

Marine Omega3 wound matrix for the treatment of complicated wounds

Experiences associated with amputations in the lower limb in diabetic patients

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Keywords

Diabetic ulcer, wound healing, wound matrix, amputation

Summary

Introduction: Complicated wounds in the lower extremity can arise as a consequence of insufficient soft-tissue coverage after amputations in diabetic patients. The Kerecis® Omega3 wound matrix is a decellularized skin matrix derived from codfish and represents an alternative treatment option to achieve wound healing.

Methods: 5 patients with diabetes mellitus and complicated wounds in the lower limb with exposed bony segments were treated with the Omega3 wound matrix between November 2014 and November 2015. Following initial debridement in the operating room, the wound matrix was applied and covered with a silicone mesh. In the further course, wound treatment was conducted on outpatient setting.

Results: In total, 7 wounds were treated with localization at the level of the thigh (n=2) and the forefoot (n=5). For the wounds at the thigh, it took 26 weeks to achieve wound closure, whereas the wounds at the level of the forefoot showed healing times between 13 and 41 weeks. In all patients, a reduction

of analgetics intake was noted when the treatment with the Omega3 wound matrix was initiated.

Conclusion: The Kerecis® Omega3 wound matrix represents a viable treatment option in complicated wounds in the lower limb of diabetic patients to circumvent an otherwise necessary proximalization of amputation level. Further studies comparing the Omega3 wound matrix with appropriate control groups of standard therapies for soft-tissue conditioning/coverage like negative pressure therapy, biosurgery and other acellular dermal matrices are warranted.

Schlüsselwörter

Diabetisches Ulkus, Wundheilung, Wundmatrix, Amputation

Zusammenfassung

Fragestellung: Problemwunden nach Amputationen bei Diabetikern können aus insuffizienter Weichteildeckung vergesellschaftet mit freiliegenden Knochenanteilen resultieren. Die Omega3-Wundmatrix (Kerecis®) stellt eine alternative Wundaufgabe dar, die aus der Haut des Kabeljau durch entsprechende Verfahren wie Dezellularisierung ge-

wonnen wird und seit kurzem in Deutschland verfügbar ist.

Methode: Wir berichten über 5 Patienten (1 Frau) mit Problemwunden nach Amputationen, bei denen eine Proximalisierung des Amputationsniveaus drohte. Bei mehreren Patienten war zuvor eine konventionelle Wundbehandlung mit Vakuumtherapie teils über mehrere Wochen ohne durchgreifenden Erfolg durchgeführt worden. Die Erstapplikation der Omega3-Wundmatrix (Kerecis®) nach Debridement und Abdeckung mittels feuchtem Verband erfolgte im OP unter stationären Bedingungen, danach wurden die Patienten einmal wöchentlich ambulant versorgt.

Ergebnisse: Insgesamt behandelten wir sieben Problemwunden mit Wundlokalisation am Oberschenkelstumpf (n=2) nach Oberschenkelamputation bzw. Vorfuß nach Vorfuß- (n=4) bzw. Zehenamputation (n=1). Die Oberschenkelwunden zeigten nach 26 Wochen eine komplette Abheilung. Die Wunden am Vorfuß waren nach 13–41 Wochen verschlossen. Zusätzlich war bei allen Patienten innerhalb der ersten 2 Behandlungswochen mit Kerecis® eine deutliche Verminderung der lokalen Wundschmerzen zu verzeichnen.

Schlussfolgerung: Die Behandlung mit dem Omega-3-fettsäurehaltigen Fischhautpräparat (Kerecis®) stellt einen wirksamen Ansatz in der Behandlung von Problemwunden nach Amputationen bei Diabetikern dar. Weitere Untersuchungen sind notwendig, um die Granulations- und Reepithelialisierungsfunktion sowie die zusätzlich vorhandene analgetische bzw. antinozizeptive Wirkung dieses Präparates genauer zu evaluieren.

