Association Between Leptin and Wound Healing: An Update

Reviewed by:
Dr. Anil Ballani
Consultant Physician,
Hinduja & Lilavati Hospital,
Mumbai

Wound healing: An overview

Wound healing is a highly modulated dynamic cascade of cellular and biochemical events that usually results in the successful repair of injured tissues.[1] Wound healing is a crucial physiological process that consists of three phases: an inflammatory phase, a proliferative phase, and a maturation phase that includes angiogenesis, extracellular matrix (ECM) biosynthesis, epithelialization, and tissue remodelling.[2]

Process of wound healing

The process of wound healing comprises of three phases which includes inflammatory phase, proliferative phase and maturation phase which is illustrated in Figure 1:[3]

Figure 1: Phases of wound healing[3]

Inflammatory phase

- Starts within seconds after injury
- Fibrin clot formation
- This phase encompasses neutrophil infiltration, monocyte infiltration and differentiation to macrophage and lymphocyte infiltration
- Cutaneous neurogenic inflammation and hemostasis
- Recruitment of neutrophils to the injured tissue- during first 24 hours

Proliferative phase

- Comprises of re-epithelialization, angiogenesis, collagen synthesis, ECM formation
- Progressive infiltration of inflammatory monocytes-macrophages to the wound starts the second day after injury and reaching its maximum during the proliferative phase
- Circulating lymphocytes migrate to the skin early after injury reaching a plateau by 4th day

Maturation phase

- Starts in the second week of injury
- Skin integrity is restored by remodelling of the tissue and organization of the scar

Factors affecting wound healing

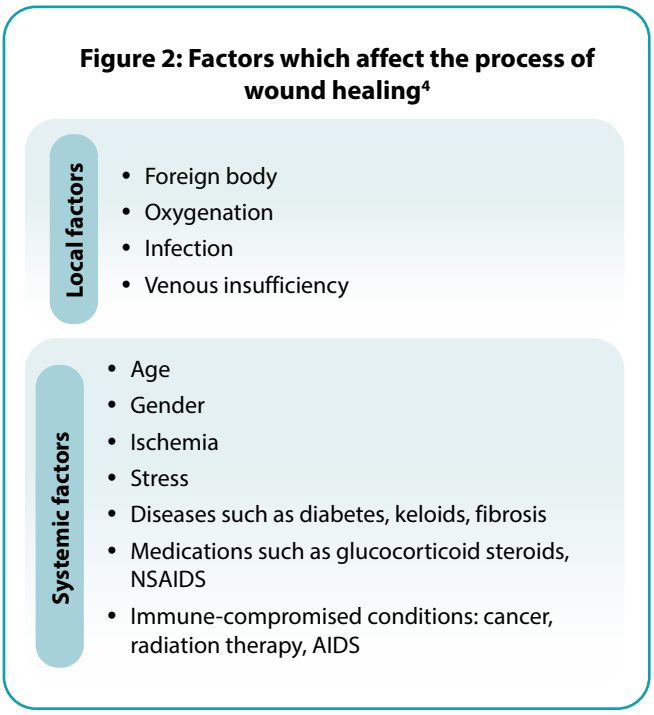
There are two factors which affect the process of wound healing which are summarized in Figure 2.[4]

Leptin: An overview

Leptin (LEP) is a hypoxia inducible pleiotropic cytokine, which is encoded by leptin gene (LEP gene) located on chromosome 7q31.3.[1,2] It is synthesized and secreted by mature adipose tissue. Leptin is an important regulator of metabolism, food intake and body mass.[1] As the leptin receptors are widely located, evidences have stated that it has a significant role in promoting angiogenesis, regulating the production of pro-inflammatory cytokines and alteration of hormonal system.[2,5] Furthermore, LEP plays a pivotal role in skin regeneration as its synthesis and secretion enhances after skin injury which results in reducing the wound healing cycle.[6]

Leptin binds to its specific receptor and stimulates the main signal pathways such as januskinanses (JAK), signal transducer and activator of transcription (STATs), mitogen-activated protein kinases (MAPK) and phosphoinositide-3-kinase pathways and thereby promoting regulation of various functions including energy metabolism and wound healing.[7]

Figure 2: Factors which affect the process of wound healing[4]



Role of leptin in wound healing

Leptin plays a crucial role in all the phases of wound healing:

Inflammatory phase

Evidences have stated that macrophages are involved in the healing process during this phase. In the initial stages of this wound repair, macrophages influx results in production of inflammatory cytokines, clearance of debris and in later stages it assists in resolving inflammation and promoting tissue repair.[8] LEP enhances the phagocytic activity of macrophages which thereby promotes wound healing.[9]

