Fish Skin Grafts with Omega-3 for Treatment of Chronic Wounds: Exploring the Role of Omega-3 Fatty Acids in Wound Healing and A Review of Clinical Healing Outcomes

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ABSTRACT

Chronic, non-healing wounds, such as diabetic foot ulcers and venous leg ulcers, have a significant economic impact on healthcare and are associated with elevated patient morbidity. Among the toolset of treatment options available to clinicians, skin grafts from other species (xenografts) are often used to promote wound closure. While porcine xenografts have been the most used skin xenograft over the years, acellular fish skin grafts from Atlantic cod (Gadus morhua) have steadily gained traction in usage. Unlike other skin grafts, acellular fish skin grafts have a substantial lipid profile primarily composed of omega-3 fatty acids, notably eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Fish oil supplementation has been shown to result in faster rates of wound epithelialization, and omega 3 fatty acids provide barrier protection against bacteria and alter the inflammatory profile of wounds. EPA and DHA have been shown to have modulatory effects on the progression of wound healing. These characteristic omega-3 fatty acids and their metabolites alter skin physiology at a cellular and molecular level. Clinically, fish skin grafts continually demonstrate increased efficacy in treatment of wounds. When applied to non-responsive diabetic foot ulcers, acellular fish skin grafts have resulted in accelerated healing rates and significantly more fully healed wounds when compared to standard options. Here, we explore the role of omega-3 fatty acids in wound regeneration and repair, with particular focus on EPA and DHA. Then, we review clinical research outcomes to address notable clinical research studies and highlight the therapeutic potential of fish skin grafts with omega-3 as a treatment for chronic, non-healing wounds.

INTRODUCTION

Chronic wounds are those that fail to progress through a timely and orderly sequence of repair and lack the normal phases of healing.[1] The most common types are venous ulcers, arterial ulcers, diabetic ulcers, and pressure ulcers.[2] Chronic wounds result in significant reductions in quality of life for those affected and have a substantial impact on global healthcare costs as well.[3] In the United States, approximately 2% of the population is estimated to be affected by chronic, non-healing wounds.[4] Given the aging population and rising prevalence of obesity and diabetes, it is expected that chronic wound management will remain an active challenge that requires considerable investment.[5-7] Advancements in wound-related research and improved clinical modalities are essential for alleviating the burden of disease.

Among an array of treatment modalities, healthcare providers often use skin grafting techniques to advance healing of large, chronic wounds and to improve the quality of newly formed skin. There are three main types of skin grafting: autografts obtained from the patient's healthy, non-wounded skin separate from the wound site, allografts extracted from an organ donor, and xenografts harvested from different species.[8] Broadly termed "tissue-based products," these grafts may also be a composite system combining allografts and xenografts and/or epidermal and dermal components (e.g., human fibroblasts and keratinocytes seeded on a bovine matrix). Tissue-based products may also be classified as containing live cells (cellular) or devoid of cells (acellular). Porcine and bovine xenografts are the most common xenografts used today; however, acellular fish skin grafts from Atlantic cod (*Gadus morhua*) have shown promise as an emerging new treatment option.

The application of acellular fish skin xenografts results in improved wound healing due to its notable biomechanical properties. Skin derived from Atlantic cod has a similar macrostructure to human skin and provides an ideal microenvironment for cellular ingrowth, incorporation of fibroblasts, and remodeling of extracellular matrix proteins.[9,10] Fish skin is also biocompatible and has not shown any allergic reaction in clinical studies assessing chronic wounds.[11] Notably, the defining property attributed to the efficacy of acellular fish skin is a unique lipid profile potent in omega-3 fatty acids.[12] Omega-3 polyunsaturated fatty acids (ω-3 PUFA) are thought to modulate the inflammatory phase of healing, due to altered expression and signaling activity of proinflammatory cytokines at wound sites.[13,14] The ω-3 PUFA content of fish skin is specifically characterized by increased concentrations of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which both have been shown to exert anti-inflammatory and antimicrobial effects.[15] Furthermore, metabolites derived from ω-3 PUFA are hypothesized to mediate the effects of fish skin xenografts. Lipid mediators biosynthesized from DHA and EPA include resolvins, maresins, and protectins, which all have been shown in experimental models to affect wound regeneration.[16-18] Numerous experimental studies focused on these lipid mediators suggest that they may promote healing by adjusting the inflammatory profile of wounds.[19,20] There is increasing support for the use of omega-3 metabolites in clinical applications related to wound healing and further research exploring this area is essential.[21]

Clinically, acellular fish skin grafts have shown improved healing rates of chronic wounds and garnered attention as a potentially efficacious treatment option.[22,23] Several clinical studies demonstrated accelerated healing of diabetic foot ulcers after application of fish skin xenografts, and a currently active clinical trial (NCT04133493) aims to determine their effect on diabetic foot ulcers compared to standard of care.[24,25] Additionally, application of acellular fish skin is an effective treatment option for healing complicated, treatment-resistant wounds of various etiology, including wounds due to diabetic, arterial, and venous disease.[26] Future studies incorporating larger patient populations and chronic wounds of diverse etiologies are necessary to further advance our understanding and assess the efficacy of fish skin xenografts as a treatment modality.

