

# The Use of Growth Factors in Wound Healing: An Update

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## ABSTRACT

**Wound healing is a complex and well-integrated process. Growth factors have an important role in modulation of wound healing steps. Because of their important role in wound healing, growth factors have been used as triggering agents in chronic wounds. In this article, we provide an up-to-date review of growth factors found to be effective in chronic ulcers and are commercially available on the market for treatment of chronic ulcers.**

**KEY WORDS:** *Basic fibroblast growth factor, Epidermal growth factor, Platelet-derived growth factor, Vascular endothelial growth factor*

## INTRODUCTION

Wound healing is a complex process consisting of well-programmed and interlocking phases. During wound healing, which can be summarized as inflammatory, proliferative, and remodeling phases, many cells and the mediators and growth factors that they secrete are effective.<sup>1</sup> Although the process is shorter in surgical wounds that are closed primarily, shrinkage and closure are expected in about 1 month when the wound is left to itself. The causes of acute wounds are mostly trauma and previous surgeries. Wounds that do not heal in 1 month are called chronic wounds. In chronic wounds, wound healing usually remains in the inflammatory or proliferative phase, and the wound healing pattern is impaired. The most common causes of chronic wounds are venous ulcers and neuropathic and ischemic wounds.<sup>2</sup> Many growth factors have been tried

as treatment, and some of them have been used for therapeutic purposes to allow wound healing to remain stable. This section will explain growth factors that are effective in wound treatment.

## GROWTH FACTORS

Growth factors are regulators in peptide structures that have roles in every stage of wound healing.<sup>3</sup> Growth factors are secreted from many cell groups, such as macrophages, platelets, fibroblasts, keratinocytes, and endothelium, which are involved in wound healing. Growth factors cause an autocrine response in the cell in which they are secreted, a paracrine response in adjacent cells, and an endocrine response in distant cells.<sup>4</sup> The activity of a growth factor secreted by any cell can be reduced by another growth factor secreted by another cell. Two different cells can affect each other's functions with the growth factors they secrete. Growth factors can be defined as the method of communication of cells with each other in mechanisms of wound healing.

### Effects of growth factors

Growth factors not only enable cells in the wound healing mechanism to communicate with each other but also trigger chemotaxis, deposition in the extracellular matrix, proliferation, and angiogenesis in the cell by binding to their respective receptors after they are secreted.

In the chronic wound healing process, growth factors may not be produced in sufficient quantities. Although the physiology of each chronic wound differs, the application of external growth factors to the chronic wound may be beneficial in transforming the wound into an acute wound.

Although their half-lives are short, the effectiveness of growth factors has been shown in chronic wounds when injected during the vicious circle of the proliferative phase and in wounds where granulation cannot be formed. Irregular uses prevent the reduction (downregulation) of receptors in cells. Growth factors can be used in combination with other treatment methods. Although growth factors are never an alternative to reconstruction options,

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such as grafts or flaps, they can be used to support other treatments in the reconstruction steps.

Growth factors used in wound healing so far include those derived from epidermal growth factor (EGF), vascular endothelial growth factor, basic fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF). The main growth factors, the cells from which they are secreted, and their functions are summarized in Table 1.

#### Epidermal growth factor

Epidermal growth factor is a growth factor that was first isolated from the salivary glands of mice.<sup>5</sup> Research has shown that EGF increases fibroblast proliferation to the wound edges, increases epithelialization by increasing keratinocyte proliferation, and improves granulation by provoking de novo angiogenesis.<sup>6</sup> Because of these effects, EGF has been used clinically in diabetic foot wounds. There are 2 EGF products used in Turkey. One product is Heberprot (Hasbiotek, Abdi İbrahim), which is applied by topical injection around the wound and is available in 75-µg preparations. The recommended therapeutic dose is injection of 75 µg into and around the wound 3 times per week for 6 or 8 weeks.<sup>7</sup> The most common side effects of the drug are nausea and vomiting.<sup>8</sup> Monitoring and pre-medication are recommended in patients with these side effects.<sup>9</sup> The conversion of a chronic wound to an acute wound and its closure are among the other effects of EGF.

The other topical preparation of EGF is Regen-D cream; this cream is recommended to be applied directly on the wound.<sup>10,11</sup> After the ulcer area is cleaned, the cream is applied as a thin layer twice per day to cover the entire area.

#### Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is a signaling protein shown to have a role in vasculogenesis and angiogenesis.<sup>12</sup> There are 5 human VEGF isoforms (A, B, C, D, E) identified so far. Receptors of VEGF have shown effects on healing. The receptors are tyrosine kinase receptors on the cell surface and are activated by transphosphorylation.<sup>13</sup> The VEGF-1 receptor activates an inflammation-related response, whereas the VEGF-2 receptor triggers an angiogenesis-related response.<sup>14</sup>

Vascular endothelial growth factors are secreted by endothelial cells, smooth muscle cells, platelets, neutrophils, keratinocytes, monocytes, macrophages, and fibroblasts. Hypoxia is one of the most important factors affecting VEGF release.<sup>15</sup>

Recombinant VEGF produced with a plasmid carrying the VEGF gene has been shown to significantly shorten wound healing time in patients with diabetes and ischemia compared with a placebo group.<sup>16</sup> A recombinant VEGF preparation called Telbermin, which is in phase 1 studies and is applied topically, has been shown to accelerate wound healing in patients with chronic neuropathic ulcers.<sup>17</sup>

**TABLE 1.** List of Growth Factors and Their Role in the Wound-Healing Process

| Growth Factor                      | Abbreviation | Origin of Secretion                                                          | Function                                                                                                     |
|------------------------------------|--------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| Platelet-derived growth factor     | PDGF         | Platelets, keratinocytes, fibroblasts, endothelial cells, perivascular cells | Proliferation of fibroblasts, chemotaxis, collagen synthesis, angiogenesis, immunomodulation                 |
| Transforming growth factor-β       | TGF-β        | Platelets, keratinocytes, fibroblasts, endothelial cells, macrophages        | Proliferation of fibroblasts, chemotaxis, collagen synthesis, angiogenesis, immunomodulation                 |
| Transforming growth factor-α       | TGF-α        | Platelets, keratinocytes                                                     | Migration and proliferation of keratinocytes                                                                 |
| Epidermal growth factor            | EGF          | Platelets, keratinocytes, fibroblasts, endothelial cells                     | Migration and proliferation of keratinocytes                                                                 |
| Interleukins                       | IL-1, IL-10  | Leukocytes, keratinocytes                                                    | Fibroblast proliferation                                                                                     |
| Tumor necrosis factor              | TNF          | Leukocytes, keratinocytes                                                    | Increases inflammation                                                                                       |
| Fibroblast growth factor           | FGF          | Keratinocytes, macrophages                                                   | Proliferation of fibroblasts and epithelial cells, deposition of the matrix, wound contracture, angiogenesis |
| Keratinocyte growth factor         | KGF          | Fibroblasts                                                                  | Keratinocyte proliferation                                                                                   |
| Insulin-like growth factor         | IGF-1        | Fibroblasts                                                                  | Proliferation and differentiation of keratinocytes                                                           |
| Vascular endothelial growth factor | VEGF         | Platelets, keratinocytes, macrophages, neutrophils                           | Angiogenesis, increasing vascular permeability, chemotaxis of macrophages                                    |

### Basic fibroblast growth factor

The fibroblast growth factor (FGF) family consists of more than 20 growth factors, such as acidic FGF (aFGF or FGF-1) and basic FGF (bFGF or FGF-2).<sup>18</sup> Heparan sulfate binds to the released FGFs in the extracellular matrix, and the inactive FGF is stored as a growth factor reserve. Keratinocytes, fibroblasts, and endothelial cells produce FGFs; FGFs are also produced by muscle cells, chondrocytes, and mast cells.<sup>19</sup> Both FGF-1 and FGF-2, which are predominately shown in inflammatory cells and dermal fibroblasts, play a role in angiogenesis and wound healing. When released from the extracellular matrix, they have a paracrine effect on endothelial cells and an autocrine effect when released from endothelial cells.<sup>20</sup> Basic FGF or FGF-2 is one of the most well-defined and studied growth factors. Basic FGF was first characterized in 1974 and plays an active role in wound healing. During the first 3 days of wound healing, the activity of basic FGF is high. Basic FGF (FGF-2) plays a role in the formation of granulation tissue.