Similarly, LEP improves wound induced inflammation by increasing lymphocyte proliferation.[2] Furthermore, LEP increases the chemotaxis of macrophages and lymphocytes and promotes T helper cells 1 (Th 1) differentiation which leads to enhanced wound healing.[10] Studies have illustrated LEP role in enhancing the CD69 expression, which is a marker for the monocyte activation and this in turn promotes wound healing.[2]

Leptin is said to enhance the production of human b-defensin-2 (hBD-2) by stimulating STAT 1 AND STAT3 secretion which further assists in wound healing.[2,9]

Proliferative phase

This phase involves angiogenesis, which is modulated by endogeneous growth factors and hormones such as leptin, vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF-2).[2]

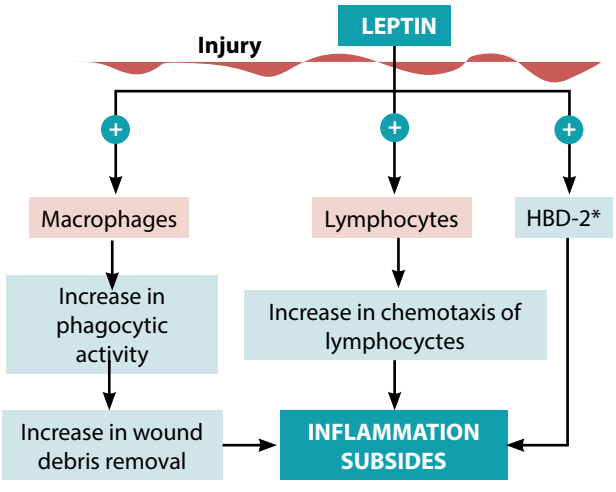
There's a plethora of evidence which supports that LEP enhances angiogenesis by increasing endothelial VEGF secretion.[11] Additionally, LEP assists in angiogenesis by improving FGF-2 function.[2] Re-epithelialization is the formation of new epidermis once the keratinocytes and fibroblasts proliferate and migrate towards the border of the wound.[12] Leptin tends to enhance re-epithelialization by increasing keratinocytes and fibroblasts proliferation through JAK/STAT pathway.[2,6,9]

Maturation phase

In addition to this, LEP amplifies scar formation by promoting fibroblast proliferation.[2] The role of leptin in different phases of wound healing is summarized in Table 1 and in Figure 3-5.

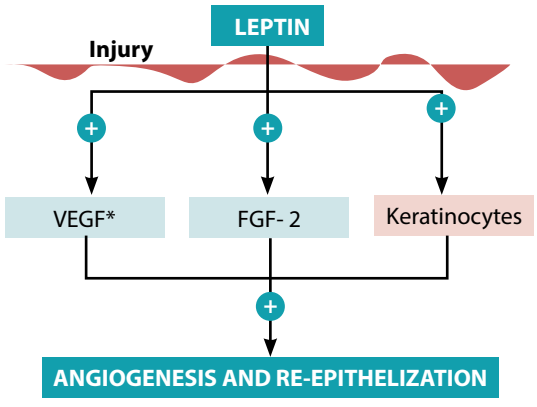
Table 1: Role of leptin in different phases in wound healing		
Wound healing phases	**Description[3]**	**Role of leptin in wound healing**
1. INFLAMMATORY PHASE	• Starts within seconds after injury • This phase encompasses neutrophil infiltration, monocyte infiltration and differentiation to macrophage and lymphocyte infiltration • Cutaneous neurogenic inflammation and hemostasis • Recruitment of neutrophils to the injured tissue- during first 24 hours	• Leptin enhances the phagocytic activity of macrophages which thereby promotes wound healing.[8] • Leptin improves wound induced inflammation by increasing lymphocyte proliferation.[2] • Leptin increases the chemotaxis of macrophages and lymphocytes and promotes T helper cells 1 (Th 1) differentiation which leads to enhanced wound healing.[9] • Leptin is said to inhibit tumor necrosis factor alpha and enhances the production of human b-defensin-2 (hBD-2) by stimulating STAT 1 AND STAT3 secretion which further assists in wound healing.[2]
2. PROLIFERATIVE PHASE	• Comprises of re-epithelialization, angiogenesis, collagen synthesis, ECM formation. • Progressive infiltration of inflammatory monocytes-macrophages to the wound starts the second day after injury and reaching its maximum during the proliferative phase. • Circulating lymphocytes migrate to the skin early after injury reaching a plateau by 4th day.	• There's a plethora of evidence which supports that LEP enhances angiogenesis by increasing endothelial VEGF secretion.[10] • Leptin assists in angiogenesis by improving FGF-2 function.[2] • Leptin tends to enhance keratinocytes and fibroblasts proliferation through JAK/STAT pathway which results in re-epithelization.[2,5,8]
3. MATURATION PHASE	• Starts in the second week of injury • Skin integrity is restored by remodelling of the tissue and organization of the scar	Leptin amplifies scar formation by promoting fibroblast proliferation.[2]

