

Insulin-like growth factor-I and wound healing, a potential answer to non-healing wounds: A systematic review of the literature and future perspectives

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Abstract. The induction of wound healing by insulin-like growth factor-I (IGF-I) has been demonstrated in several animal studies; however, there are disproportionately fewer studies assessing its value in humans. The aim of the present review is to provide a comprehensive summary of all the available evidence pertaining to the effects of IGF-I administration on the process of wound anaplasias, both in human tissues *in vivo* and in cells *in vitro*. A systematic search of Medline, Scopus and Google Scholar was performed for relevant studies published until May 2020. Overall, 11 studies were included. Of these, 2 studies were conducted in human subjects, whereas the rest of them were performed using *in vitro* models of human cell lines. All studies demonstrated a positive association between IGF-I and wound anaplasias; IGF-I promoted the migration of keratinocytes, thus playing an important role in wound epithelialization as well as enabling wound bed contraction, and it also stimulated hyaluronan synthesis. The wound healing-promoting effect of IGF-I may be a great asset in dealing with the healing of challenging wounds; thus, this type of treatment could be extremely useful in addressing patients with large burn wounds, chronic diabetic ulcers and patients with impaired wound healing. Nevertheless, the route of recombinant IGF-I administration, the recommended dosage, as well as the indications for clinical use of this growth factor remain to be determined and thus, additional clinical trials are required, with a focus on the medical use of recombinant IGF-I in wound anaplasias.

Introduction

Wound anaplasias is a dynamic and particularly complex process that involves several cell types (such as keratinocytes and fibroblasts) as well as fundamental cellular processes, including proliferation, differentiation and migration (1). The biological responses of these cells are initiated and mediated primarily by growth factors, acting solely or in combination with other factors, in a paracrine or autocrine manner (2-4).

In particular, wound healing involves both proliferation and migration of keratinocytes from the wound edges, under the influence of several growth factors (5). The insulin-like growth factor-I (IGF-I), also termed somatomedin C, is a hormone similar to insulin in terms of its molecular structure, which plays an important role during puberty and displays several anabolic effects in humans (5). Approximately 98% of IGF-I is bound to one of six binding proteins. IGFBP-3 accounts for 80% of all IGF binding (6). IGF-I promotes its effect by binding to specific receptors on the cell surface (7). There is a growing body of evidence showing that IGF-I serves an important role in the regeneration of several different tissues following injury (8-12). Interestingly, despite this growing body of literature showing the wound healing effects of IGF-I in animals (13-16), there are only a few studies investigating its effects in humans.

In this context, a systematic search of the literature was performed to provide a summary of all the available evidence regarding the effects of IGF-I administration on wound healing in humans, and to outline the perspectives for future studies and medical applications. The present review is the first systematic review summarizing the role of IGF-I in wound healing in humans.

Materials and methods

A systematic search of MEDLINE, Scopus and Google Scholar were performed using the terms 'IGF-I', 'insulin-like growth factor I' and 'wound', 'healing' and 'regeneration' combined with the Boolean operators AND/OR, to identify studies performed in humans on the effects of IGF-I in the process of wound healing published until May 2020. A priori

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selected exclusion criteria were: i) reviews, editorials and clinical vignettes; ii) animal studies; iii) studies without explicitly reported experimental details; iv) studies where the full-text was unavailable; and v) studies published in any language other than English.

Following removal of duplicate studies, the abstract list generated by the above search was independently screened by two authors for identification of potentially relevant studies. After excluding papers of obvious irrelevance, full-text evaluation of all remaining studies was performed for completeness and eligibility of reported data, according to the aforementioned inclusion/exclusion criteria. Any ensuing disagreements were resolved by a third reviewer. Reference lists of all relevant studies were further manually checked. The present review was performed according to the PRISMA guidelines (17) (Fig. S1).

Data of interest that were recorded, including the type of study and year of publication, the external administration of IGF-I or measurements of endogenous IGF-I production, the human tissue or cell type investigated, whether the study was performed *in vivo* or *in vitro*, as well as the experimental outcomes. After thorough full-text evaluation of the included studies, data of interest were inserted into Microsoft Excel 2014 (Microsoft Corporation) and were subsequently crosschecked by two of the authors for discrepancies.

Results

The initial search of the aforementioned databases yielded 765 studies. After duplicate removal, 735 studies were screened and 686 were excluded. A total of 49 full text articles were assessed for eligibility. Finally, 11 studies were included in this review, with the year of their publication ranging from 1992-2010.