The use of fish skin is an emerging and promising technology, yet the knowledge of clinicians may be limited. Therefore, in this article, we aim to improve this gap in knowledge. We first discuss acellular fish skin graft technology. We primarily explore the role of ω-3 PUFA in the physiology of wound regeneration and repair, with discussion of EPA, DHA, and other omega-3 derived metabolites. Next, we review clinical studies that have assessed fish skin grafts with omega-3 as treatment of chronic wounds and also review the associated clinical healing outcomes. We then conclude with closing remarks to provide future perspective on fish skin xenografts with omega-3 fatty acids as a useful clinical tool in wound care.

STRUCTURE AND COMPOSITION OF ACELLULAR FISH SKIN

Acellular fish skin xenografts are harvested from Atlantic cod (*Gadus morhua*). The Atlantic cod skin is then decellularized via osmotic manipulation and application of light detergent; therefore, bypassing the need for chemicals and stronger detergents that are characteristic of traditional xenografts processing.[27,28] Other commonly used xenografts require harsh chemical processing to reduce the risk of disease transfer, but no viral inactivation is necessary to process Atlantic cod skin.[29,30] This gentler processing allows acellular fish skin xenografts to retain more of its scaffold structure and to preserve molecular components that would be otherwise degraded.[28] The milder manufacturing method of Atlantic cod skin also provides a more cost-effective and environmentally friendly option when compared to traditional xenografts.[31] Additionally, the use of acellular fish skin xenografts has a low likelihood of inducing hypersensitivity when applied to participants.[11] Repeated biocompatibility testing has shown that acellular fish skin grafts are nontoxic and do not promote unwanted inflammatory responses.[32] Nevertheless, safety measures are in place; continual reports are mandated by the Food and Drug Administration (FDA) to confirm and ensure quality control of fish skin xenografts that are currently on the market.[33]

Acellular fish skin grafts have a structure and composition suited for skin grafting applications. The layers of Atlantic cod skin have a similar macrostructure to human skin, consisting of both epidermal and dermal layers. Prior to decellularization, the fish skin contains various cell types including mucous cells, club cells, and sensory cells.[34] In contrast to other decellularized membrane graft options, fish skin grafts are notably thicker with an average thickness of approximately 0.5mm.[35] Fish skin grafts have been shown to act as a bacterial barrier for up to 48–72 hours, which

has been attributed to this physical thickness as well as the molecular composition of the graft.[35] Similar to human skin, the xenograft matrix is primarily composed of type I collagen.[36] However, collagen found in Atlantic cod skin has an increased amount of proline which confers thermodynamic stability to the graft scaffolding; this results in robust quality and a longer shelf life for acellular fish skin grafts, which remain effective for several years after manufacturing.[35-37] On a microscopic level, decellularized Atlantic cod skin appears to be composed of threads that rotate perpendicular to each other with an appearance similar to that of a woven material.[32] Acellular fish skin grafts have a greater pore density and larger pore diameter, with an average of 16.7 pores per 100μm^2 and a width of 16.1μm, respectively.[38] This pore size allows for optimal attachment to graft scaffolding and permits migration of human skin fibroblasts, which have an average diameter of 10–15μm.[35,38] Interestingly, histological study demonstrates chronological remodeling of the graft scaffolding due to the infiltration of fibroblasts.[35] The highlighted structural characteristics of acellular fish skin are befitting of an effective graft tool since proper fibroblast proliferation is paramount to successful and effective wound healing. Along with collagen, the acellular matrix contains fibrin, proteoglycans, and glycosaminoglycans that provide therapeutic benefit and promote the healing of wounds.[39] However, the defining property of Atlantic cod skin is a high content of ω-3 PUFA. This unique composition separates fish skin grafts from other commonly used graft applications.[40] For example, the ω-3 PUFA percentage of mammalian graft lipid content is almost twentyfold less than that in acellular fish skin grafts.[35] In the succeeding section, we review the diverse physiological effects of ω-3 PUFA and derived metabolites within the context of wound regeneration and repair.