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Omega-3-Wundmatrix zur Behandlung komplizierter Wunden

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Table 1 Patient demographics

Patient No.	1	2	3	4	5
Gender	♀	♂	♂	♂	♂
Age (years)	76	67	74	76	80
Diabetes mellitus	+	+	+	+	+
Hypertension	+	+	+	+	+
Hyperlipoproteinaemia	+	–	+	+	–
Nicotine abuse	+	–	+	+	+
Obesity (BMI, kg/m ²)	28	21	36	24	25
Renal insufficiency	II°	II°	III°	V°	II°
Hemodialysis	–	–	–	+	–
ASA-Class	IV	IV	IV	IV	IV
Comorbidities	CML		CAD	CAD, AF	AVS

BMI: Body mass index, ASA: American Society of Anaesthesiologists, CML: Chronic myeloid leukemia, CAD: Coronary artery disease, AF: Atrial fibrillation, AVS: Aortic valve stenosis, II/III/IV: Renal insufficiency (glomerular filtration rate, GFR) Grade II: GFR 60–89 ml/min, Grade III: GFR 30–59 ml/min, Grade V: <15 ml/min.

The complicated course of wound healing in patients with diabetes mellitus has received considerable attention and studies of diabetic foot ulcers in various countries have yielded prevalence figures ranging from 2–10% whereby recurrent diabetic foot ulcers are the most likely of all to necessitate amputation (in up to 60% of cases) (1).

In the treatment of diabetic foot ulcers the efficacy of local wound debridement is supported by the available literature. However, comparative evidence of different

methods for debridement, i.e. surgical, autolytic or larval debridement is of low quality and did not reveal superiority of any of the procedures (2). With regards to efficacy of negative pressure therapy, there is very little evidence to support their use in the treatment of wounds (3, 4) and, furthermore, negative pressure therapy sometimes may be technically difficult in wounds at the forefoot with regards to achieve appropriate sealing. An alternative concept to negative pressure therapy are acellular dermal matrices that have been

used in the treatment of diabetic foot wounds as an adjunct to achieve healing with promising results (5–8).

The Kerecis® Omega3 wound patch (Kerecis Ltd., Isafjordur, Iceland) is such an acellular dermal matrix, however, it is derived from decellularized codfish skin. Nonetheless, its protein composition resembles that of human skin and the porous microstructure allows ingrowth of dermal cells and capillaries. Additionally, it contains long-chain polyunsaturated omega-3 fatty acids (9). The processed marine matrix is available as a vacuum-dried off-the-shelf product that is FDA-approved and CE certified. The Omega3 wound patch is intended to be used for treatment of chronic wounds and has unique properties and potential advantages of omega-3 fatty acid enrichment.

The aim of this pilot study was to evaluate applicability and efficacy of the Kerecis® Omega3 wound patch in the treatment of complicated wounds associated with amputations in the lower limb in patients with diabetes mellitus.

Patients and method

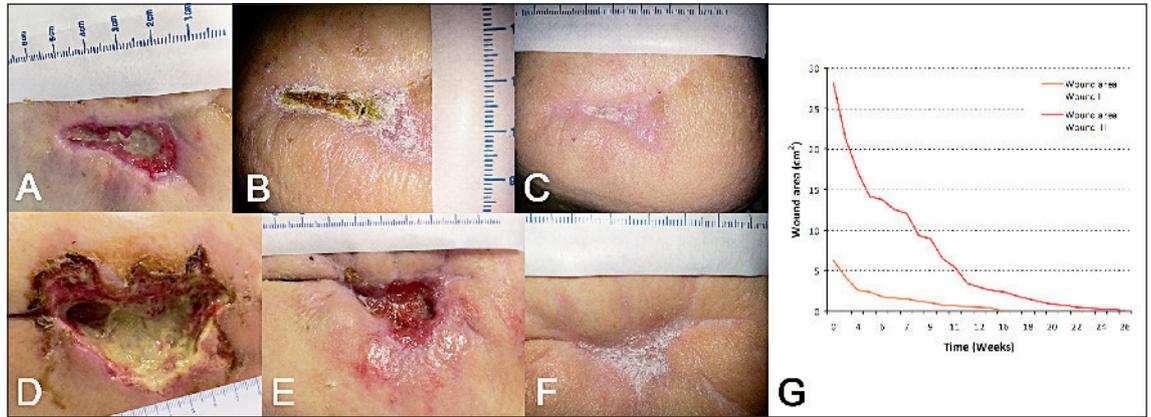
In this single-arm pilot study five patients were treated at our institution between November 2014 and November 2015. The inclusion criteria for the study were presence of a complicated lower limb wound follow-

