

## Local Treatment of Diabetic Foot Ulcers by Hyperoil™: An Unexpected Outcome

Ahmed Salah Arafa \*, Ahmed yehia , Alaa fiad

General Surgery Department, Zagazig University Hospital, Zagazig University,  
Sharkia Province, Egypt

### ABSTRACT

**Background:** Diabetes is an increasing urgent global health issue, with an increasing prevalence in those aged 65 or over. Diabetic foot ulcer (DFU) is one of the very important but most neglected complications of diabetes that affect up to 15 % of diabetic patients who are caused by an imbalance between excessive pressure on the soul of the foot and repetitive stress from walking. DFUs can become infected and lead to osteomyelitis, cellulitis and even amputation that increase the morbidity, mortality and very high cost of the health care system. The management of DFUs represents a major clinical challenge, and there remains the continuing uncertainty concerning optimal approaches to management. The aim of this present analysis was to follow a cohort of patients with diabetes in clinical practice from initial presentation of a DFU to evaluate patient management by Hyperoil™. **Methods:** 12 patients with DFU were asked to attend to the Wound Care Units (WCU) of Zagazig University Hospital between December 2016 and December 2018 followed a standardized diagnostic/ therapeutic scheme to manage the diabetes and coexisting conditions. All DFUs were treated with Hyperoil™ at home, when diabetes was well compensated at WCU. Changes in the HbA1c, blood pressure and pain have been evaluated by using the paired t-test. **Results:** All the 12 patients recovered their DFUs 2 to 10 months after starting the Hyperoil™. During this period, the HbA1c and pain improved due to DFUs disappeared in all patients. Furthermore, the hypertension was better compensated. **Conclusion:** According to the results obtained from the present study, it seems that using Hyperoil™ for advanced DFUs, together with tight diabetes control, might be a cheap and effective new option for the home management of advanced DFUs.

**Keywords:** Diabetic foot ulcer; Hyperoil™; *Hypericum perforatum*; *Azadirachta indica*; Home wound care.

### INTRODUCTION

Diabetic foot complications are common, complex, and costly. The demographic trends suggest that these complications, including ulcers, infections and amputations, will continue to be highly prevalent<sup>[1]</sup>.

The foot ulcer was defined as a full thickness lesion of the skin of the foot, according to the International Working Group on the Diabetic Foot (IWGDF)<sup>[2]</sup>.

Diabetic foot ulcers (DFUs) are a frequent and serious complication of diabetes mellitus with an annual incidence of 0.01–0.04 and a lifetime risk of 0.15–0.25<sup>[3]</sup>.

The foot ulcers eventually develop in 15 % of the chronic diabetics and give rise to further complications such as infection and amputation if

inadequately healed [4]. These wounds are typically resistant to the healing despite meticulous wound care, control of the glucose levels, and maintenance of the nutritional status of the patient<sup>[5]</sup>.

Diabetic neuropathy is considered the predominant underlying factor involved in the development of the ulcers[6]. The neuropathy results in nociception deficits and foot deformity, that together increasing the risk of ulceration triggered by the traumatic events<sup>[7]</sup>.

Patients with diabetes are twice as likely to have peripheral arterial disease (PAD) compared to those without diabetes<sup>[8]</sup>, and 5-year mortality rates of patients with both DFU and PAD are 50%<sup>[9]</sup>. The Clinical manifestations of PAD are ranged from mild claudication to limb-threatening ischemia. However, the typical symptoms of PAD in diabetic patients may be absent, due to the

---

\*Correspondence author: Ahmed Salah Arafa  
E-mail: ahmedarafa237@gmail.com  
Tel.: 00201025244965

underlying neuropathy. Therefore, all diabetics over the age of 50 should be regularly assessed with the ankle brachial pressure index (ABPI)<sup>[10]</sup>.

However, Diabetic foot ulcers (DFUs) are often hard to heal, with an increased risk for infection, which can lead to recurrent hospitalization and lower limb amputation<sup>[11]</sup>.

Hyperoil™ is a mixture of hypericum flowers extract (*Hypericum perforatum*) and nimh oil (*Azadirachta indica*), available as oil, gel, cream and gauze gel, that was tested to be used in complicated DFUs<sup>[12]</sup>.

