CYPRUS JOURNAL OF MEDICAL SCIENCES

Review

DOI: 10.5152/cjms.2016.230

Current Treatment of Diabetic Foot Infections and the Effect of Dermobor

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Cite this article as: Büke Ç. Current Treatment of Diabetic Foot Infections and the Effect of Dermobor. Cyprus J Med Sci 2017; 2: 29-34

One of the most serious chronic complications of diabetes is diabetic foot infections. Neuropathy, peripheral vascular disease and trauma are among the leading factors to development of diabetic foot ulcers and predispose to progress the diseases to diabetic foot infections. Delay of diagnosis and treatment and poor antibiotic treatment of diabetic foot infections can result in amputation. Diabetic foot ulcers and infections are the main causes of foot amputation around the world. The five-year survival rate of patients underwent foot amputation due to diabetic foot infections is low. With this review it's aimed to give information about the current epidemiology, risk factors, diagnosis and antimicrobial therapy of diabetic foot infections. In addition it's intended to give the results of Dermobor treatment in small number of cases with diabetic foot ulcers and infections.

Keywords: Diabetic foot ulcer, diabetic foot infection, antibiotic treatment, Dermobor

INTRODUCTION

Diabetes mellitus (DM) remains one of the major public health problems worldwide. The prevalence of both type I and 2 DM is increasing. Type 2 DM is responsible for almost 90% of diabetes patients. Obesity, inactivity, family history, age, gestation, high blood pressure, abnormal cholesterol and triglyceride levels and polycystic ovary syndrome play crucial role to get type 2 DM (1). The number of people living with diabetes is growing fast. In 2013 the number of patients with type 2 DM was 382 million. With this speed, it's estimated that, there will be 592 million people by 2035 (2). Turkey has the highest rate of prevalence among the European countries with 13.7% although the global prevalence is 8.5% (3). Diabetes is considered one of the devastating diseases with high mortality rate. In 2015, of the 56.4 million deaths worldwide, 1.6 million were due to DM. It remains the 7th leading cause of death. Diabetes is also very costly both for the individual and for the health systems of the countries. In 2013, the cost for diabetes and related diseases reached $ 548 billion all over the world (4).

Diabetic foot infections (DFIs) are one of the most serious chronic complications of DM. Diabetic foot ulcers complicate the disease. They occur more than 15% of diabetic patients during their lifetime (5, 6). Treatment of diabetic foot ulcers (DFUs) and subsequent infections is difficult. Multidisciplinary approach is needed for the management of DFUs and DFIs. The most dramatic end result of DFUs and DFIs are foot amputation. The number has been reaching one in every 30 second in the world. The annual number of patient, undergoing foot amputation is around 12,000 in Turkey, and mostly due to DFIs (7-9).

The aim of this review is to review the current empiric and definitive antimicrobial therapy and to discuss the effectiveness of Dermobor gel (Genbor Biyosidal Yaşam Ürünleri San.Tic.Ltd.Şti, İstanbul, Turkey) in the treatment of DFUs and DFIs. It's believed that this review may be useful to primary care physicians, infectious diseases physicians, vascular surgeons, orthopedics, nurses and podiatrists.

RISK FACTORS AND PATHOGENESIS OF DIABETIC FOOT INFECTIONS

Most diabetic foot infections begin with a wound and once an infection occurs, the risk of amputation increases significantly. The prevalence of DFUs are around 4-10% depending on age and duration of DM. The lifetime prevalence reaches 15%. Most of the DFUs (60-80%) heal, while 10-15% of them remain unhealed. The healing of DFUs also depend on the characteristics of the wounds. For example neuropathic wounds are more likely to heal over a period of 4-5 months while

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Received: 21.07.2017
Accepted: 08.08.2017

neuro-ischemic ulcers take longer period and generally result in amputation. Indeed 10-30% of patients with DFUs progress to amputation within a period of 6-18 months after the first evaluation. Among amputated patients five years mortality is around 50-60% (10, 11).

