Role of collagen in wound management

Collagen is structurally and functionally a key protein of the extracellular matrix which is also involved in scar formation during the healing of connective tissues. Many collagen dressings have been developed to enhance wound repair, particularly of non-infected, chronic, indolent skin ulcers. The use of collagen dressings is supported by relatively sparse and insufficient scientific data. This review identifies the supporting evidence for the use of the dressings which are available, often with widely different claimed advantages and modes of action, and considers future developments and assessment of collagen dressings.

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Collagen is the unique, triple helix protein molecule, which forms the major part of the extracellular dermal matrix (ECM), together with the glycosaminoglycans, proteoglycans, laminin, fibronectin, elastin and cellular components (Hopkinson, 1992a, b; Berry et al, 1998; Enoch and Leaper, 2008). Collagen is the most abundant protein in animal tissues and accounts for 70–80% of the dry weight of the dermis (Hopkinson, 1992a). Mainly produced by fibroblasts, at least 21 genetically distinct collagens have currently been identified, with six of these being present in the skin. Collagen type I comprises approximately 70% of collagen in the skin, with type III being 10%, and trace amounts of collagen type IV, V, VI and VII (Uitto et al, 1989; Hay, 1991).

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The principal function of collagen is to act as a scaffold in connective tissue, mostly in its type I, II and III forms. In early healing wounds, type III is laid down first, with the proportion of type I increasing as scar formation progresses and is remodelled. Collagen deposition and remodelling contribute to the increased tensile strength of the wound, which is approximately 20% of normal by three weeks after injury, gradually reaching a maximum of 70% of that of normal skin (Desmouliere et al, 1995). Although epithelial structures can heal by regeneration, connective tissues cannot and depend on the process of repair mostly by the formation of collagenous scar tissue (Berry et al, 1998), predominantly of type I, which serves to restore tissue continuity, strength and function. Collagen is a brittle substitute for unwounded tissue, and scar tissue rarely exceeds 70% of unwounded tissue strength.

In embryos, it has been shown that cutaneous wounds can heal without a scar (Rowlatt et al, 1979; Moulin et al, 2005; Redd et al, 2004), but this has yet to be translated into a tissue engineered alternative solution. In addition to being the main component of scar tissue, collagen has a key role in:

- The control of the inflammatory response to injury and subsequent repair with functions that influence cellular mitogenesis, differentiation and migration
- Protein synthesis in the extracellular matrix (ECM)
- Synthesis and release of inflammatory cytokines and growth factors
- Interactions between enzymes which remodel the ECM, including matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs), which are summarised in *Table 1*.

Collagen in chronic wound healing

In chronic wounds involving skin, defined as those which do not heal in optimal conditions within six weeks (Mustoe et al, 2006), the complex interactive processes described above are deranged. Conversely, there is not a lack of normal healing but often hyperactivity which is out of phase, non-progressive, and with a persistent, uncoordinated, mixed acute and chronic inflammatory response (Schultz and Mast, 1998; Trengrove et al, 1999; Hansen et al, 2003; Kim et al, 2003; Diegelmann and Evans, 2004), which has also been well summarised at molecular level (Agren and Werthen, 2007). The most common cause of this 'hard-to-heal' chronicity is infection, which can be hard to define and range from increasing microbial colonisation, which is inevitable in open wounds healing by secondary intention, through to increasing contamination and clinically overt infection. The concept of 'critical colonisation", or alternatively an excessive local bioburden, which acts as a prequel to infection, is widely accepted

but is not accurately measurable (White and Cutting, 2008). Nevertheless, control of colonisation and infection through local, topical (antiseptics) and systemic (antibiotics) antimicrobials is pivotal to preparation of the wound bed, before wound closure following contraction through formation of 'healthy' granulation tissue and epithelialisation. Other factors critical to the successful preparation of the wound bed include scrupulous debridement of non-viable tissue and foreign material, by all methodologies available (including sharp surgical debridement and topical negative pressure [TNP] therapy) (Wolcott et al, 2009). This can only be achieved in conjunction with optimal holistic care; again through local (such as attention to adequate arterial supply or pressure relief) and systemic (such as diabetic control) interventions. Once these criteria are met, with a prepared wound bed and control of any underlying pathological processes, successful healing can occur. It is at this stage that collagen or collagen-derived dressings may have a role in wound healing strategies.