Table 2 Operative History

Patient No.	1	2	3	4	5
Revascularization	CFA-TEA and stent-PTA of EIA Pop (PIII)-ped (ADP) bypass (GSV)	Pop (PIII)-ped (ATP) bypass (GSV)	–	Pop (PIII)-ped (ADP) bypass (GSV)	CFA-TEA, femorotibial (peroneal artery) in situ bypass and stent-PTA of CIA/EIA
Patency Bypass	occluded	patent	–	patent	patent
Resections	BK amputation	Distal transmetatarsal amputation forefoot	Toe amputation (D1)	Distal transmetatarsal amputation forefoot	Distal transmetatarsal amputation forefoot
	Distal OK amputation	Chopart's amputation	Transmetatarsal amputation (D1)	Proximal transmetatarsal amputation forefoot	Proximal transmetatarsal amputation forefoot
	Proximal OK amputation				
Previous duration of NPT (weeks)	10	3	4	–	–

CFA: Common femoral artery, TEA: Thrombendarterectomy, PTA: Angioplasty, EIA: External iliac artery, CIA: Common iliac artery, PIII: Segment III popliteal artery, ADP: dorsal pedal artery, GSV: greater saphenous vein, BK: below the knee, OK: above the knee, NPT: negative pressure therapy

Fig. 1
Wound healing of patient 1. A–C depicts wound I (A: prior to treatment, B: under treatment, C: healed wound) and D–F show wound II (D: prior to treatment, E: under treatment, F: healed wound). Kinetic of wound healing is shown in G.



ing amputation with exposed bony segments and impending risk for proximalization of amputation level.

Local institutional review board was waived as this is a FDA-approved/CE-certified commercially available product and the indication (chronic vascular ulcers) was within instructions for use (IFU). Nonetheless, the patients were extensively informed about the study and gave written consent.

The patient demographics are given in ► Table 1. The mean age of the study cohort was 75 ± 5 years and all of the patients had at least two risk factors of cardiovascular disease. All but 1 patient (Patient 3) suffered from peripheral arterial occlusive disease and had respective procedures for arterial revascularization prior to patch treatment (► Table 2). In patient 3, a diabetic foot syndrome with sufficient arterial perfusion was present. In patient 1, failed pedal arterial bypass resulted in lower limb amputation with subsequent proximalization of amputation level from below the knee to distal femoral and finally, proximal femoral amputation.

Sufficient arterial perfusion at all wound sites was documented by either ABI (>0.5)

or measurement of transcutaneous local tissue oxygen pressure ($tcpO_2 > 40$ mmHg).

All wounds received a standard pretreatment with a first debridement in the operating room under aseptic conditions with meticulous cleaning of the wound, exploration for viability of the exposed bony segments and testing for bacterial contamination.

The patch used for the study was the Kerecis® Omega3 wound patch, (Kerecis Ltd., Isafjordur, Iceland) at a dimension of 3×7 cm. First, the patch was tailored to the size of the wound and rinsed in sterile physiologic saline solution for 1 minute according to the instructions for use. Then, the patch was cautiously applied to the wound and fixation of the patch was achieved by coverage with a self-adherent soft silicone foam dressing (Mepilex® Border, Mölnlycke Health Care, Gotenberg, Sweden).