### AIM OF WORK

The aim of this present analysis was to follow a cohort of patients with diabetes in clinical practice from initial presentation of a DFU to evaluate patient management by Hyperoil™.

### MATERIALS AND METHODS

This prospective observational study was carried out between December 2016 and December 2018 in the general surgery department at Zagazig University Hospitals. We prospectively assessed DFU remission at 1 year after completion of the treatment by Hyperoil™ in participants with advanced DFU not yet needing surgery. We recorded the patient characteristics at the time of admission and evaluated electronic medical records for the clinical complications and outcomes over a 12 month follow-up period. Patient baseline characteristics and the diagnostic methods were shown at Table 1.

**Table 1. Patient baseline characteristics & Diagnostic methods**

Patient baseline characteristics	Diagnostic methods
Male/Female = 7 / 5 (total =12)	Echo Color Doppler
Age range: 30 – 70 years	Transcutaneous oxygen and carbon dioxide partial pressure (TCpO <sub>2</sub> -TCpCO <sub>2</sub> )
BMI range: 28-31	Laser Doppler Fluximetry and bio-microscopic evaluations
Smokers / non smokers: 7 patients / 5 patients	
HbAc1% range: 7.1%-9.8%	
Ulceration area size : 15-420 cm <sup>2</sup>	
Ulcer duration before admission (days) range: (7-90)	
<b>Comorbidities:</b> -- Hypertension 12 patients -- Ischemic Heart Failure 5 patients --Chronic Kidney Failure 2 patients -- COPD 3 patients -- HCV positive 1 patient	

BMI (Body Mass Index), COPD (Chronic Obstructive Pulmonary Disease), HCV (Hepatitis C Virus)

All patients were controlled for the metabolic parameters with the goal of optimizing glycaemic control, having target HbA1c of 7% and fasting blood glucose between 80 mg/dL and 120 mg/dL, according with the American Diabetes Association (ADA) guidelines<sup>13</sup>. All patients were asked to clarify and evaluate their perceived pain administering the Visual Analog Scale for pain (VAS)<sup>14</sup>.

All patients were asked to attend to the Wound Care Units (WCU) and followed a standardized diagnostic/ therapeutic scheme to manage the diabetes and coexisting conditions.

Patients with the critical chronic ischemia, having supine big toe pressure (Laser Doppler evaluation) <30 mmHg associated to the dorsum foot values O<sub>2</sub><20 mmHg and CO<sub>2</sub>>50 mmHg (Transcutaneous Partial Pressure) measured with

the lower limb depending <sup>15</sup> were excluded from this study.

Diabetic foot Ulcers are multifactorial, where neuropathy, angiopathy and infection are the main variables. All patients in our study had a good limb vascularity indicated by normal values of ABPI that was regularly assessed. Ulcers were predominantly neuropathic (8 patients) and some were infected (4 patients).

All patients gave their signed informed consent to be included in this case series. All patients were shifted to the intensive insulin therapy when admitted to WCU. No changes in the dietary habits were prescribed.

#### Wound Treatment

Hyperoil™ is a new therapy with low cost. Nimh oil (*Azadirachta indica*) has shown the cicatrizing, bacteriostatic, anti-inflammatory properties. The anti-inflammatory effects of the *Hypericum perforatum* extracts were recently demonstrated, thus, providing the rationale for using these extracts in lower legs wounds, together with nimh oil extract.

All patients had wound care. After adequate debridement of the necrotic and infected tissues, the wound was treated with the Hyperoil™ oil applications every three days. The skin around the wound was carefully cleaned with normal Ringer solution and gauze having Hyperoil™ oil. The ulcer's bed and undermined edges were cleaned, and the exudates and fibrin residuals or necrotic materials were removed, with a gauze with Hyperoil™. Then, a little Hyperoil™ oil was dropped in the ulcer including exposed bone. In addition, the ulcer was covered with gauze.

Patients were asked to attend the clinical medical checks in WCU, to assess the ulcer's healing progression (e.g. decrease of ulcer size or growth of granulation tissue).