Multiple risk factors can play a role in the occurrence of DFUs such as; neuropathy, peripheral vascular disease, traumas, poor glycemic control and cigarette smoking. Among these neuropathy and peripheral vascular diseases are the most important factors. Sensory neuropathy can allow diminished perception of pain, pressure and heat, thus patients cannot distinguish well an injury or temperature to their feet. Motor neuropathy can cause foot deformities by muscle weakness, atrophy and paresis, which it becomes open pressure-induced soft tissue damage. In addition, autonomic neuropathy causes dry cracked skin by diminishing sweat secretion, resulting in a disruption of skin integrity. The deficiency of blood flow due to peripheral arterial diseases can results in the development of the wound and gangrene. In this setting the entry of microorganisms into the deep skin structures and the development of microbial infection become easy (12, 13).

CLASSIFICATION OF DIABETIC FOOT ULCERS

Diabetic foot ulcers generally classified as neuropathic, ischemic or both. Neuropathic DFUs is characterized with the presence of peripheral neuropathy without ischemia while ischemic DFUs is defined with the existence of symptoms related to peripheral artery disease with no peripheral neuropathy. In neuro-ischemic DFUs neuropathy and ischemia coexist (14). In describing the extent and the severity of lesions classification of DFUs is important. There are various classification schemes including; Wagner-Meggitt, PEDIS classification, Kings College Hospital classifications, and University of Texas classification. The Wagner-Meggitt and University of Texas are the most well accepted systems (Table I). The most common possible causative microrganisms responsible from DFIs are; *Staphylococcus aureus, Staphylococcus agalactiae*, coagulase negative staphylococcus (CNS), *Streptococcus pyogenes, Escherichia coli, Klebsiella pneumoniae, Proteus* spp., *Enterobacter* spp., *Enterococcus* spp., *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.

CLINICAL SIGNS OF DIABETIC FOOT INFECTIONS

Diabetic foot infections are often accompanied by the cardinal manifestations of inflammation such as; erythema, warmth, swelling, tenderness and presence of pus in an ulcer or sinus tract. But, these signs may not be evident in all cases, especially in the presence of severe ischemia. Patients with sensory neuropathy may have diminished sensation in the involved area and may not complain of tenderness, even in the setting of infection. In such patients, infection may progress to involve deeper tissues (15). Presence of gangrene, severe ischemia, or tissue necrosis may remind the existence of a limb threatening infection. Systemic signs such as fever, chills, hypotension, and tachycardia may accompany local signs of infection and indicate an increased severity of infection, like sepsis and septic shock**.** Osteomyelitis can occur in the setting of a diabetic foot wound with or without evidence of local soft tissue infection. It should be diagnosed and aggressively treated as soon as possible.

DIAGNOSIS OF DIABETIC FOOT INFECTIONS

The diagnosis of DFIs depends on the presence of two or more cardinal manifestations of inflammation such as; erythema, warmth, tenderness, swelling and induration or the presence of pus (15). For definitive diagnosis the growth of the microorganism in culture DFIs is essential. In the absence of clinical signs and symptoms the growth of the microorganism should be assessed with caution. This situation is generally due to sample taken by superficial swabs. This method is not reliable for predicting the definitive pathogens. For the accurate diagnosis samples for culture should be aspirated from an abscess or curettage from the ulcer base following superficial debride-

TABLE I. Wagner-Meggitt and University of Texas Classifications of DFUs and causative microorganisms for diabetic foot infections

Grade	Wagner-Meggitt	University of Texas	Causative microorganisms
0	Healed or pre-ulcerative wound, pain on the foot only	Superficial ulcer, healed or pre- or post-ulcerative wound[A-D]	*S. aureus* *S. agalactiae* CNS *S. pyogenes*
I	Superficial ulcer, without reaching to the deeper layers	Full-thickness ulcer not involving tendon, capsule, or bone and without abscess formation[A-D]	*S. aureus* *S. agalactiae* CNS *S. pyogenes*
2	Deeper ulcer and penetrating tendon, bone or joint capsule	Tendon or capsular involvement without bone palpable[A-D]	+ Generally polimicrobial Enterobacteriaceae *Enterococcus* spp. *Pseudomonas aeruginosa* Anaerobes
3	Deep ulcer with bone, tendon involvement and there is abscess formation	Abscess formation and bone involvement[A-D]	+ Anaerobic *Streptococci* *Bacteroides* spp. *Clostridium* spp.
4	Gangrene on the part of the foot		
5	Gangrene on the whole foot		