Of these 11 studies, 2 were performed *in vivo* and the other 9 were performed *in vitro* using human cell cultures primarily obtained from infant foreskin. Specifically, the study by Vogt *et al* (18) was performed on split-thickness skin wounds of patients that had undergone reconstructive plastic surgery, whereas the study by Wicke *et al* (19) was performed on surgical wounds of orthopedic patients. Endogenous levels of IGF-I were measured during wound healing in the *in vivo* studies, whilst all cell culture experiments involved exogenous administration of IGF-I. Several other growth factors were studied in parallel with IGF-I, utilizing either PCR or immunassay studies.

The majority of studies revealed that IGF-I is an important mitogen involved during the process of wound healing. Specifically, both *in vitro* (13,20-22) and *in vivo* (18) studies showed that IGF-I is an important stimulant for the migration of keratinocytes, thus playing a central role in wound epithelialization. Lee *et al* (23) demonstrated that IGF-I assisted in wound bed contraction, minimizing the gap between the edges of the wound. In particular, the combination of IGF-I and IGFBP-1 promoted wound bed contraction, which is a critical step of wound healing (23). Additionally, Kuroda *et al* demonstrated that IGF-I results in the stimulation of hyaluronan synthesis *in vitro* (24). Interestingly, the aged patients appeared to exhibit lower plasma as well as wound levels of IGF-I, which resulted in delayed wound healing (19). Hyde *et al* (25) in 2004 demonstrated that IGF-I combined with extracellular matrix protein vitronectin resulted in significantly enhanced protein

synthesis and cell migration in the wound area (25). Moreover, Lee *et al* (26) demonstrated the role of IGF-I in fibroblast proliferation and keratinocyte migration. Table I summarizes the outcomes of the reviewed studies.

Discussion

Wound healing is a complex process that occurs in several phases and involves several factors. IGF-I is a hormone that plays an important role during growth and development, and is expressed in several tissues in humans where it exerts several anabolic effects (27,28). The liver is the primary source of generation of circulating IGF-I (27,28), although local secretion of IGF-I has been observed in multiple tissues (29). Beyond its central role as a promoter of growth, IGF-I is involved in the normal function of several organs, such as the kidneys, brain, skeletal muscle and bone, amongst others (30-33). Furthermore, IGF-I possesses a crucial role in wound healing via multiple mechanisms; it acts as a chemotactic agent for endothelial cells, stimulates the proliferation and migration of keratinocytes and fibroblasts, and increases the wound strength (34).

Several animal studies have been conducted to assess the role of IGF-I in the process of wound anaplasias, using both local as well as systemic administration. Lynch *et al* (3) demonstrated a 132% increase in the dermal thickness and a 300% increase in the number of connective tissue cells within the wound site as well as in the collagen content and maturity, following the application of recombinant IGF-I and platelet-derived growth factor-2 in partial thickness wounds, which were surgically induced in the back and thoracic areas of young white Yorkshire pigs. In addition, Skottner *et al* (35) studied the anabolic actions of IGF-I following systemic and local administration in mutant dwarf rats. The results of their study indicated that local administration of IGF-I had a significant positive effect on wound regeneration. Moreover, a placebo-controlled trial demonstrated that IGF-I depletion in hypophysectomized rats decreased wound protein levels and hydroxyproline content by 50%, and that IGF-I infusion returned the levels of these variables to normal (36).

Given the above findings in animal models, further studies were performed regarding the optimum means of IGF-I delivery in the wound micro-environment. Jeschke *et al* (37) concluded that liposomal IGF-I gene transfer can accelerate wound anaplasias. Moreover, another study examining the role of systemic administration of IGF-I in rats concluded that IGF-I improved the healing process in collagenous tissue (38).

Several other studies have shown that IGF-I contributes to the repair of a variety of tissues; Lu *et al* (39) demonstrated the ability of IGF-I to promote repair of skeletal muscle tissue, and Kluge *et al* (40) in myocardial tissue. Moreover, the significance of IGF-I in airway remodeling has been also found in patients with inflammatory bowel disorder (41), and IGF-I was shown to attenuate TNF- α and IL-1 β production in rat burn wounds (42).

The present study has some limitations. There were significant differences between the sample sizes and methodology of the reviewed studies. The evidence provided in the present review is limited by the heterogeneity of the included studies. Additionally, the vast majority of IGF-I studies have

Table I. Summary of the results in the reviewed studies.