Along with the critical collagen functions listed in *Table 1*, several other factors relating to poor wound healing, directly affect collagen metabolism. Included among the extrinsic factors is diabetes, in which hyperglycaemia reduces normal collagen production and induces non-enzymatic glycosylation of collagen and keratin, leading to formation of abnormal rigid collagen and adding to tissue breakdown (Black et al, 2003). Collagen over production can form abnormal scars, which impede wound healing (Gault, 1999). A chronic wound burden among the elderly has been documented (Wilkinson et al, 1993), and much of this age-related, delayed wound healing is caused by impaired collagen synthesis and increased degradation (Ashcroft et al, 2002). Smoking affects the synthesis rates of collagen, MMP and TIMP1 levels in the skin, leading to imbalances in collagen turnover (Knuutinen et al, 2002). Intrinsic factors include variations in oxygen tension which can alter fibroblast proliferation and collagen production, and also enhance the structural support required for capillary angiogenesis (Hunt and Pai, 1975), and an abnormal excessive local inflammatory response leading to abnormal, hypertrophic or keloid scarring (Wang et al, 2007).

Table 1
Influence of collagen in the inflammatory response to injury

- Cellular differentiation, angiogenesis and mitogenesis
- Protein synthesis and ECM deposition
- Cellular migration (keratinocytes and epithelialisation, fibroblasts, monocyte/macrophages, neutrophils)
- Induction of collagenases
- Wound contraction
- Platelet aggregation and induction clotting cascades
- Induction of growth factors and cytokines through degradation products
- Cell surface receptors (integrins) in cell-signalling and induction of other ECM molecules and proteins

References:
Doillon and Silver, 1986; Montesano et al, 1983; Albini and Adelman-Grill, 1985; Newman and Tucci, 1990; Petersen et al, 1990; Shaw et al, 1990; Klein et al, 1991; Schiro et al, 1991; Hynes, 1992; Madri and Marx, 1992; Scharfetter-Kochanek et al, 1992; Sudbeck et al, 1994; Krieg, 1995; Clark, 1996; Schultz and Mast, 1998; Pilcher et al, 1997, 1999; Feng et al, 1999; Davis et al, 2000; Steffensen et al, 2001; Armstrong and Jude, 2002; Ruszczak, 2003; Diegelmann and Evans, 2004; Mirastschijski et al, 2004; Schultz et al, 2005; Ulrich et al, 2005; Agren and Werthen, 2007; Cavallini, 2007; Clark et al, 2007; Hodde and Johnson, 2007; DiCosmo, 2009; Schultz and Wysocki, 2009

Collagen dressings in wound management

The use of collagen dressings may seem attractive in view of their functions to:

- Inhibit or deactivate MMPs
- Increase fibroblast production and permeation
- Aid in the uptake and bioavailability of fibronectin
- Help to preserve leukocytes, macrophages, fibroblasts, and epithelial cells
- Assist in the maintenance of the chemical and thermostatic microenvironment of the wound (Burton et al, 1978; Doillon et al, 1984, 1986, 1988; Palmieri, 1992; Brett, 2008).

These data suggest a compelling theoretical role for collagen as a dressing in wound management, but are relatively limited, being derived from experimental data and non-comparative case reports. The use of collagen in wound management has not yet been clearly translated into a platform for widespread clinical use, as these studies only offer evidence for collagen as a dressing matrix and not as an active agent.

By comparison, the use of collagen materials as a scaffold in hernia and abdominal wound repair (Holl-Allen, 1984; Buinewicz and Rosen, 2004; Parker et al, 2006; Baillie et al, 2007; Jehle et al, 2007) seems to be clinically and cost-effective, but their use as a dressing in healing indolent chronic skin wounds, healing by secondary intention, has yet to be convincingly proven, despite the fact that there are many such products already available (*Table 2*).

