

Wound dehiscence on a diabetic patient with haemophilia and high risk of further amputation successfully healed with omega-3 rich fish skin: a case report

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Article points

1. Acellular fish skin has haemostatic properties that are useful in patients with haemophilia or are on anticoagulant therapy with increased risks of wound haematomas or dehiscence.
2. Haemostatic effect is achieved through activation of the coagulation pathway by providing a non-traumatic hemostasis of the wound bed compared to commonly used caustic agents or diathermy.
3. The acellular fish skin graft has important bacterial barrier properties that were helpful in this case.

Key words

- Acellular Fish Skin Graft (Kerecis™ Omega3 Wound)
- Amputation
- Bacterial barrier
- Dehiscence
- Fish skin
- Grafts
- Haemostasis
- Omega-3
- Wounds in haemophiliacs

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Haemophiliacs have abnormal healing where the combination of bleeding disorder and peripheral neuropathy often result in repeated traumatic bleedings that are hard to control. This is a case report on a patient with haemophilia and chronic infected ulcerations of the left foot for which he had undergone multiple procedures over the past 2 years. This is the first described case of a patient suffering from haemophilia and a dehisced transmetatarsal amputation turned into a chronic wound treated with acellular fish skin. The wound healed after 14 weeks and six applications of the fish skin graft. The wound remained healed after 1 year and 10 months. This case illustrates the effectiveness of the fish skin to achieve haemostasis, rapidly incorporate and aid in wound closure in a high-risk patient with diabetes and haemophilia.

Bleeding disorders, both hereditary and as a result of anticoagulant therapy, can influence treatment options and outcomes of wound healing through multiple pathways. In the worst cases, they will inhibit the healing progression of the wound directly with excessive bleeding leading to haematoma formation and wound dehiscence. Furthermore, in wounds that have achieved haemostasis, the knowledge of underlying coagulopathy may lead to insufficient debridement and cleanup of the wound to limit risk of bleeding.

Although haemophilia is relatively uncommon among people with diabetes, projected at less than 0.01%, the problem it presents applies to patients on oral anticoagulants as well, and has been documented in a Finnish Study to be 1.64% of the general population, a large majority take those medications due to cardiovascular indications (Virjo et al, 2010).

Patients with bleeding disorders combined with those taking platelet inhibitors or other anticoagulant medication account for a significant proportion of the general patient population and current treatment options can lead to poor

outcomes or time-consuming methods for achieving haemostasis. Haemophiliacs have abnormal healing (Hoffman et al, 2006) where the combination of bleeding disorder and peripheral neuropathy often result in repeated traumatic bleedings that are hard to control.

The author reports a case where a patient is treated with an acellular fish skin graft (Kerecis™ Omega3 Wound, Kerecis) a type of cellular and/or tissue-based product (CTP) (Magnusson et al, 2015). A double-blind randomised controlled clinical trial on 162 acute punch wounds showed that fish skin grafts promoted significantly faster healing compared to a mammalian-derived product (Baldursson et al, 2015). Clinical and scientific studies have shown that fish skin promotes faster healing (Yang et al, 2016), chronic wound healing (Yang et al, 2016; Trinh et al, 2016; Clasen et al, 2017; Dorweiler et al, 2017) and pain reduction (Trinh et al, 2016; Clasen et al, 2017; Cyrek et al, 2017; Dorweiler et al, 2017) where the omega-3 fatty acids in combination with the skin-for-skin microstructure of the fish skin graft play a fundamental role.

The fish skin is minimally processed compared to CTPs from mammalian sources since there is no disease transmission risk from Atlantic cod to humans (Baldursson et al, 2015). This gentle processing method leaves the three-dimensional structure of the skin intact and its natural lipid content, including the omega-3 fatty acids.

CTPs derived from mammals, including human amniotic membrane CTPs, require heavy processing due to disease transmission risk. Such harsh processing methods, including viral inactivation, remove most of the tissue's natural components, leaving behind only a matrix of the most insoluble collagens (Crapo et al, 2011).

The three-dimensional structure of the acellular fish skin graft is highly porous offering a favourable environment for cellular ingrowth and a barrier to bacterial invasion of *Staphylococcus aureus* (Magnusson et al, 2017). This porosity and natural structure offers a very large surface area that is exposed to the blood cells and platelets in a bleeding wound and potentially facilitating a rapid haemostatic response.

Human skin and fish skin are homologous, sharing structural and functional anatomy of the epidermis, dermis and subcutis (Rakers et al, 2010). Acellular fish skin grafts are, however, naturally more rich in omega-3 polyunsaturated fatty acids (PUFAs). Omega-3 PUFAs are precursors of the pro-resolving lipid mediators that have a role in host defense, remodeling of tissue and in the mechanism of pain responses (Serhan, 2014; Trinh et al, 2016).