We defined our primary outcome, DFU remission, as wound healing leaving the skin surface smooth and the foot ulcers did not show any recurrence after one year of continuous follow up.

#### Statistical analysis

All data were described using means (standard deviations), medians (interquartile range). Only the descriptive statistic was used to evaluate outcomes. Parameters related to the wound itself such as the foot ulceration area size was varied from 15 to 420 cm<sup>2</sup> (length & width). Statistical

significance of variations (Changes in HbA1c, blood pressure and pain) between the beginning of the observation, the lesion recovery and the end of the observation have been evaluated with paired samples t-test performed with Microsoft Excel 2010 for Windows.

## RESULTS

We followed a total of 12; (7 males and 5 females) diabetic patients with advanced DFUs for a duration of 10 months follow up. The foot ulceration area size ranged from 15 to 420 cm<sup>2</sup> (length & width). Their age ranged between 30 and 70 years and 7 of them were actual smokers.

All patients completed the Hyperoil™ treatment and the wounds recovered within 10 months. None of the patients was lost to follow up. None of the patients had any new ulcer or recurrence in the 10 months follow-up period.

All patients were reported a clinically relevant and statistically significant improvement in glycated haemoglobin (HbA1) when ulcers recovered (Mean 7.55%; SD 0.85%; p=0.002) (Range =6.7-9.5) when compared to basal (Mean 8.66%; SD 0.80%) (Range =7.1-9.8).

All patients were under antihypertensive therapy. All patients were reported a clinically relevant and statistically significant improvement in Systolic Blood Pressure (SBP) when ulcers recovered (Mean 133.08; SD 7.66; p<0.001) (Range =125-150) when compared to basal (Mean 149.17; SD 9.96) (Range =130-160) without any change in antihypertensive therapy.

All patients were reported a clinically relevant and statistically significant improvement in the Diastolic Blood Pressure (DBP) when ulcers recovered (Mean 78.67; SD 4.40; p=0.002) (Range =80-100) when compared to basal (Mean 90.67; SD 6.14) (Range =75-90) without any change in the antihypertensive therapy.

All patients used the non-opioid painkillers (e.g. paracetamol tablets) as treatment. Statistically significant improvement in VAS pain was in all patients when the ulcers recovered (Mean 0; SD 0; p=0.002) when compared to basal (Mean 6.33; SD 2.06) (Range =3-9). Some examples of recovered lesions are shown in (Figures 1 & 2).

Table 2. Changes in HbA1c, Blood pressure and Pain

Patient Number	HbA1c (%)		SBP (mmHg)		DBP (mmHg)		VAS	
	Basal	End of observation	Basal	End of observation	Basal	End of observation	Basal	End of observation
1	8	6.70	130	125	80	75	3	0
2	9	8	140	126	83	78	5	0
3	9.20	7.90	135	125	85	75	6	0
4	9.40	8.10	145	130	90	81	3	0
5	8.50	7.70	150	140	94	76	5	0
6	7.10	6.70	155	128	95	83	7	0
7	7.50	6.70	160	135	98	77	9	0
8	8.40	6.70	155	138	96	78	8	0
9	9.20	7.90	150	130	89	76	7	0
10	8.80	6.90	160	140	90	80	8	0
11	9.80	9.50	150	130	88	75	6	0
12	9	7.80	160	150	100	90	9	0
Mean	8.66	7.55	149.17	133.08	90.67	78.67	6.33	0
SD	0.80	0.85	9.96	7.66	6.14	4.40	2.06	0
(Range)	(7.1-9.8)	(6.7-9.5)	(130-160)	(125-150)	(80-100)	(75-90)	(3-9)	(0-0)
Test	-3.072*		8.391*		-3.068*		-3.066*	
P-value	0.002		<0.001		0.002		0.002	
(Sig.)	(S)		(HS)		(S)		(S)	

• Wilcoxon signed ranks test. \* Paired t-test. VAS: Visual Analogue Scale, SD: Standard Deviation. P-value<0.05 is significant. Sig.: Significance, (S) Significant, (HS) Highly significant.