Basic FGF has also been used in the treatment of burns. Fu and colleagues showed accelerated wound healing in a prospective randomized multicenter study on 600 patients.<sup>21</sup> Hayashida and colleagues observed better scar healing in pediatric burns.<sup>22</sup> Spray preparations (Fiblast and Trafermin) are available abroad. Studies have shown the effectiveness of these agents for the closure of venous stasis ulcers, burn wounds, and exposed bones and tendons.<sup>23,24</sup>

### Platelet-derived growth factor

In the wound-healing process, the first cells to reach the damaged area and initiate wound healing are platelets. Platelets secrete many growth factors, especially PDGFs. Platelet-derived growth factor is a dimer protein found in platelets, macrophages, fibroblasts, and endothelial cells.<sup>25</sup> There are 3 isomers (designated AA, BB, and AB) and 2 receptors ( $\alpha$  and  $\beta$ ).<sup>26</sup> Platelet-derived growth factor is released from alpha granules in platelets in the early phase of wound healing and activates early-stage and late-stage inflammatory cells. In the late period of wound healing, PDGF increases the production of hyaluronic acid and fibronectin and increases extracellular matrix deposition.<sup>27</sup> Platelet-derived growth factor has chemoattractant and mitogenic effects on fibroblasts, smooth muscle cells, and endothelial cells.

Becaplermin, which mimics the endogenous PDGF-BB isomer, is produced by recombinant DNA technology (Regranex, Smith & Nephew). This agent, approved by the US Food and Drug Administration (FDA), is presently used in topical gel form and is widely used as a cicatrizer, especially in the United States. In randomized, prospective, placebo-controlled multicenter studies, topically applied human recombinant PDGF has been shown to accelerate

wound healing in patients with chronic diabetic foot ulcers.<sup>28</sup> Becaplermin gel is applied to an open wound once per day, and the agent is stored in the refrigerator. The treatment can be extended up to 20 weeks to observe the positive results of the application. The most common side effect is erythematous rash. However, the risk of developing malignancy is 5 times higher in patients who use 3 tubes for treatment, and the FDA has not approved the use of more.<sup>29</sup>

### Granulocyte colony-stimulating factor

Granulocyte colony-stimulating factor (G-CSF) is a cytokine found in the inflammatory phase of the wound bed. Granulocyte colony-stimulating factor is a glycoprotein growth factor that stimulates the proliferation of granulocyte cell colonies in the bone marrow.<sup>30</sup> In bacterial infections, the level of G-CSF increases and it can stimulate neutrophils and fight infection.<sup>31</sup> By calling Langerhans cells to the wound bed, G-CSF stimulates the proliferation of inflammatory cells and contraction of myofibroblasts in the wound bed.<sup>32</sup> In patients with diabetic foot wounds, where neutrophil functions such as migration and diapedesis are impaired, G-CSF may affect wound healing by increasing neutrophil and phagocytotic activity. Topical application of G-CSF has been shown to dramatically reduce wound recurrence and accelerate wound healing. Filgrastim (Neupogen) and lenograstim (Granocyte), which are G-CSF preparations, are available in Turkey as a subcutaneous application. Their application can reduce amputation rates, increases neutrophil levels in the blood, and shorten the duration of infection.<sup>33</sup>

### Insulin-like growth factor

Insulin-like growth factor 1 (IGF-1) is 7.6 kDa and consists of 70 amino acids. This growth factor is synthesized by fibroblasts in the dermis and dermal papillae.<sup>34</sup> Insulin-like growth factors are positive regulatory agents for the differentiation and proliferation of many cells, including tumor cells. Cytokines, which have cell-protective properties, are proliferation mediators for cells, and they also have a regulatory effect on cell apoptosis. Insulin-like growth factor has mitogenic and morphogenic effects on keratinocytes.<sup>35</sup> The effect of reepithelialization at the wound site and proliferation in hair follicles has been demonstrated.<sup>36</sup> Insulin-like growth factor plays a role as a progressive factor in the regeneration of fibroblast-derived tissues. Insulin-like growth factor can trigger angiogenesis via VEGF.<sup>37</sup> Research has shown that IGF-1 accelerates wound healing in diabetic models.<sup>38</sup> There is no preparation yet available.

## EFFECTS OF GROWTH FACTORS

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## CONCLUSIONS

Artificial growth factors are costly due to their protein structure and production processes. In addition, because of their short half-life, growth factors should be used at certain intervals and in multiple doses. Cold chain is one of the other factors that increase the cost.

Although the benefits have been shown in the literature, the results are not 100% effective. Therefore, the cost is the most important disadvantage in the use of growth factors.

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