The patented Kerecis Omega3 Wound is regulatory approved with commercial use in the US, Europe and Asia, under the brand Kerecis™ Omega 3 Wound.

This case report represents a unique case of a dehiscence in a person with diabetes with haemophilia in which the acellular fish skin graft was used to expedite the healing of a surgical wound.

Initial presentation

A 56-year-old male with moderate factor VIII deficiency haemophilia requiring on demand management with self-administered factor VIII replacement (Helixate FS®) presented with an infected forefoot ulcer with cellulitis and osteomyelitis. Other medical comorbidities were

a history of diabetes, a fused right knee joint and hepatitis C. Approximately 1 month prior to presentation, he had an injury to his left foot, which became infected and progressed to osteomyelitis. He was admitted to a regional (out-of-state) hospital and was started on intravenous antibiotics. He had progressive soft tissue and bone infection and was transferred to the author's hospital. It was felt he would need surgical intervention and the podiatry service was consulted.

Patient history

The inciting event occurred when the patient stepped on a nail while working on his father's farm 2 years prior. His health began to decline and, eventually, he had to leave his healthcare career on medical disability, after having several surgeries for gangrene. The wounds would heal and reopen over the next several years.

One month prior to admission, the patient had presented to a regional hospital due to worsening pain, swelling and redness to his left foot. Prior to this presentation, the patient had a 3-day history of fevers, chills, nausea and vomiting. This was, therefore, a further episode of recurrent infected ulcerations of the left foot and for which he had undergone multiple procedures over the past 2 years. The patient was then transferred to the author's hospital with a fluid collection on the dorsum of the left first metatarsophalangeal joint and active bleeding. An ulceration measuring 4 x 3.5 x 0.3 cm was noted on the first metatarsal head that probed to bone with streaking cellulitis and increased temperature in the left lower limb. A second ulceration was noted under the second metatarsal head that measured 0.3 x 0.2 x 0.5 cm and also probed to bone. There was fluctuance on the lateral and dorsal aspect of the foot with mild erythema extending up his left leg.

When the patient was admitted from the regional hospital, blood cultures had shown methicillin sensitive *Staphylococcus aureus*. Intravenous cefazolin (Kefzol) was started. Subsequent wound cultures grew *Streptococcus viridans* and methicillin-sensitive *Staphylococcus aureus*. On examination, there were palpable pulses in the dorsalis pedis and posterior tibial arteries with normal lower-extremity arterial dopplers.

Vital signs on admission demonstrated a temperature of 98.2F, heart rate of 65, respiratory rate of 18 and blood pressure measured 154/72.

Page points

1. The three-dimensional structure of the acellular fish skin graft is highly porous, offering a favourable environment for cellular ingrowth and a barrier to bacterial invasion
2. This case report represents a unique case of a dehiscence in a person with diabetes with haemophilia in which the acellular fish skin graft was used to expedite the healing of a surgical wound
3. The wound was subjected to recurrent infected ulcerations of the left foot, for which the patient had undergone multiple procedures over the past 2 years.

Biochemical results revealed a glucose of 266 and White blood cell count of 7.4, ESR was 127, haemoglobin was 7.7, haematocrit was 24.1 and HgA_{1c} was 6.8.

His medications included: Helixate FS 40 units/kg daily when needed, Celecoxib 200mg twice daily, Gabapentin 300mg three times daily, Insulin V-Go 40 units every 24 hours plus 10 units with meals, Janumet 50/500mg orally twice daily, Lisinopril 5 mg once daily, Loratadine 10 mg once daily, Meclizine 25 mg three times per day if needed, Methocarbamol 500mg three times daily if needed for muscle spasms, NovoLog depending on blood glucose, Tramadol 50mg up to six times per day if needed for pain, Tricor 45 mg daily, Vicodin 5/300 up to six times per day if needed for pain, Zantac 150m daily, and Zofran 4mg up to three times daily for nausea.

Foot X-rays showed extensive degenerative changes in multiple joints of the foot, but no acute signs of osteomyelitis, but also showed multiple areas of subcutaneous air. Intense soft tissue oedema was present. His medical history was significant for MSSA bacteremia, factor VIII haemophilia, type 2 diabetes mellitus, gastroesophageal reflux disease, obstructive sleep apnea and hepatitis C. He denied tobacco or alcohol use and had no known drug allergies. Previous surgical history included multiples debridements of the left foot, a rotator cuff injury, right knee total fusion and C-spine fusion.