Figure 3: Role of leptin in inflammatory phase[8-10]



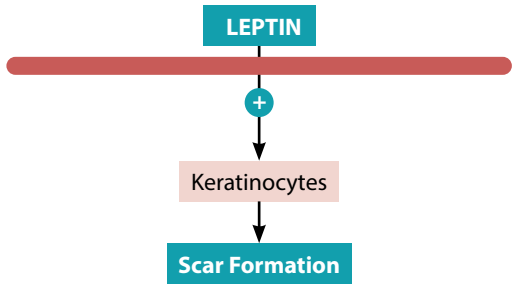
* Human b-defensin-2

Figure 4: Role of leptin in proliferative phase[2,6,9,11]



*vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF-2).

Figure 5: Role of leptin in maturation phase[2]



Conclusion

The physiological regulation of skin wound healing is a complex process that requires many cell types and mediators to interact in a highly sophisticated temporal sequence. As explained in this artefact, leptin has been shown to promote wound healing in the skin by enhancing the proliferation, differentiation/function and migration of epidermal keratinocytes and increasing angiogenesis and re-epithelialization around the injured area which justifies the association between leptin and wound healing.

CLINICAL EVIDENCE

Leptin accelerates endothelial wound healing: Role of endothelial nitric oxide synthase expression.[13]

1

A study conducted to evaluate the alterations of endothelial nitric oxide synthase on human umbilical vein endothelial cells wound healing in control group and treatment groups with leptin

2

The difference between the control and leptin treatment groups was statistically significant ($P<0.05$)

3

CONCLUSION:

The expression of endothelial nitric oxide synthase in human umbilical vein endothelial cells increased with leptin dose, with the highest increase in the group treated with 100 ng/mL leptin

References

1. Murad A, Nath AK, Cha ST, Demir E, Flores-Riveros J, Sierra-Honigmann MR. Leptin is an autocrine/paracrine regulator of wound healing. *Faseb J.* 2003;17(13):1895-7.
2. Yuan C, Liao J, Zheng L, Ding L, Teng X, Lin X, Wang L. Current knowledge of leptin in wound healing: A collaborative review. Front. *Pharmacol.* 2022;13:968142.
3. Dorantes LC, Canedo-ayala M. Skin Acute Wound Healing: A Comprehensive Review. *Int J Inflammation*. 2019.
4. Guo S, DiPietro LA. Factors Affecting Wound Healing. *J Dent Res.* 2010; 89(3):219-229.
5. Tadokoro S, Ide S, Tokuyama R, et al. Leptin promotes wound healing in the skin. *PLoS One.* 2015 Mar 23;10(3)
6. Su X, Cheng Y and Chang D. The Important Role of Leptin in Modulating the Risk of Dermatological Diseases. *Front. Immunol.* 2021;11.
7. Lin J, Yan G. Roles of leptin-mediated intracellular signaling pathways on wound healing. *Chinese Journal of Reparative and Reconstructive Surgery*. 2007;21(11):1254-1258.
8. Boniakowski AE, Kimball AS, Jacobs BN, et al. Macrophage-Mediated Inflammation in Normal and Diabetic Wound Healing. *J Immunol*. 2017;199 (1): 17-24.
9. Dopytalska K, Baranowska-Bik A, Roszkiewicz M, Bik W, Walecka I. The role of leptin in selected skin diseases. *Lipids in Health and Disease.* 2020;19(1):1-10.
10. Matarese G, Moschos S, Mantzoros CS. Leptin in Immunology. *J Immunol.* 2005; 174 (6): 3137-3142.
11. Nwadozi E, Ng A, Stromberg A, Liu H. Y, Olsson K., Gustafsson T, et al. Leptin is a physiological regulator of skeletal muscle angiogenesis and islocally produced by PDGFRα and PDGFRβ expressing perivascular cells. *Angiogenesis*. 2019;22 (1):103–115.
12. Jia N, Liu J, Zhu G, Liang Y, Wang Y, Wang W, Chen Y, Yang J, Zhang W, Zhang J. Polarization of ADAM17-driven EGFR signalling in electric field-guided collective migration of epidermal sheets. *J Cell Mol Med*. 2020;24(23):14073-14085.
13. Yiğittürk G, Önal MÖ, Subaşı E, et al. Leptin Accelerates Endothelial Wound Healing: Role of Endothelial Nitric Oxide Synthase Expression. *Anatol J Cardiol*. 2022;26(10):750-756.