In the further course, wound treatment was performed in our outpatient clinic with scheduled changement of the dressing, limited local debridement as necessary and renewal of the patch once per week. In each follow-up office visit, clinical and photographic documentation of the wound was obtained.

Statistical analysis of patient data and quantification of wound area was performed using MS Excel (Microsoft Corp. Redmond, Washington, USA) and Fiji/Image J open source software (imagej.nih.gov/ij/), respectively.

Results

Altogether, 7 wounds in 5 patients were treated. The wounds were localized at the level of the proximal thigh ($n=2$), proximal forefoot ($n=4$) and distal forefoot ($n=1$). The wounds at the level of proximal thigh (6 and 28 cm², Patient 1) took 16 and 26 weeks, respectively, to fully reendothelialize. For the wounds at the level of the proximal forefoot that were 11 cm² (Patient 2), 6/8 cm² (Patient 4) and 29 cm² (Patient 5), it took 30, 13/19 and 33 weeks, respectively, to achieve closure. The wound at the level of the distal forefoot (17 cm², Patient 3) was healed after 41 weeks. A detailed photographic documentation of each course of wound healing is depicted in the respective figure for each wound (► Fig. 1 A–C and D–F, and ► Fig. 4: A–C and D–F, ► Fig. 2 A–C, ► Fig. 3 A–C and ► Fig. 5:

Fig. 2
Wound healing of patient 2. A–C show appearance of the wound (A: prior to treatment, B: under treatment, C: healed wound). Kinetic of wound healing is shown in D.



A-C) and in addition, the kinetics of wound closure is shown (▶ Fig. 1 G, ▶ Fig. 2 D, ▶ Fig. 3 D and ▶ Fig. 4 G ▶ Fig. 5 D). The mean size of the wounds treated was $15 \pm 10 \text{ cm}^2$ and the mean duration of treatment to achieve full closure (reendothelialization of the wound) was 25 ± 10 weeks and ranged from 13 (Patient 4) to 41 (Patient 3) weeks.

In order to allow comparison of closure kinetics of the different wounds, we performed normalization of the size and duration values and the resulting normalized closure kinetic is shown in Figure 6: Here, all wound sizes were normalized to a maximum wound area of 100% and all durations were normalized to a maximum of 100%. Thereby, we were able to document,

that the overall course of wound closure kinetic does not follow a linear but an exponential course and in all wounds, a reduction of wound size of 50% could be achieved within the first third of treatment time. Vice versa, wound size was reduced to <30% in all wounds within the first half of the treatment duration. The number of patches used in total was 96 and a median of 20 patches was applied per patient (▶ Table 3).

The intraoperative microbiology testing revealed bacterial colonization in all wounds with 3 patients having singular bacteria (extended spectrum beta-lactamase-positive *E. coli*, *Enterobacter cloacae* and *Staphylococcus aureus*) and two patients showing multiple bacteria (*Strepto-*

coccus agalactiae/*Klebsiella oxytoca*/*Staph. aureus* and *Pseudomonas aeruginosa/enterobacter cloacae*). Initially, all patients received targeted antibiotic therapy either intravenously (Imipenem, Sulbactam/Piperacillin) or per os (Ciprofloxacin, Clindamycin). In 3 patients, antibiotic therapy was discontinued at discharge, whereas in two patients, oral antibiotics were administered until complete closure of the wound.

We observed an interesting potential side-effect of the omega-3 patches: In all patients, a markedly reduced level of local pain was noted within the first two weeks of treatment. In addition, the amount of analgetic consumption could be lowered, especially in patient 1 where the adminis-



Fig. 3 Wound healing of patient 3. A–C show appearance of the wound (A: prior to treatment, B: under treatment, C: healed wound). Kinetic of wound healing is shown in D.



Fig. 4 Wound healing of patient 4. A–C depicts wound I (A: prior to treatment, B: under treatment, C: healed wound) and D–F show wound II (D: prior to treatment, E: under treatment, F: healed wound). Kinetic of wound healing is shown in G.