The patient was taken to the operating room 5 days after admission when his medical condition had been optimised. Preoperatively, Helixate FS was administered on recommendation of his hematologist due to severely low levels. Following the administration of Helixate FS, his factor VIII levels returned to a normal level, and subsequently he underwent a transmetatarsal amputation with excision of the plantar ulcers and the incision was partially closed in a T fashion. At the initial operation, a fetal bovine tissue was used to reinforce the incision and soft tissue defect that was unable to be completely closed.

His intra-operative cultures had positive growth of methicillin sensitive *S. aureus*. His pathology came back with acute and chronic inflammation of the distal metatarsal heads consistent with osteomyelitis. He did well postoperatively and negative pressure wound therapy was placed over the

incision and initial tissue graft. He was discharged home on his fourth postoperative day on IV Kefzol. It should be noted that at this point there was no active bleeding, the incision was intact and the initial graft was in place and fixated with skin staples.

Three weeks postoperatively, the patient presented to the office with active bleeding and a dehiscence of his incision. The centre portion of the incision line was open and measured 10 x 8 x 3mm. At 5 weeks postoperatively, he had ongoing bleeding. He ultimately received more factor VIII to control that and once the bleeding was controlled, he presented for the initial Kerecis Omega3 Wound application. On assessment, the dehisced ulcer now measured 5.0 x 3.0 x 1.0cm. No acute sign of infection was noted. The initial Kerecis Omega3 Wound was placed 5 weeks after the initial operation.

He continued to have follow up every 1–3 weeks for further Kerecis Omega3 Wound applications. A total of six pieces were used to completely close the wound. Significant improvement in control of the bleeding was noted, as well as a decrease in hypergranulation tissue. The wound size continually decreased at each visit until it was ultimately healed by week 14.

Methods

Wound area was measured in triplicate at each time point with the software ImageJ (Wayne Rasband, National Institute of Health). The ImageJ freehand tool was used to mark the borders of the wound and then the wound pixel area was calculated with the ImageJ area measure tool. The pixel area was then converted to cm² by using scale bar on the wound image (Schindelin et al, 2015).

Results

Week 0

The initial application of Kerecis Omega3 Wound (Figure 1a–1b). The ulcer measured 5.0 x 3.0 x 1.0cm and was probing close to the distal cut ends of the metatarsal bones.

Week 1

Due to risk of bleeding the initial dressing was left in place. The patient was still receiving Helixate® FS Antihemophilic Factor (recombinant) for haemophilia.



Figures 1a (above left) and Figure 1b (above second left). Initial visit – debridement and first application of Kerecis Omega3 Wound.

Figure 2. Wound at week 3.

Figure 3. Wound at week 5.



Figure 4. Wound at week 7.

Figure 5. Wound at week 18.

Figure 6. Wound at week 20.

Figure 7. Wound at week 32.

Week 3

Ulcer at second application (Figure 2). The ulcer measured 4.0 x 2.5 x 1.0 cm

Week 5

The ulcer at third application (Figure 3) measured 4.0 x 1.5 x 0.5 cm. There were no further bleeding episodes. The patient had positive blood cultures for klebsiella oxitoca, which was attributed to a peripherally inserted central catheter that was replaced. There was no clinical infection of the foot.

Week 7

There were no further bleeding episodes (Figure 4) at fourth application. The ulcer measured 3.0 x 1.0 x 0.3 cm.

Week 9

The ulcer at fifth application measured 2.8 x 0.8 x 0.2 cm.

Week 11

The ulcer at sixth (final) application measured 2.5 x 0.7 x 0.2 cm.

Week 14

The wound was healed.

Week 18

The wound remained healed (Figure 5).

Week 20

The wound remained healed (Figure 6).

Week 32

The wound remained healed (Figure 7). The patient was dispensed extra depth inlay shoes and custom foot orthoses with toe filler.

One year, 10 months

The patient's foot remained healed and was



Figure 8. Wound at 1 year and 10 months.

ambulating in extra-depth shoes and custom inserts (Figure 8).

Conclusion

The fish skin product was effectively used to treat a patient with haemophilia suffering from a chronic wound that was unresponsive to previous treatments.

This is the first case report of the use of this fish skin product where the hemostatic properties of the fish skin were used to address the difficulties in the care of the haemophilic patient with a dehisced post-amputation wound.

Fish skin graft treatment is a promising option for a wide variety of patients, where there is an increased risk of bleeding or hematoma formation. Current treatment options for such patients are limited.

Combined with treating the underlying shortage of clotting factors in a haemophilic patient, the acellular fish skin promotes quick hemostasis and promotes a healing response. The fish skin graft possesses bacterial barrier properties, that can allow for more rapid progression of the wound

through the healing cascade and wound healing in high-risk patients.

This case illustrates the effectiveness of the product to achieve haemostasis, rapidly incorporate and aid in wound closure in a high-risk patient with diabetes and haemophilia. ■

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