**Plate 1** showing **figure 1**; infected DFU at the medial aspect of the left foot. **Figure 2** showing the using of Hyperoil™ in treating the ulcer. **Figure 3 and 4** showing the necrosis was cleaned & appearance of granulation tissue with reduction of the ulcerated area and the wound become superficial. **Figure 5** showing that the ulcer was completely healed without scar retraction.



**Plate 2 showing figure 1;** DFU at the sole of the right foot. **Figure 2 and 3** showing the appearance of granulation tissue with reduction of the ulcerated area and the wound become superficial. **Figure 4** showing that the ulcer was completely healed without scar retraction.

## DISCUSSION

Advanced complications of the diabetes including DFUs, constitutes a major challenge, especially in low-income countries, and can have a huge impact on patients, families, and society<sup>16</sup>.

Individuals who develop a DFU are at greater risk of premature death, myocardial infarction and fatal stroke. It has been estimated that every 20 seconds a lower limb is limb is amputated due to complications of diabetes<sup>17</sup>.

The risk of death at 5 years for a patient with a diabetic foot ulcer is 2.5 times as high as the risk for a patient with diabetes who does not have a foot ulcer<sup>18</sup>.

Diabetes influence foot wound healing by an impairment of the peripheral circulation, altered leukocyte function, disturbed balance of cytokines and proteases and even chronic hyperglycemia itself<sup>19</sup>.

This delay in healing is associated with serious impairment of lifestyle and mood and exposes the patient to limb-threatening complications, such as the development of secondary infection and gangrene<sup>20</sup>.

Neely et al.<sup>21</sup> found that a transcutaneous oxygen tension (TcPO<sub>2</sub>) of less than 30 mmHg, absence of the Achilles' tendon reflex, and foot insensitivity are 3 factors that are strong predictors of ulceration.

The improvements in foot ulceration diagnosis and prevention can reduce the amputation risk and health care costs<sup>22</sup>.

Benefits of wound debridement include removal of necrotic tissue, reduction of pressure, inspection of underlying tissue, drainage of pus, optimisation of topical preparations and stimulation of healing [23].

Where ulcers are not infected and predominantly neuropathic, the use of antibiotics may be withheld as Chantelauet al.<sup>24</sup> have shown that with appropriate wound management, patients do equally well with or without systemic antibiotics in a randomized controlled trial.

A case report on the successful using of Hyperoil™ in an elderly patient with advanced bilateral diabetic foot has been recently published<sup>12</sup>. The using of Hyperoil™ in this patient allowed wound home care, when the patient received only a 2 times a week cleaning of the lesions,

performed by relatives, without any other surgical or clinical intervention<sup>12</sup>.

## CONCLUSIONS

The observed results of the case series support that Hyperoil™ might be used for the management of DFUs with satisfactory results.

Properly designed and controlled studies are needed to confirm these preliminary observations where Hyperoil™ has to be compared with available standard treatments.

### Conflict of interest

The authors report no any proprietary or commercial interest in any product mentioned or concept discussed in this paper.

### Abbreviations:

Negative Pressure Wound Therapy(NPWT), Ankle Brachial Pressure Index (ABPI), Peripheral Arterial Disease (PAD), Hyperbaric Oxygen Therapy (HBOT), International Working Group on the Diabetic Foot (IWGDF), Randomised Controlled Trial(RCT), American Diabetes Association (ADA), Wound Care Units (WCU), Visual Analogue Scale (VAS)

### Acknowledgment

The authors gratefully acknowledge all the members of staff of the Vascular Surgery Unit, Zagazig University for their valuable assistance and guidance throughout this work. We appreciate all patients who participated in the study.