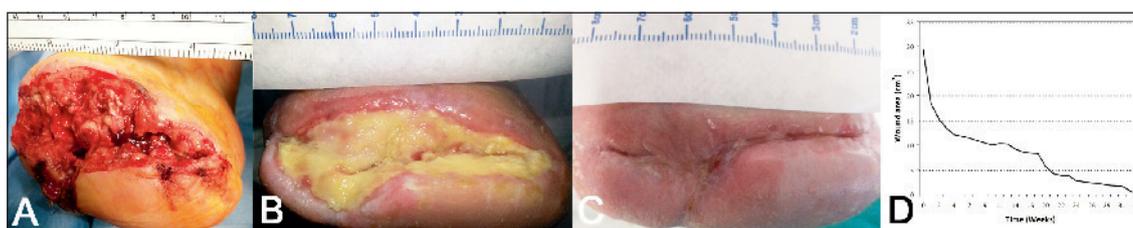


Fig. 5 Wound healing of patient 5. A–C show appearance of the wound (A: prior to treatment, B: under treatment, C: healed wound). Kinetic of wound healing is shown in D.

tration of opioids could be discontinued after one week of Omega3 wound matrix treatment.

Discussion

In the course of amputations performed in the forefoot or lower limb for diabetic foot or distal gangrene, situations may arise where the surgeon is confronted with complicated wounds with exposed bony segments. This may occur as a consequence after arterial perfusion was restored successfully by a revascularization procedure and nonviable tissue was debrided (minor amputation) but soft tissue coverage of the forefoot is insufficient to achieve primary closure. Here, treatment options include a proximalization of amputation level that in most cases will convert a minor into a major amputation with limb loss. However, this will completely counteract and nullify the previous efforts being made by a vascular reconstructive procedure, especially in cases where a pedal bypass has been placed. Therefore, different option for soft-tissue conditioning and wound coverage have been established as mentioned before with their individual unique advantages but also drawbacks.

With regards to the wound matrix used in this study, we were able to achieve wound closure in five cases of complicated wounds with exposed bony segments. The kinetics of soft-tissue regeneration however, certainly needs some form of patience with a mean time to closure of 6 months. But it has to be stressed, that the treatment itself was endowed with high level of acceptance by the patient as well as the physician because of the handling characteristics of the patch with outpatient office visit only once a week. And as pointed out, the wound area could be decreased by 50% within the first third of the treatment in all cases thereby markedly reducing the efforts for wound debridement as well as size and application time of the dressing. The kinetics of wound closure that we found (► Fig. 6) closely resembles the curve of wound area of a study published by Zimny (10) where wounds of neuropathic diabetic foot ulcers were analyzed.

Table 3 Quantity of Omega3 matrix patches ($N_{\text{total}}=96$)

Patient No.	Patches (wound I)	Patches (wound II)
1	6	20
2	18	
3	20	
4	3	7
5	22	

Interestingly, this study also evaluated the course of wound area of ischemic diabetic foot ulcers and there, a strikingly different pattern with a linear and prolonged course was noted. This clearly highlights the necessity of optimization of arterial perfusion in diabetic wounds to achieve healing. In our institution, negative pressure wound therapy represents a mainstay for soft-tissue conditioning, however, it only can be performed under inpatient set-

tings. Therefore, the use of the Omega3 wound matrix enabled us to convert the treatment to an outpatient setting. Another important advantage of the marine matrix compared to vacuum therapy is the avoidance of skin mazeration and sealing problems especially in cases of long-lasting treatment. Those initial results are corroborated by another study where the omega-3 wound patch was used in a series of 81 volunteers with forearm wounds. Here, the fish skin product was noninferior at the primary end point of healing at 28 days and the wounds treated with fish skin acellular matrix healed significantly faster than the control group (intestinal submucosa) (11).