This review looks at the currently available data to explore and substantiate any case for the development and clinical use of collagen sheet dressings, paste or fleece for the stimulation of closure in indolent 'hard-to-heal' chronic wounds.

Skin, with its inherent epidermis and dermis, provides the ideal cover for any wound. For this reason, a whole range of autologous skin graft techniques are available to replace lost skin, from split-thickness skin grafts to complex pedicle or free microvascular myocutaneous flaps, but these may not be sufficient to cover the widespread skin loss which may occur after extensive burns (Purna and Babu, 2000). All these grafts give primary cover with an optimal chance of healing, and have also been widely used to cover chronic wounds in which healing is stalled despite adequate preparation of the wound bed to optimise closure by secondary intention. Nevertheless, these grafted wounds are at risk of failure or infection (of both donor and recipient sites), with considerable subsequent morbidity. Several techniques have been designed to extend the area of split-thickness grafts available, such as meshing, or to make harvest simpler and accessible, as in pinch grafting, but they still inflict an injury to healthy, intact skin (Horch et al, 2005).

The use of dermal allografts still has a place (Pianigiani et al, 2004), but progress has turned to the evolution of tissue engineering from the development of monolayer culture of keratinocytes through to the use of collagen, hyaluronic acid or synthetic polymers as carriers of live, human-derived fibroblasts and keratinocytes (Horch et al, 2000). Even freeze-dried cellular dressings with a carrier matrix have been shown to be effective in healing wounds of diverse origins (Nanchahal and Ward, 1992; Gentzkow et al, 1996; Munster, 1996; Sabolinski et al, 1996; Leigh et al, 1987; Polak et al, 1997; Falanga and Sabolinsky, 1999; Tay et al, 2000; Veves et al, 2002; Bello and Falabella, 2002; Omar et al, 2002; Curran and Plosker, 2002; Caravaggi et al, 2003; Krishnamoorthy et al, 2003; Ehrlich, 2004; Harding et al, 2005; Cavorsi et al, 2006; Shealy and DeLoach, 2006; Ehrenreich and Ruszczak, 2006; Vanschiedt et al, 2007).

These advances in the production of artificial skin substitutes have the potential to replace lost functional cells, which can also successfully orchestrate the dysfunctional wound healing process found in chronic wounds. However, they come at an expensive price for introduction into wide clinical practice and it could be argued that much more extensive evidence is needed for their adoption. It has also been argued that there is no replacement for an autograft (Paul, 2008). The application of these skin substitutes vary from simple direct application as cell monolayers to polymer, or animal-derived collagen scaffolds, and their diversity deserves a separate review. The interaction of collagen alone within the wound is also considerable and is the basis of this review.

Collagen and acellular dermal skin substitute dressings

Promogran® (Systagenix)

This product deserves special interest, as it has been the subject of prolonged and in-depth research and marketing. It is a matrix dressing containing regenerated cellulose and collagen which has been shown experimentally to modulate proteases, metalloproteinases and elastase in open wounds (Cullen et al, 2002a; Hart et al, 2002) by 'protecting' platelet-derived growth factor (PDGF) and other growth factors in the wound. There is also clinical trial evidence that Promogran may be able to handle exudate and accelerate healing in venous and diabetic ulcers (Vin et al, 2002; Veves et al, 2002), but the clinical significance of this is open to doubt (Cullen et al, 2002b). There is a plethora of case reports and small patient series, which are supportive, but these have a high risk of publication bias.

In the authors' opinion, the difficulty with the clinical studies and attempts at randomised controlled trials (RCTs) is that:

- They are underpowered, with randomisation which is poor or not defined
- They often compare the dressing with an ineffective 'standard' therapy (often bland Vaseline gauze)
- Evaluations are unblinded and subjective (and therefore biased), and made by untrained, unvalidated observers and methodology.