A: not infected nor ischemic; B: infected; C: ischemic; D: ischemic and necrotic; CNS: Coagulase negative staphylococcus

ment of necrotic tissue (15, 16). Definitive diagnosis of osteomyelitis generally depends on isolation of bacteria from a sterilely obtained bone biopsy sample with histologic evidence. But bone biopsy is not always routinely available or practical. In such instances, the presumptive diagnosis is based on clinical and radiological assessment. The following factors increase the likelihood of osteomyelitis; grossly visible bone or ability to probe to bone, ulcer size larger than 2 cm^2, ulcer duration longer than one to two weeks, and erythrocyte sedimentation rate (ESR) >70 mm/h. On the presence of one or more findings the suitable changes in conventional radiograph can be helpful in making the diagnosis of osteomyelitis. Magnetic resonance imaging (MRI) is highly sensitive and specific for the diagnosis of osteomyelitis. If bone is grossly visible, radiographic examination is not necessary (17).

ANTIMICROBIAL TREATMENT OF DIABETIC FOOT INFECTIONS

For the success of the treatment of DFIs, multidisciplinary approach plays a key role. Management of DFIs requires attentive wound care, glycemic control, good nutrition, supply of fluid and electrolyte balance and appropriate antimicrobial therapy (18, 19). Patients with ulcerations that are not infected should not receive antibiotic therapy. In this situation local wound care and reducing the pressure on the foot is adequate. The selection of empiric antibiotic therapy should be considered based on the severity of infection and the likelihood of involvement of resistant organisms. If it is needed empiric therapy can be changed to definitive antibiotic treatment depending on culture and susceptibility results.

EMPIRIC ANTIBIOTIC THERAPY OF DIABETIC FOOT INFECTIONS

Clinical signs, epidemiological data and antimicrobial susceptibility results should be taken into the consideration for the choice of antibiotics in the empirical treatment of DFIs. Mild diabetic foot infections, manifesting with cellulitis or erythema extends ≤ 2 cm around the ulcer and without systemic signs of infection, can be treated as in outpatient. Oral single antibiotic therapy is convenient for mild DFIs. If there is no history of antibiotic use in the last one month empiric therapy should cover the activity against staphylococci and streptococci. In patients with previous hospitalization and prior antibiotic use, methicillin-resistant *Staphylococcus aureus* (MRSA) should be taken into the consideration. In patients with moderate DFIs, in which cellulitis or erythema extends >2 cm around the ulcer and infection with abscess, involving deep tissue such as muscle, tendon, joint and bone but without systemic signs of infection, antibiotics should include activity against staphylococci (including MRSA if risk factors are present), streptococci, aerobic gram-negative bacilli and anaerobes. In patients with deep ulcer, involving only fascia, antibiotics can be administered by oral route while patients presenting with extensive infections that involve deep tissues like joint and bone, should receive intravenous treatment and combination therapy should be given as point out in severe infections. In severe, limb-threatening diabetic foot infections and those that are associated with systemic toxicity combined broad-spectrum parenteral antibiotic therapy should be given. Surgical debridement is also necessary in most of these cases. Streptococci, MRSA, aerobic gram-negative bacilli such as; *E. coli, K. pneumonia, P. aeruginosa*, and anaerobes should be covered by empiric antibiotic therapy (15, 20, 21). In patients with life threatened DFIs, long term chronic wound, prior antibiotic use, and exudative wounds, *P. aeruginosa* should be considered and covered in empiric antibiotic therapy (22). The choice of empiric antibiotic therapy is summarized in Table 2.