ROLE OF OMEGA-3 FATTY ACIDS IN WOUND HEALING

Structurally, ω-3 PUFA are characterized by a double bond three atoms away from the terminal methyl group and play an important role in human physiology.[41] The two types of ω-3 PUFA notably prevalent in fish skin grafts are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Fig. 1).[41] The known effects of EPA and DHA include inflammatory modulation, skin barrier and anti-microbial enhancement, adjustments in perceived pain, and more.[42] These lipids have been shown to mediate many aspects of skin physiology, however, the role of ω-3 PUFA within chronic, non-healing wounds is poorly understood. Therefore, further exploration of this class of compounds has been a growing area of interest in the medical literature. Current research efforts focused on ω-3 PUFA within chronic wounds have produced variable findings and further study is essential to elucidate their therapeutic potential.

Notably, ω-3 PUFA have been shown to affect the inflammatory stage of skin healing by altering the synthesis and activity of proinflammatory cytokines such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α.[43] These pro-inflammatory cytokines are secreted by a variety of immune cells and play essential roles in signaling transduction throughout the wound healing process.[42] They assist in controlling infection and mediate tissue repair by upregulating phagocytic activity, stimulate keratinocyte migration at the wound periphery, augment fibroblast infiltration, induce the structural breakdown and rearrangement of extracellular matrix proteins, and promote or diminish the release of additional cytokines via feedback mechanisms.[44,45] Conversely, pro-inflammatory cytokines during the onset of wound healing have been associated with decreased rates of healing.[44] In the medical literature, results from experimental studies assessing the inflammatory effects of ω-3 PUFA on wound healing are inconsistent. Wounds treated with ω-3 PUFA heal less effectively, partly due to resultant downstream inflammatory mediators. For instance, experimental research conducted by Burger et al. demonstrated decreased quality and rate of wound closure in mice receiving increased oral intake of EPA; further analysis identified increased M2 macrophage population counts and expression of markers specific for M2 macrophages, as well as elevated levels of interluekin-10 (IL-10), which serves as a key anti-inflammatory cytokine.[46] Interestingly, these findings contradict the results of previous studies using macrophage deficient mice models, which highlight M2 macrophages as effectors of improved healing outcomes.[47-49] Knowing that treating wounds with fish skin grafts does not slow healing, these results can be reconciled by recognizing that the macrophage response in wound healing is not dichotomous and likely depends heavily on the time at which each macrophage phenotype is active in the wound healing cascade. Additionally, increased concentrations of ω-3 PUFA in the diet of beagle dogs also diminish epithelialization and wound contracture associated with lower concentrations of prostaglandin E_2 (PGE_2) and reduced tissue perfusion.(50) In contrast, intravenous administration of lipid supplementation with notably elevated concentrations of

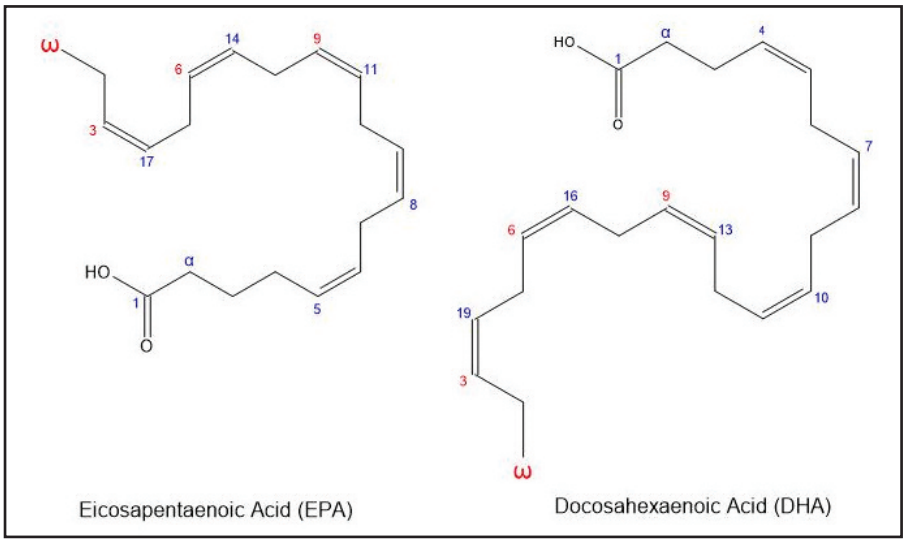

Figure 1. Two-dimensional molecular structures of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Blue notation initiates at the carboxyl groups and identifies the α (alpha) carbon of each compound. Red notation initiates at the terminal methyl groups and identifies the ω (omega) carbon of each compound. The double bond beginning at the third carbon from the terminal methyl group is the defining structural characteristic of ω-3 PUFA.[98–100]