Interestingly, we also observed a potential beneficial side-effect of the Omega3 wound matrix that is associated with reduction of analgetics during the course of the treatment. Of note, this was not one of the primary endpoints of this feasibility study and therefore has not been systemati-

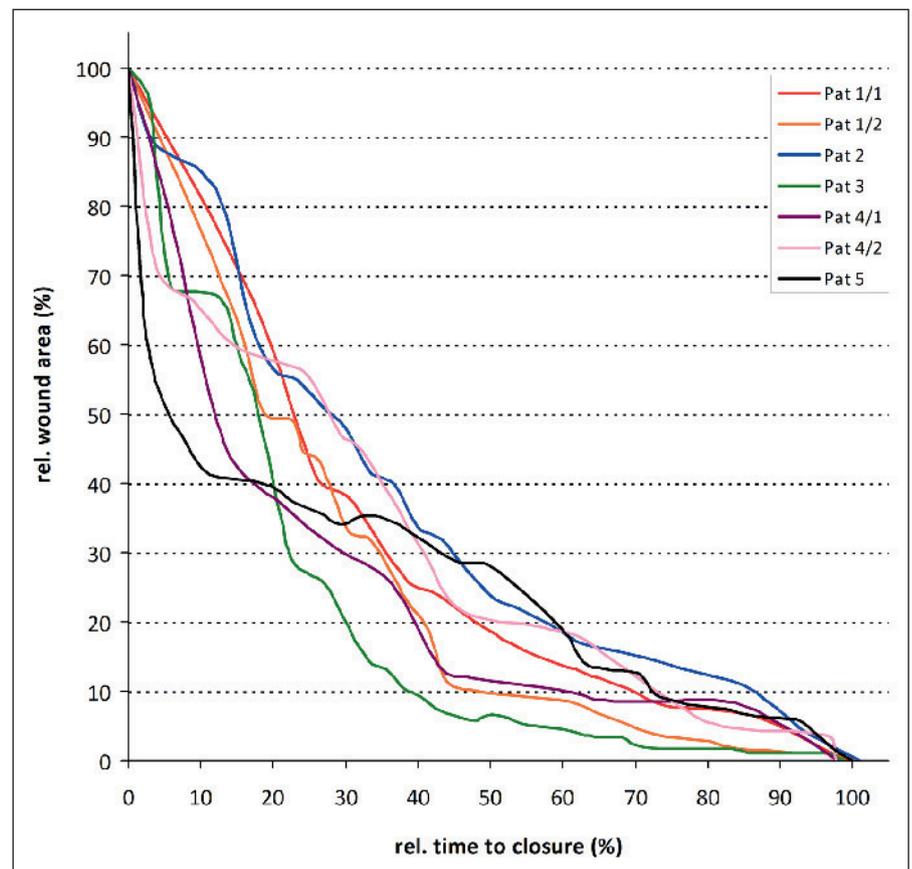


Fig. 6 All seven individual curves for kinetics of wound healing were normalized to 100% with regards to wound area and time to closure and shown in one diagram.

Conclusion

In our experience the Omega3 wound matrix represents a viable treatment option in complicated wounds in the lower limb of diabetic patients to circumvent an otherwise necessary proximalization of amputation level. It definitely is a specialized treatment option for complex cases with additional potential benefits in terms of outpatient treatment and reduction of analgetic medication due to antinociceptive properties of omega-3-fatty acids.

cally quantified and analyzed statistically. However, there is evidence in the literature, that omega-3 fatty acids may indeed influence pain sensation by an antinociceptive property (12, 13). This interesting feature should therefore be in the focus of further investigations.

There are notably some limitations of this study and one is the small sample size of the study group. However, this study was designed as a pilot study to evaluate safety and efficacy of the method. As a perspective, further studies comparing the Omega3 wound matrix with appropriate control groups of standard therapies for soft-tissue conditioning/coverage like negative pressure therapy, biosurgery and other acellular dermal matrices are warranted.

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Conflict of interest

The authors declare no conflict of interest.

Ethical guidelines

All national guidelines were met as well as the current declaration of Helsinki. Informed consent by the patients is signed.

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