Often there are high dropout rates so that assessment even up to 12 weeks is compromised. While it is appreciated that the gold standard of complete healing has to be replaced by surrogates of healing rates (Gelfand et al, 2002) using, for example, computerised planimetry, there is often too much emphasis on poor clinical assessments of presence of infection or inflammation, pain, handling of exudate, odour, numbers of dressing changes and dressing acceptability or tolerance, and inadequate 'add-on' attempts at cost-effectiveness (although one study, using a Markov-based health economic analysis did suggest that Promogran may be cost-effective; Ghatnekar et al, 2002). These are, of course, criticisms that can be levelled at almost all trials involving the healing of chronic ulcers and, ideally, more high quality research is genuinely needed.

Nevertheless, there is a consistency in the clinical trials involving Promogran to faster healing rates and better outcomes. Like so many other dressings, it has also been combined with silver to improve control of bioburden.

Other collagen acellular dermal matrix dressings

There have been several sources of collagen for use as a dermal matrix (*Table 2*). Some have been used as temporary dressings in burn care therapy for many years to optimise the wound healing process or improve post-burn scarring (Robson et al, 1973; Purna and Baboo, 2000; Ehrenreich and Rusczak, 2006; Shores et al, 2007). The dermal skin substitute Integra® (Integra Life Sciences), which is a bi-layer bovine collagen and polysiloxane dressing, has been extensively used for this purpose, but there have been few prospective RCTs comparing it with other available skin substitutes (Nguyen and Dickson, 2006).

AlloDerm® (Life CellCorp), an acellular dermal matrix derived from cadaveric skin, and Biobrane®, (Smith and Nephew), a porcine collagen with a layer of silicone, have also been widely used for burn management (McHugh et al, 1986; Wainwright, 1995). Adequate trials studying their use, and other similar dressings, in different wound types other than burns are also awaited. All these biological dressings, including porcine and bovine collagen as well

Table 2

Currently available acellular collagen and dermal matrix products for wound care (the list is not exhaustive)

Permacol®	porcine dermis	Tissue Science Laboratroies
Integra®	bovine tendon/synthetic polysiloxane	Integra Lifesciences
Puracol	Bovine collagen	Medline Industries
Promogran®	collagen/regenerated cellulose	Systagenix
Fibracol®	collagen/alginate	Systagenix
Promogran Prisma®	collagen/Ag	Systagenix
Oasis®	porcine small intestine submucosa	Cook Biotech
Biostep®	porcine collagen/alginate/CMC +/- Ag	Smith and Nephew
Colactive	porcine collagen/alginate +/- Ag	Smith and Nephew
Catrix®	bovine carilage (powder)	Lescarden Inc
Cellerate®	bovine collagen	Wound Care Innovations
Collieva™	bovine collagen	CollMed Laboratories
Medifil®	bovine collagen gel	BioCore
Skintemp	bovine collagen	BioCore
Matriderm®	collagen/elastin	Suwelak
Decutastar®	equine collagen	ADL
Septocoll® E	collagen fleece/gentamicin	Biomet
Colladerm	bovine/equine/gentamicin	Innocoll
AlloDerm®	human cadaver de-epithelialised skin	LifeCell Corp
Cymetra®	particulate alloderm	LifeCell Corp
Mediskin	porcine dermis	Brennan Medical
EZ-Derm™	aldehyde linked porcine dermis	Brennan Medical
Biobrane®	porcine collagen/silicone membrane	Smith and Nephew
GraftJacket®	human cadaver dermal matrix	Wright Medical Technology

* Dermagraft® (Advance Tissue Sciences) is freeze dried bovine collagen used as a carrier for human fibroblasts
* Apligraf® (Organogenesis) is a bi-layered dressing of cultured human epidermis bonded to bovine collagen containing human fibroblasts

as that from human origin, have been refined and prepared through several different processes of purification to render them non-antigenic and sterile (Huang et al, 2004; Rosales et al, 2004; Rudnick, 2006; Nataraj et al, 2007). Like Promogran, they have since been linked with other materials, for example, alginates and antimicrobial agents, such as silver and gentamicin. There are several types of availability ranging from fleeces, sponges, films and pastes to bi-layered sheet dressings, which have all been previously well-reviewed (Shores et al, 2007; Brett, 2008).