ω-3 PU.FA increase the rate of wound healing in mice.[51] In this study, the IL-10 concentration was elevated in the treatment group and the wounds demonstrated increased rates of fibroblast distribution and collagen fiber organization on histology.[51] Furthermore, topical application of DHA accelerated wound healing associated with reduced expression of IL-1β and increased expression of IL-6 and transforming growth factor β (TGF- β).[52] However, an experimental study of mice that received increased oral intake of DHA demonstrated slower rates of healing, particularly during the late inflammatory phase of wound repair, and produced newly formed tissue of lower quality.[53] Interestingly, poor healing outcomes are more often demonstrated in efforts examining oral intake of ω-3 PUFA while improved healing measures tend to be associated with studies that utilize other modes of administration.

In addition to a multitude of inflammatory effects, ω-3 PUFA can modulate other functions closely tied to wound regeneration and repair. For instance, application of ω-3 PUFA has been associated with alterations to skin barrier function that aid wound repair. Intake of flaxseed oil, which increases the ratio of ω-3 PUFA to other fatty acids in blood plasma, decreases skin roughness and sensitivity and improves skin hydration.[54] Furthermore, experimental studies investigating the effects of DHA on keratinocytes demonstrated increased filaggrin expression and improved keratinocyte differentiation.[55,56] Filaggrin is integral to epidermal homeostasis and barrier function and serves as an identifier of wound healing, with levels elevated being found in skin that has undergone recent re-epithelization.[57] Notably, both experimental models and clinical trials have also found decreased trans epidermal water loss (TEWL) in skin receiving increased quantities of ω-3 PUFA.[58] TEWL measurements in wound healing are a direct measure of the progress of epidermal wound healing, which suggests that ω-3 PUFA-induced barrier changes may result in improved wound repair.[59] Additionally, an *ex-vivo* study assessing skin content after ω-3 PUFA supplementation demonstrated increased ceramide levels in the epidermis of skin explants exposed to EPA.[57] Experimental lipid studies have shown that ceramides, along with many other eicosanoids, regulate wound healing at the level of cellular signaling.[58,59] Interestingly, application of hydrocolloid dressings containing ceramide to erosions induced on mice demonstrated improved recovery and significantly reduced TEWL measurements versus controls.[60]

Moreover, ω-3 PUFA added protection against pathogenic microorganisms and reduced the activity of bacterial biofilms.[61] Bacterial biofilms consist of sticky multi-layered conglomerates of microbes adherent to each other via extracellular matrix mucopolysaccharides (Fig. 2). These encased bacteria attach to human tissue and are often difficult to treat with conventional therapies. Understanding and managing biofilm formation in wound care, particularly for advancing the treatment of chronic wounds, is a rapidly growing area of study.[62] Numerous *in-vitro* studies have noted anti-bacterial and anti-biofilm effects of both EPA and DHA, including activity against *Staphylococcus* pyogenes, both Methicillin-resistant *Staphylococcus aureus* (MRSA) and non-resistant *S. aureus*, *Vibrio vulnificus*, *Candida albicans,* and more.[63-66] There are several proposed mechanisms for the anti-microbial and anti-biofilm effects attributed to ω-3 PUFA. Through alterations in the lipid profile of cellular membranes, ω-3 PUFA modify membrane hydrophobicity, electric potential, and structural integrity resulting in the cell death of vulnerable microorganisms.[67,68] Cellular distortions of both *Fusobacterium nucleatum* and *Porphyromonas gingivalis* in the presence of DHA and EPA have been identified through electron microscopy, highlighting the ability of ω-3 PUFA to induce protective structural changes.[69] Lastly, ω-3 PUFA modulate antioxidant activity has been studied extensively in diseases like atherosclerosis and neurodegenerative disorders.[70] Antioxidant compounds have been hypothesized to mediate anti-microbial effects through disruptions in electron donor synchrony and suppression of growth and division.[71] Specifically, DHA and EPA suppress the generation of reactive oxygen species and substantially down-regulate the expression of oxidative stress-related inflammatory mediators.[72] Extension of these mechanisms to skin physiology suggest that ω-3 PUFA may serve as a potential target for improved wound therapies, particularly for the care of infected and chronic wounds.