TABLE 2. Empiric antibiotic choice for diabetic foot infections

Severity	Choice of antibiotics	Dosages
Mild	Amoxicillin-clavulanate	875/125 mg twice a day PO or
	Co-trimoxazole	160/800 mg twice a day PO or
	Klindamycin	600 mg three times a day PO or
	Doxycycline	100 mg twice a day PO
	Fucidic acid*	500 mg three times a day PO or
	Linezolide*	600 mg twice a day PO
Moderate	Co-trimoxazole +	160/800 mg twice a day PO +
	Amoxicillin-clavulanate	875/125 mg twice a day PO
	or	or
	Clindamycin +	450 mg every 8 h PO +
	- Ciprofloxacin	- 750 mg twice a day PO or
	- Levofloxacin	- 750 mg once a day PO or
	- Moxifloxacin	- 400 mg once a day
	Fucidic acid*	500 mg three times a day PO or
	Linezolide*	600 mg twice a day PO
Severe	- Ampicillin-sulbactam	- 3 g every 6 h IV or
	- Piperacillin-tazobactam	- 4.5 g every 6-8 h IV or
	- Imipenem-cilastatin	- 500 mg every 6 h IV or
	- Meropenem	- 1 g every 8 hours IV or
	- Ertapenem	- 1 g every 24 hours IV or
	- Moxifloxacin	- 400 mg every 24 h IV
	+	+
	- Vancomycin	- 1g every 12 h IV or
	- Linezolid	- 600 mg every 12 h IV or
	- Daptomycin	- 4-6 mg/kg every 24 h IV

* In case of MRSA infection; PO: Peroral; IV: Intravenous

DURATION OF ANTIMICROBIAL THERAPY

Patients with mild infection oral antibiotic therapy should be given for about one to two weeks. Antibiotics do not need to be given until wound closure. Patients with moderate or severe infection, requiring surgical debridement, intravenous antibiotic therapy is usually adequate for two to four weeks without osteomyelitis. If there is a good response to parenteral therapy, oral agents can be used to complete the course of treatment. In patients with osteomyelitis, surgical resection is generally beneficial. In same studies it is demonstrated that antibiotic therapy for longer period without resection succeed the healing about 60 to 90%, which is comparable to those reported with surgery. The optimal duration is uncertain. But four to six weeks is an appropriate course if there is residual infected bone following debridement of necrotic bone. However, if necrotic bone remains, clinical cure may require several months with antibiotic therapy (15, 20).