The use of pig, small intestinal, submucosa (Oasis® Wound Matrix) has been experimentally studied as an ECM graft with subsequent successful use in multicentre clinical trials (Mostow et al, 2005; Niezgoda et al, 2005). Although showing a difference in healing rates, favouring the ECM matrix dressing, both studies were relatively underpowered. The first involved 120 patients with relatively small venous ulcers and reached a statistically significant difference compared with standard compression alone ($p<0.02$); but the second, involving 73 patients with diabetic foot ulcers, did not reach significance compared with topically-applied platelet-derived growth factors (PDGF). In the venous leg ulcer study, more healed ulcers remained healed at six months after treatment with the ECM matrix dressing, compared with the patients treated with compression alone.

The use of growth factors has proven to be inconsistent, and seems to have fallen off the wound healing formulary (Fu et al, 2005). However, the clinical evaluation of collagen still promises that there may be a therapeutic role to orchestrate the healing of 'hard-to-heal', uninfected, chronic wounds which have a prepared wound bed. The many interactions with the ECM (*Table 1*) suggest that collagen is a suitable candidate to initiate healing or restore the cellular milieu in stalled wounds (Agren and Werthen, 2007). Again, more research is needed, but the cost of further adequate RCTs in multicentre trials for clear scientific proof and meta-analysis is prohibitive. There are plenty of case reports or short patient series that have evaluated collagen matrix dressings to heal chronic ulcers, indicating success (Sabolinski, 1996; Yamada et al, 1999; Shealy and DeLoach, 2006).

Conclusions

Functionally, collagen has a pivotal role by means of its wide-ranging functions, spanning the spectrum of processes involved in a healing wound. However, collagen dressings have only been scientifically proven to be effective exogenously, as a substrate and viable biomaterial. Its appealing endogenous functions by means of a dressing are yet to be proven. Is it then worth the effort

of producing a new collagen dressing, or evaluating collagen dressings further, ideally supported by a multicentre, randomised, controlled trial? From a cost point of view alone, it would be prohibitive; let alone the logistics of mounting such a trial to show any clear-cut advantage. There are several, possibly already too many, collagen dressings available, so why should another, which offers no particularly special or extra effectiveness or price advantage be worth marketing? Some collagen products have been widely exposed in symposia or 'special issues' of journals, presented throughout this review, without becoming integrated into wound management in general, and may follow the fate of the wide range of growth factors and cellular/skin substitutes that are hardly enjoying widespread use (Fu et al, 2005).

There is, in addition, considerable pressure from the need for evidence-based medicine to prove the value of drugs and devices. The Cochrane systematic review has proven to be unhelpful in the field of wound care, with each foray into different aspects coming up with the conclusion that 'more research is needed' (Leaper, 2009). For similar reasons, it is unlikely that guidelines can be expected from institutions such as the National Institute of Health and Clinical Evidence (NICE) or the Scottish Intercollegiate Guidelines Network (SIGN). The likely lack of any forthcoming guidelines for the use of collagen dressings in clinical wound management also militates against the introduction of another to an already crowded field.

In the field of a bioengineered skin substitute, collagen is proving effective for skin constructs (such as Dermagraft® and Apligraf®). The authors foresee this as the future for collagen-based wound management. Nevertheless, the compelling experimental data around the value and potential influence of collagen in the healing of stalled traumatic and surgical wounds, or 'hard-to-heal' chronic ulcers of all types, including diabetic, venous leg and pressure ulcers, clearly remains attractive for many scientific groups and manufacturers. WUK

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Key points

- Collagen is a key protein in connective tissue and in the process of wound healing by repair and formation of scar.
- Collagen is intimately involved in many tissue physiological processes.
- Collagen dressings, particularly to promote healing in chronic wounds, are clearly attractive and several experimental and clinical studies have shown promise.
- The evaluation of collagen dressings with an unequivocal result in adequately powered, randomised clinical trials may be prohibitive.