patient is exposed & allowed to breathe in 100% oxygen in a high pressure chamber. The barometric pressure can be increased up to three times normal atmospheric pressure (3ata). When patients breathe oxygen at two to three times atmospheric pressure, the amount of dissolved oxygen in the blood significantly increases; subsequently more oxygen is delivered to the affected area thereby alleviating the wound hypoxia. HBOT has a bactericidal effect through the oxygen free radicals which are generated along with increased leukocyte activity [62]. Clinical evidence strongly emphasize the role of HBOT in reducing the risk of amputation in patients with DFU compared to those managed without HBOT (13.63% versus 30.07%) [63].

Low-level laser therapy in wound healing:

Low level laser therapy (LLLT) or low-intensity laser therapy (LILT) is also known as cold laser therapy, photobiomodulation, or monochromatic infrared light therapy which shows positive effect on

the three overlapping phases of wound healing which can reduce inflammation, cause earlier initiation of the proliferative phase, and augments the rate of contraction as angiogenesis increases [62]. There are also a significant number of research articles describing the effects of LLLT on mast cells, macrophages and fibroblasts, all of which are critical for optimum wound healing. Several reports & literature suggests that most chronic wounds like diabetic neuropathic foot ulcers, pressure ulcers, venous insufficiency and arterial insufficiency respond well to this treatment intervention (**Fig-9**) [62,64].

Fig-9:
Multi-cluster diode probe for use in low-level laser therapy for wound healing.

Conclusion

The incidences of DFUs are increasing and require a high cost of care; since, it often takes long time to heal due to polymicrobial infection & biofilm complication. DFU, if not managed well can lead to amputation in several cases and thus exacerbating patients quality of life. Wound healing requires infection control, inflammatory repair, regeneration of connective tissue matrix, & finally wound constriction and re-epithelization. Infection control & inflammatory repair can be achieved successfully with the use of appropriate topical &/or systemic antimicrobials. However, while managing wounds complicated with biofilm, a newer generation iodine formulation, cadexomer iodine could be the first-line treatment option in addition to debridement. Subsequently, regeneration of connective tissue matrix, & finally wound constriction and re-epithelization can be aided with newer treatment strategies like HBOT, NPWT & use of epidermal

growth factors. Although, commendable efforts in recent years have been taken in the diagnosis and treatment of DFU, it still remains a major public health concern. Therefore, primary prevention should be the main strategy for reducing the burden of the diabetic foot. Despite significant medical and surgical improvements, more research is currently required to define optimal treatment approaches in clinical practice.

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22

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