In human physiology, the metabolism of ω-3 PUFA can produce an array of enzymatic derivatives, including many that belong to a growing class of cell signaling molecules known as specialized pro-resolving mediators (SPM). SPM are formed as polyunsaturated fatty acids and are processed by lipoxygenase, cyclooxygenase, and cytochrome P450 enzymes.[73] Elucidating the potential of SPM has been a rapidly growing area of

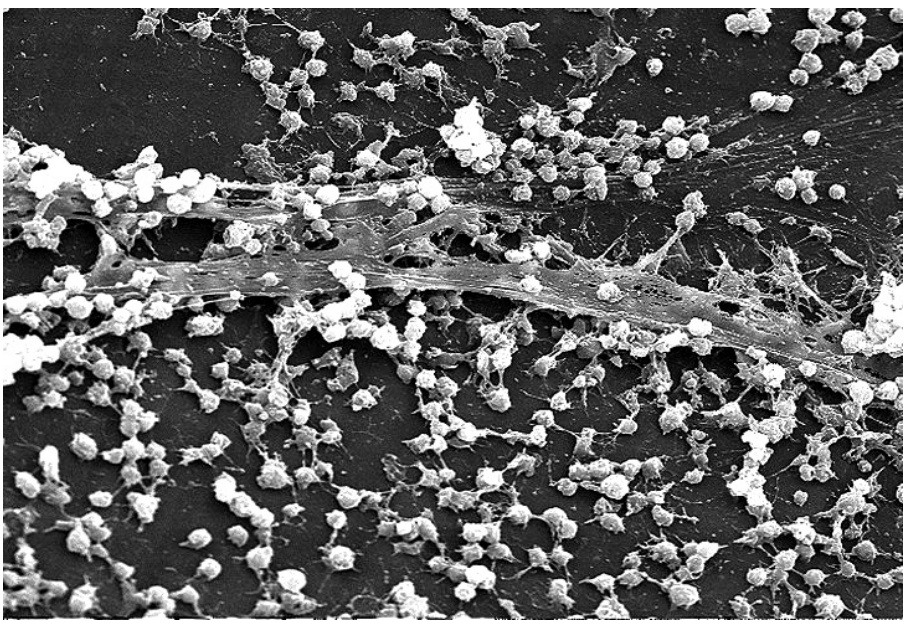

Figure 2. A scanning electron microscope (SEM) image depicting multiple conglomerates of Staphylococcus aureus bacteria which constitute a biofilm on the surface of an in-dwelling catheter.[101] Biofilms are characterized by multi-layered, interbacterial adhesions primarily comprised of extracellular matrix mucopolysaccharides. Developing improved treatments for biofilm growth is a growing area of research crucial to improved wound care, particularly for management of chronic wounds.

research interest in the study of inflammation and disease.[74,75] Both experimental and clinical research efforts have demonstrated the efficacy of SPM to resolve inflammation and serve as pharmacological targets.[76,77] Specifically, the most notable and well-studied SPM derived from EPA and DHA include resolvins, protectins, and maresins.[78,79] Insight into the physiological role and effects of these compounds has extended to wound regeneration and repair. Notably, DHA- and EPA-derived resolvins, protectins, and maresins have been identified in skin wounds from both mice and pigs.[80,81] Topical application of resolvins to mice has resulted in significant enhancements in rate of re-epithelialization, and the cellular mechanisms involved in resolvin mediated enhancements of keratinocyte migration are beginning to be elucidated.[80] Additionally, investigation of models of wounded intestinal mucosa has highlighted resolvins as promoters of accelerated wound repair due to downstream signaling effects that increase cell migration and proliferation.[82] Maresins also effect wound healing. In mice models of diabetic wounds, specific maresins have been shown to restore the inflammatory action of previously impaired macrophages and thus consequently suppress chronic inflammation of diabetic wounds.[83] Furthermore, protectins have been shown to improve inflammation and were identified in macrophages, with a significantly higher amount of M2 macrophages.[84] In diabetic wound models, decreased production of protectins has also been associated with impaired healing due to attenuation of pro-healing M2 macrophages and a diminished response to inflammation and oxidative stress.[84] These results suggest that both maresins and protectins have the potential to advance healing by converting the inflammatory profile of a chronic wound to an acute phase amenable to resolution. Novel clinical research focused on furthering understanding of SPM and inflammation in the setting of wound healing is also underway. A currently active clinical trial (NCT04308889) aims to discern the SPM profile of acute tissue inflammation by assessing fluid from exudative blisters induced by cantharidin (a terpenoid toxin produced by various beetle species); additionally, the same trial utilizes a crossover study design in which participants are randomized to an initial treatment of oral ω-3 PUFA supplementation or non-supplementation, to determine the influence of ω-3 PUFA on the production of SPM in acute inflammation.[85] All in all, SPM show promise as potential molecular targets for the development of improved therapies in wound healing, and continued experimental research—along with increased clinical trials—will help elucidate SPM as a future remedy for chronic, treatment-resistive wounds.