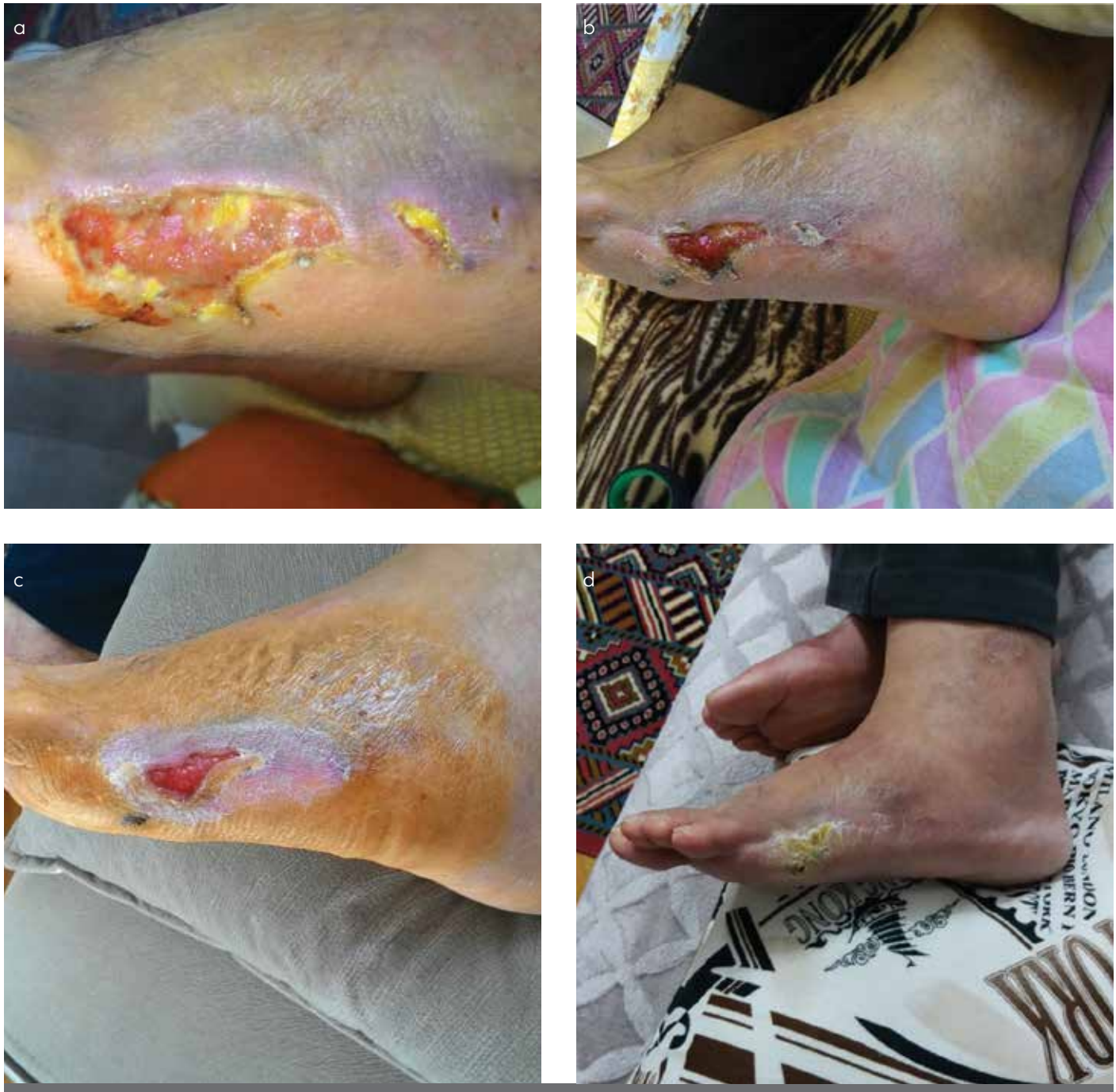

FIGURE I. a-d. The complete closure of DFIs in a 57 years old male patients with Dermobor gel within 50th days. (a) before Dermobor treatment, (b) 16th days of Dermobor treatment, (c) 38th days of Dermobor treatment, (d) 50th days of Dermobor treatment

The treatment of DFIs with local antimicrobial agents depends on several factors. General health of the patient, the process of tissue repair, and description and classification of the wound should be considered when deciding. Generally both local and systemic antimicrobials are using together in the treatment of patients with DFIs. Dermobor gel is licenced as a local treatment agents for DFIs in 2014. It contains 0.2% chlorhexidine digluconate and 3% sodium pentaborate pentahidrate (NaB), Chlorhexidine digluconate 0.2% has strong antibacterial and antiviral effect. This product has not only antimicrobial properties but also has wound closure effect with NaB.

We used Dermobor gel (Genbor Biyosidal Yaşam Ürünleri San. Tic.Ltd.Şti, İstanbul, Turkey) in ten patients with DFIs. Seven of them were male and the mean ages of patients were 64.12±12.16. The duration of diabetes mellitus was 15 years. In four patients the causative microorganisms were grown (*Staphylococcus aureus* in two patients, *Escherichia coli* and *Klebsiella pneumonia* in one patient respectively) from deep of ulcers taken by sterile biopsy techniques. In six patients the wound area was 10-19 cm^2 while in four it was more than 20 cm^2. Most of the patients (n: 6) were moderate and severe diabetic foot infections. Patients with severe diabetic foot infections (n: 2) antibiotics were given parenteral route. Patients with moderate diabetic foot infec-