## REFERENCES

1. Skrepnek GH, Mills JL, Lavery LA, Armstrong DG. Health care service and outcomes among an estimated 6.7 million ambulatory care diabetic foot cases in the US. *Diabetes Care*. 2017;dc162189.
2. Jones NJ, Harding K. 2015 International Working Group on the Diabetic Foot Guidance on the prevention and management of foot problems in diabetes. *Int Wound J*. 2015;12(4):373-374.
3. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA* 2005;293:217–28.
4. Molvær AK, Graue M, Espehaug B, Østbye T, Midthjell K, Iversen MM. Diabetes-related foot ulcers and associated factors: Results from the Nord-Trøndelag Health Survey (HUNT3) (2006–2008). *J Diabetes Complications*. 2014; 28(2):156-161.
5. Fowler EM, Vesely N, Johnson V, Harwood J, Tran J, Amberry T. Wound care for patients with diabetes. *Adv Skin Wound Care*. 2003;16(7):342-346.
6. Caravaggi C, Sganzaroli A, Galenda P, Bassetti M, Ferraresi R, Gabrielli L. The management of the infected diabetic foot. *Curr Diabetes Rev*. 2013;9(1):7-24.
7. Rathur HM, Boulton AJM. The neuropathic diabetic foot. *Nat Rev Endocrinol*. 2007;3(1):14.
8. Gregg EW, Sorlie P, Paulose-Ram R, et al. Prevalence of lower-extremity disease in the US adult population ≥ 40 years of age with and without diabetes: 1999–2000 national health and nutrition examination survey. *Diabetes Care*. 2004;27(7):1591-1597.
9. Dolan NC, Liu K, Criqui MH, et al. Peripheral artery disease, diabetes, and reduced lower extremity functioning. *Diabetes Care*. 2002;25(1):113-120.
10. Mayfield JA, Reiber GE, Sanders LJ, Janisse D, Pogach LM. Preventive foot care in people with diabetes. *Diabetes Care*. 1998;21(12):2161-2177.
11. Alavi A, Sibbald RG, Mayer D, et al. Diabetic foot ulcers: part II. Management. *J Am Acad Dermatol*. 2014;70(1):21-e1.
12. Iabichella ML. The use of an extract of *Hypericum perforatum* and *Azadirachta indica* in advanced diabetic foot: an unexpected outcome. *BMJ Case Rep*. 2013;2013:bcr2012007299.
13. American Diabetic Association (ADA). Glycemic targets: standards of medical care in diabetes—2018. *Diabetes Care*. 2018;41(Supplement 1):S55-S64.
14. Mosti G, Iabichella ML, Partsch H. Compression therapy in mixed ulcers increases venous output and arterial perfusion. *J Vasc Surg*. 2012;55(1):122-128.
15. Melillo E, Ferrari M, Balbarini A, Pedrinelli R. Transcutaneous gases determination in diabetic critical limb ischemia. *Diabetes Care*. 2005;28(8):2081-2082.
16. Bos M, Agyemang C. Prevalence and complications of diabetes mellitus in Northern Africa, a systematic review. *BMC Public Health*. 2013;13(1):387.

17. Young MJ, Mc Cardle JE, Randall LE, et al. Improved survival of diabetic foot ulcer patients 1995-2008: possible impact of aggressive cardiovascular risk management. *Diabetes Care* 2008; 2143-47.
  18. Walsh JW, Hoffstad OJ, Sullivan MO, Margolis DJ. Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom. *Diabet Med* 2016; 33: 1493-8.
  19. Boulton AJM. The diabetic foot: from art to science: the 18<sup>th</sup> Ca-millow Golgi lecture. *Diabetologia* 2004; 47: 1343-1353.
  20. Nabuurs-Franssen MH, Huijberts MS, Nieuwenhuijzen Kruseman AC, Willems J, Schaper NC. Health-related quality of life of diabetic foot ulcer patients and their caregivers. *Diabetologia* 2005; 48:1906–1910.
  21. Reiber G, Lipsky B, Gibbons G. The burden of diabetic foot ulcers. *Am J Surg.* 1998;176(2):5S-10S.
  22. Chan JCN, Gagliardino JJ, Baik SH, et al. Multifaceted determinants for achieving glycemic control: the International Diabetes Management Practice Study (IDMPS). *Diabetes Care.* 2009;32(2):227-233.
  23. Steed DL, Donohoe D, Webster MW, Lindsley L, Diabetic ulcer study group. Effect of extensive debridement and treatment on healing of diabetic foot ulcers. *J Am Coll Surg.* 1996;183:61–4.
  24. Müller M, Trocme C, Lardy B, Morel F, Halimi S, Benhamou PY. Matrix metalloproteinases and diabetic foot ulcers: the ratio of MMP-1 to TIMP-1 is a predictor of wound healing. *Diabet Med.* 2008;25(4):419-426.
-