The roles of ω-3 PUFA in wound healing are diverse and numerous. DHA, EPA, and ω-3 PUFA metabolites may have the potential to serve as a therapeutic target for improved therapies in wound care. They induce a wide range of immunomodulatory effects, transform the structural dynamics of skin, and strengthen defenses against microbial pathogens. These findings shine a spotlight on ω-3 PUFA and may generate future involvement in wound care therapies. However, it is important to distinguish between acute and chronic wounds when interpreting research findings. The physiological and inflammatory profile of chronic, non-healing wounds differs significantly from that of acute wounds, which properly undergo hemostasis, inflammation, proliferation, and maturation.[86] Clinically, chronic wounds often require diverse treatment plans and necessitate a systematic approach to care. Despite a multitude of advanced therapies available to clinicians, there is a demand for more tools backed by evidence of efficacy and effectiveness.[87] Clinical studies and trials are thus paramount to discern the therapeutic utility of new treatments and fill this knowledge gap. Exploring clinical studies that evaluate acellular fish skin grafts with ω-3 PUFA provides the medical community an opportunity to better gauge the ability of this treatment to effectively treat chronic wounds.

ASSESSING CLINICAL HEALING OUTCOMES OF FISH SKIN GRAFTS WITH OMEGA-3 FATTY ACIDS

In view of these considerations, we discuss published and peer-reviewed clinical research studies that investigate acellular fish skin grafts with ω-3 PUFA as a treatment option for chronic wounds. We focus our attention to reported healing outcomes to further appraise the clinical efficacy of this graft technology and highlight noteworthy clinical studies (Table I). Most previous and ongoing clinical studies evaluating acellular fish skin grafts have concentrated on diabetic foot ulcers or other wounds of diabetic etiology. Accordingly, we first center our discussion on the healing outcomes of these clinical research efforts and also provide discussion of currently active clinical trials. Next, we move forward to studies examining fish skin grafts for the treatment of venous leg ulcers or chronic wounds in the setting mixed etiology. Lastly, we call attention to a unique randomized controlled trial that investigated fish skin grafts with ω-3 PUFA in comparison to a widely used skin substitute.

The majority of clinical research assessing fish skin grafts with ω-3 PUFA as a treatment of chronic wounds has investigated healing outcomes in participants with diabetic foot ulcers. Published literature in this field includes clinical studies of varied design. For instance, a noteworthy case report published in 2018 details the successful use of an acellular Atlantic cod skin graft with ω-3 PUFA to treat a patient with diabetes and hemophilia experiencing a chronic wound unresponsive to prior treatments.[88] The patient initially sustained an injury to his left foot that resulted in infectious complications, warranting multiple treatments with antibiotics and surgical interventions over the course of two years. After metatarsal amputation and excision of multiple plantar ulcers, negative pressure wound therapy was placed postoperatively alongside tissue grafting, but the incision proceeded to dehisce three weeks later, leading clinicians to apply a fish skin graft with ω-3 PUFA. The wound healed 14 weeks after first graft application at an initial size of 5.0 x 3.0 x 1.0cm, and remained healed at two-year follow up without any instance of wound dehiscence. Interestingly, this case report exemplifies efficacious use of a fish skin graft with ω-3 PUFA to heal a treatment-resistive, chronic wound and also demonstrates consistent healing quality, attributed to the lack of post-healing dehiscence or complication. Moreover, there are also retrospective and prospective clinical studies which provide expanded insight into this treatment modality for use in diabetic foot ulcers and wounds of diabetic etiology. One example is a retrospective study performed by Michael et al. that measured wound area reduction in a 16-week time period in patients with full-thickness

Table I
Notable clinical studies investigating the healing outcomes of fish skin grafts with omega 3 fatty acids