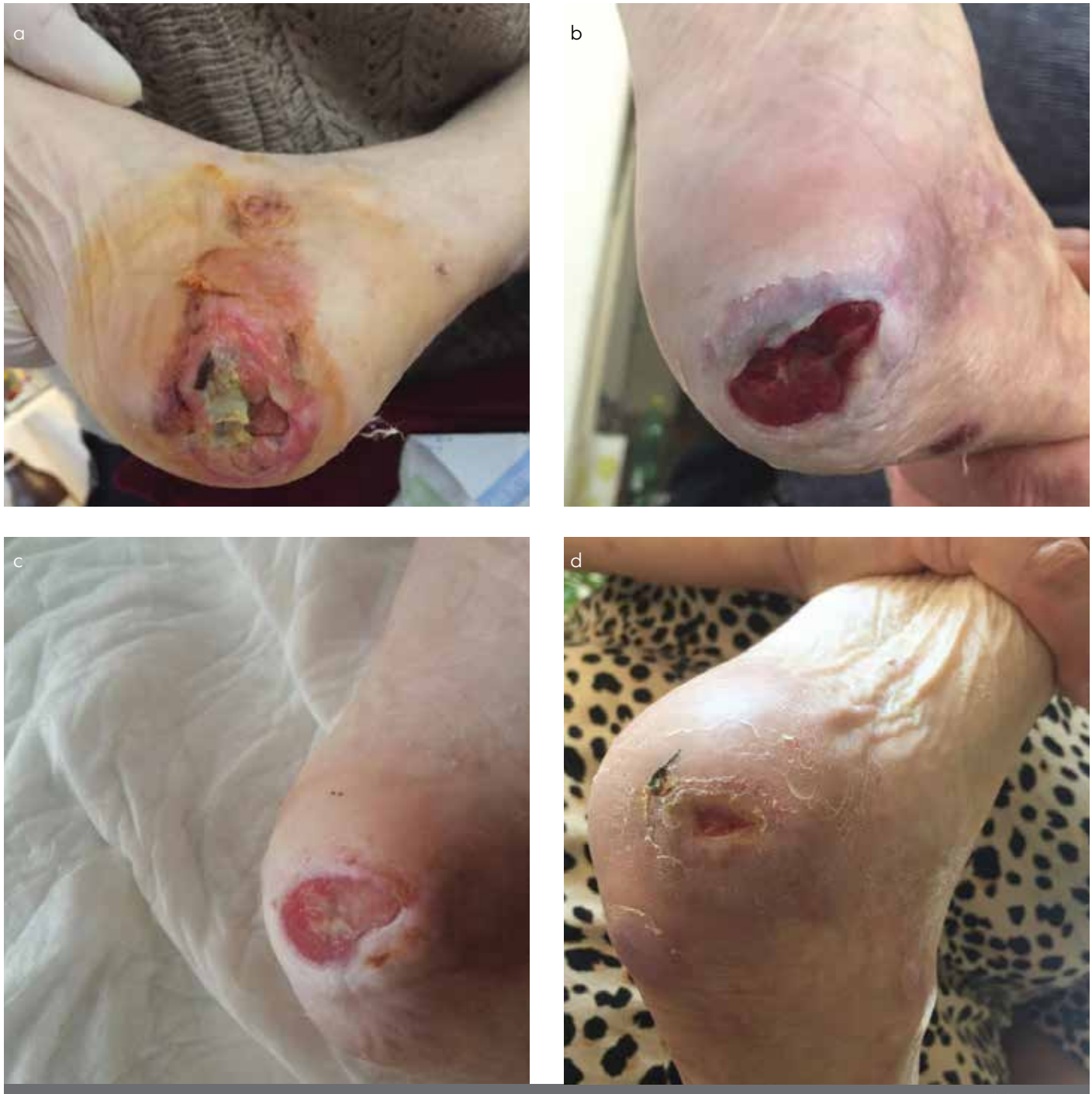

FIGURE 2. a-d. The formation of granulation tissue ≥75% of DFIs in a 72 years old female patient with Dermobor gel within 40th days. (a) before Dermobor treatment, (b) 10th days of Dermobor treatment, (c) 16th days of Dermobor treatment, (d) 40th days of Dermobor treatment

tions and wound culture results positives were used oral antibiotics also. All of the patients received Dermobor gel two times a day. Dermobor gel pomaded around and into the wounds' areas. Granulation tissue formation > 75%, were seen in six patients in 4-5 weeks, wound closure has occurred in two patients in 6-7 weeks. The treatment has been continuing in remaining four patients.

In the first picture complete closure in the DFI was seen at the end of 50th days of Dermobor gel, twice a day, in a 57 years old male patient with DFI. In the second picture 75% granulation tissue formation was occurred at the 16th days of Dermobor gel treatment in a 72 years old female patient with DFI (Figure 1 and Figure 2).

CONCLUSION

Diabetic foot ulcers and infections are the one of the most hopeless chronic complications for diabetic patients since the healing of the wounds and infections generally take longtime. On the other hand sometimes the efforts of treatment cannot be resulted in success and can progress to the need of amputation. But currently it is believed that most of the DFUs and DFIs can be managed and the foot amputation can be prevented with careful patient management. According to the

results of the small number of cases with Dermobor in DFIs, it's seen that Dermobor is seen one of the hopeful choice in DFIs. It acts as both antibacterial and formation of granulation tissue. But for the assessment of the effect of Dermobor, multicentric studies are needed.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the author.

Financial Disclosure: The author declared that this study has received no financial support.

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