First author, year	<i>In vitro/ in vivo</i>	Method	Tissue/cell type (origin)	Growth factors assessed	Results	Refs.
Barreca <i>et al.</i> , 1992	<i>In vitro</i>	Northern blot	Cell culture (human keratinocytes-skin biopsy)	IGF-I, IGF-II	Human fibroblasts synthesize IGF peptides, whereas keratinocytes do not. Fibroblast-derived IGFs stimulate keratinocyte growth in a paracrine fashion, highlighting their potential role in the regulation of keratinocyte proliferation, in skin growth and in wound healing.	(44)
Tsuboi <i>et al.</i> , 1992	<i>In vitro</i>	Sato and Rifkin method	Cell culture (human keratinocytes-infant foreskins)	IGF-I, TGF- α , aFGF, bFGF, KGF	TGF- α , aFGF, bFGF, KGF and IGF-I stimulate the migration of keratinocytes, whereas as TGF- β 2 suppresses it.	(20)
Kratz <i>et al.</i> , 1994	<i>In vitro</i>	Estimation of re-epithelialization	Sterile human skin	IGF-I, IGF-II, IGFBP-1 (mastectomy specimens)	IGF-1 stimulates efficient re-epithelialization of the wounds both alone and in the presence of recombinant IGFBP-1.	(21)
Bhora <i>et al.</i> , 1995	<i>In vitro</i>	Immuno-histochemistry	Full thickness skin (amputated lower extremities)	IGF-I, FGF	Important mitogens	(13)
Lee <i>et al.</i> , 1996	<i>In vitro</i>	Estimation of gel contraction	Cell culture (human keratinocytes-infant foreskins)	IGF-I, IGFBP-1	The combination of IGF-I and IGFBP-1 promotes the contraction of fibroblast-embedded collagen gel	(23)
Vogt <i>et al.</i> , 1998	<i>In vivo</i>	ELISA	Split-thickness skin wounds (reconstructive surgery)	IGF-I, TGF- β 2	Stimulation of epithelialization during the first day	(18)
Kuroda <i>et al.</i> , 2001	<i>In vitro</i>	PCR	Cell culture (normal adult skin)	IGF-I, FGF	Stimulation of hyaluronansynthesis, with important implications for tissue remodeling, such as in development and wound healing.	(24)
Wicke <i>et al.</i> , 2002	<i>In vivo</i>	ELISA	Surgical trauma (orthopedic surgery)	IGF-I, IGF-II, IGFBP-3	Aged patients had lower plasma levels and correspondingly lower wound localized levels of IGF-I, IGFBP-3 on all 4 postoperative days. Plasma and wound fluid levels were reduced by 25-70% in the aged patients	(19)
Haase <i>et al.</i> , 2003	<i>In vitro</i>	PCR	Cell culture (human keratinocytes-infant foreskins)	IGF-I	IGF-I can influence different components of the keratinocyte migration machinery that determines the speed of wound epithelialization.	(22)
Hyde <i>et al.</i> , 2004	<i>In vitro</i>	PCR	Cell culture (HaCAT-human keratinocytes)	IGF-II:VN and IGF-I:IGFBP-5:VN	Functional assays demonstrated that both the IGF-II:VN and IGF-I:IGFBP-5:VN complexes resulted in significantly enhanced protein synthesis and cell migration through Transwell pores in skin keratinocytes (HaCAT).	(25)
Lee <i>et al.</i> , 2010	<i>In vitro</i>	PCR	Cell culture (human keratinocytes-foreskins)	GH	GH enhances the local formation of IGF-I, which activates fibroblast proliferation and keratinocyte migration	(26)

aFGF, acidic fibroblast growth factor; bFGF, basic FGF; TGF, transforming growth factor; KGF, keratinocyte growth factor; HGF, hepatocyte growth factor; IGF, insulin-like growth factor; PDGF, platelet derived growth factor; IGFBP, insulin-like growth factor binding protein; GH, growth hormone; VN, vitronectin.

been performed in animals, not humans. Currently, large burn wounds as well as chronic diabetic ulcers are challenging clinical issues that are poorly addressed. Given the apparently beneficial role of IGF-I in wound healing, it would be of great value to utilize the clinical effects of IGF-I in such patients. In addition, since the main concern in chronic, partially healed wounds is an inappropriately excessive inflammatory response that fails to resolve (43), the research findings included in this systematic review suggest that local IGF-I administration would be of benefit in chronic, difficult-to-heal wound patients.

In conclusion, IGF-I is a hormone with profound anabolic activities and an important role in wound anaplasias. The IGF-I-induced stimulation of wound healing has been demonstrated in several animal studies. The present systematic review reports a potentially promising, evidence-based practice favoring the use of IGF-I in addressing patients with large burn wounds, chronic diabetic ulcers and patients with impaired wound healing, as IGF-I has been found to positively influence important outcomes of the wound healing process. However, several issues regarding IGF-I administration in those patients remain to be specified, such as the route of recombinant IGF-I administration, the recommended dosage, as well as the indications for its clinical use. Hence, more consistent clinical trials are needed, focusing on the medical use of recombinant IGF-I in patients whose healing process has been compromised.

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Authors' contributions

ZG conceived the subject of the review. EK and DV performed the literature search. APa and APh analyzed and interpreted the data. ZG wrote the manuscript. GK and DM critically revised the manuscript. All the authors have read and approved the final version of this manuscript. Data sharing is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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