Clinical Study	Wound Etiology	Study Design	Healing Outcomes
Winters[88]	Post-infectious chronic wound in patient with diabetes and hemophilia	Case report	Complete healing 14 weeks post-graft application; no dehiscence or complication for 2 years
Michael et al.[89]	Full thickness DFU	Retrospective study	Mean reduction of wound surface area by 87.57% and 35 wounds fully healed 16 weeks post-graft application
Woodrow et al.[24]	Postoperative DFU	Prospective study	Median reduction of wound surface area by 84.9% six weeks post-graft application on wounds with less than 3-month duration (n=6). Median reduction of wound surface area by 42% six weeks post-graft application on wounds with greater than 3-month duration (n=2)
Lullove et al.[91]	Chronic, treatment-resistive, superficial DFU	Randomized controlled trial	Group treated with fish skin grafts demonstrated complete healing in 16 of 24 (67%) ulcerations opposed to the control arm, which comprised of complete healing in 8 of 25 (32%) ulcerations (n=49, p<0.047) (101).
Omega3 Wound Fish Skin Graft in the Treatment of DFUs (NCT04133493)[93]	DFU	Randomized controlled trial	Pending (Currently Active)
Kerecis Omega3 Wound Plus SOC vs. SOC Alone in Treating Severe Diabetic Foot Ulcers and Forefoot Amputations (Odinn) (NCT04257370)[6]	DFU, chronic and/or post-surgical wounds in patients with diabetes	Randomized controlled trial	Pending (Currently Active)
Dorweiler et al.[94]	Chronic wounds secondary to chronic venous insufficiency, diabetic foot disease, peripheral artery occlusive disease, or metatarsal amputation	Multicenter case series report	25 wounds showed effective healing post-graft application and time to heal varied between 9 and 41 weeks
Yang et al.[95]	Chronic wounds secondary to diabetic, venous, and/or arterial disease	Prospective clinical study	After 5 weekly applications, they reported a 40% decrease in wound surface area (p<0.05) and a 48% decrease in wound depth (p<0.05) across 18 ulcerations (n=18)
Kirsner at al.[97]	Acute full-thickness wounds induced on healthy volunteers (post-debridement chronic wound model)	Randomized controlled trial	Wounds treated with fish skin healed significantly faster (hazard ratio 2.37; 95% confidence interval: (1.75–3.22; p=0.0014) compared with wounds treated with amnion skin substitute

diabetic foot ulcers treated with fish skin grafts with ω-3 PUFA; in 51 patients with a total of 58 wounds, there was a mean reduction of wound surface area of 87.57% and 35 wounds fully healed.[89] Furthermore, a prospective study completed by Woodrow et al. evaluated healing outcomes six weeks after application of fish skin with ω-3 PUFA to eight patients with postoperative diabetic foot wounds, and found a median percentage wound area reduction of over 84.9% in wounds with less than three months of duration opposed to less than 42% in wounds with a duration greater than three months.[24] These two aforementioned studies both report measures of central tendency with significant decreases in wound surface area at follow up and thus highlight fish skin graft technology as a seemingly efficacious treatments for chronic diabetic wounds. However, both of these observational clinical research studies lack control groups for comparative analysis, which is essential to investigate the efficacy of fish skin grafts versus standard-of-care options. Classically, randomized controlled trials are considered the most robust form of scientific evidence used to influence clinical decision making since randomization diminishes bias and provides a basis to explore causality.[90] Nonetheless, there is a deficit of published medical literature from randomized control trials that have evaluated fish skin grafts with ω-3 PUFA as an improved treatment option for diabetic wounds.

In July 2021, Lullove et al. published their findings from a multicenter, randomized controlled clinical trial evaluating the effect of fish skin with ω-3 PUFA on the healing of treatment-resistive, chronic diabetic foot ulcers.[91] They compared the percentage of wounds closed in patients randomized to receive solely standard of care versus patients randomized

to receive fish skin graft application in addition to standard of care. At 12 weeks follow up, a statistically significant difference in healing between the two groups was found; the group randomized to receive fish skin grafts demonstrated complete healing in 16 of 24 (67%) ulcerations opposed to the control arm, which comprised of complete healing in eight of 25 (32%) ulcerations ($n=49$, $p<0.047$).[91] This trial presents a great opportunity for clinicians to deduce if acellular fish skin grafts with ω-3 PUFA are an efficacious option to promote improved wound closure, particularly for patients with chronic diabetic wounds that fail to respond to standard-of-care options like offloading, debridement, and adequate dressings. Excitingly, two randomized clinical trials investigating fish skin grafts with ω-3 PUFA as a treatment for diabetic foot ulcers and wounds of diabetic etiology are currently underway. In the United States, an active trial is comparing healing outcomes after 12 weeks of treatment of participants with partial thickness diabetic foot ulcers receiving acellular Atlantic cod skin grafts with ω-3 PUFA versus those of participants with similar wounds receiving standard of care (NCT04133493).[92] An additional multicenter randomized control trial across several European countries is investigating healing outcomes of acellular Atlantic cod skin grafts with ω-3 PUFA in diabetic patients with chronic lower extremity wounds, specifically wounds that penetrate to either tendon or capsule (Grade 2) or to bone or into joint (Grade 3), and wounds of diabetic patients post-ankle amputation (NCT04257370).[93] The trial aims to recruit 330 participants to assess the percentage of patients with complete wound epithelialization 16 weeks post-graft application versus standard of care. Completion of both trials will add greatly to the limited published data available, and greater sample sizes improve statistical power. If both trials reach their designated recruitment goals, the healing outcomes collected and analyzed as a result of randomized controlled trials in this wound context will increase in number substantially and also diversify to include a wider range of measures such as wound epithelialization. Thus, in light of this, the aforementioned clinical trials have considerable potential to enrich medical knowledge and provide future guidance for investigators and clinicians interested in using fish skin grafts with ω-3 PUFA to treat chronic wounds in diabetic patients.

In addition to clinical research focused primarily on diabetic wounds, there are various clinical studies in the medical literature that assess fish skin grafts with ω-3 PUFA as a potentially efficacious treatment for chronic wounds of other etiology. Dorweiler et al. described healing outcomes of fish skin grafts on complicated wounds across three vascular surgery centers located in Germany.[94] Inclusion criteria for consideration as a complicated wound included ulcerations secondary to chronic venous insufficiency, diabetic foot disease, peripheral artery occlusive disease, or metatarsal amputation. Altogether, 25 wounds were documented as successfully treated with fish skin grafts containing ω-3 PUFA and time to heal varied between nine and 41 weeks. Uniquely, this study incorporates a wide range of wound etiologies and practice from separate medical centers, which grants access to a diverse set of results and data. Yang et al. prospectively evaluated 18 hard-to-heal ulcers for the changes in wound area after treatment with fish skin graft containing ω-3 PUFA.[95] Hard-to-heal ulcers consisted of chronic wounds due to diabetic, venous, and/or arterial disease. After five weekly applications, they reported a 40% decrease in wound surface area ($p<0.05$) and a 48% decrease in wound depth ($p<0.05$). These results once again highlight fish skin grafts as a solution for these types of wounds. Nevertheless, this study lacked a control group and the associated healing outcomes should, therefore, not be extrapolated to compare fish skin technology with other treatments. Currently, there are no published or active randomized controlled trials assessing fish skin grafts with ω-3 PUFA as a treatment for chronic wounds outside of diabetic etiology. The most relevant clinical research effort aligning to fill this knowledge gap is a currently active trial investigating the effect of oral EPA and DHA therapy on the healing of chronic venous leg ulcers (NCT03576989).[96]

Intriguingly, Kirsner et al. conducted a randomized clinical trial to compare healing outcomes of wounds treated with acellular fish skin grafts containing ω-3 PUFA to wounds treated with dehydrated amnion/chorion membrane allograft (dHACM), a commonly used skin substitute in wound care.[97] To investigate and assess outcomes in the setting of chronic wound care, they imitated a recently debrided chronic wound by inducing an acute full-thickness wound, 4mm in diameter, on healthy volunteers. Interestingly, they found that wounds receiving fish skin graft treatment healed significantly faster (hazard ratio 2.37; 95% confidence interval: [1.75–3.22; $p=0.0014$]) compared to wounds treated with dHACM. This clinical research study exhibits exemplary components that future research efforts could incorporate when establishing study structure and design. Firstly, comparing the efficacy of fish skin grafts with ω-3 PUFA to other commonly used graft options provides valuable information for wound care clinicians. Additionally, utilizing a double-blind, randomly controlled trial study design model mitigates bias and helps establish causality. Importantly, a distinction must be made between acute wounds which are likely to heal normally to chronic wounds which, by definition, will not heal without intervention. Therefore, it is difficult to apply the results of this study to the treatment of chronic ulcers. Ultimately, improved quality and quantity of clinical studies will strengthen the impact of medical literature on clinical decision making in wound care.

CONCLUSION

Accumulating clinical and basic science data consistently demonstrates a beneficial role for ω-3 PUFA and acellular fish graft technology in wound healing. The structure and composition of acellular fish skin grafts derived from Atlantic cod have unique properties that make it suitable as an efficacious and eco-friendly graft option for treatment of chronic wounds. However, there is a critical need for large randomized, controlled trials of common chronic wounds such as venous ulcers and diabetic foot ulcers to definitively establish the role of fish skin grafts containing ω-3 PUFA as a clinical treatment option. STI

AUTHORS' DISCLOSURES

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